Topics in Heterocyclic Chemistry 45
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Synthesis and Modification of Heterocycles by Metal-Catalyzed Cross-coupling Reactions

Springer

45
Topics in Heterocyclic Chemistry

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The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

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Tamás Patonay • Krisztina Kónya
Editors

Synthesis and Modification of Heterocycles by Metal-Catalyzed Cross-coupling Reactions

With contributions by

Á. Balázs · G. Dormán · J. Gerencsér · M. Koley · A. Kotschy · M.D. Mihovilovic · Z. Novák · L. Rycek · M. Schnürch · R.S.G.R. Seixas · A.M.S. Silva · V.L.M. Silva · L. Wimmer

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Dedicated to the memory of Professor Tamás Patonay

Preface

This volume is focused on new and innovative metal-catalysed reactions that lead to the formation of a carbon–carbon or a carbon–nitrogen bond. In the first chapter entitled 'Metal-Catalyzed Cross-Coupling Reactions in the Decoration of Pyridines', Moumita Koley, Michael Schnürch and Marko D. Mihovilovic outline cross-coupling reactions of pyridine derivatives applying the approaches that involve pyridine as organometal or as (pseudo)halide species. A lot of research is dedicated to cross-coupling reactions in aqueous medium that is of particular importance for environmental reasons. This chapter brings all types of cross-coupling methods covering mainly the literature from the past decade.

The chapter 'Metal-Catalyzed Cross-Coupling Reactions in the Decoration of Pyrimidine, Pyridazine, and Pyrazine' by Laurin Wimmer, Lukas Rycek, Moumita Koley and Michael Schnürch provides us with the comprehensive review on the cross-coupling chemistry of electron-deficient N-heterocycles containing two nitrogen atoms. The focus lies on new developments in the field, e.g. regarding new catalytic systems, and covers literature from 2008 until late 2013.

The third chapter entitled 'Metal-Catalysed Cross-Coupling Reactions in the Synthesis and Transformations of Quinolones and Acridones' by Raquel S. G. R. Seixas, Vera L. M. Silva and Artur M. S. Silva is an overview of the applications of cross-coupling reactions in the synthesis and transformations of quinolones and acridones. These compounds are widely recognized by their diverse bioactivity being useful structural moieties for drug candidates. Furthermore, they hold significant interest due to their host–guest chemistry; applications in chemical, biochemical and environmental analyses; and utility in synthetic methods' development.

The chapter 'Synthesis and Transformations of Oxygen Heterocycles' by Zoltán Novák and András Kotschy deals with the recent developments in the transition metal-catalysed synthesis and transformations of such oxygen-containing heteroaromatic systems where the oxygen is part of a five-membered ring.

The last chapter 'Transition Metal-Catalyzed Coupling Reactions in Library Synthesis' authored by János Gerencsér, Árpád Balázs and György Dormán describes the recent progress in utilizing carbon–halogen bonds for a variety of transition metal-catalysed reactions, including Suzuki–Miyaura, Sonogashira,

Buchwald–Hartwig, Stille, Negishi and Heck couplings. Furthermore, several C–H activation/arylation protocols are reported for a direct derivatization of the heterocyclic cores. Cross-coupling reactions are also implemented into domino and cascade reactions that enable the construction of novel ring systems.

Let me take this opportunity to express my sincere thanks to the authors for their outstanding contributions as well as to Elizabeth Hawkins, Judith Hinterberg and other people from Springer that are involved in the project for their patience and for their dedicated support in completing this volume.

The volume was edited by Professor Tamás Patonay. He was extremely motivated in accepting this challenge and immediately invited several distinguished authors to contribute the chapters of their expertise. Unfortunately, he passed away on June 23, 2015.

Professor Patonay was born in Debrecen, Hungary, on September 26, 1951. After finishing his undergraduate education at the University of Debrecen, he continued his studies at the same institution to reach the M.Sc. degree (1976) and Ph.D. in chemistry (1980). Furthermore, he was promoted to the D.Sc. in chemistry at the Hungarian Academy of Sciences in 2002. He was employed as a research associate at the Research Group for Antibiotics of HAS, Debrecen, from 1976 till 1982. Then, he joined the Department of Organic Chemistry, University of Debrecen, as a senior lecturer, where he became an associate professor in 1990 and was promoted to professor of organic chemistry in 2004. He served as a head of the department from 2008 onwards. He spent some time abroad. Namely, he was a visiting research associate with Professor R. V. Hoffman at the Department of Chemistry, New Mexico State University, Las Cruces, USA (1993–1994), and with Professor L. Hevesi at the Departement de Chimie, Facultes Universitaire Notre-Dame de la Paix, Namur, Belgium (1996). He also developed very intensive collaborations with several other laboratories in Europe and in the USA.

Although his research interest was very broad, let me mention only some of his favourite topics: metal-catalysed C–C and C–N cross-coupling reactions of oxygen heterocycles; synthesis of oxygen- and sulphur-containing heterocycles; the chemistry of 2-azido-, 2-halo- and 2-sulphonyloxy ketones; an application of new oxidizing and reducing agents for heterocyclic compounds; asymmetric oxidations and reductions; and highly efficient synthetic methods involving microwave-assisted and parallel syntheses. He published about 125 papers in the peer-reviewed international journals, 17 review articles and book chapters, as well as 3 patents. As an invited speaker, he delivered a number of lectures at international conferences, at universities and at research institutes. He also served as a guest editor of the special issue published in 2009 by the *Current Organic Chemistry* entitled ‘Nitrogen

Heterocycles and Their Acyclic Precursors: New Routes and Methods'. His successful and fruitful career was recognized by several honours: Higher Education Medal (1977), Outstanding Work (1986), FUNDP Scholarship (1996), Széchenyi Professor Scholarship (1998), Novicardin Prize (2006) and Academy Award (2015).

His sense of humour and direct style of communication were well known among his students. His extremely practical way of thinking in solving different problems was also legendary as he always reached the most elegant solutions to the research problems. While he carried out an extensive work in organic chemistry, he also served as an outstanding supervisor of students to reach their degrees. He always supported their experimental work giving them the opportunities to enjoy the beauty of the research experiences. It happened very often that even his former students visited him to get support or a friendly advice. Whenever possible, he spent the holidays discovering the wilderness of nature. He particularly loved the mountains, and he was an excellent teammate not only during the hiking trips but also on other occasions. I met Tamás for the first time about two decades ago at the University of Ljubljana when he delivered an outstanding lecture devoted to his research work. He came back to Slovenia several times and I had also a pleasure of visiting him twice at his department. We also met each other at several conferences around the world. I have had always the privilege to discuss with him various aspects of organic chemistry and numerous other topics as well.

The organic chemistry community has lost an excellent scientist and a man who was able to accept challenges and solve them with optimism and positive approach. He is greatly missed not only by his family but also by numerous colleagues and friends around the world. He will be always remembered but never replaced.

Ljubljana, Slovenia Slovenko Polanc
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Metal-Catalyzed Cross-Coupling Reactions in the Decoration of Pyridines

Moumita Koley, Michael Schnürch, and Marko D. Mihovilovic

Abstract Cross-coupling reactions involving pyridine derivatives are discussed for both approaches involving pyridine as organometal or as (pseudo)halide species. All types of cross-coupling methods are included, and mainly literature from the past decade is covered. Older landmark contributions are included as well whenever it is necessary to communicate key concepts. This chapter is organized according to the coupling type and the role of the pyridine derivative, either as (pseudo)halide or as organometal species.

Keywords (Pseudo)halide · Boronic acid · Cross-coupling · Metal organyl · Palladium

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Abbreviations

9-BBN	3-Borabicyclo[3.3.1]nonane
acac	Acetylacetonate
BMIM	1-Butyl-3-methylimidazolium
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-tri-*i*-propyl-1,1′-biphenyl
cBRIDP	Di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine
CM-phos	2-[2-(Dicyclohexylphosphino)phenyl]-1-methyl-1*H*-indole
cod	Cyclooctadiene
C-Phos	2-(2-Dicyclohexylphosphanylphenyl)-*N1,N1,N3,N3*-tetramethyl-benzene-1,3-diamine
CuMeSal	Copper(I) 3-methylsalicilate
CuTC	Copper(I) thiophene-2-carboxylate
Cy	Cyclohexyl
CyPF-*t*Bu	(*R*)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
DABCO	Diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DPE-Phos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
DSC	Dye-sensitized solar cell
D-*t*-BPF	1,1′-Bis(di-*t*-butylphosphino)ferrocene
EDG	Electron donating group
EWG	Electron withdrawing group
HASPO	Heteroatom-substituted secondary phosphine oxide
IMes HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPr	Bis(2,6-diisopropylphenyl)imidazol-2-ylidene

IPrNi(allyl)Cl	Allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] chloropalladium(II)
JosiPhos	(*R*)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
MIDA	*N*-Methyliminodiacetic acid
MTBE	Methyl *t*-butyl ether
NHC	*N*-Heterocyclic carbene
NMP	*N*-Methyl-2-pyrrolidone
OLED	Organic light-emitting diode
PEG	Polyethylene glycol
PEPPSI-IPent	Dichloro[1,3-bis(2,6-Di-3-pentylphenyl)imidazol-2-ylidene] (3-chloropyridyl)palladium(II)
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene] (3-chloropyridyl)palladium(II) dichloride
PMB	*p*-Methoxybenzyl
PTS	Polyoxyethanyl-α-tocopheryl sebacate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
Salen	2,2′-Ethylenebis(nitrilomethylidene)diphenol
SDPP	Silicadiphenylphosphinite
SES-NH_2	2-(Trimethylsilyl)ethanesulfonyl
S_NAr	Substitution nucleophilic aromatic
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SPO	Secondary phosphine oxide
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBS	Tert-butyldimethylsilyl
Tedicyp	*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclopentane
t-BuJosiPhos	(*R*)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
tmp	Tetramethylpiperidide
TON	Turnover number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

Nitrogen-containing heterocycles are compounds of high relevance in many areas of chemistry and in everyday life. Among them, pyridine can be regarded as a privileged structure. Highly functionalized pyridines, including aryl and heteroaryl

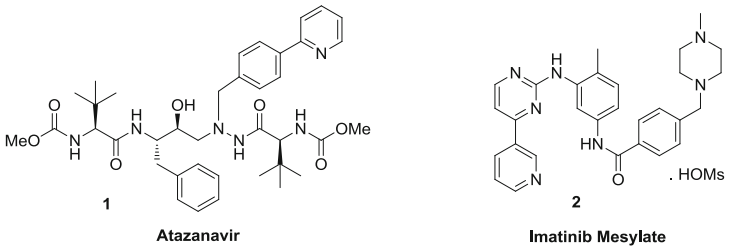


Fig. 1 Pyridine containing drugs on the market

substituted derivatives, are among the most prevalent heterocycles encountered in natural products, pharmaceutical and agrochemical industry, as well as in material science [1–4]. According to a recent MDL Drug Data Report, the most common heterocycle in pharmaceutically active compounds is pyridine. Examples of drugs based on pyridine are atazanavir (Reyataz) (**1**) [5] and imatinib mesylate (Gleevec) (**2**) [6] (Fig. 1) which are prescribed against human immunodeficiency virus (HIV) and chronic myelogenous leukemia, respectively.

As pyridines are the most common heterocyclic motif found in pharmaceutically active compounds, preparative methods of pyridine derivatives remain an essential research topic in organic synthesis. Besides constructing the pyridine core via classical cyclization strategies, decoration of pyridine building blocks via different types of reactions is applied frequently. As an electron poor heterocycle, nucleophilic substitutions can be carried out in a relatively facile fashion. Via this method, a C-heteroatom bond is formed between a pyridine C (most commonly in position 2 or 4) and the heteroatom of a nucleophile. For introducing a C-residue, other types of reactions are better suited, one example being metal-catalyzed cross-coupling reactions [7]. The success story of these reactions started in the 1970s and peaked in 2010 by awarding the Nobel Prize in chemistry to Akira Suzuki, Ei-ichi Negishi, and Richard Heck. Cross-coupling reactions have been applied on heterocyclic systems and, naturally, also on pyridine with a substantial number of examples being reported.

Within this chapter, the various types of cross-coupling reactions applied on pyridine will be discussed. The chapter is organized according to the coupling type and the role of the pyridine derivative, either as (pseudo)halide or as organometal species. We believe that this will be convenient for readers in order to most effectively find an answer to a specific question. Regarding the timeframe covered, focus was put on the past decade. Older landmark contributions are included as well whenever it is necessary to communicate key concepts.

2 Pyridine in Suzuki–Miyaura Reactions

The palladium-catalyzed cross-coupling reaction between different types of organoboron compounds and various electrophiles such as halides and triflates was initially described by Suzuki and Miyaura in 1979 [8]. It is now generally referred to as the Suzuki–Miyaura reaction (often only the Suzuki reaction). Since then, continuous advances have been made with respect to reaction scope, including coupling partners, catalyst loading, temperature profile, etc. It is nowadays also possible to couple sterically demanding substrates, and even asymmetric variants have been reported. Suzuki–Miyaura coupling is now considered as one of the most powerful, versatile, and general methodologies for the construction of C–C bonds via metal catalysis. Among the attractive features of the Suzuki–Miyaura reaction are the wide availability, stability (to air and moisture), and low toxicity of boronic acids, as well as the facile removal of the boron-containing side products of the coupling process.

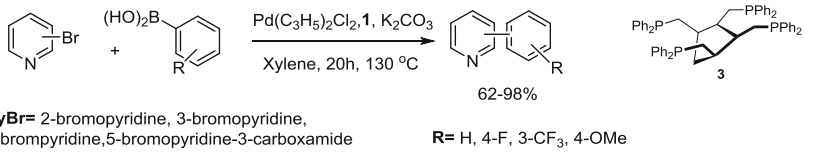
2.1 Pyridine as (Pseudo)halide in Suzuki–Miyaura Reactions

Many pyridine halides are commercially available or easily accessible, and hence, they have found widespread application in cross-coupling chemistry. Pyridine is considered as a privileged structure, and hence, it is not surprising that pyridine halides have been applied in Suzuki reactions frequently. Within this subchapter, new developments regarding functional group tolerance, coupling of less reactive (pseudo)halides (mainly chlorides), and regioselective or one-pot procedures are particularly highlighted.

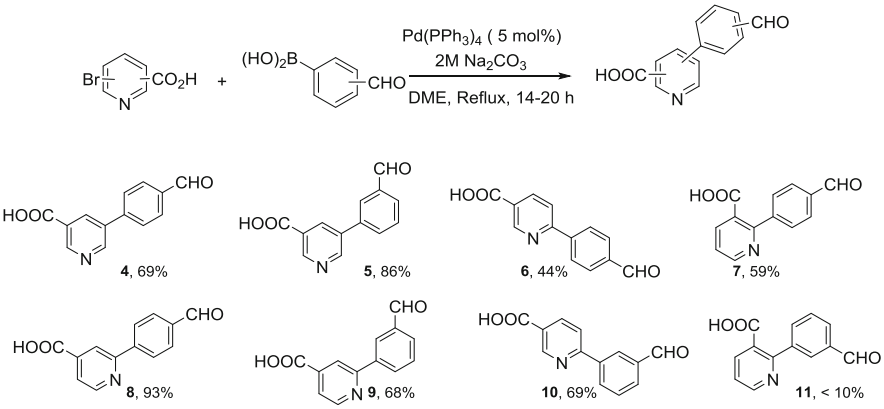
2.1.1 Recent Developments in Suzuki–Miyaura Coupling of Pyridine Bromides

Santelli and coworkers reported an efficient catalyst system for the coupling of bromopyridine derivatives giving high yields of the coupling products [9, 10]. As the phosphine ligands used in Suzuki–Miyaura coupling have important influence on stability and rate of the catalytic reaction, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclopentane (Tedicyp) (**3**) [11–13] was tested in Suzuki–Miyaura reactions as novel phosphine ligand. The ligand contains a cyclopentane ring to which four diphenylphosphinoalkyl groups are stereospecifically bound to the same face. In combination with $[PdCl(C_3H_5)]_2$, a catalyst system is formed which proved to be very efficient in Suzuki–Miyaura reactions, especially for heterocyclic substrates, including a number of bromopyridines (Scheme 1).

Extremely low catalyst loadings could be applied. 3-Bromopyridine as best performing pyridine halide required a substrate to catalyst ratio of 10,000,000



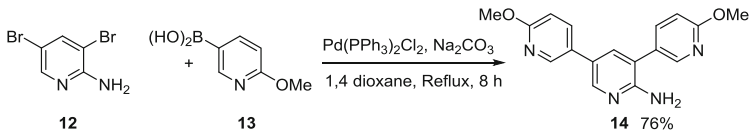
Scheme 1 Tedicyp as ligand in Suzuki-Miyaura couplings



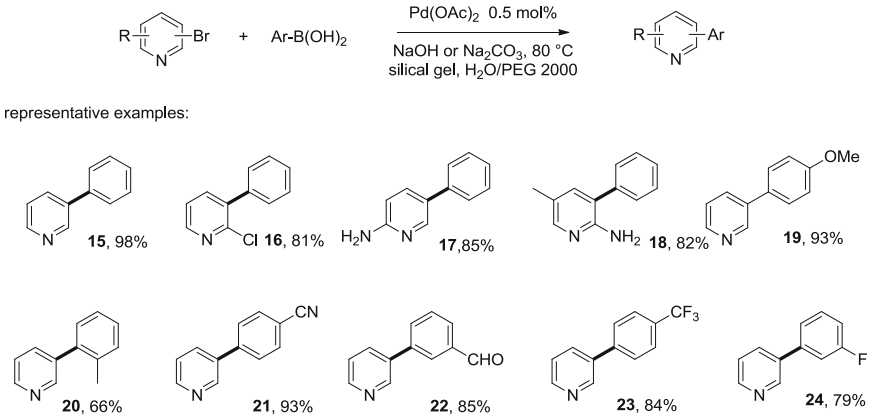
Scheme 2 Coupling between formylphenylboronic acids and bromobyridine carboxylic acids

only. This is rather counterintuitive since due to the electronegativity of the nitrogen atom, the 2- and 4-positions of halopyridines are expected to be more reactive towards oxidative addition to Pd(0). The highest TON was observed for 3-bromopyridine (2,500,000) followed by 4-bromopyridine (810,000) and 2-bromopyridine (62,000).

Suzuki–Miyaura coupling reactions of unprotected bromopyridine carboxylic acids with formylphenylboronic acids were reported by Schaub and coworkers [14]. $Pd(PPh_3)_4$ was applied as catalyst in a mixture of an aqueous Na_2CO_3 solution and 1,2-dimethoxyethane. The coupling products were synthesized in multi-gram scale. Conversions and yields of the coupling reactions depended on electronic effects (substitution pattern of the bromopyridine carboxylic acids). *Meta*-bromo-substituted-carboxylic acids gave the highest yields of coupling products with 4- and 3-formylphenylboronic acids (Scheme 2, examples **4**, **5**, **8**, **9**) and also 2-bromopyridine-4-carboxylic acid gave reasonable good yields (Scheme 2, examples **6** and **10**). 2-Bromopyridine-3-carboxylic acid gave a reasonable yield of 59% of **7** with 4-formylphenylboronic acid, but was inefficient (<10%, **11**) with 3-formylphenylboronic acid, most likely due to the increased steric hindrance. 5-Bromopyridine-2-carboxylic acid gave a similarly poor result with all three boronic acids due to unfavorable electronic effects. The sterically demanding 2-formylphenylboronic acid gave a good yield only with 5-bromopyridine-3-carboxylic acid (75%, not shown), and all other bromides gave low yields (Scheme 2).



Scheme 3 Suzuki-Miyaura coupling in presence of a free amine functionality

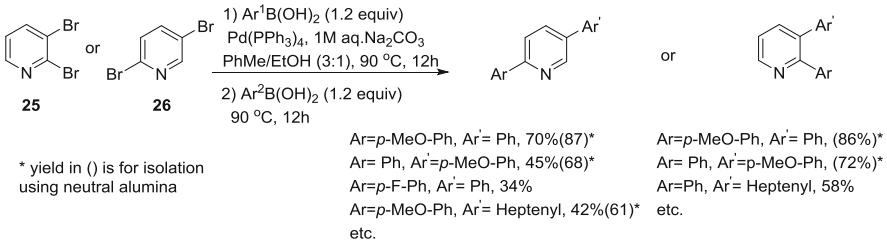


Scheme 4 Suzuki-Miyaura coupling in a PEG/water mixture

Bryce and coworkers reported a systematic study of a Suzuki–Miyaura coupling method which tolerates free primary amine functionality [15]. Within standard conditions, Na_2CO_3 (aqueous 1 M) was used as base and $Pd(PPh_3)_2Cl_2$ was employed as catalyst (5 mol%) in 1,4-dioxane at reflux for 8 h. In this work, pyridine was applied as halide and as boronic acid component as well. Both, pyridine bromides and chlorides were tested with generally good results. Besides the amine, other functional groups were tolerated, as well, such as NO_2, CF_3, OMe, or acetamide. One remarkable example is depicted in Scheme 3: in this case, both coupling partners **12** and **13** were pyridines, and double coupling gave a good yield of 76% of **14** (Scheme 3).

One convenient feature of the Suzuki reaction is the possibility to carry out reactions in aqueous medium. Zhang disclosed such a protocol under phosphine-free conditions (Scheme 4) [16]. A mixture of H_2O and PEG (3:3.5) was used as solvent. Interestingly, silica gel had a beneficial effect on the transformation. A series of pyridine bromides (and other heteroaryl bromides) could be coupled with good yields of arylated pyridine (**15**–**24**) in general.

A site-selective one-pot double Suzuki–Miyaura cross-coupling on dihalogenated pyridines was reported by Handy and coworkers (Scheme 5) [17], using 2,5-dibromopyridine **26** as the most suitable substrate. Naturally, the first substitution occurs at the more reactive 2-position. A series of 2,5-bisarylated pyridines (in some cases hepteneboronic acid was used as one coupling partner) were synthesized successfully with yields around 40% in most cases with no

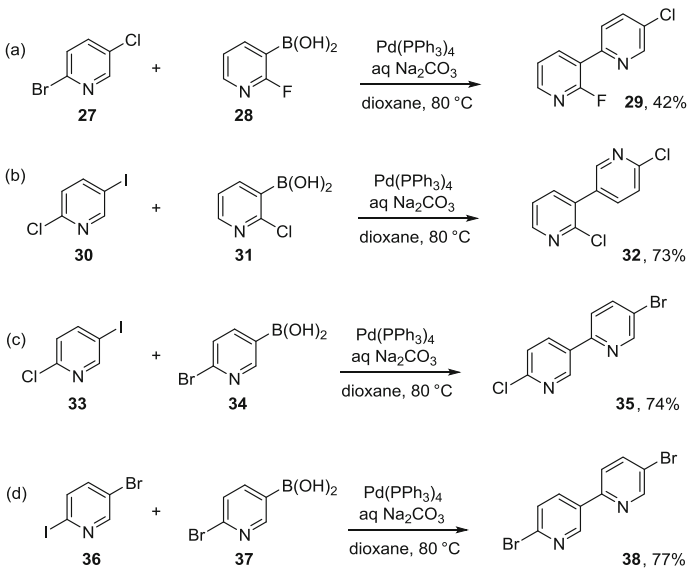


Scheme 5 Sequential Suzuki-Miyaura coupling of dibromopyridines

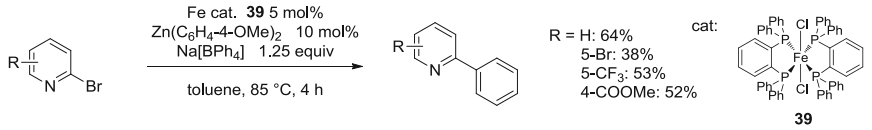
obvious influence of the substitution pattern of the boronic acids. Interestingly, improved yields could be observed by use of neutral alumina instead of silica for purification of the crude reaction mixtures (typically ~20% increase). The same protocol can be applied to 2,3-dibromopyridine **25** with similar effectiveness, and as expected, the first coupling took place in position 2 (Scheme 5). The reaction conditions can be considered as standard for a Suzuki–Miyaura reaction. The use of a ternary solvent mixture consisting of EtOH, toluene, and water (derived from the Na_2CO_3 solution) is noteworthy, since this is critical for the success of the protocol.

Using the same reaction conditions and 2-bromo-3-iodopyridine as substrate, the one-pot protocol led to initial cross-coupling in position 3 based on the enhanced reactivity of the C–I bond in position 3 overcoming the electronic effect of the pyridine ring which would actually favor cross-coupling in position 2 (not shown). However, no yield was reported for this specific transformation, and hence, the efficiency and utility cannot be assessed.

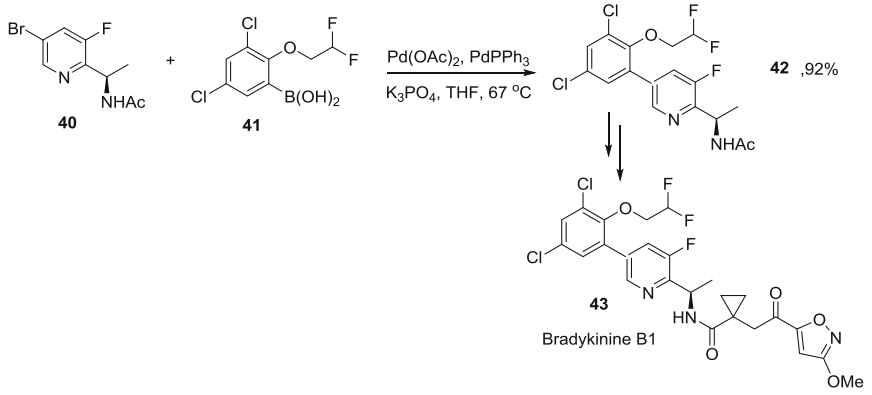
Rault and coworkers published an interesting study on the cross-coupling behavior of dihalopyridines bearing two different halogen atoms with halopyridylboronic acids, whereas the carbon–halogen bond on the boronic acid coupling partner had a lower reactivity than the carbon–halogen bonds in the dihalopyridines [18]. They found the heteroarylation reaction to occur at the more reactive carbon–halogen bond of the halopyridine substrates irrespective of its position on the ring. A few examples are displayed in Scheme 6. When typical reaction conditions were used (dioxane, aqueous Na_2CO_3, $Pd(PPh_3)_4$, reflux), the reaction of 2-bromo-5-chloropyridine **27** with 2-fluoro-3-pyridylboronic acid **28** gave 5-chloro-2′-fluoro-2,3′-bipyridine **29** in 42% yield (Scheme 6, Eq. (a)). Moreover, 2,6′-dichloro-3,3′-bipyridine **32** was synthesized in 73% yield from 2-chloro-5-iodopyridine **30** and boronic acid **31** (Scheme 6, Eq. (b)) and the Suzuki–Miyaura reaction between **33** and boronic acid **34** gave 6-bromo-6′-chloro-3,3′-bipyridine **35** in 74% yield (Scheme 6, Eq. (c)). When 5-bromo-2-iodopyridine **36** was coupled with compound **37** 5,6-dibromo-2,3′ bipyridine **38** was obtained in 77% yield. This shows that bromine in the presence of iodine remains inert. The procedure has its limitations when all halides are of identical nature (e.g., all bromides). In such cases, low yields and mixtures of products were obtained.



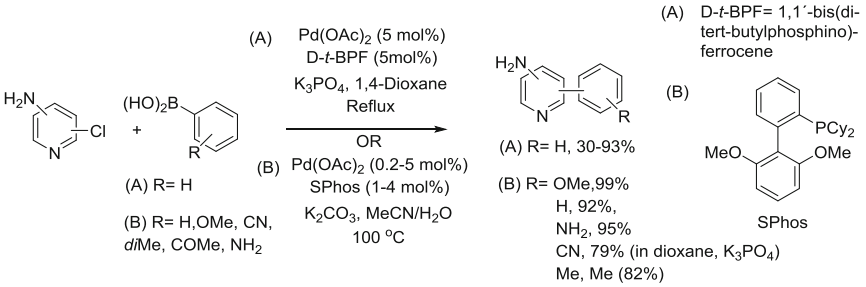
Scheme 6 Coupling of dihalopyridines with halopyridineboronic acids



Scheme 7 Iron catalyzed Suzuki-Miyaura coupling of bromopyridines



Scheme 8 Suzuki-Miyaura coupling as key step in the synthesis of Bradykinine B1



Scheme 9 Suzuki-Miyaura coupling of chloropyridineamines

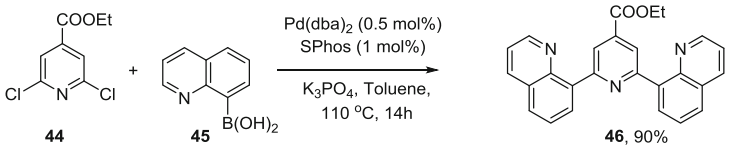
Catalytic systems based on non-precious metals are of increasing interest. Bedford and coworkers disclosed such an example with their iron–zinc co-catalyzed Suzuki reaction. Also, the organometal coupling partner is unusual since sodium tetraphenylborate gave the best results. Several bromopyridines were subjected to the coupling conditions; however, only moderate yields were obtained (Scheme 7).

Many interesting applications of Suzuki–Miyaura coupling can be encountered in crucial steps of natural products synthesis. The compound responsible for the physiological processes accompanying inflammation and chronic pain is bradykinin B1 (**43**). The synthesis of (**43**) involves a Suzuki–Miyaura coupling to generate intermediate (**42**) where arylboronic acid (**41**) and bromopyridine amide (**40**) are coupled using $Pd(OAc)_2$ and PPh_3 in a 1:2 ratio with 2 M K_3PO_4 in THF (Scheme 8). This intermediate (**42**) can then be converted to bradykinin B1 in two more synthetic steps, (Scheme 8) [19].

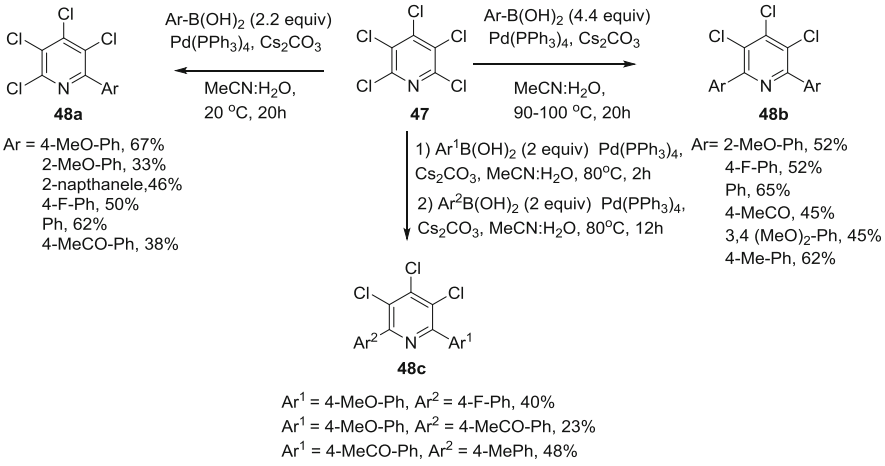
2.1.2 Recent Developments in Suzuki–Miyaura Coupling of Pyridine Chlorides

(Hetero)aryl chlorides are even more attractive coupling partners since there are more examples commercially available, often at a cheaper price, and additionally, the atom efficiency is significantly higher when chlorides are used instead of bromides or iodides. Hence, significant efforts are undertaken to develop general protocols for the coupling of (hetero)aryl chlorides including pyridine chlorides.

Chloro-aminopyridines are considered as difficult substrates in Pd-catalyzed cross-coupling processes since the free amino group is often not well tolerated. Itoh reported the Suzuki–Miyaura reaction of 2-chloropyridine-3-amine, 6-chloropyridine-3-amine, 6-chloropyridine-2-amine, and 5-chloropyridine-2-amine with phenylboronic acid in good yields (68–93%). 2-Chloropyridine-4-amine was less successful and gave only 30% yield (Scheme 9, conditions A) [20]. The key to successful coupling is the use of the sterically demanding ligand 1,1′-bis(di-*tert*-butylphosphino)-ferrocene (D-*t*-BPF). The choice of ligand proved to be crucial also in other cases as demonstrated by Buchwald and coworkers, who



Scheme 10 Twofold Suzuki-Miyaura coupling of ethyl 2,6-dichloroisonicotinate

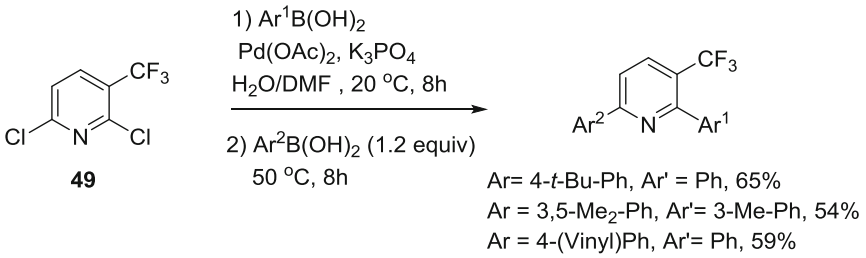


Scheme 11 Pentachloropyridine in Suzuki-Miyaura couplings

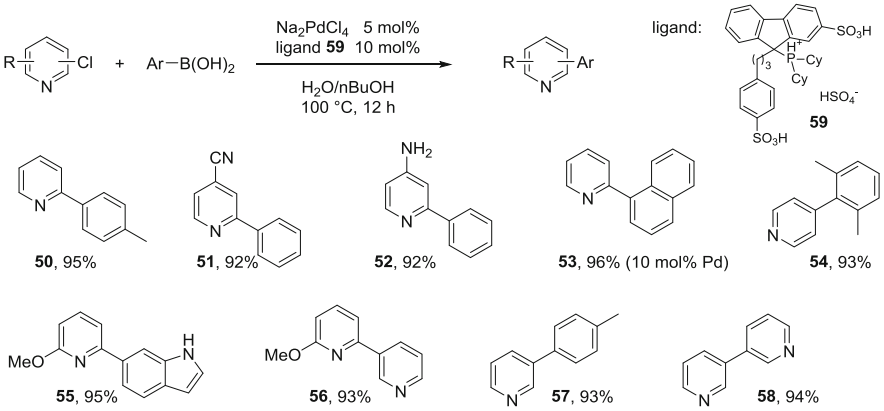
had used the highly active dialkylbiphenylphosphino ligand SPhos (Scheme 9, conditions B) which then again did not require protection of the amino group [21].

SPhos is also effective in the preparation of 2,6-di(quinolin-8-yl)-pyridine compounds, an excellent tridentate ligand for Ru(II), providing complexes with microsecond luminescent lifetimes. Johansson et al. reported the synthesis of this compound class by the double Suzuki–Miyaura coupling of a heteroarylboronic acid and halopyridine derivatives [22]. As shown in Scheme 10, an ester group of **44** was unaffected while coupling with **45** under the applied reaction conditions (Scheme 10).

Site-selective arylation reactions of pentachloropyridine (**47**) with arylboronic acids were reported by Langer and coworkers (Scheme 11) [23]. Optimization of the selective mono-arylation in position 2 revealed that simple $Pd(PPh_3)_4$ outperformed more advanced catalytic systems such as $Pd(OAc)_2$/XPhos, significantly (Scheme 11, **48a**). Using acetonitrile/water as solvent mixture and Cs_2CO_3 as base, the coupling can be achieved at room temperature while only 2.2 equiv. of boronic acid are required. 4-Methoxyphenylboronic acid gave the highest yield of 67% which is even better than for phenylboronic acid (62%). Sterically demanding boronic acids are ineffective indicated by lower yields as expected (2-naphtyl 46%, 2-MeO-phenyl 33%). Also, electron withdrawing groups are less tolerated (4-F-phenyl 50%, 4-AcO-phenyl 38%) in the reaction. Doubling the amount of boronic



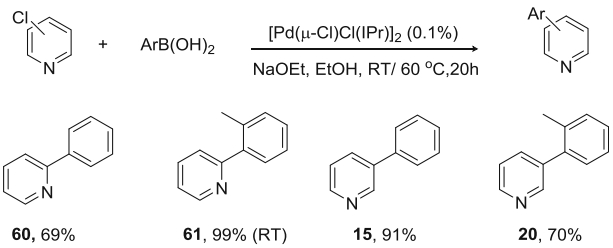
Scheme 12 Sequential Suzuki-Miyaura coupling of 2,6-dichloro-3-(trifluoromethyl)pyridine



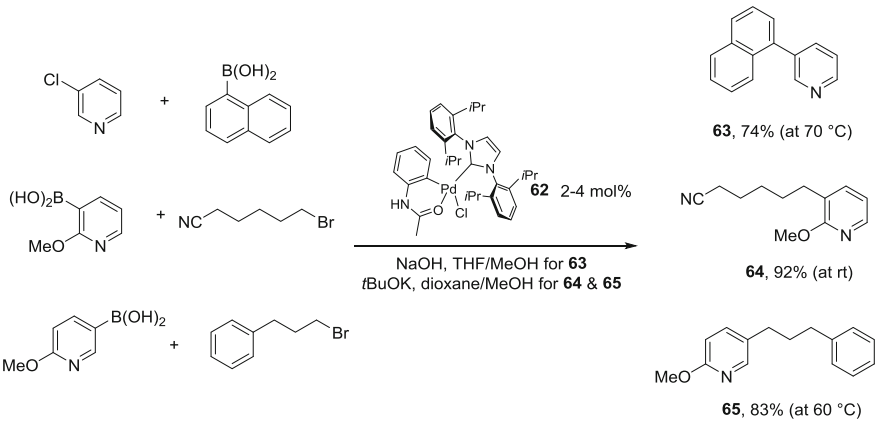
Scheme 13 A water soluble ligand in Suzuki-Miyaura coupling of pyridine chlorides

acid to 4.4 equiv. led to bis-arylation in positions 2 and 6 with moderate yields, ranging between 45% and 64% (Scheme 11, **48b**). A one-pot reaction with consecutive introduction of two different boronic acids can be performed successfully as well, and three examples were reported (Scheme 11, **48c**). In the best performing example, 48% yield was achieved, corresponding to approximately 70% yield for each individual cross-coupling step.

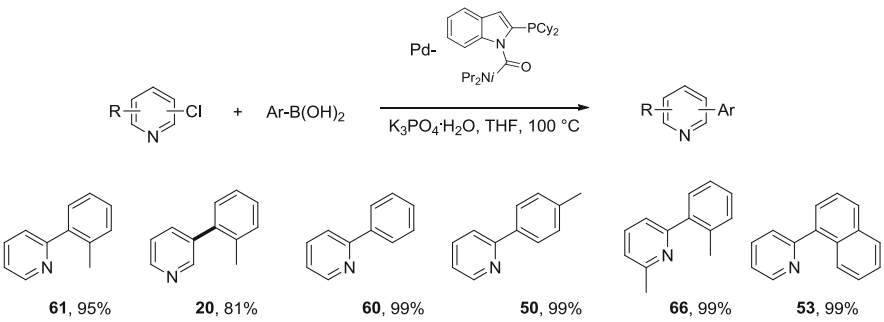
An example of Suzuki–Miyaura coupling on pyridine derivatives containing a CF_3 group is displayed in Scheme 12. This is an important result as trifluoromethylated pyridines [24], along with other fluorinated and trifluoromethylated heterocycles [25], are of special relevance in medicinal and agricultural chemistry due to the metabolic stability of the C–F bond. In general, palladium-catalyzed cross-coupling reactions of polyhalogenated substrates usually proceed regioselectively in favor of the sterically less hindered and electronically more deficient position. In the case of pyridine halide **49**, the Suzuki–Miyaura reaction proceeded regioselectively in favor of the electronically more deficient position 2, which is sterically more hindered than position 6, due to the proximity of the CF_3 substituent (Scheme 12) [26].



Scheme 14 NHC-assisted Suzuki-Miyaura coupling of pyridine chlorides

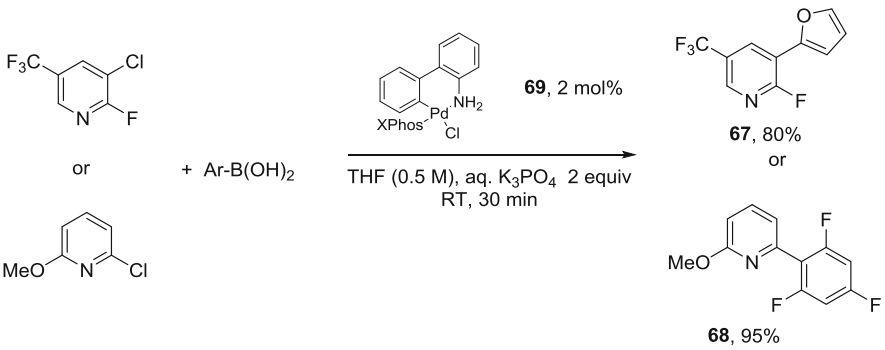


Scheme 15 A Pd-NHC catalyst in Suzuki-Miyaura coupling of pyridine derivatives



Scheme 16 An indolyl-based ligand in the coupling of pyridine chlorides

Plenio and coworkers designed water-soluble phosphine ligands (e.g., **59**) which gave excellent results in the coupling of pyridine and quinolone chlorides [27]. A water/n-BuOH mixture was used as reaction medium and Na_2PdCl_4 served as palladium source. In all reported cases involving pyridine and quinolone, yields >90% were achieved (Scheme 13, e.g., **50**–**58**)! Both aromatic and heteroaromatic



Scheme 17 Suzuki-Miyaura coupling towards flurinated building blocks

boronic acids could be applied leading to valuable bi-heteroaryls (e.g., asymmetrically substituted bipyridines). Functional group tolerance was excellent as well since NH_2, CF_3, OMe, CN, and CHO were well accepted. Representative examples are given in Scheme 13.

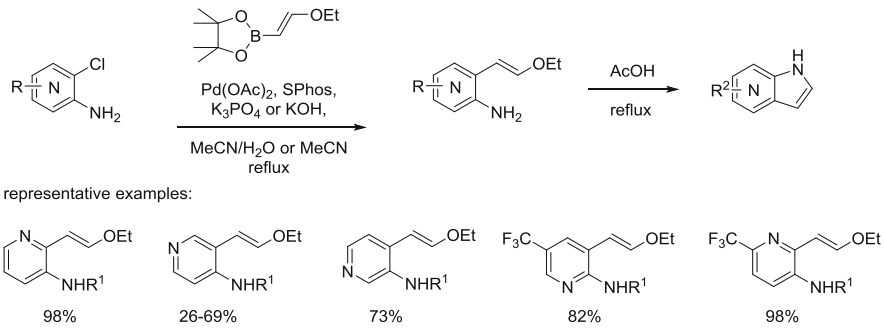
N-Heterocyclic carbenes (NHC) as different class of ligands were applied to Suzuki–Miyaura transformations as well. In recent years, well-defined mono-NHC palladium complexes have been developed which promote Suzuki–Miyaura reactions with low catalyst loading and under mild reaction conditions. One such NHC–Pd complex, the air- and moisture-stable $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ (IPr=bis (2,6-diisopropylphenyl)imidazol-2-ylidene), has been reported as an efficient precatalyst for coupling of 2- and 3-chloropyridines at room temperature with very low catalyst loading of only 0.1 mol% (Scheme 14, e.g., **15**, **20**, **60,** and **61**) [28].

Kantchev and Ying reported an example in which 3-chloropyridine and 2-chloro-3-methoxypyridine were coupled with boronic acids, successfully [29]. Additionally, the same catalyst **62** was able to promote coupling of pyridineboronic acid (esters) as well, in two case (**64** and **65**) even with an alkyl bromide which is a rare example of a sp^2–sp^3 coupling of pyridine under Suzuki–Miyaura conditions (Scheme 15).

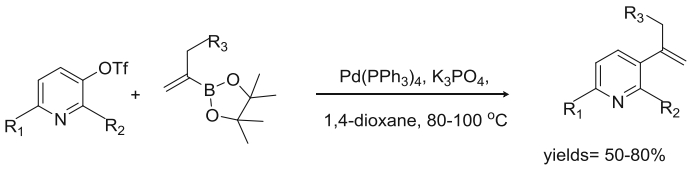
Kwong and coworkers applied an indolyl-based ligand in the coupling of several pyridine chlorides with boronic acids [30]. Remarkably low catalyst loadings (0.01–0.067 mol% Pd) were sufficient to achieve almost quantitative product yields in most cases (Scheme 16).

Fluorine is a recurring substituent in commercialized and developmental drugs. Coupling methods which tolerate multiply fluorinated reaction partners are hence of great importance. One such example was reported by the group of Buchwald in 2010 [31]. They described new Pd-precatalysts **69** which were able to give the desired polyfluorinated coupling products (**67** and **68**). Two different pyridine chlorides were coupled as well in both cases with excellent yield (Scheme 17).

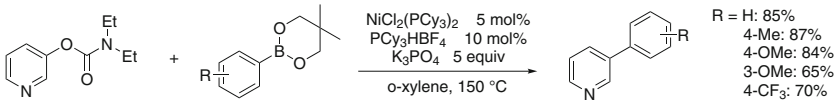
Most Suzuki couplings are dedicated to the coupling of two arene systems. However, also alkenylboronic acid derivatives are useful coupling partners. In their efforts towards pyrrole-fused pyridines, Hoelder and coworkers applied such



Scheme 18 Alkenylboronic esters in Suzuki-Miyaura couplings of pyridine chlorides



Scheme 19 Alkenylboronic esters in Suzuki-Miyaura couplings of pyridine triflates

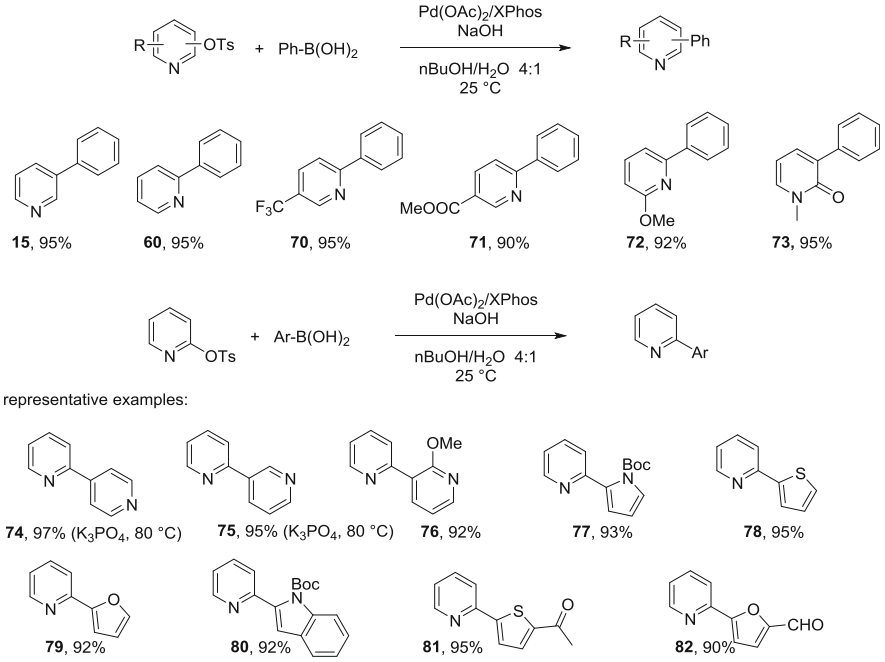


Scheme 20 *N*,*N*-Dietylcarbamate as leaving group in Ni-catalyzed Suzuki-Miyaura coupling

a reaction on different halogenated pyridine amines (Scheme 18) [32]. The catalytic system utilized ($Pd(OAc)_2$/SPhos) can be considered as well established by now. Yields in the alkenylation step were usually good to excellent. The same is true for the final cyclization.

2.1.3 Other Leaving Groups in Suzuki–Miyaura Reactions

Due to the better availability of 3-hydroxypyridines as compared to the corresponding halides, this substance class would be an interesting alternative in cross-coupling reactions. The hydroxyl group can be converted to triflates easily [33], which is an excellent leaving group in Suzuki–Miyaura reactions. In this regard, 3-alkenyl-substituted pyridines can be synthesized via Suzuki–Miyaura coupling as described by Vyvyan and coworkers using 3-pyridyl triflates with alkenylpinacolboronates as coupling partners (Scheme 19). The reactions proceed in moderate to good yields using simple $Pd(PPh_3)_4$ (10 mol%) as catalyst with K_3PO_4 (3 equiv.) as base in 1,4-dioxane [34]. The method can be applied to the



Scheme 21 Pyridine tosylates in Suzuki-Miyaura couplings

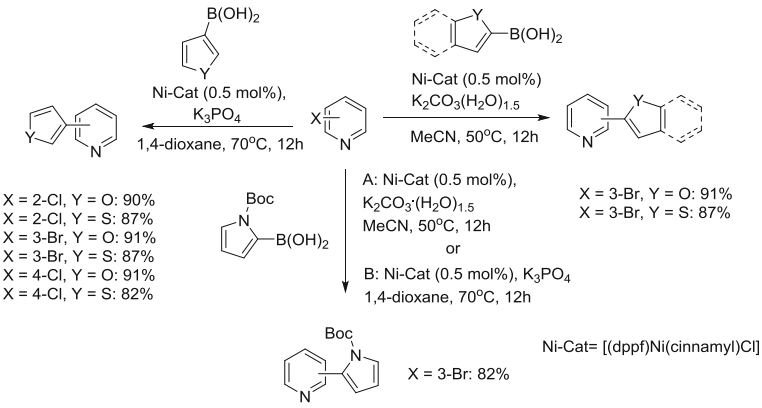
synthesis of a potential precursor for the synthesis of the natural product cananodine.

The group of Snieckus pioneered directed ortho metalation methods in which the directing group is used as leaving group (i.e., the pseudohalide) in cross-coupling reactions [35]. When employing *N*,*N*-diethyl *O*-carbamate as directing group in position 3 of pyridine, coupling with several boronic acid esters worked well, independent of the electronic nature of the organometal compound (Scheme 20). Noteworthy, nickel catalysis proved to be efficient which is often neglected in cross-coupling chemistry.

Tosylates are another potential leaving group accessible from readily available hydroxyl pyridines. Inamoto and Doi reported a nickel-catalyzed protocol in which pyridine-3-tosylate was coupled with phenylboronic acid (69%), 4-MeO-phenylboronic acid (86%), and 4-CN-phenylboronic acid (83%) with good results (not shown) [36].

A pyridine-bridged bis-benzimidazolylidene pincer nickel(II) complex was very effective in Suzuki coupling of various (hetero)aryl halides and pseudohalides. Regarding pyridine, 3-bromopyridine, 3-chloropyridine, as well as 3-pyridyl tosylate and 3-pyridyl mesylate were coupled with phenylboronic acid. The latter two gave 3-phenyl pyridine in 95% and 91%, respectively (not shown) [37].

Mesylates are rarely applied as leaving groups in cross-coupling chemistry since their leaving group ability is less pronounced as compared to other (pseudo)halides.



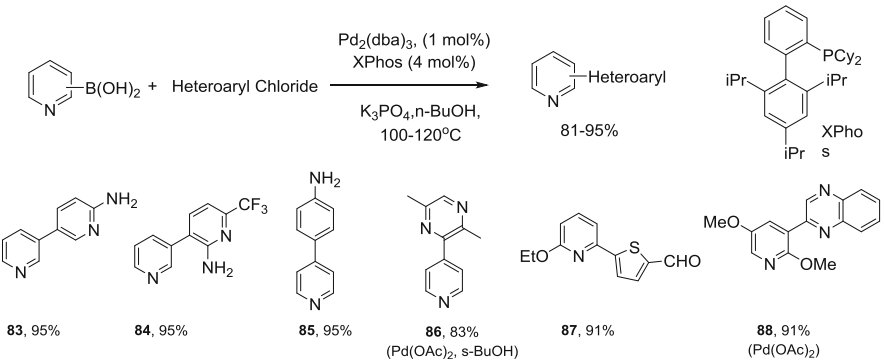
Scheme 22 Pyridine halides in Suzuki-Miyaura couplings with heterocyclic boronic acids

Again, Kwong and coworkers established a general protocol for Suzuki–Miyaura coupling of potassium aryltrifluoroborates and aryl mesylates [38]. In one example, they coupled 3-pyridyl mesylate with thiophene-3-potassium trifluoroborate which gave 66% of the coupling product (not shown). A catalytic system consisting of $Pd(OAc)_2$ and the indole-based phosphine ligand CM-Phos proved to be efficient.

A comprehensive study of pyridine chlorides but also pyridine tosylates was reported by Zhou and coworkers [39]. Yields >90% were reported within short reaction time (5 min–1 h) no matter whether pyridine chlorides or tosylates were applied. In this study, various pyridine tosylates were coupled with phenylboronic acid (Scheme 21, products **15**, **60**, **70**–**73**). Additionally, 2-pyridyl tosylate was coupled with a number of heterocyclic boronic acids, always with excellent yields (Scheme 21, products **74**–**82**). A simple catalytic system of $Pd(OAc)_2$ and XPhos proved to be ideal, and in most cases, room temperature was sufficient.

2.2 Nickel-Catalyzed Suzuki–Miyaura Coupling

Reduction of cost associated with metal-catalyzed reactions is important for industrial application. In this regard, replacement of palladium by the cheaper and more abundant metal nickel is an interesting option. Hartwig and coworkers reported the well-defined nickel catalyst dppf-ligated cinnamylnickel(II) chloride (dppf=1,1′-bis(diphenylphosphanyl)-ferrocene) [40]. This catalyst allows coupling of pyridine halides along with pyrimidine, pyrazine, and quinoline halides with five-membered heteroarylboronic acids (Scheme 22). These coupling reactions can be carried out with as low as 0.5% catalyst loading, and very high yields (37 examples, 81–97% yield) were obtained with no additional ligand necessary. Additionally, 50°C was sufficient to promote the reaction. Scheme 22 shows coupling



Scheme 23 Pyridineboronic acids in Suzuki-Miyaura couplings with heteroaryl chlorides

examples of simple pyridine halides. However, also substituted pyridine halides were applied (MeO, Me, CF_3, CHO, acetyl, CN) with similar efficiency.

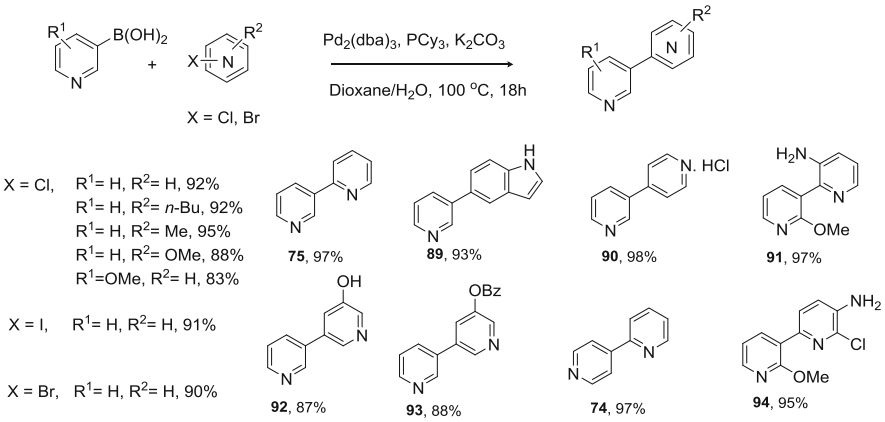
2.3 Pyridine as Boronic Acid Derivatives

Pyridine-derived boronic acids have proven to be a particularly difficult class of substrate for the Suzuki–Miyaura coupling due to a relatively low stability (especially 2-pyridylboronic acid) and the formation of trimeric anhydrides which display low reactivity.

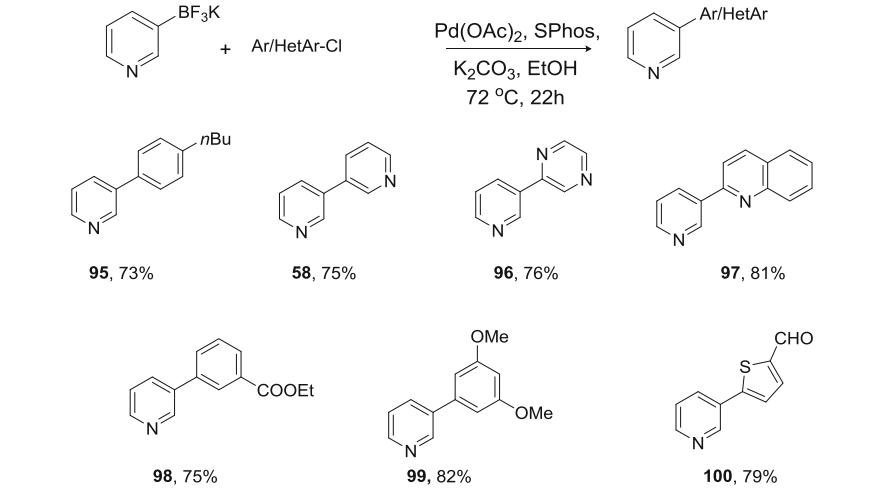
Buchwald and coworkers reported a successful utilization of pyridine boronic acids in Suzuki–Miyaura coupling. A $Pd(OAc)_2$/Xphos catalyst system provided good yields for the reaction of pyridine boronic acids with activated heteroaryl chlorides (Scheme 23, products **83**–**88**), although in selected cases Sphos is more effective as ligand [21].

Fu and coworkers have reported a versatile coupling method for a variety of heteroarylboronic acids, including 3-pyridineboronic acid, with a range of chlorobenzenes, including ortho-substituted and electronically deactivated substrates [41]. Using bulky trialkylphosphines, including $P(^tBu)_3$ and PCy_3, as effective ligands along with Pd as catalyst, good yields were obtained [42]. PCy_3 is relatively cheap compared to other ligands such as $P(^tBu)_3$, aryldialkylphosphines, and carbenes and shows high reactivity in Suzuki–Miyaura coupling. After some optimization efforts, the authors could establish $Pd/PCy_3/K_3PO_4$/dioxane/H_2O as effective catalytic system to promote cross-coupling of 3-pyridylboronic acids with different halides, especially aryl/heteroaryl chlorides in excellent yield. This catalyst system is also effective for Suzuki–Miyaura cross-couplings towards bipyridyls providing these products (**74**, **75**, **89**–**94**) generally in good yield (Scheme 24). Free NH_2 and OH groups were well tolerated as well as MeO or benzoyl.

This $Pd/PCy_3/K_3PO_4$/dioxane/H_2O-based method is effective not only for Suzuki–Miyaura cross-couplings of heteroarylboronic acids but also for boronate



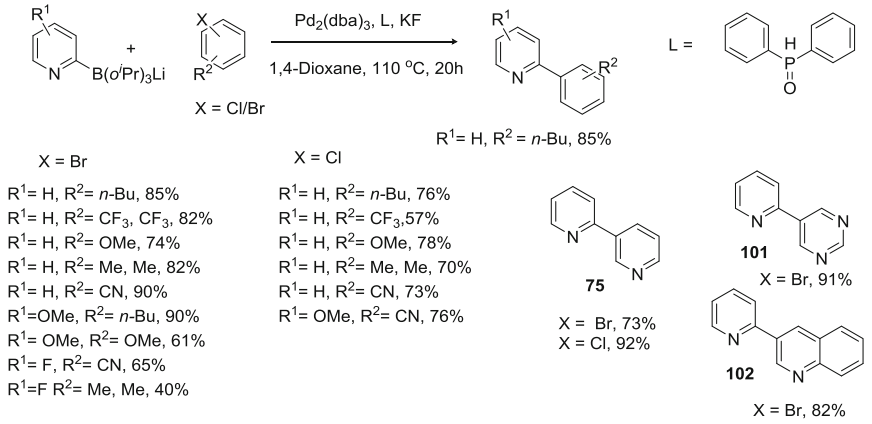
Scheme 24 Pyridineboronic acids in Suzuki-Miyaura couplings with pyridine halides



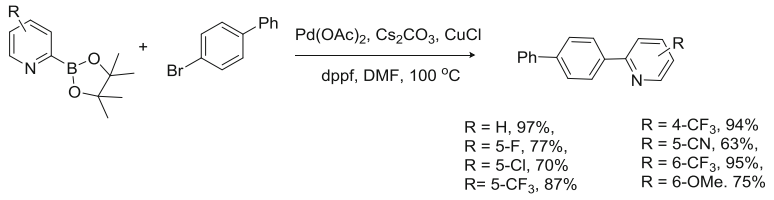
Scheme 25 Potassium pyridine-3-trifluoroborate in Suzuki-Miyaura couplings

esters and trifluoroborates as well, as demonstrated in the two examples (not shown).

The drawbacks associated with the use of boronic acids can be overcome by using boronate esters and trifluoroborates. A coupling method of (hetero)aryl potassium trifluoroborates was reported by Buchwald and coworkers including potassium 3-pyridyl trifluoroborate. Different aryl and heteroaryl chlorides including 3-pyridyl chloride can be applied as coupling partners, giving rise to 3,3′-bipyridine (**58**) (75% yield). Several other (hetero)aryl potassium trifluoroborates were used as coupling partners as well in generally good yield (Scheme 25,



Scheme 26 Lithium triisopropyl 2-pyridylborates in Suzuki-Miyaura couplings

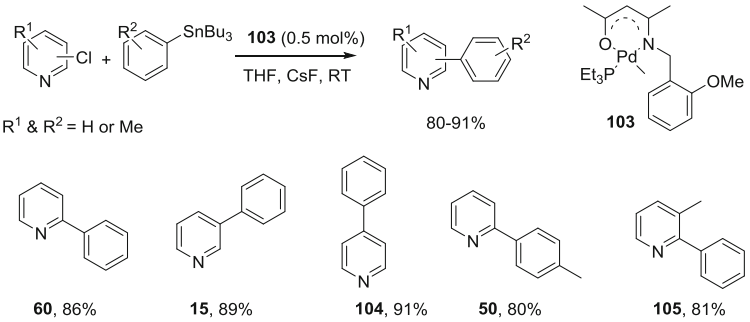


Scheme 27 2-Pyridyl pinacolboronates in Suzuki-Miyaura couplings

products **95**–**100**) [43]. $Pd(OAc)_2$, SPhos, K_2CO_3 in ethanol was applied as catalytic system. A similar study was published in 2012 by the group of Wu and Zou [44].

There are certain issues attributed for difficulties in Suzuki–Miyaura coupling of 2-pyridyl nucleophiles with aryl halides: (1) slow transmetalation rate of electron-deficient heteroaryl boron species and (2) rapid decomposition of reagents via protodeboronation. An efficient method to overcome these difficulties is by using lithium triisopropyl 2-pyridylborates as reported by Buchwald and coworkers. The borates required in Suzuki–Miyaura coupling can be obtained readily in one step from the corresponding 2-bromo- or 2-iodopyridine derivatives. Suzuki–Miyaura coupling reaction of these borates with different aryl/hetaryl halides is a general method for the synthesis of 2-substituted pyridine derivatives such as **75**, **101,** and **102** (Scheme 26) [45]. A similar method was reported by Ackermann and coworkers later on [46].

Another approach to overcome instability of 2-pyridineboronic acid is its conversion into the corresponding boronate. Generally, the use of pinacolboronates is attractive due to their commercial availability and stability towards air and moisture. Deng and coworkers have reported a protocol for coupling of 2-pyridyl pinacolboronate as nucleophile with aryl bromide (Scheme 27) [47]. Yields were generally good, and electron donating and electron withdrawing substituents were



Scheme 28 Pyridine chlorides in the Stille coupling with arylstannanes

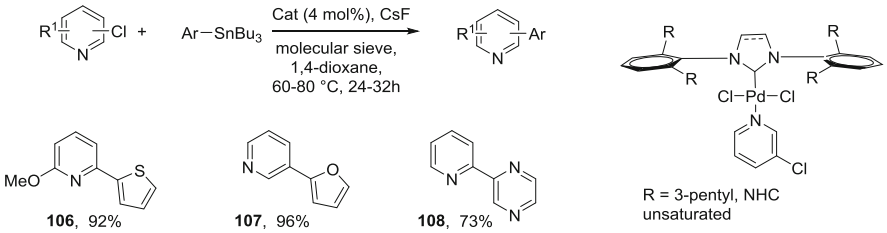
well tolerated. CuCl was required as additive, and the authors suggested that in its presence, the pyridine boronic ester might be transmetalated to a cuprate species.

3 Stille–Migita Coupling

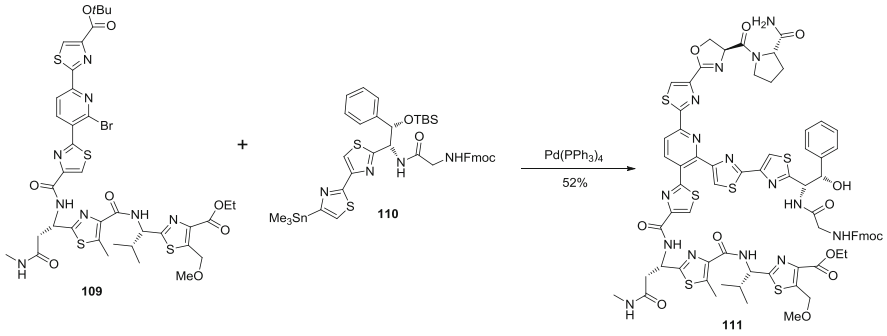
The palladium-catalyzed cross-coupling of aryl or vinyl (pseudo)halides with organostannanes is known as the Stille–Migita coupling reaction [48, 49] more often referred to as Stille coupling, only. This is another widely used method for C–C bond formation offering the advantage that air and moisture stable organotin reagents can be used, along with an excellent functional group tolerance. In contrast to Suzuki, Kumada, and Heck reactions, which operate under basic conditions, usually neutral conditions are employed for Stille couplings (although in some cases base may be required). The main drawback associated with the Stille cross-coupling procedure is toxicity of the tin compounds which make them problematic for industrial applications. Stille coupling, using aryl bromide and iodide, is already well established, but use of aryl chloride as coupling partner is not well developed [50, 51]. Examples of recent applications of Stille couplings of pyridine halides are discussed in this chapter. Simple applications of pyridine in Stille reactions under well-established reaction conditions are not discussed unless the substrates or products are of special interest or complexity. As will be demonstrated, most new developments are based on the establishment of new ligands which are able to create a more reactive metal species.

3.1 Pyridine as (Pseudo)halide in Stille–Migita Reactions

A Stille coupling at room temperature is achieved using a phosphanyl–βketoiminate palladium complex (**103**). Chloropyridines bearing a chloride in 2-, 3-, or 4-position can be coupled with tributylphenylstannane in high yields of 80–91% within 4–6 h, with low catalyst loading of 0.5% (Scheme 28). Although the coupling process of



Scheme 29 Pyridine chlorides in the Stille coupling with heteroarylstannanes

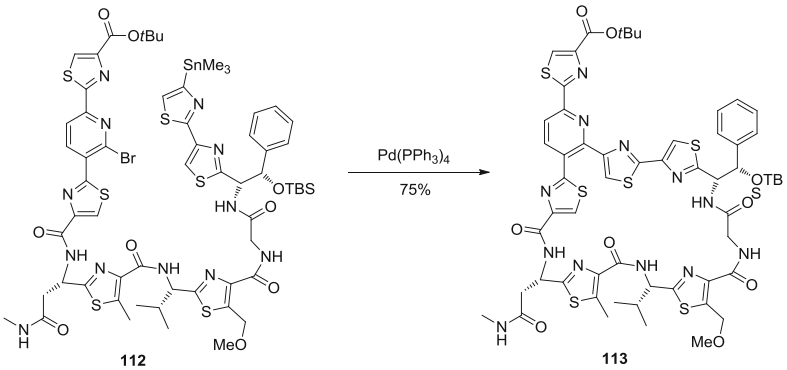


Scheme 30 Stille coupling of highly complex precursors

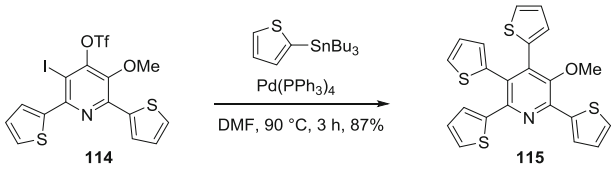
sterically hindered 2-chloro-3-methylpyridine is slower compared to other substrates, the desired coupling product **105** can be obtained with 81% isolated yield by prolonging the reaction time to 8 h [52].

The group of Organ reported an extremely efficient catalytic system for the coupling of heterocyclic halides with heterocyclic stannanes under Stille conditions. In three examples, pyridine chlorides were used: 2-chloro-6-methoxypyridine reacted with 2-(tributylstannyl)thiophene in 92% yield (**106**), whereas 3-chloropyridine coupled with 2-(tributylstannyl)oxazole and 2-chloropyridine with 2-(tributylstannyl)pyrazine in 96% (**107**) and 73% (**108**), respectively (Scheme 29) [53]. The Pd-PEPPSI-iPent catalyst proved to be most efficient. The reaction temperature was elevated but below the boiling point of the reaction solvent. One drawback is the relatively long reaction time.

The group of Bach applied Stille coupling of a very complex pyridine halide in a late stage of the synthesis of the thiazolylpeptide antibiotic GE2270 A [54]. This compound consists of a complex macrocycle which contains five thiazole and one pyridine ring. In an early approach towards the total synthesis of the target, the Stille reaction was used to connect two advanced fragments which set the stage for the macrocyclization. Pyridine bromide **109** was coupled with thiazole stannane **110** using simple $Pd(PPh_3)_4$ as catalyst in 52% yield (Scheme 30). This yield is actually quite good considering the complexity of the structures and the presence of several amide moieties.



Scheme 31 Mocrocyclization via intramolecular Stille coupling



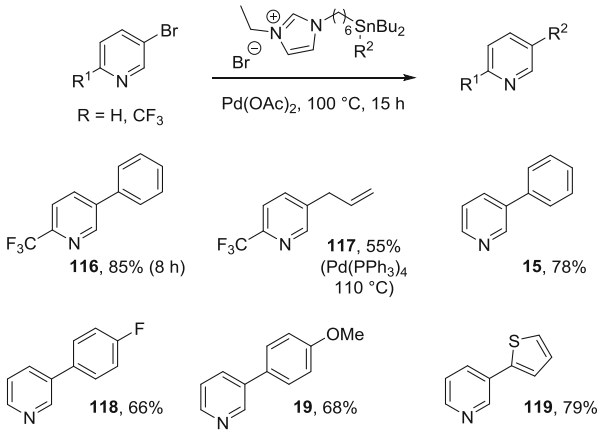
Scheme 32 Per(2-thienyl)pyridines via Stille cross-coupling

In the second variant, the Stille reaction was used specifically for the macrocyclization step of **112** to **113** (Scheme 31). Applying the same conditions, the yield was even better with 75% which makes up for the long reaction time of 3 days. In order to favor intramolecular Stille coupling, the reaction had to be carried out in high dilution (0.001 M).

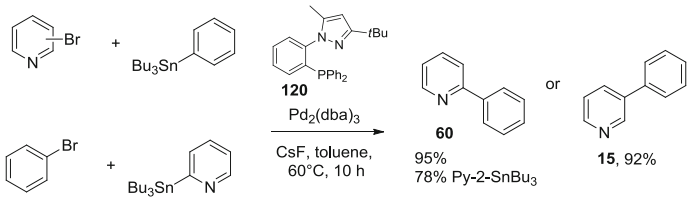
In subsequent work, the structurally closely related natural products amythiamicin C and D were synthesized applying the same strategy [55]. The group of Alvarez applied Stille coupling reactions as well in their synthetic efforts towards natural products structurally related to amythiamicin. However, they applied the method at different stages in the synthesis, i.e., on smaller precursors [56].

Reissig and coworkers reported the synthesis of several per(2-thienyl)pyridines since they were interested in their photophysical properties [57]. Two out of five thienyl residues were introduced via Stille coupling in one-pot giving a good yield of 87% of product **115** starting from **114** (Scheme 32).

An unusual example of a Stille coupling reaction was reported by Legoupy and coworkers [58]. They used ionic liquid supported organotin reagents for the decoration of various (hetero)aryl bromides or alkenylbromides. Reaction optimization was carried out using 3-bromopyridine as coupling partner. It turned out that homo-coupling of the arylation reagent was a major problem which had to be overcome. In the end, they identified a relatively simple catalytic system since $Pd(OAc)_2$ without any ligand gave the best results. Suppression of homo-coupling was



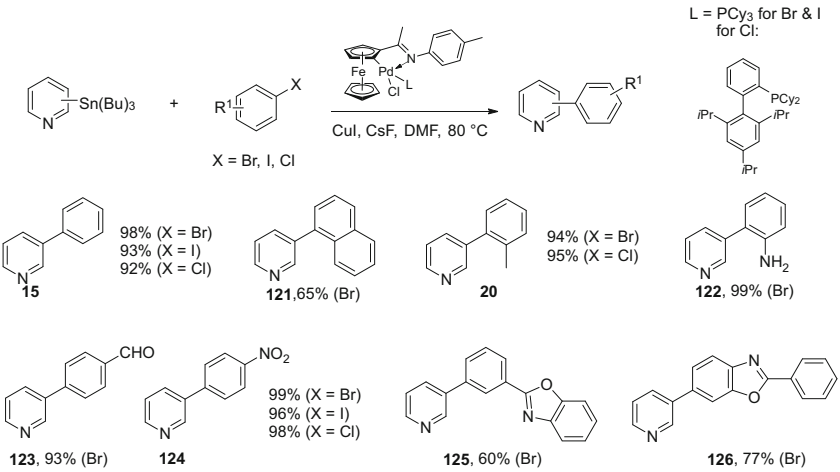
Scheme 33 Ionic liquid supproted tin reagents in the Stille coupling with pyridine bromides



Scheme 34 A pyrazole-tethered phodphine ligand enables milder Stille coupling

achieved largely by optimizing the reaction temperature; 100°C proved to be optimal with higher or lower temperature giving larger quantities of homo-coupling products. The examples involving pyridine halides are compiled in Scheme 33. As can be seen, products **15**, **19**, and **116–119** were obtained in good yields.

In order to obtain even milder and more generally applicable catalytic systems, efforts towards new ligands for coupling reactions are undertaken, continuously. Sarkar and coworkers developed pyrazole-tethered phosphine ligand **120** for Pd (0) which could be applied successfully in Stille, Hiyama, and Kumada coupling reactions [59]. Examples employing pyridine as halide and organometal species were reported, as well. The reaction proceeds at 60°C in toluene in excellent yields for the studied pyridine examples **15** and **60**. However, the reaction time of 10 h is rather long (Scheme 34).

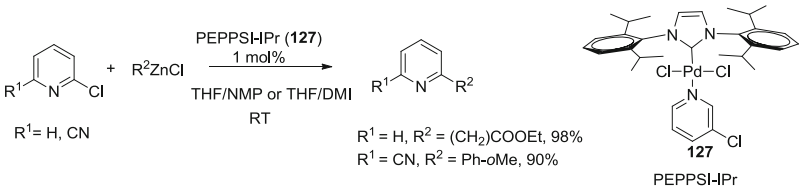


Scheme 35 A ferrocene-palladium species for Stille coupling of pyridinstannanes

3.2 *Pyridine as Organometal Species in Stille–Migita Reactions*

In 2008, Hocek and coworkers exploited the Stille protocol in the synthesis of certain 4- and 3-substituted benzene and aniline C-ribonucleosides (not shown) [60]. They used 3- or 4-bromophenyl C-nucleoside intermediates as substrates carrying TBS protecting groups on the hydroxyl functions. In two examples, 2-Bu_3Sn-pyridine was used as coupling partner. Reaction conditions can be considered as conventional ($Pd(PPh_3)_2Cl_2$, DMF, 100°C), and good yields were obtained.

A ferrocene-based palladacyclic system was reported to promote the Stille coupling between 3-alkylstannylpyridines and aryl halides (Cl, Br, I) (Scheme 35) [61]. In contrast to many other examples of Stille reactions, a base had to be applied and CsF turned out to be most suitable. Additionally, CuI was required as additive (but its role not further commented), and reactions were carried out in DMF as solvent. The requirement for base and additive can be understood as drawback; however, the reaction is quite robust giving yields often >90% independent of the halide species (see examples **15**, **20**, **121**–**126**). Sterically demanding halides are well tolerated as well as functional groups such as NH_2, MeO, Me, CHO, COOR, CF_3, NO_2, COMe, and OH. Selected examples are depicted in Scheme 35.



Scheme 36 Room temperature Negishi coupling of pyridine chlorides

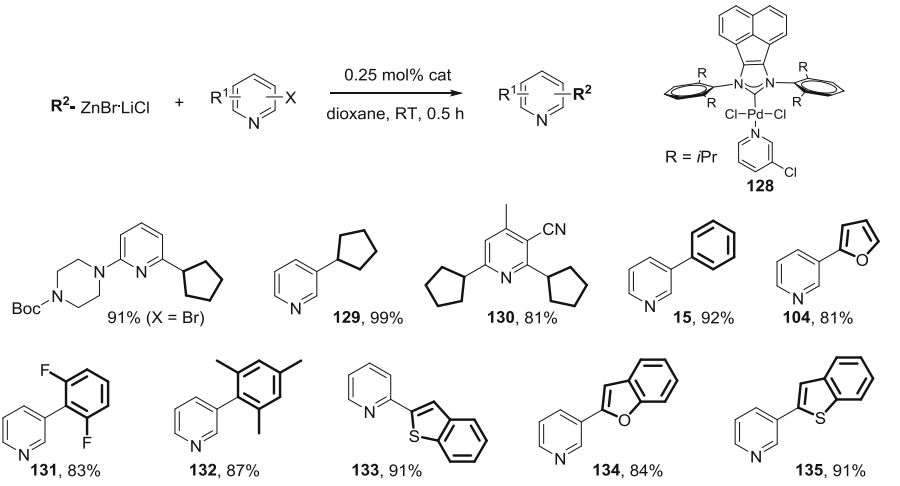
4 Negishi Coupling

Pd-catalyzed cross-coupling of organozinc reagents with organohalides or triflates is known as the Negishi reaction. Reported by Negishi in 1977 for the first time, this was the first reaction that allowed the preparation of unsymmetrical biaryls in reasonably good yields [62–64]. The advantages associated with Negishi reactions are employment of mild reaction conditions and broad functional group compatibility, including ketones, esters, amines, and nitriles. The organozinc reagents can be generated and used in situ by transmetalation of Grignard or organolithium reagents with $ZnCl_2$ [65]. New developments in the field of application of pyridine in Negishi reactions are reported in this chapter independent of the role of pyridine (halide or organometal). Simple applications of pyridine in Negishi reactions under well-established reaction conditions are not discussed.

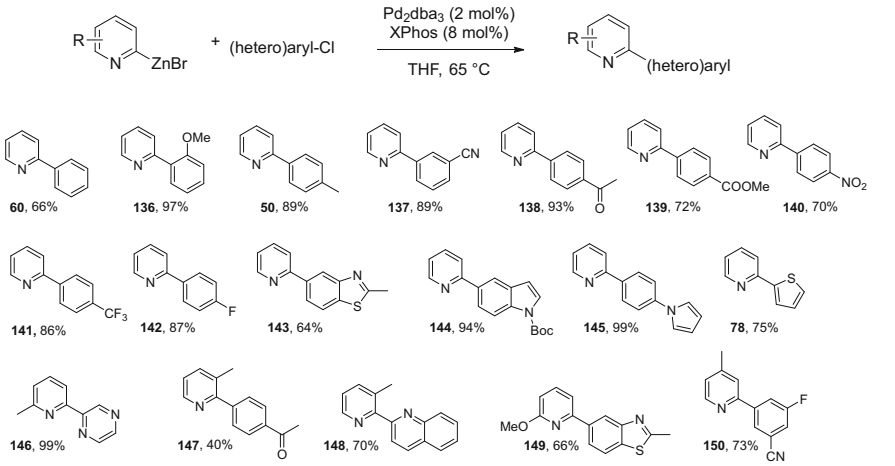
4.1 Pyridine as (Pseudo)halide

A widely applicable Negishi cross-coupling protocol must fulfill several criteria, such as ease of handling of reagents or broad substrate scope. In this regard, an *N*-heterocyclic carbene (NHC)-based precatalyst (**127**) (PEPPSI-IPr) is reported to be useful in Negishi coupling with a broad substrate scope which includes pyridines as well. Utility of precatalyst **127** was demonstrated in various types of cross-coupling reactions in recent years. It can be synthesized easily, is air stable and highly active as well as structurally defined, and can surpass the phosphine-ligated Negishi processes in terms of activity and usefulness. Both alkyl and arylzinc reagents can be coupled with pyridine-2-chlorides (Scheme 36) using this active catalyst system at room temperature [66]. The so termed Pd–PEPPSI complexes have been very successful in Negishi reactions in recent years, and the field was reviewed previously [67].

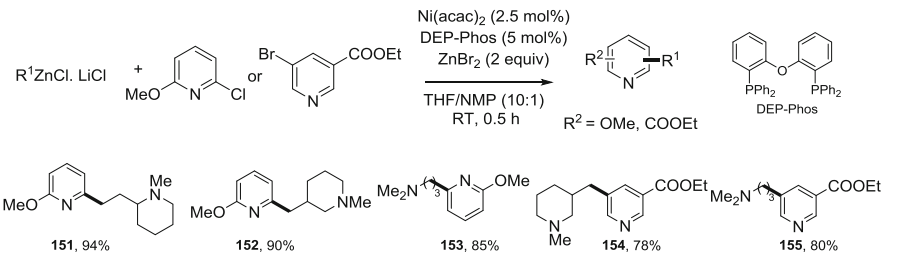
In 2013, Tu and coworkers disclosed another catalyst type structurally closely related to the PEPPSI systems [68]. Their Pd–NHC complexes **128** were designed to have strong σ-donor and π-acceptor properties. Using these catalysts, Negishi couplings could be carried out at room temperature with low catalyst loading (0.25 mol%) within 30 min (Scheme 37). Cyclopentylzinc bromide reacted well with aryl bromides and even chlorides including pyridine derivatives (towards **129**



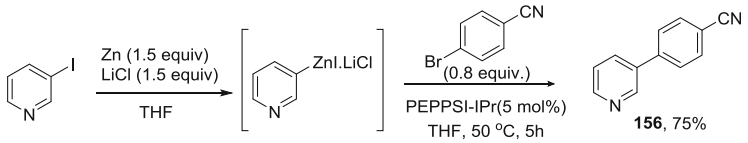
Scheme 37 Pyridine chlorides were used as coupling partners unless indicated differently



Scheme 38 Negishi coupling of pyridine zinc bromides with (hetero)aryl chlorides



Scheme 39 Nickel catalyzed Negishi coupling at room temperature



Scheme 40 Improving stability of pyridinezincates - 1

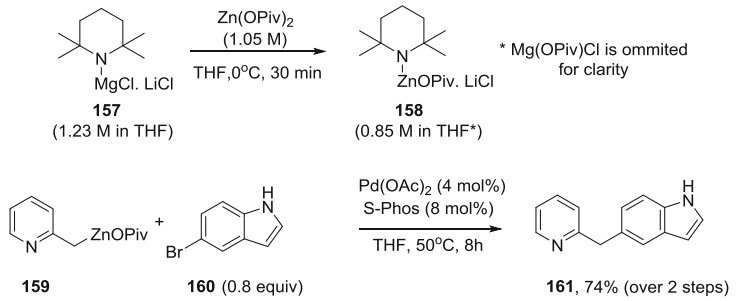
and **130**). For the coupling with arylzinc species, higher catalyst loading, reaction time, and temperature were required (Scheme 37, products **15**, **104**, **131**–**135**).

In recent years, sterically demanding biaryl-ligands (Buchwald ligands) were demonstrated as highly useful in cross-coupling reactions, most importantly in cases when sterically demanding substrates or less reactive aryl chlorides were employed. One such study dedicated to pyridinezinc bromides was reported by the group of Yin [69]. Under their conditions, a series of aryl chlorides were coupled to pyridinylzinc species, and typically good to excellent yields were obtained (Scheme 38, products **50**, **60**, **78**, **136**–**150**). Functional groups (NO_2, CF_3, OMe, CN, Ac, COOMe, Boc) were well tolerated as well as ortho substitution of the halide species (Scheme 38). Naturally, the group of Buchwald contributed to the field as well. In their recent report of Negishi cross-couplings on structurally quite diverse systems, few examples employing pyridine in one role or the other were reported as well (not shown) [70].

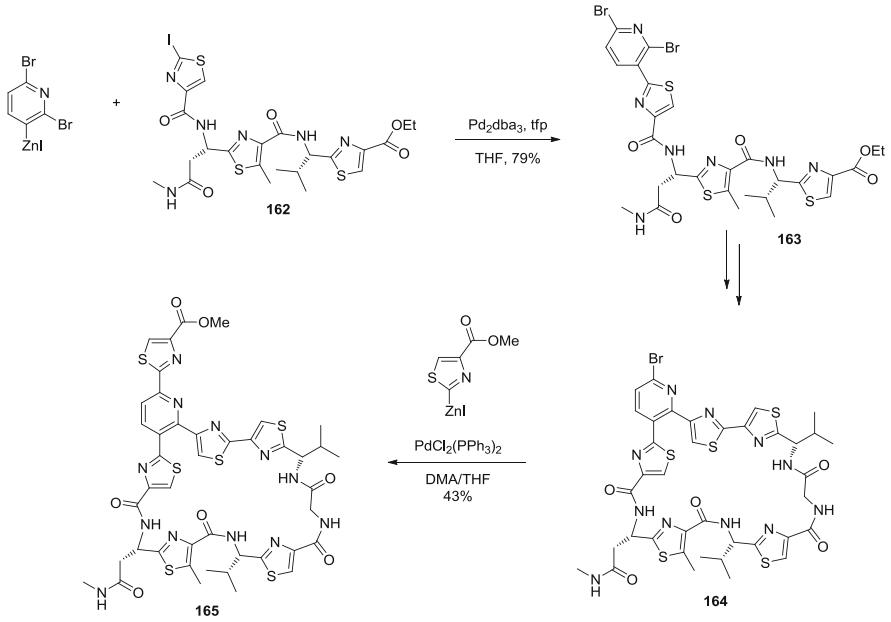
The aminoalkyl moiety is one of the most frequently occurring structural motives in biologically active molecules. In this regard, Ni-catalyzed Negishi coupling for aminoalkylation of heteroarenes including pyridine is a valuable method for decorating a pyridine scaffold (Scheme 39) [71, 72]. The alkylzinc species required as nucleophile for Negishi cross-coupling can be prepared easily from the corresponding chlorides via a Grignard reagent and transmetalation with $ZnCl_2$. The optimal ratio of Ni-catalyst to ligand is 1:2. Both bromo- and chloropyridine derivatives can undergo cross-coupling with aminoalkylzinc reagents at room temperature, for example, towards compounds (**151**–**153**). An ester functionality on pyridine is reported to be tolerated also under the reaction conditions (Scheme 39, products **154** and **155**).

4.2 Pyridine as Zinc Species

Due to high reactivity, environmentally friendly organozinc reagents are a suitable choice for cross-coupling chemistry. However, zinc reagents are labile and sensitive to air and water. This drawback can be overcome by in situ generation of the zinc reagent from the corresponding iodide by addition of zinc and LiCl, followed by cross-coupling with bromide, chloride, and triflate using PEPPSI-IPr as catalyst. This method is a one-pot protocol, and handling of sensitive zinc reagents can be



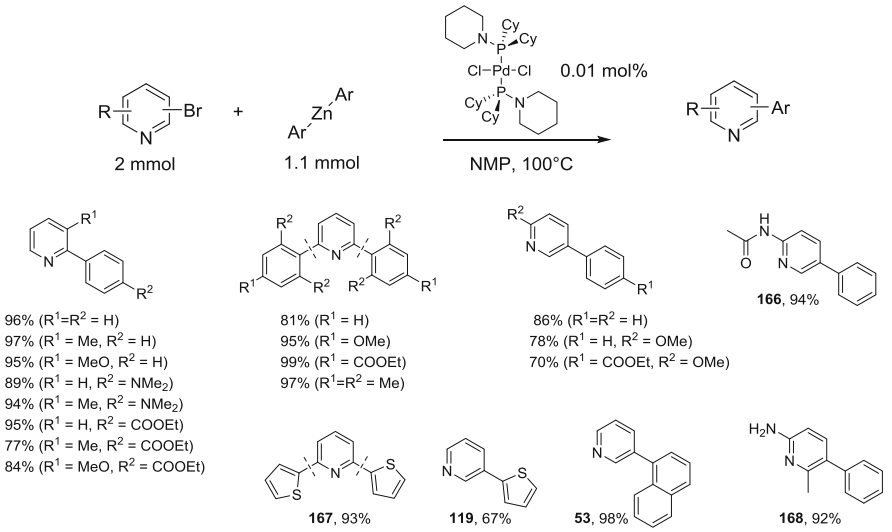
Scheme 41 Improving stability of pyridinezincates - 2



Scheme 42 Negishi coupling in the synthesis of amythiamicin D

avoided that way. The following reaction scheme describes the overall procedure with 3-iodo pyridine as starting material (Scheme 40) [73].

Zinc reagents are usually unstable towards air and moisture, but aryl- and heteroarylzinc pivalates are easy to handle solids and moderately stable (up to 4 h in air) even when handled in air. Moreover, zinc pivalates can be prepared easily either via Mg insertion in the presence of $Zn(OPiv)_2$ 2LiCl [74] or directed metalation using TMP-MgCl LiCl (TMP = 2,2,6,6-tetramethylpiperidyl) and subsequent transmetalation to $Zn(OPiv)_2$ [75]. Still, both methods are incompatible with the presence of electron withdrawing functional groups such as nitro, aldehyde, etc. In this regard, the milder reagent TMP-ZnOPiv LiCl proved to be



Scheme 43 Diarylzinc reagents in Negishi coupings with pyridine bromides

successful for the metalation at the benzylic position of five- and six-membered heterocycles and is tolerated by sensitive functionalities such as nitro and aldehyde as well. TMP-ZnOPiv LiCl (**158**) is prepared by the addition of $Zn(OPiv)_2$ (1.05 equiv., 0°C) to a solution of TMP-$MgCl_3$ LiCl (**157**, 1.23 M in THF) followed by dilution with dry THF until a clear solution is achieved (final concentration: 0.85 M; Scheme 26). For example, 2-picoline can be zincated smoothly using this reagent after 1 h at 25°C to provide the corresponding zinc pivalate **159** which can then be used effectively in a Negishi cross-coupling with 5-bromoindole **160** using Pd $(OAc)_2$ and SPhos as the catalytic system. The desired product **161** can be obtained in 74% yield over two steps (Scheme 41) [76].

The total synthesis of the thiopeptides amythiamicin C and D proved to be a fruitful area for cross-coupling chemistry. The group of Bach reported a total synthesis in which they carried out three cross-coupling reactions on the pyridine scaffold [55], one Stille reaction (see Sect. 3.1) and two Negishi reactions. In the case of amythiamicin D (**165**), pyridine served as the zinc organyl in the first Negishi reaction and was coupled to a complex thiazole-peptide building block **162** to intermediate **163**. The second Negishi coupling represented the last step in the synthesis of amythiamicin D where the remaining bromine on pyridine of substrate **164** was coupled to a 2-thiazolyl-zinc species (Scheme 42). In both reactions, the coupling conditions can be considered as standard, but the complexity of the target product is remarkable. Removal of triphenylphosphine oxide proved to be tricky in the last step which lowered the yield of **165** to 43%. In the synthesis of amythiamicin C, the order of events was slightly different, but overall the same coupling reactions were applied.

Frech reported a new Pd-catalyst with extremely high activity in Negishi reactions [77]. The catalyst is readily prepared from commercially available $[Pd(cod)(Cl)_2]$ (cod=cyclooctadiene) with 1-(dicyclohexylphosphanyl)piperidine. The authors demonstrated a wide substrate scope and excellent functional group tolerance at low catalyst loading (0.01 mol%), and often the reactions were completed within minutes (Scheme 43). Among the many examples, several coupling reactions of pyridine bromides with diarylzinc reagents were reported (Scheme 43, e.g., **166–168**). Also in these cases, good yields were obtained demonstrating the power of this new catalytic system.

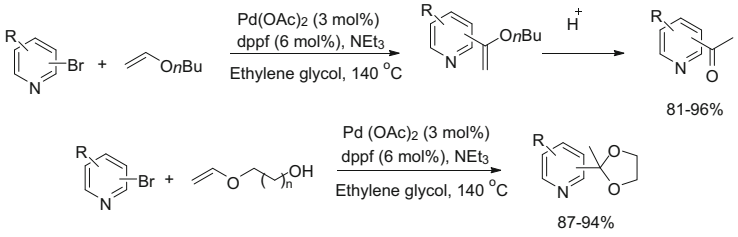
The group of Twieg showed that a Negishi reaction can be carried out in the presence of a stannyl group employing simple $Pd(PPh_3)_4$ as catalyst [78]. Alkyl- and arylzinc chlorides were used as coupling partners, and it was demonstrated that the Bu_3Sn group can be further converted in a Stille coupling reaction (not shown).

5 Mizoroki–Heck Reaction on Pyridine

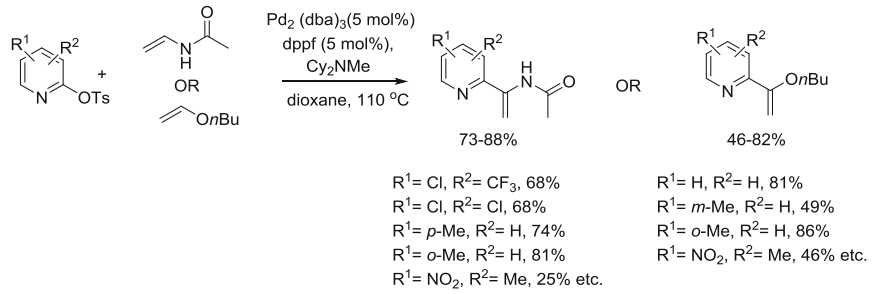
Palladium-catalyzed replacement of vinylic hydrogen by aryl, alkenyl, or benzyl moieties, independently discovered by Mizoroki and Heck in the early 1970s, is known as the Mizoroki–Heck (MH) coupling reaction, often referred to as the Heck reaction only [79, 80]. This reaction has special value for industrial and academic research as mild conditions are sufficient to activate the olefin. This procedure is now broadly defined as the Pd(0)-mediated cross-coupling of an aryl or vinyl halide or triflate with an alkene, and many catalytic systems were reported to catalyze this cross-coupling reaction [81–83].

Reactive aryl halides (Br or I) and activated alkenes are used frequently in cross-coupling processes. Aryl chlorides are definitely more attractive substrates due to their more facile availability. However, due to the relatively strong C–Cl bond, oxidative addition is difficult to achieve. So far, considerable advances in terms of catalytic systems used in MH coupling have been reported, but poor regioselectivity is one of the major disadvantages in synthetic utility. Regioselectivity of this reaction is defined by the resulting substitution pattern on the olefins. As a general rule, electron poor alkenes selectively provide products of β-substitution, whereas linear β- and branched α-substituted products are formed with electron-rich alkenes [84–87]. To achieve selective α-substitution with electron-rich olefins, a cationic palladium (II) complex need to be generated in situ under the reaction conditions, to promote an ionic pathway [88, 89]. So far, several methods have been successfully developed to circumvent the problem of regioselectivity, but concomitant disadvantages are the use of expensive substrates such as triflates or toxic additives (halide scavengers like silver and thallium) or applications limited to particular olefins [90, 91].

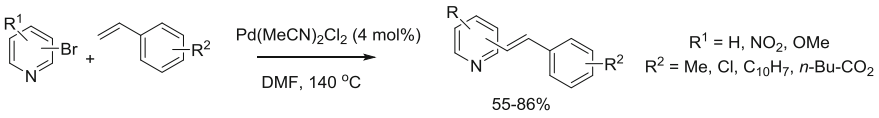
A general and efficient method for coupling of pyridine bromides with vinyl ethers and hydroxyalkyl vinyl ethers in ethylene glycol was reported (Scheme 44) [92]. In this green solvent, highly regioselective heteroarylation of electron-rich



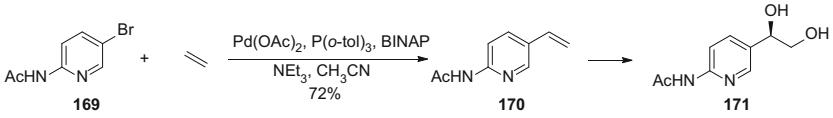
Scheme 44 Coupling of vinyl ethers with pyridine bromides



Scheme 45 Coupling of vinyl ethers and enamides with pyridine tosylates



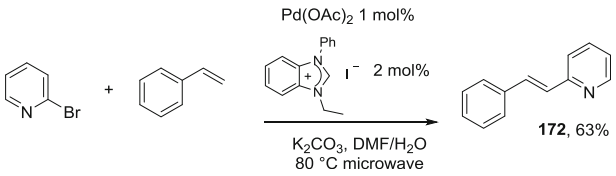
Scheme 46 Ligandless Heck coupling of pyridine bromides



Scheme 47 Heck coupling of 169 with ethylene

olefins was achieved with pyridyl bromides. The advantages of this method are that there is no necessity for using expensive triflates, halide scavengers, or ionic liquids (which often help to promote an ionic pathway). Ethylene glycol supposedly facilitates the formation of the ionic palladium intermediate, which promotes the ionic route and preferentially affords the branched products.

Heck coupling of pyridine tosylates with electron-rich enamides and vinyl ethers was reported by the group of Skrystrup [93]. Excellent regioselectivity for the desired products and no loss in reactivity of the applied olefin are observed (Scheme 45). 2-Pyridyl tosylate derivatives used in this protocol can be synthesized easily from the corresponding commercially available 2-hydroxy pyridines by



Scheme 48 Microwave assisted Heck coupling of styrene with 2-bromopyridine

simple treatment with tosylchloride (TsCl) and a base. Coupling of 2-pyridyl tosylates with *N*-vinyl acetamide using $Pd(dba)_2$ as catalyst precursor and dppf (1,1′-bis(diisopropylphosphino) ferrocene) as ligand provides the desired product with good yields of 68–79% within 22 h (Scheme 45). In the case of electron withdrawing nitro-substituted pyridines, the yield drops to 25%. In the case of bistosylates, double MH coupling is observed with *N*-vinyl acetamide. Couplings of butyl vinyl ether with 2-pyridyl tosylates are also successful under the same reaction conditions giving 49–85% yield of the desired products. Electron withdrawing groups are well tolerated as well in this case. Usually, a slightly lower yield was observed with substituents in the 3-position of the 2-pyridyl tosylates.

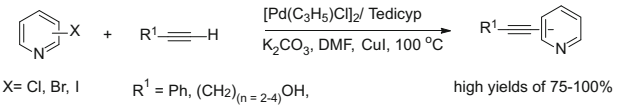
Pyridine bromides and substituted pyridine bromides (Scheme 46) are reported to undergo Heck reaction with styrene derivatives under ligand and base-free conditions. This makes the transformations more convenient and economic, although a high temperature of 140°C is mandatory to obtain the maximum yield of the products [94]. MH coupling of styrene with 3-bromopyridine gives higher yields than 2-bromopyridine, which is a bit counterintuitive.

The MH reaction is not only widely investigated for small-scale applications in laboratory, but also some industrial applications are reported [95]. For example, 2-acetamido-5-vinylpyridine **171**, a key intermediate for drug candidates at Pfizer, can be synthesized by Sharpless dihydroxylation of **170**, which is obtained effectively in multi-kilogram scale by MH coupling of **169** with ethylene using rac-BINAP as ligand in combination with $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ (Scheme 47) [96].

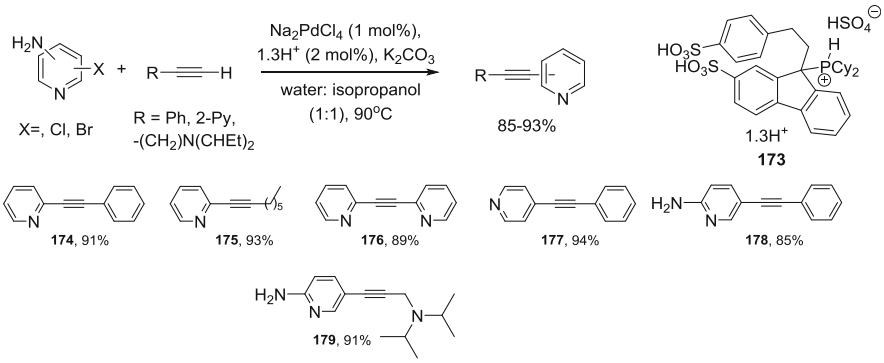
Küçükbay and coworkers investigated Suzuki–Miyaura and MH reactions in the presence of *N*-phenylbenzimidazolium salts [97]. Their catalytic system proved to be very reactive in the case of aryl bromides and aryl iodides. Unfortunately, coupling of styrene with 2-bromopyridine gave a significantly lower yield. Still, around 60% of product **172** could be obtained within 10 min of reaction time (Scheme 48).

6 Sonogashira Coupling

The palladium (or copper)-catalyzed coupling of aryl or vinyl halides with terminal acetylenes is known as Sonogashira coupling reaction which was first published in 1975 by Sonogashira, Tohda, and Hagihara [98]. This cross-coupling reaction is



Scheme 49 Generally applicable Sonogashira coupling of pyridine halides

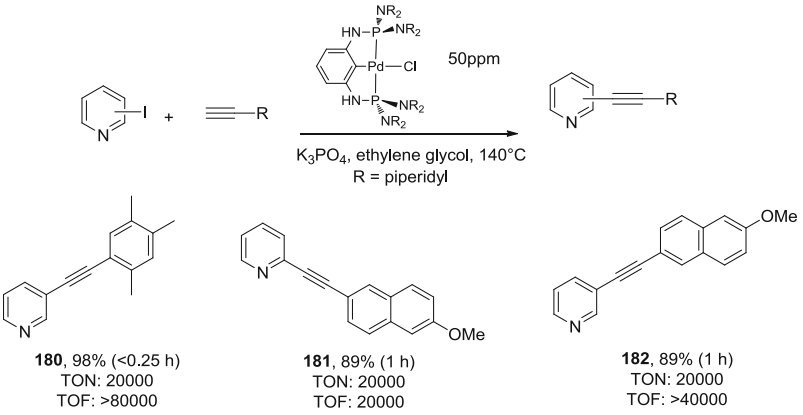


Scheme 50 Sonogashira coupling in aqueous media

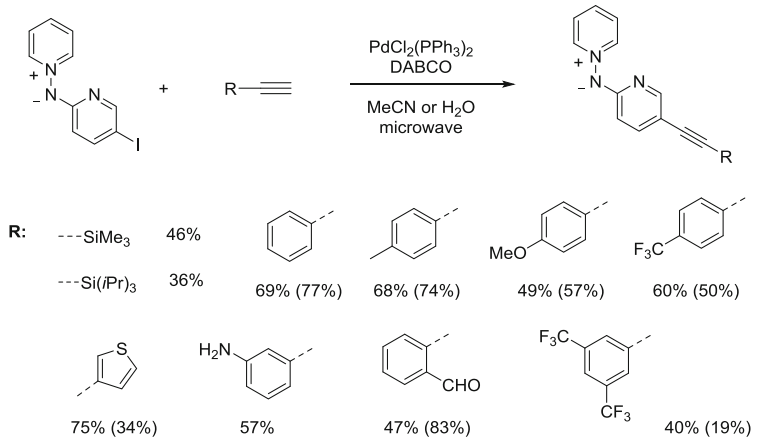
one of the most synthetically significant routes to achieve sp^2–sp C–C bond formation. Application of Sonogashira coupling includes natural product synthesis, synthesis of heterocyclic and biologically active compounds, conjugated polymers, molecular electronics, etc. [99]. In this section, new developments in Sonogashira coupling of recent years are reported. Only reactions are reported in which pyridine acts as halide coupling partner.

A general protocol for coupling of pyridyl halides with terminal alkynes (Scheme 49) with low catalyst loading was reported by Santelli and coworkers [100, 101]. This group employed a stable and efficient palladium catalyst based on a phosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)-cyclopentane or TedicyP [11]. As general trend, pyridyl iodides are more reactive than bromides, whereas chlorides showed the slowest kinetic profile. Due to the electronegativity of the nitrogen atom, the 2 and 4 positions of halopyridines are expected to be most susceptible to the oxidative addition to palladium. However, with this reported catalytic system, in the case of pyridyl bromides, the position of halide has generally a minor effect. In contrast, in the case of chloropyridines, reactions of 2- and 4-chloropyridines are faster than with 3-chloropyridine. This indicates that the oxidative addition of chloropyridines to palladium is the rate-limiting step.

On a more environmentally friendly note, Sonogashira coupling of pyridyl halides with terminal alkynes was reported in aqueous media without use of any copper cocatalyst [102]. 2-Chloropyridine and 5-bromopyridine-2-amine were coupled with phenyl, 2-pyridyl acetylene, or oct-1-yne in good yields (Scheme 50, products **174**–**179**). Interestingly, there is no need for protection of amine in the



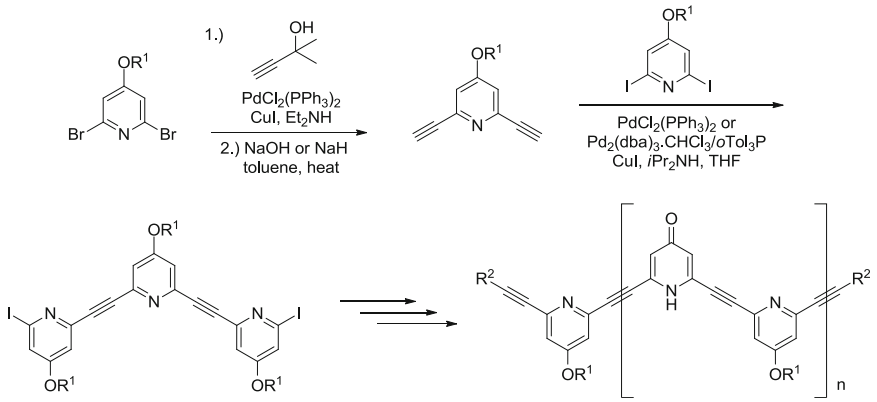
Scheme 51 Low catalyst loading Sonogashira coupling of pyridine iodides



Scheme 52 Yields in brackets correspond to the reaction in water

case of 2-amino-5-bromopyridine, which gives almost quantitative yield upon coupling with phenylacetylene **178**. The active Pd-catalyst used in this transformation is generated in situ from Na_2PdCl_4, and two equivalents of triply protonated ligand $1.3H^+$ (**173**), in the presence of 5 equiv. of K_2CO_3 (Scheme 50). Ligand **173** is commercially available as well.

Another copper-free example was reported by Frech and Bolliger who disclosed amino-phosphine-based pincer complexes of palladium which promote the Sonogashira coupling of aryl bromides and aryl iodides in the absence of cocatalyst at extremely low catalyst loadings [103]. The examples including pyridine halides required only 50–100 ppm of catalyst and were completed between 0.25 and 6 h. TOF of up to >80,000 and TON up to 20,000 were measured. Conversions were complete in almost all cases. Eleven examples were reported involving pyridine



Scheme 53 Sonogashira coupling in the synthesis of pyridine–pyridone alternate oligomers

halides, but in only three cases (**180–182**), a yield was reported (although then excellent; Scheme 51).

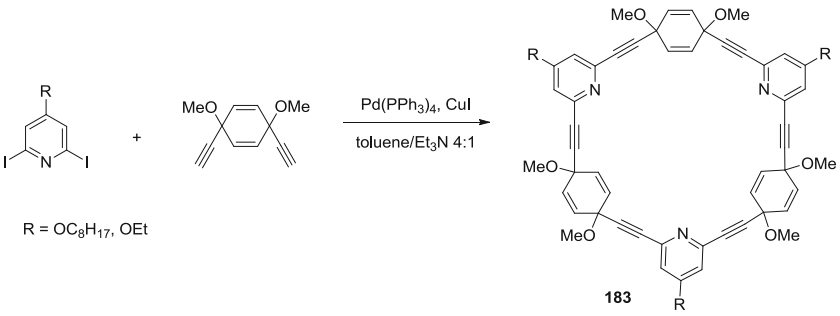
Another copper-free method came from the laboratory of Alvarez-Builla [104]. In this report, pyridinium *N*-heteroarylaminides were used as substrates, and it was found that a simple catalytic system ($PdCl_2(PPh_3)_2$, DABCO, acetonitrile) proved to be sufficient to promote the desired coupling process (Scheme 52) even though yields were mediocre (30–75%).

Other copper (and amine)-free conditions were reported over the past years. For example, it was demonstrated that carboxylate-based ionic liquids are suitable media for that purpose. Simple $PdCl_2$ as metal source and KOAc as base at 100–120°C proved to be sufficient to give a good yield of 85–88% in the coupling of 3-bromopyridine and phenylacetylene depending on the IL applied (not shown) [105].

Li and coworkers investigated the tetradentate phosphine ligand *N*,*N*,*N*′,*N*′-tetra (diphenylphosphinomethyl)pyridine-2,6-diamine in Cu-free Sonogashira couplings in combination with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as metal source [106]. As coupling partners, 2- and 3-bromopyridine were used as well as 3-chloropyridine in the reaction with phenylacetylene. In the case of bromides, 96% yield was obtained after 3 h, whereas chloride gave only 12% after 20 h.

Palladium-free Sonogashira reactions have been reported as well. Bolm and coworkers investigated such a variant [107]. Initially, they tested the coupling between iodobenzene and phenylacetylene in the presence of various copper sources and an excess of DMEDA as ligand. Interestingly, all Cu sources gave the desired product in high yields after 22 h. When applied to 2-iodo and 3-iodopyridine as halide coupling partner, the corresponding products were obtained in good yields of 86% and 84%, respectively.

The Sonogashira reaction is well established on pyridine systems and has been applied to the synthesis of compounds with interesting properties in recent years. Abe and Inouye exploited the Sonogashira methodology in the synthesis of



Scheme 54 Macrocycle synthesis via Sonogashira coupling

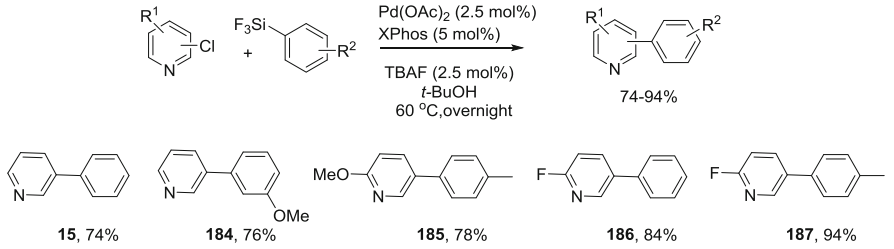
pyridine–pyridone alternate oligomers (Scheme 53) [108]. The target compounds displayed self-dimerization and glucoside recognition properties.

Ohe reported the synthesis of an interesting compound class applying standard Sonogashira coupling conditions. Pyridine-containing strained cyclynes were synthesized from 2,6-diiodopyridines and *cis*-3,6-diethynyl-3,6-dimethoxycyclohexa-1,4-diene as coupling partner (Scheme 54, product **183**) [109]. Not surprisingly, the yield in the macrocyclization was low (3–10%). Further transformation of these intermediates led to a product with strong fluorescence around 500 nm with a good fluorescence quantum yield.

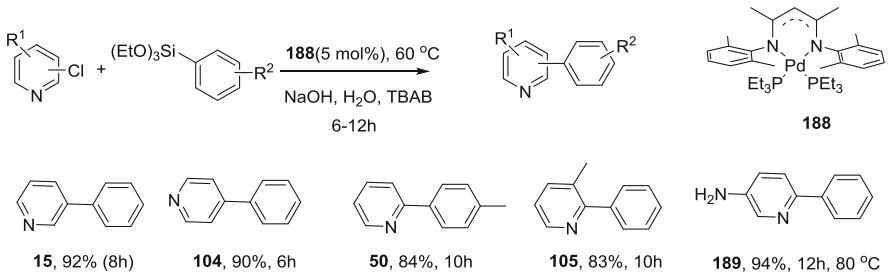
7 Hiyama Coupling

Coupling of organosilanes with organohalides and triflates as coupling partners to generate biaryls and alkyl and vinyl aromatics is known as Hiyama coupling and has emerged to be a powerful synthetic method in organic chemistry. Compared to organoborons (Suzuki–Miyaura reaction) and organostannanes (Stille reaction), organosilanes have several advantages of being lower in toxicity, ease of handling, and comparatively high stability [110–114]. Previously, the application of organosilane derivatives as coupling partners was not attractive due to the weak polarization of the carbon–silicon bond. This problem has been solved through the generation of a penta-coordinate silicon intermediate in situ, using a fluoride activator [115] such as tetra-*n*-butylammonium fluoride (TBAF) or an inorganic base [116–120]. Subsequently, other efficient partners such as organo(trialkoxy) silanes [121, 122], organosilanolates [123, 124], and organohalosilanes [125, 126] have been utilized in Hiyama cross-coupling also referred to as Hiyama–Denmark coupling.

A variety of palladium catalysts have been studied extensively for Hiyama coupling. Aryl iodides and bromides have been predominantly used as the coupling partners of organosilanes. However, the use of aryl chlorides is highly desirable, due to ready availability and cost effectiveness. So far, only few examples of the



Scheme 55 Pd-catalyzed Hiyama coupling of pyridine chlorides



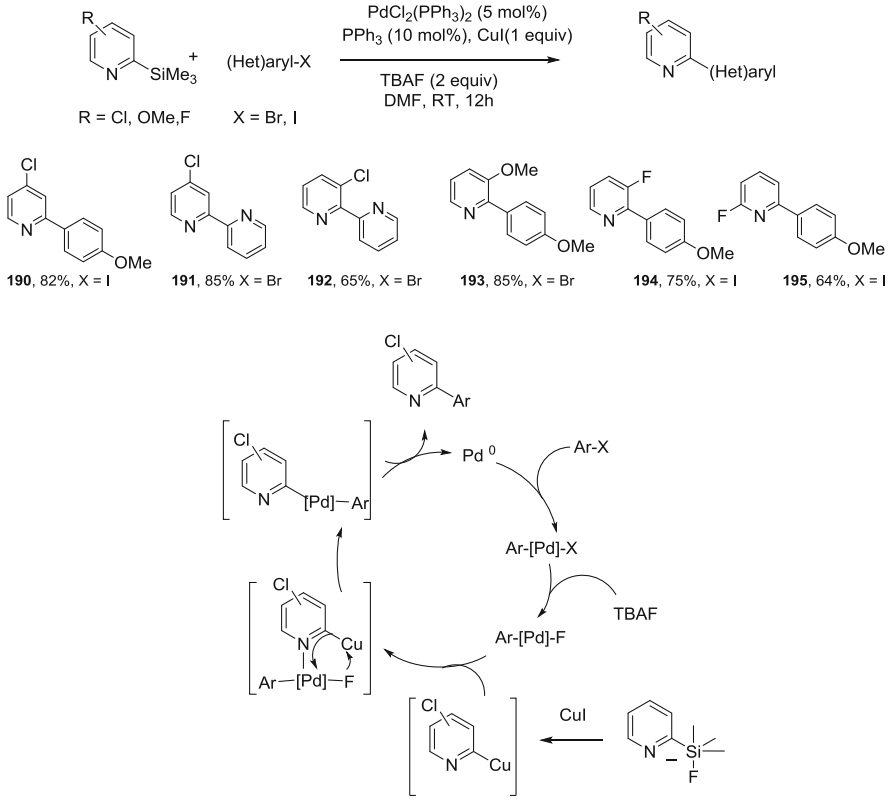
Scheme 56 Hiyama-Denmark coupling of pyridine chlorides

Hiyama coupling with aryl chlorides are reported, and they often proceed under microwave heating or high catalyst loading [120, 127, 128].

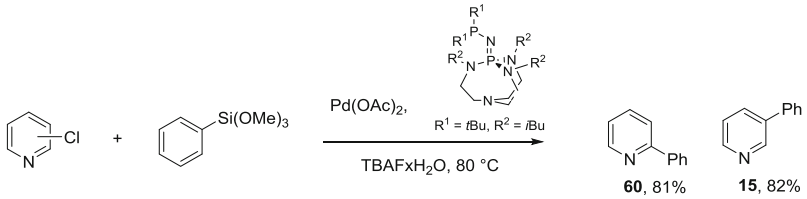
An effective Hiyama coupling of aryltrifluorosilanes with pyridyl chlorides (Scheme 55) has been reported by Molander and Iannazo [129]. Aryltrifluorosilanes are interesting as coupling partners in Hiyama coupling because of their stability to heat, air, and moisture, as well as their easy handling. Moreover, synthesis of these triflurosilanes is straightforward and can be achieved easily from commercially available trichlorosilanes. The substrate scope of pyridyl chloride includes electron donating (as in **185**) and withdrawing (as in **186** and **187**) substrates which make this method more attractive.

β-Diketiminatophosphane palladium complex **188** is reported to be a highly active catalyst for a fluoride-free Hiyama coupling of un-activated aryl and heteroaryl chlorides including chloropyridines and also substituted chloropyridines in aqueous media. 2-, 3-, and 4-chloro-substituted pyridines are known to undergo coupling with arylsilanes, and very basic and electron-rich 5-amino-2-chloropyridine is also found to participate in coupling to give the desired products **15**, **50**, **104**, **105**, and **189** in high yield (Scheme 56) [130]. This is remarkable since catalyst deactivation has often been an issue for coupling of electron-rich substrates, owing to the presence of free amino group, which allows it to bind to the Pd and thus deactivate the catalyst.

Halogenated 2-trimethylsilylpyridines have been reported to undergo Hiyama coupling with aryl and heteroaryl halides at room temperature as reported by Gros and coworkers (Scheme 57) [131]. The electron withdrawing effect of chlorine and

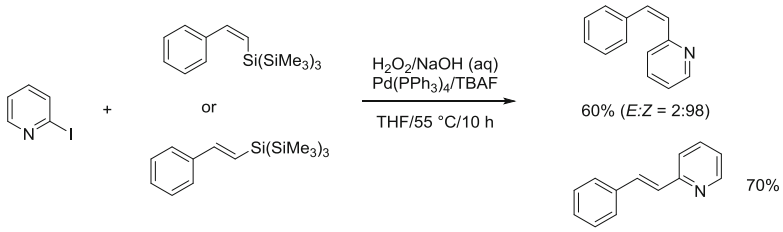


Scheme 57 Room temperature Hiyama coupling of (trimethylsilyl)pyridines



Scheme 58 Hiyama-Denmark coupling of 2- and 3-chloropyridine

other electron withdrawing substituent such as fluorine on the pyridine ring is believed to increase polarization of the C–Si bond, thus favoring the formation of the intermediate ate complex by reaction with fluoride ions, from TBAF (see products **190–192**, **194** and **195**). Interestingly, the authors observed that a methoxy group in 3 position was also tolerated (**193**), and they attributed an electron withdrawing effect to this group as well even though it is generally considered to be electron donating. Complexation of palladium by the pyridine nitrogen in transmetallation step (assisted by fluorine and copper) is an important factor in



Scheme 59 Tris(trimethylsilyl)silanes in the Hiyama coupling of 2-iodopyridine

this reaction as suggested by the proposed mechanism, and thus the pyridine nitrogen must be α- to the trimethylsilyl group in the substrate.

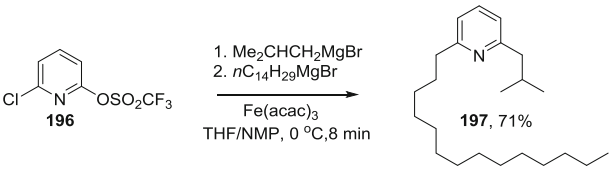
Sarkar and coworkers developed pyrazole-tethered phosphine ligands for Pd(0) which were already discussed in the Stille section. One case of a Hiyama reaction was disclosed as well in that contribution. Coupling of 3-bromopyridine with trimethoxy(phenyl)silane gave 3-phenylpyridine in 88% yield [59].

Another class of ligands was applied by the group of Verkade [132]. They synthesized electron-rich amino-phosphines which promoted the Hiyama–Denmark coupling of aryl bromides but also of aryl chlorides. 2- and 3-chloropyridine gave 81% **60** and 82% **15**, respectively, in the reaction with trimethoxy(phenyl)silane (Scheme 58).

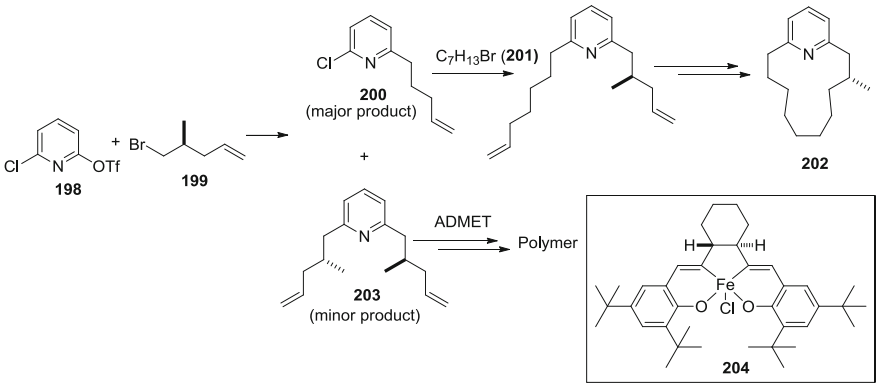
The trend in Hiyama-type coupling reactions clearly goes into the direction of fluoride-free conditions as realized in Hiyama–Denmark coupling. There, silanols deprotonated under the reaction conditions are applied as organosilicon species. The group of Wnuk reported vinyl tris(trimethylsilyl)silanes as suitable substrates for Hiyama coupling in the absence of fluoride anions [133]. In this case, a reactive silanol or siloxane species is generated due to the presence of aq. H_2O_2 and NaOH. *Z*-Tris(trimethylsilyl)silanes and *E*-tris(trimethylsilyl)silanes were reported as substrates (Scheme 59). In the first case, coupling with 2-iodopyridine gave 60% yield with an *E*:*Z* ratio of 2:98, the best of all investigated halides. In the case of *E*-substrates, the *E* product was formed exclusively in all cases investigated.

8 Kumada–Corriu–Tamao Coupling

The success story of modern cross-coupling chemistry started with the discovery of the nickel-catalyzed reactions of Grignard reagents with alkenyl and aryl halides, independently described by Kumada and Corriu in 1972. This transformation is now generally referred to as Kumada coupling, less frequently as Kumada–Corriu–Tamao reaction [134–136].



Scheme 60 Iron catalyzed Kumada coupling with simple $Fe(acac)_3$

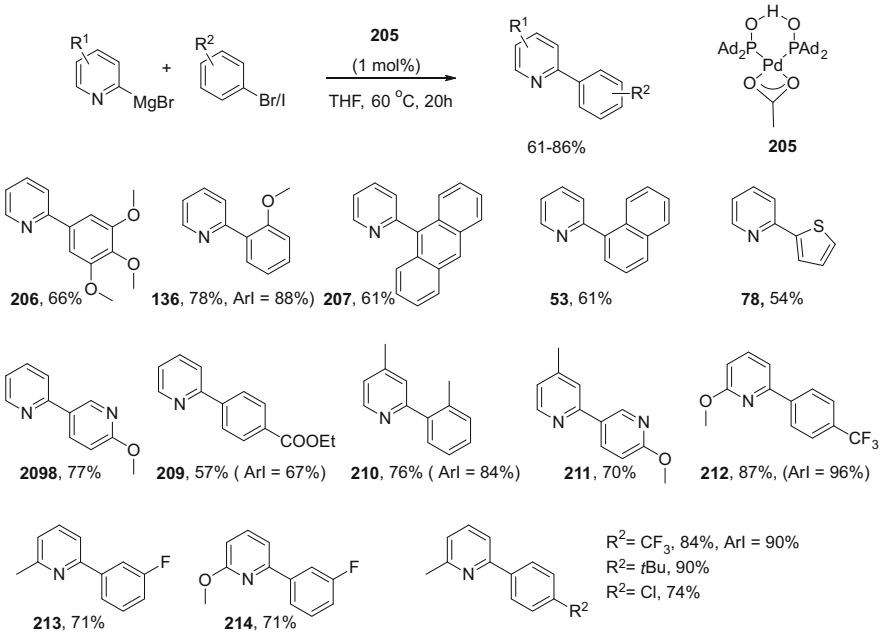


Scheme 61 Iron complex 204 in Kumada coupling of 198

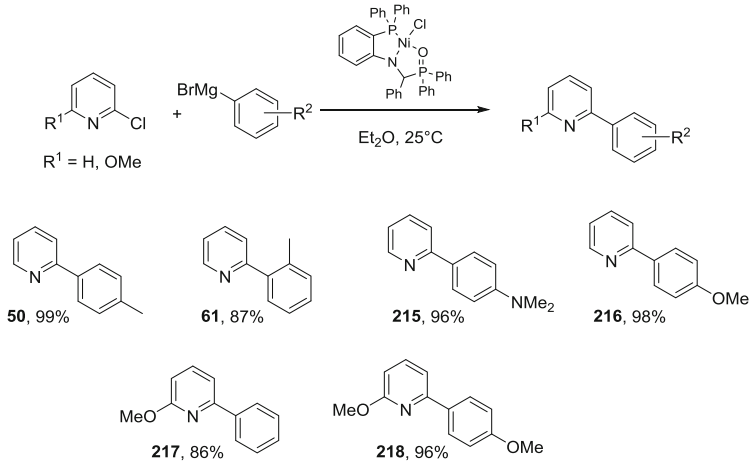
8.1 Pyridine as (Pseudo)halide

Fürstner and coworkers described an iron-catalyzed cross-coupling process of alkylmagnesium halides and aromatic electrophiles, including pyridyl chlorides and sulfonates. The latter compounds are distinctly more reactive: the first coupling in pyridine substrate **196** proceeded at the sulfonate site and only then the chloride reacted, giving the desired product **197** in 71% in a one-pot protocol [137]. Cheap and nonhygroscopic $Fe(acac)_3$ is used as alternative to replace the expensive palladium catalysts usually used for such coupling procedures. Additionally, this catalyst shows unprecedentedly high reaction rates even at or below room temperature. This Fe-catalyzed method does not require any addition of special ligand, making it very attractive for coupling of pyridyl chlorides with alkyl, alkenyl, and alkylmagnesium bromides, as cheap and environmentally benign method. Only for *sec*-alkyl Grignard reagents, the use of [Fe(salen)Cl] (**204**) is recommended [138].

The utility of this iron-catalyzed method is illustrated in the synthesis of the alkaloid (R)-(+)-muscopyridine by the same research group [139]. The enantiomerically pure Grignard reagent **199** is converted with the difunctional pyridine derivative **198**, and the iron–salen complex **204** (5 mol%) in THF/NMP at 0°C for 20 min. Compound **200** is formed selectively by reaction at the triflate site accompanied by small amounts of the dialkylation product **201**. Without

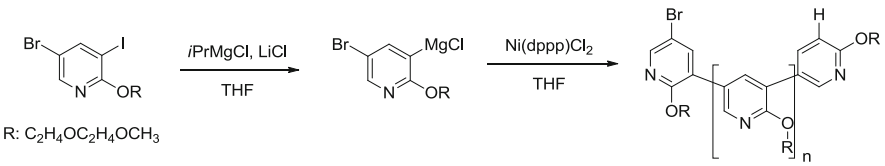


Scheme 62 Palladium catalyzed Kumada coupling of pyridine Grignards



Scheme 63 Nickel catalyzed Kumada coupling of pyridine chlorides

intermediate purification to remove the dialkylated product, 6-heptenylmagnesium bromide **202** and additional catalyst **204** (5 mol%) are introduced and stirring can be continued for 30 min at 0°C. Subsequent ring-closing metathesis and reduction of the resulting double bond gives the natural product **203** (Scheme 61), while the



Scheme 64 Pyridine polymerization via Kumada cross-coupling

byproduct generated from the dialkylated intermediate can be transformed into a polymer by acyclic diene metathesis (ADMET) to facilitate easy separation.

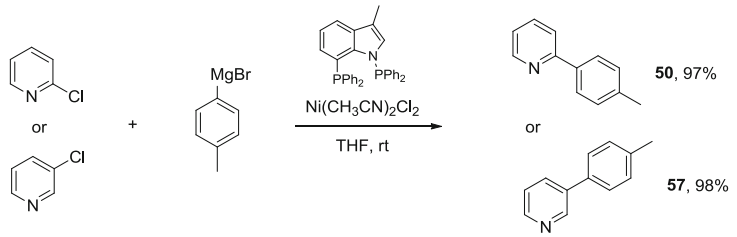
8.2 Pyridine as Grignard Species

Generally applicable Kumada cross-coupling reactions of easily available 2-pyridyl organomagnesium reagents using $(1\text{-Ad})_2P(O)H$ as ligand were reported by Ackerman et al. [140]. The ligand forms the active catalyst (**205**) in the presence of $Pd_2(dba)_3$ in situ. The air- and moisture-stable secondary phosphine oxide $(1\text{-Ad})_2P(O)H$ turned out to be the ideal choice as pre-ligand. The generated catalyst is very active and gives good yields of desired products in the absence of any base. A variety of substituted 2-pyridyl nucleophiles and aryl halides (iodide and bromide) can be coupled using the reaction conditions described in Scheme 62. Generally, iodides give better yield than bromides. Interestingly, functional group tolerance is high as well for this cross-coupling process (see examples in Scheme 62).

Palladium is the predominant metal in cross-coupling chemistry. However, nickel is often an interesting alternative, and also in the original contribution on Kumada couplings, nickel was used as catalyst. Such catalysts can be extremely valuable as demonstrated by the group of Wang [141, 142]. They introduced amido pincer nickel complexes to promote biaryl formation of a series of halides including 2-chloropyridine. In all examples, excellent yields >90% were obtained at room temperature, even for sterically demanding *o*-tolyl Grignard coupling partners (Scheme 63, products **50**, **61**, **215**–**218**).

Yokozawa and coworkers reported two examples of pyridine polymerization via Kumada cross-coupling. Both 2,5-dihalopyridine [143] and a 3,5-dihalopyridine (Scheme 64) [144] served as substrates. Upon "mono-Grignardation," the polymerization proceeded under nickel (or Pd) catalysis. These are rare examples in which cross-coupling chemistry is exploited for a desired polymerization reaction.

As already mentioned in the Stille and Hiyama sections, pyrazole-tethered phosphine ligands are quite versatile in promoting various coupling reactions, in particular also Kumada coupling [59]. Sarkar disclosed indole-based bidentate compounds as alternative type of ligands for the nickel-catalyzed Kumada coupling of aryl chlorides including 2- and 3-chloropyridine [145]. Both halides were



Scheme 65 Nickel catalyzed Kumada coupling of pyridine chlorides

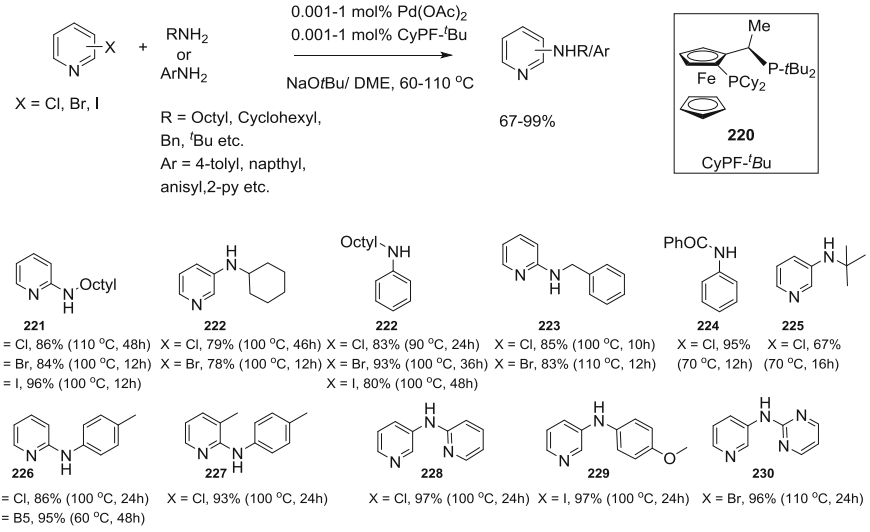
coupled with 4-tolyl magnesium bromide at room temperature in almost quantitative yields (Scheme 65, products **50** and **57**).

NHC systems can be considered as privileged ligand class, and they were applied in nickel-catalyzed Kumada couplings, as well [146]. The activity of the metal complexes was excellent. Un-activated aryl chlorides could be reacted even at room temperature. The reaction of 2-chloropyridine with 4-tolyl magnesium bromide gave a quantitative yield, and also 2,6-dichloropyridine gave the bis-coupling products with phenylmagnesium bromide and 4-toluyl magnesium bromide in 81% and 88%, respectively (not shown).

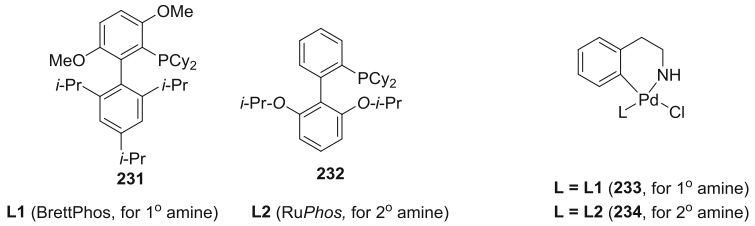
9 Buchwald–Hartwig Amination Reactions on Pyridine

Palladium-catalyzed amination of aryl and heteroaryl (pseudo)halides is known as the Buchwald–Hartwig (B–H) reaction [147–150]. Since the discovery of this coupling process in 1995, significant progress has been made regarding improvement of substrate scope, lowering catalyst loading, application of highly active ligands for better yields, improved catalyst stability towards air and hydrolysis, or milder reaction conditions. Even after such progresses, a generalized procedure to couple any aryl/heteroaryl halides (or pseudohalides) with any nitrogen nucleophile is still lacking. Industrial applicability of Buchwald–Hartwig coupling is also limited, so far.

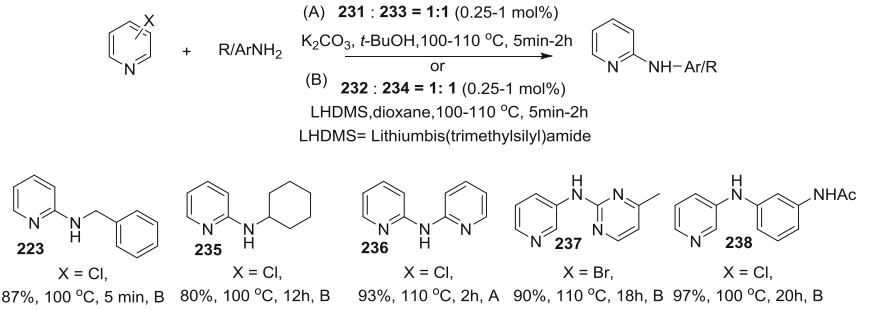
One possible side reaction in B–H coupling can be encountered due to the replacement of phosphine ligands in the active catalyst system by primary amine nucleophiles or by heteroaryl substrates through basic heterocyclic nitrogen. As a consequence, the lifetime of the catalyst is reduced. Therefore, a ligand which binds the palladium strongly to prevent ligand replacement but possesses the properties to promote oxidative addition and reductive elimination is ideally suited for Buchwald–Hartwig reactions. In this regard, commercially available, air- and moisture-stable CyPF-*t*Bu **219** reported by Hartwig is a versatile ligand. Its backbone is conformationally rigid due to the orientation of the methyl and ferrocenyl group, thus directing the phosphorous electron pair towards the metal center. A generalized and highly efficient method for coupling of aryl halides, including pyridyl chloride and bromides using $Pd(OAc)_2$ as catalyst along with CyPF-*t*Bu



Scheme 66 Buchwald-Hartwig coupling of pyridine halides at low catalyst loading

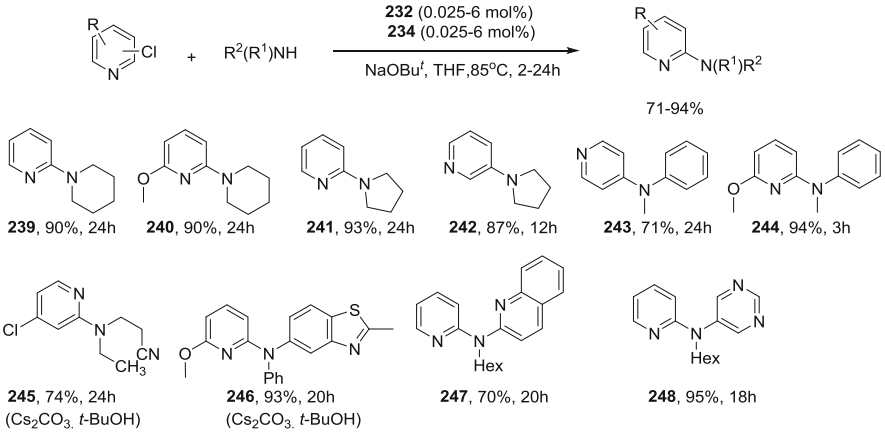


Scheme 67 Priviledged ligands in for Buchwald-Hartwig amination

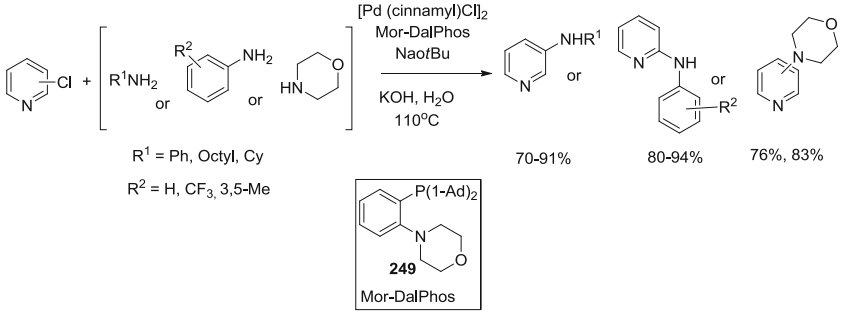


Scheme 68 Buchwald-Hartwig coupling of pyridine halides using BrettPhos and Ruphos ligands

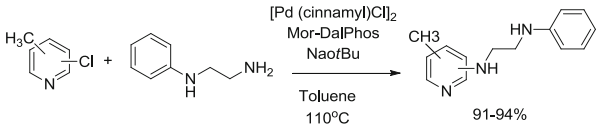
as ligand (**220**), is described in Scheme 66 [151]. This reaction exhibits broad substrate scope with a variety of functional groups, including cyano, keto, free-carboxylate, amido, carbalkoxy, aromatic, and aliphatic hydroxyl and amino groups



Scheme 69 Buchwald-Hartwig amination of pyridine chlorides



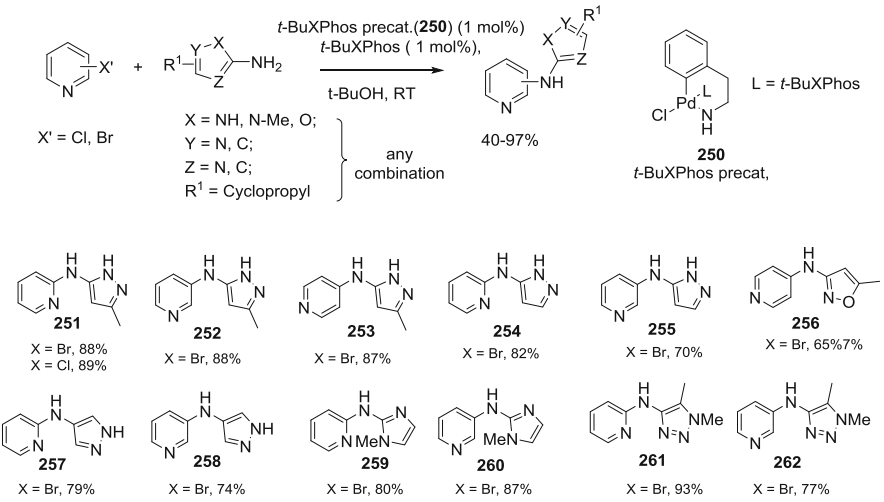
Scheme 70 Buchwald-Hartwig amination of pyridine chlorides in water



Scheme 71 Chemoselective Buchwald-Hartwig amination

employing very low catalyst loading (typically 0.001–1% with respect to both catalyst and ligand). Usually, high yields are obtained (Scheme 66, **221**–**230**). Secondary amines were also reported to couple under such conditions making this process more general.

Another generalized method for coupling of a wide variety of amines, including pyridyl amines, with aryl and heteroaryl halides including pyridine halides has been reported by Buchwald and coworkers using only the ligand systems BrettPhos (**231**), for primary amines, and RuPhos (**232**), for secondary amines (Scheme 67)



Scheme 72 Buchwald-Hartwig amination of pyridine halides with heterocyclic amines

[152]. Usually, a catalyst loading of 0.05–0.5 mol% is sufficient to accomplish the coupling, but in the case of pyridyl chlorides, a typical catalyst loading ranges from 0.25 to 1 mol%.

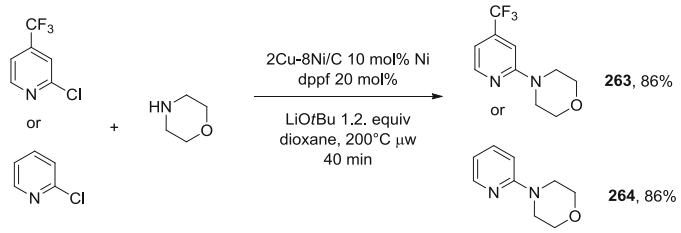
Coupling of 2-chloropyridine with primary amines (both aliphatic and aromatic) can be achieved using the BrettPhos ligand with Pd-catalyst system. Pyridine amines are usually considered as difficult substrate class due to lower nucleophilicity of the amine nitrogen and potential coordination to Pd with the pyridine nitrogen. The BrettPhos–Pd-catalyst system **233** proved to be useful in such cases. Representative examples of coupling are shown below (Scheme 68, products **223**, **235**–**238**).

Coupling of 2-chloropyridine with secondary amines requires lower catalyst loading (0.025–0.1 mol%), whereas 3-chloropyridines are more difficult substrates which require 1 mol% catalyst loading. Reaction conditions and examples (**239**–**248**) are given in Scheme 69.

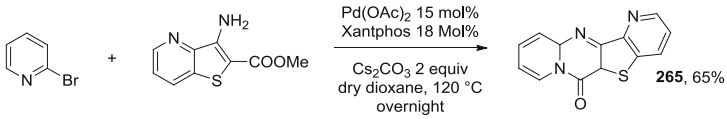
The commercially available $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos **249** catalyst system can be used for coupling of readily available and cheap pyridyl chlorides with primary or secondary amines in water, making the coupling of pyridyl chlorides more environmentally friendly. Details on reaction conditions along with substrates are given in Scheme 70 [153].

It is noteworthy that the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos system is effective in chemoselective amination with distinct preference for unhindered nucleophilic amine reaction partners (Scheme 71) [154].

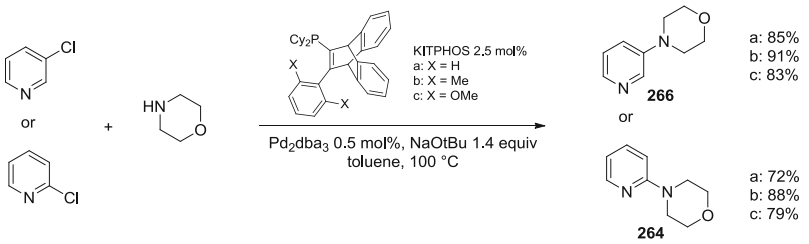
Coupling of a wide range of five-membered heteroaryl amines with pyridyl chlorides and bromides at room temperature can be achieved, with a general set of reaction conditions using the *t*-BuXPhos precatalyst **250** (Scheme 72) [155]. Precatalyst **250** can be readily converted to the active monoligated



Scheme 73 Cu/Ni particles in the Buchwald-Hartwig amination



Scheme 74 Tandem C–N coupling - intramolecular cyclization



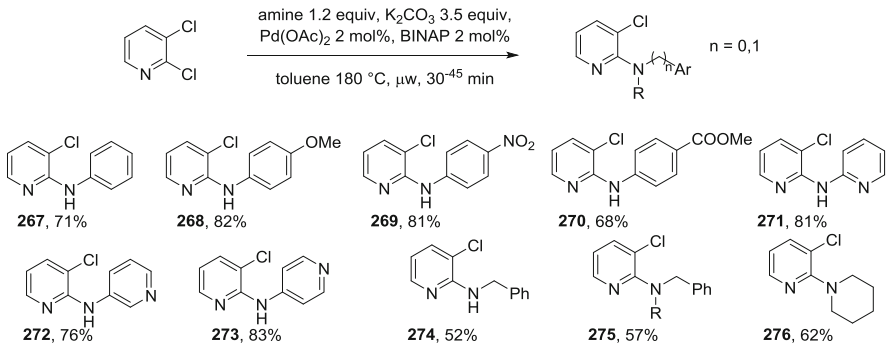
Scheme 75 KITPHOS ligands in Buchwald-Hartwig aminations

Pd(0) species within 2–3 min at or below room temperature. This allows subsequent room temperature C–N coupling at low catalyst loadings towards a series of products (Scheme 72, products **251**–**262**).

In the case of coupling of pyridyl halides and 1-*H*pyrazoles, coupling is completely selective for the exocyclic amine (**251**–**255**, **257**); no arylation of the N(H) heterocycle can be detected, so protection of –NH is not necessary, making the above transformation more attractive for industrial applications.

The group of Lipshutz developed a heterogeneous catalytic system composed of copper and nickel oxide particles which are supported on charcoal [156]. The additional ligand dppf had to be used in a relatively large amount of 20 mol%. The system proved to be an efficient catalyst for a number of metal-catalyzed reactions, including the Buchwald–Hartwig amination of two pyridine chlorides towards **263** and **264** (see Scheme 73). As can be seen, the reaction time was short, and good yields were obtained with morpholine as the amine coupling partner. Additional ligand and base were required as well. The advantage lies in the potential for recyclability of this heterogeneous catalyst.

Tandem C–N coupling and subsequent intramolecular cyclization was reported by Queiroz and coworkers [157]. A well-established catalytic system was employed



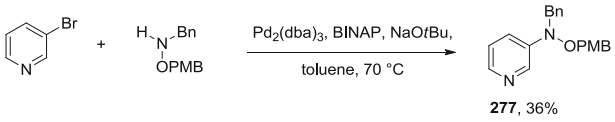
Scheme 76 Buchwald-Hartwig coupling of 2,3-dichloropyridine

for the C–N coupling, but high catalyst loading was required (Scheme 74). Overall, the reaction leads to interesting tetracyclic scaffolds (such as **265**) with good efficiency. An interesting feature of this transformation is the loss of aromatic character for the pyridine core.

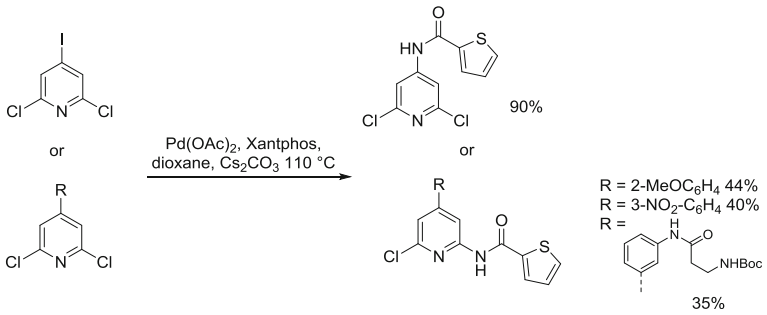
The group of Doherty reported the synthesis of a ligand class called KITPHOS and their application in Buchwald–Hartwig reactions [158]. Both 2- and 3-chloropyridines were successfully coupled with morpholine (giving **264** and **266**), and depending on the applied phosphine ligand, up to 91% yield was obtained with low catalyst loading within 1–2 h reaction time (Scheme 75).

Schnürch, Mihovilovic, and coworkers disclosed a microwave-promoted Buchwald–Hartwig amination procedure for 2,3-dichloropyridine [159]. The amine was introduced selectively in 2 position (Scheme 76, products **267**–**276**). This protocol was an improvement to earlier reports by the group of Maes [160]. In this case, conventional heating was applied and 20 equiv. of K_2CO_3 was required to achieve high conversions. By applying microwave irradiation at higher reaction temperature, this amount could be reduced to 3.5 equiv.; moreover, reaction times could be shortened significantly (typically 30 min). Aniline derivatives, benzylic amines, and piperidine were applied as amine coupling partners. Additionally, 2-, 3-, and 4-aminopyridine were used as well, representing the highest yielding examples with coupling product yields at 81% (**271**), 76% (**272**), and 83% (**273**), respectively (Scheme 76). 3-Iodo-2-(methylthio)pyridine was employed as alternative substrate as well (not shown). Naturally, C–N coupling took place in position 3. The conditions differed in the applied base (Cs_2CO_3), and conventional heating was used instead of microwave irradiation. Again, aniline derivatives were used as coupling partners, and the remaining methylthio group was used as leaving group in a subsequent Liebeskind–Srogl coupling (see Sect. 10).

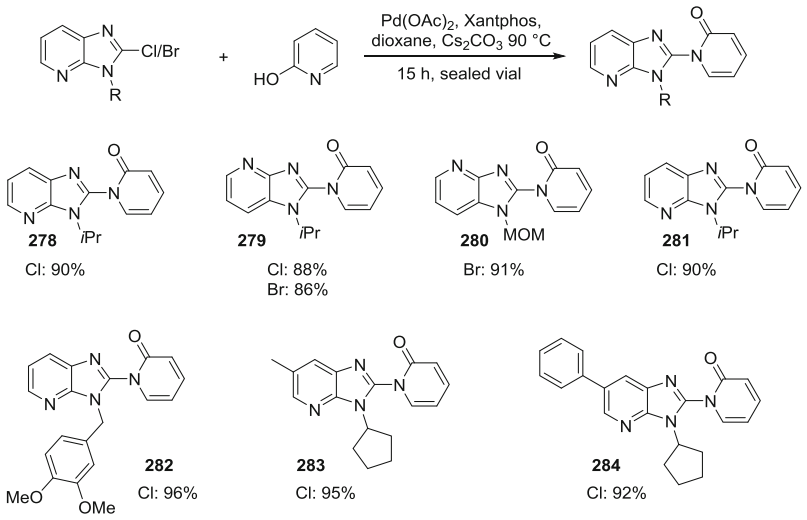
Miller and coworkers used Buchwald–Hartwig-type coupling reactions in their efforts to synthesize *N*-alkyl-*N*-(pyridin-2-yl)hydroxylamine scaffolds as selective antibacterial agents [161]. Reaction conditions applied were typical for such transformations, but the amine source was exceptional. Most frequently, primary or



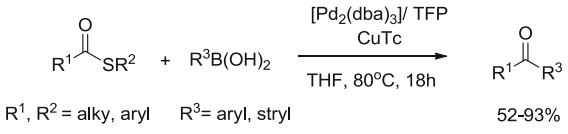
Scheme 77 PMB-protected benzylhydroxylamine in Buchwald-Hartwig coupling with 3-bromopyridine



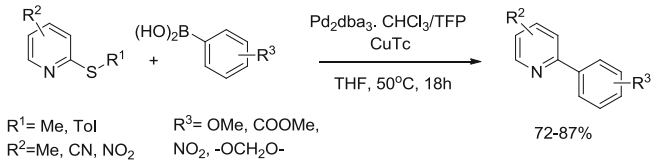
Scheme 78 Buchwald-Hartwig coupling with thiophene-2-amide



Scheme 79 Buchwald-Hartwig coupling of 2-hydroxypyridine



Scheme 80 The Liebeskind-Srogl reaction towards ketones



Scheme 81 Liebeskind-Srogl coupling of methylthio- or p-tolylthio-pyridine

secondary amines are used as coupling partners, but in this case, PMB-protected benzylhydroxylamine was applied. However, the yield was low with 36% of **277** (Scheme 77).

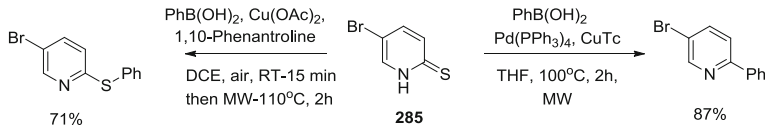
Also amides have been established as coupling partners for B–H type reactions. One such example was disseminated by Bihel and coworkers in 2013 [162]. 2,6-Dichloro-4-iodopyridine could be coupled with thiophene-2-amide in position 4 in 90% yield using $Pd(OAc)_2$ and Xantphos as catalytic system. If position 4 or positions 4 and 6 were already decorated, thiophene-2-amide or benzamide could be introduced in position 2 (Scheme 78). Besides Buchwald–Hartwig coupling, Sonogashira and Suzuki couplings were reported as well in this contribution. The three methods were exploited in sequential couplings towards 2,4,6-trisubstituted pyridines.

An unusual example came from the lab of Padusha [163]: In their synthesis of C2-substituted imidazo[4,5-*b*]pyridine, analogues 2-hydroxypyridine was coupled with various imidazo[4,5-*b*]pyridine halides leading to N-substitution of the pyridine nitrogen and formation of (imidazo[4,5-*b*]pyridin-2-yl)pyridin-2(1*H*)-ones **278**–**284**. Again, $Pd(OAc)_2$, Xantphos, and Cs_2CO_3 were used as catalytic system. A large number of examples were prepared giving yields >90% typically. Scheme 79 shows representative examples.

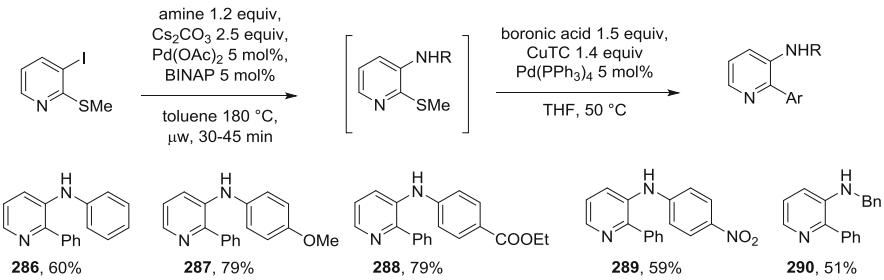
10 Liebeskind–Srogl Coupling

Liebeskind and Srogl reported in 2000 a palladium-catalyzed, Cu(I)-mediated, cross-coupling protocol for the synthesis of ketones from thioesters and boronic acids under neutral conditions (Scheme 80) [164]. A key feature of this coupling method is the requirement of stoichiometric amounts of a copper(I) carboxylate species, for example, copper(I) thiophene-2-carboxylate (CuTC), as a thiophilic metal cofactor.

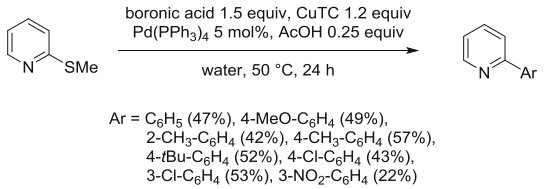
Initially, the reaction scope was limited to thioesters as an organosulfur building block and a boronic acid as the organometallic reagent to access ketones. Since then, considerable advances have been made in terms of substrate scope and reaction conditions. A variety of thio-organic reagents, such as thioethers, thioamide, etc., are now known to undergo selective C–C cross-coupling, not only with boronic acids but also with other organometallic substrates, such as



Scheme 82 Complementary couplings under Liebeskind-Srogl conditions



Scheme 83 A sequential Buchwald-Hartwig - Liebeskind-Srogl coupling sequence



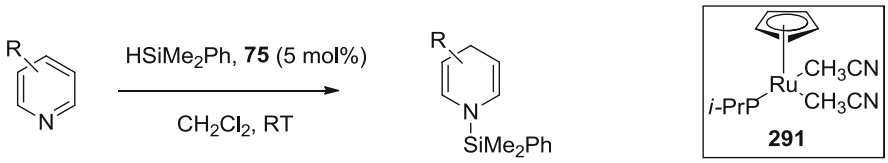
Scheme 84 Liebeskind-Srogl coupling in water

organostannes and organoindium reagents, with high yields and selectivity [165–167]. Heteroaromatic thioethers can be used as substrate in this Pd(0)-catalyzed, Cu (I)-mediated base-free desulfitative coupling to form biaryls.

2-Methylthio- and 2-tolylthio-pyridine derivatives (Scheme 81) are reported to undergo palladium-catalyzed copper(I) thiophene-2-carboxylate (CuTc)-mediated Liebeskind–Srogl(L–S) reaction as reported by Liebeskind and Srogl with the Pd_2dba_3/tris(2-furyl)phosphine (TFP) catalytic system in THF as solvent [168].

Five- and six-membered heterocycles, including pyridine, bearing a thioamide motif are also reported to undergo L–S coupling, but a high loading of CuTC (2–3 equiv.) is required [169, 170]. Using thioamide **285** as starting materials offers the advantage to tune reactivity from C–C coupling to C–S coupling by changing the catalyst system. Anaerobic Pd(0)/Cu(I) system favors C–C coupling, whereas aerobic Pd(II) system is directed towards C–S coupling as demonstrated for pyridine derivative **285** (Scheme 82).

Schnürch and coworkers exploited the orthogonality of the Liebeskind–Srogl coupling reaction vis-à-vis other methods such as Buchwald–Hartwig coupling [159]. Starting from 3-iodo-2-(methylthio)pyridine, first a Buchwald–Hartwig



Scheme 85 Ruthenium catalyzed hydrosylation of pyridines

coupling was carried out. The reaction mixture was cooled to room temperature, diluted with DCM and filtered through a pad of Celite. After evaporation of DCM, anhydrous THF was added, followed by the boronic acid and the catalytic system for the Liebeskind–Srogl step. Via this facile protocol, a number of 2-arylated-3-aminated pyridines (**286**–**290**) could be prepared with reasonable good yields over two steps (Scheme 83).

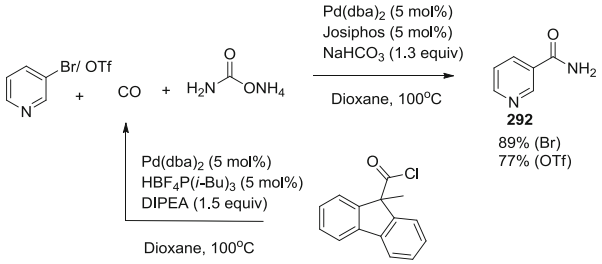
Later, the same authors published the first Liebeskind–Srogl coupling in aqueous medium [171]. Using 2-(methylthio)pyridine as substrate yields of around 50% were obtained with a series of boronic acids. A strongly coordinating NO_2 substituent gave significantly lower yield (Scheme 84). Overall, reactions proceeded rarely beyond 50% conversion, and long reaction times were required in water as solvent. By addition of AcOH, the rate could be enhanced, but still 24 h was required. The authors hypothesized that the rate-enhancing effect originates from protonation of pyridine which increases the positive charge and speeds up the reaction.

11 Miscellaneous Reactions

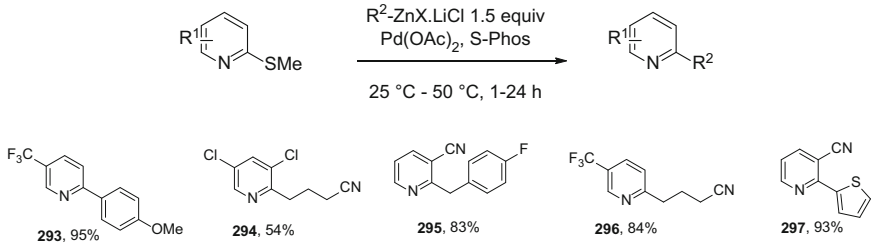
11.1 Hydrosilylation of Pyridine

Few synthetic methods are available for the introduction of silyl groups in pyridine [172–175]. Silylated partially reduced pyridine derivatives are often used as selective reducing agents [176] and can be important as building blocks for organic synthesis [177].

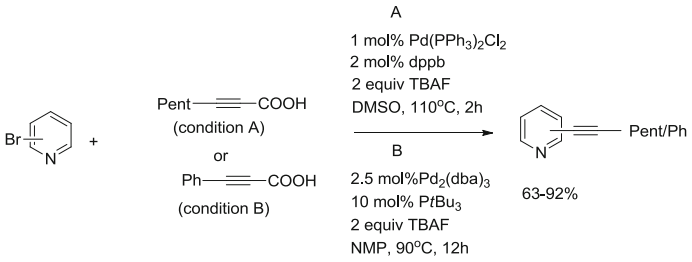
A facile catalytic hydrosilylation method of pyridine is reported by Nikonov and coworkers using cationic ruthenium complex $[Cp(i\text{Pr}_3\text{P})\text{Ru}(\text{NCCH}_3)_2]^+$ (**291**) [178] (Scheme 85). The advantageous features of this method are that the transformation proceeds at room temperature and selectively generates 1,4-addition products; this behavior is of high significance, as conventional reduction methods usually give mixtures of 1,2- and 1,4-dehydropyridines [177].



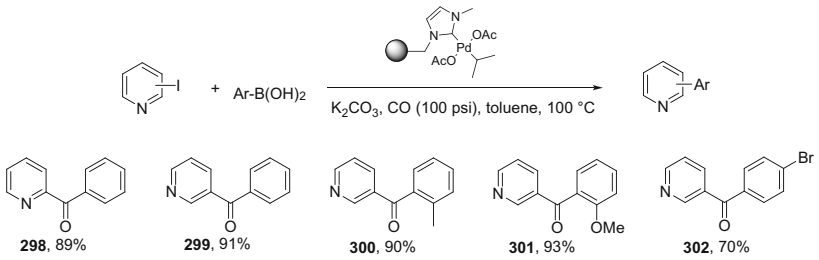
Scheme 86 Pd-catalyzed formation of nicotinamide



Scheme 87 Coupling of (methylthio)pyridine with organozinc reagents



Scheme 88 Decarboxylative alkynylation of pyridine bromides



Scheme 89 Carbonylative Suzuki-Miyaura coupling towards ketones

11.2 Primary Amide Formation from Pyridine

A palladium-catalyzed method for the direct transformation of primary aryl amides from aryl bromides, including pyridyl bromides (or triflates), is reported by Skydstrap and coworkers (Scheme 86, product **292**) [179]. A two-chamber system is used for carrying out the reaction, where the solid precursors and the gaseous components, carbon monoxide, and ammonia are kept separately and allowed to react subsequently. Functional group tolerance of this methodology is also a noteworthy factor.

Knochel and coworkers reported a transformation which can be considered as a hybrid between a Liebeskind–Srogl and Negishi coupling reaction [180–183]. The methylthio group is employed as leaving group, whereas the organometal counterpart is a zinc organyl. A number of heterocyclic methylthio ethers were reacted including 2-(methylthio)-5-(trifluoromethyl)pyridine and 3-cyano-2-(methylthio) pyridine. In both cases, good to excellent yields of products (**293–297**) were obtained (Scheme 87).

A decarboxylative coupling of 2-octynoic- and phenyl propiolic acids with 2- and 3-bromopyridine was reported in 2009 by Moon and coworkers (Scheme 88) [184]. The reaction was catalyzed by a combination of either $Pd(PPh_3)_2Cl_2$ and dppb or $Pd_2(dba)_3$ and the bulky phosphine P*t*Bu_3 in the presence of tetrabutylammonium fluoride (TBAF), to yield the corresponding diarylated acetylene.

Bhanage and coworkers subjected 2- and 3-iodopyridine to carbonylative Suzuki coupling leading to the corresponding ketones (**298–302**) (Scheme 89) [185]. The reaction proved to be robust since steric bulk was well tolerated and also a bromo-substituted acid gave a good yield of 70%. A polymer-supported Pd–NHC complex served as catalyst amendable to recycling: It was demonstrated in the reaction of iodobenzene and phenylboronic acid that the catalyst can be used four times without a significant drop in yield and minor loss in activity as only observed within the fifth repetition. A CO pressure of 100 psi was applied representing relatively moderate reaction conditions.

12 Conclusion

The field of reaction optimization in cross-coupling chemistry is still a very active area. This is also reflected by the ongoing activities applying pyridine derivatives as coupling partners. Given the importance of the pyridine motif, this is not surprising, and we expected further research to be published on a regular basis. Recent trends focus on the development of milder and more environmentally benign reaction conditions. This goes in line with the general trend towards “green chemistry” in all chemical research fields.

One important aspect is the development of new ligands. We have seen in the recent years that ligand fine-tuning is a valuable tool to achieve the aforementioned

goals in cross-coupling chemistry, with great discoveries to be expected in the future.

Another trend aims at the application of less reactive coupling partners such as chlorides or tosylates (derived from alcohols). This would lead to a broader range of potential coupling partners since much more chlorides and alcohols are commercially available as compared to bromides or iodides besides an often favorable cost issue.

Furthermore, a lot of research is dedicated to the reaction medium, most importantly, towards cross-coupling reactions in aqueous medium, again for environmental reasons. Also here significant advances have been made in recent years for several cross-coupling methods.

Finally, heterogeneous catalyst systems (metal nanoparticles or immobilized catalyst systems) have gained importance as well. They allow for catalyst recycling and would be compatible with continuous flow techniques, even though in this field research is scarce still.

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Metal Catalyzed Cross-Coupling Reactions in the Decoration of Pyrimidine, Pyridazine, and Pyrazine

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Abstract This chapter treats the cross-coupling chemistry of electron-deficient N-heterocycles containing two nitrogen atoms. The chapter is ordered according to heterocycle, coupling method, and the role of the N-heterocycle within the coupling process. The focus lies on new developments in the field, e.g., regarding new catalytic systems, and covers literature from 2008 until late 2013.

Keywords Cross-coupling • Metal catalysis • Palladium • Pyrazine • Pyridazine • Pyrimidine

Contents

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Abbreviations

9-BBN	3-Borabicyclo[3.3.1]nonane
acac	Acetylacetonate
BMIM	1-Butyl-3-methylimidazolium
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-tri-*i*-propyl-1,1′-biphenyl
cBRIDP	Di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)phosphine
cod	Cyclooctadiene
CPhos	2-(2-dicyclohexylphosphanylphenyl)-*N1*,*N1*,*N3*,*N3*-tetramethyl-benzene-1,3-diamine
CuMeSal	Copper(I) 3-methylsalicilate
CuTC	Copper(I) thiophene-2-carboxylate
Cy	Cyclohexyl
CyPF-*t*Bu	(*R*)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
DABCO	Diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DPE-Phos	Bis[(2-diphenylphosphino)phenyl] ether
dppf	1,1′-Bis(diphenylphosphino) ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
DSC	Dye-sensitized solar cell
dtbpf	1,1′-Bis(di-*t*-butylphosphino)ferrocene
EDG	Electron donating group
EWG	Electron withdrawing group
HASPO	Heteroatom-substituted secondary phosphine oxide
IMes·HCl	1,3-Bis(2,4,6-trimethylphenyl)imidazolium chloride
IPrNi(allyl)Cl	Allyl[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]chloropalladium(II)
JosiPhos	(*R*)-1-[(S_P)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
MIDA	*N*-methyliminodiacetic acid

MTBE	Methyl *t*-butylether
NHC	N-heterocyclic carbene
NMP	*N*-methylpyrrolidone
OLED	Organic light-emitting diode
PEG	Polyethylene glycol
PEPPSI-IPent	Dichloro[1,3-bis(2,6-di-3-pentylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II)
PEPPSI-IPr	[1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
PMB	*p*-Methoxybenzyl
PTS	Polyoxyethanyl-α-tocopheryl sebacate
PyBroP	Bromotripyrrolidinophosphonium hexafluorophosphate
rt	Room temperature
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
Salen	2,2′-Ethylenebis(nitrilomethylidene)diphenol
SDPP	Silicadiphenyl phosphinite
SDS	Sodium dodecylsulfate
SES-NH_2	2-(trimethylsilyl)ethansulfonyl
S_NAr	Substitution nucleophilic aromatic
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
SPO	Secondary phosphine oxide
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBS	*Tert*-butyldimethylsilyl
t-BuJosiPhos	(*R*)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
tmp	Tetramethylpiperidide
TON	Turnover number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

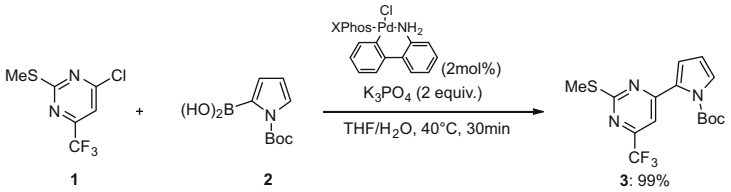
1 Pyrimidine in Cross-Coupling Reactions

1.1 Pyrimidine in Suzuki–Miyaura Reactions

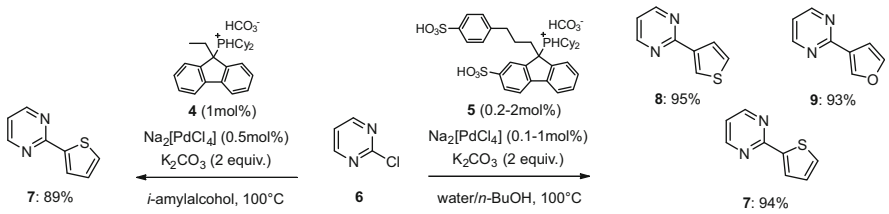
1.1.1 Pyrimidine as (Pseudo)Halide

Catalyst Design

The coupling of 2-heteroaryl as well as polyfluoro-substituted (hetero)arylboronic acids is a long-standing problem due to the tendency of these compounds to



Scheme 1 Low temperature Suzuki coupling of pyrimidine chloride **1**

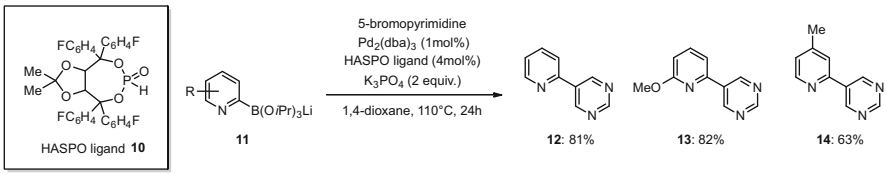


Scheme 2 Palladium-catalyzed cross-coupling of **6** towards biheteroaryls

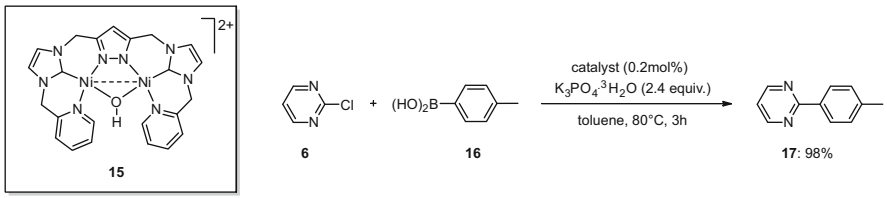
undergo protodeborylation. In an effort to solve this problem, Buchwald and coworkers tried to find a catalytic system, where coupling occurs significantly faster than the concomitant decomposition of boronic acids [1]. They identified Pd(biphenyl-NH_2)Cl-XPhos as a suitable precatalyst, which forms the active XPhos-catalyst instantaneously in the presence of weak bases already at room temperature. Generally coupling products were obtained in excellent yields under these exceptionally mild conditions within 30 min up to 2 h. Substituted 4-chloropyrimidine **1** reacted smoothly with *N*-Boc-pyrrole boronic acid **2** and gave 99% yield of **3** (Scheme 1).

Fleckenstein and coworkers reported the coupling of furan- and thiopheneboronic acids under application of fluorenylphosphines **4** and **5** as highly active ligands [2]. Conditions employing the sulfonated and thus water-soluble ligand **5** proved highly effective, giving excellent yields for these challenging substrates (e.g., 2-chloropyrimidine with furan- and thiopheneboronic acid, 93–95% of products **7**–**9**, Scheme 2, right) (**5** is also active in the Sonogashira reaction; see Sect. 1.4.6). Under nonaqueous conditions, excellent yields were achieved for the coupling with many heteroaryl chlorides, but in the case of 2-chloropyrimidine, *i*-amyl alcohol had to be used instead of *n*-butanol to avoid the formation of the S_NAr product (Scheme 2, left).

Ackermann and Potukuchi reported heteroatom-substituted secondary phosphine oxides (HASPO, **10**) to be bench-stable and effective preligands for Suzuki–Miyaura coupling reactions of lithium 2-pyridylborates **11** [3]. During the formation of the active catalyst, the preligand undergoes a P–O hydride shift and forms a phosphorous-bound Pd–phosphite complex. A range of biaryls were obtained with typical yields in the range of 60–70%. Coupling of 5-bromopyrimidine with



Scheme 3 HASPO-assisted Suzuki coupling of lithium 2-pyridylborates



Scheme 4 An unusual nickel catalyst in Suzuki coupling of **6**

4-methylpyridinylborate and 6-methoxypyridinyborate gave 63% and 82% yield of **14** and **13**, respectively (Scheme 3).

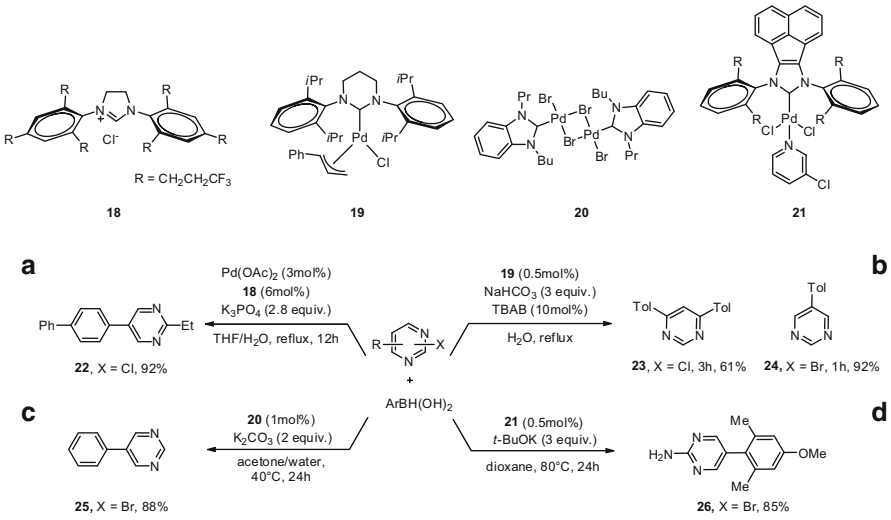
An interesting example of a Ni-catalyzed Suzuki–Miyaura coupling was published by Zhou et al. [4]. The di-nickel complex **15** showed impressive catalytic activity: at catalyst loadings as low as 0.2–0.8 mol%, yields for the coupling of aryl chlorides and bromides were excellent, often quantitative (Scheme 4, **17**). This and similar complexes were also found to be a highly competent catalysts for the Kumada–Corriu reaction (see Sect. 1.6).

Liu et al. prepared air and moisture-stable NHC-preligand **18** bearing 3,3,3-trifluoropropyl groups for the tuning of electronic properties [5]. The authors rule out a steric effect and claim that the electron-withdrawing nature of the 3,3,3-trifluoropropyl substituents facilitates the formation of monocarbene-palladium complex as well as the reductive elimination by decreasing the electron density of the carbene. Upon treatment with a base in situ, the actual ligand is generated by elimination of HCl (Scheme 5a, **24**).

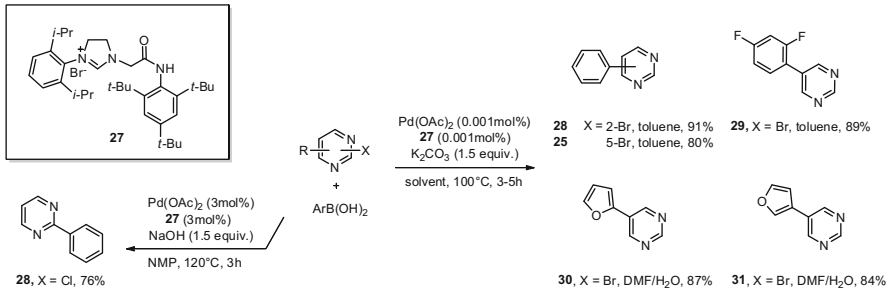
The synthesis of novel N-heterocyclic carbenes **19** with expanded rings (6- or 7-membered rings) was reported by Kolychev et al. [6]. These air and moisture-stable ligands showed good catalytic activity for the coupling of heteroaryl chlorides and tolylboronic acid. The diarylation product **23** of 4,6-dichloropyrimidine was obtained in only 61%. The arylation product **24** of 5-bromopyrimidine, however, was formed in 92% yield (Scheme 5b).

The benzimidazole-based NHC complex **20** was reported to efficiently catalyze the formation of 2-phenylpyrimidine **25** in 88% yield after 12 h at 40°C (Scheme 5c) [7].

The coupling of highly sterically demanding boronic acids was achieved by Tu et al. using acenaphthoimidazolylidene palladium complexes **21** with *t*-BuOK in dioxane at 80°C [8]. This catalyst tolerated a free NH_2 group and coupling of



Scheme 5 Various ligands in palladium-catalyzed Suzuki couplings



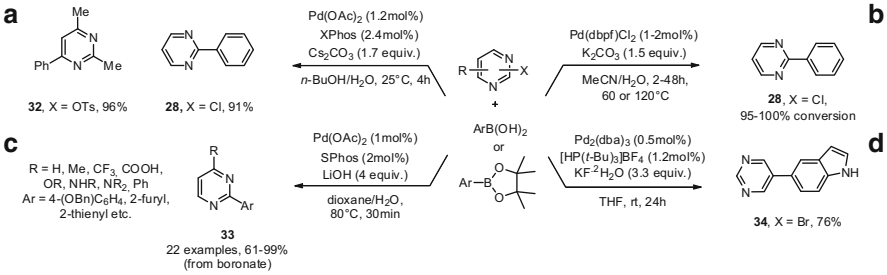
Scheme 6 Sterically demanding NHC ligands in the Suzuki coupling of pyrimidine halides

2-amino-5-bromopyrimidine with 2,6-dimethyl-4-methoxyphenylboronic acid gave 85% yield of **26** (Scheme 5d).

Kumar et al. reported the synthesis of palladium-amido-*N*-imidazolium salts and their application as NHC ligand precursors. Especially when these complexes contained ligands with great steric bulk (e.g., **27**), TON of up to 850,000 could be achieved in Suzuki–Miyaura coupling reactions (Scheme 6, catalyst loading 0.001%, 3 h, 100°C, products **25**, **28**–**31**) [9].

New Catalytic Systems

Yang et al. reported the combination of palladium acetate and XPhos together with cesium carbonate and aqueous butanol at room temperature to be a highly effective catalyst system for the coupling of chlorides and tosylates [10]. The authors



Scheme 7 Examples for palladium-catalyzed Suzuki coupling of pyridine halides and tosylates

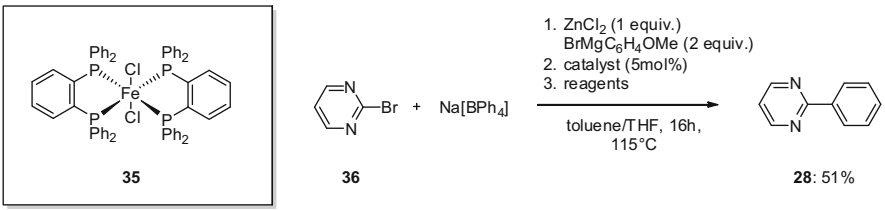
demonstrated the applicability of their protocol for a wide range of heterocyclic substrates: 2-chloropyrimidine was converted into 2-phenylpyrimidine **28** in 91% yield within 4 h. In case of tosylates, sodium hydroxide proved to be slightly more effective. Under these modified conditions, 2,6-dimethylpyrimidinyl tosylate reacted smoothly with phenyl boronic acid to give 96% yield of **32** within 1 h (Scheme 7a).

Asano et al. developed a method for the efficient arylation of 2-chloropyrimidine [11]. He reported the use of a combination of palladium(II) acetate with the S-Phos ligand and lithium hydroxide in dioxane/water at 80°C to be highly effective for the coupling with a wide range of electron-rich boronic acid pinacolates. The authors showed that 2-heteroaryl boronates such as 2-furanyl and thienylboronic acid esters offer the advantage of being significantly more stable than the corresponding boronic acids (Scheme 7c, **33**).

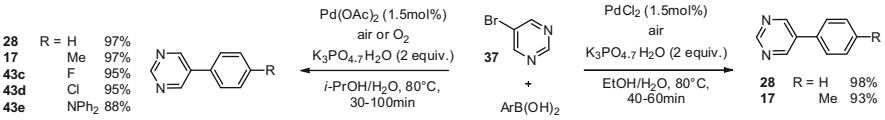
Moseley and coworkers identified a robust protocol for the coupling of aryl bromides and chlorides utilizing the air-stable $Pd(dbpf)Cl_2$ catalyst in acetonitrile/water mixtures [12]. The protocol requires 1.5 equiv. of potassium carbonate and a slight excess of boronic acid. At 60°C the reaction reaches completion with a wide range of aromatic and heteroaromatic bromides and gave the coupling product **28** in excellent yield. In the case of aryl chlorides, long reaction times (up to 48 h at 60°C) were observed. This could be reduced to about 2 h by running the reaction in superheated solvent at 120°C (Scheme 7b).

Batches of boronic acids can contain significant amount of anhydrides, which goes in line with lower coupling efficiencies when no water is used as cosolvent [13]. Lou and Fu addressed this problem, by developing a protocol where simple $KF \cdot 2H_2O$ is employed, in order to introduce just enough water to hydrolyze potentially present anhydrides. At the same time, they suggest the use of a mixture of $Pd_2(dba)_3$ and *t*-butylphosphonium tetrafluoroborate as a convenient source of palladium and *t*-butylphosphine. Coupling products were obtained in good to excellent yields under mild conditions (THF, rt). Coupling of 5-bromopyrimidine with 5-indoleboronic acid afforded the product **34** in 76% yield (Scheme 7d).

An iron-catalyzed Suzuki cross-coupling of tetraarylborate salts with benzylbromides and 2-bromoheteroaryls was reported by Bedford et al. [14]. The catalytically active Fe(II) complex **35** requires diarylzinc as an additive, in which



Scheme 8 Iron-catalyzed Suzuki coupling of **36**



Scheme 9 Ligandless Suzuki coupling of pyrimidine bromide **37**

only minimal incorporation of these aryl residues into the product was found. Yields depend strongly on the combination of substrates and range from 38 to 88%. In case of the arylation of 2-bromopyrimidine **36** with sodium tetraphenylborate, a yield of 51% of **28** was achieved (Scheme 8).

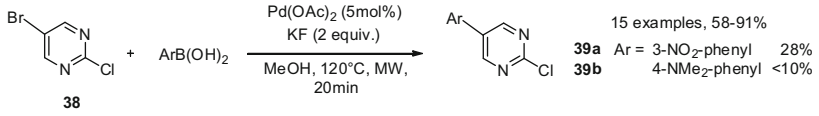
Ligand-Free Coupling

An interesting example of an oxygen-promoted ligand-free coupling reaction was published by Liu and Wang [15]. N-heterocyclic bromides reacted very effectively with arylboronic acids in the presence of palladium acetate and air in absence of a ligand (Scheme 9, left). This protocol proved effective for the coupling of triarylamine-derived boronic acids as well [16]. Coupling also occurs if palladium(II) chloride and aqueous ethanol is employed [17], providing 5-phenylpyrimidine **28** in 98% yield (80°C, 40 min) (Scheme 9, right).

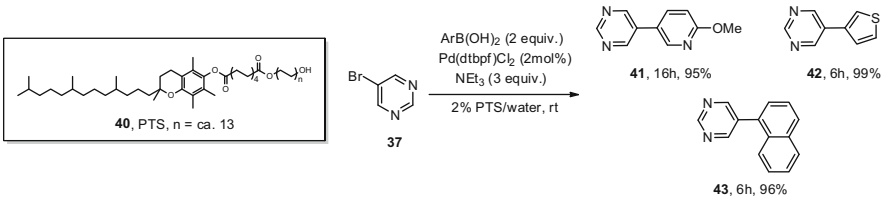
A protocol sparing the phosphine ligand was also published by Colombo and coworkers [18]. They used palladium acetate in combination with potassium fluoride under microwave conditions (120°C, MeOH, 20 min) to couple 2-chloro-5-bromopyrimidine with a variety of boronic acids with good yield. In the case of 3-nitrophenylboronic acid, only a low yield of 28% of **39a** could be achieved, and 4-dimethylaminophenylboronic acid gave only trace amounts of coupling product **39b** (Scheme 10).

Water as Reaction Medium

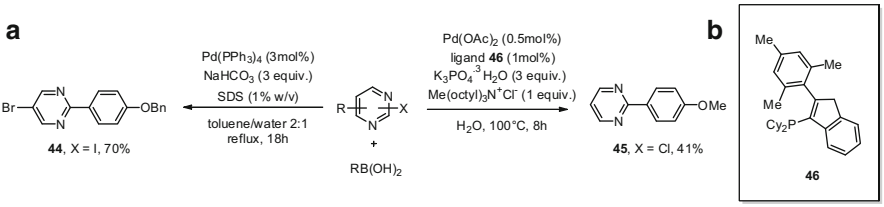
Lipshutz et al. reported the efficient coupling of heteroaryl bromides with boronic acids in water without cosolvent [19]. The coupling reaction takes place in micelles formed from the water-insoluble starting materials and tocopherol-modified PEG



Scheme 10 Ligandless Suzuki coupling of pyrimidine chlorides



Scheme 11 Micellar catalysis in Suzuki couplings

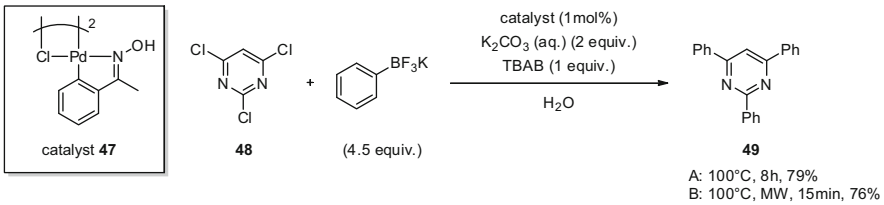


Scheme 12 Palladium-catalyzed Suzuki coupling in aqueous medium I

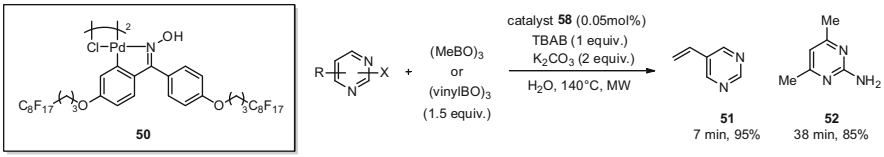
40 as tenside (2%) under mild conditions. As catalyst a bidentate ferrocenylphosphine was used. Among other examples, 5-bromopyrimidine **37** was coupled to naphthylboronic acid in 96% yield of **43** after 6 h at rt, showing that steric bulk is well tolerated (Scheme 11).

Vashchenko et al. demonstrated that the efficiency of coupling reactions in biphasic solvent systems such as toluene/water or DME/water can be improved, if surfactants like SDS and *n*-butanol are added [20]. These allow the formation of microemulsions which are believed to solubilize hydrophobic coupling partners. Under these conditions, coupling of benzyloxyphenylboronic acid with 4-bromo-2-iodopyrimidine gave the desired product **44** only in moderate 70% yield (Scheme 12a).

Mao and coworkers reported (mesitylindenyl)dicyclohexylphosphine **46** in the presence of $Me(octyl)_3N^+Cl^-$ as a remarkably active catalyst for the Suzuki–Miyaura reaction under aqueous conditions [21]. A catalyst loading as low as 0.0005 mol% gave the coupling product of chlorobenzene and 4-methoxyphenylboronic acid in 61%, which corresponds to a TON of 120,000. Good to excellent yields were obtained for a high number of examples with electron-rich or neutral boronic acids and a broad range of aryl- and heteroaryl chlorides. Coupling of 2-chloropyrimidine performed significantly worse than pyridine derivatives. In this case, the reaction required 0.5 mol% of catalyst and



Scheme 13 Palladium-catalyzed Suzuki coupling in aqueous medium II



Scheme 14 Palladium-catalyzed Suzuki coupling in aqueous medium III

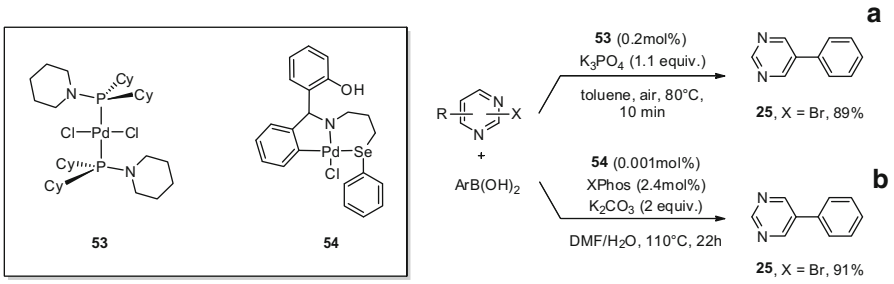
gave the product 2-(4-methoxyphenyl)pyrimidine **45** in only 41% yield (Scheme 12b).

Oxime-derived palladacycle **47** was reported to efficiently catalyze the coupling of aryltrifluoroborates under aqueous conditions [22]. In microwave heating with concomitant cooling of the reaction vessel in an airstream, shorten reaction times from several hours to minutes giving good yields of **49** were found (Scheme 13).

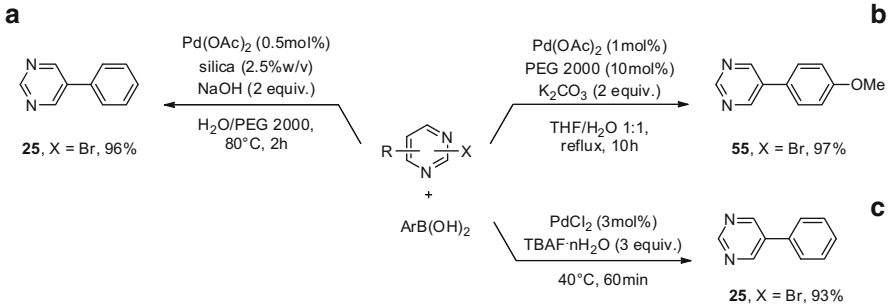
Lam and coworkers developed a fluorous, oxime-based palladacycle **50**, optimized for coupling chemistry in water under microwave irradiation [23, 24]. The catalyst was successfully employed for a range of Pd-catalyzed coupling reactions, e.g., Suzuki–Miyaura, Stille, Kumada, Heck, and Sonogashira coupling in aqueous or organic medium (see also Sect. 1.4.4). The catalyst can be recovered from the reaction mixture by fluorine solid-phase extraction and reused up to five times with no significant loss of activity. For the majority of coupling reactions, excellent recovery rates and very low levels of Pd-leeching were observed. Examples involving pyrimidine were the vinylation of 5-bromopyrimidine with trivinylboroxine (**51**, 95% yield) and the reaction of substituted 4-chloropyrimidine with trimethylboroxine to give 2-amino-4,6-dimethylpyrimidine **52** (140°C, 38 min, 85%) (Scheme 14).

Nanoparticles as Catalytically Active Species

Sing and coworkers synthesized an air and moisture-stable palladacycle precatalyst **54**, which was reported to form well-defined $Pd_{17}Se_{15}$ nanoparticles of ~8 nm size [25]. These efficiently promote the coupling of bromoaryls with boronic acids. While this protocol requires elevated temperatures, it allows, in the case of the reaction of 5-bromopyrimidine with phenyl boronic acid, the use of an



Scheme 15 Pd nanoparticles for Suzuki coupling reactions I



Scheme 16 In situ formation of Pd nanoparticles for Suzuki coupling reactions

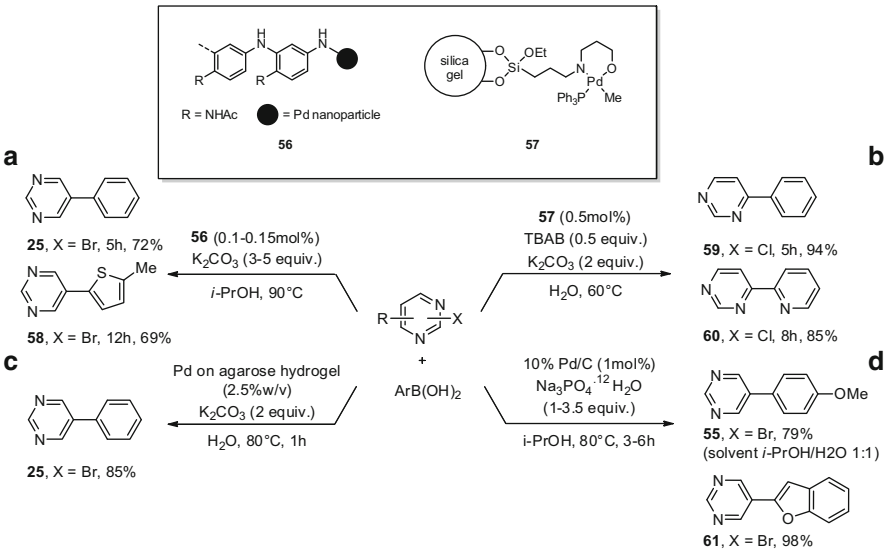
exceptionally low catalyst loading of only 0.001 mol%. Product **25** was obtained with a yield of 91%, which corresponds to a TON of 91,000 (Scheme 15b).

Bolliger and Frech reported the use of dichlorobis[1-(dicyclohexylphosphanyl) piperidine]palladium **53** as a stable depot form of Pd nanoparticles with extremely high catalytic activity [26]. For the reaction of 5-bromopyrimidine with phenylboronic acid, 89% yield of **25** was achieved after 10 min at 80°C and with a catalyst loading of only 0.2 mol% (Scheme 15a).

Various methods for the in situ generation of catalytically active nanoparticles without the use of precatalysts have been published: $Pd(OAc)_2$ in water/PEG 2000 with addition of silica (Scheme 16a) [27], $PdCl_2$ with PEG 2000 in aqueous THF at reflux (Scheme 16b) [28], and $PdCl_2$ with TBAF at 40–100°C (Scheme 16c) [29]. The nanoparticles obtained by these methods efficiently catalyze Suzuki–Miyaura reactions.

Catalysts on Solid Support

Ul Islam et al. reported the synthesis of Pd nanoparticles **56** embedded in poly-acetanilide and the use of this material in a ligand-free coupling reaction [30]. For heterocyclic substrates, this catalyst gave a yield of 72% of **25** in the reaction of 5-bromopyrimidine with phenylboronic acid (Scheme 17a).

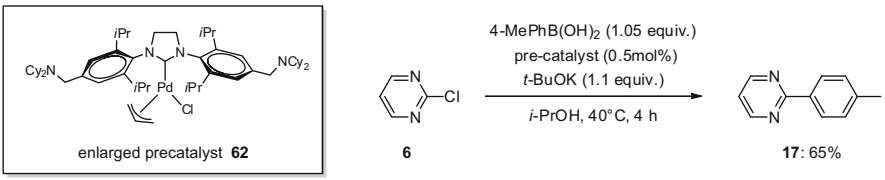


Scheme 17 Examples for solid supported catalysts in Suzuki coupling of pyrimidine derivatives

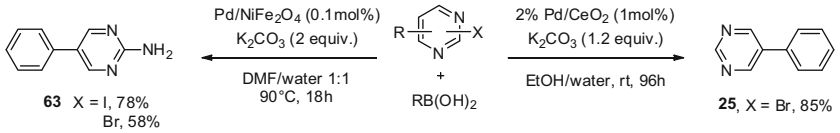
Lee et al. reported the immobilization of palladium on mesoporous zeolite [31]. Reaction of a silylated Pd complex with zeolite gave rise to catalyst **57**. The coupling reaction was conducted at 60°C in water and gave the products in excellent yield. The catalyst was recovered by simple filtration and could be reused at least ten times with no significant drop of catalytic activity (Scheme 17b). Later Lee et al. showed that this catalyst is also highly active in the Stille and the Sonogashira cross-coupling reaction [31].

Kitamura et al. showed that Pd/C can catalyze coupling reactions in combination with sodium phosphate in aqueous *i*-PrOH at 80°C [32]. Excellent yields were obtained for many heteroaryl bromides. Coupling of 5-bromopyrimidine with 4-methoxyphenylboronic acid proceeded only in 79% yield of **55** after 6 h. When heteroaryl boronic acids were employed, only low yields could be obtained under these conditions. This drawback was eliminated by using nonaqueous *i*-PrOH instead of the *i*-PrOH/H_2O mixture: 5-(benzofuran-2-yl)pyrimidine **61** was isolated in 98% with a catalyst loading of only 1 mol% Pd after 3 h. The authors showed that during the reaction, the palladium leaches into the reaction mixture until a maximum was reached after about 20 min. After that time, the dissolved palladium was again deposited on the active charcoal and a decrease of Pd-levels in solution could be observed. The catalyst could be reused for at least five runs with no loss of catalyst activity (Scheme 17d).

Firouzabadi et al. demonstrated that agarose hydrogel could be used as a stabilizing support and bioorganic ligand for Pd nanoparticles [33]. The hydrogel was prepared by heating $Pd(OAc)_2$ together with agarose in the presence of citric acid. It catalyzes the formation 5-phenylpyrimidine **25** from the corresponding



Scheme 18 Easily removable Pd catalyst for Suzuki coupling



Scheme 19 Mixed metal species in Suzuki couplings

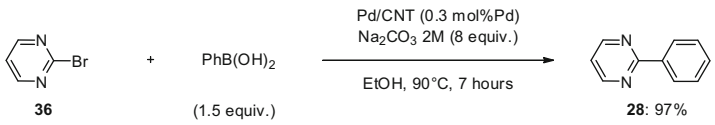
bromide in 85% yield (Scheme 17c). The same authors also published the use of an aminopropyl-functionalized clay as a solid support for nanoparticles [34]. The exfoliated layers of the clay are believed to wrap around the nanoparticles which are then easily dispersed in water. Compared to the immobilization in the agarose hydrogel, a similar high catalytic activity was achieved, and, additionally, an extension of the scope towards the Heck reaction was achieved. 5-Phenylpyrimidine was obtained in 88% yield after 10 h.

A different approach for recovering the catalyst was chosen by Schoeps et al. [35]. They designed imidazolium salts with a molecular weight of about 800 g/mol. The Pd-NHC complexes **62** prepared from these compounds were employed in Suzuki–Miyaura reaction as well as Buchwald–Hartwig reactions. After completion of the reaction, the catalyst could be successfully removed from the reaction mixture by solvent-resistant nanofiltration removing 97–99.9% of the Pd complex (Scheme 18, product **17** obtained in 65% yield).

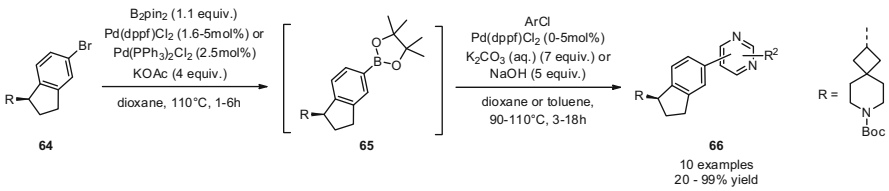
Borhade et al. reported the application of Pd on ferrite (Fe_2O_3) as a heterogeneous catalyst in DMF/water at 90°C [36]. The reaction of boronic acids with aryliodides and bromides gave the coupling products in good to excellent yield. The coupling product **63** of 2-aminopyrimidin-5-boronic acid with bromobenzene was obtained in only 58% but with iodobenzene in 78% after 1 h. Due to the magnetic properties of ferrite, it is possible to recover the catalyst material from the reaction mixture by applying a magnetic field (Scheme 19, left).

Amoroso et al. developed conditions for the use of Pd/CeO_2 as cross-coupling catalyst [37]. Excellent yields were obtained for a selection of electron-rich and electron-poor substrates. 5-Bromopyrimidine, as the only heteroaromatic example, gave the arylation product **25** in 85% yield after a prolonged reaction time of 96 h (Scheme 19, right).

Lin and coworkers synthesized a heterogeneous catalyst for the Suzuki–Miyaura coupling reaction by depositing Pd on carbon nanotubes [38]. A catalyst loading of only 0.3% (based on Pd) was sufficient to achieve excellent yields for a variety of



Scheme 20 Heterogeneous palladium in Suzuki couplings



Scheme 21 Example for a one-pot borylation/coupling sequence

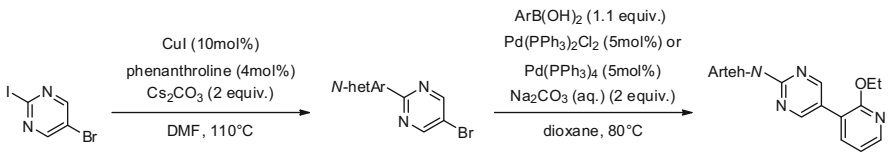
substrates. Reuse of the catalyst up to three times was demonstrated to proceed without significant loss of reaction efficiency. Coupling of 2-bromopyrimidine **36** with phenylboronic acid gave the coupling product **28** in 97% yield (Scheme 20).

Coupling Sequences

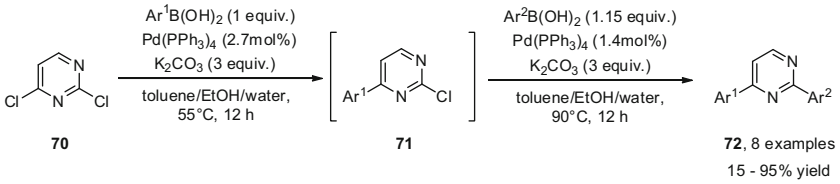
In the course of their effort to synthesize a library of indanes, workers at Pfizer developed a one-pot borylation/coupling sequence [39]. Starting from an amino-substituted 5-bromoindane **64**, first a borylation with bis(pinacolato)diboron gave the intermediate boronic acid ester **65**, which was subsequently coupled with heteroaromatic halides. Several substituted 2-chloro- and 4-chloropyrimidines reacted smoothly and gave the coupling products **66** in 81–99% yield with exception of the unsubstituted 4-chloropyrimidine (63% yield) and 6-chloro-4-cyanopyrimidine (20% yield) (Scheme 21).

Siddle et al. disclosed a sequential coupling procedure of 5-bromo-2-iodopyrimidine **67** and other aromatic dihalides [40]. In a first step, a Cu/phenanthroline-catalyzed C–N coupling in 2-position took place. The intermediate product **68** was isolated with yields ranging from 57% for the reaction with benzimidazol to 84% for pyrrole. In the second reaction step, the intermediate was coupled with boronic acids under standard Suzuki–Miyaura conditions to **69** in 43–79% yield. For two selected examples, the authors demonstrated that the reaction sequence can be performed in a one-pot manner with an overall yield of >50% (Scheme 22).

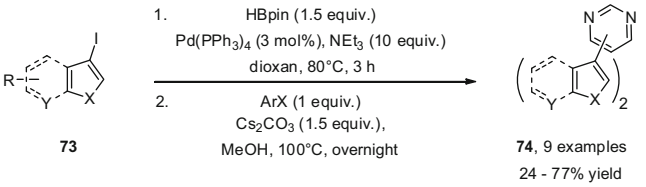
Anderson and Handy published a protocol for the sequential one-pot Suzuki–Miyaura coupling of 2,4-dichloropyrimidine **70**, utilizing the reactivity differences of the 2- and 4-position of pyrimidine [41]. The first step is carried out at 55°C in a mixture of ethanol, toluene, and water. Once full conversion was reached, the second boronic acid and additional base were added and the temperature was raised



Scheme 22 Sequential coupling of pyrimidine dihalide **67**



Scheme 23 Sequential coupling of pyrimidine dihalide **70**

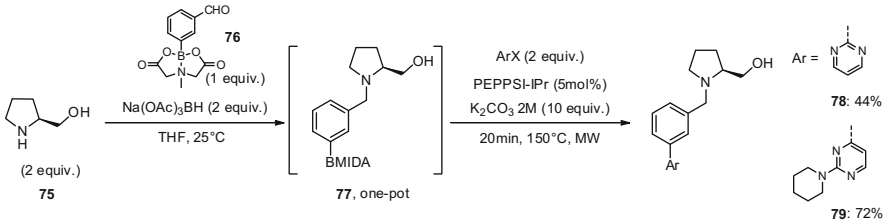


Scheme 24 Borylation/cross-coupling sequence towards **74**

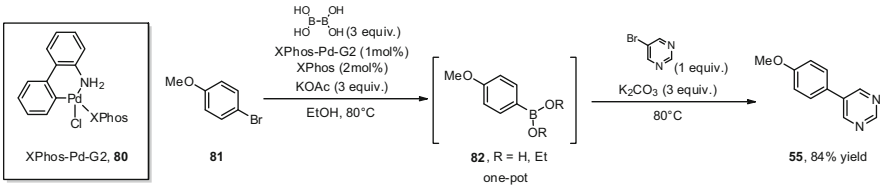
to 90°C. The reaction gave good to excellent yields over two steps (**72**, 62–95%) for different phenylboronic acids. The reaction proved sensitive to 2-substituted boronic acids; in these cases, the yields dropped to 15–21% (Scheme 23).

Tasch and coworkers developed a double Masuda borylation/Suzuki–Miyaura cross-coupling sequence for synthesizing symmetrically substituted bis(indolyl) diazines **74** [42]. The method was used to synthesize the marine alkaloid hyrtinadine A and a library of derivatives. Substituted 3-iodoindoles **73** were first reacted with pinacolborane to give the corresponding boronates. Then dry methanol to quench excess borane, dihalodiazines, and cesium carbonate was added for the coupling step. Depending on the substitution pattern of the indole coupling partner and the coupling position, yields of 24–77% of **74** were achieved when dihalopyrimidines were employed (Scheme 24).

The same group also applied very similar conditions to the synthesis of natural products meridianin A and meriolin 1 as well as a library of derivatives [43]. It is worth mentioning that coupling partners containing the 2-aminopyrimidine or 2-hydroxypyrimidine moiety are well tolerated without the need for a protecting group.



Scheme 25 Reductive amination/Suzuki–Miyaura sequence towards **78** and **79**



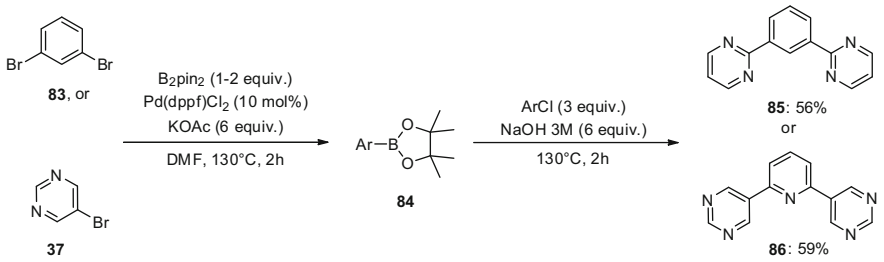
Scheme 26 One-pot borylation/Suzuki coupling towards **55**

Grob et al. used a one-pot reductive amination/Suzuki–Miyaura sequence for library synthesis [44]. For this purpose, they transformed formyl-substituted arylboronic acid into the corresponding MIDA boronates. These compounds were subjected to reductive amination conditions using triacetoxyborohydride. After completion of the reaction, the coupling partner, aq. potassium carbonate and PEPPSI-IPr, were added, and the reaction was heated to 150°C in the microwave. The reaction was assessed for a great variety of substrates with yields ranging from 14 to 63%. When 3-formylphenylboronic MIDA ester **76** was reacted with prolinol **75** and 2-chloropyrimidine, product **78** was obtained in 44% overall yield (Scheme 25).

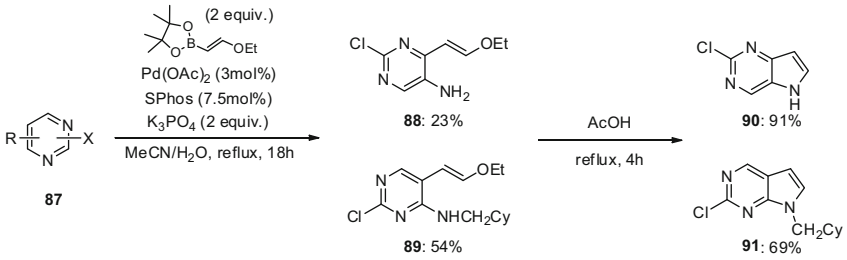
An interesting one-pot borylation/Suzuki–Miyaura sequence was developed by Molander et al. using diboronic acid as borylation agent [45]. The method employs XPhos-Pd-G2 catalyst **80** and ethanol at 80°C. Efficient coupling was demonstrated for a large number of different substrates. Among the examples, the reaction of 4-bromopyrimidine and 4-bromoanisol **81** was reported to give the coupling product **55** in 84% yield (Scheme 26).

Kelson and coworkers published sequential borylation/Suzuki–Miyaura coupling for the synthesis of polyazatriaryl ligands [46]. Starting from bromoarenes, $Pd(dppf)Cl_2$-catalyzed borylation with bis(pinacolato)diboron as borylating agent gave the intermediate boronates **84**. After completion of the reaction, the coupling partner and sodium hydroxide were added. Among a number of other examples, the reaction of 1,3-dibromobenzene with 2-chloropyrimidine and 2,6-dibromopyridine with 5-chloropyrimidine gave the bisarylated product **85** in 56% and **86** in 59% yield, respectively (Scheme 27).

A coupling/cyclization sequence leading to (aza)indoles was developed by Hoelder and coworkers [47]. They coupled (ethoxyvinyl)borolane with aryl halides



Scheme 27 Sequential borylation/Suzuki coupling towards **85** and **86**

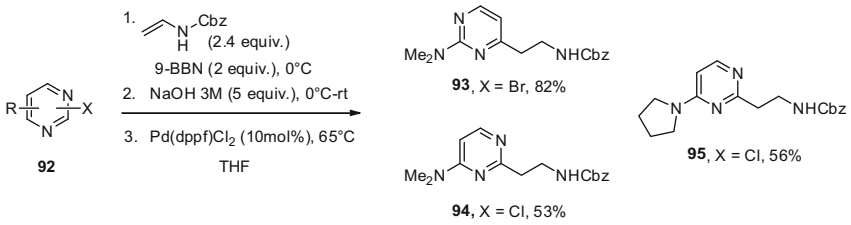


Scheme 28 A coupling/cyclization sequence leading to (aza)indoles

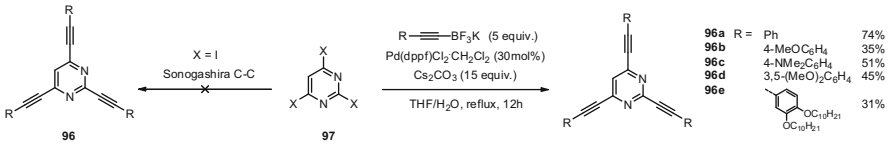
bearing an amino group in ortho-position to the halide. The coupling products **88** and **89** underwent then acid-catalyzed cyclization to (aza)indoles. This methodology was also applied to two isomeric dihalopyrimidine amines which gave the corresponding pyrrolopyrimidines in 91% (**90**) and 69% (**91**), respectively (Scheme 28).

Conditions for the coupling of an alkylborane generated in situ from benzylvinylcarbamate and 9-BBN were developed by Roy et al. [48]. The method was utilized for the synthesis of a small library of disubstituted N-heterocycles with moderate yields for the coupling with 2-chloropyrimidines but good to excellent yields for 2-bromopyridines (Scheme 29, products **93**–**95**).

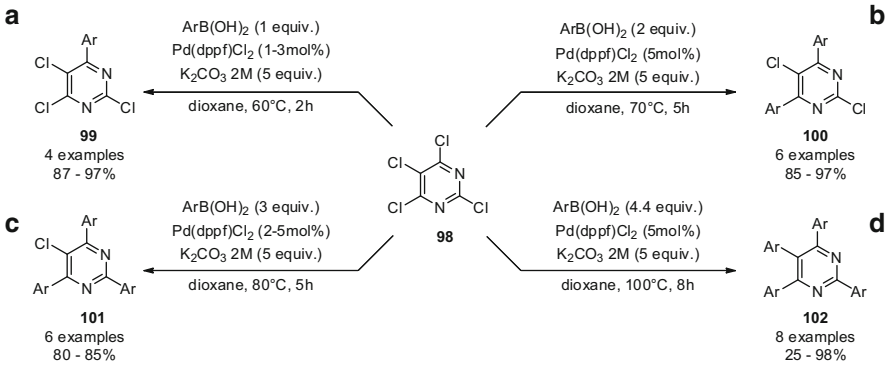
In order to study their fluorescence properties, Ple and coworkers attempted to synthesize di- and trialkynylpyrimidines starting from di- or triiodopyrimidines **97** [49]. In case of 2,4-diiodo- and 4,6-diiodopyrimidine, coupling proceeded smoothly under standard Sonogashira coupling conditions. On the contrary, 2,4,6-triiodopyrimidine did not afford the expected trialkynylpyrimidine **96**, possibly due to the low stability of the starting material. The trialkynyl products **96** were then prepared successfully via Suzuki and Negishi alkynylation starting from 2,4,6-trichloropyrimidine (see also Sect. 1.4.6). Later this method was used to synthesize the star-shaped trialkynylpyrimidine **96e** with blue light-emitting properties (Scheme 30) [50].



Scheme 29 In situ generation of alkylboranes and subsequent Suzuki coupling with pyrimidine halides



Scheme 30 Suzuki coupling as alternative to the Sonogashira protocol

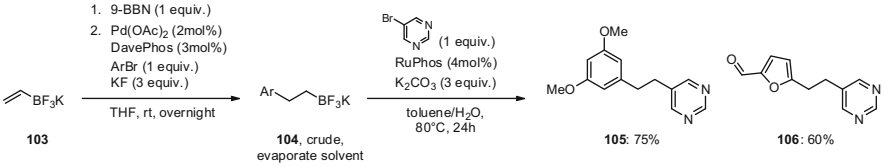


Scheme 31 Exploring site-selective Suzuki coupling of **98**

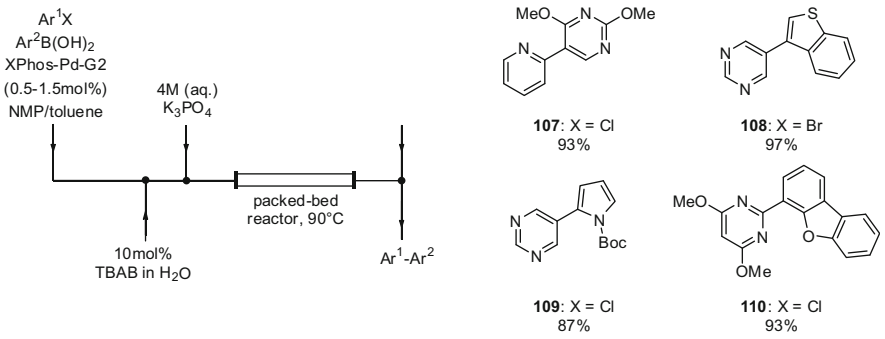
Selective Coupling

A site-selective coupling method starting from tetrachloropyrimidine **98** was published by Hussain et al. [51]. By careful tuning of the reagent loading, reaction time, and temperature, the authors synthesized the mono-, di-, tri- and tetraarylation products **99**–**102** in good to excellent yields (Scheme 31).

Molander et al. developed a "1,2-dianion equivalent" based on the addition of 9-BBN to vinyltrifluoroborate **103** [52]. The resulting diboraethane couples first on the borane side in the presence of KF and DavePhos to give **104**. After addition of potassium carbonate, RuPhos, and the second coupling partner, the remaining trifluoroborate was coupled. A broad scope of aromatic, heteroaromatic compounds, as well as bromoalkenes were coupled in one-pot fashion in 56–83% yield, including pyrimidine products **105** and **106** (Scheme 32).



Scheme 32 Vinyltrifluoroborate **103** as 1,2-dianion equivalent

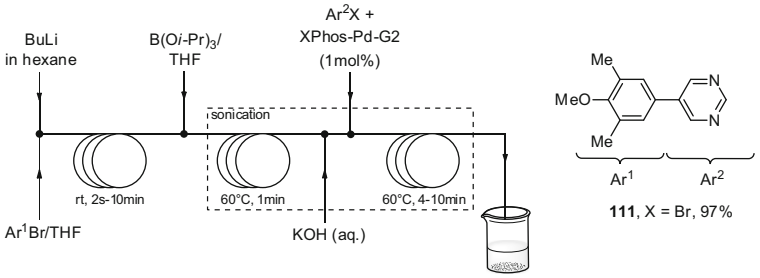


Scheme 33 Pyrimidine derivatives in continuous flow Suzuki couplings I

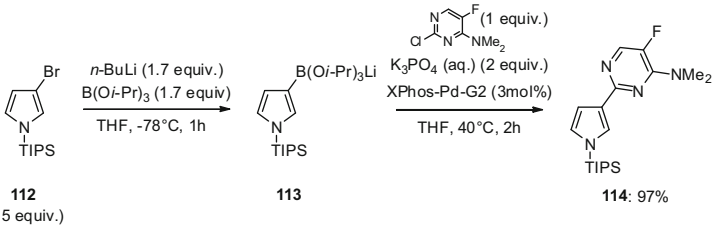
Continuous Flow

General conditions for the cross-coupling of heteroaryl chlorides under continuous flow conditions were developed by Noël and coworkers [53]. For this purpose, the homogenous XPhos precatalyst was used in a biphasic solvent mixture. A packed-bed reactor was used to increase the contact of the two immiscible phases. With a residence time of only 3 min, excellent yields of biaryls were achieved. For example, coupling of 2-chlorodimethoxypyrimidine with dibenzofuran gave the coupling product **110** in 94% yield (Scheme 33, **107**–**110**).

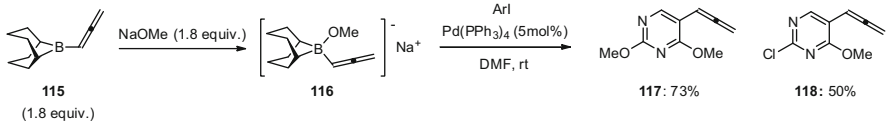
An impressive example of a lithiation/borylation/Suzuki–Miyaura cross-coupling reaction sequence in continuous flow was published by Shu et al. [54]. Starting from aryl bromides, in the first step, the aryllithium species was generated by metal-halogen exchange with residence times between 10 s up to 2 min. Alternatively, the aryllithium was generated by direct lithiation of thiophene or furan within 4–10 min. The organolithium species was trapped by combining the stream with triisopropylborate in THF for 1 min. After addition of base and a solution of XPhos precatalyst, the temperature was raised to 60°C for 10 min. Generally good to excellent yields were achieved. The reaction of 5-bromo-2-methoxyxylene and 4-bromopyrimidine yielded 97% of the coupling product **111** (Scheme 34). Later also a one-pot procedure with conditions optimized for running the reaction in batch was published by Oberli and Buchwald [55] (Scheme 35).



Scheme 34 Pyrimidine derivatives in continuous flow Suzuki couplings II



Scheme 35 Pyrimidine derivatives in continuous flow Suzuki couplings III

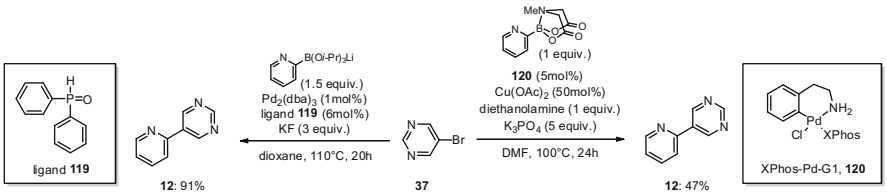


Scheme 36 Cross-coupling of pyrimidine iodides with **115**

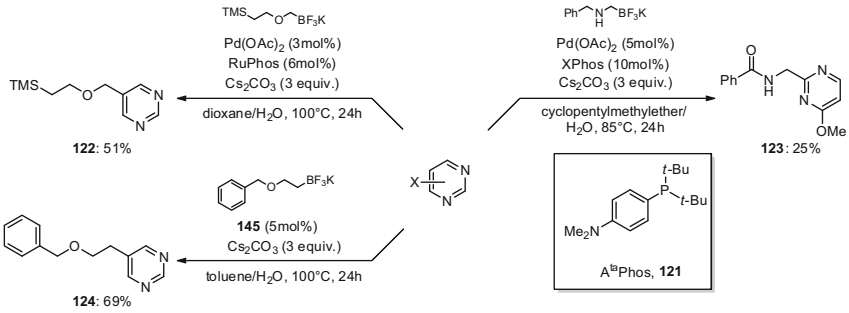
Alternative Coupling Partners

Radkowski et al. discovered a new type of B-allenyl-9-BBN complex **115** which allows for the efficient allenylation of aryliodides [56]. The reaction requires sodium methoxide, $Pd(PPh_3)_4$, and proceeds smoothly at rt, giving the allenylation products in 50–95% yield. Two examples employing substituted 5-iodopyrimidines were reported giving the coupling products in 73% (**117**) and 50% yield (**118**) (Scheme 36).

Billingsley and Buchwald addressed a long-standing problem of Suzuki–Miyaura coupling of 2-pyridyl-boron compounds [57]. These substrates are particularly challenging due to their low reactivity in the transmetallation step as well as their propensity to decompose via a protodeborylation pathway. The authors found that lithium triisopropylborates in combination with diphenylphosphine oxide **119** as ligand react smoothly, giving the coupling products in moderate to excellent yields. When lithium 2-pyridylisopropylborate was coupled with



Scheme 37 Stable 2-pyridyl-boron compounds for Suzuki coupling reactions



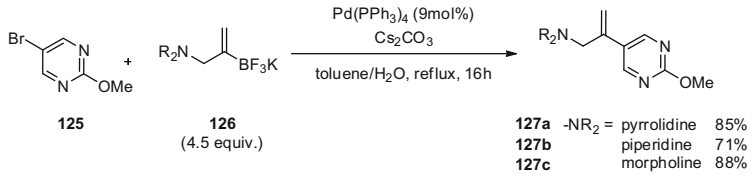
Scheme 38 Various ligands in Suzuki couplings of pyrimidine halides

5-bromopyrimidine **37**, the product **12** was obtained in 91% yield after 20 h (Scheme 37, left).

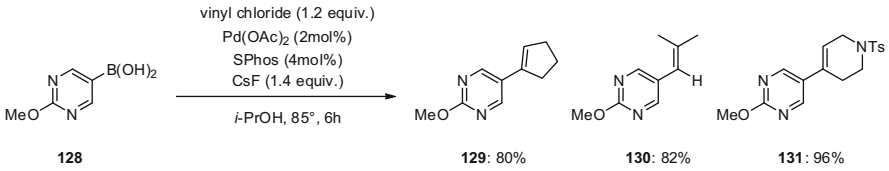
Very recently, Dick et al. reported another solution to that problem [58]. They converted the 2-pyridintriisopropylborate into its MIDA ester, an air-stable and storable compound. The ester is hydrolyzed under the reaction conditions, slowly releasing the boronic acid at a rate slower than the coupling reaction. The Cu-mediated XPhosPd-G1 (**120**)-catalyzed coupling reaction proceeds with aryl halides as well as triflates in generally good to excellent yields. For some examples, lower yields in the range of only 50% were achieved. For example, the coupling product **12** of 5-bromopyrimidine **37** was obtained in only 47% (Scheme 37, right).

Molander and coworkers reported the preparation and cross-coupling of alkoxymethyl [59], amidomethyl [60], and alkoxyethyl trifluoroborates [61]. Reaction conditions were optimized separately for these reagents: while a combination of $Pd(OAc)_2$/RuPhos was used for the alkoxymethyl reagent, $Pd(OAc)_2$/XPhos was employed for the amidomethyl trifluoroborates. In the case of the alkoxyethyl reagent, $PdCl_2A^{ta}Phos$ **121** was identified as a suitable catalyst. Generally good yields could be achieved in the transformations, but halopyrimidines reacted only sluggishly and gave low or moderate yields (Scheme 38, **122–124**).

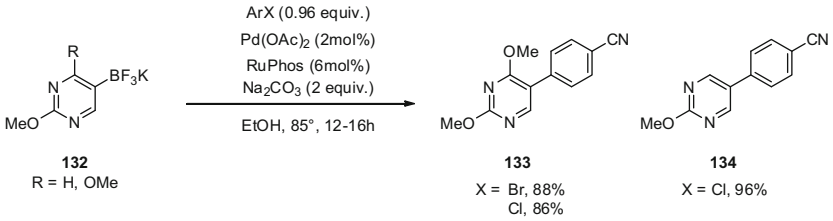
The preparation and coupling of substituted vinyl-BF_3K salts was investigated by Math et al. [62]. Internal vinyl-BF_3K salts **126** and a variety of electron-deficient (hetero)aryl bromides formed the coupling products in 67–88% yield. Three examples involving the coupling of 5-bromo-2-methoxypyrimidine **125** gave the



Scheme 39 Vinyl-BF_3K salts in the cross-coupling with **125**



Scheme 40 Cross-coupling of **128** with various vinyl chlorides



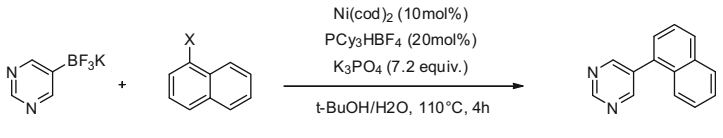
Scheme 41 Palladium-catalyzed Suzuki coupling of pyrimidine-BF_3K salts

products **127a–c** in 71–88% yield depending on the BF_3K-coupling partner (Scheme 39).

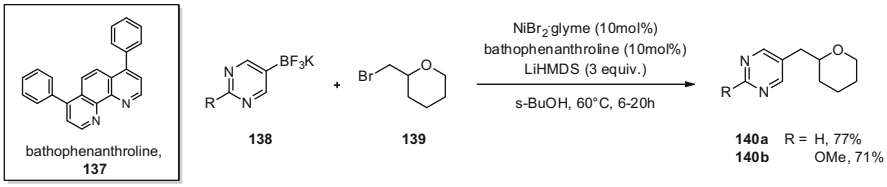
1.1.2 Pyrimidine Boron Compounds as Coupling Partners

Thakur et al. published the coupling of heteroaryl boronic acids with vinyl chlorides employing the SPhos ligand in conjunction with potassium fluoride in *i*-PrOH [63]. Under these conditions, minimal protodeboronation was observed. Electron-rich and electron-poor heterocycles as well as open-chain and cyclic vinyl chlorides are within the scope of the reaction. 4-Pyrimidineboronic acids such as **128** coupled with vinyl chlorides in 80–96% yield of **129–131** within 6 h (Scheme 40).

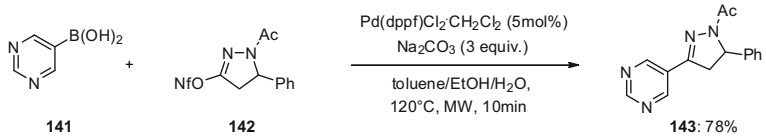
Molander et al. prepared a variety of heteroaromatic potassium trifluoroborate salts and explored their scope as coupling partners in Suzuki–Miyaura coupling [64]. As catalyst, a combination of RuPhos and $Pd(OAc)_2$ proved to be effective. Among other examples, they investigated coupling of substituted 5-pyrimidine trifluoroborates **132** with 4-halobenzonitrile. For these reactions, yields of 86–96% of **133** and **134** could be achieved (Scheme 41). Coupling of



Scheme 42 Nickel-catalyzed Suzuki coupling of pyrimidine-BF_3K salts with aryl donors



Scheme 43 Nickel-catalyzed Suzuki coupling of pyrimidine-BF_3K salts with alkyl halides



Scheme 44 Nonaflate as leaving group in Suzuki–Miyaura coupling of **141**

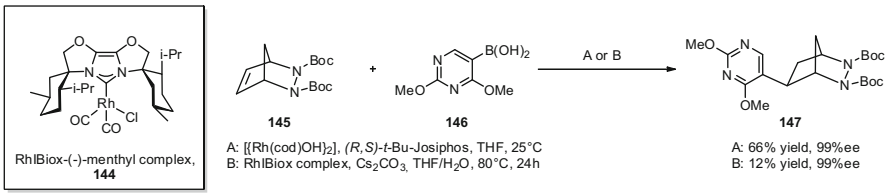
2-chloropyrimidine with thiophene-3-trifluoroborate and furan-2-trifluoroborate gave the coupling products in 52% and 92%, respectively.

The group of Molander also reported conditions for the coupling of phenolmethanesulfonates with aryl tetrafluoroborates [65]. Coupling was effected in the presence of $Ni(cod)_2/PCy_3HBF_4$ in generally good to excellent yields. Arylation of 5-pyrimidine potassium tetrafluoroborate **135** with 1-naphtol methanesulfonate **136** gave the product **25** in 83% after 4 h at 110°C (Scheme 42).

The same group found that alkyl halides are efficiently coupled with (hetero)aryl tetrafluoroborates in the presence of $Ni(II)Br_2$ and bathophenanthroline **137** [66]. The use of the more stable potassium tetrafluoroborates **138** allows the coupling of challenging substrates such as 2-thiophenetetrafluoroborates. Reported yields are typically in the range of 50–80% (Scheme 43, **140**a, b).

An example of a nonaflate as the coupling partner was reported by Grimm et al. [67]. The substituted pyrazoline nonaflate **142** reacted smoothly under microwave conditions and gave 78% of the coupling product **143** within 10 min (Scheme 44).

Menard and Lautens reported a rhodium-catalyzed desymmetrization of 2,3-bicyclic hydrazines such as **145** with arylboronic acids [68, 69]. The reaction could be tuned to give either cyclopentenes after ring-opening, or, especially in case



Scheme 45 Rhodium-catalyzed hydroarylation of **146**

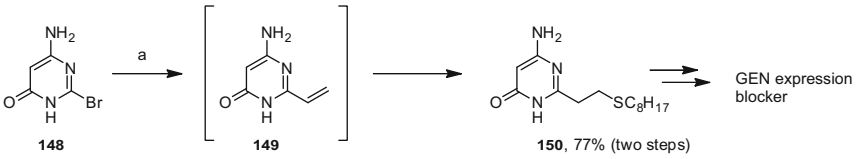
of heteroaromatic coupling partners, the hydroarylation product with excellent stereoselectivity. The combination of $[Rh(cod)OH]_2$ with *t*-Bu-Josiphos catalyzed the hydroarylation reaction of substituted 5-pyrimidineboronic acid **146** in 66% yield of **147** with 99% *ee*. In the initial protocol, 2-substituted boronic acids were required in order to obtain high stereoselectivity. This limitation was overcome with the use of a Rh-IBiox-catalyst **144**, now allowing for a broader range of compounds to be coupled with 94–99% *ee* [70] (Scheme 45).

1.2 Pyrimidine in Stille Reactions

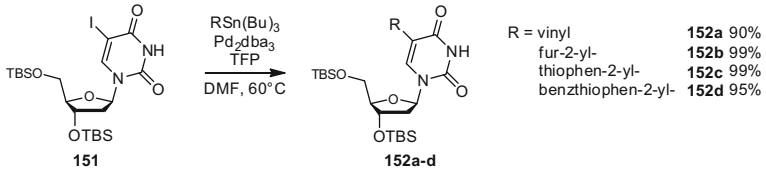
1.2.1 Pyrimidine as (Pseudo)Halide

Intrastrand cross linking-forming oligonucleotides are an interesting class of molecules, since they are capable of blocking DNA replication; thus, gene expression can be suppressed. Therefore, such compounds have found application as chemotherapeutic agents. Hattori et al. have designed and synthesized oligodeoxinucleoside, which was in a later stage incorporated into the DNA chain and cross-linked to thymine and served purpose of gene expression blocker [71]. The synthesis of oligodeoxinucleoside started with Stille coupling between pyrimidine derivative **148** and tributyl(vinyl)stannane which was without purification treated with octanethiol, giving rise to compound **150** in 77% yield over two steps (Scheme 46). Octanethiol served the purpose of a protecting group of the vinylic double bond, which was restored in a later stage, since it was anticipated not to tolerate the synthesis conditions for the nucleotide (Scheme 46).

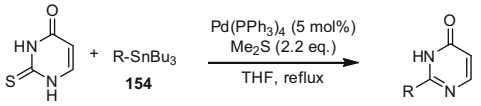
Wicke and Engels have investigated Stille coupling as potential tool for post-synthetic modification of synthetic RNA oligonucleotides [72]. Initially, optimization of the reaction conditions was performed on the monomeric uridine **151**, and under the optimal conditions (Pd_2dba_3, $P(fur)_3$, DMF, 60°C), they were able to couple tributyl(vinyl)stannane with 5-iodouridine in 90% yield of **152a**. Furthermore, 2-furyl, 2-thienyl and 2-benzothienyl moieties were introduced in the same way, providing derivatized mononucleotides in yields up to 99% (Scheme 47, **152b–d**). Moreover, they were able to carry out the developed modification on the oligonucleotide as well. Penta- and dodecamers were decorated with the functionalities mentioned above at both terminal and nonterminal positions.



Scheme 46 (*a*) (i) $Bu_3SnCHCH_2$, $Pd(PPh_3)_2Cl_2$, DMF; (ii) $C_8H_{17}SH$



Scheme 47 Post-synthetic notification of RNA nucleotide

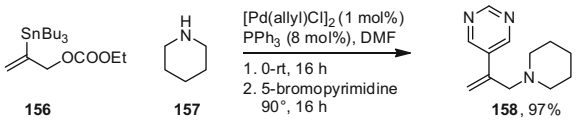


Entry	R	time (h)	Product	Yield (%)
1	Phenyl	24	**155a**	68
2	3-nitrophenyl	24	**155b**	63
3	4-methoxyphenyl	24	**155c**	52
4	2-furyl	14	**155d**	64
5	2-thienyl	14	**155e**	62
6	3-pyridinyl	24	**155f**	53
7	PhCH=CH-	48	**155g**	36

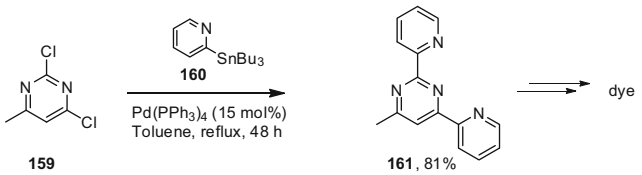
Scheme 48 Desulfative Stille cross-coupling

Desulfitative cross-coupling of 2-thiouracil **153** and its derivatives was described by Sun et al. [73]. The method does not require protection of free nitrogen (unlike in the case, when boronic acid is used for coupling). Under optimized conditions, tributylstannylbenzene **154** couples with 2-thiouracil in the presence of $Pd(PPh_3)_4$ and $CuBr{\cdot}Me_2S$ yielding 68% of product **155a**. Electron donating and electron-withdrawing substitution of the organotin reagent is tolerated, as well as utilization of diverse heterocycles and styrene as tin electrophile, providing derivatized uracil in yields from 36 to 64% (**155b–g**). Substitution of uracil is tolerated as well (Scheme 48).

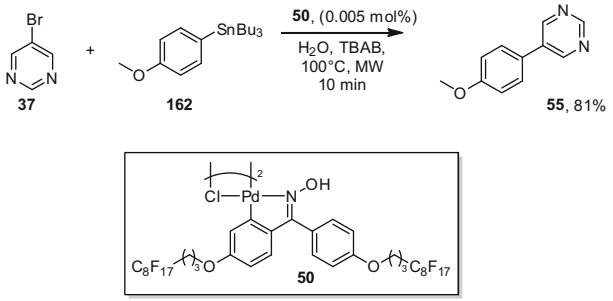
Kazmier and Bukovec have investigated the synthetic utility of stannylated ally carbonates [74]. They have demonstrated that a carbonate moiety can serve as leaving group for palladium-catalyzed amination reactions and resulting stannylated allyl amines can undergo further coupling under Stille conditions. Moreover, the amination/Stille coupling sequence can be performed in a one-pot fashion. 5-bromopyrimidine was utilized for the second step of the sequence as well. Initially, ethyl (2-(tributylstannyl)allyl) carbonate **156** is coupled with piperidine **157**, providing 2-(tributylstannyl)allylpiperidine, which subsequently undergoes Stille



Scheme 49 Stille coupling of pyrimidine with stannylated allyl amines



Scheme 50 Derivatization of pyrimidine via Stille coupling in the synthesis of dyes



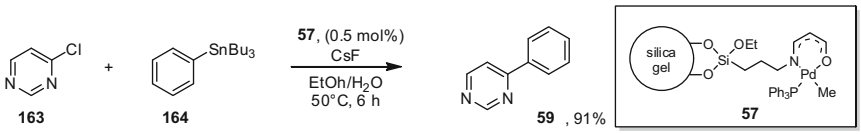
Scheme 51 Microwave-assisted Stille coupling of **37**

coupling upon addition of 5-bromopyrimidine. The final product **158** was obtained in 97% of overall yield (Scheme 49).

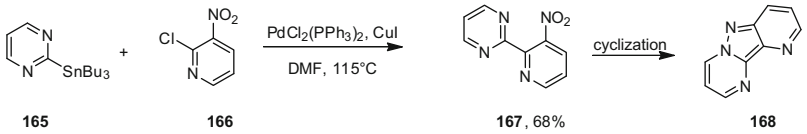
Synthesis and evaluation of optical properties of 4-arylvinyl-2,6-di(pyramid-2-yl)pyrimidines were performed by Hadad et al. [75]. The synthetic strategy comprises of double Stille coupling between 2,4-dichloro-6-methylpyrimidine **159** with 2-tributylstannylpyridine **160** and subsequent aldol condensation of formed 4-methyl-2,6-di(pyramid-2-yl)pyrimidine. Under the reaction conditions (15 mol%, $Pd(PPh_3)_4$, toluene), double Stille coupling provided 81% of **161** (Scheme 50).

Few new catalytic systems were developed and evaluated for Stille coupling. Susanto et al. described oxime-based palladacycle **50** [23]. Extremely low catalyst loading (0.005 mol%) proved to be sufficient for the reaction to proceed successfully. 5-Bromopyrimidine **37** provided 91% yield of **55** in the reaction with tributyl-4-methoxyphenylstannane **162** (Scheme 51).

A silica-anchored catalyst **57** was reported by Lee et al. [31]. Ketoiminato-phosphan-Pd complex was able to catalyze Stille coupling between



Scheme 52 Stille coupling via immobilized catalyst **166**



Scheme 53 Two-step synthetic approach towards polyaza tricycles via Heck reaction and subsequent nitrene-mediated cyclization

4-chloropyrimidine **163** and tributylphenyl stannane **164** towards **59** in 91% yield (Scheme 52).

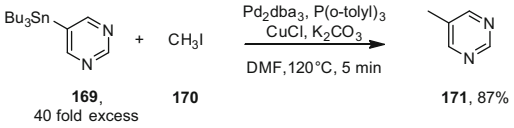
1.2.2 Pyrimidine as Organometal Species

Many papers describe the synthesis of various structural motives, involving Stille coupling of pyrimidine, as a main or one of the main steps. Herein, pyrimidine could play a role of both, electrophile and nucleophile.

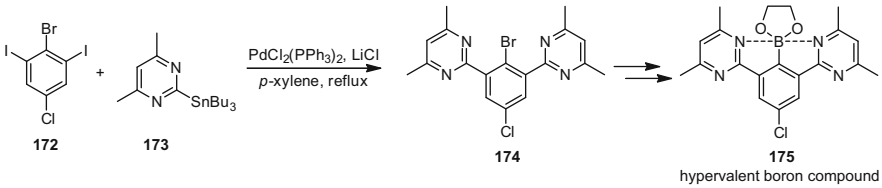
Nyffenegger et al. have developed a two-step synthesis towards polynitrogen-fused tricycles [76]. The sequence consists of Stille coupling of diverse electrophiles with various *o*-nitro(hetero)aryl chlorides and subsequent nitrene-mediated cyclization in the presence of triethylphosphite. Employing 2-tributylstannylpyrimidine **165** in the reaction with 2-chloro-3-nitropyridine **166** provided 68% of **167**, which upon treatment with triethylphosphite provided final fused tricyclic structure **168** in 86% yield (Scheme 53).

With the aim of developing a method for the production of ^{11}C-labeled radio pharmaceuticals for positron emission tomography (PET), Doi and coworkers have investigated the methylation of common heterocycles with methyl iodide via Stille coupling.[77] Due to the short half-life of ^{11}C ($t_{1/2} = 20.4$ min), fast synthesis of labeled species is a prerequisite. The strategy, reported by Doi, relies on the coupling of iodomethane with excess of the stannylated heteroaryl. However, previously developed reaction conditions (CH_3I/stannane/Pd_2dba_3/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 in a ratio of 1:40:0.5:2:2:2) turned out to be inefficient when applied to the selected heterocycles. After reoptimization of conditions (CH_3I/stannane/Pd_2dba_3/P(*o*-tolyl)$_3$/CuCl/K_2CO_3 in ratio 1:40:0.5:16:2:5 at 100°C in NMP for 5 min), trapping of iodomethane **170** with 5-tributylstannylpyrimidine **169** provided 87% of 5-methylpyrimidine **171** (Scheme 54).

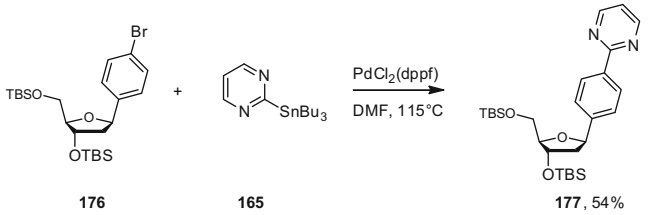
Hirano et al. have investigated the properties of hypervalent pentacoordinated boron compounds [78]. For this purpose, compound **175** was synthesized. Within the synthetic sequence, Stille coupling on intermediate **172** was reported with



Scheme 54 Methylation of pyrimidine with MeI via Stille coupling



Scheme 55 Synthesis of the hypervalent-boron species via Stille coupling



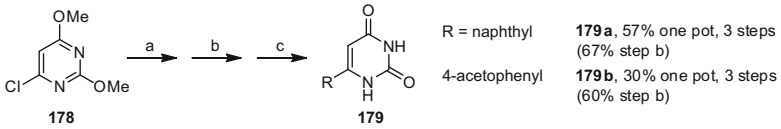
Scheme 56 Synthesis of 4-aryl substituted phenylene *C*-2′-deoxyribonucleosides

2-tributylstannyl-4,6-dimethylpyrimidine **173** as coupling partner in the presence of $PdCl_2(PPh_3)_2$ and LiCl. Compound **174** was obtained in rather poor yield of 13%. Low efficiency of the last step was ascribed to insufficient reactivity of the starting material and instability of the product at the high reaction temperature. **174** was then further elaborated to the desired hypervalent-boron compound **175** (Scheme 55).

Several reports have been published, describing either modification of pyrimidine containing nucleic bases or even a synthesis of artificial nucleosides, taking advantage of Stille coupling either as one step in the linear synthesis or as tool to introduce diversity at a specific position.

Hocek and coworkers have developed a synthesis of 4-arylsubstituted benzene *C*-2′-deoxyribonucleosides [79]. As a starting point for the derivatization at position 4 of the benzene ring, compound **176** was synthesized (Scheme 56) first and subsequently submitted to cross-coupling. Several aryl groups were introduced via coupling with **165**, including 2-pyrimidinyl. This reaction yielded 54% of **177**, which placed pyrimidine among the challenging substrates.

In 2008 Bargadí and Rossi have developed a novel approach towards 6-substituted uracils [80]. Synthesis was carried out as a one-pot procedure, consisting of stannylation of 4-chloro-2,6-dimethoxypyrimidine **178**, subsequent Stille coupling with aryliodide or benzoyl chloride, and hydrolysis. Stille coupling was carried out in the presence of $PdCl_2(PPh_3)_2$. The overall yields of the 6-substituted uracils **179a–b** were in the range between 30 and 57% (after three steps, Scheme 57).



Scheme 57 One-pot synthesis of substituted uracils; (*a*) stannylation (*b*) $PdCl_2(PPh_3)_2$, toluene, reflux (*c*) hydrolysis

1.3 Pyrimidine in the Negishi Reaction

1.3.1 Pyrimidine as (Pseudo)Halide

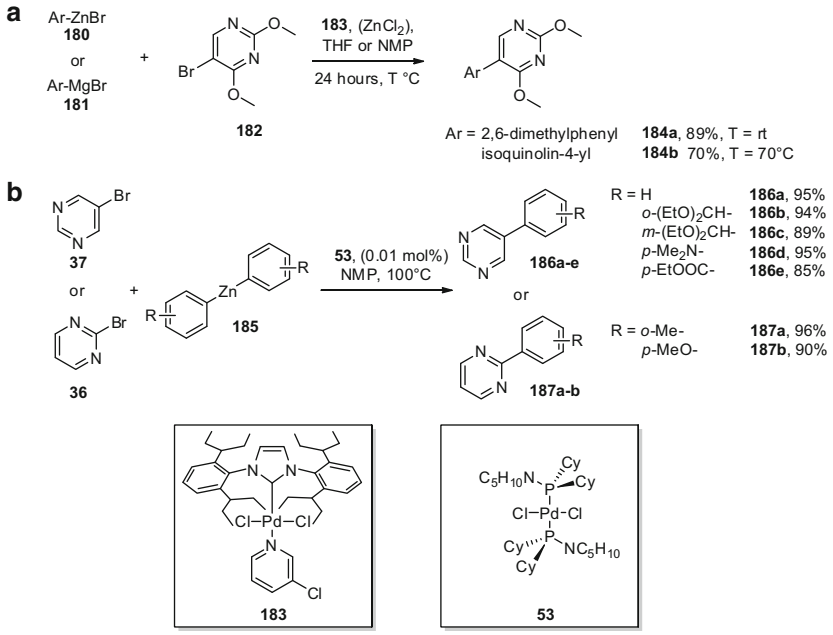
Catalyst Development

Several new catalytic systems were investigated for Negishi coupling. Organ and coworkers have shown that Pd-PEPPSI-IPent (**183**), a NHC-based palladium complex, is a potent catalyst capable of coupling of a variety of (hetero)aryls, including sterically hindered 2,6-substituted substrates [81]. The corresponding Grignard reagents were first treated with $ZnCl_2$ and subsequently mixed with the (hetero) aryl halide coupling partner. Reaction between 2,6-dimethylphenylzincbromide **180** with 2,4-dimethoxy-5-bromopyrimidine **182** led to 89% of **184a**. Reaction of the same pyrimidine derivate with 4-bromoisoquinoline **181** provided 70% of product **184b** (Scheme 58a).

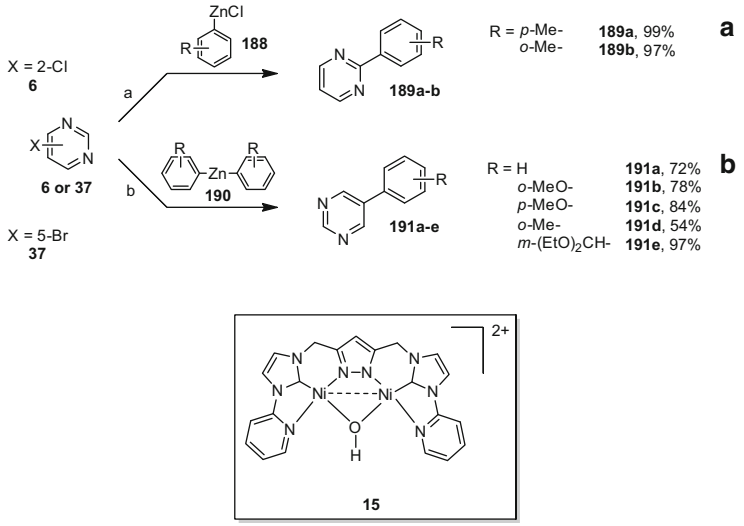
Another palladium-based catalyst was designed by Boliger and Frech [82]. Treatment of $Pd(cod)_2Cl_2$ with 1-(dicyclohexylphosphanyl)piperidine led to the formation of dichloro{bis[1-(dicyclohexylphosphanyl)piperidine]} complex **53**, which was subsequently evaluated in Negishi coupling. Various 2- or 5-bromopyrimidines were coupled with different diarylzinc reagents, giving yields in the range of 86–96% (**186a–e**, **187a**, **b**). Attractive features of this method are very low catalyst loadings (0.01 mol%) and short reaction times (in the range of minutes for all pyrimidines) (Scheme 58b).

Besides the investigation on palladium as a catalyst for Negishi coupling, also nickel has attracted some attention. Binuclear cationic nickel catalyst **15** ligated by NHC was described by Xi et al. as the first Ni/NHC catalyst for Negishi coupling [83]. At the relatively mild reaction conditions (80°C, 5 h), various (hetero)aryls were coupled with diverse arylzinc species. 2-chloropyrimidine **6** provided 99% of **189a**, when coupled with *p*-tolyl zinc chloride. Reaction with *o*-tolyl zinc chloride provided 97% of the biaryl **189b** (Scheme 59a).

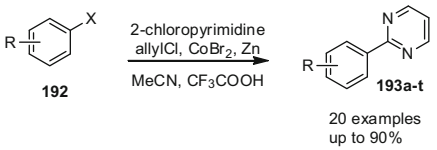
Gerber and Frech have synthesized an aminophosphine-based nickel catalyst and applied it in Negishi coupling [84]. $NiCl_2$ was treated with 2 equiv. of tri (piperidin-1-yl)phosphine, and the catalyst formed was found to be highly active in the coupling reaction already at low catalyst loading of 0.1 mol%. The reaction was carried out at a temperature of 60°C for up to 2 h. Several 5-bromopyrimidines were tested with various diarylzincs giving yields between 54 and 97% (Scheme 59b).



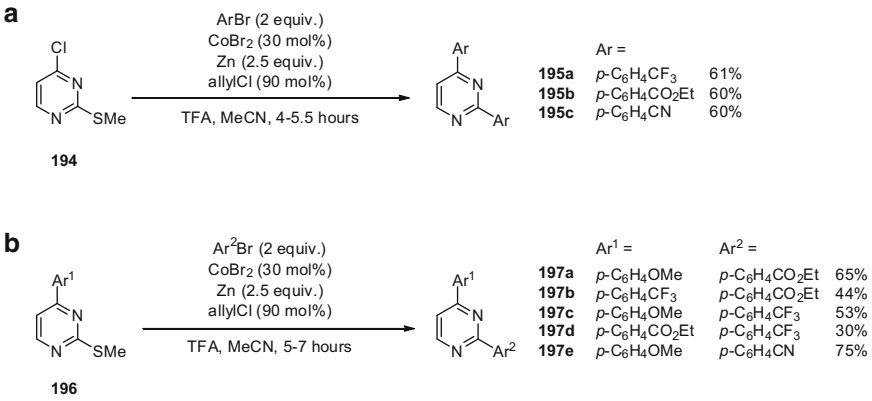
Scheme 58 New catalytic systems based on palladiums (**183**) and (**53**) and their application



Scheme 59 Negishi coupling catalyzed by nickel complex 15; (*a*) 15 (0.1 mol%), THF/NMP (1:1), 80°C, 2 or 3 h; (*b*) $NiCl_2$ (0.1 mol%), $P(NC_5H_{10})_3$ (0.2 mol%), THF/NMP, (1:2), 60°C, 0.5–2 h



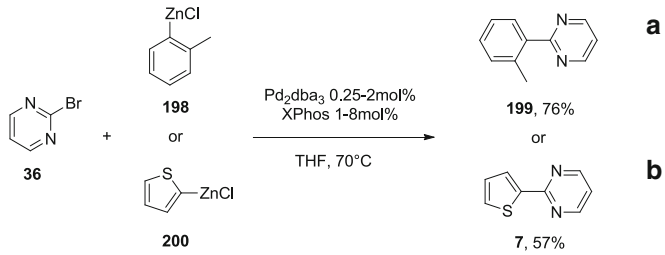
Scheme 60 Cobalt-catalyzed Negishi coupling



Scheme 61 $CoBr_2$-catalyzed desulfitative Negishi coupling

Cobalt as a catalyst for Negishi coupling was reported by Bégouin and Gosmini [85]. Various electron-rich and few electron-poor aryl halides were in situ transformed into arylzinc reagents and coupled with 2-chloropyrimidine in the presence of the catalytic system, comprising of $CoBr_2$, allyl chloride (of which the role within the reaction was not clarified yet), and traces of trifluoroacetic acid. At 50°C in acetonitrile, the reaction provided satisfactory yields up to 90% when electron-poor or electron-rich substrates were reacted. *O*-substitution of aryl halides caused a slight drop in reaction yields. Aryl chlorides were investigated in the coupling with 2-chloropyrimidine as well. The final products were obtained in yields from 50 to 60%, with no obvious effect of electronic properties of aryls (Scheme 60).

Begouin et al. also disclosed the $CoBr_2$-catalyzed desulfitative coupling of heteroaromatic methylthioethers and arylzinc reagents [86]. The authors found trace amounts of bis-coupling product when they treated 4-chloro-2-methylthiopyrimidine **194** with various arylzinc reagents in the presence of 10 mol% $CoBr_2$. When the catalyst loading was increased to 30 mol%, the bis-coupling product became the major product, even if only one equiv. of coupling partner was employed. With 2 equiv. of coupling partner, yields of about 60% were achieved (Scheme 61a). Also the synthesis of unsymmetrically substituted pyrimidines was successful: when the crude reaction mixture of the first arylation was subjected to bis-arylation conditions (30 mol% $CoBr_2$), products **197a–e** were isolated in 30–75% yield (Scheme 61b).



Scheme 62 Pd-XPhos-catalyzed arylation of 2-bromopyrimidine

Methodology

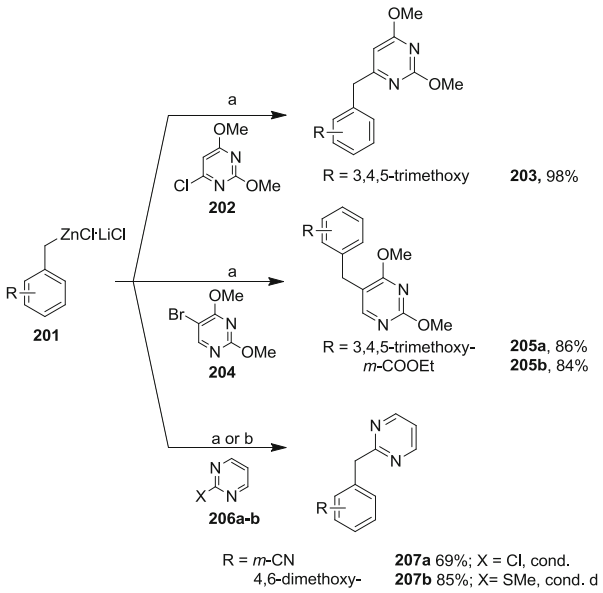
In 2004, the group of Buchwald published a Negishi coupling between arylzinc chlorides and aryl bromides (Scheme 62a) [87]. Scope study included reaction between 2-tolylzinc chloride **198** with 2-bromopyridine **36**. Employing a proper catalytic system, consisting of Pd_2dba_3 and XPhos as ligand, allowed using conveniently low catalyst loadings as low as 0.25% of palladium source with 4 equiv. of ligand. The coupling product was obtained in 76% yield. Similarly, only using 2 mol% catalyst loading, 2-bromopyridine **36** was coupled with thiophen-2-yl zinc chloride **200**, yielding 57% of **7** as shown by Luzung et al. [88] (Scheme 62b).

It was also demonstrated that cross-coupling between benzylic zincates and aryl halides can be mediated by nickel. Both pyrimidine chlorides and pyrimidine bromides were employed, providing the desired products in yields up to 98% using Ni $(acac)_2$ and PPh_3 as ligand. Moreover, employing thioether as leaving group is possible as well when PPh_3 is replaced with DPE-Phos. 4,6-dimethoxy benzylzinc chloride reacted with 2-methylthiopyrimidine **206b** in 85% yield (Scheme 63).

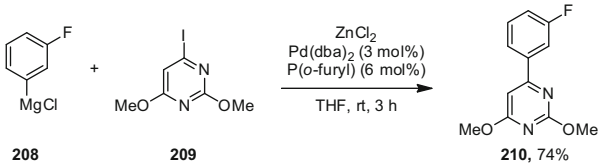
Dunst and Knochel developed LiCl-mediated insertion of Mg into an aryl–Cl bond and its subsequent transmetalation with $ZnCl_2$ and Negishi coupling [89]. In this reaction, 1-chloro-3-fluorobenzene was reacted with 4-iodo-2,6-dimethoxypyrimidine **209**, providing the desired product **210** in 74% yield (Scheme 64).

In the same group, direct metalation of protected uracils and thiouracils was developed [90]. Similarly as in the previous case, a Grignard reagent was transmetalated with $ZnCl_2$ and subjected to Negishi coupling. 3-Trifluoromethyl iodide **212a** and 4-(ethoxycarbonyl)phenyl iodide **212b** underwent coupling with 2,6-dimethoxypyrimidin-4-yl magnesium chloride **211** with 80% and 71% yield respectively (Scheme 65).

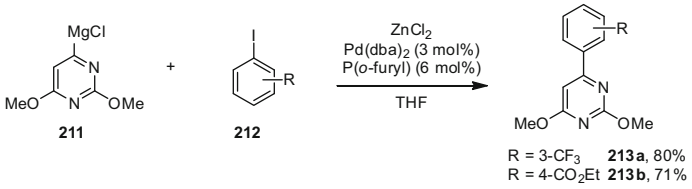
Knochel and coworkers also reported the first example of a direct insertion of aluminum into C–X bonds [91]. This process is rendered possible by the presence of certain metal salts (e.g., $InCl_3$/LiCl or $BiCl_3$/LiCl). The organoaluminum reagents **215** were transmetalated using $Zn(OAc)_2$. The resulting organozinc reagents smoothly underwent Pd-catalyzed cross-couplings with aryliodides. Among many other examples, it has been demonstrated that a substituted 6-iodopyrimidine bearing an ester (**216**) coupled with 4-iodotrifluorotoluene **214**



Scheme 63 Coupling of (pseudo)halopyrimidine with benzylic zinc reagents; (*a*) $Ni(acac)_2$ 0.5 mol %), PPh_3 (2 mol%), THF, 60°C; (*b*) $Ni(acac)_2$ (2.5 mol%), DPE-Phos (5 mol%), THF, 25°C



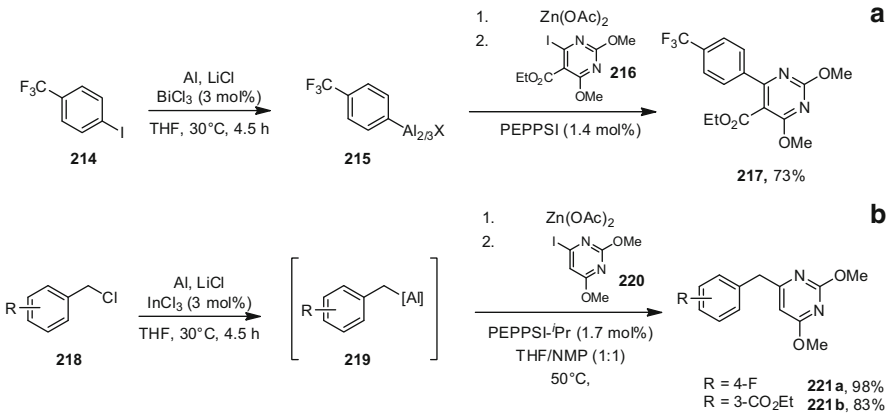
Scheme 64 Coupling of organozinc reagents, generated in situ via magnesium insertion and transmetalation



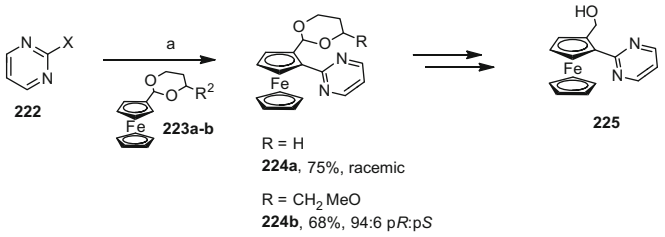
Scheme 65 Synthesis of uracil derivatives via Negishi coupling

in 73% yield after 4.5 h at 30°C (Scheme 66a). Later, this methodology was extended to substrates containing benzylic chlorides (Scheme 66b) [92].

Synthesis of hydroxymmethyl-2-(2′-pyrimidyl)ferrocene was described by Omedes et al. [93]. After acetal protection of the carbonyl group, the compound was treated with *s*-BuLi and $ZnBr_2$. Addition of $PdCl_2(PPh_3)_2$ and 2-iodopyrimidine led to the formation of racemic product **224a** in 75%. Hydrolysis



Scheme 66 Coupling of organozinc reagents, prepared in situ via direct Al-insertion and transmetalation



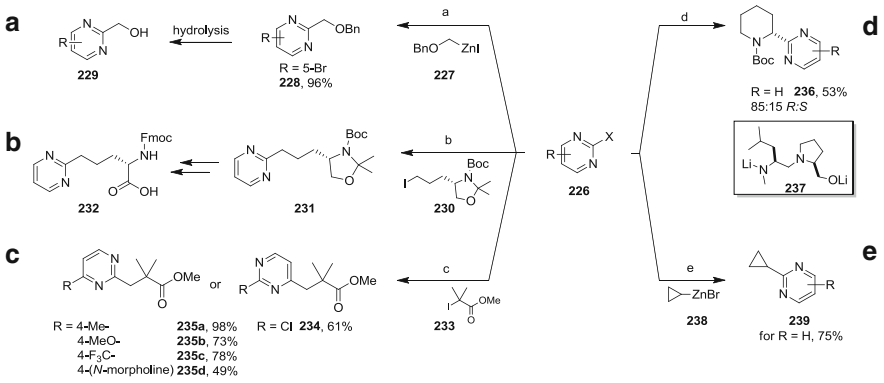
Scheme 67 Negishi coupling of ferrocenylzinc bromides; (*a*) (1) ferrocene, *s*-BuLi, THF, −78°C; (2) $ZnBr_2$, THF, −30°C to rt, 1 h; (3) 2-iodopyrimidine, $PdCl_2(PPh_3)_2$, THF, reflux, overnight

and reduction provided the corresponding alcohol **225**. When enantiopure starting material **223b** was used instead, the reaction gave enantiomerically enriched **224b** in 68% yield with an enantiomeric ratio 94:6 (*pR*:*pS*) (Scheme 67).

Hasnik et al. have reported hydroxymethylation of (hetero)aryls via Negishi coupling of the corresponding (hetero)aryl halide with (benzoxymethyl)zinc iodide **227** [94]. Coupling with 5-bromo-2-iodopyrimidine in the presence of $Pd(PPh_3)_4$ proceeds selectively into the iodine position and **228** is isolated in 96%. Further deprotection yields 75% of 5-bromo-2-hydroxymethyl pyrimidine **229** (Scheme 68a).

Suhartono et al. have developed a synthetic method towards nonnatural amino acids containing an aryl moiety [95]. Key intermediate **230** was obtained from glutamic acid in four steps. Treatment of **230** with Zn and I_2 and subsequent $NiCl_2(PPh)_3$ promoted Negishi coupling with with 2-bromopyrimidine towards arylated intermediate **231** in 86% yield. **231** was further converted to the desired amino acids **232** (Scheme 68b).

Preparation of 3-aryl-2,2-dimethylpropanoates via Negeshi coupling was described by Kwak et al. [96]. Firstly, methyl-3-iodo-2,2-dimethylpropanoate **233**



Scheme 68 Negishi coupling of alkylzinc reagents with halopyrimidines; (*a*) $Pd(PPh_3)_4$, THF, rt (*b*) (1) 268, Zn, I_2; (2) 2-bromopyrimidine, $NiCl_2(PPh_3)_2$ (*c*) X=Cl; Zn-Cu, toluene, DMA, Pd $(PPh_3)_4$ 110°C (*d*) X=Br; (1) N-Boc-piperidine, s-BuLi, TMDEA (4 eq.), Et_2O, −78°C; (2) (*S*,*S*)-237, −45°C, 5 h; (3) −78°C, $ZnCl_2$ warm to rt; (4) 2-bromopyrimidine, $Pd(OAc)_2$, *t*-$Bu_3P{\cdot}HBF_4$ (*e*) X=Br; $Pd(OAc)_2$ (1 mol%), CPhos (2 mol%), THF, rt, 30 min

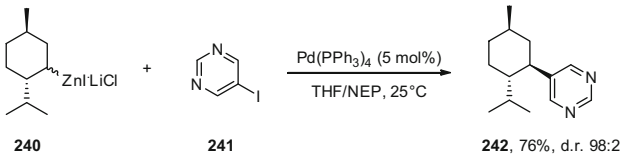
is treated by Zn-Cu couple, and the resulting zincated species is subjected to Negishi conditions ($Pd(PPh_3)_4$, 110°C) and addition of (hetero)aryl chloride). Series of diversely substituted 2-chloropyrimidines was tested, and corresponding products **235a–d** were isolated in 49–98% yields. The reaction tolerates both electron-withdrawing and electron-donating substituents (Scheme 68c).

Beng and Gawley reported highly enantioselective (hetero)arylation of Boc-protected piperidine [97]. Treatment of the starting material with *s*-BuLi and chiral additive **237**, followed by addition of $ZnCl_2$ and finally submission of the formed zinc species to the coupling condition ($Pd(OAc)_2$/*t*-$Bu_3P{\cdot}HBF_4$) in the presence of 2-bromopyrimidine, leads to the formation of **236** in 53% yield. Enantiomeric ratio (*R*:*S*) was determined to be 85:15 (Scheme 68d).

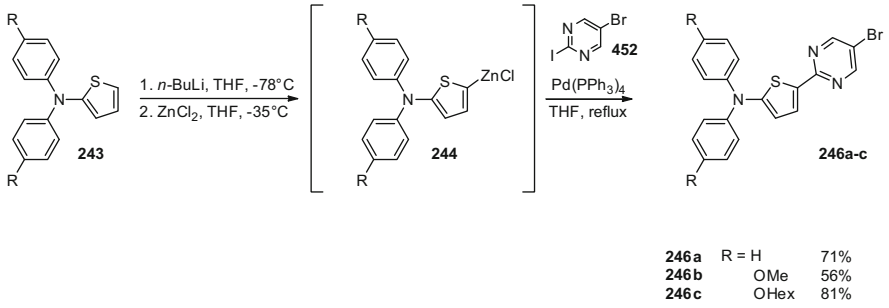
Negishi coupling of a secondary sp^3-C-zinc center with (hetero)aromatic halides was investigated by Han and Buchwald [98]. Out of the tested ligands, CPhos performed the best. Reaction of cyclopropylzinc chloride **238** with 2-bromopyrimidine, catalyzed by $Pd(OAc)_2$ and CPhos in a THF/toluene mixture, provided 75% of **239**. Although carried out under very mild conditions (room temperature), full conversion was reached after only 30 min (Scheme 68e).

Thaler et al. have investigated diastereoselective $C(sp^3)$-$C(sp^2)$ Negishi coupling [99]. Related to this chapter, iodomenthol was firstly converted to the corresponding zincated species by treatment with zinc and lithium chloride. 240 was then reacted with 5-bromopyrimidine in the presence of $Pd(PPh_3)_4$. Product **242** was obtained in 76% with 98:2 diastereomeric ratio (Scheme 69).

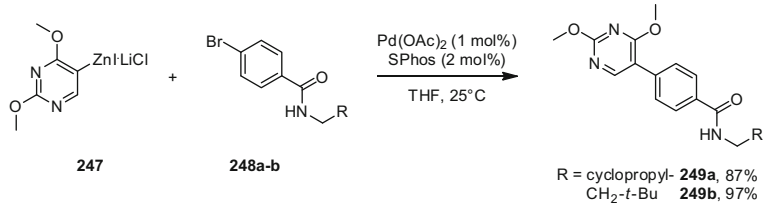
Negishi coupling of pyrimidine was applied within the synthesis of DSC sensitizers [100]. First, 2-(*N*,*N*-diaryl)thiophene **243** was metalated using *n*-BuLi and subsequent addition of $ZnCl_2$. Reaction with 5-bromo-2-iodopyrimidine **345** in the presence of $Pd(PPh_3)_4$ provides formation of desired products **246a–c** in yields between 56 and 81%. Subsequent modifications led to the desired derivatives, which were investigated for their optical properties (Scheme 70).



Scheme 69 Diastereoselective introduction of pyrimidine to menthol



Scheme 70 Synthesis of the precursor of dye for DSSC

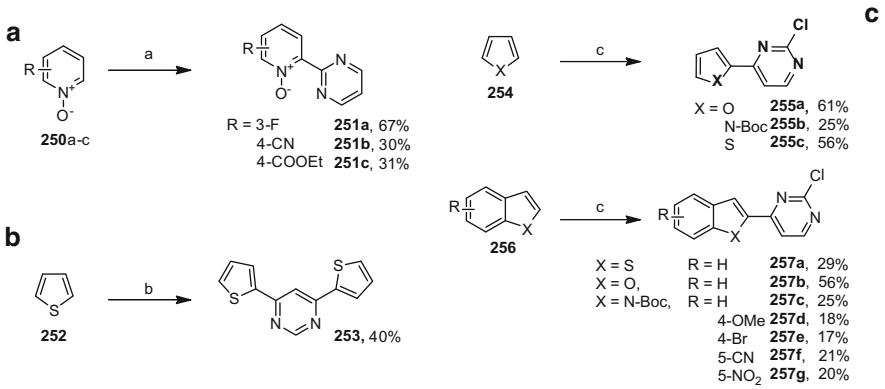


Scheme 71 Negishi cross-coupling in the presence of free amide

Monolikakes et al. have investigated the possibility of Negishi coupling between various zinc nucleophiles and aryl halides bearing unprotected amides [101]. Using $Pd(OAc)_2$/S-Phos and mild reaction conditions (25°C), reaction between 2,4-dimethoxypyrimid-5-yl zinc iodide **247** and 4-bromo-*N*-(cyclopropylmethyl) benzamide **248a** provided 87% of the desired biaryl **249a**. In the reaction with 4-bromo-*N*-(3,3-dimethylbutyl)benzamide **248b**, the same nucleophile provided 97% of **249b** (Scheme 71).

Several reports were published dealing with direct metalation of aromatic species and subsequent Negishi coupling. Utilizing the proper metalating agent allows regioselective metalation even in the presence of chlorides or bromides. In most cases, pyrimidine is used as electrophile; nevertheless, direct metalation of pyrimidine is described as well.

Staben and coworkers have developed a method of regioselective metalation of azine *N*-oxides with TMPZnCl·LiCl [102]. Subsequent treatment of the metalated species with heteroaryl bromides in the presence of Pd catalyst leads to formation of biaryls. A mixture of 2-bromopyrimidine with 3-fluoropyridine *N*-oxide **250a**,



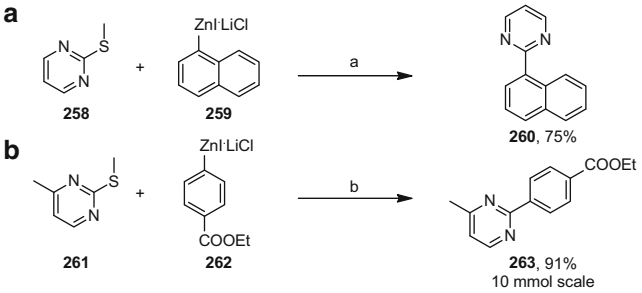
Scheme 72 Direct metalation and Negishi coupling of heterocyclic substrates (*a*) TMPZnCl·LiCl, 2-bromopyrimidine, $PdCl_2(dppf)\cdot CH_2Cl_2$, THF, rt to 60°C (*b*) (1) $ZnCl_2$·TMEDA (0.5 eq.), Li (tmp), THF, rt, 2 h; (2) heteroaryl chloride, $PdCl_2$ (2 mol%), dppf (2 mol%), reflux 24 h (*c*) (1) LiTMP. THF, −78° or −90°C, 1 h; (2) $ZnCl_2$·TMEDA, rt. 1 h; (3) $PdCl_2$ (2 mol%), dppf (2 mol %), heteroaryl chloride; (4) Hydrolysis

4-(methoxycarbonyl)pyridine *N*-oxide **250b** or 4-cyanopyridine *N*-oxide **250c** was initially treated with metalation agent and subsequently $PdCl_2(dppf)$-CH_2Cl_2 was added. The resulting biaryls **251a–c** were isolated in 67%, 31%, and 30%, respectively. Compared to other investigated heterocycles, pyrimidines turned out to be difficult substrates to couple (Scheme 72a).

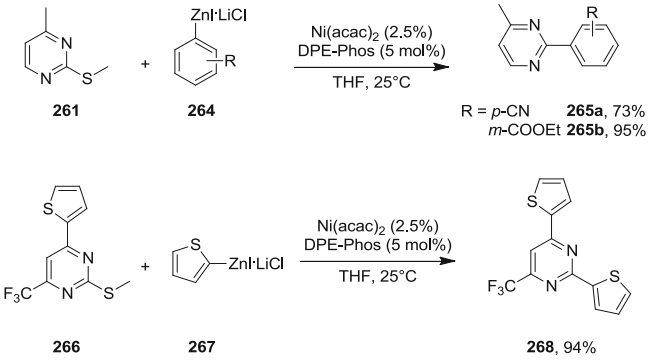
The same conclusion can be drawn from the work of Snégaroff et al. [103], who have developed a deprotonative metalation using amino/alkyl mixed lithium-zinc combinations. When thiophene was subjected to the metalation conditions with $ZnCl_2$·TMEDA and Li(tmp) and subsequently reacted with 4,6-dichloropyrimidine, the desired 4,6-(dithiophen-2-yl)pyrimidine **253** was isolated in 40% yield (Scheme 72b).

Seggio et al. investigated deprotonative lithiation of several heterocycles followed by transmetalation with $ZnCl_2$·TMDEA and cross-coupling with (hetero)aryl chlorides [104]. Furan, thiophene, and their benzo-fused analogs were metalated and reacted with 2,4-dichloropyrimidine. All couplings proceeded into position 4 of pyrimidine. In general, fused heterocycles provided comparable yields. 2-Chloro-4-(2-furyl)pyrimidine **255a** was obtained in 61%, while the yield of 2-chloro-4-(2-benzofuryl)pyrimidine **257b** was slightly lower with 56%. 2-Chloro-4-(2-thienyl)pyrimidine **255c** was isolated in 56% yield as well and analogous 2-chloro-4-(2-benzothiophenyl)pyrimidine **257a** in rather poor 29% yield (Scheme 72c).

The scope of the transformation was extended in a follow-up work [105]. Boc-protected imidazole, benzimidazole, and variously substituted benzimidazole derivatives were coupled as well. However, obtained yields did not exceed 25%, independently on the electronic properties of the substrate (Scheme 72c).



Scheme 73 Desulfitative Negishi coupling of methylthiopyrimidines; (*a*) Pd_2dba_3 (0.25–2 mol%), XPhos (1–8 mol%), THF, 70°C; (*b*) $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 25°C



Scheme 74 Nickel-catalyzed Negishi cross-coupling, involving pyrimidine sulfides

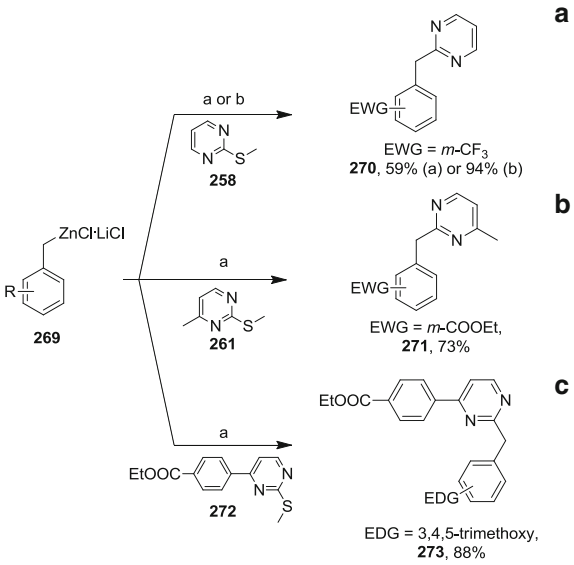
Pyrimidine Sulfides in Negishi Reactions

More recently, coupling between arylzincates and aromatic sulfides was developed in the group of Knochel [106, 107]. The reaction is catalyzed by Pd(OAc)/SPhos as catalytic system, employing 2.5 mol% of catalyst and 5 mol% of ligand. Reaction between 2-thiomethylpyrimidine **258** and naphthylzinc iodide **259** yields 75% of **260** and reaction between 4-(ethoxycarbonyl)phenylzinc iodide **262** with 4-methyl-2-thimethylpyrimidine **261** provides 91% of the biaryl **263** (Scheme 73a, b).

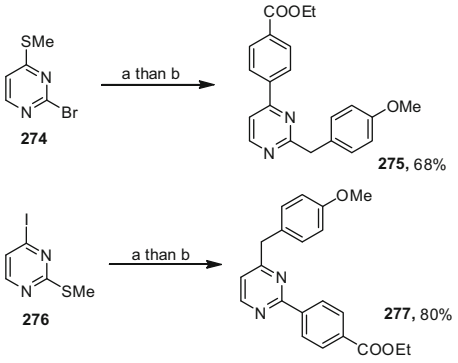
Nickel-catalyzed coupling of arylzincates and aromatic thiols was reported as well, again by Knochel and coworkers [106, 107]. Employing $Ni(acac)_2$ and DPE-Phos leads to coupling of various 2-thiomethylpyrimidines with arylzinc chlorides in yields up to 95% (Scheme 74).

Besides $C(sp^2)$-nucleophiles, benzylic $C(sp^3)$-zincates were investigated as well [108–110]. Under palladium catalysis, diverse 2-methylthiopyrimidines (**258**, **261**, **272**) couple with substituted benzylzinc chlorides (**269**) in yields up to 94% under mild conditions (25–50°C, Scheme 75a, b, c). It has been shown that the reaction conditions are compatible with substrates bearing an ester functionality (Scheme 75c).

In addition, a method for selective decoration of the pyrimidine ring was described. Employing different starting materials **274** and **276** led to the formation



Scheme 75 Desulfitative Negishi coupling of benzylic zinc reagents; (*a*) $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 25°C; (*b*) $Pd(OAc)_2$ (2.5 mol%), SPhos (5 mol%), THF, 50°C

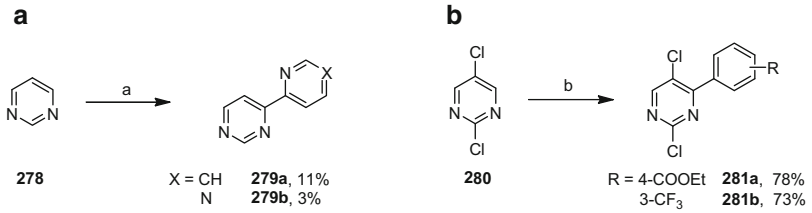


Scheme 76 Selective, sequential Negishi couplings on pyrimidine; (*a*) $Pd(dba)_2$ (2 mol%), TFP (5 mol%), 25°C, *p*-(methoxy)benzylzinc chloride; (*b*) $Pd(OAc)_2$ (2.5 mol%), S-Phos (5 mol%), 25°C, *p*-(ethoxycarbonyl)phenylzinc chloride

of regioisomers **275** and **277** via consecutive introduction of benzylic and aromatic moieties in yields of 68% and 80% over two steps (Scheme 76).

1.3.2 Pyrimidine as Organometal Species

In the same report of Snégaroff et al. discussed above (see section "Methodology") [103], pyrimidine **278** was treated with $ZnCl_2$·TMEDA and Li(tmp) and subsequently coupled with 2-chloropyridine or 4-chloropyrimidine in the presence of



Scheme 77 Direct metalation and cross-coupling of pyrimidine; (*a*) (1) $ZnCl_2 \cdot TMEDA$ (0.5 eq.), Li(tmp), THF, rt, 2 h, (2) heteroaryl chloride, $PdCl_2$ (2 mol%), dppf (2 mol%), reflux 24 h; (*b*) (1) $TMP_2Zn \cdot 2MgCl_2 \cdot 2LiCl$, THF, 25°C, 45 min, (2) ArI, $Pd(dba)_2$ (3 mol%), P(*o*-furyl)$_3$ (6 mol%), THF, 65°C, 45 min

$PdCl_2$ and dppf under reflux. The resulting products **279a** and **279b** were obtained in 11% and 3%, respectively (Scheme 77a).

A more successful method of direct regioselective metalation of 2,5-dichloropyrimidine **280** (into position 4) and subsequent Pd-catalyzed cross-coupling was reported by Morsin and Knochel [111]. Using $TMP_2ZnCl_2 \cdot 2LiCl$ at 25°C, followed by treatment with either ethyl 4-iodobenzoate or 3-3-iodotrifluoromethylbezene in the presence of $Pd(dba)_2$ and P(*o*-furyl)$_3$, led to the coupled products **281a** and **281b** in 78% and 73% yield, respectively (Scheme 77b).

1.4 Pyrimidine in the Sonogashira Reaction

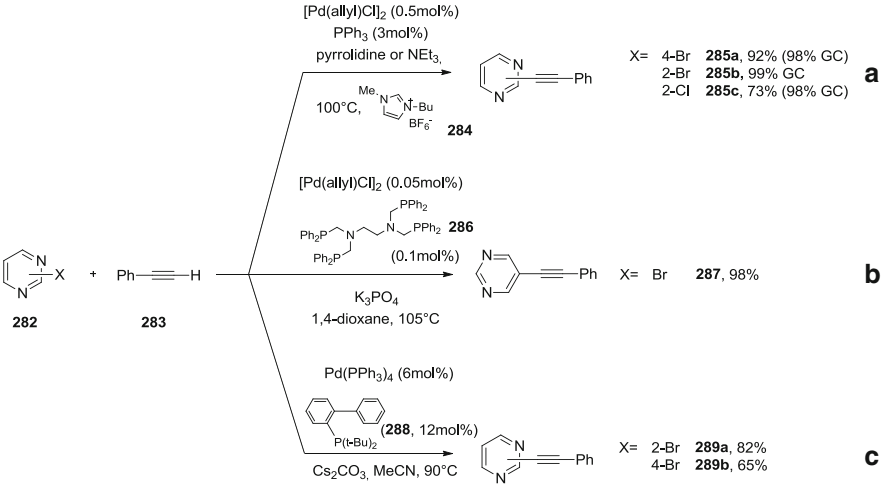
1.4.1 Copper-Free Sonogashira Reactions

Several Cu-free variants have been published throughout the last years. If performed in the ionic liquid BMIM tetrafluoroborate **284**, high yields in absence of Cu-salts have been obtained (Scheme 78a) [112].

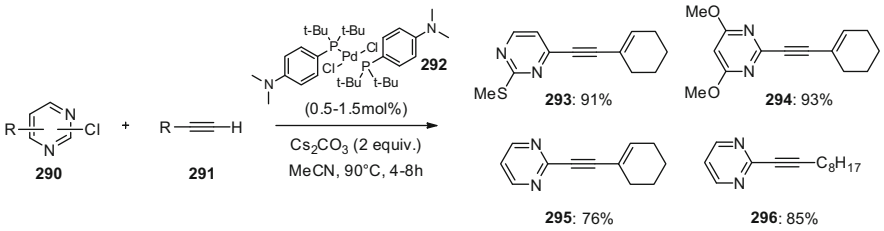
Highly efficient und Cu-free coupling was also facilitated by tetradentate *N*,*N*,*N*′,*N*′-tetra(diphenylphosphinomethyl)-1,2-ethylenediamine **286**/$[Pd(C_3H_5)Cl]_2$. In the presence of this catalyst, 5-bromopyrimidine reacted with phenylacetylene **283** to give 98% yield after 20 h (Scheme 78b) [113].

Under conditions developed by Ngassa et al., a variety of aryl bromides and phenylacetylene reacted in the presence of $Pd(PPh_3)_4$, ligand 2-(di-*t*-butylphosphino)-1,1′-biphenyl **288**, and cesium carbonate. 2- and 5-bromopyrimidine gave the coupling products **289** in 82% and 65%, respectively (Scheme 78c) [114].

Recently, Pu et al. reported $[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P]_2Pd(0)$ **292** and $[p\text{-}Me_2NC_6H_4(t\text{-}Bu)_2P]_2PdCl_2$ to be excellent precatalysts for Cu-free alkynylations [115]. Aryl bromides reacted with phenylacetylene in the presence of cesium carbonate within 4 h in acetonitrile at 80°C (e.g., 2-bromopyrimidine, 93%; 5-bromopyrimidine, 93%). Some aryl chlorides required DMF as a solvent, reaction temperatures 90–110°C and up to 8 h (e.g., methyl 6-chloronicotinate and



Scheme 78 Copper-free Sonogashira reactions of halopyrimidines



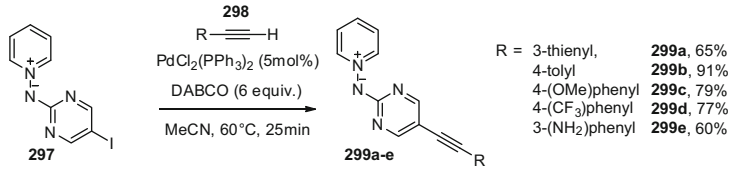
Scheme 79 Copper-free Sonogashira coupling of chloropyrimidines

1-decyne, 95%). However, chloropyrimidines **290** reacted smoothly in acetonitrile, yielding the coupling products **293**–**296** in 76–93% yield (Scheme 79).

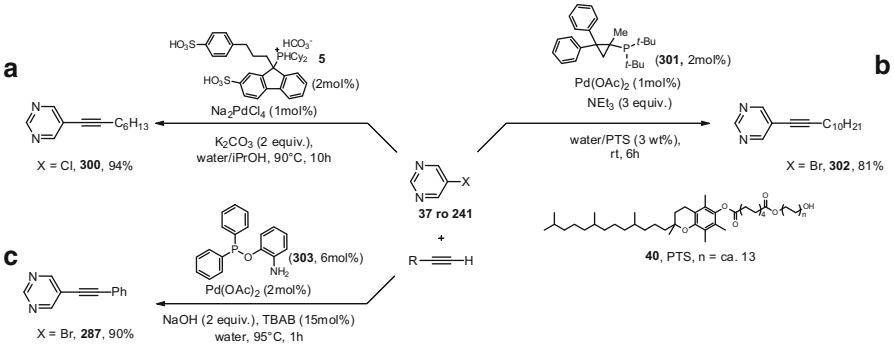
1.4.2 Aqueous Sonogashira Reactions

Alkynylation of a number of pyrimidinylamidines **297** in the presence of $PdCl_2(PPh_3)_2$/DABCO was achieved in acetonitrile as solvent [116]. For substrates containing other heterocycles, coupling could also be carried out in aqueous medium (Scheme 80).

Fleckenstein and Plenio employed the doubly sulfonated and thus water-soluble fluorenyldicyclohexylphosphine ligand **5** for the coupling reaction of (hetero)aryl chlorides and bromides with a variety of terminal alkynes [117]. Using environmentally benign potassium carbonate as base and a water/isopropanol mixture as solvent, the reaction proceeded smoothly with excellent yields (e.g., 2-chloropyrimidine and 1-octyne, 94% yield of **300**) (Scheme 81a).



Scheme 80 Sonogashira coupling reactions of pyrimidinylamidines



Scheme 81 Novel catalysts for the Sonogashira reaction in aqueous solutions

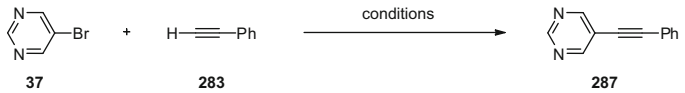
In order to overcome the problem of substrate solubility in aqueous reaction media, Lipshutz et al. used the nonionic amphiphile PTS as an agent for the formation of nano-micelles [118]. Among other catalysts Pd(dtbpf)Cl_2 and Pd $(OAc)_2$/cBRIDP **301**, a cyclopropylphosphine ligand catalyzed the coupling reaction efficiently at room temperature in the absence of a Cu source and gave excellent yields for most examples (5-bromopyrimidine and 1-decyne, 6 h, 81% of **302**) (Scheme 81b).

Successful coupling in neat water was achieved with the ligand 2-aminodiphenyl phosphinite **303** in a heterogeneous reaction mixture [119]. The catalyst could be recovered by centrifugation and was reused up to six times without significant loss of activity (Scheme 81c).

1.4.3 Ligand-Free Sonogashira Reactions

Several catalytic systems have been reported to couple halopyrimidines in absence of ligands (Scheme 82): The combination of PdEnCat™/KOH/EtOH represents an environmentally benign catalytic system [120]. Isolated yields vary widely (22–94%), with 52% for the reaction between 5-bromopyrimidine and phenylacetylene. The relatively harsh conditions limit the applicability of this method to robust coupling partners (Table 1, Entry 1).

An investigation of gelatin as supporting material for Pd nanoparticles showed that these particles constitute an effective catalyst in the presence of KOAc/TBAB



Scheme 82 Sonogashira reaction under ligand-free conditions

Table 1 Examples for the Sonogashira reaction under ligand-free conditions

Entry	Conditions	Time (h)	Yield (%)	References
1	PdEnCat™ 30 (2 mol%), KOH (2 equiv.), EtOH, reflux	24	52	[120]
2	Pd(0) nanoparticles on gelatin, KOAc (1.5 equiv.), TBAB, 100°C	2	77	[121]
3	Fe_2O_3 nanoparticles (5 mol%), K_2CO_3 (2 equiv.), ethylene glycol, 125°C	72	76	[122]
4	CuI (10 mol%),  (20 mol%), Cs_2CO_3 (2 equiv.), DMF, 130°C	24	96	[123]

[121]. Among 17 examples, reactivity decreased in the order aryliodides (80–94% yield), bromides (74–85%), and chlorides (53–60%). 5-Bromopyrimidine was coupled with phenylacetylene in 77% (Table 1, Entry 2).

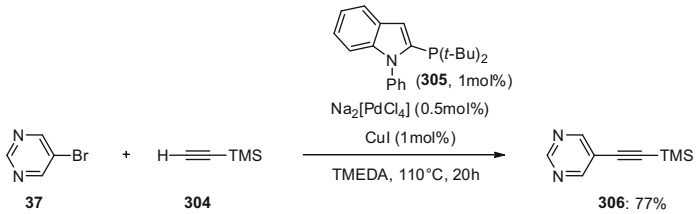
Under conditions developed by Hoseini and coworkers, coupling occurs in the presence of magnetite nanoparticles as the sole catalyst in ethylene glycol without ligand or Cu source present [122]. Due to their magnetic properties, catalyst particles can easily be separated from the reaction mixture and reused. Good to excellent yields were obtained after extended reaction times (e.g., 5-bromopyrimidine and phenylacetylene, 72 h, 76%) (Scheme 82) (Table 1, Entry 3).

8-Hydroxyquinoline was used as a bifunctional N,O-ligand in conjunction with CuI, allowing for coupling reactions to take place in the absence of Pd in moderate to very good yields (5-bromopyrimidine and phenylacetylene, 130°C, 24 h, 96%) [123] (Table 1, Entry 4).

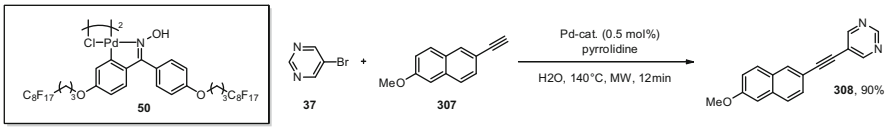
1.4.4 New Catalysts

Beller and coworkers identified the indolylphosphine ligand CatacXium®PIntB **305** in conjunction with Na_2PdCl_4, CuI, and TMEDA as a powerful catalytic system, especially suited for the Sonogashira reaction of electron-rich heterocycles [124]. Nevertheless, coupling of 5-bromopyrimidine with trimethylsilylacetylene gave the coupling product **306** in only 77% yield (Scheme 83).

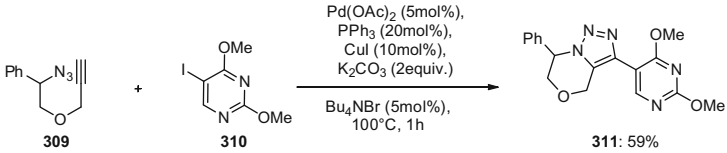
The oxime-based Pd-cycle **50**, which is also a competent catalyst in Suzuki–Miyaura, Heck, Stille, and Kumada–Corriu–Tamao coupling reactions (see also section "Water as Reaction Medium"), was successfully employed for the coupling



Scheme 83 Application of CatacXium®PlntB ligand



Scheme 84 Coupling catalyzed by an oxime-based palladacycle



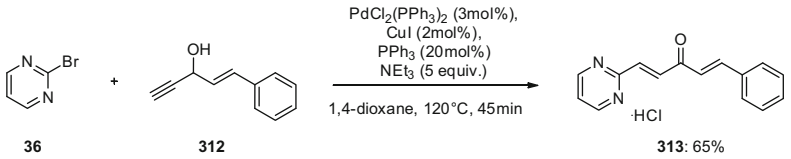
Scheme 85 Sonogashira-click cascade

of 5-bromopyrimidine and 2-ethynyl-6-methoxynaphthalene **307** (90% yield) [23, 24] (Scheme 84).

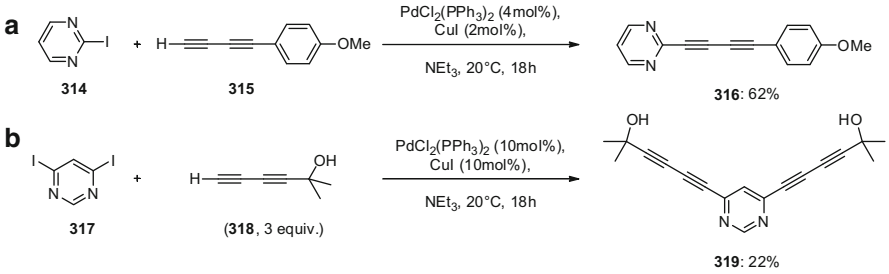
1.4.5 New Reactions

Achari and coworkers combined a Sonogashira coupling reaction with an azide-click reaction in a one-pot protocol to synthesize a library of triazole-fused morpholines in 53–90% yield [125]. The combination of $Pd(OAc)_2/PPh_3/CuI$ proved effective, catalyzing the coupling reaction as well as the heteroannulation reaction. The authors showed that the corresponding acyclic intermediate coupling products can be isolated when the reaction is run in the absence of CuI. They therefore proposed a mechanism, where coupling occurs first, followed by the copper(I)-catalyzed heteroannulation. When 2,4-dimethoxy-5-iodopyrimidine **310** was employed as coupling partner, the fused ring system **311** was obtained in 59% yield after 1 h at 100°C (Scheme 85).

Gendron et al. described a novel protocol for the synthesis of diarylidene acetone **313** via a Sonogashira/isomerization reaction of propargylic alcohols **312** [126]. Coupling was effected with $PdCl_2(PPh_3)_2/CuI/NEt_3$ in THF, heated to 120°C under microwave irradiation (Scheme 86).



Scheme 86 Sonogashira/isomerization reaction



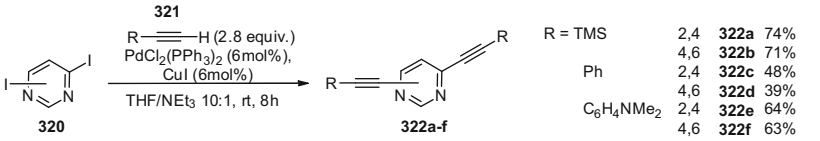
Scheme 87 Sonogashira coupling of diynes

1.4.6 Various

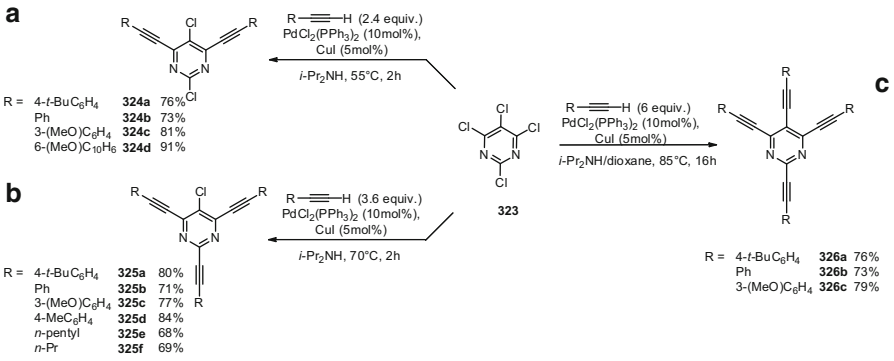
Bryce and coworkers reported the synthesis of terminal aryldiynes [127]. Heteroatoms on the aryl group lead to a significant increase in stability of these compounds due to H-bonding with the terminal alkyne proton. Unlike other compounds of the same class, the reported examples could be isolated and purified. As a prototypical example of how these compounds can be employed, the coupling of 2-iodopyrimidine **314** with (4-methoxy)phenylbutadiyne **315** under classical Sonogashira conditions was carried out in 62% yield. In an effort to synthesize oligo-butadiynes as molecular wires, 2-hydroxypropyl-protected butadiyne **318** was reacted with 4,6-diiodopyrimidine **317** under similar conditions and afforded the bis-coupled product **319** in 22% yield [128] (Scheme 87).

Plé and coworkers synthesized a number of dialkynylpyrimidines as precursors for organic electronic materials starting from the diiodopyrimidines **320** [49]. However, coupling of 2,4,6-triiodopyrimidine failed under Sonogashira conditions, presumably due to the limited stability of the starting material. This problem was circumvented by employing 2,4,6-trichloropyrimidine instead, which was successfully alkynylated under Suzuki–Miyaura or Negishi conditions (see section "Coupling Sequences") (Scheme 88).

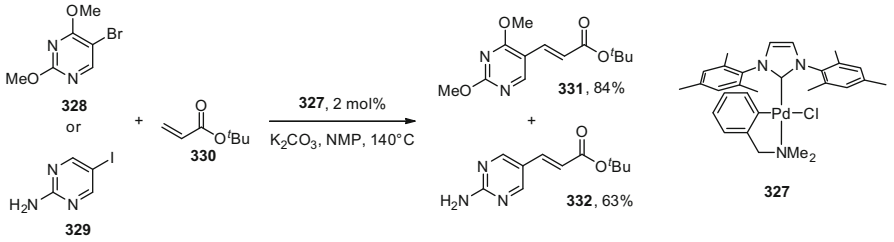
Sequential coupling of 2,4,5,6-tetrachloropyrimidine with arylacetylene gave rise to di-, tri-, and tetraynepyrimidines with a high degree of regioselectivity [129]. The obtained products showed promising fluorescence properties (Scheme 89).



Scheme 88 Double alkynylation of diiodopyrimidines



Scheme 89 Regioselective di-, tri-, and tetraalkynylation of tetrachloropyrimidine

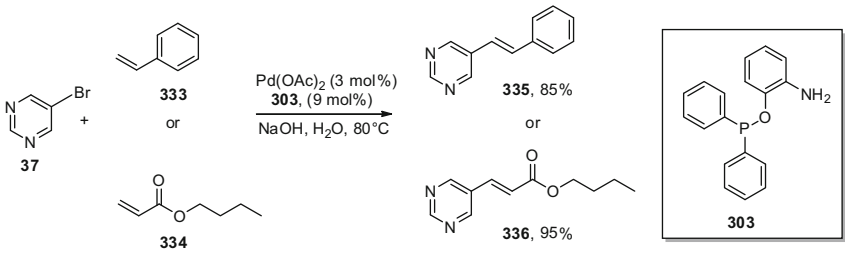


Scheme 90 NHC-based palladium catalyst for the Heck reaction and its application in coupling involving various pyrimidines

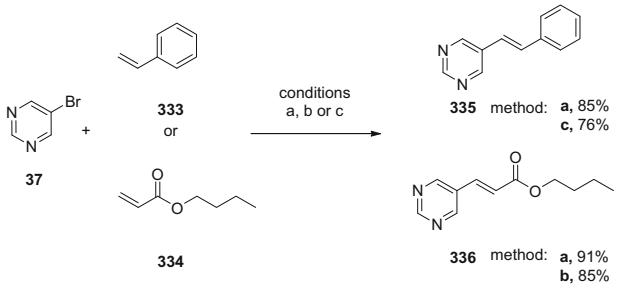
1.5 Pyrimidine in the Heck Reaction

1.5.1 Catalyst Development

Several new catalytic systems were developed for the Heck reaction. Ying and coworkers have developed an NHC-ligated palladacycle **327** which can be prepared in a simple one-pot three-component reaction starting from *N*,*N*-dimethybenzylamine, $PdCl_2$, and IMes·HCl [130, 131]. This precatalyst can be successfully utilized in the Heck reaction between *t*-butylacrylate **330** and 5-bromo-2,4-dimethoxypyrimidine **328** or 5-iodo-2-aminopyrimidine **329**. At 140°C in NMP and in the presence of K_2CO_3, the reaction provided 84% and 63% yield, respectively (Scheme 90).



Scheme 91 Application of phosphinite ligand 303 in alkenylation reactions of 5-bromopyrimidine

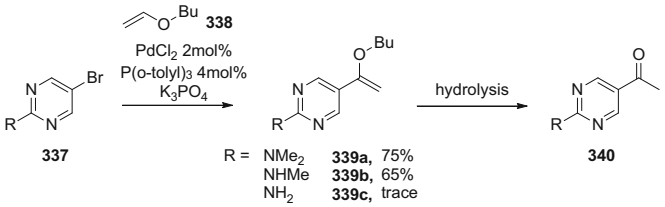


Scheme 92 Gels as support for Pd nanoparticles; (*a*) $PdCl_2$ on gelatin, nPr_3N, neat, 140°C, 100–200 min; (*b*) Pd(0) on SDPP, nPr_3N, neat, 130°C, 100 min; (*c*) $Pd(OAc)_2$ on agarose, Et_3N, 120°C, 12 h

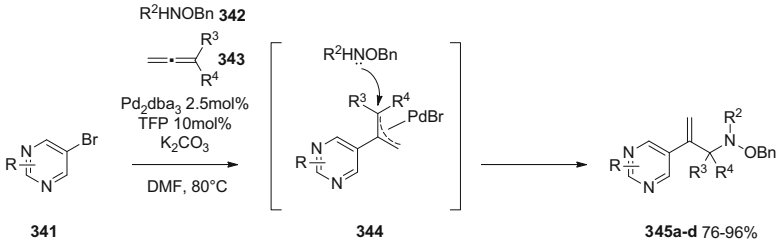
The novel ligand 2-aminophenyldiphenylphosphinite **303** was synthesized from 2-aminophenol and chlorodiphenyl phosphine and evaluated in Heck coupling by Gholinejad et al. [132]. Its utility has been demonstrated in reactions between (hetero)aryl halides and either styrene **333** or *n*-butylacrylate **334**. Using 3 mol% of $Pd(OAc)_2$ and 6 mol% of ligand in water and with NaOH or Cs_2CO_3 as base, **37** provided 85% yield of product **335** and 75% yield in case of 5-*n*-butylacrylate-pyrimidine **336** (Scheme 91).

Several nanoparticle-based catalysts were developed by the Iranpoor group (Scheme 92). The effect of different solid supports for palladium nanoparticles was investigated. In the earliest work, nanoparticles were deposited on gelatin, a nontoxic, degradable, and easily accessible natural product support [133]. Heck reaction could then be conducted under solvent-free conditions at 140°C using tri (*n*-propyl)amine as base. 5-Bromopyrimidine **37** was coupled with styrene **333** or *n*-butylacrylate **334**, providing 91% and 85% yield, respectively.

Silicadiphenylphosphinite (SDPP) is another solid support for palladium nanoparticles which was investigated [134]. Its utilization in the Heck coupling reaction between **37** and **334** under the defined conditions (solvent-free, 130°C, *n*-Pr_3N) provided 85% of the desired product.



Scheme 93 Acylation of arenes: Pd-catalyzed vinylation followed by hydrolysis



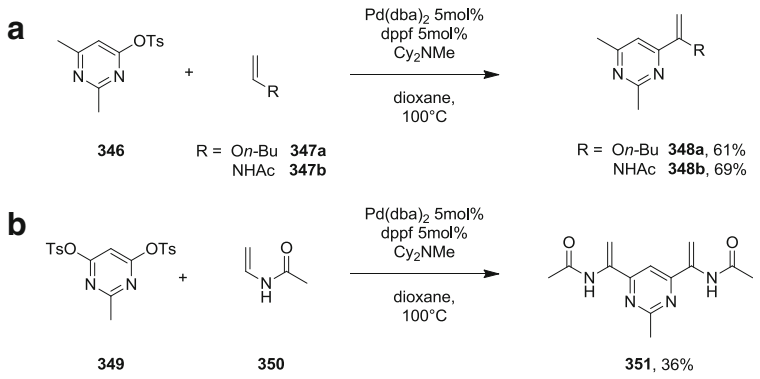
Scheme 94 Trapping of allene-derived Pd-allyl complexes with hydroxylamines

The last investigated support material was agarose [135]. Even though it was possible to lower the temperature to 120°C, a slight drop of the reaction yield in the reaction between **37** with **333** (solvent-free, Et_3N) to 76% was observed. Moreover, significantly longer time was required for the completion of the reaction than in case of gelatin (12 h in case of agarose vs. 200 min in case of gelatin).

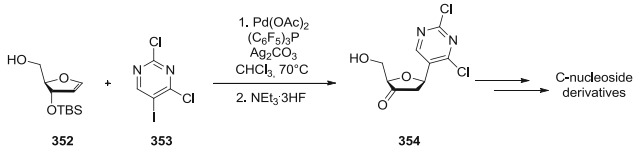
1.5.2 Synthetic Methods

He et al. have developed a method for preparation of acetylated heteroaryls via Heck reaction of heteroaryl bromides with vinyl(*n*-butyl)ether and subsequent acid hydrolysis of the Heck products [136]. Substituted 2-amino-4-bromopyrimidines (**337**) were evaluated as substrates for this transformation. Under the reaction conditions, 75% of desired 5-acetyl-2-(*N*,*N*-dimethylamino)pyrimidine **339a** was isolated. The drop of the yield to 65% (**339b**) was observed when monomethylated 5-bromo-2-(*N*-methylamino)pyrimidine was used. Only traces of the product were detected when 4-bromo-2-aminopyrimidine was coupled (Scheme 93).

Elboray et al. have developed a palladium-catalyzed three-component reaction between (hetero)aryl halides, allenes, and protected hydroxylamines, formally consisting of Heck and Tsuji–Trost allylation [137]. In the first step, (hetero)aryl halide **341** couples with allene **343**, providing η^3-coordinated allylic species **344**, which undergoes a nucleophilic attack of hydroxylamine giving rise to 1,1-disubstituted olefines **345**. Several pyrimidine-based substrates were also submitted to this reaction, providing reaction yields in the range from 76% to 96% (Scheme 94).



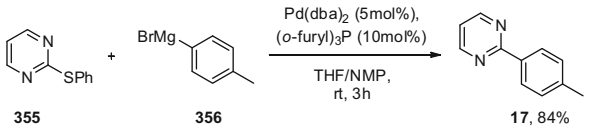
Scheme 95 Vinylation of pyrimidine tosylates



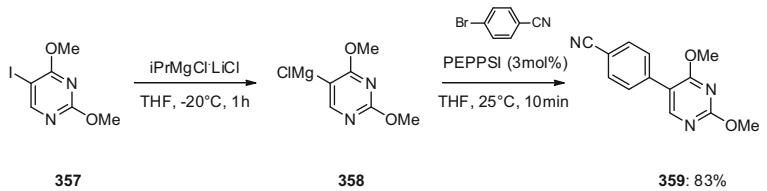
Scheme 96 Arylation of glycals towards artificial C-nucleosides

Skrydstrup and coworkers have investigated regioselective Heck coupling of heteroaryl tosylates with electron-rich olefins [138]. Several pyrimidine derivatives were coupled with electron-rich vinyl(*n*-butyl)ether or *N*-vinylacetamide, using Pd_2dba_3, Cy_2NMe as base, and dppf as ligand in dioxane at 100°C. All the couplings took place on the more substituted olefinic carbon. 2,4-Dimethyl-6-tosylpyrimidine **346** provided 61% of desired product when coupled with vinyl(*n*-butyl)ether **347a** and 69% when *N*-vinylacetamide **347b** was used. 2-Methyl-4,6-ditosylpyrimidine **349** underwent bis-olefination under the reaction conditions, providing product **351** in 36% yield (Scheme 95).

Heck reaction was utilized to synthesize artificial nucleosides by Kubelka et al. [139, 140] (Scheme **96**). Synthesis started with the reaction between 2,4-dichloro-5-iodopyrimidine **353** and 3′-TBS-protected glycal **352**. Under the reaction conditions ($Pd(OAc)_2$, $(C_6F_5)_3P$, Ag_2CO_3 in $CHCl_3$ at 70°C), partial desilylation was observed. Therefore, the Heck product was directly deprotected by the treatment with triethylamine trihydrofluoride. Reaction yielded acceptable 42% (after two steps) and could be successfully upscaled to 5 g. Halopyrimidine **354** was further elaborated towards artificial nucleosides (see also Sect. 1.8.4).



Scheme 97 Desulfidative variant of Kumada coupling



Scheme 98 Kumada coupling of iodopyrimidines, employing *i*-PrMgCl

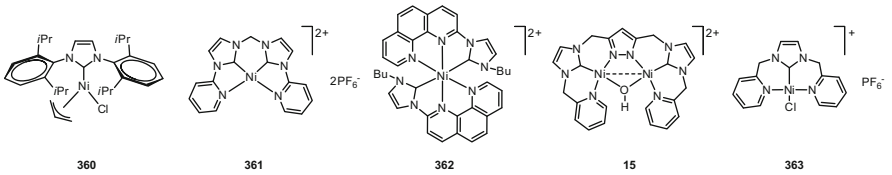
1.6 Pyrimidine in Kumada–Corriu–Tamao Reactions

Van der Eycken and coworkers reported a development of a desulfitative variant of the Kumada coupling reaction [141]. $Pd(dba)_2$/(*o*-furyl)$_3$P efficiently catalyzed the addition of aryl Grignard reagents to thioesters and 2-heteroarylsulfides. 2-Phenylthiopyrimidine **355** reacted smoothly with 4-tolylmagnesium chloride to give the coupling product **17** in 84% yield after 3 h. In contrast to many other desulfitative couplings (i.e., Liebeskind–Srogl coupling [142, 143]), the reaction does not require a Cu source as an additive (Scheme 97).

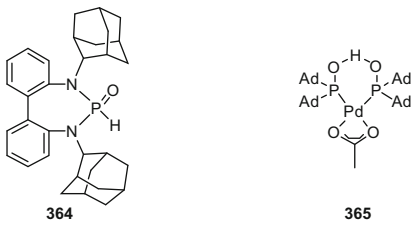
Manolikakes and Knochel found that the rate of the Kumada coupling reaction was greatly enhanced, when reagents derived from *i*-PrMgCl via Mg/I-exchange were used [144]. Following this finding, the role of isopropyl iodide which is formed in the reaction was investigated. The authors reasoned that a change in the mechanism towards a radical mechanism was responsible for the increase in reaction rate. Among other examples, 5-iodo-2,4-dimethoxypyrimidine **357** was transformed into the corresponding Grignard reagent. Coupling with 4-bromobenzonitrile catalyzed by the PEPPSI catalyst (3 mol%) afforded the product **359** in 83% yield after only 10 min at room temperature(Scheme 98).

The complex (IPr)Ni(allyl)Cl **360** was employed as a catalyst for the Kumada coupling of aryl chlorides [145]. The reaction gave excellent yields for a range of products, but 2-chloropyrimidine performed worse than most substrates under the reaction conditions: when reacted with phenyl or tolyl Grignard reagent, it gave 72% or 74% yield, respectively. More importantly, the catalyst also proved to be competent in activating arylethers, but no examples employing pyrimidine were shown.

As a continuation of their work in the Suzuki–Miyaura cross-coupling reaction [146], Xi et al. reported nickel(II) complex **361** of a pyridine-functionalized NHC ligand to be highly active catalysts for the coupling of aryl- and vinyl chlorides in Kumada coupling [147]. Products were obtained in very good to excellent yields after 12 h at room temperature. When 2-chloropyrimidine was reacted with



Scheme 99 New nickel-based complexes, used to catalyze Kumada coupling of pyrimidines



Scheme 100 New phosphine oxide-based ligands

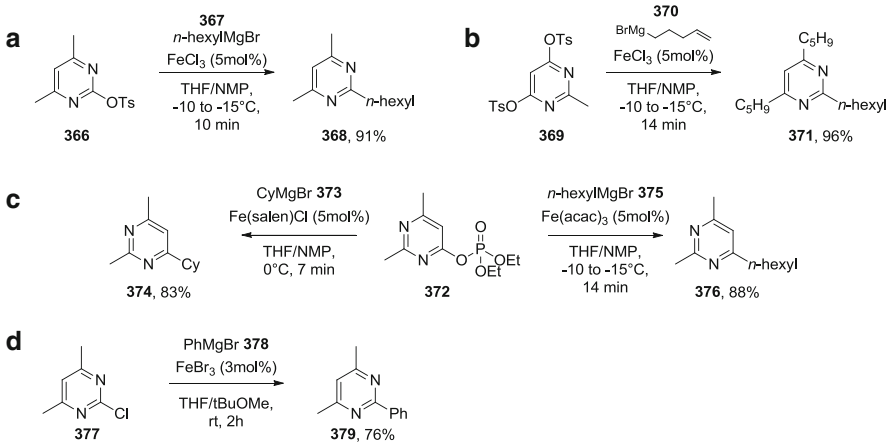
o-tolylmagnesium bromide, 89% of the coupling product could be isolated. Also unsymmetrical pincer complex **362** showed a comparable activity [148]. Binuclear nickel complex **15** proved to be highly active for the coupling of 2-chloropyrimidine with tolylmagnesium chloride [4]. Even the sterically demanding *o*-tolylpyrimidine coupling product could be isolated in quantitative yield after 12 h at rt. Complex **15** also catalyzes the Suzuki–Miyaura coupling reaction (see section "Catalyst Design").

Ni(II)-complex **363**, which was derived from a trinuclear Cu-complex, lead to a further improvement in reaction efficiency, especially for chloro-N-hetercyclic coupling partners: 2-chloropyrimidine gave a quantitative yield of the coupling product when reacted with *p*-tolylmagnesium bromide [149] (Scheme 99).

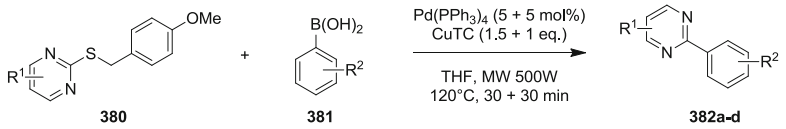
Schulzke and coworkers developed a coupling protocol employing bisadamantylphosphine oxide **364** as ligand which allowed for the coupling of 2-pyridinylmagnesium bromide [150]. Using $Pd(dba)_2$/ligand (1 mol%), good to excellent yields were achieved within 20 h at 60°C in THF. 5-(Pyridin-2-yl) pyrimidine was isolated in 81% yield.

Secondary phosphine oxides (SPOs) **365** (Scheme 100) were also used as air-stable preligands for nickel(II) by Fang and coworkers [151]. During the formation of the active catalyst, the preligand undergoes a P–O hydride shift and forms phosphorous-bound Ni-phosphite complex. Very good to excellent yields were achieved in the coupling of aryl chlorides, fluorides, and tosylates. When 4,6-dichloropyrimidine was reacted with 2 equiv. of phenylmagnesium bromide, the bisarylated product was obtained in 88% yield after 20 h at room temperature.

The group of Skrydstrup reported – among other heterocyclic substrates – the employment of pyrimidine tosylates and phosphonates (**372**) in iron-catalyzed cross-coupling reactions with alkyl Grignard reagents [152]. Coupling occurred at −10 to −15°C within minutes and very good to excellent yields were achieved. As catalyst, either $Fe(acac)_3$, $FeCl_3$, or a Fe-salen complex was employed. Pyrimidine



Scheme 101 Utilization of iron catalysts in Kumada reaction on pyrimidines



382a	R^1 = H	R^2 = 4-OMe	73%
382b	H	4-Me	85%
382c	4,6-dimethoxy	4-OMe	88%
382d	4,6-dimethoxy	4-Me	73%

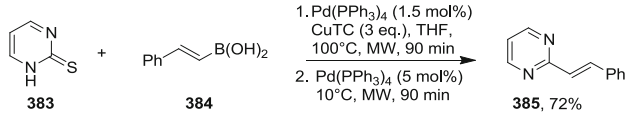
Scheme 102 MW-accelerated LSC utilizing *p*-methoxybenzyl sulfide as leaving group

containing substrates performed particularly well in the reaction. 4,6-Dimethylpyrimidyltosylate **366** reacted with *n*-hexylmagnesium bromide in 91% yield and 2-methylpyrimidin-4,6-ditosylate **369** bis-coupled with 4-pentenylmagnesium bromide in 96% yield (Scheme 101a–c).

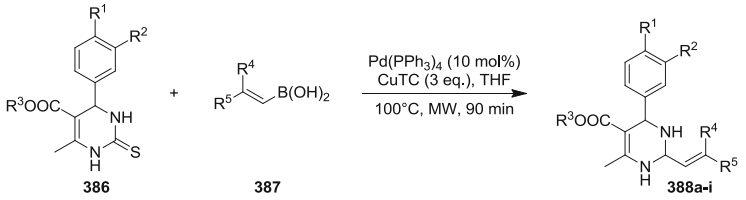
Later, Knochel and coworkers found that in a mixture of THF and MTBE, iron (III)bromide acts as a highly efficient catalyst for the arylation of N-heterocyclic halides [153]. 4,6-Dimethyl-2-phenylpyrimidine **379** was obtained in 76% after 2 h at room temperature, from corresponding 4,6-dimethyl-2-chloropyrimidine and **377** and phenylmagnesium bromide **378**.

1.7 Pyrimidine in Liebeskind–Srogl Coupling Reactions

Modha et al. investigated microwave-accelerated LSC utilizing *p*-methoxybenzyl sulfide as leaving group [154]. Several pyrimidine derivatives were subjected to the reaction conditions ($Pd(PPh_3)_4$, CuTC) and coupled with boronic acids. Reaction provided desired coupling products in yields between 73 and 88% (Scheme 102).



Scheme 103 MW-accelerated desulfitative LSC of pyrimidinethiones and vinylboronic acids



Entry	Dihydropyrimidine	Boronic acid	Product	Yield single mode [%]	Yield multimode [%]
1	($R^1 = R^2 = H$, $R^3 = Et$)	($R^4 = H$, $R^5 = Ph$)	**388a**	65	65
2	($R^1 = R^2 = H$, $R^3 = Et$)	($R^4 = H$, $R^5 = Ph$)	**388b**	64	66
3	($R^1 = R^2 = H$, $R^3 = Et$)	($R^4 = R^5 = Me$)	**388c**	55	60
4	($R^1 = R^2 = Me$, $R^3 = H$)	($R^4 = H$, $R^5 = Ph$)	**388d**	68	65
5	($R^1 = R^2 = Me$, $R^3 = H$)	($R^4 = H$, $R^5 = {}^t Bu$)	**388e**	71	69
6	($R^1 = R^2 = Me$, $R^3 = H$)	($R^4 = R^5 = Me$)	**388f**	61	62
7	($R^1 = H$, $R^2 = OH$, $R^3 = Et$)	($R^4 = H$, $R^5 = Ph$)	**388g**	65	63
8	($R^1 = H$, $R^2 = OH$, $R^3 = Et$)	($R^4 = H$, $R^5 = {}^t Bu$)	**388h**	60	67
9	($R^1 = H$, $R^2 = OH$, $R^3 = Et$)	($R^4 = R^5 = Me$)	**388i**	63	65

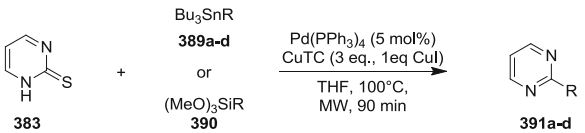
Scheme 104 MW-accelerated desulfitativ LSC of 3,4-dihydropyrimidine-2(1H)-thiones and vinylboronic acids

Another protocol, employing microwave irradiation upon the LSC of pyrimidine, was developed by Arshad et al. [155]. Various vinyl boronic acids could undergo desulfitative coupling with pyrimidinethiones in the presence of palladium catalyst and copper(I) cofactor. Under the optimized conditions, utilizing $Pd(PPh_3)_4$ and CuTC, styrylboronic acid **384** could be coupled with pyrimidine-2(*1H*)-thione **383** in 72% yield (Scheme 103).

Moreover, series of highly substituted 3,4-dihydropyrimidine-2(*1H*)-thiones **386** was examined in the LSC as well. In the reaction with substituted vinyl boronic acids **387**, desired products were obtained in 55–71% when single-mode microwave irradiation was applied and in 60–69% when reaction was carried out in multimode, demonstrating that the application of both modes is feasible and not significant difference is observed (Scheme 104).

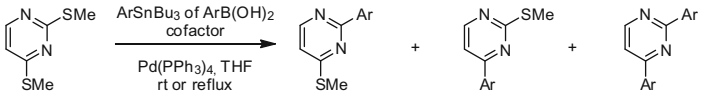
Additionally, pyrimidine-2(*1H*)-thione **383** can undergo Liebeskind–Srogl type coupling with tributylstannanes **389a–d** and trimethoxyphenylsilane **390**. Desired products are obtained in yields between 60 and 80% (Scheme 105).

A reaction with an unusual regioselectivity was reported by Farahat and Boykin [156]. Submitting 2,4-dimethylthiopyrimidine **392** and diverse boronic acids or arylstannanes to the Liebeskind–Srogl conditions ($Pd(PPh_3)_4$, CuTC or CuMeSal) can lead potentially to three different products, 2-arylated **393**, 4-arylated **394**, or



Entry	Reagent	R	Product	Yield [%]
1	**389a**	Ph	**391a**	80
2	**389b**	2-pyridzl	**391b**	72
3	**389c**	2-furyl	**391c**	69
4	**389d**	vinyl	**391d**	63
5	**390**	Ph	**391a**	60

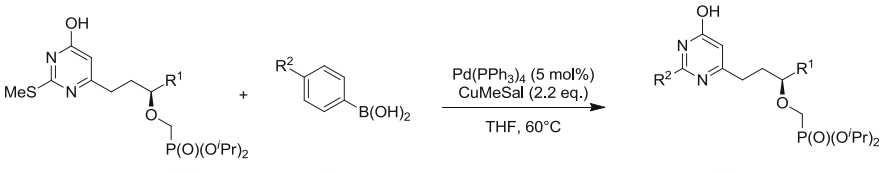
Scheme 105 MW-accelerated desulfitative LSC of pyrimidinethiones and stannanes or silanes



Entry	Reactant	Temperature	Cofactor	**393** [%]	**394** [%]	**395** [%]
1	$PhB(OH)_2$	rt	CuMeSal	55	3	2
2			CuTC	1	0	0
3	4-MeOPhB$(OH)_2$	rt	CuMeSal	57	4	5
4			CuTC	2	0	0
5	4-CNPhB$(OH)_2$	rt	CuMeSal	59	4	5
6			CuTC	2	0	0
7	tributyl(2-furyl)stannan	rt	CuMeSal	63	0	6
8			CuTC	15	0	0
9	tributyl(2-thienyl)stannan	rt	CuMeSal	61	0	5
10			CuTC	20	0	0
11	$PhB(OH)_2$	reflux	CuMeSal	4	0	41
12			CuTC	3	3	49
13	4-MeOPhB$(OH)_2$	reflux	CuMeSal	2	0	70
14			CuTC	5	3	48
15	4-CNPhB$(OH)_2$	reflux	CuMeSal	4	0	69
16			CuTC	4	2	51
17	tributyl(2-furyl)stannan	reflux	CuMeSal	5	0	79
18			CuTC	2	0	55
19	tributyl(2-thienyl)stannan	reflux	CuMeSal	4	0	74
20			CuTC	3	0	52

Scheme 106 Unusual regioselective reaction of bismethylsulfanylated pyrimidines

bisarylated **395**. In spite of the usually observed enhanced reactivity of position four over position two in pyrimidine, the reaction provided mostly 2-arylated products at rt. When the temperature was increased to reflux (in THF), 2,4-bisarylated products were formed (Scheme 106).



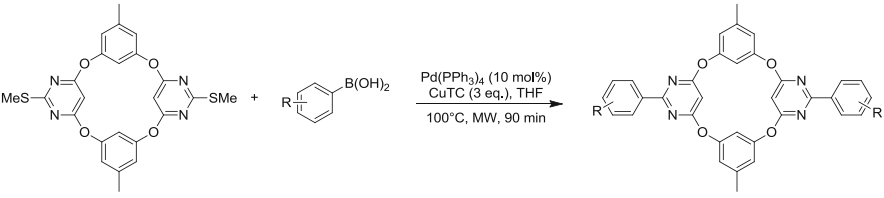
R = H, **396a**
R = *(R)*-CH_2OH **396b**

397a-l

398a-l

Entry	R^1	R^2	Product	Yield [%]
1	H	H	**398a**	89
2	H	F	**398b**	64
3	H	OMe	**398c**	57
4	H	NO_2	**398d**	56
5	H	CF_3	**398e**	50
6	H	OH	**398f**	41
7	*(R)*-CH_2OH	H	**398g**	75
8	*(R)*-CH2OH	F	**398h**	54
9	*(R)*-CH2OH	OMe	**398i**	60
10	*(R)*-CH2OH	NO_2	**398j**	41
11	*(R)*-CH2OH	CF_3	**398k**	65
12	*(R)*-CH2OH	OH	**398l**	63

Scheme 107 Synthesis of acyclic nucleoside phosphonates via LSC



399

400a R = 4-^{t}Bu
400b 4-OMe
400c 4-CN
400d 2-Me

401a R = 4-^{t}Bu 68%
401b 4-OMe 78%
401c 4-CN 75%
401d 2-Me 76%

Scheme 108 Decoration of oxacalix[2]arene[2]pyrimidines via LSC

An efficient synthesis of acyclic nucleoside phosphonates via LSC was reported by Brehova et al. [157]. Optimization of the reaction conditions revealed CuMeSal to be superior to CuTC. Under optimized conditions, intermediates **396a**, **b** were coupled with several phenylboronic acid derivatives providing desired phosphonate esters in yields up to 89% (Scheme 107). Subsequent hydrolysis led to the desired phosphonates.

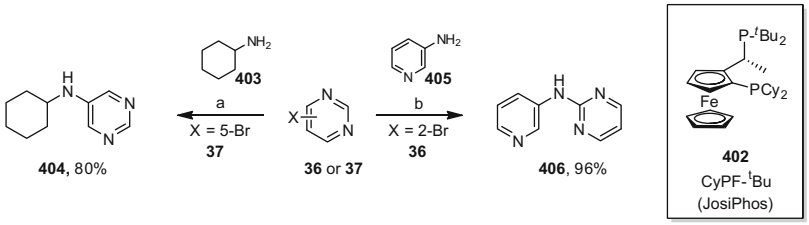
Post-macrocyclization functionalization of oxacalix[2]arene[2]pyrimidines via LSC was investigated by Van Rosson et al. [158]. Under the standard conditions employing $Pd(PPh_3)_4$ and CuTC, pyrimidine-based macrocycle **399** can be decorated with various phenylboronic acids with yields between 68 and 78% (Scheme 108).

1.8 C–Heteroatom Coupling

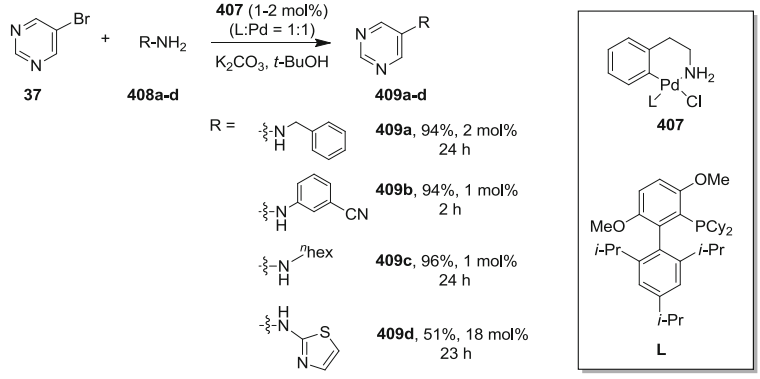
1.8.1 Ligand Promoted C–N Couplings on Pyrimidine

Shen et al. reported the C–N coupling of aliphatic amines with different heteroaryl halides in their comprehensive study of CyPF-*t*Bu ligand (**402**, also called JosiPhos) [159]. In general, JosiPhos, in combination with $Pd(OAc)_2$, mediated a coupling of various substrates with strikingly low catalyst loadings, as low as 0.0005 mol%. However, upon the couplings of 2- or 5-bromopyrimidines (**36 or 37**) with different electrophiles, catalyst loading had to be increased to 1 mol%. Coupled products **404** and **406** were obtained in yields up to 96% (Scheme 109).

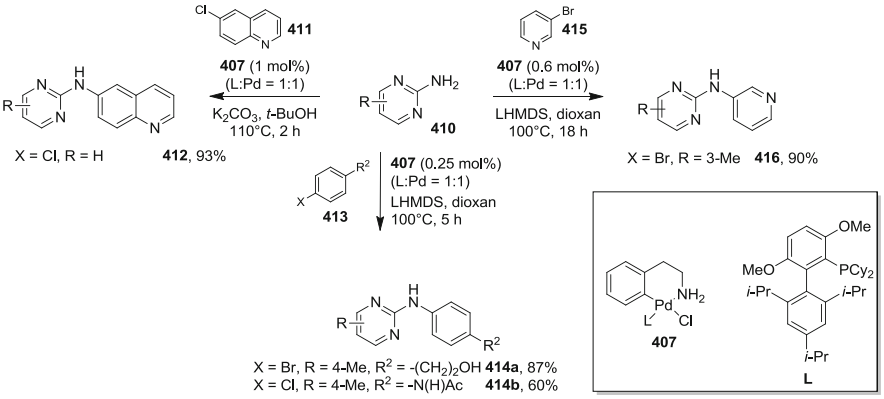
Several phosphine ligands were developed in the group of Buchwald and tested in a variety of C–N couplings. Two new ligands were reported BrettPhos (Schemes 110 and 111) for couplings with primary amines and RuPhos for coupling with secondary amines (Scheme 112). Their application included coupling of pyrimidines with both aliphatic and aromatic amines [160]. A general advantage of these ligands over JosiPhos, reported by Hartwig, is a increase of reaction rate. Nevertheless, direct comparison of the three ligands in the C–N coupling on pyrimidines (and also in general) is not possible due to the fact that different



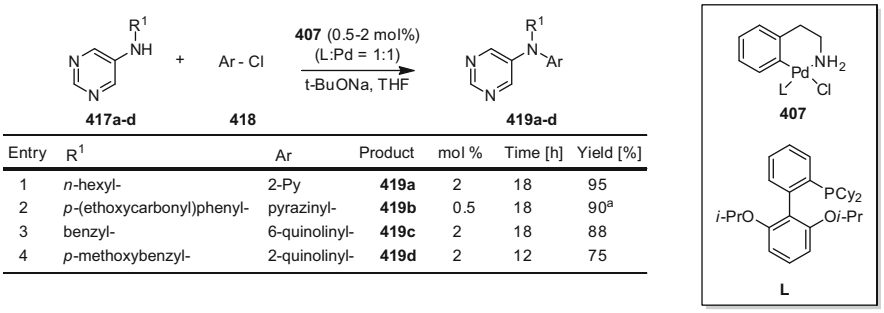
Scheme 109 Structure and application of Hartwig's JosiPhos (*a*) $Pd(OAc)_2$ (1 mmol%), CyPF-*t*Bu (1 mol%), 100°C or 110°C, 48 h or 20 h



Scheme 110 Structure and application of Buchwald's BrettPhos



Scheme 111 Application of Buchwald's BrettPhos



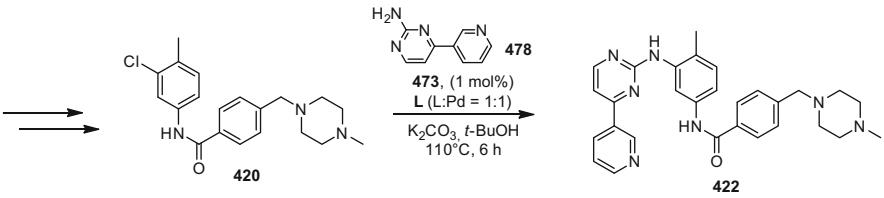
Entry	R^1	Ar	Product	mol %	Time [h]	Yield [%]
1	*n*-hexyl-	2-Py	**419a**	2	18	95
2	*p*-(ethoxycarbonyl)phenyl-	pyrazinyl-	**419b**	0.5	18	90[a]
3	benzyl-	6-quinolinyl-	**419c**	2	18	88
4	*p*-methoxybenzyl-	2-quinolinyl-	**419d**	2	12	75

Scheme 112 Structure and application of Buchwald's RuPhos, [a]Cs_2CO_3/^{t}BuOH

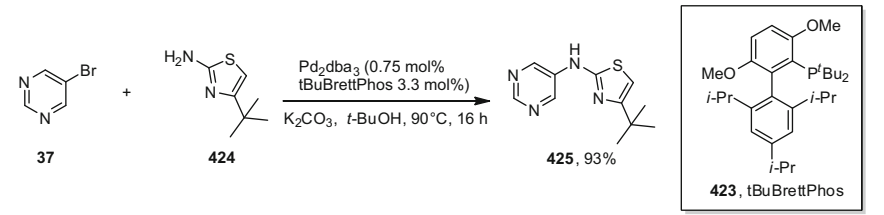
substrates and conditions were applied. Moreover, when aliphatic benzylamine **408a** and *n*-hexylamine **408c** were utilized in the coupling with 5-bromopyrimidine **37** (Scheme 110), shortening of the reaction time to 24 h could be possible only at the cost of increasing the catalyst loading to 2 mol%. The reaction yielded 94% and 96% of desired products, respectively. When aromatic 3-cyanoaniline **408b** was used, 94% of product was isolated after 2 h, utilizing 1 mol% of catalyst. Coupling with 2-aminothiazole **408d** was also possible, but very difficult. 18 mol% of catalyst was necessary and the reaction provided only 51% of desired 5-*N*-(2-aminothizolo)pyrimidine **409d** (Scheme 110).

Additionally, 2-aminopyrimidine and 4-methyl-2-aminopyrimidine were investigated as nucleophiles. 0.25–1 mol% of catalyst loading was required for the coupling with different aryl chlorides. In the range of 2–18 h, reaction afforded 60–93% of desired products (Scheme 111).

A series of secondary amines (**417a-d**) was investigated as well [160]. They were coupled with different heteroaryl chlorides, providing yields from 75 to 95% with catalyst loadings in the range from 0.5 to 2 mol%. Reactions were completed within 12–18 h (Scheme 112).



Scheme 113 Synthesis of Imatinib (Gleevec®) using Buchwald's BrettPhos



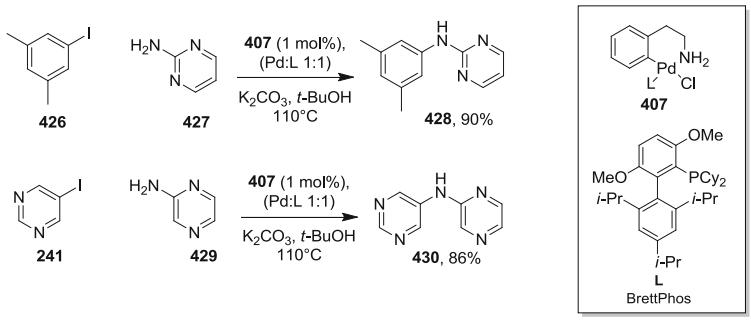
Scheme 114 *t*-BuBrettPhos as a ligand for aminothiazolization of pyrimidine

Finally, the methodology was applied to the synthesis of Imatinib (Gleevec®) **422**, a compound used for the treatment of chronic myelogenous leukemia (Scheme 113).

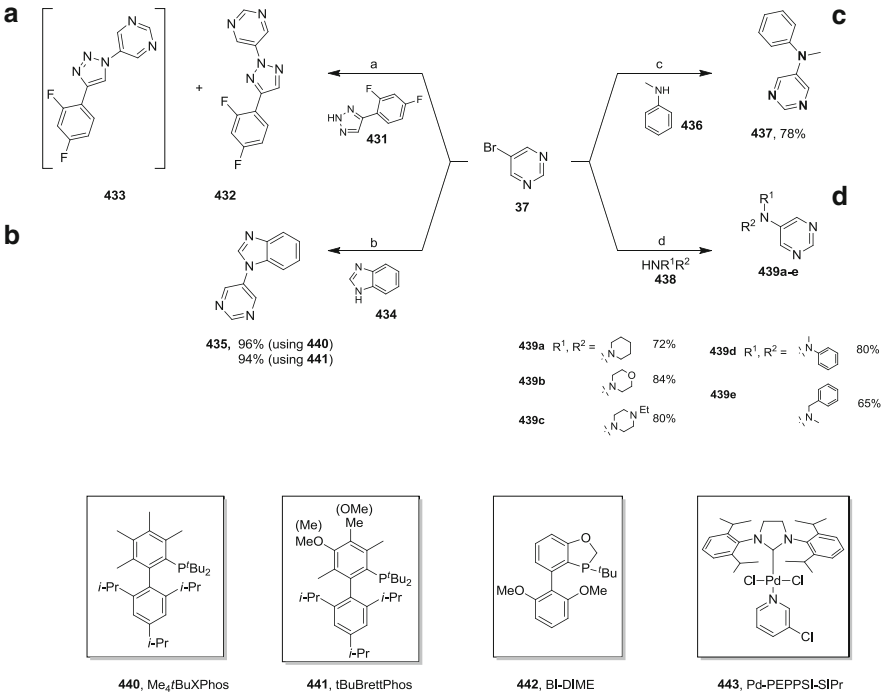
Another report from Buchwald's laboratory describes *N*-arylation of 2-aminothiazoles utilizing *t*-BuBrettPhos **423**, [161] a ligand initially developed for C–N coupling of amides [162]. The pK_A values of 2-aminothiazoles are closer to amides than to anilines or other (hetero)aromatic amines; therefore, application of **423** proved to be beneficial. Coupling of 4-*t*-butyl-2-aminothiazole **424** with 5-bromopyrimidine **37** catalyzed by $Pd(OAc)_2$ and **423** in water afforded 93% of product (Scheme 114).

Fors et al. showed that BrettPhos can be applied successfully for C–N bond-forming processes, starting from various amines and aryliodides [163]. It has to be mentioned that in Pd-catalyzed C–C cross-coupling reactions, (hetero)aryliodides are the most reactive aryl halides, whereas the same substrates are the least reactive in Pd-catalyzed C–N couplings. Employing BrettPhos turned out to be beneficial, and its performance is superior to the performance of some other common Buchwald-type ligands (DavePhos, XPhos, and RuPhos). Under the optimized conditions, 2-aminopyrimidine **427** coupled with 3,5-dimethyliodobenzene **426** in 90% yield. Employing 5-iodopyrimidine **241** in the coupling with aminopyrazine **430** led to the formation of the desired product in 86% yield (Scheme 115).

Udea et al. developed a method for regioselective (hetero)arylation of triazoles [164]. In the presence of Pd_2dba_3, Me$_4$*t*BuXPhos **440**, and K_3PO_4, coupling between 5-bromopyrimidine **37** and 4-(2,4-difluorophenyl)-2*H*-1,2,3-triazole **431**



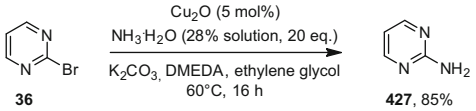
Scheme 115 Utilization of BrettPhos for C–N coupling of aryliodides



Scheme 116 (*a*) Pd_2dba_3 (0.5 mol%), Me_4tBuXPhos (**440**, 1.0 mol%), K_3PO_4, toluene, 120°C, 5 h; (*b*) Pd_2dba_3 (0.5 mol% Pd:L 1:1), Me_4tBuXPhos (**440**) or Me_3(OMe)tBuXPhos (**441**), K_3PO_4, toluene/dioxane (5:1), 120°C, 5 h; (*c*) Pd_2dba_3 (2.5 mol%), BI-DIME (**442**, 10 mol%), NaOt-Bu, toluene, 110°C, 20 h; (*d*) Pd-PEPPSI-SIPr (**443**, 4 mol%) , Cs_2CO_3, DME, 80°C, 24 h

was realized in 90% yield with 98:2 ratio of N^2 to N^1 substituted triazole (**432**:**433**, Scheme 116a).

In the report of Ueda et al., the synthesis and application of Me_3(OMe)*t*BuXPhos (**441**) is discussed [165]. **441** is described as a surrogate for Me_4*t*BuXPhos (**440**) previously reported as efficient ligand for various C–N bond formations.



Scheme 117 Copper-catalyzed amination of 2-bromopyridine using aqueous ammonium

The performance of both ligands was comparable for all examined examples, involving the coupling of **37** with benzimidazole **434** (96% using **440** and 94% using **441**, Scheme 116b). The advantage of the new ligand **441** is a better availability of the precursors for its synthesis.

Rodriguez et al. described the synthesis and application of several oxaphosphole-based monophosphorus ligands [166]. Among them, ligand **442** shown excellent efficiency in C–N coupling of sterically hindered starting materials with low catalyst loadings (0.05–2.5 mol% Pd_2dba_3 and 0.3–10 mol% ligand). Reaction between **37** and *N*-methylaniline **436** was carried out as well. Herein, 2.5 mol% of catalyst together with 10 mol% of ligand were necessary, giving the final product **437** in 78% yield (Scheme 116c).

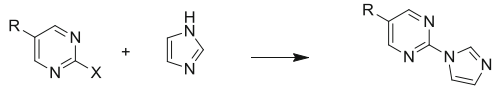
N-heterocyclic carbens proved to be very successful alternatives to phosphine ligands for various kinds of cross-couplings such as Suzuki–Miyaura or Buchwald–Hartwig amination [167]. Organ et al. [168] synthesized and characterized a series of new Pd-NHC precatalysts, where **443** (Pd-PEPPSI-*i*-Pr) showed the best performance in Buchwald–Hartwig amination. **37** was coupled with several secondary amines. Using 4 mol% of precatalyst, the corresponding coupling products were obtained in yields between 65 and 84% in 24 h at 80°C (Scheme 116d).

Several ligand classes were developed for a copper metal center. Elmkaddem et al. reported copper-catalyzed amination of 2-bromopyridine **36** using aqueous ammonium [169]. Employing Cu_2O and bidentate dimethylethylenediamine (DMEDA) as ligand, they were able to convert **36** into 2-aminopyrimidine **427** in 85% yield under relatively mild conditions (Scheme 117).

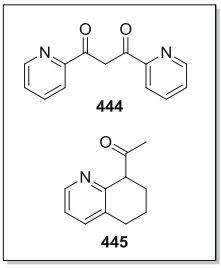
Different ligands with similar structural features, containing a pyridine moiety in close proximity to carbonyl function, were reported by Xi et al. [170] and Chen et al. [171]. Xi et al. utilized pyridine-functionalized 1,3-diketone (**444**) as a ligand for CuI. Such a catalytic system turned out to be a powerful tool for an introduction of different arenes and/or heteroarenes into the position 1 of imidazole. Employing 2-chloropyrimidine provided 96% of 2-*N*-imidazolopyrimidine **448a** (Scheme 118, entry 1). Among the tested substrates, 2-chloropyrimidine belonged to the best-performing (hetero)arens, even comparable to (hetero)aryl bromides. Coupling products served as precursors for the synthesis of NHC as ligands for a metal center.

Chen et al. investigated **445** as a ligand for copper (I) bromide. Application of such a catalytic system on the reaction between imidazole **447** and 5-chloro-2-bromopyrimidine provided 76% of 5-chloro-2-*N*-imidazolopyrimidine **448b** (Scheme 118, entry 2).

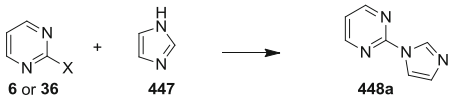
Cao et al. [172]. reported a catalytic system, based on CuI and hexamethyltetramine. This allowed the formation of 2-*N*-imidazolopyrimidine **448a** from



Entry	R	X	Ligand	Conditions	Product	Yield [%]
1	H	Cl	**444**	a	**448a**	96
2	Cl	Br	**445**	b	**448b**	76



Scheme 118 Ligands for copper metal center for an effective Ullmann-type amination. (*a*) CuI (10 mol%), **446** (10 mol%), K_2CO_3, DMF, 110°C, 24 h, under N_2; (*b*) CuBr (5 mol%), 446 (10 mol %), Cs_2CO_3, DMSO, 60°C, 5 h, under N_2



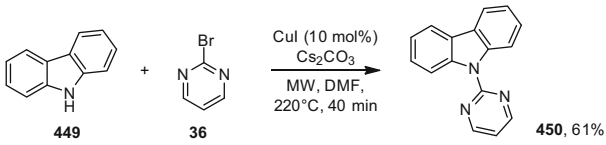
Entry	X	Product	Ligand	Conditions	Yield [%]
1	Cl	**448a**	HMTA	a	96
2	Cl	**448a**	D-Glucseamine	b	95
3	Br	**448a**	per-6-ABCD	c	98

Scheme 119 Amination of pyrimidine, utilizing nanoparticles on solid support, (*a*) CuI (5 mol%), HMTA (5 mol%), K_2CO_3, DMF, 140°C, 20 h; (*b*) CuI (20 mol%), D-Glucosamine (40 mol%), Cs_2CO_3, 110°C, 24 h; (*c*) CuI (20 mol%), per-6-ABCD (10 mol%), K_2CO_3, DMSO, 110°C, 24 h

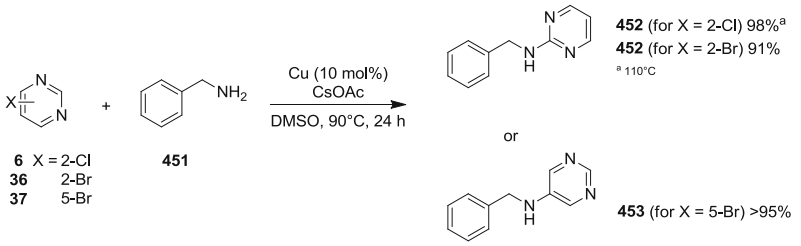
2-chloropyrimidene and imidazole in very good 96% yield. 5 mol% of CuCl and the additive were necessary, and compared to other tested substrates, 2-chloropyrimidine gave very good results (Scheme 119, entry 1).

Natural sugars or sugar derivatives were examined as environmentally friendly ligands for *N*-arylation of imidazoles by Cheng et al. [173]. Among the investigated catalytic systems CuI/D-Glucosamine promoted *N*-arylation most efficiently. Coupling between 2-chloropyrimidine with imidazole, catalyzed with this system, provided 95% of desired 2-imidazolopyrimidine **448a** (Scheme 119, entry 2).

Per-6-amino-B-cyclodextrine (per-6-ABCD) was reported by Surech and Pitchumani as another sugar-based ligand capable of enhancing the performance of copper catalysts [174]. Utilizing CuI/per-6-ABCD, 5-bromopyrimidine was coupled to position 1 of imidazole in 98% yield. Besides its role as a ligand for the copper metal center, per-6-ABCD acts as a cavity for transitory binding of the substrate as well as via combined electrostatic and hydrophobic interactions (Scheme 119, entry 3).



Scheme 120 Ligand-free *N*-(hetero)arylation of carbazole



Scheme 121 Cu-catalyzed ligand-free amination of pyrimidine

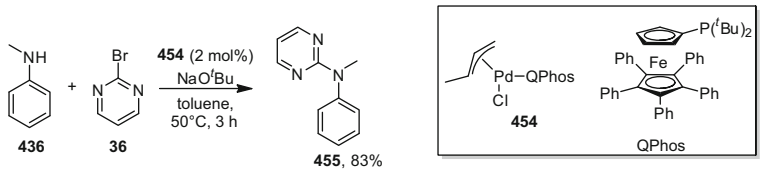
1.8.2 Ligand-Free Copper-Catalyzed C–N Coupling of Pyrimidines

Several examples of ligand-free copper-catalyzed C–N bond-forming processes were described as well. Kwon et al. reported CuI-catalyzed, ligand-free microwave-accelerated *N*-(hetero)arylation of carbazoles with various (hetero) aryl halides [175]. A general drawback of the reported method is a very high temperature (220°C) and still long reaction time. Coupling of carbazole **449** with 2-bromopyrimidine **36** provided 61% of **450**. Compared to other investigated examples within the study, 2-bromopyrimidine turned out to be rather a difficult substrate (Scheme 120).

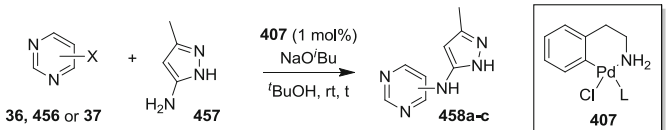
Another example of copper-catalyzed, ligand-free C–N coupling was reported by Bolm and coworkers [176]. They investigated coupling of various primary and secondary aliphatic or aromatic amines with heteroaryl halides. In this case, reactions were heated conventionally, resulting in prolongation of reaction times (24 h). However, transformations could be carried out at significantly lower temperatures (90°C in most cases). Relevant examples involve is coupling of benzylamine **451** with 2-chloropyrimidine 6 (required 110°C), 2-bromopyrimidine **36**, and 5-bromopyrimidine **37**. The corresponding products could be isolated in 98%, 91%, and >95% yield, respectively (Scheme 121).

1.8.3 Other Catalytic Systems

Seechurn et al. have examined a series of π-allyl-based palladium complexes (most of them showing good air stability) in C–C/N couplings [177]. They found complex **454** as the best-performing catalyst and carried out a wide substrate scope investigation. Coupling of 2-bromopyrimidine **36** with *N*-methylaniline **436** provided 83%



Scheme 122 New palladium complex for Buchwald–Hartwig amination



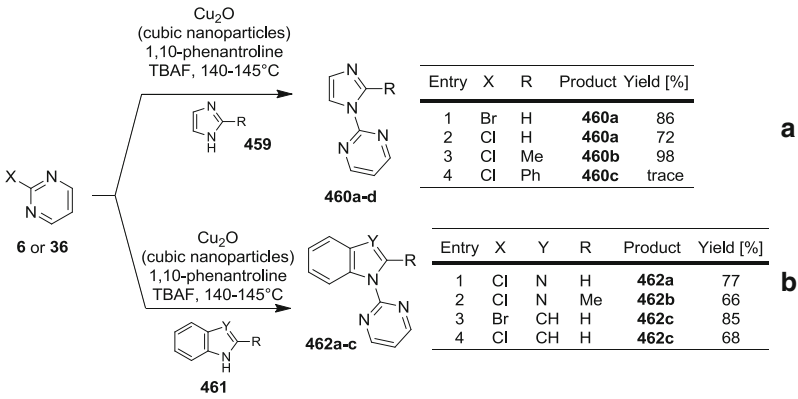
Entry	Starting material	X	Amine position	Time [h]	Product	Yield [%]
1	**36**	2-Br	2	6	**458a**	61
2	**465**	4-Br	4	6	**458b**	0
3	**37**	5-Br	5	4	**458c**	70

Scheme 123 Buchwald–Hartwig amination of pyrimidine, utilizing palladacycle 407 with *t*BuXPhos as the ligand

of the coupling product **455** using 2 mol% of the complex. The reaction could be carried out at relatively mild conditions, requiring only 50°C and 3 h (Scheme 122).

3-Methyl-5-aminopyrazole **457** can be coupled with 2-, 4-, and 5-bromopyrimidine, employing precatalyst **407** in combination with *t*BuXPhos, NaO*t*-Bu in *t*-butanol, as reported by Waring et al. [178]. Reaction takes place at room temperature. While coupling of 2- and 5-bromoryrimidine proceeded in good yields (61 and 70%, resp.), 4-bromopyrimidine did not undergo the desired transformation at all (Scheme 123).

Cubic copper(I) oxide nanoparticles turned out to be a useful catalytic system for C–N bond-forming transformations in combination with 1,10-phenantroline [179]. Series of imidazole and indole derivatives were coupled with either 2-bromo- or 2-chloropyrimidine (**36** or **6**). 2-bromopyrimidine generally performed better. Reaction between imidazole and 2-bromopyrimidine **36** yielded 86% of biaryl, whereas 2-chloropyrimidine afforded only 72% of coupling product (Scheme 124a, entries 1 and 2). A methyl group in position 2 of imidazole had a positive influence on the reaction with **6**, and the coupling product **460b** was obtained in 98% (Scheme 124a, entry 3). In the case of 2-phenylimidazole, only traces of product were detected (Scheme 124a, entry 4). A fused benzene ring as in benzimidazole did not influence the reaction significantly (77% in the coupling with **6**, Scheme 124b, entry 1). Switching to *N*-methyl-benzimidazole gave a notably lower yield of 66% (Scheme 124b, entry 2). Employing indole provided good results as well as giving 85% and 68% yield in reactions with 2-bromo- and 2-chloropyrimidine, respectively (Scheme 124b, entries 3 and 4).



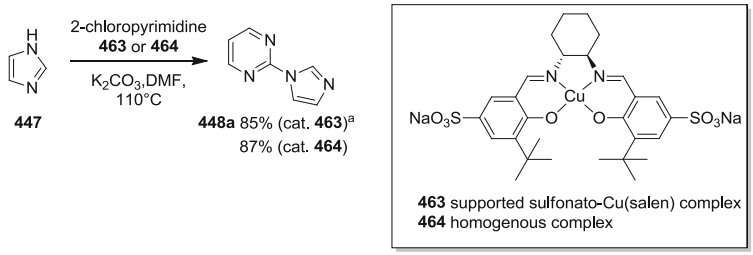
Entry	X	R	Product	Yield [%]
1	Br	H	**460a**	86
2	Cl	H	**460a**	72
3	Cl	Me	**460b**	98
4	Cl	Ph	**460c**	trace

a

Entry	X	Y	R	Product	Yield [%]
1	Cl	N	H	**462a**	77
2	Cl	N	Me	**462b**	66
3	Br	CH	H	**462c**	85
4	Cl	CH	H	**462c**	68

b

Scheme 124 Utilization of copper oxide nanoparticles on C–N coupling involving pyrimidine



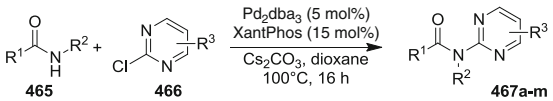
Scheme 125 New copper complex and its utilization in Ullmann-type reaction. [a]Stated yield after the third catalytic cycle, after the recovery by filtration

Kantam et al. reported a Merrifield resin-supported sulfonato-Cu(salen) complex (**463** and **464**) for the C–N coupling reactions of (hetero)aryl chlorides [180]. Applying this catalytic system to the reaction between 2-chloropyrimidine and imidazole led to the formation of the desired product **448a** in 85% yield (third cycle after recovery by filtration). At 110°C, with 1 mol% of the catalyst, the reaction was finished in 3 h. For comparison, the corresponding homogeneous reaction with unsupported catalyst gave 87% yield (Scheme 125).

1.8.4 Miscellaneous C–N Couplings on Pyrimidines

Vimolratana et al. investigated palladium-catalyzed introduction of various amides into position 2 of 2-chloropyrimidine [181]. Employing bidentate ligands turned out to be crucial, and particularly XantPhos provided an excellent yield of 94% in the coupling reaction between benzamide and 2-chloropyrimidine (Scheme 126, entry

Scheme 126 Coupling of amides and 2-chloropyrimidine



465 466 467a-m

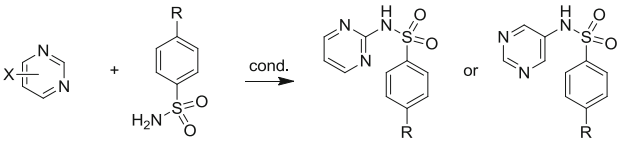
Entry	R^1	R^2	R^3	Product	Yield [%]
1	Ph	H	H	**467a**	94 (71)[a]
2	*p*-F_3C-phenyl	H	H	**467b**	71
3	*p*-MeO-phenyl	H	H	**467c**	87
4	*o*-tolyl	H	H	**467d**	80
5	Me	H	H	**467e**	91
6	^{t}Bu	H	H	**467f**	96
7			H	**467g**	93
8	Me	Me	H	**467h**	38
9	Ph	Me	H	**467i**	32
10	Ph	H	5-Et	**467j**	65
11	Ph	H	4-CF_3	**467k**	96
13	Ph	H	4-OMe	**467l**	82
13	Ph	H	4-Me	**467m**	27

1). A series of primary (entries 1–6, 10–13) and secondary (entries 7–9), aromatic (entries 1–4, 9–13) and aliphatic (entries 5–8) amides were examined. Notably, both electron-rich and electron-deficient aromatic amides coupled efficiently (entries 2–4). Also primary aliphatic amides provided good results (entries 5–6). Cyclic pyrrolidin-2-one underwent coupling smoothly as well, providing **467g** in 93% (entry 7). However, the coupling of acyclic secondary amides suffered from lower yields (entries 8–9). Variation of the halopyrimidine component was permitted as well, but 2-bromopyrimidine provided a lower yield when coupled to benzamide (71% vs. 94% of **467a**, entry 1). Both electron-rich and electron-deficient pyrimidines were well accepted (entries 9–13).

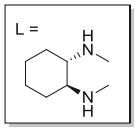
Sulfonamides are particularly important functionalities in pharmaceutical industry. Several reports were published, dealing with metal-catalyzed C–N cross-coupling reactions between (hetero)aryl halides and sulfonamides as an alternative to the commonly applied coupling of sulfonylchlorides with aromatic amines.

In 2010 Baffoe et al. published a copper-catalyzed Ullman-type reaction between various (hetero)aryl bromides and different sulfonamides (Scheme 127, entries 1 and 3) [182]. Among the tested substrates, 2-bromopyrimidine and 4-bromopyrimidine coupled with rather poor yields, providing 35% of **469a** and 60% of **470** in respective manner. Wang et al. reported coupling between 2-bromopyrimidine and benzensulfonamide catalyzed by CuI/DMEDA catalytic system [183]. In this case, the coupling product **469b** was obtained in 86% yield (Scheme 127, entry 2).

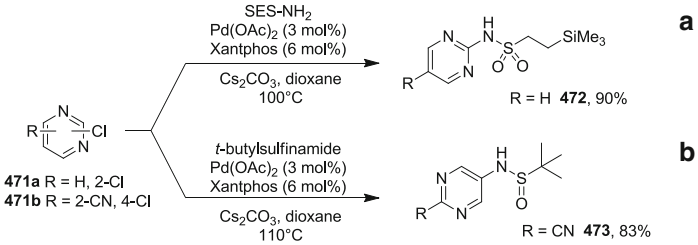
Anjanappa et al. investigated palladium-catalyzed 2-(trimethylsilyl) ethanesulfonyl (SES-NH_2) amidation of (hetero)arenes [184]. SES-NH_2 can be used as an ammonia surrogate, since it can be easily cleaved to liberate free amine by reaction with fluoride ions. Applying $Pd(OAc)_2$ and XantPhos as ligand,



Entry	X	R	Conditions	Product	Yield [%]
1	2-Br	H	a	**469a**	35[a]
2	2-Br	Me	b	**469b**	86[b]
3	4-Br	H	a	**470**	60[a]



Scheme 127 Decoration of sulfonamides via Ullmann-type reaction. (*a*) CuI (5 mol%), DMEDA (0.5 eq.), K_2CO_3, rt; (*b*) CuI (15 mol%), L (30 mol%), K_2CO_3, DMF, 100°C



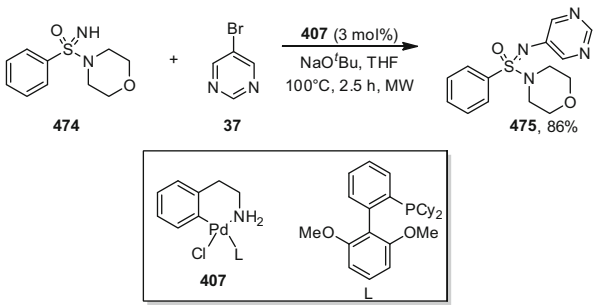
Scheme 128 Pd-catalyzed amination using ammonia surrogates

introduction of SES-NH_2 into position 2 of 2-chlropyrimidine provided 90% of product **472** (Scheme 128a).

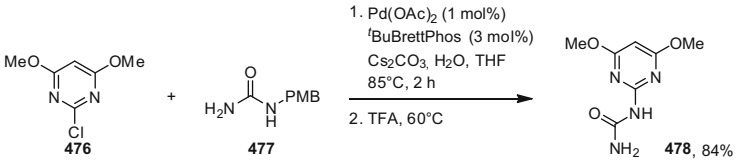
Another ammonium surrogate is *t*-butylsulfinamide which was developed in the same research group [185]. In this moiety, the central sulfur atom occurs in oxidation state two lower than in sulfonamides. Anjanappa et al. have developed palladium-catalyzed C–N coupling between various (hetero)aryl halides and *t*-butylsulfinamide, allowing an easy introduction of divers (hetero)aryls. Reaction with 2-cyano-5-chloropyrimidine provided 83% of desired product **473** (Scheme 128b).

Sulfonimidamides are aza analogs of sulfonamides, in which one oxygen atom is replaced by nitrogen. This enables further derivatization on the additional nitrogen atom. Arvidsson and coworkers have described a synthesis of sulfonimidamides and developed a method to arylate the nitrogen atom via palladium-catalyzed C–N coupling [186]. Employing precatalyst **407** (L=RuPhos), coupling between sulfonimidamide **474** and 5-bromopyrimidine proceeded with 86% yield (Scheme 129).

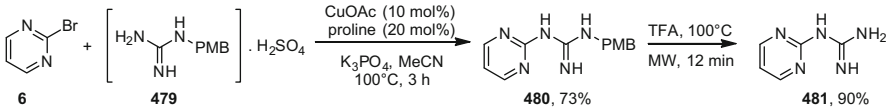
A method for preparation of unsymmetrically *N*,*N*-diarylated ureas was described by Breitler et al. [187]. The process comprises of a one-pot Pd-catalyzed arylation/deprotection of mono-protected urea, followed by a second arylation. Under the optimized reaction conditions, 2-chloro-4,5-dimethoxypyrimidine **476** and *N*-PMB-urea **477** provided in the coupling/deprotection sequence 84% of the



Scheme 129 Decoration of sulfonimidamides



Scheme 130 Monoarylation o urea via Buchwald–Hartwig amination

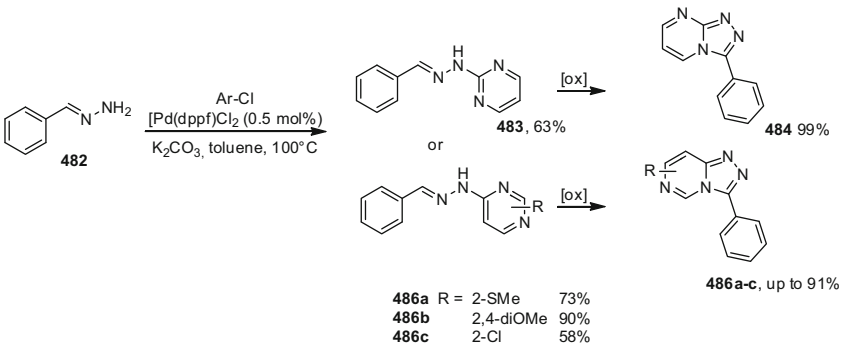


Scheme 131 Monoarylation of guanidine

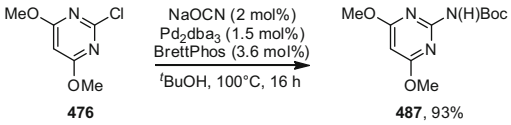
desired mono-arylated product **478** (Scheme 130). Unfortunately, this substrate was not submitted to the further *N*-derivatization.

Monoarylation of guanidine was described by Hammoud et al. [188]. They found a copper catalyst to be superior to palladium catalysts. The combination of CuOAc with proline as additive turned out to be crucial. Employing mono-PMB-guanidine **479** in guanidination of 2-bromopyrimidine provided 73% of the desired product **480** which was successfully deprotected to give **481** (Scheme 131).

Another moiety able to undergo palladium-catalyzed C–N coupling with pyrimidine, is benzaldehyde-derived hydrazone **482**. Such a reaction yields *N*,*N*′-diarylated hydrazones, which under oxidative conditions are able to cyclize to provide triazolopyrimidines [189]. Four pyrimidine derivatives were examined within the substrate scope investigation in the reaction with benzophenone hydrazone **482**. Among them, 2-chloropyrimidine provided 63% of the *N*,*N*′-diarylated hydrazone **483**. 4-chloro-2-methylthio- and 4-chloro-2,6-dimethoxypyrimidine provided 73% and 90% of product respectively (**485a**, **b**, Scheme 132, entries 1 and 2). Coupling of 2,4-dichloropyrimidine proceeded into position 4 giving 58% yield (**485c**, Scheme 132, entry 3). A clear trend for the preference of electron-rich substrates



Scheme 132 Synthesis of triazolopyrimidines via coupling of hydrazones and subsequent oxidation



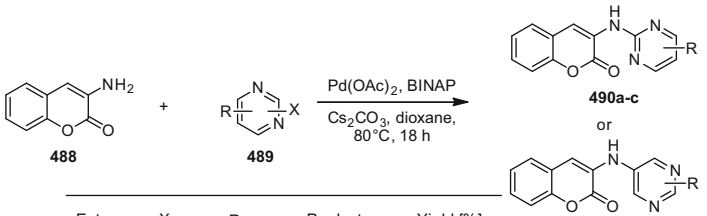
Scheme 133 Unconventional preparation of Boc-protected 2-aminopyrimidine

was observed. All intermediates underwent smooth oxidations towards the corresponding heterocycles in yields between 77 and 99% (Scheme 132).

Carbamates are important functionalities, as they occur in pharmacologically active compounds, polymers and last but not least, they are important protective groups in organic synthesis. Vinogradova et al. have reported one pot multicomponent synthesis of various carbamates via palladium catalyzed reaction of (hetero)arylhalides or triflates with sodium isocyanide and an alcohol as a trapping nucleophile[190]. Employing 2-chloro-4,6-dimethoxypyrimidine **476**, sodium isocyanide and *t*-butanol led to the formation of Boc-protected 2-amino-4,6-dimethoxypyrimidine **487** in 93% yield (Scheme 133).

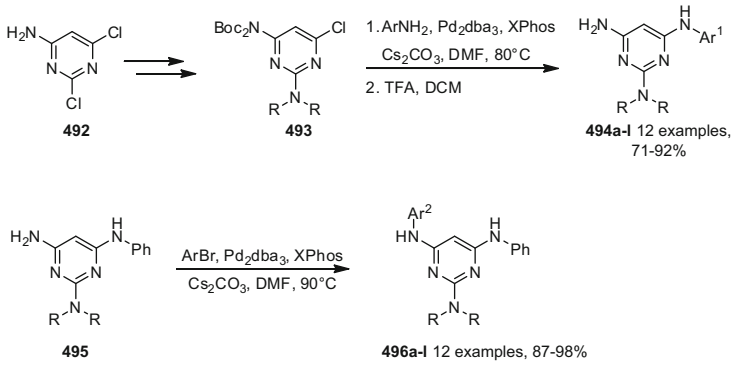
Several reports were published describing the synthesis of organic compounds, utilizing C–N cross-coupling reactions as a key step. Das et al. synthesized a series of 3-(heteroaryl)aminocoumarines via Buchwald–Hartwig amination of 3-aminocoumarin **488** and halopyrimidines [191]. Utilizing $Pd(OAc)_2$ and BINAP as catalytic system and Cs_2CO_3 as base five examples was reported giving the corresponding products in 77–90% yield (Scheme 134).

A practical four step route towards 2-dialkylamino-4-arylamino-6-aminopyrimidines was developed by Li and Rosenau [15]. At a late stage, Buchwald–Hartwig amination into position 6 was carried out before Boc-deprotection gave the final products. Cross-coupling was conducted in the presence of Pd_2dba_3, XPhos, and Cs_2CO_3, giving yields between 71 and 92%. In addition, obtained structures can be utilized in a second Buchwald–Hartwig amination as nucleophiles in reaction with aryl bromides. Applying the same reaction conditions (at slightly



Entry	X	R	Product	Yield [%]
1	2-Br	H	**490a**	77
2	2-Cl	4-OMe	**490b**	88
3	2-Br	4-Me	**490c**	80
4	5-Br	H	**491a**	86
5	5-Cl	5-N(Me)$_2$	**491b**	90

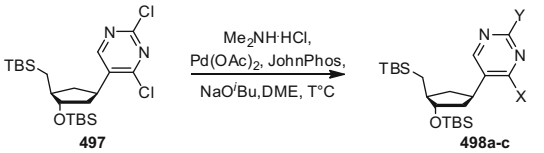
Scheme 134 Decoration of aminocoumarines with pyrimidines



Scheme 135 Synthesis of unsymetric triaminopyrimidines

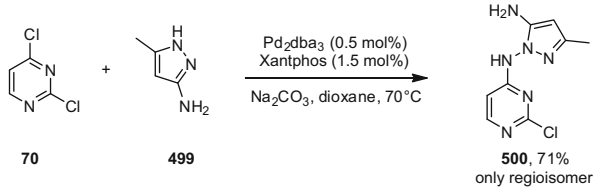
elevated temperature) led to interesting nonsymmetrical diarylaminopyrimidines **496a–l** in yields up to 98% (Scheme 135).

Artificial *C*-nucleosides are an important compound class. Kubelka et al. investigated the synthesis of 2,4-disubstituted pyrimidin-5-yl *C*-2-deoxyribosides via selective functionalization of 2,4-dichloropyrimidin-5-yldeoxyribose or its TBS-protected analog **497** [139]. The substrate was subjected either to conditions suitable for nucleophilic substitution or metal-catalyzed cross-coupling. The selectivity of the transformation is caused by the difference in reactivity of positions 2 and 4 of the pyrimidine ring. A dimethylamino group was introduced via Buchwald–Hartwig amination, utilizing $Pd(OAc)_2$, JohnPhos, and sodium *t*-butanoate (TBS-protected nucleoside was used). Notably, at room temperature, coupling proceeded preferentially into position 4. However, a minor amount of the regioisomer was isolated as well (71% vs. 16% respectively, Scheme 136, entry 1). At higher temperature, the amination took place in both positions giving diaminated product in 84% yield (Scheme 136, entry 2).



Entry	Temperature [°C]	X	Y	Product	Yield [%]
1	rt	$N(Me)_2$	Cl	**498a**	71
		Cl	$N(Me)_2$	**498b**	16
2	80 °C	$N(Me)_2$	$N(Me)_2$	**498c**	84

Scheme 136 Derivatization of 2,4-disubstituted pyrimidin-5-yl *C*-2-deoxyriboses



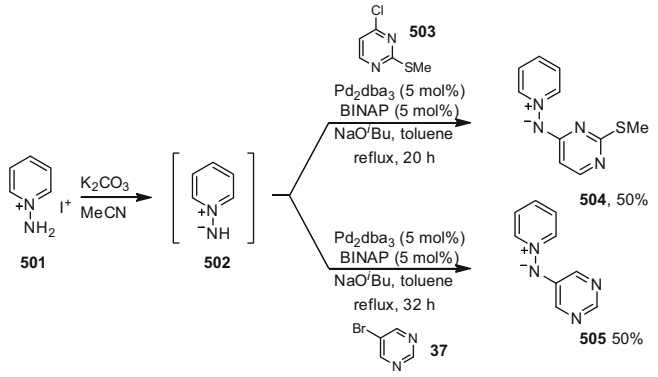
Scheme 137 Regioselective coupling of 2,4-dichloropyrimidine and 3-amino-1*H*-pyrazoles

Shen et al. investigated the regioselectivity of cross-coupling between 2,4-dichloropyrimidine **70** and 3-amino-1*H*-pyrazoles [192]. They discovered that submission of the substrates to cross-coupling conditions (Pd_2dba_3, Xantphos, Na_2CO_3) led to coupling with the endocyclic secondary amino group. It was demonstrated that coupling of 2,4-dichloropyrimidine proceeded exclusively into position 4 of pyrimidine and position 2 of the pyrazole yielding 71% of **500**, (Scheme 137). Alternatively, treatment of reactants with HCl in dioxane led to S_NAr of chloride preferably with the exocyclic primary amino group of 3-amino-1*H*-pyrazole into the position 4 of pyrimidine.

The method for preparation of pyridinium heteroaryl-stabilized amidines based on palladium-catalyzed C–N cross-coupling utilizing Pd_2dba_3, BINAP, and NaO*t*-Bu was developed by Cordoba et al. [193]. *N*-aminopyridinium iodide **501** and 4-methyl-2-metylthiopyrimidine **503** or 5-bromopyrimidine **37** provided 50% of the desired products **504** and **505** in both cases (Scheme 138).

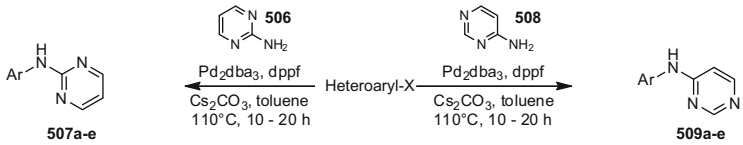
A method to couple electron-deficient heteroaryl amines with heteroaryl halides was developed in the group of Yin [194]. Optimization of reaction conditions revealed that the combination of Pd_2dba_3 with bidentate dppf ligand and Cs_2CO_3 in toluene was the best condition. In the study, pyrimidines were employed as electrophiles and nucleophiles as well. Aminopyrimidines **506** and **508** were coupled with different heteroaryls, including pyrimidine halides, providing coupling products in 62–87% yield (Scheme 139a, b).

Lach et al. developed a general route to unsubstituted *N*-(heteroaryl)aryl-aminobenzensulfonamides, relying on aminobenzensulfonamide and (hetero)aryl halides coupling [195]. The synthetic route consists of synthesis of bis-PMB protected 3- or 4-aminobenzensulfonamide **514** (PMB group protects the



Scheme 138 Preparation of pyridinium heteroaryl-stabilized amidines via Pd-catalyzed C–N cross-coupling

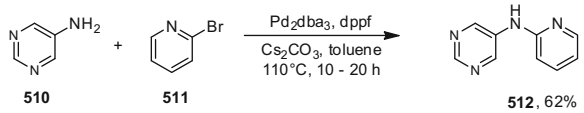
a



Entry	Heteroaryl	X	Product	Yield [%]
1		Br	**507a**	86
2		Cl	**507a**	82
3		Cl	507b	76
4		Br	507c	63
5		Cl	**507d**	83
6		Br	507e	78

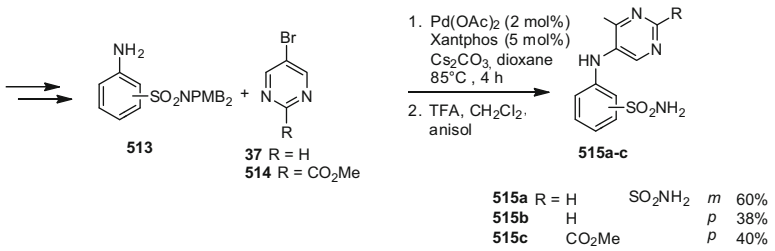
Entry	Heteroaryl	X	Product	Yield [%]
1		Br	**509a**	87
2		Cl	**509a**	82
3		Cl	509b	75
4		Br	509c	80
5		Cl	**509d**	76
6		Br	509e	67

b



Scheme 139 Coupling of electron-deficient heteroaryl amines with heteroaryl halides

sulfonamide moiety) and its subsequent Buchwald–Hartwig amination/deprotection sequence. Employing 5-bromopyrimidine and 2-methoxycarbonyl-5-bromopyrimidine afforded the desired products **515 a–c** in up to 60% yield (Scheme 140).



Scheme 140 A general route to unsubstituted *N*-(heteroaryl)aryl-aminobenzensulfonamides

1.8.5 Other than C–N Coupling

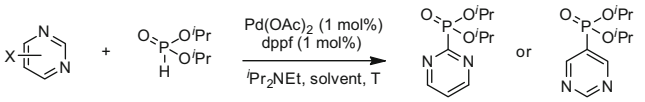
Besides the reports, dealing with C–N coupling, several papers were published, discussing reactions between carbon-based electrophiles and nucleophiles other than nitrogen. Herein, carbon–phosphorus, carbon–sulfur, and carbon–oxygen cross-coupling reactions are summarized.

C–P Coupling

Since Hirao's pioneering work in the area of C–P coupling in 1982 [196], many follow-up papers have been published modifying the original procedure, extending the scope of reagents, etc., and research in the field continues till today. In some of the reports, pyrimidine halides served as substrate for coupling with different phosphorus-based moieties.

Balabassi et al. carried out some reinvestigation of the original Hirao conditions [197]. They focused on the elimination of the main problems of the transformation, namely, rather high catalyst loadings and dealkylation of the desired products occurring as a side reaction. The latter problem was solved by replacing the original base, triethylamine, with more sterically hindered secondary amine (*N*,*N*-diisopropylethyl amine), since the dealkylation proceeds via a S_N2 mechanism. Applying DMF or MeCN as solvent and $Pd(OAc)_2$ in combination with the dppf ligand as a catalytic system allowed to reduce the catalyst loading from 5 to 1 mol%. Moreover, the first example of a (hetero)aryl chloride able to undergo C-P bond formation was reported. Diisopropylphosphite **517** was then reacted with many (hetero)aryl halides, including 2-bromopyrimidine **36**, 2-chloropyrimidine **6**, 5-bromopyrimidine **37**, and 5-chloropyrimidine **516**, yielding desired products in up to 83% (Scheme 141).

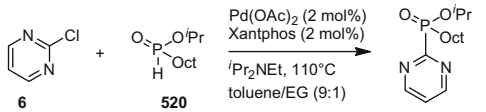
Another report from the Montchamp laboratory dealt with the coupling of (hetero)aryl chlorides and phosphorus nucleophiles, in this particular case *H*-phosphinate esters [198]. Under the optimized conditions (2 mol% of $Pd(OAc)_2$ and Xantphos, *i*-Pr_2Net), reaction between 2-chloropyrimidine **6** and ethyl octylphosphinate **520** provided 52% of **521**. 2-Chloropyrimidine turned out to be a rather difficult substrate in comparison to others (Scheme 142).



6, 36, 37 or 516 | 517 | 518a-b | 519a-b

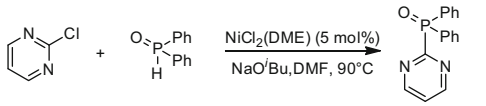
Entry	X	Solvent	Temperature	Product	Yield [%]
1	2-Br	CH_3CN	reflux	**518a**	67
2	2-Cl	DMF	85°C	**518b**	28
3	5-Br	CH_3CN	reflux	**519a**	83
4	5-Cl	DMF	105°C	**519b**	62

Scheme 141 Reinvestigation of the original Hirao conditions



6 | 520 | **521**, 52%

Scheme 142 Coupling of *H*-phosphinate esters with 2-chloropyrimidine



6 | 522 | **523**, 79%

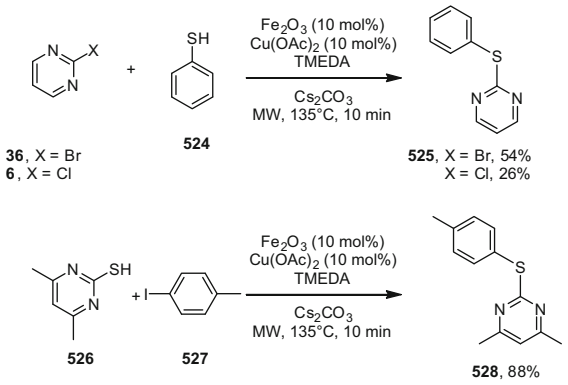
Scheme 143 Cross-coupling of diphenylphosphine oxide with 2-chloropyrimidine

Zhang et al. developed nickel-catalyzed cross-coupling of diphenylphosphine oxide with various (hetero)aryl chlorides [199]. In the presence of $NiCl_2$(DME) and *t*-BuONa at 90°C, 2-chloropyrimidine **6** was able to undergo reaction with diphenylphosphine oxide **522** to yield 79% of corresponding diphenylpyrimidin-2-ylphosphine oxide **523** (Scheme 143).

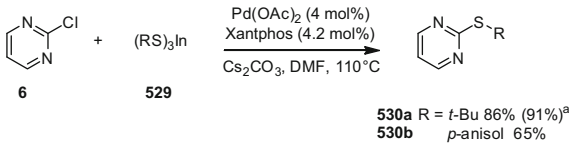
C–S and C–O Coupling

In general, utilizing sulfur nucleophiles in cross-coupling reactions is rather challenging due to the ability of sulfur to strongly coordinate to the metal center, which can possibly lead to catalyst poisoning. First reports of C–S couplings appeared in the 1980s when Migita et al. published palladium-catalyzed cross-coupling of aryl bromides or iodides and stannyl sulfides leading to arylsulfides [200]. The transformation has been subject to many investigations, and nowadays C–S coupling is still an active area of research.

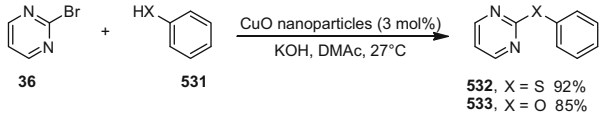
In 2009, Liu and coworkers developed Fe/Cu co-catalyzed cross-coupling of aryl halides and thiols [201]. A variety of substrates, including aromatic and aliphatic thiols and different (hetero)aryl halides, were coupled under the optimized conditions (10 mol% Fe_2O_3, $Cu(OAc)_2$, 20 mol% TMEDA). Among them,



Scheme 144 Cu/Fe catalyzed C–S bond formation reaction on pyrimidines



Scheme 145 Indium catalyzed cross-coupling on pyrimidine, [a]DIPEA used



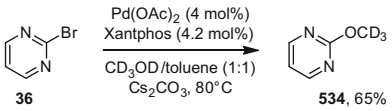
Scheme 146 Copper(II)oxide nanoparticles for C–S/C–O cross-coupling on pyrimidine

2-bromopyrimidine and 2-chloropyrimidine were coupled with thiophenol **524**, yielding 54% and 26% of **525**, respectively. In addition, 4,6-dimethylpyrimidine-2-thiol **526** was coupled with *p*-iodotoluene **527**, providing 88% of cross-coupling product **528** (Scheme 144).

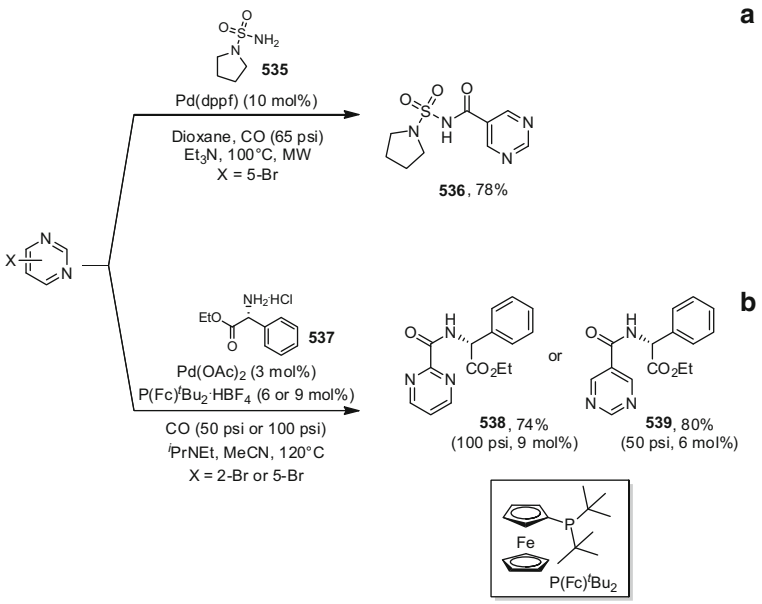
Mo et al. developed palladium-catalyzed cross-coupling, utilizing indium tris (organothiolates) as nucleophiles and aryl chlorides [202]. Under optimized conditions, 2-chloropyrimidine underwent coupling with indium tris(*t*-butylthiolate) **529** yielding 91% of sulfide **530a**. Reaction of 2-chloropyrimidine with aromatic indium tris(*p*-anisylthiolate) provided 65% of sulfide **530b** (Scheme 145).

Recently, Kervembu and Babu have demonstrated the utilization of CuO nanoparticles as an active catalyst for cross-coupling reactions between (hetero) aryl bromides and aryl chlorides with (thio)phenols leading to C–S or C–O bond formation [203]. The reactions were carried out in absence of ligand at rt. This makes the procedure attractive since additionally a relatively low catalyst loading (3 mol%) could be applied. Thiophenol gave in the reaction with 2-bromopyrimidine 92% of **532**, whereas phenol delivered 85% of the desired ether **533** (Scheme 146).

In 2012, Dash et al. developed palladium-catalyzed d_3-methoxylation of diverse (hetero)aryl bromides [204]. An optimization study revealed that using $Pd(OAc)_2$,



Scheme 147 Pd-catalyzed d_3-methoxylation of pyromodine



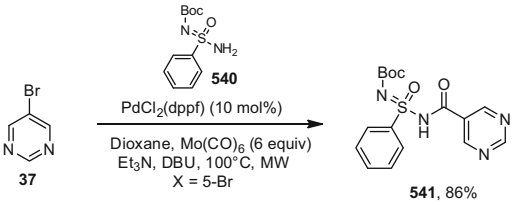
Scheme 148 Carbonylation of pyrimidine using gaseous CO

*t*BuXPhos, and Cs_2CO_3 leads to the best results. Applying such conditions to the reaction of 2-bromopyrimidine with an excess of MeOD led to formation of the desired product **534** in 65% (Scheme 147).

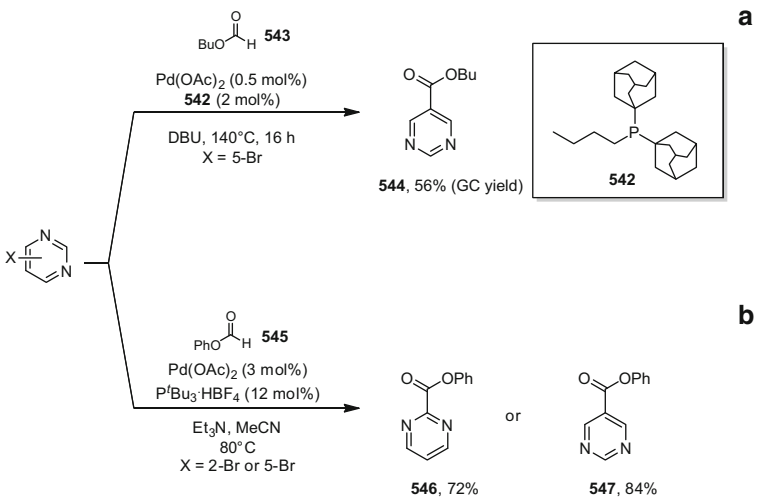
1.9 Carbonylation

Carbonylations proved to be synthetically very useful reactions since they allow simple access towards a variety of chemical functionalities such as amides, esters, and others. Since the pioneering work published by Heck in 1974 [205], many variations of the reaction were carried out and research in the field continues. In recent times, several papers were published, dealing with carbonylation reactions on the pyrimidine core.

Roberts et al. have reported microwave-accelerated carbonylation of (hetero) aryl halides in the presence of sulfamide **535** and 65 psi gaseous CO [206]. The reaction was catalyzed by Pd/dppf and coupling of 5-bromopyrimidine provided the corresponding compound **536** in 78% yield (Scheme 148a).



Scheme 149 Carbonylation of pyrimidine using gaseous $Mo(CO)_6$ as CO source

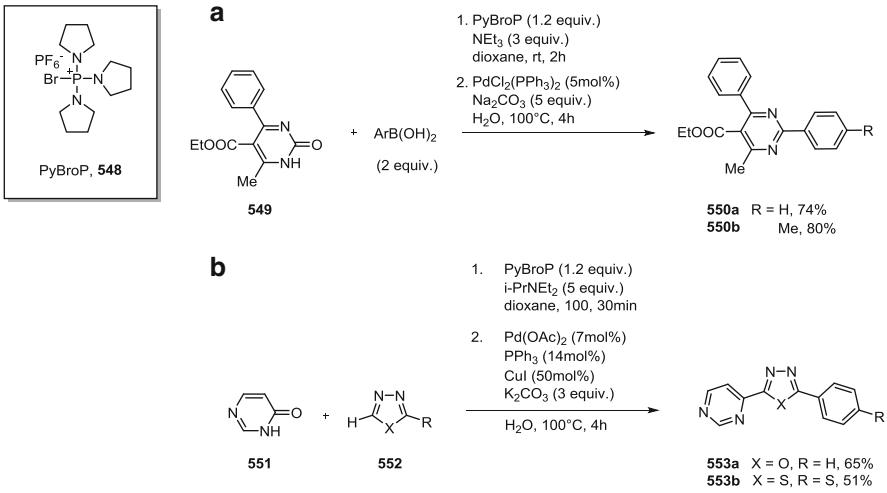


Scheme 150 Carbonylation of pyrimidine using formates

Aminocarbonylation of pyrimidine was described by Qu et al. [207] applying $Pd(OAc)_2$ together with monodentate di-*t*-butyl ferrocene phosphine. In the presence of (*R*)-ethyl 2-amino-2-phenylacetate hydrochloride **537** and under 50 or 100 psi pressure of CO, 2-bromopyrimidine or 5-bromopyrimidine provided the corresponding products **538** and **539** in 74% and 80% yield, respectively (Scheme 148b).

Developing a surrogate for gaseous CO is of interest mainly because of the toxicity of carbon monoxide. Borhade et al. have utilized $Mo(CO)_6$ as CO source for palladium-catalyzed carbonylation of various (hetero)aryl halides in the presence of nucleophilic sulfonamides [208]. 5-Bromopyrimidine was treated with mono Boc-protected benzenesulfonamide **540** in the presence of Pd catalyst and the molybdenum complex. Desired aminocarbonylated product **541** was obtained in 86% (Scheme 149).

Besides using gaseous CO or surrogate, carbonylation reactions utilizing formates were reported as well. Beller and coworkers investigated carbonylation of (hetero)aryl halides using butyl formate **543** [209]. The reaction was catalyzed by $Pd(OAc)_2$/(diadamantyl)butylphosphine (**542**). 5-Bromopyrimidine provided 56% of **544** (GC yield, Scheme 150a).



Scheme 151 Direct arylation of tautomerizable hydroxyl pyrimidines

5-Bromopyrimidine and 2-bromopyrimidine were carbonylated with phenyl formate by Udea et al. as well [210]. Under the catalysis of $Pd(OAc)_2/P^tBu_3$, products **546** and **547** were obtained in 84% and 72%, respectively (Scheme 150b).

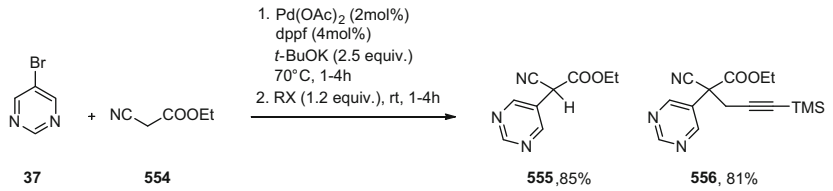
1.10 Miscellaneous Reactions

An interesting direct arylation reaction of tautomerizable hydroxy-N-heterocycles with arylboronic acids was reported by Kang et al. [211]. Biaryl products were obtained in good to excellent yields. The authors assume that the OH group is activated via formation of a phosphonium salt with PyBroP **548** followed by insertion of the Pd catalyst into the C–O bond. Two examples of the reaction of highly substituted 2-pyrimidone **549** were reported, giving the coupling products **550** in 74% and 80% yield respectively (Scheme 151a).

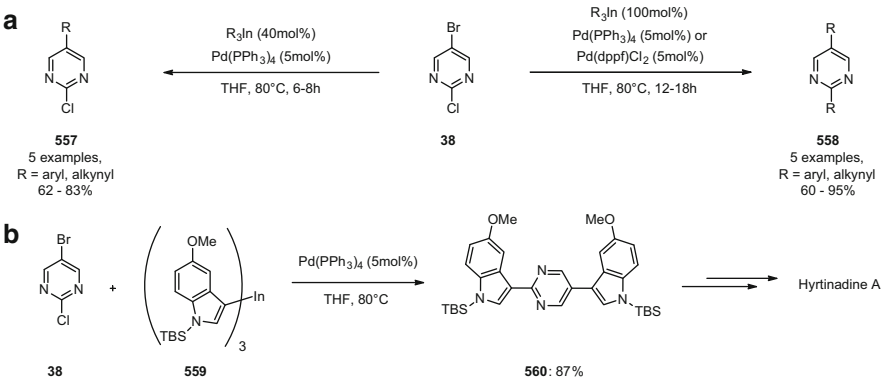
Sharma et al. disclosed a variant of the reaction described above. Here, an organocuprate, which is formed in situ by metalation of an acidic methylene group with CuI, serves as the organometallic coupling partner. As substrates benzoxazoles, oxadiazoles, and thiadiazoles were reported (Scheme 151b) [212].

Faul and coworkers have developed a one-pot protocol for the synthesis of 2-allyl-2-arylcyanoacetates. The process consists of a sequential $Pd(OAc)_2$/dppf-catalyzed arylation of the enolate, followed by in situ trapping of the tertiary carbanion with an alkyl halide [213]. 4-Bromopyrimidine **37** reacted smoothly, giving the final products **555** and **556** in 81–85% yield (Scheme 152).

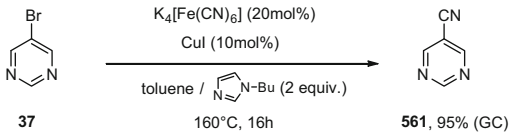
Mosquera et al. investigated the Pd-catalyzed coupling of triarylindium reagents with 5-bromo-2-chloropyrimidine **38** [214]. Double arylation towards **558** as well



Scheme 152 Synthesis of 2-allyl-2-arylcyanoacetates in one pot



Scheme 153 Pd-catalyzed cross-coupling of pyrimidines with triaryl indium

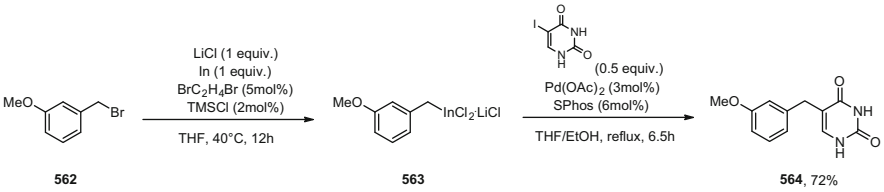


Scheme 154 Copper-catalyzed cyanation of 4-bromopyrimidine

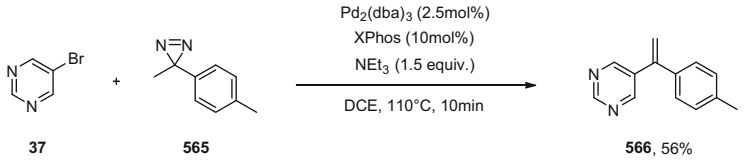
as selective arylation in 4-position towards **557** was achieved in 60–95% yield (Scheme 153a). The method was applied to the synthesis of **560**, a key intermediate in the synthesis of hyrtinadine A (Scheme 153b).

Schareina et al. reported a Cu(I)-catalyzed coupling reaction of aryl bromides with potassium hexacyanoferrate as a nontoxic cyanide source [215]. The authors identified alkylimidazoles as highly effective ligands for the Cu catalyst in this transformation. Although harsh reaction conditions are required (140–180°C, 16 h) for most substrates, the reaction proceeded cleanly and gave the corresponding benzonitriles in 60–99% yield, e.g., 5-cyanopyrimidine **561** was obtained in 95% yield (Scheme 154).

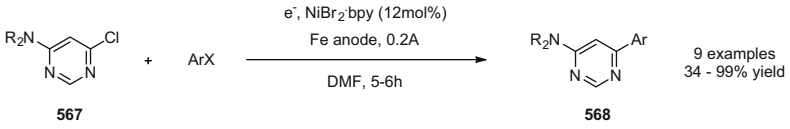
Extending his previous work on the preparation of organoindium compounds [216] by direct insertion of In(0) into C–X bonds, Knochel and coworkers reported a general method for the preparation of benzylic In(III) reagents [217]. The insertion was found to be much faster for benzylbromides (0°C, up to



Scheme 155 Preparation and application of benzylic In(III) reagents



Scheme 156 Pd-catalyzed coupling of diaziridine and 5-bromopyridine



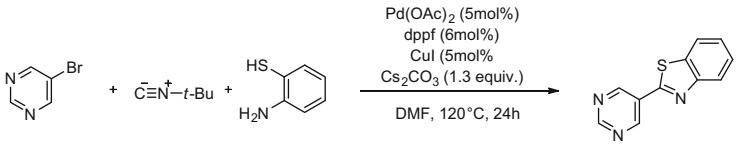
Scheme 157 Electrochemical reductive coupling of pyrimidine

30 min) compared to benzyl chlorides (up to 16 h, 40°C). The reactivity of the resulting In(I) reagents towards cross-coupling reactions could be significantly increased by a transmetallation step with *i*PrMgCl · LiCl, giving rise to a mixed alkylbenzyl In(III) species. These reagents (e.g., **563**) react smoothly with aryliodides and bromides in the presence of $Pd(OAc)_2$/SPhos at 25–40°C. 5-Iodouracil was coupled with the substituted benzylindium compound **563** giving 72% yield of **564** (Scheme 155).

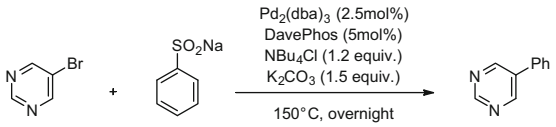
The use of diaziridines such as **565** as coupling partners in a Pd-catalyzed cross-coupling reaction was investigated by Zhao et al. [218]. The products of this reaction are 1,1-diarylalkenes. The combination of $Pd_2(dba)_3$/XPhos in conjunction with microwave heating was found to be highly effective in this transformation towards 1-arylstyrenes. Products were generally obtained in good to excellent yields after only 10 min. 5-Bromopyrimidine, as the only heteraromatic example, gave a moderate 56% yield of **566** (Scheme 156).

An example of electrochemical reductive coupling was reported by Sengmany et al. [219]. 4-Amino-6-chloropyrimidines **567** were coupled with aryl halides in the presence of $NiBr_2$bpy and a sacrificial iron anode. Yields vary strongly depending on the nature of the amine substituent and the coupling partner giving compounds of type 568 in 34–99% yield (Scheme 157).

A three-component reaction of amino(thio)phenols **570** with isocyanide **569** and an aryl halide was published by Lang and coworkers [220]. In the presence of a Pd



Scheme 158 Pd- and Cu-catalyzed 3-component coupling



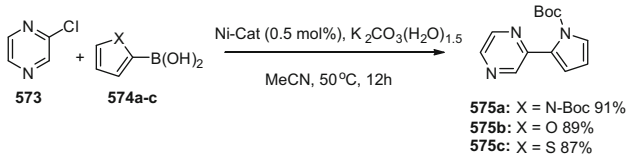
Scheme 159 Pd-catalyzed desulfitative cross-coupling of phenylsulfinate and bromo pyrimidine

catalyst, 2-aryl benzoxazoles and benzothiazoles were obtained. The authors noted an interesting difference in the reaction mechanism: aminophenols are believed to react via isocyanide insertion into the aryl-Pd bond followed by coupling with the amine nucleophile. The reaction conditions used for aminophenols proved ineffective for aminothiophenols: Here the starting material is believed to undergo a noncatalyzed reaction with the isocyanide, giving rise to 2-unsubsituted benzothiazoles. When CuI was added, formation of organocuprates and subsequent coupling with an aryl halide gave 2-arylbenzothiazoles. One example involving pyrimidine is presented in Scheme 158.

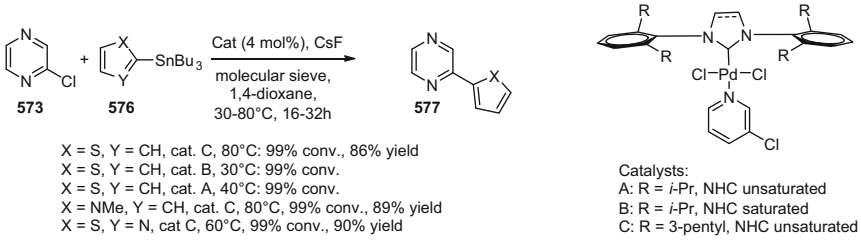
The Pd-catalyzed desulfitative cross-coupling of phenylsulfinate **572** with aryl halides was reported by Colomb and Billard [221], thus extending the scope of a previously reported reaction with arlytriflates [222] towards heteroaromatic substrates under similar conditions (Scheme 159).

2 Pyrazine in Cross-Coupling Reactions

Pyrazines are widely used intermediates in medicinal chemistry [223–230]. Hence, their decoration to increase complexity at a late stage of a synthetic sequence is of significant interest to synthetic chemists in general and medicinal chemists in particular. Naturally, cross-coupling reactions have been used in pyrazine chemistry, however not to the same extent as in pyrimidine chemistry. In the following chapters, the recent progress in this field is reviewed (2008 to mid-2013).



Scheme 160 Ni-catalyzed Suzuki coupling on pyrazine



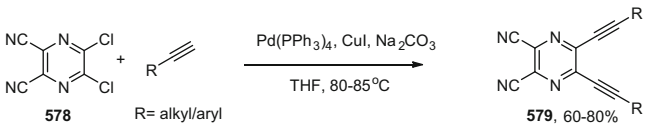
Scheme 161 NHC-Pd complex-catalyzed Stille coupling of pyrazine

2.1 Pyrazine in Suzuki–Miyaura Reactions

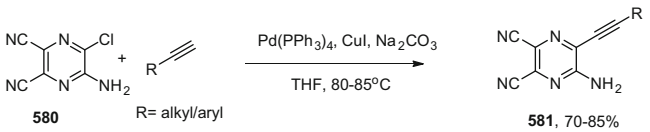
The replacement of the precious metal palladium with the first-row, abundant metal nickel for Suzuki–Miyaura couplings could significantly reduce the cost of the catalyst. Recently, Ge and Hartwig reported a single-component nickel catalyst, the dppf-ligated cinnamylnickel(II) chloride [(dppf)Ni(cinnamyl)Cl], which promoted coupling of heteroaryl halides with heteroaryl boronic acids towards biheteroaryls (Scheme 160). Among the more than three-dozen examples, pyrazine was used as well: pyrazine chloride **573** was coupled with *N*-Boc-2-pyrroleboronic acid, 2-benzofuranboronic acid, and 2-benzothiopheneboronic acid to give **575a** in 91%, **575b** in 89%, and **575c** in 87% yield. These high yields were obtained with 0.05% nickel catalyst only and no additional ligand was required [231].

2.2 Pyrazine in Stille Reactions

Stille cross-coupling reactions with NHC-palladium complexes as catalysts have been reported on **573** with a series of heterocyclic stannanes **576** (Scheme 161). Catalyst C, containing 3-pentyl residues, proved to be most general which was attributed to the flexible steric bulk of the 3-pentyl group. However, Pd-PEPPSI precatalysts were equally efficient in coupling of **573** with a thiophene stannane. Generally, all examples reported for pyrazine gave full conversion and high yield of **577** at relatively low temperatures as low as 30°C in one example. Low temperatures are beneficial since decomposition of organostannanes or heteroaryl halides is minimized [232].



Scheme 162 Sonogashira coupling of substituted pyrazine



Scheme 163 Sonogashira coupling of pyrazine and alkyl/aryl alkyne

2.3 Pyrazine in Sonogashira Reactions

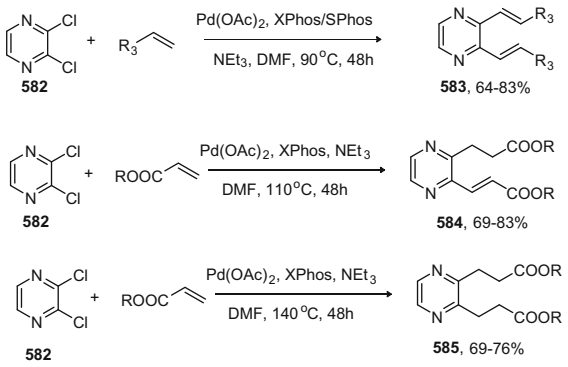
The palladium-catalyzed coupling of terminal alkynes with aryl or vinyl halides and triflates, usually in the presence of a copper co-catalyst, is commonly known as the Sonogashira reaction [233–236].

Van Lier published a paper dedicated to the investigation of Sonogashira cross-coupling on pyridazine derivatives [237]. Readily available 2,3-dicyano-5,6-bis-chloropyrazine **578** was coupled with a series of alkynes in positions 2 and 3 (Scheme 162). In a typical reaction, **578** was coupled with 1-hexadecyne using $Pd(PPh_3)_4$, copper iodide, and sodium carbonate as a base in THF at 80–85°C for 4 h giving **579** in 60% yield. A variety of different alkynes was applied including aliphatic (1-hexyne, hex-5-yn-1-ol, undec-10-yn-1-ol) and aromatic ones (phenylacetylene, 4-*n*-Bu-phenylacetylene, 4-CF_3-phenylacetylene, 4-NMe_2-phenylacetylene, 2-naphthylacetylene, and ferrocenylacteylene). Yields were in the range from 60 to 80%.

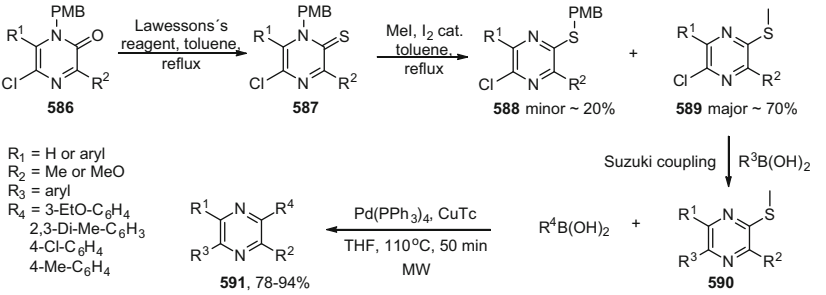
As second substrate 5-amino-6-chloro-2,3-dicyanopyrazine **580** was submitted to Sonogashira couplings with a similar range of alkynes (Scheme 163). In this case, coupling took place in position 6 and the free amino group was well tolerated. Yields of **581** up to 85% were reported in many cases.

2.4 Pyrazine in Heck Reactions

Langer and coworkers reported Heck cross-coupling reactions of 2,3-dichloropyrazine **582**. Three different reaction conditions were disclosed giving rise to three different product classes, namely, 2,3-dialkenyl-, 2-alkenyl-3-alkyl-, or 2,3-dialkylpyrazines **583**, **584**, and **585**, respectively (Scheme 164) [238]. The reaction of **582** with an alkene (ethyl acrylate and various styrenes) and a catalytic system comprising of $Pd(OAc)_2$ (5 mol%) and XPhos or SPhos (10 mol%) afforded



Scheme 164 Heck reaction on pyrazine



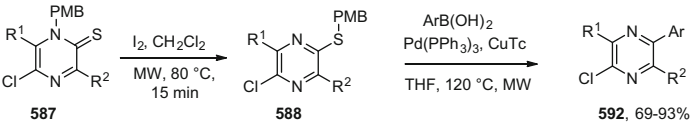
Scheme 165 Example of orthogonality: Suzuki and Liebeskind–Srogl reaction on pyrazine

the 2,3-dialkenylpyrazine **583** in good yield. Already in these reactions, partial dehydrogenation was observed, especially at higher temperatures. Using various acrylates (2.5 equiv.) as coupling partners and 110°C rather than 90°C, 2-alkenyl-3-alkylpyrazines **584** were obtained in yields ranging from 69 to 83%. As explanation for the reduction, protodemetalation was proposed. Raising the temperature further to 140°C gave complete reduction to **585**, again tentatively via protodemetalation.

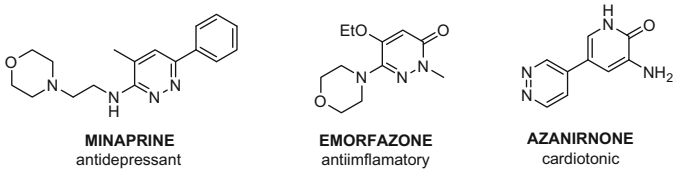
2.5 Pyrazine in Liebeskind–Srogl Reactions

The Liebeskind–Srogl reaction is the coupling of a thioester or thioether with an organometal compound, in most cases a boronic acid. A palladium catalyst and a copper salt (in stoichiometric amount, most often copper(I) thiophene-2-carboxylate) are required. Due to the absence of base in this transformation, it is orthogonal to Suzuki–Miyaura cross-couplings since in the absence of base, the thiospecies acts as a leaving group while C-X bonds remain unaffected.

This orthogonality of methods was exploited in the synthesis of asymmetrically 2,3,5,6-tetrasubstituted pyrazines **591**, starting from N1-PMB-protected 3,5-dichloro-2(*1H*) pyrazinone **586** (Scheme 165). Initially, the thioether moiety



Scheme 166 Liebeskind–Srogl reaction of pyrazine



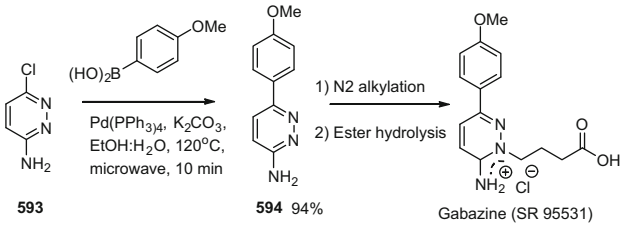
Scheme 167 Pyridazine and pyridazinone-based drugs

had to be introduced which was achieved via formation of the thio-pyrazinone intermediate using Lawesson's reagent to give **587**, followed by iodine-catalyzed methylation and concomitant aromatization to generate the thiomethyl-substituted pyrazines **589** which can be used as substrate for the Liebeskind–Srogl reaction [239]. Methylation reaction was always accompanied by the transfer of the PMB group to form para methoxylbenzyl thioether **588**. Coupling reactions of **589** under Suzuki conditions (or Sonogashira) gave substrates **590** for Liebeskind–Srogl coupling. This last step of the sequence works very well with various boronic acids to give **591** in excellent yields.

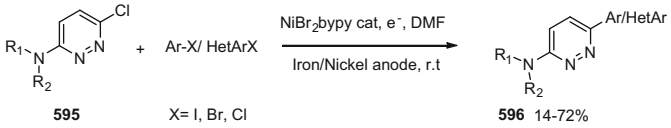
The protocol described above could be streamlined by eliminating the methylation step and directly using PMB-thioether **588** as substrate instead (Scheme 166). Liebeskind–Srogl coupling between **588** and arylboronic acids towards **592** proceeded in high yields also with this starting material. Initially, the reactions were sluggish due to reagent decomposition. This difficulty was overcome by adding the reagents in two portions aryl boronic acids of different electronic properties could be applied [240].

3 Pyridazine in Cross-Coupling Reactions

Pyridazine derivatives display diverse biological activities such as anticancer [241] or analgesic effects [242] and can be applied for the treatment of urinary incontinence [243], inflammatory pain [244], obesity [245, 246], and neurodegenerative diseases potentially [247–249]. Examples of some pyridazine and pyridazinone-based drugs are shown in Scheme 167.



Scheme 168 Suzuki coupling of pyridazine



Scheme 169 Ni-catalyzed electrochemical arylation of pyridazine

3.1 Suzuki Coupling on Pyridazine

Broad substrate scope and high efficiency for the Suzuki coupling of unprotected 3-amino-6-chloropyridazine **593** can be achieved using a microwave-assisted protocol (Scheme 168) [250]. This method offers excellent reactivity for a variety of electron-deficient, electron-rich, and sterically hindered arylboronic acids, as well as heteroaromatic boronic acids with yields being uniformly good to excellent (17 examples, 75–95%). Chloro- and amino-substituents on the boronic acid and the amino substituent on the pyridazine ring are well tolerated under the reaction conditions, which can extend the scope for further functionalization of the pyridazine scaffold. In Scheme 168, synthesis of **594** is displayed which is a precursor for gabazine (SR-95531), which shows high specificity and potency towards both $GABA_A$ and $GABA_C$ receptors [251, 252].

Recently, a nickel-catalyzed electrochemical arylation of 3-amino-6-chloropyridazines **595** at r.t. is described, using an iron/nickel electrode as the sacrificial anode (Scheme 169). In total 27 examples of **596** were disclosed, and also the scope of the amine residue was investigated (e.g., morpholino, pyrrolo, imidazole, and series of dialkylamino). Substituents on the halide coupling partner such as methoxy, methyl, CF_3, chloro, cyano, and COOEt were tolerated. Pyridine and quinoline halides gave relatively low yield. 3-Bromothiophene gave a good yield of 71%, but additionally 1 equiv. of halide was added after 2.5 h. Comparable transformations involving classical reactions, such as Suzuki or Stille cross-couplings, revealed that the electrochemical method constitutes an alternative tool due to a broad substrate scope, use of ambient reaction condition, and a cheaper catalyst as compared to palladium [253].

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Metal-Catalysed Cross-Coupling Reactions in the Synthesis and Transformations of Quinolones and Acridones

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Abstract Metal-catalysed cross-coupling reactions have had a large impact on synthetic organic chemistry and have found many applications in target-oriented synthesis. Their widespread use in organic synthesis is due to the mild conditions associated with the reactions together with their tolerance of a wide range of functional groups. The cross-coupling reactions have been applied to the synthesis of a large number of natural products and bioactive compounds of complex molecular structures. This chapter presents an overview of the applications of cross-coupling reactions in the synthesis and transformations of quinolones and acridones. These compounds are widely recognized by their diverse bioactivity being useful structural moieties for drug candidates. Furthermore they hold significant interest due to their host–guest chemistry; applications in chemical, biochemical and environmental analyses and utility in synthetic methods' development.

Keywords Acridones · Carbonylation · Copper · Cross-coupling · Cyclization · Metal-catalysed · Palladium · Quinolones · Reaction mechanisms

Contents

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Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Alk	Alkyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bppm	*tert*-Butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine
Bu	Butyl
CH	Classical heating
cod	Cyclooctadiene
CuTC	Copper(I)-thiophene-2-carboxylate
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIOP	2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane
DIPEA	Diisopropylethylamine
DMA	Dimethylacetamide
DMEDA	Dimethylethylenediamine
DMF	Dimethylformamide
DMPU	Dimethylpropylene urea
DMSO	Dimethyl sulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl]ether
dppe	Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene

dppp	1,3-Bis(diphenylphosphino)propane
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
ee	Enantiomeric excess
er	Enantiomeric ratio
Et	Ethyl
HMPA	Hexamethylphosphoramide
Hx	Hexyl
LDA	Lithium diisopropylamide
Me	Methyl
MOM	Methoxymethyl
Ms	Mesyl
MW	Microwave
NBS	*N*-Bromosuccinimide
Pent	Pentyl
Ph	Phenyl
Piv	Pivaloyl
PMHS	Polymethyl-hydrosiloxane
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
R,*R*-BDPP	(2*S*,3*S*)-(−)-Bis(diphenylphosphino)butane
rac	Racemic
R-JOSIPHOS	(*R*)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl] ethyldicyclohexylphosphine
rt	Room temperature
SPHOS	2-Dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl
TBAB	Tetrabutylammonium bromide
THF	Tetrahydrofuran
THP	Tetrahydropyran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TMSA	Trimethylsilylacetylene
tol	4-Methylphenyl(tolyl)
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

Carbon–carbon bond formation through transition metal-catalysed cross-coupling reactions remains one of the most powerful methods in organic synthesis. In this chapter a review of metal-catalysed cross-coupling reactions applied to the synthesis and transformation of quinolin-2(1*H*)- and quinolin-4(1*H*)-ones up to 2012 is presented, highlighting the reaction conditions, including the catalysts, ligands, bases and selectivity, evidencing the representative C–C bond-forming reactions

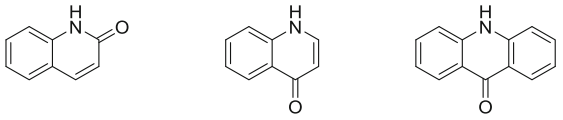


Fig. 1 Compounds discussed in this chapter

(e.g. Sonogashira, Suzuki, Buchwald–Hartwig, Stille, Heck reaction, among others). In the same period, publications concerning these types of reactions in the synthesis of acridin-9(10*H*)-ones are very scarce, with a combined Buchwald–Hartwig aryl amination-directed remote metalation (DreM) protocol, an aryl amination followed by an intramolecular Friedel–Crafts acylation using polymer-supported Pd and Sc catalysts and more recently the electrocyclization of (*E*,*E*)-2,3-distyrylquinolin-4(1*H*)-ones being only known. To the best of our knowledge, there is no report about their chemical transformations.

Quinolin-2(1*H*)- and quinolin-4(1*H*)-ones are benzo-α- and benzo-γ-pyridones, respectively, since they are constituted by a α- or γ-pyridone *ortho*-fused with a benzene ring (Fig. 1). The quinolone motif is common in nature, particularly in alkaloids from Rutaceae family but can also be produced by different animal and bacterial species (e.g. [1, 2]). These compounds represent privileged moieties in medicinal chemistry and are ubiquitous substructures associated with biologically active natural products. Quinolin-4(1*H*)-ones are well-known drugs used as antibiotics (e.g. fluoroquinolones) due to their excellent antimicrobial activity (e.g. [3]), but they also possess other interesting biological properties such as antimalarial (e.g. [4]) and antitumoural (e.g. [5, 6]) activities, among others. Considerable interest in studying the isomeric quinolin-2(1*H*)-ones is also related to the different kinds of important biological activities demonstrated. These compounds were reported as antiulcer (e.g. rebamipide), antihistaminic (e.g. repirinast) (e.g. [7]) and anticancer (e.g. tipifarnib) (e.g. [8, 9]) agents and have also been evaluated, for example, as inhibitors of HIV-1 reverse transcriptase (e.g. [10, 11]) and antivirals (e.g. [12]). Up to now several methods for the synthesis of quinolones have been reported in the literature, but the most commonly used involve the condensation of anilines with β-ketoesters followed by cyclization to give quinolin-4(1*H*)-ones (Conrad–Limpach synthesis) or quinolin-2(1*H*)-ones (Conrad–Limpach–Knorr synthesis). Other classical methods leading to the formation of the C3–C4 bond include the Friedländer synthesis, Camps modification and Niementowski reaction [13–15].

Acridin-9(10*H*)-ones, also called dibenzo-γ-pyridones, are tricyclic compounds presenting a γ-pyridone with two *ortho*-fused benzene rings (Fig. 1). Several naturally occurring and synthetic acridin-9(10*H*)-one derivatives are known due to their biomedical potential including antiviral [16], antimalarial (e.g. [17]), antitumoural and anticancer activities (e.g. [18, 19]). Besides medicinal applications, acridin-9(10*H*)-ones are also used in host–guest interactions and in chemical, biochemical, and environmental analysis as fluorescence probes and as analytical tools in biomimetic chemistry [20–26]. Acridin-9(10*H*)-ones are commonly prepared by the acid-induced ring closure of *N*-arylanthranilic acids, themselves usually obtained from the Ullmann condensation of anilines with *ortho*-halogen-substituted benzoic acids [27–31]. Other methods involve the intermolecular

nucleophilic coupling of arynes with *ortho*-aminobenzoates and subsequent intramolecular nucleophilic cyclization [32, 33] and the anionic *N*-Fries rearrangement of *N*-carbamoyldiarylamines to anthranylamides followed by cyclization with triflic anhydride [34].

Most of these methods often require harsh conditions, tedious workup and purification procedures and are regioselectivity compromised, and the variety of substrates is limited. The drawbacks of the conventional methods can be overcome by metal-catalysed reactions in the synthesis and transformation of these types of compounds. This is a recent topic but several methods have already been established meaning that it is an important and upward research field.

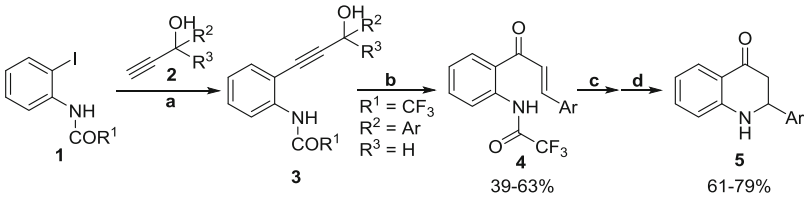
2 Synthesis of Quinolin-4(1*H*)-ones

2.1 Sonogashira Reaction

2-Iodoanilides **1** reacted with terminal propargyl alcohols **2** under Pd-catalysed conditions to yield the corresponding 2-substituted anilides **3** [35, 36]. Among several catalysts, $PdCl_2(PPh_3)_2$ was found to be the best, and the addition of CuI was not found to give any additional advantage. Propargyl alcohols **2** in the presence of Et_3N appear to be capable to reduce Pd(II) to Pd(0) before the oxidative addition of Pd(0) to the aryl halide could occur. Only in one case (R^1=CF_3; R^2=R^3=H) the corresponding indole, obtained by spontaneous cyclization of 2-substituted anilides **3**, was isolated.

2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones **5** were synthesized from the 2-substituted anilides **3** by acid-catalysed Meyer–Schuster rearrangement leading to *N*-substituted 2′-aminochalcones **4** followed by alkaline hydrolysis, deprotection and cyclization under acidic conditions (Scheme 1).

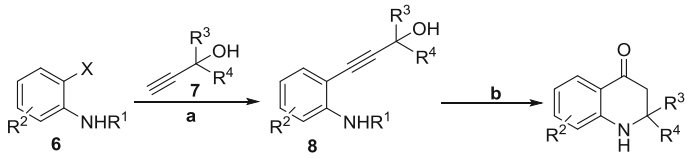
Recently, Spivey and co-workers reported a similar general and straightforward method to prepare 2,3-dihydroquinolin-4(1*H*)-ones **9** starting from 2-(pseudo) halogenated anilines **6** by a two-step procedure involving a Sonogashira coupling with propargyl alcohols **7** followed by a Brønsted acid-catalysed cyclization (Scheme 2) [37]. Anilines **8** were converted into quinolin-4(1*H*)-ones **9** by acid-catalysed tandem Rupe rearrangement–Donnelly–Farrell ring-closure reaction upon treatment with concentrated HCl, followed by basic workup. The Rupe rearrangement involves a regioselective hydration–dehydration rearrangement of the alkyne moiety, probably via aldol **10**, to give the corresponding α,β-unsaturated ketone, which by acid-catalysed 6-*endo*-trig Michael-type ring closure is converted into the dihydroquinolin-4(1*H*)-ones **9** (Scheme 2). For the cyclization of the *N*-acetyl derivatives, the authors proposed the Rupe rearrangement followed by the in situ acetamide hydrolysis immediately prior to cyclization [37].



R^1 = Me, CF_3; R^2 = H, Me, Ar; R^3 = H, Me; Ar = Ph, 4-MePh, 2-MePh, 4-OMePh

a: $PdCl_2(PPh_3)_2$ (1-2 mol%), Et_3N, DMF, rt, 24 h; **b:** PTSA, benzene, rt, 48 h; **c:** NaOH, EtOH, rt, 40 h; **d:** HOAc, H_3PO_4, 90 ºC, 25 min

Scheme 1 Synthesis of 2,3-dihydroquinolin-4(1*H*)-ones **5** from 2-substituted anilides **3** obtained by Pd-catalysed reaction of 2-iodoanilides **1** with propargyl alcohols **2** [35, 36]



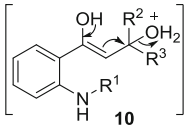
X = Br, I, OTf

R^1 = H, Ac

R^2 = H, 5-Cl, 5-Me, 4-OCF_3, 4-CF_3

R^3 = H, Me; R^4 = Ph

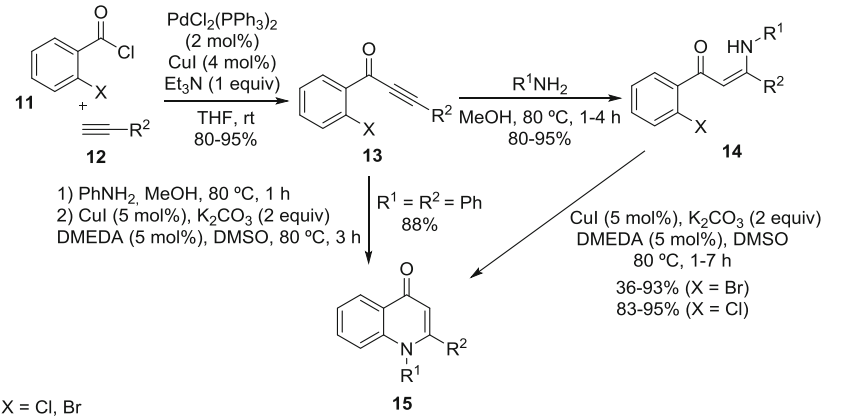
a: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), PPh_3 (0.5 equiv), Py, Et_3N, 90 ºC, 1.5-3 h; **b:** 1) concentrated HCl, H_2O, 120 ºC, 1.5-8 h; 2) K_2CO_3



Scheme 2 Synthesis of 2,3-dihydroquinolin-4(1*H*)-ones **9** via Sonogashira coupling of 2-(pseudo)haloanilines **6** with propargyl alcohols **7** followed by acid-catalysed cyclization [37]

This reaction allows the introduction of different groups at C-2 of the quinolin-4(1*H*)-one skeleton (e.g. R^3=H, Me; R^4=Ph), thus providing access to a wider variety of 2-substituted 2,3-dihydroquinolin-4(1*H*)-ones **9**.

1,2-Disubstituted quinolin-4(1*H*)-ones **15** have been prepared by Cu-catalysed heterocyclization of 1-(2-halophenyl)-2-en-3-amin-1-ones **14**, readily obtained by conjugate addition of primary amines to α,β-ynones **13** prepared by Sonogashira cross-coupling of terminal alkynes **12** with commercially available 2-bromo- and 2-chlorobenzoyl chlorides **11** (Scheme 3) [38]. Best results were obtained when the cyclization of 1-(2-bromophenyl)-2-en-3-amin-1-ones **14** was carried out in the presence of CuI, DMEDA and K_2CO_3 in DMSO at 80°C. Under the same conditions, 1-(2-chlorophenyl)-2-en-3-amin-1-ones **14** can also be used for this synthesis although reaction rates are lower. The reaction tolerates a variety of useful functionalities (ester, keto-, cyano- and chloro-substituents), although alkyl substituents are tolerated with some limitations and enaminones derived from primary alkylamines require a stronger base (NaO*t*-Bu) and those containing 3-alkyl substituents did not afford quinolin-4(1*H*)-ones. Quinolin-4(1*H*)-ones **15** can also be



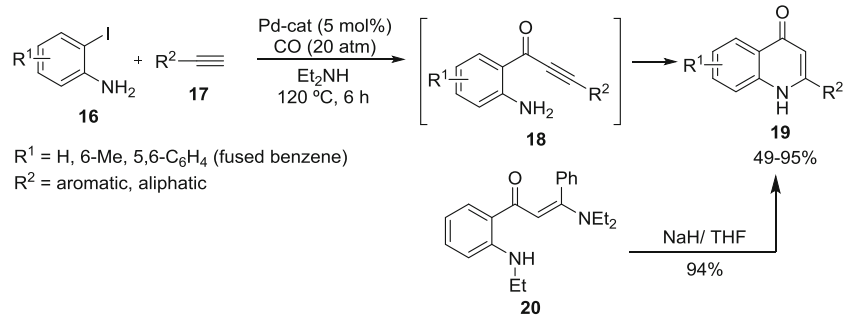
Scheme 3 Synthesis of 1,2-disubstituted quinolin-4(1*H*)-ones **15** via Sonogashira cross-coupling/Cu-catalysed cyclization [38]

prepared via a sequential process from α,β-ynones **13** and primary amines, omitting the isolation of the enaminone intermediates.

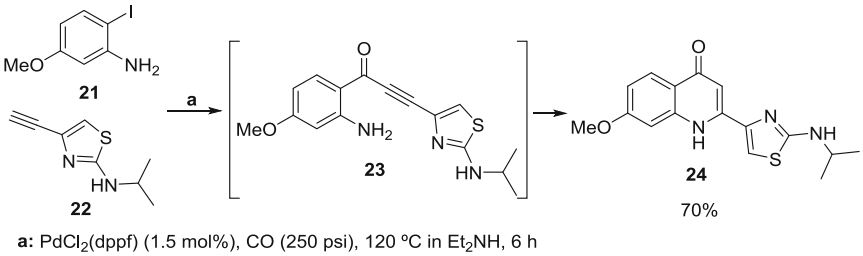
The mechanism proposed by the authors involves the initial coordination of nitrogen to copper, and the resulting complex undergoes an oxidative addition of the C–X bond to copper to afford the Cu(III) intermediate. Subsequent reductive elimination releases the product with concomitant regeneration of the Cu(I) species.

2.1.1 Carbonylative Sonogashira Reaction

Among the different methods described for the synthesis of 2-substituted quinolin-4(1*H*)-ones **19**, the Pd-catalysed carbonylative coupling of **2**-iodoanilines **16** with terminal arylacetylenes **17**, initially reported by Torii and Kalinin [39–41], appears to be the most versatile. The desired compounds were obtained in good yields using either $PdCl_2(PPh_3)_2$ or $PdCl_2$(dppf) in the presence of an excess Et_2NH which acts as solvent and base and plays a key role in the cyclization step (Scheme 4). 2-Iodoanilines are preferred to 2-bromoanilines and react both as a free base and in the hydrochloride form although the latter in lower yield [40]. The reaction of arylacetylenes generally gave better yields than aliphatic acetylenes, and functional groups such as thiophenyl, acetal, THP, ester, keto and ether tolerate the reaction conditions. Reaction with alkylated aniline under the same conditions led to the corresponding enamine **20** as main product (52%), and only 20% of quinolin-4(1*H*)-one **19** was obtained, although subsequent treatment of the enamine with sodium hydride in THF led to quinolin-4(1*H*)-one **19** quantitatively [39, 41]. Decrease of CO pressure or temperature drops the reaction yield.



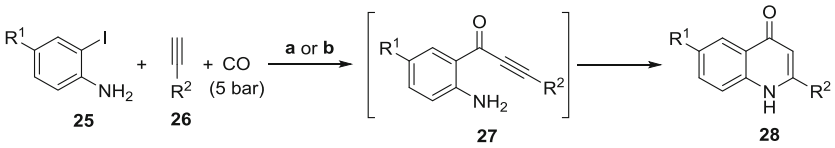
Scheme 4 Synthesis of 2-substituted quinolin-4(1*H*)-ones **19** by Pd-catalysed carbonylative coupling of 2-iodoanilines **16** with arylacetylenes **17** according to Torii [39, 41]



Scheme 5 A convergent synthesis of the quinolin-4(1*H*)-one **24** by Pd-catalysed carbonylative Sonogashira coupling of 2-iodo-5-methoxyaniline **21** with thiazolylacetylene **22** [42]

Quinolin-4(1*H*)-one **24**, a key substructure of the hepatitis C virus NS3 protease inhibitor BILN2061, was synthesized via a Pd-catalysed carbonylative Sonogashira coupling of 2-iodo-5-methoxyaniline **21** with thiazolylacetylene **22** (Scheme 5) [42].

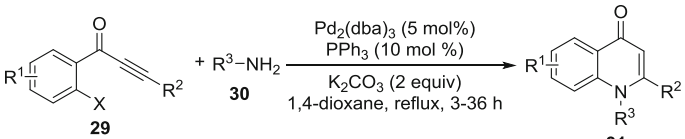
Djacovitch and co-workers have found that 2-substituted quinolin-4(1*H*)-ones could be selectively obtained through a one-pot two-step multi-catalysis using sequentially $PdCl_2$(dppp) and Et_2NH as catalysts (Scheme 6, **a**) [43]. The intermediate **27** is selectively produced by a Pd-catalysed carbonylative Sonogashira coupling between 2-iodoanilines **25**, alkynes **26** and CO (5 bar), using Et_3N as the base in the presence of $PdCl_2$(dppp) as catalyst. In the second step, an organocatalysed cyclization occurs after the addition of Et_2NH to give the expected quinolin-4(1*H*)-ones **28** in high yields and selectivity. This method although successful still suffers from the need of homogeneous catalysts which are tedious to remove and could result in high Pd and ligand contamination of the final products that is not acceptable when dealing with animal and human health. More recently the same authors extended the procedure to the use of heterogeneous catalysts associating the [Pd(PNP)]@SBA-15 catalyst to a grafted amine catalyst as [NH_2]@SBA-3 in a one-pot tandem [Pd/amine] mode that allowed, for example, the selective synthesis of 2-phenylquinolin-4(1*H*)-one in a suitable 61% isolated yield (Scheme 6, **b**) [44]. Interestingly, such an approach resulted in a strong decrease of



a: Homogeneous catalysis: R^1 = H, NO_2, Cl, F; R^2 = Ph, 4-OMePh, Bu; 26-98%
2-iodoaniline (3 mmol), alkyne (1.2 equiv), $PdCl_2$(dppp) (1 mol%), Et_3N (4 equiv), toluene, 80 °C, 6 h; then Et_2NH (4 equiv), rt, 2 h.

b: Heterogeneous catalysis: R^1 = H; R^2 = Ph; 60-72%
run 1: 2-iodoaniline (3 mmol), phenylacetylene (1.2 equiv), Pd(PNP)@SBA-15 (0.1 mol%), $[NH_2]$@SBA-3 (1 mol%), Et_3N (2.5 equiv), anisole (5 mL), 80 °C. For the next runs 2-3: the same stoichiometry was used but the amount of reactants and solvent was adjusted according to the collected amount of recovered catalysts mixture.

Scheme 6 Synthesis of 2-substituted quinolin-4(1*H*)-ones **28** by a carbonylative Sonogashira coupling reaction under homogeneous and heterogeneous Pd catalysis [43–45]



R^1 = H, Br
R^2 = 4-EtPh, 4-OMePh, 4-ClPh, 4-FPh, 3-ClPh, Ph, pyridin-3-yl
R^3 = Ph, 4-MePh, 3-MePh, 2-MePh, 4-OMePh, 2-OMePh, 4-NH_2Ph, 4-OHPh, 4-ClPh, 4-BrPh, 4-NO_2Ph, 4-CO_2EtPh, 4-AcPh, BuNH_2, naphtalen-1-yl, pyrimidin-5-yl

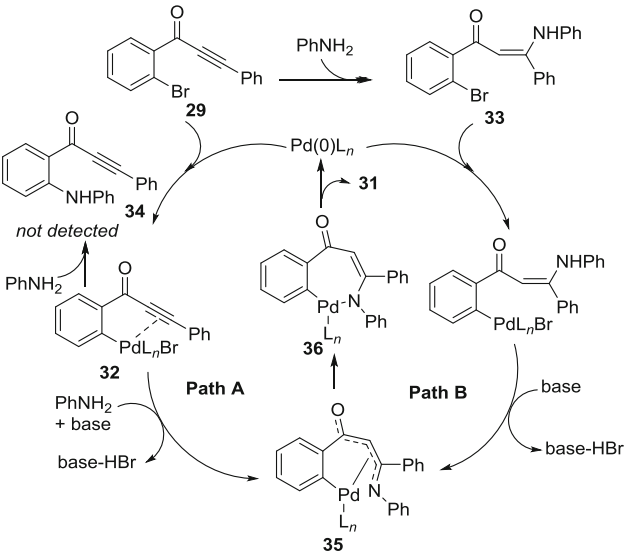
Scheme 7 Synthesis of functionalised quinolin-4(1*H*)-ones **31** through an efficient Pd-catalysed tandem amination approach [47]

Pd contamination in the final products since only 3–5 ppm of Pd was found in the crude quinolin-4(1*H*)-ones, while 40 ppm was measured when using homogeneous catalytic system. The overall reaction time was also reduced from 7 to 3 days (in the same reaction conditions). Recycling of the {[Pd(PNP)]@SBA-15/[NH_2]@SBA-3} catalyst mixture was successful for 3 runs [45, 46].

2.2 *Buchwald–Hartwig Reaction*

Functionalized quinolin-4(1*H*)-ones **31** were synthesized in good to excellent yields in one step through an efficient Pd-catalysed tandem amination approach, starting from easily accessible 2-haloaryl acetylenic ketones **29** and primary amines **30**, involving a sequential double C–N bond formation (Scheme 7) [47].

The reaction of **29** (X=Br, R^1=H) with aniline in the presence of $Pd(PPh_3)_4$ in 1,4-dioxane using K_2CO_3 as base afforded the corresponding quinolin-4(1*H*)-one **31** in 71% yield. A similar result was obtained using the $PdCl_2$(dppf)–CH_2Cl_2

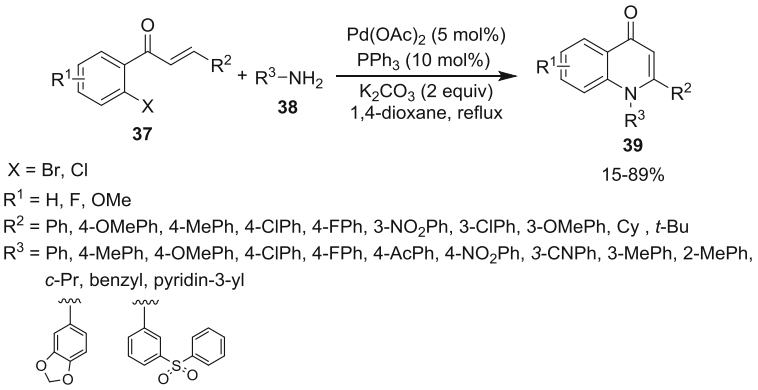


Scheme 8 Plausible mechanism for the synthesis of quinolin-4(1*H*)-ones **31** [47]

complex as catalyst. Improvements were made using $Pd_2(dba)_3$-$CHCl_3$ as catalyst combined with Xantphos or dppp, but PPh_3 proved to be the best ligand. A range of commercially available aryl amines can be employed to give the corresponding products in moderate to good yields (61–93%); however, with aliphatic amines such as butylamine, the product was obtained in moderate yield (42%). This reaction is also compatible with a variety of ynones substituted with aryl and pyridyl groups.

Two pathways are proposed as a possible mechanism for this reaction (Scheme 8), which may involve either oxidative addition of Pd(0) to the C–Br bond in **29** (intermediate **32** in Path A) or conjugate addition of aniline to **29** (intermediate **33** in path B) in the first step. The formed intermediate **32** presumably leads to **34** through Buchwald–Hartwig amination, or activation of a C≡C bond in **32** through coordination to the Pd and attack by aniline to form intermediate **35** can occur. Both pathways will go through intermediates **35** and **36**, followed by reductive elimination of Pd(0) to give the desired quinolin-4(1*H*)-one. On the basis of some experiments conducted by Xu and Zhao [47], path A could be the major pathway to afford the target quinolin-4(1*H*)-one.

More recently, Zhu and Shen reported an efficient Pd-catalysed tandem amination protocol for the synthesis of 1,2-disubstituted quinolin-4(1*H*)-ones **39** from easily accessible chalcones **37** and primary amines **38** in which the Pd catalyst [$Pd(OAc)_2$] plays a dual role, namely, in the Buchwald–Hartwig coupling and catalytic dehydrogenation (Scheme 9) [48]. $Pd_2(dba)_3$ that was a good catalyst in the Pd-catalysed tandem amination of 2-haloaryl acetylenic ketones and primary amines [47] proved to be less effective than $Pd(OAc)_2$ in this transformation (55% and 74%, respectively). A procedure using PPh_3 as a ligand in refluxing anhydrous



Scheme 9 Synthesis of 1,2-disubstituted quinolin-4(1*H*)-ones **39** through a Buchwald–Hartwig coupling/Michael addition sequence [48]

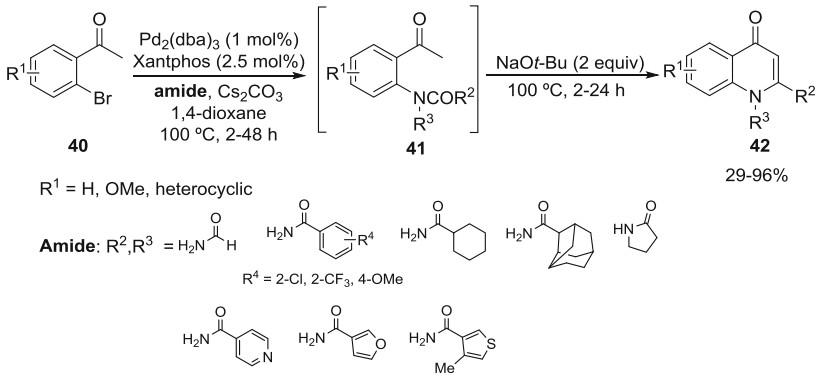
1,4-dioxane and K_2CO_3 as base was efficient with aromatic, heteroaromatic and aliphatic amines, the later in slightly lower yields. Due to the low oxidative addition reactivity of the C–Cl bond, 2-chloro-substituted chalcones gave quinolin-4(1*H*)-ones in lower yield than the correspondent bromo derivatives, even upon raised temperature.

2.3 *Sequential Pd-Catalysed Amidation and Base-Promoted Cyclization*

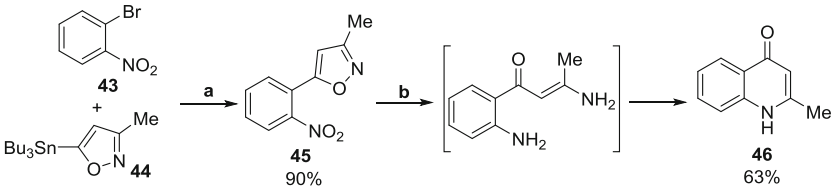
A variety of 2-substituted quinolin-4(1*H*)-ones **42** were obtained via sequential Pd-catalysed amidation of 2′-bromoacetophenones **40** followed by base-promoted intramolecular cyclization in a one-pot procedure under mild conditions (Scheme 10) [49]. The best solvent–base combination for this reaction was 1,4-dioxane/Cs_2CO_3. The addition of a strong base, either NaOH or NaO*t*-Bu, was found to be necessary to avoid the hydrolysis of the amide before cyclization. The scope of the reaction was quite general for both coupling partners although acyclic secondary amides were not successful.

2.4 *Stille Reaction*

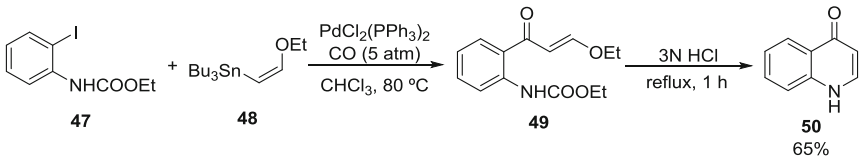
Yamanaka and co-workers described the synthesis of 2-methylquinolin-4(1*H*)-one **46** in 57% overall yield from the Pd-catalysed cross-coupling reaction of 3-methyl-5-(tributylstannyl)isoxazole **44** with 2-bromonitrobenzene **43** followed by the catalytic hydrogenation of **45** over Raney nickel (Scheme 11) [50].



Scheme 10 Synthesis of 2-substituted quinolin-4(1*H*)-ones **42** via sequential Pd-catalysed amidation followed by base-promoted intramolecular cyclization [49]

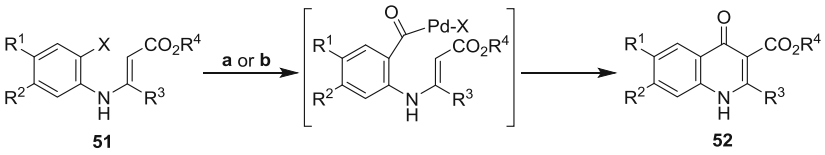


Scheme 11 Synthesis of 2-methylquinolin-4(1*H*)-one **46** via Stille reaction followed by catalytic hydrogenation [50]



Scheme 12 Synthesis of quinolin-4(1*H*)-one **50** via carbonylative Stille reaction followed by cyclization [51]

Later, the same author reported the Pd-catalysed carbonylative coupling of ethyl 2-iodophenylcarbanylate **47** with (*Z*)-tributyl(2-ethoxyvinyl)stannane **48** under CO atmosphere [51]. The obtained ethyl (*E*)-2-(3-ethoxy-1-oxoprop-2-en-1-yl)phenyl carbanilate **49** underwent cyclization under acidic conditions to give quinolin-4 (1*H*)-one **50** (Scheme 12).



X = Br, I; R^1= H, F; R^2 = H, Cl, F; R^3 = Me, CO_2Me, CH_2CO_2Me; R^4 = Me
a: 1) $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), CO (20 $kgcm^{-2}$ for X = I and 30 $kgcm^{-2}$ for X = Br), K_2CO_3, DMF, 120 ºC, 20 h; 2) diazomethane; 24-82%

X = Br, I; R^1 = CN, CO_2Et, NO_2; R^2 = H; R^3 = CF_3; R^4 = Et
b: $Pd(OAc)_2$ (1 mol%), PPh_3 (19 mol%), CO, $NaHCO_3$, DMF, 120 ºC, 2 h; 54-77%

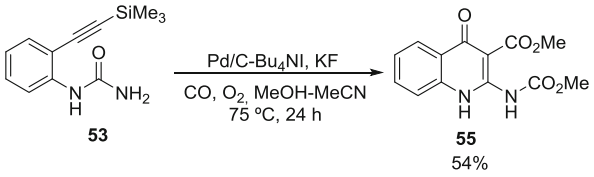
Scheme 13 Synthesis of quinolin-4(1*H*)-ones **52** via Pd-catalysed carbonylative cyclization of 2-haloenamines **51** [52–54]

2.5 Cyclocarbonylation Reaction

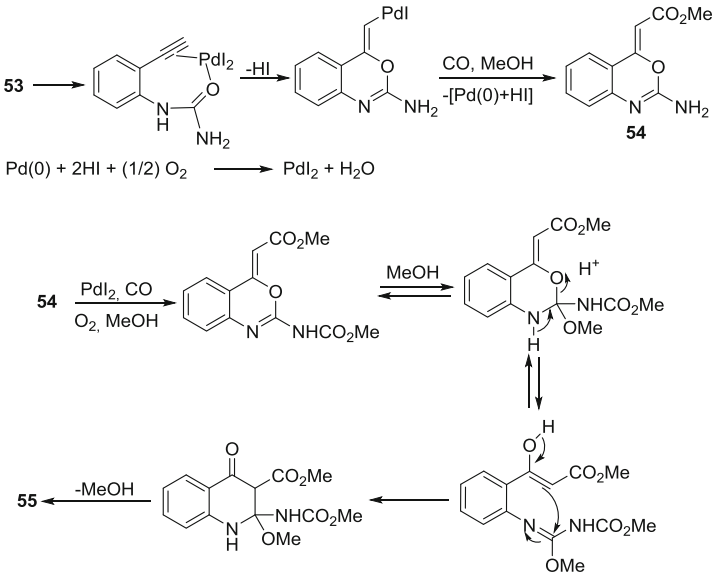
Carbonylation of 3-substituted 3-(2-haloarylamino)prop-2-enoates **51** in the presence of Pd catalyst under CO atmosphere resulted in heterocyclization to form a variety of 2-substituted quinolin-4(1*H*)-one-3-carboxylates **52** [52]. Cyclocarbonylation of iodoenamine **51** was effective at 20 kg cm^{-2}, whereas 30 kg cm^{-2} was required for the bromoenamine **51**. After treatment with diazomethane, to avoid the presence of quinolin-4(1*H*)-one-3-carboxylic acid, quinolin-4(1*H*)-ones **52** were obtained in moderate to good yields (55–82%) although derivatives involving 2-methoxycarbonyl group or 6,7-difluoride gave lower yields (24% and 37%, respectively) (Scheme 13, **a**). Under the same conditions, but using CO at atmospheric pressure, Stanforth et al. reported the synthesis of three 2-trifluoromethylated quinolin-4(1*H*)-ones (Scheme 13, **b**) [53, 54].

Gabriele and co-workers isolated quinolin-4(1*H*)-one **55** from Pd-catalysed cyclization–alkoxycarbonylation of 1-[2-(trimethylsilylethynyl)phenyl]urea **53** using Pd/C-Bu_4NI as catalyst in the presence of KF for the in situ deprotection (Scheme 14) [55, 56]. Formation of quinolin-4(1*H*)-one **55** is quite intriguing, and the authors described it from some sort of rearrangement, probably via intermediate formation of the benzoxazine derivative **54**. A reasonable mechanistic hypothesis, proposed by the authors, that requires further investigation is depicted in Scheme 15. The nature of the substituent is crucial for the product formation. In the case of an unsubstituted urea **53**, quinolin-4(1*H*)-one **55** was the only isolated reaction product, but when it is substituted, no quinolin-4(1*H*)-one was obtained [55].

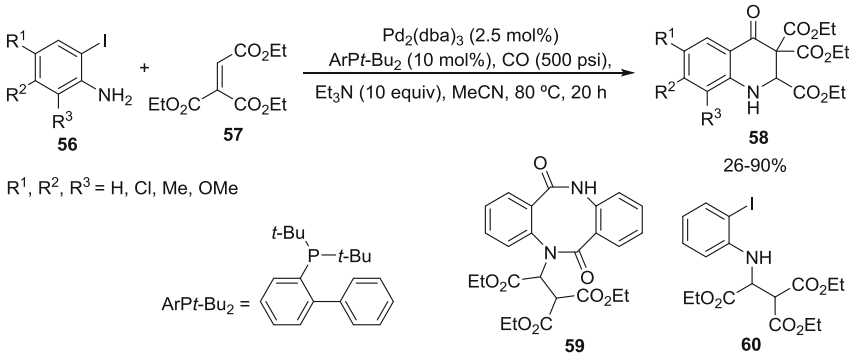
Alper and co-workers reported a Pd-catalysed intermolecular cyclocarbonylation of 2-iodoanilines **56** with diethyl ethoxycarbonylbutendienoate **57** to produce highly functionalized 2,3-dihydroquinolin-4(1*H*)-ones **58** in one step with moderate to good yields (Scheme 16) [57]. The method involves a Michael addition and subsequent carbonylation reactions using the catalytic system of $Pd_2(dba)_3$/2-(di-*tert*-butylphosphino)biphenyl in MeCN at 80°C under 500 psi of CO. The use of CH_2Cl_2 or THF as solvent favours the formation of the Michael



Scheme 14 Synthesis of quinolin-4(1*H*)-one **55** via Pd-catalysed oxidative carbonylation of 1-[2-(trimethylsilylethynyl)phenyl]urea **53** [55, 56]



Scheme 15 Proposed reaction mechanism for the formation of quinolin-4(1*H*)-one **55** via Pd-catalysed oxidative carbonylation of 1-[2-(trimethylsilylethynyl)phenyl]urea **53** [55, 56]



Scheme 16 Synthesis of 2,3-dihydroquinolin-4(1*H*)-ones **58** by Pd-catalysed intermolecular cyclocarbonylation of 2-iodoanilines **56** and diethyl ethoxycarbonyl butendienoate **57** [57]

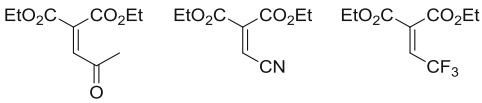


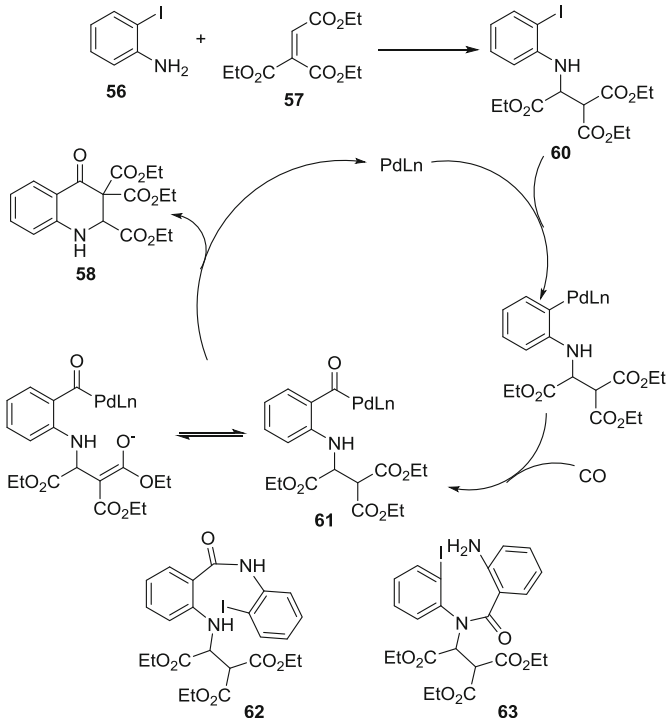
Fig. 2 Michael acceptors [57]

addition product **60** in more than 80% yield being the unique reaction product with no carbonylation taking place. Electron-donating phosphines, such as trialkylphosphines and dialkylarylphosphines, tend to give better yields; however, the authors found that 2-(di-*tert*-butylphosphino)biphenyl was the better ligand. Xantphos behaved differently and led to the formation of **59** much more selectively than when using any other ligands. The reaction is sensitive to the electronic nature of the substituents at the *para*-position relatively to the iodide group. Highly electron-donating or electron-withdrawing groups, such as methoxyl and chlorine, afforded **58** in lower yields (39% and 26%, respectively). The substituents influence the rate of the carbonylation and Michael addition steps and both can take place independently. Thus a favourable balance of the rate between these two reactions led to the successful results. No product was isolated in the reaction of **56** with a tetrasubstituted olefin indicating that initial Michael addition cannot take place probably due to steric effects. Other types of Michael acceptors (Fig. 2) were examined leading to unsatisfactory yields even after a brief screening (phosphines and bases) to optimize the reaction conditions (14–35%).

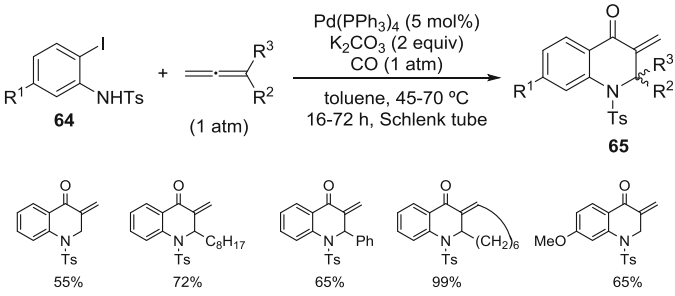
The formation of **58** involves the Michael addition of 2-iodoaniline **56** to diethyl ethoxycarbonylbutendienoate **57** as the first step to produce the Michael adduct **60**. Then the phosphine-ligated Pd(0) species undergoes oxidative addition to the C–I bond of **60**, followed by insertion of CO giving the aroyl–Pd intermediate **61**. Nucleophilic attack of the internal malonate anion on the aroyl-Pd intermediate **61** completes the catalytic cycle affording quinolin-4(1*H*)-ones **58** regenerating the Pd(0) species. Formation of **59** was explained by intermolecular double carbonylation of **56** with **60** formed in situ. First intermolecular carbonylation takes place between **56** and **60** affording an acyclic amide **62** and/or **63**, which can then undergo a second intramolecular carbonylation to give the final product **59** (Scheme 17).

A Pd(0)-catalysed termolecular queuing process involving oxidative addition of an aryl iodide **64** followed by carbonylation, allene insertion and capture of the resulting π-allyl-Pd(II) species by an internal *N*-nucleophile was described [58]. CO at atmospheric pressure was employed in contrast to Alper's reported cascades of a similar type [59] which were carried out at high pressures of CO (20 atm). Under optimal conditions, a (3+1+2)-cycloaddition reaction of 2-iodo-1-tosylaniline was undertaken using allene (1 atm) and CO (1 atm) to afford quinolin-4(1*H*)-ones **65** in good yields (55–99%) (Scheme 18). This reaction tolerates substituents on both allene and aryl iodide allowing access to an array of heterocycles with *s-cis* enone moieties.

In the first step of the catalytic cycle, the Pd(0) catalyst undergoes oxidative addition to the aryl iodide **64** bond followed by coordination and insertion of CO. The acyl–Pd(II) intermediate **66** adds to the allene at the central carbon atom



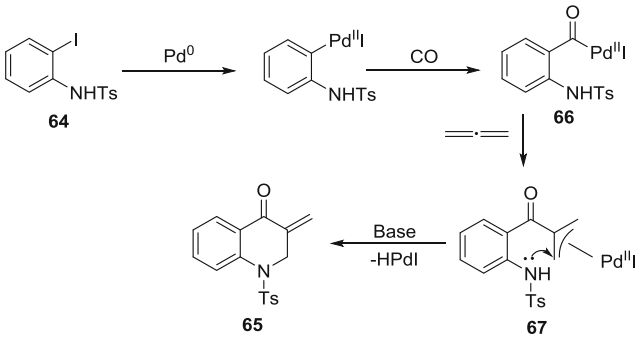
Scheme 17 Probable reaction mechanism for the formation of 2,3-dihydroquinolin-4(1*H*)-ones **58** by Pd-catalysed intermolecular cyclocarbonylation of 2-iodoanilines **56** and diethyl ethoxycarbonyl butendienoate **57** [57]



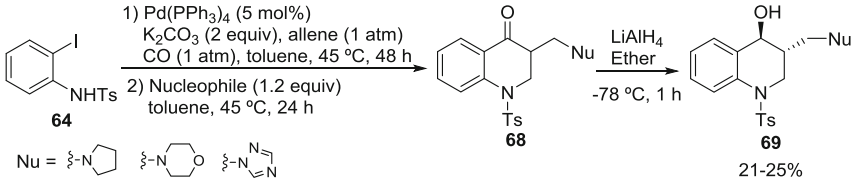
Scheme 18 Synthesis of quinolin-4(1*H*)-ones **65** via a Pd-catalysed cascade carbonylation–allene insertion [58]

to furnish a π-allyl-Pd(II) species **67** which undergoes nucleophilic attack by the internal nucleophile to give the enone product **65** (Scheme 19) [58].

These authors also described a one-pot quinolin-4(1*H*)-one synthesis–Michael addition starting from 2-iodo-1-tosylaniline **64**, CO (1 atm) and allene (1 atm) in toluene at 45°C during 48 h (Scheme 20) [58]. Both aliphatic and heteroaromatic



Scheme 19 Proposed reaction mechanism for the formation of quinolin-4(1*H*)-ones **65** via a Pd-catalysed cascade carbonylation–allene insertion [58]

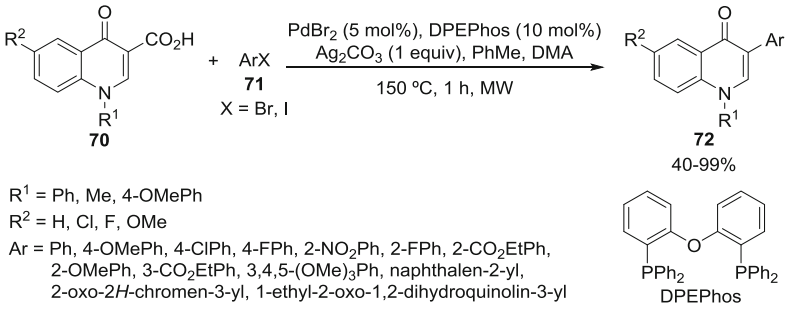


Scheme 20 Synthesis of γ-amino alcohols **69** via Pd-catalysed cascade carbonylation–allene insertion–Michael addition followed by reduction of the corresponding quinolin-4(1*H*)-ones **68** [58]

N-nucleophiles were effective, and in the case of 1,2,4-triazole, only the 1-substituted triazole was observed. As the obtained Michael adducts **68** were sensitive to retro-Michael addition, the authors performed the reduction with $LiAlH_4$, without prior isolation, obtaining the corresponding γ-amino alcohols **69** as single stereoisomers.

2.6 Others

An efficient metal-catalysed decarboxylative cross-coupling reaction of quinolin-4(1*H*)-one-3-carboxylic acids **70** with various (hetero)aryl halides **71** has been described (Scheme 21) [60]. An extensive screening of various reaction parameters (Pd, ligand, solvent, base and temperature) showed that PdI_2, $Pd(OAc)_2$ and $PdCl_2$ were less effective than $PdBr_2$. The nature of phosphine ligand has an important influence on selectivity and optimal conditions on the reaction of **70** (R^1=Ph; R^2=H) with 4-iodoanisole **71** involved the combination of the bidentate phosphine DPEphos with $PdBr_2$ in toluene/DMA at 150°C. The use of microwave irradiation provided shortening of reaction time and increase of quinolin-4(1*H*)-one **72** yield (MW, 1 h, 81%; CH, 8 h, 77% and 1 h, 60%). The bimetallic system $PdBr_2/Ag_2CO_3$ is necessary for the coupling to occur; no product could be formed in the absence of

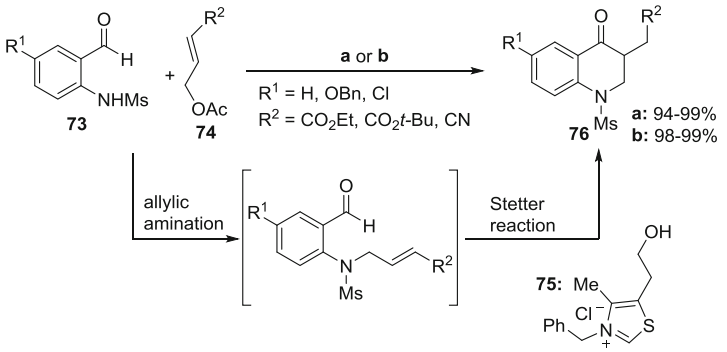


Scheme 21 Metal-catalysed decarboxylative coupling reaction of quinolin-4(1*H*)-one-3-carboxylic acids **70** with (hetero)aryl halides **71** [60]

$PdBr_2$ or when Ag_2CO_3 was replaced by other bases. Using optimal conditions under microwave irradiation, electron-rich and electron-deficient *ortho*-, *meta*- and *para*-substituted aryl iodides and bromides all efficiently underwent decarboxylative coupling in good yields (40–99%), and the coupling with heterocyclic halides was also successful [40% for 3-bromocoumarin and 57% for 3-bromoquinolin-2(1*H*)-one]. Both *N*-alkyl- and *N*-arylquinolin-4(1*H*)-one-3-carboxylic acids **70** having electron-donating or electron-withdrawing groups on the aromatic nucleus led to the formation of the corresponding coupled products **72** in good yields (60–90%). Excellent chemical selectivity was observed for **70** (R^2=Cl), preserving the C–Cl bond, which could undergo further metal-catalysed functionalization reactions. This protocol is an attractive alternative to the existing methods for the synthesis of 3-(hetero)arylquinolin-4(1*H*)-ones **72** and was also applied to the synthesis of 1-methyl-3-phenylquinolin-2(1*H*)-one (44%).

Y. Hamada and co-workers reported an interesting method for the synthesis of 3-substituted 2,3-dihydroquinolin-4(1*H*)-ones starting from 2-aminobenzaldehydes and allylic acetates, using a one-pot multi-catalytic cascade process: Pd-catalysed allylic amination–thiazolium salt-catalysed Stetter reaction (Scheme 22) [61, 62]. Under optimized conditions the one-pot sequential two-step multi-catalytic cascade process afforded 2,3-dihydroquinolin-4(1*H*)-ones **76** in excellent yields (94–99%) and is applicable for 2-aminobenzaldehydes **73** bearing electron-donating and electron-withdrawing substituents on the aromatic ring, although, in contrast to that of γ-acetoxy α,β-unsaturated esters **74** (R^2=CO_2Et, CO_2*t*-Bu), the reaction did not proceeded for γ-acetoxy α,β-unsaturated nitrile **74** (R^2=CN) (Scheme 22, **a**). When performing the one-pot sequential multi-catalytic cascade process in the presence of both catalysts (one-step procedure), the reaction proceeded well with the three different allylic acetates **74** giving 2,3-dihydroquinolin-4(1*H*)-ones **76** in excellent yields (98–99%), but, on the other hand, the allylic amination occurred only for the unsubstituted 2-aminobenzaldehyde **73**: R=H (98%) (Scheme 22, **b**).

A range of 2,3-dihydroquinolin-4(1*H*)-ones were synthesized by Pd(0)-catalysed intramolecular coupling of β-(2-iodoanilino)esters in moderate to good

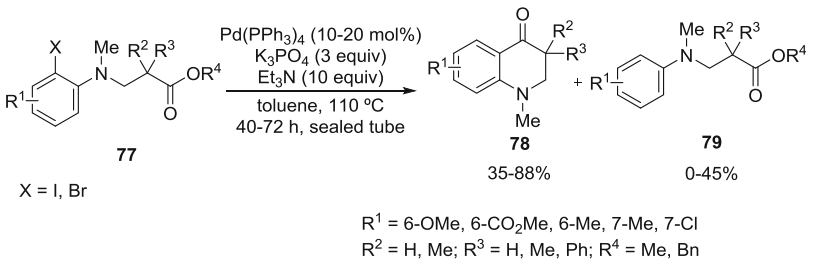


a: *Two-step procedure:* 1) $Pd(OAc)_2$ (5 mol%), PPh_3 (12 mol%), *i*-Pr_2NEt (5 equiv), *t*-BuOH (0.1 M), rt, 6-16 h; 2) **75** (20-30 mol%), 50 °C, 12-24 h;
b: *One-step procedure:* **75** (20-30 mol%), $Pd(OAc)_2$ (5 mol%), PPh_3 (12 mol%), *i*-Pr_2NEt (5 equiv), *t*-BuOH (0.1 M), 50 °C, 12-24 h.

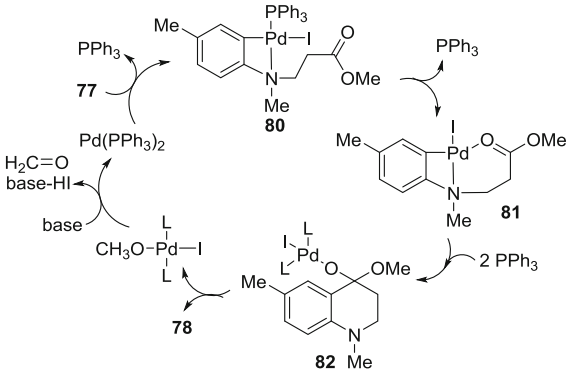
Scheme 22 Synthesis of 3-substituted 2,3-dihydroquinolin-4(1*H*)-ones **76** by Pd-catalysed allylic amination/thiazolium salt-catalysed Stetter cascade reaction [61]

yields (Scheme 23) [63]. The use of $Pd(PPh_3)_4$ as the catalyst and Cs_2CO_3 as base in THF resulted exclusively in the reduction product **79** (40%) although using K_3PO_4 as base in combination with Et_3N and toluene led to an increase in the yield of ketone **78** to 65%. These compounds resulted from the nucleophilic substitution at the alkoxycarbonyl group. Substituents on the aromatic ring have little effect on the carbopalladation reaction evidencing that the nucleophilicity of the aryl–Pd species does not appear to be affected by the electronic properties of the substituent. The low yield for the product derived from **77** (R^1=6-CO_2Me) is mainly a consequence of the competitive retro-Michael fragmentation of the β-amino ester. The benzyl ester counterpart of **77** (R^4=Bn) can also be used as substrate; however, the desired product is formed in better yields when a methyl ester, R^4=Me, is used (50% and 65%, respectively). The reaction of amino esters **77** without hydrogen atoms α to the carbonyl group proceeded smoothly to give exclusively the corresponding ketones **78** in high yields (79–88%). On the other hand, no competition between nucleophilic attack at the carbonyl group and α-arylation was observed in the reactions of amino esters **77** which contain hydrogen atoms α to the carbonyl group; however, ketones **78** (35–67%) were obtained together with the reduction products **79** (25–45%).

This Pd(0)-catalysed cyclization involves the oxidative addition of the aryl iodide to a Pd(0) species affording a four-membered azapalladacycle **80**. A carbopalladation between the α-aryl–Pd moiety and the alkoxycarbonyl group would then lead to the alkoxide-Pd(II) chelate **82**. The coordination of the N atom to the Pd centre in **80** brings the carbonyl group nearer to the metal to facilitate the formation of a transient chelated intermediate **81** in which the carbonyl group is coordinated to the Pd centre and increases the electron density on the Pd centre to enable the otherwise unfavourable carbopalladation reaction to occur. β-Alkoxide elimination from **82** would afford ketone **78** and a Pd(II) alkoxide, which would finally undergo β-hydride elimination to regenerate the Pd(0) catalyst. The



Scheme 23 Synthesis of 2,3-dihydroquinolin-4(1*H*)-ones **78** by Pd(0)-catalysed intramolecular coupling of β-(2-iodoanilino)esters **77** [63]



Scheme 24 Proposed Pd-catalysed acylation reaction mechanism in the formation of 2,3-dihydroquinolin-4(1*H*)-ones **78** [63]

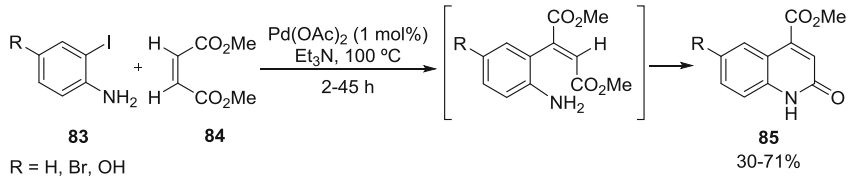
reduction sequence is supported by the isolation of significant amounts of benzaldehyde in the reaction of benzyl ester **77** (R^4=Bn) (Scheme 24).

3 Synthesis of Quinolin-2(1*H*)-ones

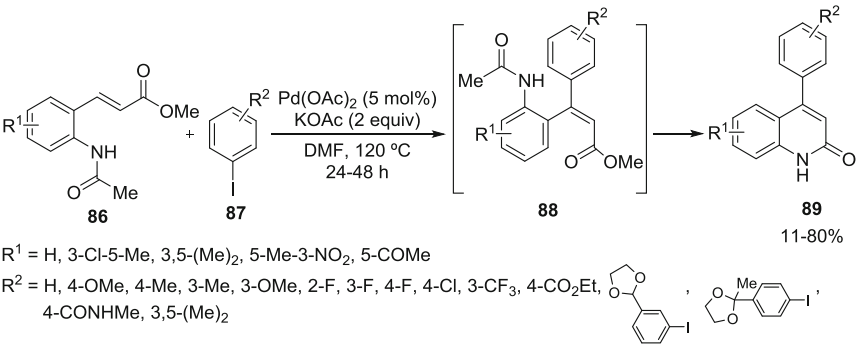
3.1 Pd-Catalysed Cross-Coupling Reactions

3.1.1 Heck Reaction

In 1978, Heck and co-workers reported for the first time the synthesis of quinolin-2(1*H*)-ones from vinylic substitution of 1,2-disubstituted olefins with 2-iodoanilines [64]. Reaction of 2-iodoanilines **83** with dimethyl maleate **84** using $Pd(OAc)_2$ as catalyst and Et_3N as base in acetonitrile at 100°C afforded, as expected from previous reaction with 4-iodoaniline, the appropriate intermediate amino esters that in situ cyclize to the quinolin-2(1*H*)-ones **85**, in moderate to good yields (71%, 55% and 30% for R=H, Br and OH, respectively), because the β-carboxymethyl group was very close to the amino group (Scheme 25). If diethyl



Scheme 25 Synthesis of quinolin-2(1*H*)-ones **85** from the Heck reaction of 2-iodoanilines **83** with dimethyl maleate **84** [64]



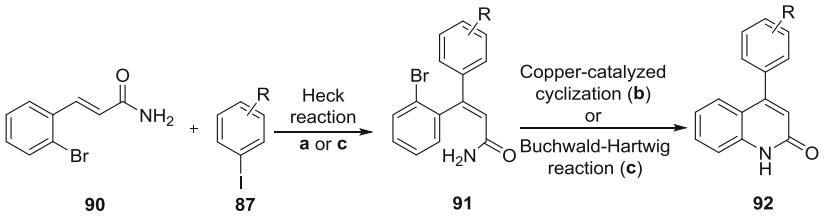
Scheme 26 Synthesis of 4-arylquinolin-2(1*H*)-ones **89** from methyl β-(2-acetamidoaryl)acrylates **86** through a domino Heck cyclization with aryl iodides **87** [65]

fumarate is used, instead of dimethyl maleate, the stereochemistry of the intermediate amino ester did not allow cyclization, because the β-carboxymethyl group was far from the amino group, without first isomerizing, although quinolin-2(1*H*)-one **85** was isolated in 47% yield along with 20% of aniline. In this case, isomerization of the intermediate should occur fairly easily or the σ-bonded Pd intermediate cyclizes readily in this reaction.

4-Phenylquinolin-2(1*H*)-one was also prepared using this methodology. First, reaction of 2-iodoaniline with (*Z*)-*N*-phenylcinnamamide led to 4-phenylquinolin-2(1*H*)-one in good yield (66%), and, as described above, the use of (*E*)-*N*-phenylcinnamamide afforded the 4-phenylquinolin-2(1*H*)-one but only in 15% yield. Another way to prepare 4-phenylquinolin-2(1*H*)-one was the reaction of (*E*)-2-aminocinnamic acid with iodobenzene, which gives the expected quinolin-2(1*H*)-one in good yield (71%).

Cacchi and co-workers described a straightforward approach to free NH 4-arylquinolin-2(1*H*)-ones **89** (30–80%) from readily available methyl β-(2-acetamidophenyl)acrylates **86** through a domino Heck cyclization reaction with aryl iodides **87** in the presence of $Pd(OAc)_2$ and KOAc in DMF at 120°C (Scheme 26) [65]. The vinylic substitution intermediate **88** was only observed when the reaction was performed at lower temperatures (25% at 80°C and 30% at 60°C).

The same authors have also shown that β-(2-bromophenyl)acrylamide **90** can also be used in the synthesis of 4-arylquinolin-2(1*H*)-ones **92** through a sequential Heck reaction–Cu-catalysed cyclization, using neutral, electron-rich

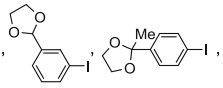


a: $Pd(OAc)_2$ (1-5 mol%), Et_3N, 100 ºC, 12-48 h; **b:** CuI, NaI, K_3PO_4, DMEDA, dioxane, 120 ºC, 24 h;

c: $Pd(OAc)_2$ (5 mol%), Bu_4NOAc (3 equiv), Bu_4NBr (3 equiv), 120 ºC, 24-48 h.

a,**b:** R = H, 4-OMe, 3-OMe, 3-F, 4-CO_2Et

c: R = H, 4-OMe, 4-Me, 3-OMe, 3-F, 3-CF_3, 4-CO_2Et, 2-F, 3-$CON(Me)_2$, 4-$CON(Me)_2$

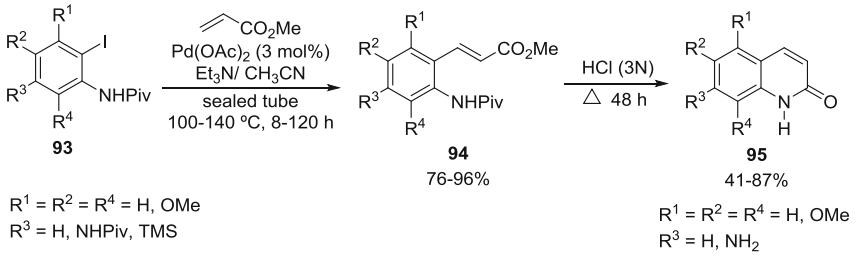


Scheme 27 Synthesis of 4-arylquinolin-2(1*H*)-ones **92** through a sequential Heck–Cu-catalysed cyclization process (**a**,**b**) or through a pseudo-domino Heck–Buchwald–Hartwig process (**c**) [66, 67]

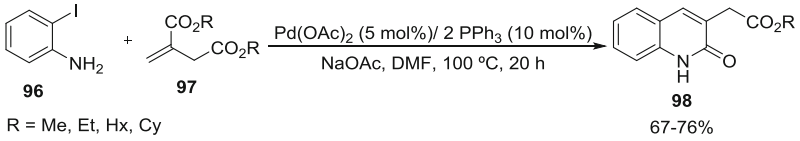
and electron-poor aryl iodides (Scheme 27, **a**,**b**). The optimized cyclization conditions involve 20 mol% CuI, 2 equiv. NaI, 2 equiv. K_3PO_4 and 0.4 equiv. DMEDA in 1,4-dioxane at 120°C; the reaction did not work in the absence of CuI [66]. Later they have shown that the reaction sequence can also be done using a pseudo-domino process that involves two mechanistically independent catalytic cycles, a Heck reaction of 2-bromocinnamamide with aryl iodides followed by an intramolecular Buchwald–Hartwig C–N bond-forming reaction (Scheme 27, **c**) [67]. Phosphine-free $Pd(OAc)_2$ is used as the pre-catalyst and a molten tetrabutylammonium acetate/tetrabutylammonium bromide as the reaction medium, at 120°C, in the Heck reaction.

Methoxyquinolin-2(1*H*)-ones were prepared from methoxylated pivaloylaminobenzenes via metalation, Heck coupling reaction and cyclization [68]. The quinolin-2(1*H*)-one ring was obtained in two steps from the iodo derivatives **93**, which were synthesized by metalation of the corresponding polymethoxypivaloylaminobenzenes with BuLi. Then the methyl methoxypivaloylaminocinamates **94** were prepared via Heck coupling reaction of **93** with methyl acrylate using Pd $(OAc)_2$ as catalyst and Et_3N as base in acetonitrile at 100°C. Cyclization to quinolin-2(1*H*)-one **95** was then performed in acidic medium in fairly good overall yields (19–62%) (Scheme 28).

The coupling–cyclization of 2-iodoaniline **96** with α,β-unsaturated carbonyl compounds **97** in DMF at 100°C in the presence of a catalytic amount of a Pd catalyst along with a base afforded 3-substituted quinolin-2(1*H*)-ones **98** in moderate to good yields (67–76%) (Scheme 29) [69]. The best conditions found were the use of 5 mol% $Pd(OAc)_2$ as catalyst, 10 mol% PPh_3 as ligand and 6 equiv. NaOAc as base. In the same conditions, $PdCl_2(PPh_3)_2$ was also effective. If a ketone group is linked to the vinyl carbon of the starting alkenes instead of a carboalkoxyl group, 2,3- or 2,4-disubstituted quinolines were obtained, depending if the α- or the β-position of the alkene is substituted.



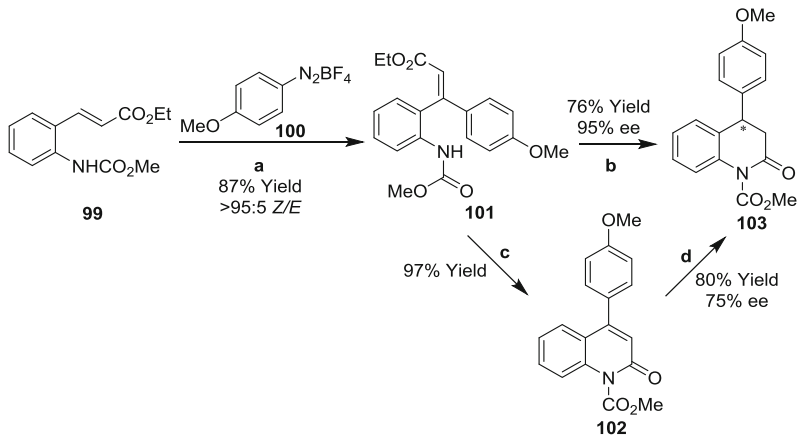
Scheme 28 Synthesis of methoxyquinolin-2(1*H*)-ones **95** from methoxylated iodopivaloylaminobenzenes **93** via Heck coupling reaction and cyclization [68]



Scheme 29 Synthesis of 3-substituted quinolin-2(1*H*)-ones **98** via Heck coupling–cyclization of 2-iodoaniline **96** with α,β-unsaturated carbonyl compounds **97** [69]

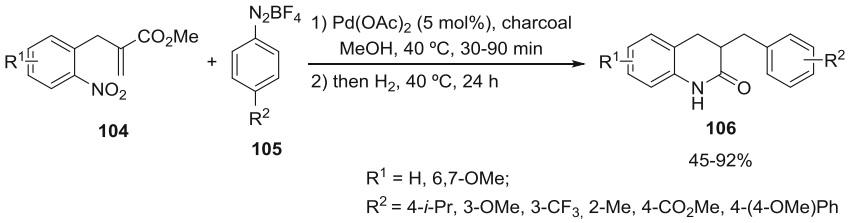
4-Methoxyphenylquinolin-2(1*H*)-one **102** was prepared via a ligand-free Pd-catalysed Heck–Matsuda reaction of cinnamate ester **99** with arene diazonium-tetrafluoroborate **100** followed by a Cu-catalysed asymmetric 1,4-reduction–cyclization of the obtained *β*,*β*-diaryl acrylate **101** (Scheme 30, **a**) [70]. The presence of the base (in this case 2,6-di-*tert*-butyl-4-methylpyridine) is important for the excellent stereoselectivity (>95:5 *Z*/*E*) due to the scavenging of PdH, preventing its reinsertion which is responsible for isomerization of the Heck adducts. Based on the enantioselective synthesis of *β*,*β*-diaryl propanoates by Cu-catalysed 1,4-reduction of β,β-diaryl acrylate using $Cu(OAc)_2$ and *R*-JOSIPHOS as ligand in the presence of an excess of PMHS, the cyclization of intermediates **101** gave almost quantitatively quinolin-2(1*H*)-one **102** using 4 equiv. of PHMS/*t*-BuOH (an intramolecular amidation reaction took place in preference to the 1,4-reduction) (Scheme 30, **c**). By using 10 equiv. of PHMS/*t*-BuOH, the expected dihydroquinolin-2(1*H*)-one **103** is obtained in good yield (Scheme 30, **b**). Dihydroquinolin-2(1*H*)-one **103** can also be prepared by subjecting quinolin-2(1*H*)-one **102** to a second Cu-catalysed 1,4-reduction (Scheme 30, **d**).

A Pd-catalysed one-pot sequential Heck–reduction–cyclization (HRC) methodology led to a selective synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **106** and **109** using either heterogeneous catalysts (Scheme 31) or mixed homogeneous–heterogeneous catalysts (Scheme 32) with in situ generated Pd/C [46, 71]. The overall reaction sequence proceeds under mild conditions providing good to high isolated yields starting either from 2-(2-nitrobenzyl)acrylates **104** and aryldiazonium salts **105** or 2-nitrobenzenediazonium salts **107** and acrylates **108**. Recycling experiments showed that the reused heterogeneous Pd/C catalyst was not able to promote another HRC sequence, but was still highly active for hydrogenation reactions.

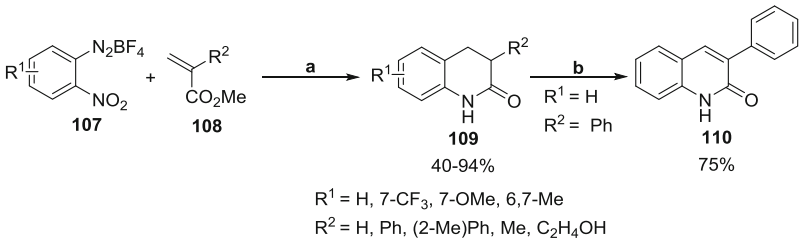


a: $Pd(OAc)_2$ (5 mol%), DTBMP (1.2 equiv), EtOH:BnCN (1:1), 60 °C, 14 h; **b:** $Cu(OAc)_2$ (3 mol%), *R*-JOSIPHOS (4 mol%), PHMS (10 equiv), *t*-BuOH (10 equiv), toluene, rt, 16 h; **c:** $Cu(OAc)_2$ (3 mol%), *R*-JOSIPHOS (4 mol%), PHMS (4 equiv), *t*-BuOH (4 equiv), toluene, rt, 16 h; **d:** $Cu(OAc)_2$ (3 mol%), *R*-JOSIPHOS (4 mol%), PHMS (10 equiv), *t*-BuOH (10 equiv), toluene, rt, 16 h.

Scheme 30 Synthesis of 4-methoxyphenylquinolin-2(1*H*)-one **102** via a Pd-catalysed Heck–Matsuda reaction of cinnamate ester **99** with arene diazoniumtetrafluoroborate **100** followed by a Cu-catalysed asymmetric 1,4-reduction-cyclization [70]

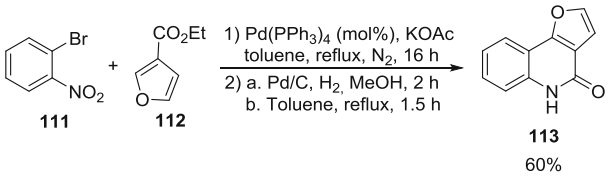


Scheme 31 Heterogeneous tandem HRC synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **106** from 2-(2-nitrobenzyl)acrylates **104** and aryldiazonium salts **105** [71]

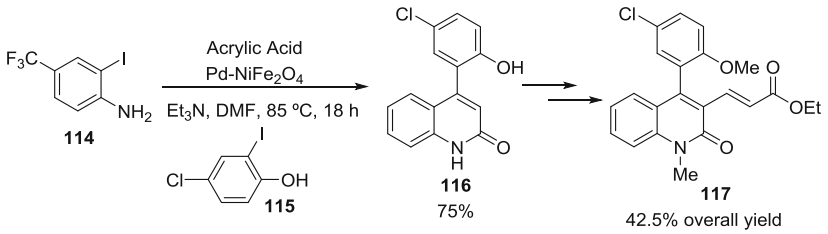


a: 1) $Pd(OAc)_2$ (5 mol%), 1,4-dioxane, 40 °C, 30-90 min; 2) then charcoal, H_2, 40 °C, 24 h
b: *t*-BuOH, KO*t*-Bu, DMSO, 25 °C, 24 h

Scheme 32 Homogeneous–heterogeneous sequential HRC synthesis of 3,4-dihydroquinolin-2(1*H*)-one **109** from 2-nitrobenzenediazonium salts **107** and acrylates **108** [71]



Scheme 33 Synthesis of furo[3,2-*c*]quinolin-4(5*H*)-one **113** through two sequential Pd-catalysed reactions of ethyl 3-furoate **112** with 1-bromo-2-nitrobenzene **111** [72]



Scheme 34 Synthesis of 4-arylquinolin-2(1*H*)-one **116** by Heck reaction of 2-iodoanilines **114** with acrylic acid and 2-iodophenol **115** followed by in situ cyclization [73]

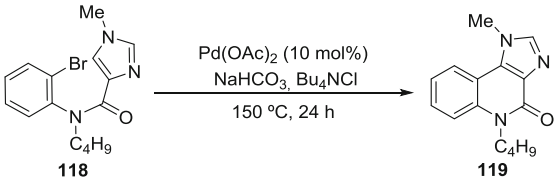
3,4-Dihydroquinolin-2(1*H*)-ones could be easily dehydrogenated under mild oxidative conditions (Scheme 32).

Two efficient sequential Pd-catalysed reactions for synthesis of furo[3,2-*c*]quinolin-4(5*H*)-one **113** in 60% overall yield were reported as shown in Scheme 33 [72]. Arylation of ethyl 3-furoate **112** with 1-bromo-2-nitrobenzene **111** in the presence of $Pd(PPh_3)_4$ afforded 2-aryl furoate (80%). Hydrogenation of the nitro group with Pd/C as catalyst and subsequent cyclization occurred uneventfully to provide furo[3,2-*c*]quinolin-4(5*H*)-one **113** (75%).

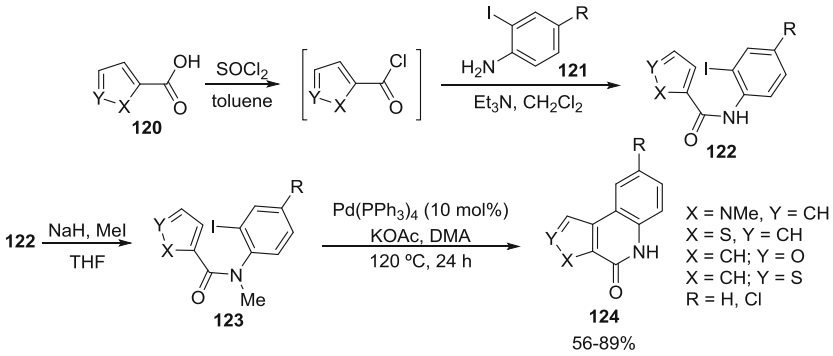
A convenient one-pot method for the synthesis of 4-arylquinolin-2(1*H*)-one **116** has been described [73]. The successive Heck reaction on substituted 2-iodoaniline **114** with acrylic acid and 2-iodophenol **115** catalysed by a Pd/nickel ferrite catalyst followed by in situ cyclization was the key step in the synthesis of 4-arylquinolin-2(1*H*)-one **116**. The scope of this methodology was extended to the synthesis of bioactive 3-alkenyl derivatives of 4-arylquinolin-2(1*H*)-ones **117** (Scheme 34).

5-Butyl-1-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **119** was obtained by the Pd-catalysed intramolecular Heck cyclization of *N*-phenyl-1*H*-imidazole-4-carboxamide **118** (Scheme 35) [74].

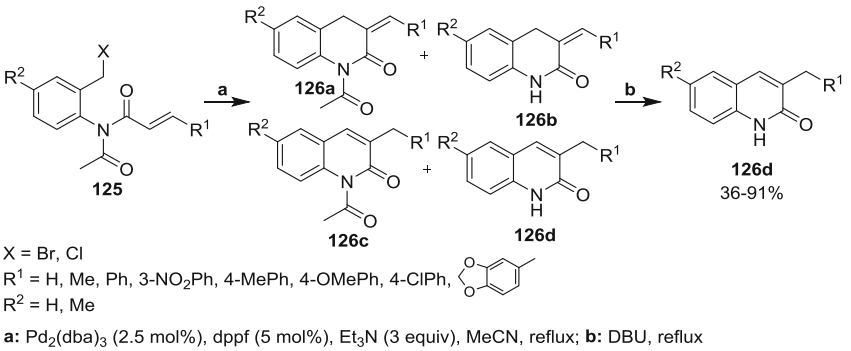
Tricyclic fused quinolone derivatives were prepared in three steps, an intramolecular Heck cyclization of *N*-(hetero)arylcarboxamides **123** being the key transformation [75]. These compounds were prepared by treatment of the acyl chlorides, generated in situ from the commercially available pyrrole-, thiophene- and furan-2- and 3-carboxylic acids **120**, with the appropriated 2-iodoanilines **121**, followed by *N*-methylation to avoid N–Pd complexation. Heck cyclization at the position 2 or 3 of the heterocyclic nucleus was performed with $Pd(PPh_3)_4$ as catalyst and KOAc as base affording the correspondent tricyclic fused quinolones **124** in moderate to high yields (Scheme 36).



Scheme 35 Synthesis of 5-butyl-1-methyl-1*H*-imidazo[4,5-*c*]quinolin-4(5*H*)-one **119** by an intramolecular Heck cyclization reaction [74]

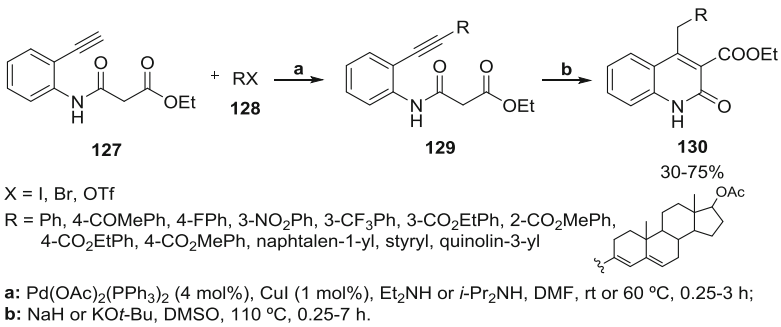


Scheme 36 Synthesis of tricyclic fused quinolones **124** by an intramolecular Heck cyclization of *N*-(hetero)arylcarboxamides **123** [75]



Scheme 37 Synthesis of 3-alkylquinolin-2(1*H*)-ones **126d** by intramolecular Heck cyclization of *N*-acetyl-*N*-[2-(halomethyl)aryl]acrylamides **125** [76]

3-Alkylquinolin-2(1*H*)-ones **126d** were synthesized by the Pd-catalysed intramolecular Heck cyclization of *N*-acetyl-*N*-[2-(halomethyl)aryl]acrylamides **125** [76]. Besides the expected and obtained 3-alkylquinolin-2(1*H*)-one **126d**, another three cyclization products **126a–126c** were also isolated. Compounds **126a** and **126c** are the acetylated products of **126b** and **126d**, respectively. Treatment of the reaction mixture with DBU successfully converted **126a–126c** into 3-alkylquinolin-2(1*H*)-one **126d** (Scheme 37). The combination of $Pd_2(dba)_3$ and



Scheme 38 Synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones **130** by a Pd-catalysed reaction of ethyl *N*-(2-ethynyl)malonanilide **127** followed by an intramolecular carbocyclization [77]

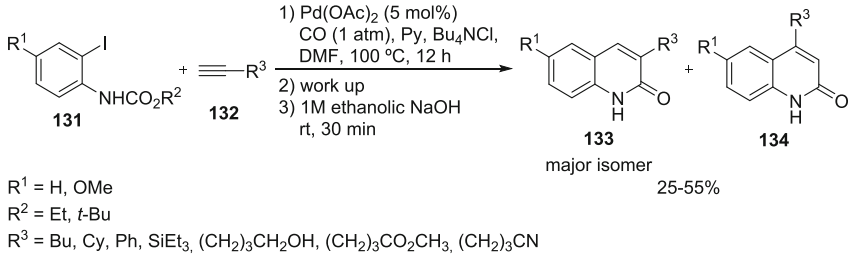
dppf in the presence of Et_3N in refluxing MeCN followed by treatment of the reaction mixture with DBU leads to 3-alkylquinolin-2(1*H*)-ones **126d** in good to excellent yields.

3.1.2 Sonogashira Reaction

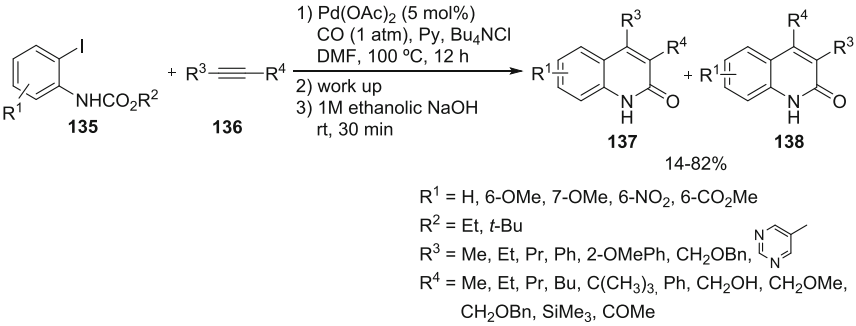
3,4-Disubstituted quinolin-2(1*H*)-ones **130** have been prepared through a Pd-catalysed reaction of the easily available ethyl *N*-(2-ethynyl)malonanilide **127** with aryl, heteroaryl and vinyl halides or vinyl triflates **128** followed by an intramolecular cyclization of the resulting coupling derivatives **129** under basic conditions [77]. This carbocyclization involves an intramolecular nucleophilic attack of the carbanion, generated from **129**, on the carbon–carbon triple bond affording, after protonation, a six-membered ring methylidene intermediate that isomerizes to the quinolin-2(1*H*)-one **130** (Scheme 38). The nature of the substituent in the acetylenic moiety is crucial for the success of the cyclization step. Best results were obtained in the presence of aromatic rings bearing electron-withdrawing substituents (60–75%), and no quinolin-2(1*H*)-ones were obtained in the presence of the electron-donating *p*-methoxyphenyl or butyl groups.

3.1.3 Carbonylative Annulation

A Pd-catalysed carbonylative annulation of terminal alkynes **132** by 2-iodoaniline derivatives **131** under CO in the presence of pyridine and $Pd(OAc)_2$ afforded 3- and 4-substituted quinolin-2(1*H*)-ones **133** and **134** (Scheme 39) [78]. Terminal alkynes bearing alkyl, phenyl, silyl, hydroxyl, ester and cyano substituents can be used in this process affording quinolin-2(1*H*)-ones in moderate yields. Reaction with phenylacetylene and triethylsilylacetylene afforded only the 3-substituted quinolin-2(1*H*)-one **133**. Removal of the carbamate protecting group by treating the crude reaction with 1 M of ethanolic NaOH is necessary; otherwise, mixtures of



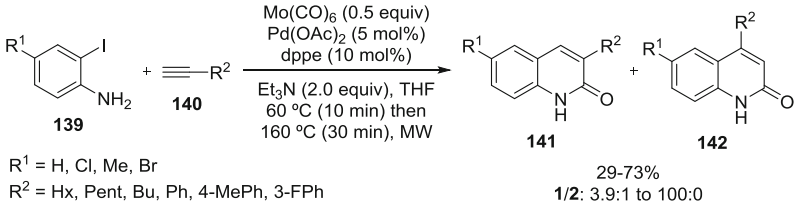
Scheme 39 Synthesis of 3- and 4-substituted quinolin-2(1*H*)-ones **133** and **134** via Pd-catalysed carbonylative annulation of terminal alkynes **132** by 2-iodoanilines **131** [78]



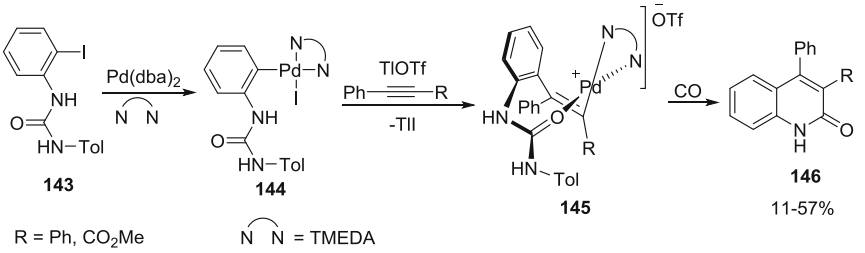
Scheme 40 Synthesis of quinolin-2(1*H*)-ones **137** and **138** via Pd-catalysed carbonylative annulation of internal alkynes **136** by 2-iodoanilines **135** [79]

unprotected and protected quinolin-2(1*H*)-ones were obtained. Both 3- and 4-substituted quinolin-2(1*H*)-ones **133** and **134** were isolated in the reactions with terminal alkynes bearing long alkyl chains. Such unusual behaviour for terminal alkynes indicates that the key step in this process is the insertion of the terminal alkyne into the carbon–Pd bond and not the Sonogashira-type coupling [39, 41] leading to quinolin-2(1*H*)-ones and not quinolin-4(1*H*)-ones. This reactivity pattern was unambiguously proven by an isotope-labelling experiment.

Later, the same authors described the synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones **137** and **138** from ligand-free Pd-catalysed carbonylative annulation of internal alkynes **136** by 2-iodoanilines **135** under CO (Scheme 40) [79]. Best results were obtained using mild electron-withdrawing substituents as *p*-toluenesulfonyl, trifluoroacetyl and alkoxycarbonyl. The nitrogen substituent is lost during the course of the reaction leading to the formation of *N*-unsubstituted quinolin-2(1*H*)-ones, save for aminocarbonyl and ethoxycarbonyl groups being the correspondent protected quinolin-2(1*H*)-one isolated in 7% and 11% yields, respectively. Ethoxycarbonyl group was removed with 1 M ethanolic NaOH. A wide variety of internal alkynes were effective in this process although the use of unsymmetrical alkynes leads to the formation of mixtures of regioisomers **137** and **138** with low regioselectivity, which arise from the two possible modes of alkyne insertion into the aryl–Pd bond. Electron-deficient alkynes are very poor



Scheme 41 Synthesis of 3- and 4-substituted quinolin-2(1*H*)-ones **141** and **142** via microwave-assisted Pd-catalysed carbonylative annulation of 2-iodoanilines **139** with terminal alkynes **140** [80]

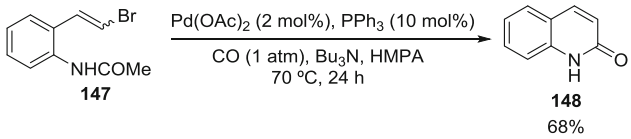


Scheme 42 Synthesis of 3-substituted 4-phenylquinolin-2(1*H*)-ones **146** through reaction of vinyl–Pd complexes **145** with CO [81]

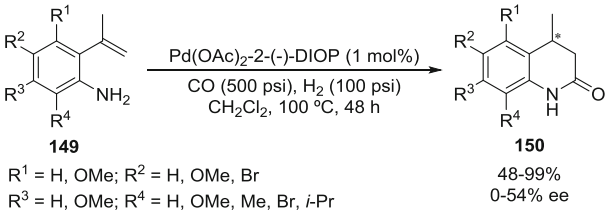
substrates for the carbonylative annulation. Electron-rich 2-iodoanilines can be employed as annulating agents, but if the substitution is *para* to the iodine, the yield is lower. Carbonylative annulation of electron-poor 2-iodoanilines afforded the corresponding quinolin-2(1*H*)-ones in lower yields than the parent system.

The synthesis of 3- and 4-substituted quinolin-2(1*H*)-ones **141** and **142**, the latter ones as minor products, was achieved from Pd-catalysed carbonylative annulation of unprotected 2-iodoanilines **139** and terminal alkynes **140** using the commercially available molybdenum hexacarbonyl as a convenient and solid CO source (Scheme 41) [80]. The reactions were conducted at 160°C for 30 min under microwave irradiation. Et_3N proved to be the best base in terms of yield and regioselectivity. $Pd(OAc)_2$ exhibited good catalytic activity, and dppe and THF were the best ligand and solvent choice for regioselectivity and yields. Different substituted 2-iodoanilines and alkyl alkynes were used without significant loss in reaction yield or efficiency. Aryl-substituted alkynes gave only the 3-substituted quinolin-2(1*H*)-one **141**. Neither internal alkynes nor *N*-protected 2-iodoanilines can be used in this carbonylative annulation.

Vinyl–Pd complexes **145**, obtained from the oxidative addition of 1-(2-iodophenyl)-3-*p*-tolylurea **143** to $Pd(dba)_2$ in the presence of 1 equiv. of TMEDA and subsequent reaction of **144** with internal alkynes, react with CO to give Pd and two 3-substituted 4-phenylquinolin-2(1*H*)-ones **146** (R=Ph, 11% and R=CO_2Me, 57%) (Scheme 42) [81]. The reaction mechanism should follow CO insertion into the Pd–C–vinyl bond of **145** to give an acyl–Pd derivative, which undergoes a C–N coupling with loss of Pd and *p*-tolyl isocyanate.



Scheme 43 Synthesis of quinolin-2(1*H*)-one **148** by Pd-catalysed carbonylation of vinyl bromides **147** [82]

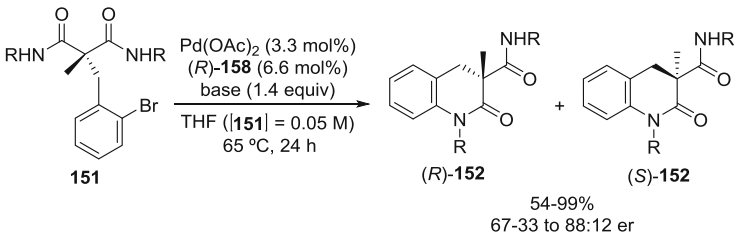


Scheme 44 Synthesis of 3,4-dihydro-4-methylquinolin-2(1*H*)-ones **150** by asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines **149** [83]

3.1.4 Cyclocarbonylation Reaction

In 1979 Ban and co-workers described the Pd-catalysed carbonylation of vinyl bromides bearing an internal amide group [82]. The (*Z*)-isomer **147** of the vinyl bromide smoothly gave, in the presence of the catalytic system $Pd(OAc)_2$ and PPh_3, quinolin-2(1*H*)-one **148** with loss of the *N*-acetyl group (Scheme 43). The corresponding (*E*)-isomer in the same reaction conditions gave only 7.7% yield of the same quinolin-2(1*H*)-one **148** because palladation occurs at the position of the halogen atom of the vinyl halide.

Chiral 3,4-dihydro-4-methylquinolin-2(1*H*)-ones **150** were prepared by asymmetric cyclocarbonylation of 2-(1-methylvinyl)anilines **149** (up to 54% ee) using a catalyst system consisting of $Pd(OAc)_2$-2(−)-DIOP [83] [$Pd(OAc)_2$ (1 mol%), (−)-DIOP (2 mol%)], in CH_2Cl_2 at 100°C for 48 h, under CO (500 psi) and hydrogen pressure (100 psi) (Scheme 44). Other chiral ligands [(−)-bppm, (+)-BINAP and *R*, *R*-BDPP] proved to be inferior to (−)-DIOP in terms of enantioselectivity. Enantioselectivity was not influenced by the amount of (−)-DIOP (1, 2, 6 equiv.) or Pd precursors [$Pd_2(dba)_3{\cdot}CHCl_3$, $Pd(acac)_2$, $Pd(CF_3COO)_2$, π-allyl-Pd chloride dimer] employed, while it was slightly sensitive to the ratio of CO and hydrogen pressure. In the absence of hydrogen, the yield is very low (37%) although optical purity was still maintained (33% ee). Substituents at the 4- and 5- position of 2-(1-methylvinyl)anilines **149** showed some effect on enantioselectivity (**150**, R^2=R^3=OMe, 20% ee; R^2=Br, 31% ee). Stronger effects were found in the case of **149** (R^1=OMe); the reaction was not enantioselective affording the correspondent racemic mixture, while the carbonylation of **149** (R^4=OMe) proceeded in a more enantioselective manner affording the correspondent quinolone **150** in nearly quantitative yield (99%, 54% ee). For 6-substituted anilines **149**, excellent yields of



R = Me, Bu, *i*-Pr, Bn, 4-OMeBn, Ph, 2,6-Me_2Ph, naphthalen-1-yl

Scheme 45 Synthesis of enantiopure 3,4-dihydroquinolin-2(1*H*)-ones **152** by an enantioselective Buchwald–Hartwig reaction [84]

150 (R^4=Me, 98%) and **150** (R^4=*i*-Pr, 99%) were obtained, whereas the carbonylation of **149** (R^2=R^4=Br) afforded the correspondent 3,4-dihydro-4-methylquinolin-2(1*H*)-one **150** in moderate yield (48%).

3.1.5 Buchwald–Hartwig Reaction

Desymmetrized 3,4-dihydroquinolin-2(1*H*)-ones **152** were synthesized by an unusual enantioselective Buchwald–Hartwig reaction involving symmetrical α-(2-bromobenzyl)malonamides **151**, in nearly quantitative yields and enantiomeric ratios up to 88:12 (Scheme 45) [84].

Using enantiopure (*R*)-**153** as ligand, **152** (R=Bn) was isolated in 85% yield but in a 57:43 er. Other ligands [(*R*)-xylyl BINAP **154**, (*R*)-H8-BINAP **157**, (*S*)-**155** and (*R*)-**156** (Fig. 3)] and more polar solvents (MeCN and DMSO) demonstrated detrimental effects or inferior results in the yield of the reaction without any enhancement in the enantiomeric ratios. Different ratios of Pd to (*R*)-**158** were investigated from 1:1 to 1:3 because this monophosphine may complex Pd differently from the bisphosphines represented in Fig. 3. The yield was slightly lower for 1:3 ratio, but enantioselectivity was nearly the same for all ratios studied. A series of bases were screened using refluxing THF, but the best results were obtained with K_3PO_4 and Cs_2CO_3 affording the product in nearly quantitative yield with good enantioselectivity. While most of quinolin-2(1*H*)-ones **152** were obtained in 99%, more sterically demanding amide nitrogen substituents led to lower reaction yields (*i*-Pr, 90%; 2,6-Me_2Ph, 54%; naphthalen-1-yl, 79%), although enantioselectivity increased with the steric bulk of the substituent (ranging from 69:31 er for Me up to 85:15 er and 88:12 er for *i*-Pr and 4-OMeBn, respectively). In the case of *N*-aryl substrates, the authors observed the same enantiomeric ratios of *N*-phenyl and *N*-benzylquinolin-2(1*H*)-ones (79:21 er).

Enantioselective intramolecular double *N*-arylation of malonamides **159** bearing 2-bromoarylmethyl groups catalysed by a Pd–BINAP complex furnished C2-symmetric spirobis[3,4-dihydroquinolin-2(1*H*)-ones] **160** in up to 70% ee (Table 1) [85]. The scope of this reaction was investigated using a variety of

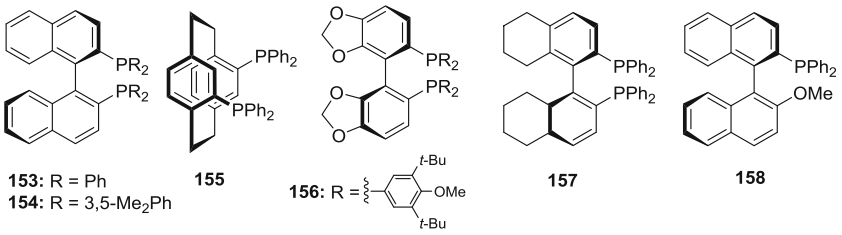


Fig. 3 Phosphine ligands discussed in Sect. 3.1.5 [84]

malonamides **159**, and it was demonstrated that substrates having a 2-chlorobenzyl groups were less reactive, although the reaction with the iodide and bromine analogues took place smoothly to give quinolin-2(1*H*)-ones **160** in high yield and moderate enantioselectivity (Table 1, entries 1–3). The reaction enantioselectivity is also affected by the substituent on the aromatic ring, moderate optical purity being obtained for 5-Cl substituents, whereas nearly racemic products were produced for 5-OMe- and 3-NO_2-substituted malonamides (Table 1, entries 6–8). It was also possible to introduce a 1,3-benzodioxole ring leading to quantitative formation of the corresponding spirobis[3,4-dihydroquinolin-2(1*H*)-one], in 57% ee, and no selectivity was observed for sterically more demanding substrates (Table 1, entries 9 and 10).

According to Sasai and co-workers, the formation of **160** seems to be initiated by the oxidative addition of one of the bromoarenes in **159** to a catalytically active Pd (0) complex. Then desymmetrization of the amide groups in the resulting Pd (II) complex **161** proceeds affording palladacycle **162**. The following C–N bond-forming reductive elimination yields monocyclized compound **163** and regenerates the Pd catalyst. The subsequent intramolecular *N*-arylation of **163** furnishes the desired spirobis[3,4-dihydroquinolin-2(1*H*)-one] **160**, enantioselectivity being determined in the first cyclization. The authors also confirmed that a kinetic resolution process is involved in the second cyclization (Scheme 46).

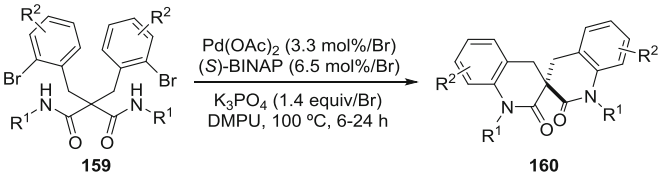
3.1.6 Ullmann Reaction

A simple, economical and effective two-step procedure for the synthesis of quinolin-2(1*H*)-ones was described [86]. The Pd(0)-mediated Ullmann cross-coupling reaction of ester **164** with 1-bromo-2-nitrobenzene gives the nitro ester **165** which engages in reductive cyclization on exposure to hydrogen in the presence of Pd/C affording the quinolin-2(1*H*)-one **166** (Scheme 47).

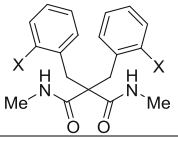
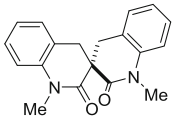
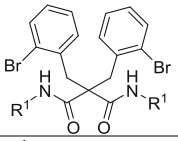
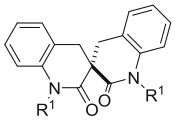
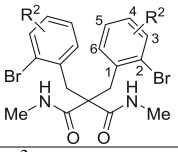
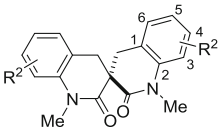
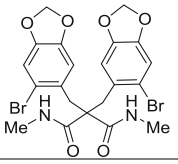
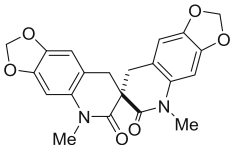
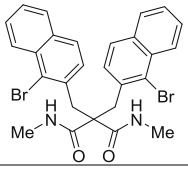
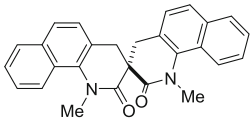
3.1.7 Others

Benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **169** were synthesized starting from 2-haloanilines **167** and alkyl 3-bromobenzo[*b*]thiophene-2-carboxylates **168** by

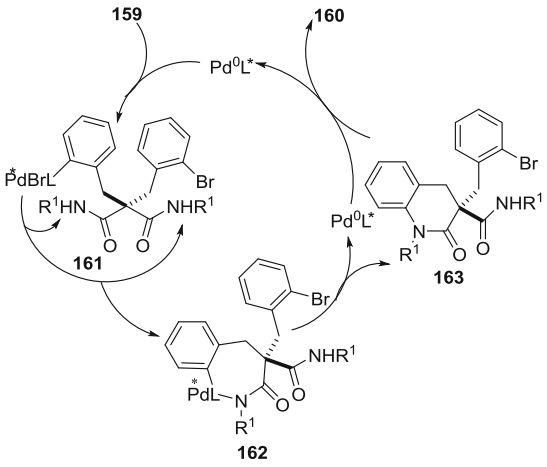
Table 1 Synthesis of spirobis[3,4-dihydroquinolin-2(1*H*)-ones] **160** by intramolecular double *N*-arylation of malonamides **159** [85]



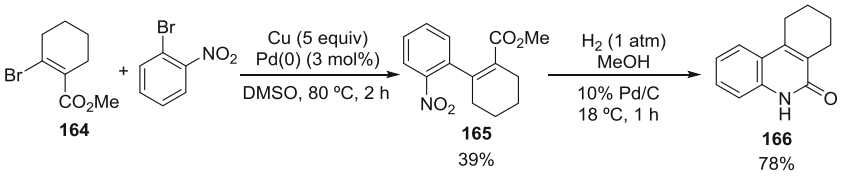
159 **160**

Entry	Substrate **159**	Product **160** Yield%[a]	ee%[b]
			
1	X=Br	99	70
2	X=Cl	8	6
3	X=I	94	38
			
4	R^1=Et	99	52
5	R^1=Bn	99	49
			
6[c]	R^2=5-Cl	85	48
7[c]	R^2=5-OMe	90	6
8	R^2=3-NO_2	42	5
			
9		99	57
			
10[c]		95	*rac*

[a]Isolated yield
[b]Determined by HPLC analysis
[c]The reactions were performed in toluene using Cs_2CO_3 as the base for 24–72 h



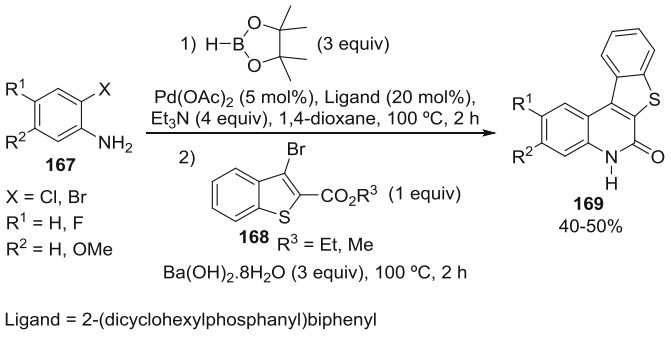
Scheme 46 Plausible catalytic cycle to give quinolin-2(1*H*)-ones **160** [85]



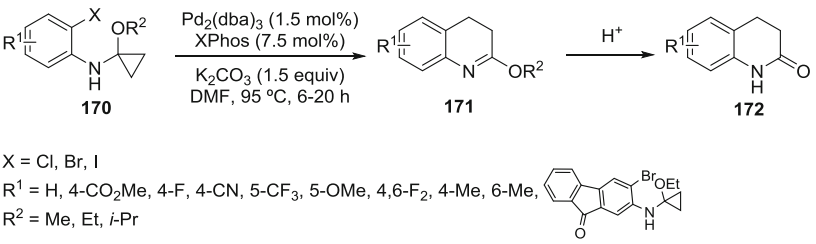
Scheme 47 Synthesis of quinolin-2(1*H*)-one **166** via Pd(0)-mediated Ullmann cross-coupling reductive cyclization sequence [86]

one-pot three-step Pd-catalysed borylation, Suzuki coupling and amidation (lactamization) (Scheme 48) [87]. The amidation reaction probably occurs in the Suzuki coupling intermediate through a nucleophilic attack of the nitrogen atom of the amine on the carbonyl of the ester group with loss of methanol or ethanol giving the corresponding tetracyclic quinolone. The use of an electron-rich sterically hindered ligand, such as 2-(dicyclohexylphosphanyl)biphenyl and $Ba(OH)_2{\cdot}8H_2O$ as base, is convenient for sterically hindered substrates. In addition the borylation should be performed in the component bearing an *ortho*-electron-donating group with the other Suzuki coupling component having an *ortho*-electron-withdrawing group. The in situ Pd-catalysed borylation avoids the preparation and isolation of boronic acids or esters and occurs with atom economy. The borylation occurred either using 2-bromo or 2-chloroanilines enhancing the scope of the reaction.

Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **172** was achieved starting from *N*-(1′-alkoxy)cyclopropyl-2-haloanilines via Pd-catalysed cyclopropane ring expansion (Scheme 49) [88]. Good yields of **171** were obtained using electron-rich biphenyl-based phosphine ligands; however, the more sterically demanding XPhos provides the better yield. The use of K_2CO_3 as base led to the best result, while KO*t*-Bu did not give the desired compound, and DMF provided better yields than toluene or 1,4-dioxane. Bromo- and iodoaniline derivatives gave better yields with a shorter reaction



Scheme 48 Synthesis of benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **169** by one-pot three-step Pd-catalysed borylation, Suzuki coupling and amidation [87]



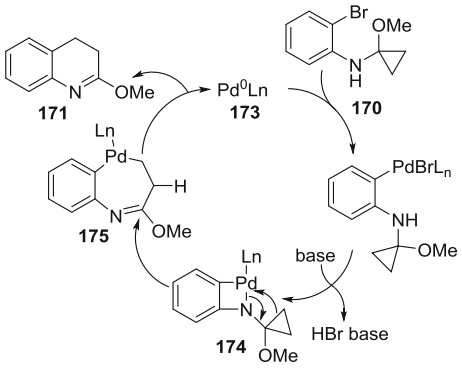
Scheme 49 Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **172** via Pd-catalysed cyclopropane ring expansion [88]

time than chloroaniline. Hydrolysis of 2-alkoxy-3,4-dihydroquinoline **171** resulted in the formation of 3,4-dihydroquinolin-2(1*H*)-ones **172** in good yields. The reaction tolerates a variety of functional groups such as ester, nitrile, ether and ketone. The substrate bearing a nitro substituent did not give the desired compound.

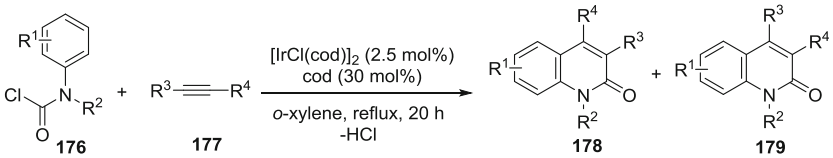
The formation of **171** starts with the oxidative addition of aryl halide **170** to Pd (0) **173** followed by intramolecular ligand exchange to give the four-membered azapalladacycle **174**. Further Pd rearrangement accompanied with cyclopropane ring opening furnishes the energetically favourable seven-membered azapalladacycle **175**. Finally, reductive elimination produces 2-methoxy-3,4-dihydroquinoline **171** and the regeneration of the reactive Pd(0) species **173** (Scheme 50).

3.2 Ir- and Rh-Catalysed Cross-Coupling Reactions

3,4-Disubstituted quinolin-2(1*H*)-ones **178** and **179** were prepared through an efficient annulation of *N*-arylcarbamoyl chlorides **176** with internal alkynes **177** in the presence of an iridium complex [89]. The reaction scope was investigated and showed that various aliphatic and aromatic internal alkynes can be employed affording the corresponding quinolin-2(1*H*)-ones **178** and **179** in 57–95% yield



Scheme 50 Plausible reaction mechanism for the formation of 2-methoxy-3,4-dihydroquinolines **171** [88]

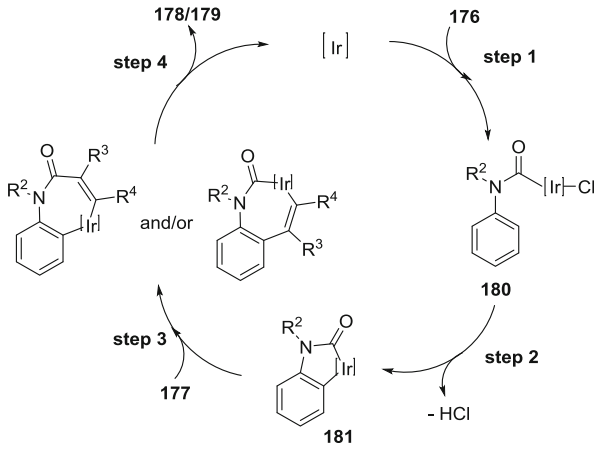


R^1 = H, 7-OMe, 6-OMe, 8-Me, 7-Me, 6-Me, 6-Cl, 6-Br, 6-CF_3, 6-CO_2Me, 6-NO_2, 6-CN
R^2 = Me, Bn, 4-OMeBn, Cy, Ph
R^3 = Bu, MeOCH_2, Ph, 4-OMePh, 4-ClPh, Me
R^4 = Bu, MeOCH_2, Ph, 4-OMePh, 4-ClPh, Cy, Me, C_5H_{11}, 2-MeOPh

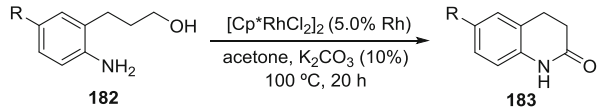
Scheme 51 Synthesis of quinolin-2(1*H*)-ones **178/179** by iridium(I)-catalysed annulation of *N*-arylcarbamoyl chlorides **176** with internal alkynes **177** [89]

(Scheme 51). When using unsymmetrical alkynes such as 1-cyclohexylpropyne and 1-phenylpropyne, the corresponding quinolin-2(1*H*)-ones were obtained in high yields albeit with low regioselectivities (**178/179**: 55/45 and 58/42, respectively). The use of unsymmetrical alkynes bearing an ether functionality improved the regioselectivity of the products (**178/179**: 72/28 and 82/18), possibly as a result of the directing effect of the oxygen atom. Terminal alkynes such as 1-decyne and phenylacetylene did not afford neither **178** nor **179**. Various carbamoyl chlorides can be employed in the reaction. Electron-rich and electron-poor aryl moieties on the nitrogen smoothly participated in the cyclization to afford the corresponding quinolin-2(1*H*)-ones in good to excellent yields (57–93%).

According to the authors, the reaction mechanism involves the oxidative addition of **176** to the iridium(I) species (Scheme 52, step 1), generating carbamoylchloroiridium(III) intermediate **180**. Next, an intramolecular cyclization (Scheme 52, step 2) affords five-membered iridacycle **181**. The authors demonstrated that cyclization must be electrophilic. The construction of the iridacycle



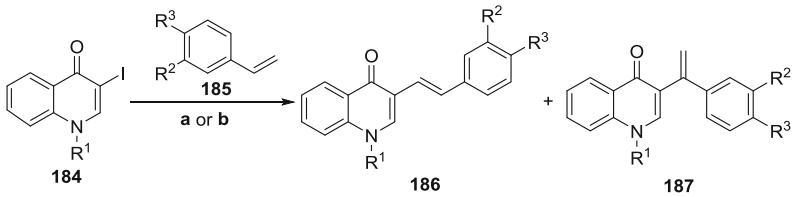
Scheme 52 Plausible reaction mechanism for the formation of 3,4-disubstituted quinolin-2(1*H*)-ones **178/179** [89]



Scheme 53 Synthesis of 3,4-dihydroquinolin-2(1*H*)-ones **183** from 3-(2-aminophenyl)-1-propanols **182** catalysed by $[Cp^*RhCl_2]_2/K_2CO_3$ system [90]

181, the key intermediate in the catalytic reaction, plays a crucial role in suppressing the decarbonylation. Subsequent insertion of **177** (Scheme 52, step 3) followed by reductive elimination (Scheme 52, step 4) affords the quinolin-2(1*H*)-one and regenerates the iridium(I) species.

Transition metal-catalysed hydrogen transfer reactions of amino alcohols using a Cp*Rh complex as catalyst afforded 3,4-dihydroquinolin-2(1*H*)-ones [90]. Oxidative *N*-heterocyclization of 3-(2-aminophenyl)-1-propanol **182** (R=H) under the optimized conditions, in the presence of $[Cp^*RhCl_2]_2$ (0.0125 mmol, 5.0% Rh) and acetone as solvent, gave selectively 3,4-dihydroquinolin-2(1*H*)-one **183** (R=H) in 81% yield (Scheme 53). Decreasing reaction temperature (80°C) as well as the amount of acetone resulted in a lower yield. The authors concluded that acetone plays a key role as hydrogen acceptor and that other rhodium catalysts {$Cp^*Rh(OAc)_2{\cdot}H_2O$, $RhCl(PPh_3)_3$, $[RhCl(CO)_2]_2$} showed lower activity than $[Cp^*RhCl_2]_2$. Electron-donating substituent (OMe) afforded **183** in moderate yield (63%), while electron-withdrawing substituents gave excellent yields (96–97%) with the exception of CN group (71%), probably due to deactivation of the catalyst by coordination of CN substituent to the rhodium centre.



a: *Classical heating conditions:* styrene **185** (5 equiv), Pd-catalyst (5 mol%), PPh_3 (10 mol%), Et_3N (1 equiv), NMP, 100 °C, 5 h;
b: *Microwave conditions:* styrene **185** (5 equiv), Pd-catalyst (5 mol%), PPh_3 (10 mol%), Et_3N (1 equiv), NMP, 2 min ramp to 100 °C and 1.5 h hold at 100 °C in closed glass vessels.

Scheme 54 Synthesis of (*E*)-3-styrylquinolin-4(1*H*)-ones **186** by Heck reaction of 3-iodoquinolin-4(1*H*)-ones **184** with styrene derivatives **185** [91]

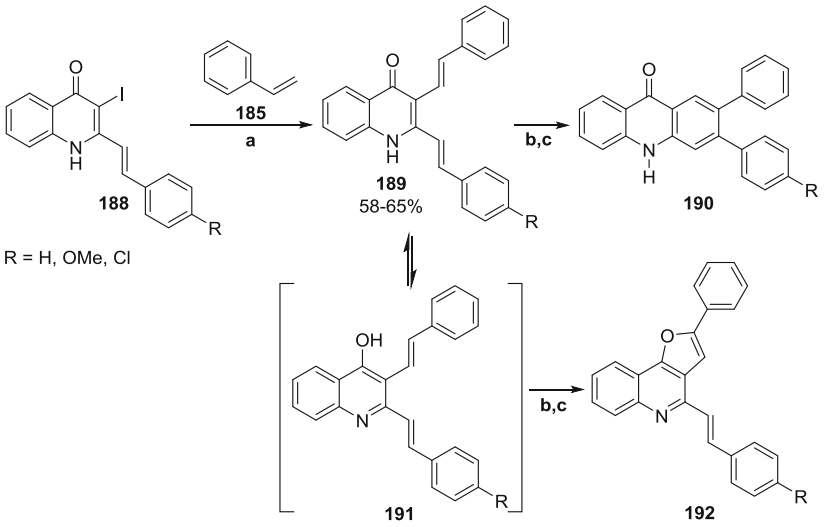
4 Transformation of Quinolin-4(1*H*)-ones

4.1 Pd-Catalysed Cross-Coupling Reactions

4.1.1 Heck Reaction

(*E*)-3-Styrylquinolin-4(1*H*)-ones **186** were prepared from the Heck reaction of 3-iodoquinolin-4(1*H*)-ones **184** with styrene derivatives **185** (Scheme 54) [91]. The reaction of 3-iodoquinolin-4(1*H*)-one **184** (R^1=H) with styrene afforded the (*E*)-3-styrylquinolin-4(1*H*)-one **186** (R^1=R^2=R^3=H) in moderate yield (46%) using $Pd(PPh_3)_4$ as catalyst, PPh_3 as ligand and Et_3N as base in NMP at 100°C. Change of the Pd source [$Pd(OAc)_2$ or Pd/C], the ligand [P(*o*-tol)$_3$] or the base (NaOAc or K_2CO_3) did not improve the yields; instead when P(*o*-tol)$_3$ was used, the branched regioisomer 3-(1-phenylethenyl)quinolin-4(1*H*)-one **187** was obtained as the main product (**186**, 10%; **187**, 16%). This Heck procedure revealed to be efficient only when 3-iodoquinolin-4(1*H*)-one was *N*-methylated. The Heck reaction of 3-iodo-1-methylquinolin-4(1*H*)-one **184** led to the (*E*)-1-methyl-3-styrylquinolin-4(1*H*)-one **186** in better yield (55%) although the branched regioisomer **187** was also isolated (14%). When the reaction was performed under microwave irradiation, shortening of the reaction time occurred but lower yields were obtained (40% in 1.5 h). The best catalyst found for the unsubstituted styrene [$Pd(PPh_3)_4$] did not work well with substituted styrenes with the exception of styrene **185** (R^2=NO_2; R^3=H) (CH, 65%; MW, 45%). For other styrenes **185**, $PdCl_2$ proved to be more efficient (R^2=H; R^3=OMe, CH 59%, MW, 36%; R^2=R^3=OMe, CH 55%, MW 30%; R^2=H; R^3=F, CH 56%; MW 48%).

Later, the same authors described the Heck reaction of (*E*)-3-iodo-2-styrylquinolin-4(1*H*)-ones **188** with styrene **185**, leading to (*E*,*E*)-2,3-distyrylquinolin-4(1*H*)-ones **189** in good yields (58–65%) (Scheme 55) [92]. $Pd(PPh_3)_4$

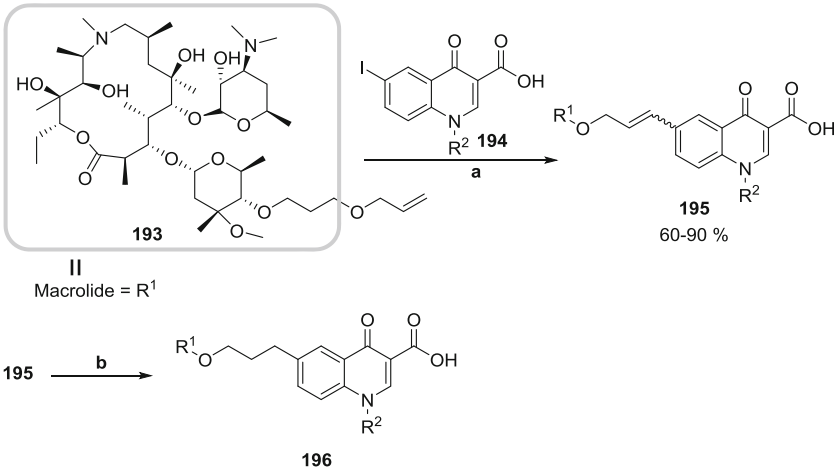


Scheme 55 Synthesis of 2,3-diarylacridin-9(10*H*)-ones **190** and (*E*)-2-aryl-4-styrylfuro[3,2-*c*]quinolines **192** via Heck reaction of (*E*)-3-iodo-2-styrylquinolin-4(1*H*)-ones **188** with styrene **185** followed by cyclization [92]

was the best catalyst [$Pd(OAc)_2$ and $PdCl_2$ proved to be unsuccessful], MeCN the most appropriated solvent and Et_3N the most suitable base.

The obtained (*E*,*E*)-2,3-distyrylquinolin-4(1*H*)-ones **189**, when heated at high temperatures, cyclize in two different ways. Electrocyclization and further in situ oxidation lead to 2,3-diarylacridin-9(10*H*)-ones **190**, while tautomerization and cyclization by nucleophilic attack of the hydroxyl oxygen atom to the β-position of the 3-styryl group and further in situ oxidation produce (*E*)-2-phenyl-4-styrylfuro[3,2-*c*]quinolines **192**. When the reaction was performed in refluxing 1,2,4-trichlorobenzene, acridin-9(10*H*)-ones **190** were obtained in low yields (16–37%) and (*E*)-2-phenyl-4-styrylfuro[3,2-*c*]quinolines **192** as the main products (35–66%). The use of an acidic medium (PTSA), in order to displace the tautomerism of 4-hydroxyquinoline **191** to the quinolone **189**, and the presence of iodine to favour the isomerization of the double bonds improved the yield of acridin-9(10*H*)-ones **190** (35–40%) although (*E*)-2-phenyl-4-styrylfuro[3,2-*c*]quinolines **192** were again obtained as the main products (41–56%).

The Heck reaction of 6-iodoquinolin-4(1*H*)-ones **194** with macrolides (from azithromycin) **193** was studied, aiming the preparation of compounds with high antibacterial activity [93]. Macrolones (macrolide + quinolone) **195** were isolated in good to excellent yields when using the catalytic system $Pd(OAc)_2/P(o\text{-tol})_3$. The optimized protocol required 2.5 mol excess of quinolone in DMF as the solvent and two different temperatures (65°C and 75°C). The desirable macrolones **196** were



Scheme 56 Synthesis of macrolones **196** via Heck reaction of macrolide **193** with 6--iodoquinolin-4(1*H*)-ones **194** followed by Pd/C hydrogenation [93]

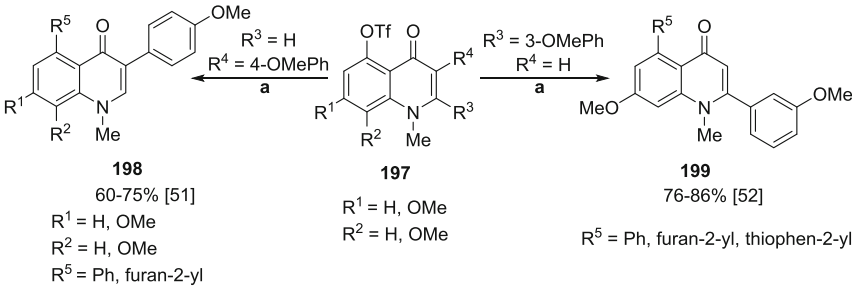
isolated with > 92% purity after complete hydrogenation of **195** catalysed by Pd/C (Scheme 56).

4.1.2 Suzuki–Miyaura Reaction

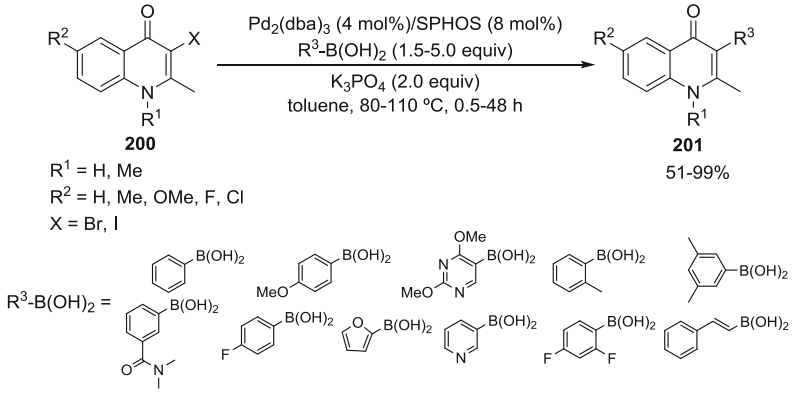
3-(4-Methoxyphenyl)-5-trifluoromethanesulfonatequinolin-4(1*H*)-ones **197** were transformed into derivatives **198** through a modified Suzuki methodology, the desired quinolin-4(1*H*)-ones **198** being obtained in moderate to good yields (Scheme 57) [94]. This protocol was applied successfully to the synthesis of 2-(3-methoxyphenyl)quinolin-4(1*H*)-ones **199** analogues [95].

The synthesis of novel and medicinally important quinolin-4(1*H*)-ones via mono and/or sequential Suzuki–Miyaura cross-coupling reactions was reported [96]. Coupling of quinolin-4(1*H*)-one **200** using a Pd/SPHOS catalytic system led to 3-substituted quinolin-4(1*H*)-ones **201** in high yields (Scheme 58), better yields being obtained with 3-iodo- than with 3-bromoquinolin-4(1*H*)-ones. For the less soluble quinolin-4(1*H*)-one, DMF was required as solvent. This reaction was effective for coupling quinolin-4(1*H*)-ones with all major subclasses of substrates with moderate to excellent yields.

To highlight the divergent nature of this synthetic route, the authors used 6-chloro-3-iodoquinolin-4(1*H*)-ones **200**, taking advantage of the reactivity differences between the iodo- and chloro-substituents. Previously the 3-position was subjected to Suzuki–Miyaura coupling (Scheme 58), and then a subsequent



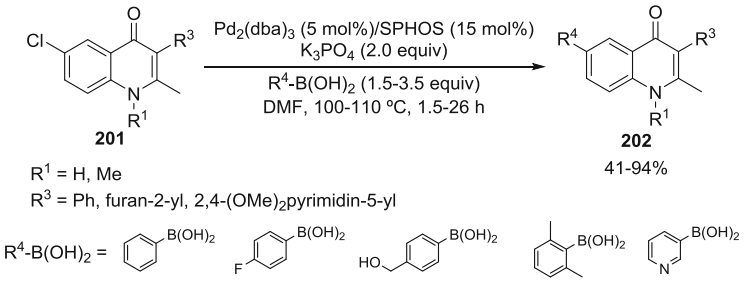
Scheme 57 Synthesis of quinolin-4(1*H*)-ones **198** and **199** by Suzuki coupling reaction of 5-trifluoromethanesulfonatequinolin-4(1*H*)-ones **197** with boronic acids [94, 95]



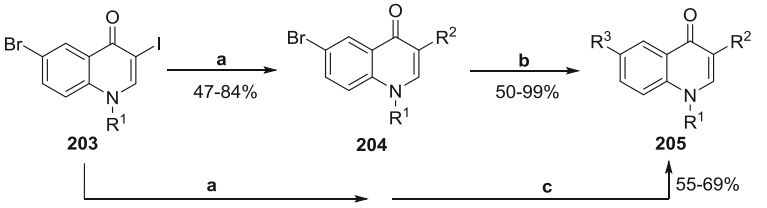
Scheme 58 Synthesis of 3-substituted quinolin-4(1*H*)-ones **201** via Suzuki–Miyaura cross-coupling reaction of quinolin-4(1*H*)-ones **200** with boronic acids [96]

coupling with different boronic acids at the 6-position was performed, generating complex quinolin-4(1*H*)-ones **202** (Scheme 59). Very good yields were obtained for 1-methylquinolin-4(1*H*)-ones (70–94%), while the NH containing 6-chloro-3-(2-furanyl)quinolin-4(1*H*)-ones only produces modest yields of the coupling product (41–47%) [96].

Sequential Suzuki–Miyaura arylation at the 3- and 6-positions of 1-substituted 6-bromo-3-iodoquinolin-4(1*H*)-ones **203** can be carried out regioselectively under standard conditions and controlled reaction temperature [97]. The chemoselective functionalization of C-3 position of the 6-bromo-3-iodoquinolin-4(1*H*)-one **203** with arylboronic acids afforded 3-aryl-6-bromoquinolin-4(1*H*)-ones **204** in good yields (80–84%), except when 2-furanboronic acid (49%) and 4-methoxyphenylvinylboronic acid (47%) were employed, without concurrent formation of regioisomeric and/or bis-coupling products (Scheme 60, **a**).



Scheme 59 Synthesis of quinolin-4(1*H*)-ones **202** via Suzuki–Miyaura cross-coupling reaction of 3-aryl-6-cloroquinolin-4(1*H*)-ones **201** with boronic acids [96]

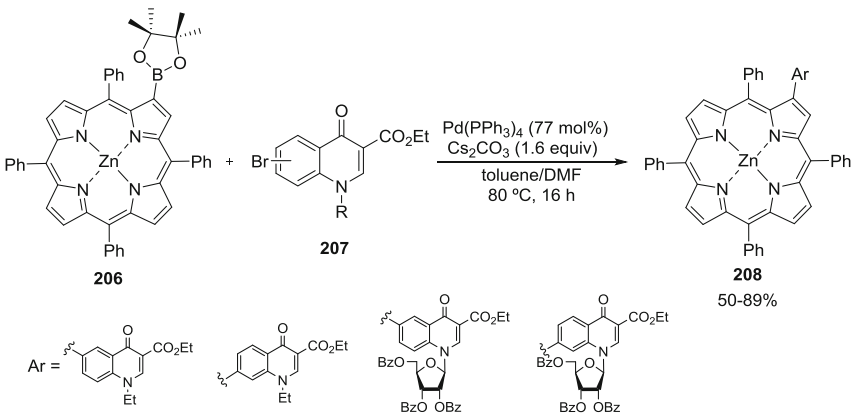


Sequential Suzuki-Miyaura arylation (**a**,**b**): R^1 = Me, Et, CH_2*c*-Pr; R^2 = Ph, 4-tol, furan-2-yl, 4-ClPh, (*E*)-2-(4-OMePh)vinyl; R^3 = 4-OCF_3Ph, 3-Py, 3-ClPh, 4-CNPh
One-pot sequential Suzuki-Miyaura arylation (**a**,**c**): R^1 = Me; R^2 = Ph, 4-tol; R^3 = 3-ClPh, 4-CNPh

a: R^2-$B(OH)_2$ (1.2 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), 2.0 M Na_2CO_3 (2.5 equiv), DME/EtOH (1.5:1), MW, 70 ºC, 5 min; 90 ºC in the case of R^2 = (*E*)-2-(4-OMePh)vinyl;
b: same conditions as **a** but with R^3-$B(OH)_2$ (1.2 equiv) at 80 ºC;
c: R^3-$B(OH)_2$ (1.2 equiv), PPh_3 (30 mol%), 2.0 M Na_2CO_3 (2.5 equiv), MW, 80 ºC, 5 min.

Scheme 60 Synthesis of trisubstituted quinolin-4(1*H*)-ones **205** by sequential Suzuki–Miyaura (**a**,**b**) or one-pot double Suzuki–Miyaura (**a**,**c**) reactions of 1-substituted 6-bromo-3-iodoquinolin-4(1*H*)-ones **203** with arylboronic acids [97]

Further elaboration of compounds **204** into trisubstituted quinolin-4(1*H*)-ones **205** was carried out through sequential Suzuki–Miyaura cross-coupling reaction by exploiting the reactivity of a 6-bromine substituent (Scheme 60, **b**). The authors performed the reaction under the same conditions used to generate compounds **204** by increasing the reaction temperature to 80°C. The trisubstituted quinolin-4(1*H*)-ones **205** were obtained in good yields (67–99%) with complete conversion of the substrate **204** with the exception of the reaction employing 4-(trifluoromethoxy) phenylboronic acid (50%) [97]. These authors also investigated the one-pot sequential Suzuki–Miyaura reaction and obtained the desired trisubstituted derivatives **205** in overall yields comparable or slightly lower than those obtained in the stepwise synthesis [Scheme 60, **a**,**b**; 70% for **205** (R^1=Me, R^2=Ph, R^3=3-ClPh) and 72% for **205** (R^1=Me, R^2=4-tol, R^3=3-CNPh)] in a total reaction time of 10 min, without the isolation of the monoarylated intermediate (Scheme 60, **a**,**c**).

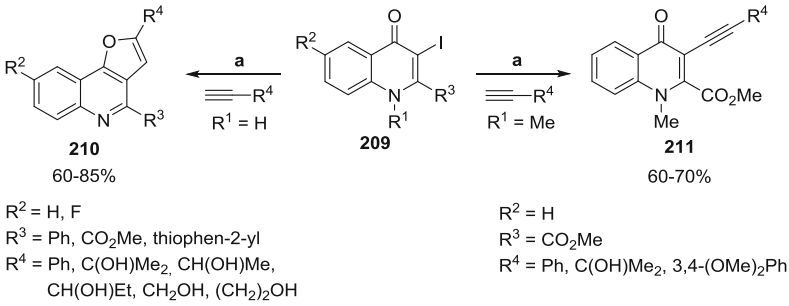


Scheme 61 Synthesis of porphyrin-quinolin-4(1*H*)-one conjugates **208** by Suzuki–Miyaura reaction of β-borylated porphyrin **206** with 6- or 7-bromoquinolin-4(1*H*)-ones **207** [98]

Porphyrin-quinolin-4(1*H*)-one conjugates were synthesized from the Suzuki–Miyaura coupling reaction of a β-borylated porphyrin **206**, prepared by borylation of the correspondent 3-bromotetraphenylporphyrinatozinc(II) with pinacolborane in the presence of $PdCl_2(PPh_3)_2$, with 6- or 7-bromoquinolin-4(1*H*)-ones **207** containing *N*-ethyl and *N*-D-ribofuranosyl substituents (Scheme 61) [98]. Quinolones **207** bearing an *N*-ethyl substituent were more reactive than those bearing *N*-ribonucleosides providing the corresponding porphyrin-quinolin-4(1*H*)-one conjugates **208** in very good yields (82–89%). The other conjugates **208** were isolated in lower yields (50–51%), but nearly 50% of the starting porphyrin **206** was recovered in both cases. Attempts to improve the outcome of the coupling process between **206** and *N*-ribonucleosides quinolone derivatives **207** were not successful [e.g. by increasing both the reaction time and the amount of bromoquinolin-4(1*H*)-ones] probably due to steric effects caused by the ribofuranosyl group. Basic hydrolysis and deprotection of the ester and benzoyl groups of ribose moieties in conjugates **208** followed by the acid demetalation afforded the correspondent conjugates that were evaluated as singlet oxygen generators.

4.1.3 Sonogashira Reaction

Diverse 2-substituted furo[3,2-*c*]quinolines **210** were prepared by a one-pot process involving Sonogashira-type coupling followed by the electrophilic or transition metal-mediated cyclization of the resulting alkynes possessing a suitable nucleophilic group in the proximity of the triple bond (Scheme 62) [99]. Better yields were obtained when using $Pd(PPh_3)_4$ (85%) or $PdCl_2(PPh_3)_2$ (80%) in place of Pd/C-PPh_3 (70%), although the latter is cheaper. DMF was found to be a better solvent when compared to THF or MeCN, and CuI is crucial in this reaction; otherwise,



Scheme 62 Pd/C-PPh_3-mediated synthesis of 2-substituted furo[3,2-*c*]quinolines **210** and 3--alkynylquinolin-4(1*H*)-ones **211** [99]

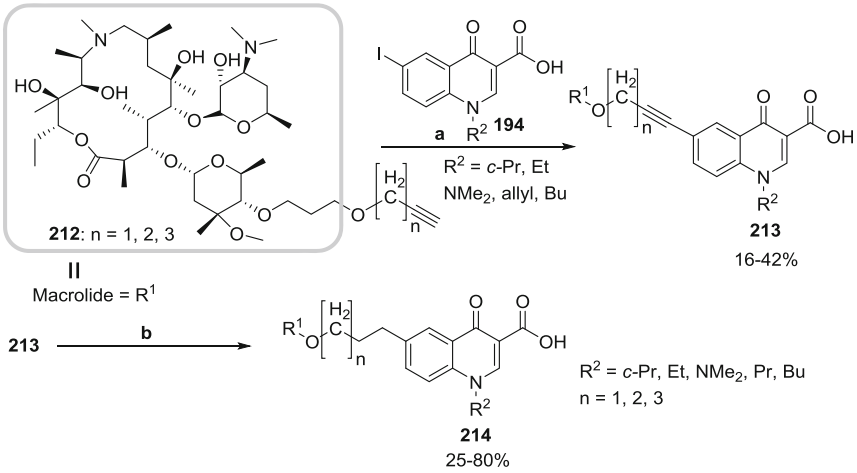
only deiodinated product was formed. Absence of PPh_3 when using Pd/C resulted in a poor yield (22%). Good yields of the desired furo[3,2-*c*]quinolines **210** were obtained regardless the nature of terminal alkynes used.

The key features of the present tandem coupling–cyclization process are the transition metal-mediated activation of the triple bond of the 3-alkynylquinoline generated in situ followed by an intramolecular attack of the oxygen on the activated triple bond with subsequent proton transfer and release of the metal ion to give the desired furoquinoline **210**. The NH of the quinolin-4(1*H*)-one ring has a critical role in facilitating the participation of C-4 quinoline oxygen in the cyclization step. Indeed when the authors performed the reaction of methyl 3-iodo-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylate **209** with terminal alkynes under the same conditions, only 3-alkynylquinolin-4(1*H*)-ones **211** were isolated as a result of a normal Sonogashira coupling reaction, and formation of furoquinolines **210** was not observed, even in trace amounts (Scheme 62).

Sonogashira protocol was used to synthesize different macrolone derivatives with high antibacterial activity, starting from 6-iodoquinolin-4(1*H*)-ones [93, 100, 101]. An example is shown in Scheme 63 where Sonogashira reaction of macrolides **212** with 6-iodoquinolin-4(1*H*)-ones **194** leads to macrolones **213** in moderate yields. Pd/C-catalysed hydrogenation was performed to obtain the desirable macrolones **214**.

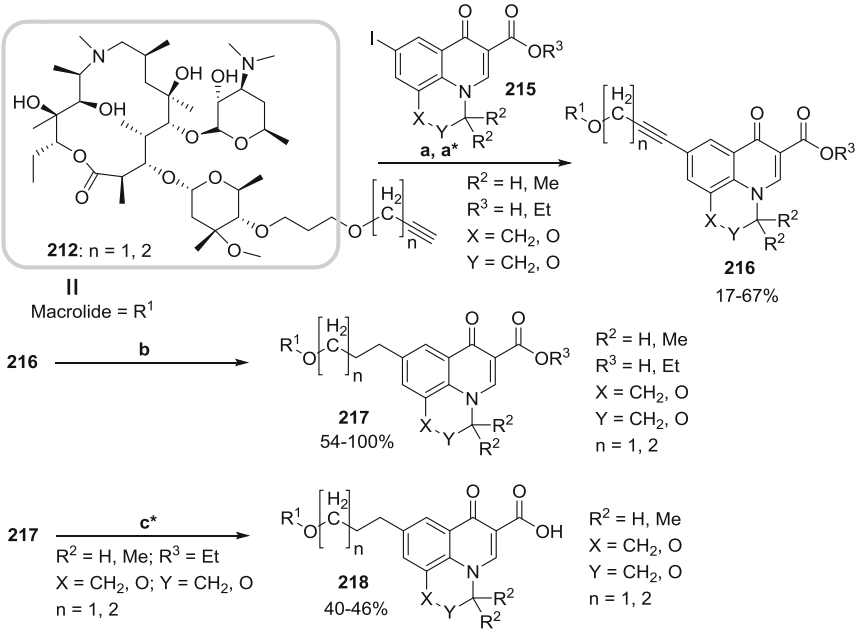
Another group of macrolones (with tricyclic quinolone moiety) **217** (R^3=H) and **218** was also synthesized by Sonogashira approach although, only when ethyl esters **215** of the parent acids were used, the reaction proceed in shorter reaction times and better yields (Scheme 64, **a**: R^3=H, **a***: R^3=Et). After hydrogenation (Scheme 64, **b**), esters **217** (R^3=Et) were hydrolysed to the corresponding carboxylic acids **218** (Scheme 64, **c***).

The Sonogashira reaction of 6-bromo-3-iodoquinolin-4(1*H*)-one **219** with TMSA yielded the expected coupling products in very satisfactory yields, with no further conversion to furo[3,2-*c*]quinoline derivatives (Scheme 65) [97]. Subsequently, Suzuki and Sonogashira cross-coupling reactions at the 6-position of



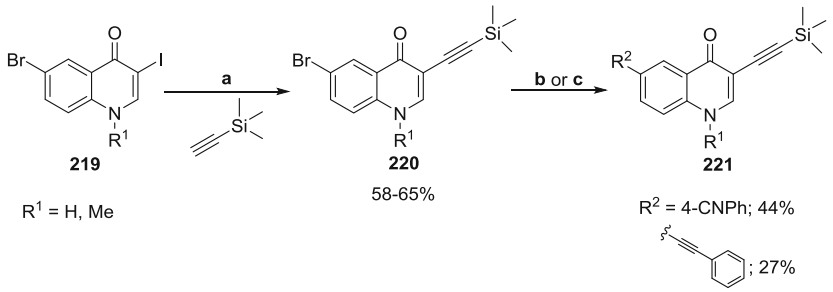
a: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (20 mol%), **194** (1.8 equiv), Et_3N (10 equiv), MeCN, 50 ºC, 16 h;
b: Pd/C 20 wt % (10 mol%), H_2 (2.2 bar), MeOH, 15 h.

Scheme 63 Synthesis of macrolones **214** via Sonogashira reaction of macrolide **212** with 6--iodoquinolin-4(1*H*)-ones **194** followed by Pd/C hydrogenation [93]



a: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (20 mol%), **215**: R^3 = H (2.5 equiv), Et_3N (10 equiv), EtOH, 50 ºC, 16 h;
a*: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (20 mol%), **215**: R^3 = Et (2.0 equiv), Et_3N (10 equiv), MeCN, 50 ºC, 1 h; **b:** Pd/C 10 wt % (10 mol%), H_2 (2 bar), MeOH, 16 h; **c*:** THF/H_2O 2:1, 0.5 M LiOH 2.5 equiv, 3 h.

Scheme 64 Synthesis of macrolones **217** and **218** via Sonogashira reaction followed by Pd/C hydrogenation and hydrolysis of the corresponding esters **217** [93]



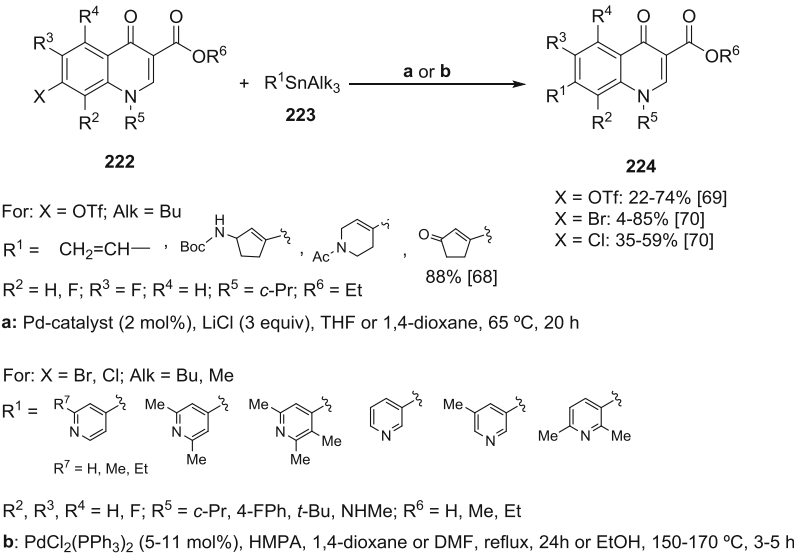
a: $PdCl_2(PPh_3)_2$ (10 mol%), CuI (20 mol%), *i*-Pr_2NH, 1,4-dioxane, MW, 120 ºC, 5 min;
b: *Suzuki-Miyaura coupling:* 4-cyanophenylboronic acid, $Pd(OAc)_2$ (10 mol%), PPh_3 (30 mol%), Na_2CO_3, DME/EtOH, MW, 80 ºC, 5 min;
c: *Sonogashira coupling*: same conditions as **a** using phenylacetylene at 150 ºC, 30 min.

Scheme 65 Sonogashira reaction of 6-bromo-3-iodoquinolin-4(1*H*)-one **219** and subsequent Suzuki and Sonogashira reactions at the 6-position of quinolin-4(1*H*)-ones **220** [97]

substrates **220** were performed to afford the trisubstituted quinolin-4(1*H*)-ones **221**. Generally, harder conditions were necessary to functionalize the 6-position due to the lower reactivity of bromine compared to iodine, while, on the other hand, the increased structural complexity made substrates **220** more prone to decomposition and side products' formation. Therefore, cross-coupling reactions at the 6-position proceeded with slightly lower efficiency, leading to products **221** in moderate to low yields.

4.1.4 Stille Reaction

In a programme to develop new antibacterial agents, Laborde and co-workers described a series of 1-cyclopropylquinolin-4(1*H*)-ones **224** (R^5=*c*-Pr), bearing at C-7 a vinyl, a 1-cyclopentenyl or a 1,2,3,6-tetrahydropyridin-4-yl group, synthesized by Pd cross-coupling of 7-quinolyltriflate **222** (X=OTf) with an appropriately functionalized vinylstannane **223** (Scheme 66, **a**) [102, 103]. The reaction with a range of vinylstannanes **223** bearing different functional groups afforded the corresponding quinolin-4(1*H*)-ones **224** in moderate to good yields (22–88%) with complete chemo- and regioselectivity; the coupling takes place exclusively at the C-7 position of the quinolone nucleus even in the presence of the C-6 fluorine or the C-2 α,β-unsaturated keto-ester moiety. In some cases, additional amounts of the tin reagent and/or the catalyst [either $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$] were necessary to improve the yield of the coupled product. The low yield obtained when using the cyclopentenylstannane possessing a bulky *tert*-butoxycarbonyl group at the 3-position (31%) was attributed to unfavourable steric demands. Later, Reuman



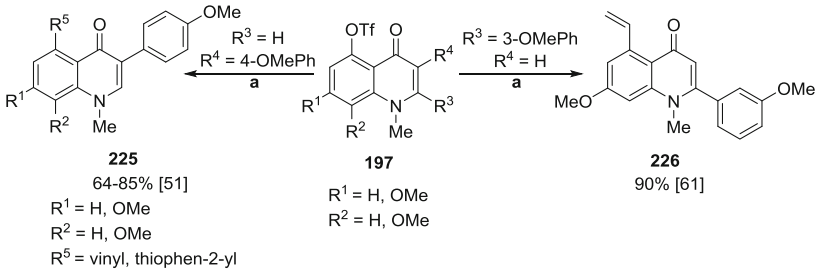
Scheme 66 Pd-catalysed Stille cross-coupling reaction of quinolin-4(1*H*)-ones **222** with functionalized stannanes **223** [102–104]

and co-workers reported a new series of 7-pyridinylquinolin-4(1*H*)-ones applying the same methodology but starting from 7-bromo- or 7-chloroquinolin-4(1*H*)-ones **222** (X=Br or Cl) (Scheme 66, **b**) [104]. The quinolin-4(1*H*)-one esters **224** were hydrolysed to the corresponding acids (50–73%) with sodium hydroxide or hydrochloric acid with concomitant removal of the *N*-protecting groups.

5-Substituted 3-(4-methoxyphenyl)quinolin-4(1*H*)-ones **225** have been synthesized in good yields via Stille cross-coupling reaction of the corresponding 3-(4-methoxyphenyl)-5-trifluoromethanesulfonatequinolin-4(1*H*)-ones **197** with tributyl(vinyl)stannane (67–85%) or with tributyl(thiophen-2-yl)stannane (64%) (Scheme 67) [94]. This protocol was successfully applied to the synthesis of 2-(3-methoxyphenyl)quinolin-4(1*H*)-one **226** [95].

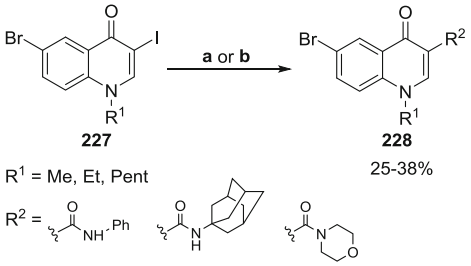
4.1.5 Aminocarbonylation Reaction

A Pd-catalysed carbonylation of 6-bromo-3-iodoquinolin-4(1*H*)-ones **227** with amines, using $Pd(OAc)_2$ as catalyst and $Mo(CO)_6$ as CO source, provides compounds **228** in low yields (25–38%) (Scheme 68, **a**) [97]. Slight modifications of the experimental conditions did not improve the reaction yield. Even when gaseous CO and Pd/C as the catalyst were used (Scheme 68, **b**), the aminocarbonylation product was obtained in similar yield (35%).



a: R^5SnBu_3 (1.5 equiv), $Pd(PPh_3)_4$ (6 mol%), LiCl (2.8 equiv), DMF, 90 ºC, 1.5 h

Scheme 67 Synthesis of quinolin-4(1*H*)-ones **225** and **226** by Stille coupling reaction of 5--trifluoromethanesulfonatequinolin-4(1*H*)-ones **197** with tributyl(vinyl)stannanes [94, 95]

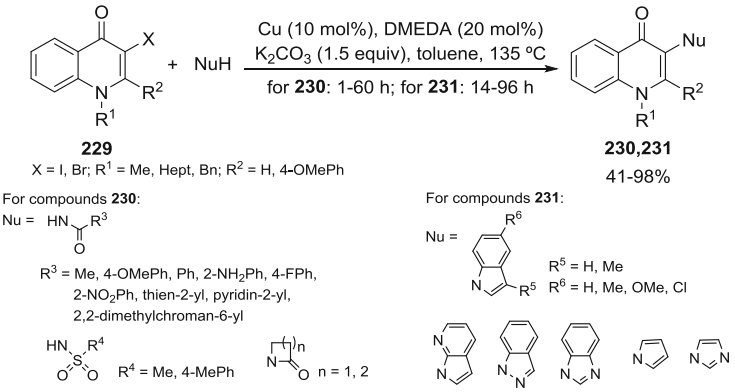


a: amine (1.5 equiv), $Pd(OAc)_2$ (10 mol%), $Mo(CO)_6$ (0.5 equiv), DBU (3 equiv), THF, MW, 110 ºC, 10 min;
b: morpholine (1 equiv), 10% Pd/C (2 mol%), CO (130 psi), DBU (3 equiv), DMF, MW, 100 ºC, 10 min.

Scheme 68 Pd-catalysed aminocarbonylation of 6-bromo-3-iodoquinolin-4(1*H*)-ones **227** [97]

4.2 Cu-Catalysed Ullmann-Type Reaction

Ullmann-type reactions of 3-haloquinolin-4(1*H*)-ones **229** with various *N*-containing nucleophiles using an inexpensive copper catalyst system proceed rapidly under relatively mild conditions providing direct access to various 3-(1-substituted)-quinolin-4(1*H*)-ones **230** and **231** in good to excellent yields (Scheme 69) [105]. The reaction was dramatically facilitated when using K_2CO_3 or Cs_2CO_3 as bases, using Cu powder as catalyst and using DMEDA as the ligand in toluene at 135°C. The use of other ligands [e.g. (±)-*trans*-cyclohexane-1,2-diamine-based ligands, TMEDA, 1,10-phenanthroline, L-proline or ethyl 2-oxocyclohexanecarboxylate] induced a lowering of the conversion rate. The authors also found that in the coupling of 3-iodo-1-methylquinolin-4(1*H*)-one **229** (X=I) with 4-methoxybenzamide, the source of copper used has no influence on the reaction rate, since $CuSO_4$, CuI, CuBr and CuTC gave similar results than that of Cu powder. This Ullmann-type reaction proved to be general for the coupling with a large variety of nucleophiles, being compatible with primary



Scheme 69 Synthesis of quinolin-4(1*H*)-ones **230** and **231** by Cu-catalysed Ullmann-type reactions of 3-haloquinolin-4(1*H*)-ones **229** with various *N*-containing nucleophiles [105]

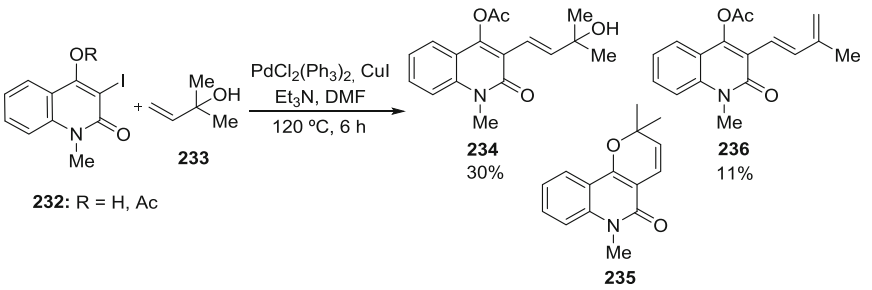
substituted (hetero)aromatic, aliphatic and cyclic amides, alkyl or arylsulfonamides, indoles, pyrroles, azaindoles, imidazoles and indazoles although in the case of less nucleophilic reagents, a longer reaction time was required. The efficiency of this catalytic system was also tested in the coupling of various nitrogen nucleophiles with other electrophilic coupling partners, such as 3-bromoquinolin-2(1*H*)-ones, and these electrophilic substrates efficiently undergo the coupling reaction giving the corresponding coupling products moderate to excellent yields (41–98%) [105]. When using 3,6-dibrominated quinolin-2(1*H*)-ones, the amination proceeded at the more activated C-3 position and yielded the monoaminated products in satisfactory yields (42–68%) under the conditions indicated in Scheme 69.

5 Transformation of Quinolin-2(1*H*)-ones

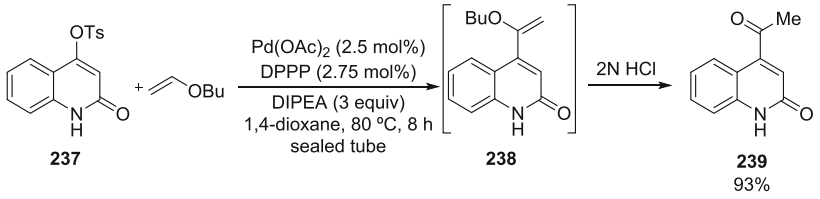
5.1 Heck Reaction

The precursor **234** of quinolone dimers paraensidimerins was synthesized by a Pd-catalysed Heck reaction of 3-iodoquinolin-2(1*H*)-one **232** with 2-methyl-3-buten-2-ol **233** (Scheme 70) [106]. The reaction of 4-acetoxyquinolin-2(1*H*)-one **232** (R=Ac), obtained by acetylation of 4-hydroxy-3-iodo-1-methylquinolin-2(1*H*)-one **232** (R=H), gave three products: the expected quinolone allylic alcohol **234** (30%); the diene **236** (11%), probably obtained by dehydration of allylic alcohol **234** by the Et_3NHI salt by-product formed in the reaction mixture; and the known alkaloid *N*-methylflindersine **235**, probably formed by deacetylation and subsequent intramolecular cyclization during the course of the reaction.

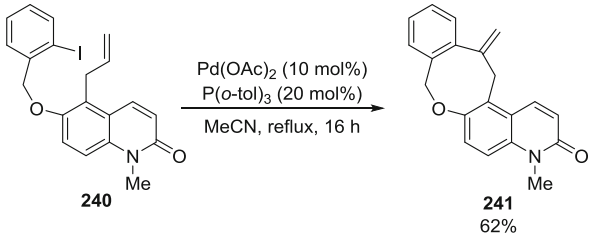
4-Acetylquinolin-2(1*H*)-one **239** was prepared via a very high α-regioselective Heck coupling of 4-tosylquinolin-2(1*H*)-one **237** with butyl vinyl ether (Scheme 71) [107]. The α-product **238** was obtained in very high α/β



Scheme 70 Heck reaction of 3-iodoquinolin-2(1*H*)-one **232** with 2-methyl-3-buten-2-ol **233** [106]



Scheme 71 Synthesis of 4-acetylquinolin-2(1*H*)-one **239** via Heck reaction of 4-tosylquinolin-2(1*H*)-one **237** with butyl vinyl ether followed by acidic treatment [107]

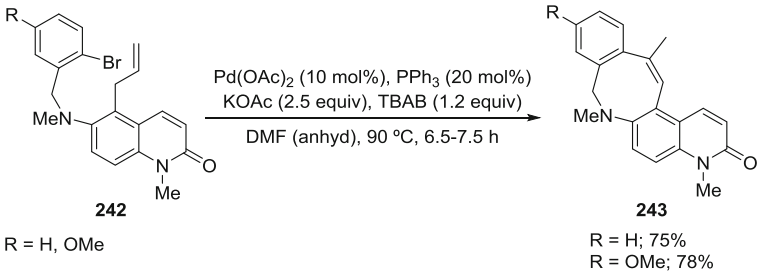


Scheme 72 Synthesis of benzoxocine-fused quinolin-2(1*H*)-one **241** from intramolecular Heck reaction of benzylallylquinolin-2(1*H*)-one **240** [108]

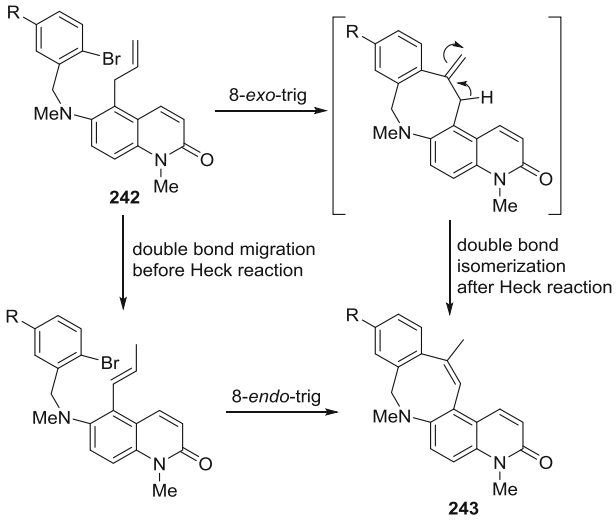
regioselectivity (>99/1) and after acidic treatment led to 4-acetylquinolin-2(1*H*)-one **239**.

One benzoxocine-fused quinolin-2(1*H*)-one **241** was prepared from the intramolecular Heck reaction of the benzylallylquinolin-2(1*H*)-one precursor **240** (Scheme 72) [108]. The reaction led to the regioselective formation of the 8-*exo* cyclization product **241**, and no 9-*endo* product was observed in this case.

Quinolin-2(1*H*)-one annulated benzazocines **243** were obtained from the Pd-catalysed intramolecular Heck reaction of unactivated allylquinolin-2(1*H*)-ones **242** (Scheme 73) [109]. The intramolecular Heck reaction afforded exclusively the *endo*cyclic product **243** in good yields. Once the exclusively 8-*exo* mode of cyclization is unusual, in this case, the authors believe that the formation of the *end*ocyclic products may occur via two possible pathways, namely, proceeding by



Scheme 73 Synthesis of quinolin-2(1*H*)-one annulated benzazocines **243** by intramolecular Heck reaction of allylquinolin-2(1*H*)-ones **242** [109]

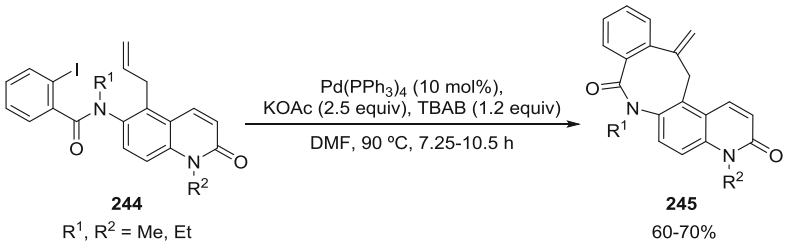


Scheme 74 Probable mechanistic path of the intramolecular Heck reaction of allylquinolin-2 (1*H*)-ones **242** [109]

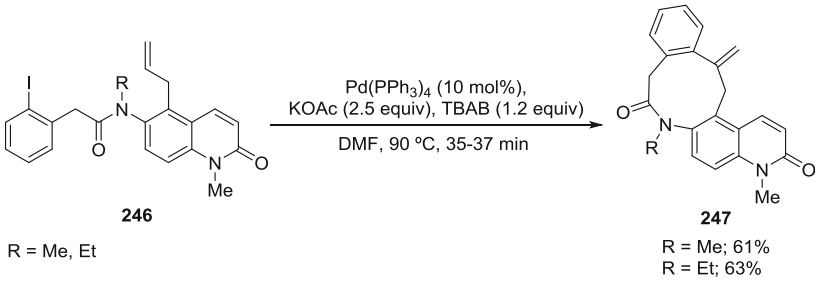
the 8-*exo* mode of cyclization followed by double-bond isomerization and, alternatively, a double-bond isomerization prior to the Heck reaction leading to the subsequent 8-*endo*-Heck cyclization (Scheme 74).

Later, the same authors described the synthesis of quinolin-2(1*H*)-one annulated benzazocinones **245** applying the same methodology at unactivated allylquinolin-2 (1*H*)-ones **244** (Scheme 75) [110]. In this case, the optimal reaction conditions were identified using $Pd(PPh_3)_4$ as the catalyst. This ligand-free Heck coupling reaction leads exclusively to the expected 8-*exo*-Heck product **245**, in good yields, without any contamination of the 9-*endo*-Heck or 8-*exo*-isomerized product.

Using the methodology described above, two quinolin-2(1*H*)-one annulated benzazoninones **247** were synthesized starting from unactivated allylquinolin-2 (1*H*)-ones **246** (Scheme 76) [111]. The Heck reaction proceeded in reasonable



Scheme 75 Synthesis of quinolin-2(1*H*)-one annulated benzazocinones **245** by intramolecular Heck reaction of allylquinolin-2(1*H*)-ones **244** [110]



Scheme 76 Synthesis of quinolin-2(1*H*)-one annulated benzazoninones **247** by intramolecular Heck reaction of allylquinolin-2(1*H*)-ones **246** [111]

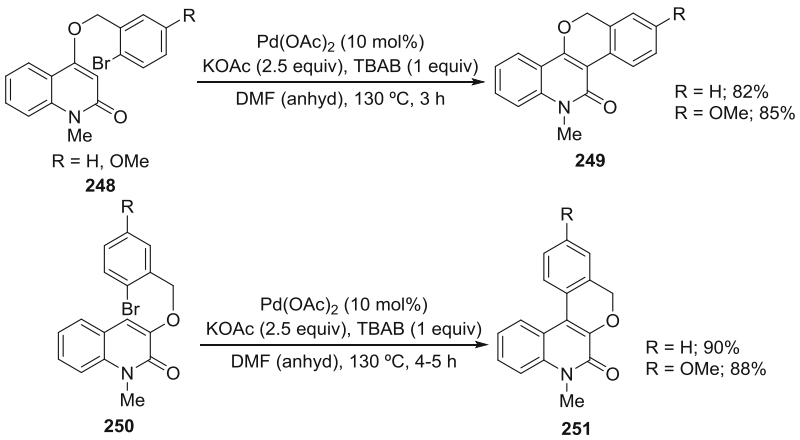
good yields with shorter reaction times, and only the product corresponding to the 9-*exo* mode of cyclization was obtained.

Pd-catalysed intramolecular Heck reaction of 3- and 4-(2-bromobenzyloxy) quinolin-2(1*H*)-ones **248** and **250**, previously synthesized [112, 113], under Jeffery's two-phase protocol afforded four tetracyclic quinolones **249** and **251** in very good yields (Scheme 77) [114].

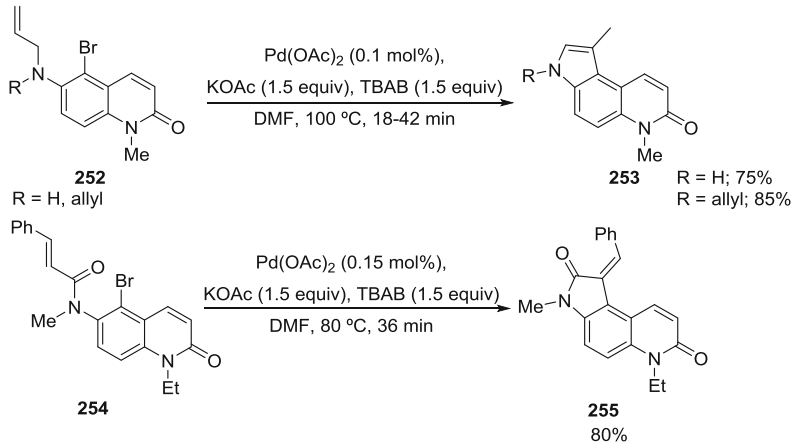
A ligand-free intramolecular Heck reaction of 6-amino-5-bromoquinolin-2(1*H*)-ones **252** catalysed by $Pd(OAc)_2$ gave new pyrrole-fused quinolin-2(1*H*)-ones **253** (Scheme 78) [115]. This methodology is applicable to secondary and tertiary amines. Under similar reaction conditions, the intramolecular Heck reaction of quinolin-2(1*H*)-one **254** afforded the corresponding pyrrol-2(3*H*)-one fused quinolin-2(1*H*)-one **255**.

Later, another synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **257** in very good yields was reported, by a ligand-free $Pd(OAc)_2$-catalysed intramolecular Heck reaction of enamines, prepared in situ from the condensation of 6-amino-5-bromo-1-methylquinolin-2(1*H*)-one **256** with cyclic and acyclic ketones (Scheme 79) [116]. The reaction is only effective when DMF is used as solvent and other Pd sources [$PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$] were less efficient than Pd $(OAc)_2$.

First, substrates **256** condense with the ketone to generate **258** and produce the enamines **259** in the presence of a base. The formed enamines subsequently



Scheme 77 Synthesis of tetracyclic quinolones **249** and **251** by intramolecular Heck reaction of 3- and 4-(2-bromobenzyloxy)quinolin-2(1*H*)-ones **248** and **250** [114]

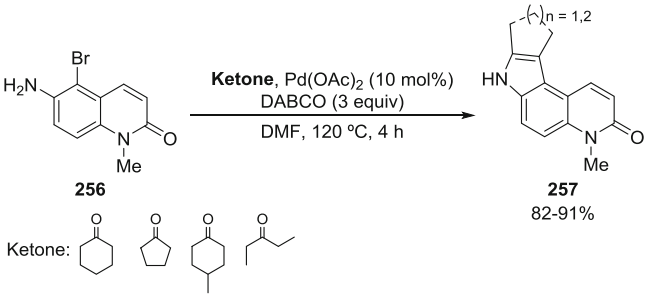


Scheme 78 Synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **253** and **255** by intramolecular Heck reaction of 5-bromoquinolin-2(1*H*)-ones **252** and **254** [115]

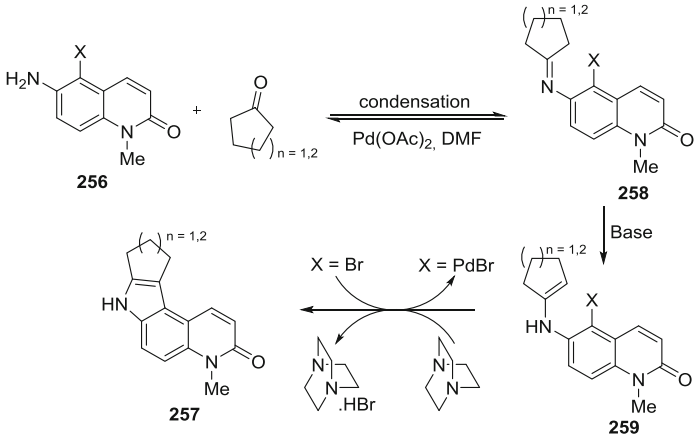
underwent intramolecular palladium-catalysed Heck reaction to afford the products **257** (Scheme 80).

5.2 Suzuki–Miyaura Reaction

The synthesis of 4- and 3,4-substituted quinolin-2(1*H*)-ones **261** and **262** via Pd-catalysed regioselective cross-coupling reactions of 3-bromo-4-trifloxy-quinolin-2(1*H*)-ones **260** with arylboronic acids was described (Scheme 81)



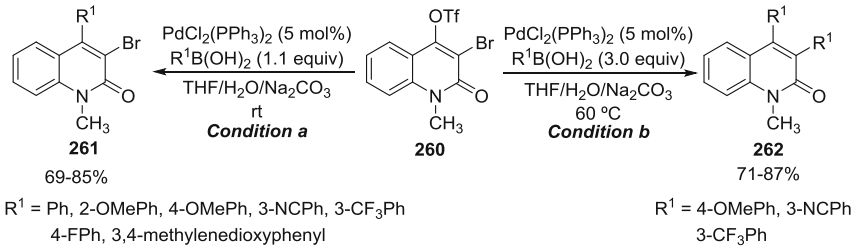
Scheme 79 Synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **257** from an intramolecular Heck reaction of the in situ prepared enamines [116]



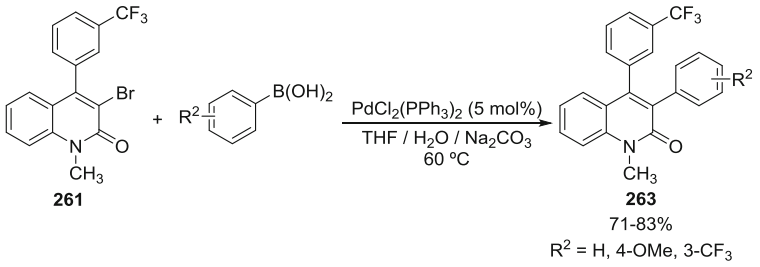
Scheme 80 Proposed mechanism for the synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **257** [116]

[117]. Regiocontrolled cross-coupling of 3-bromo-4-trifloxyquinolin-2(1*H*)-one **260** could be achieved by tuning the temperature and the amount of arylboronic acid. When using $PdCl_2(PPh_3)_2$ as catalyst in the reaction with 4-methoxyphenylboronic acid (1.5 equiv.) at 50°C, the corresponding product **261** was obtained in 20% yield together with disubstituted compound **262** (60%). At room temperature **261** was obtained as the major product (78%) and only traces of **262** were detected. Reducing the amount of 4-methoxyphenylboronic acid to 1.1 equiv., **261** was the only product (81%). At 60°C with a higher excess of 4-methoxyphenylboronic acid (2.5–3.0 equiv.), only **262** was generated (87%). Both electron-withdrawing and electron-donating-substituted arylboronic acids are suitable coupling partners, giving similar reaction yields.

Compound **261** (R^1=3-CF_3Ph) was further elaborated under the conditions shown in Scheme 82, and when it was employed as substrate in the Suzuki–Miyaura



Scheme 81 Synthesis of 4- and 3,4-substituted quinolin-2(1*H*)-ones **261** and **262** via regioselective Suzuki–Miyaura reactions of 3-bromo-4-trifloxyquinolin-2(1*H*)-ones **260** [117]



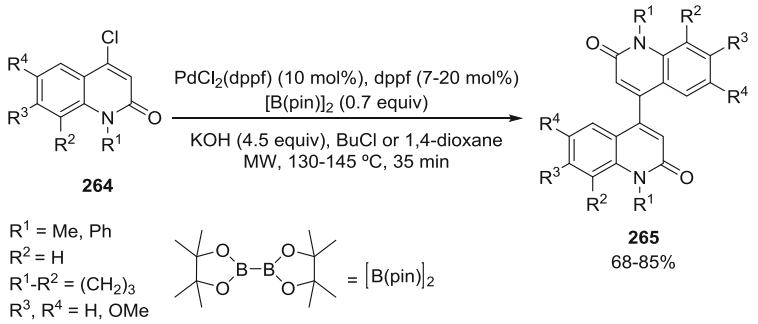
Scheme 82 Synthesis of 3,4-disubstituted quinolin-2(1*H*)-ones **263** by Suzuki–Miyaura coupling reaction of **261** with arylboronic acids [117]

reaction with different arylboronic acids, good yields of the corresponding products **263** were obtained [117].

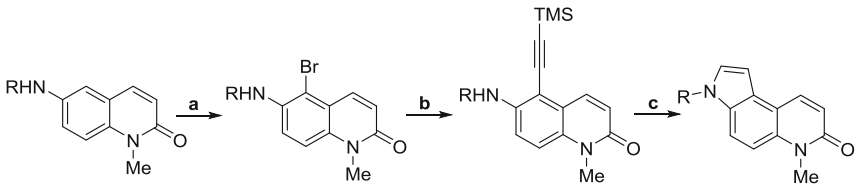
Functionalized 4,4′-bisquinolones **265** were prepared in good to excellent yields through Pd-catalysed one-pot borylation–Suzuki cross-coupling reaction of 4-chloroquinolin-2(1*H*)-one precursors **264** employing controlled MW irradiation (Scheme 83) [118]. A strong base such as KOH in combination with $PdCl_2$(dppf) as catalyst is needed to achieve excellent conversions. Solvents such as DMSO, DMF and toluene promoted the formation of the dehalogenated product, while 1,4-dioxane, dichloromethane and 1,2-dichloroethane minimized dehalogenation. 1-Chlorobutane proved to be the best solvent in this particular case.

5.3 *Sonogashira Reaction*

Pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **269** were synthesized in excellent yields by sequential coupling and cyclization reactions of aryl halides with (trimethylsilyl) acetylene with concurrent elimination of the TMS substituent (Scheme 84) [119]. Acetylenic amines possessing an electron-donating group on the nitrogen atom also underwent Cu(I)-catalysed cyclization. Quinolones **266** were prepared



Scheme 83 Synthesis of 4,4′-bisquinolones **265** by one-pot borylation–Suzuki cross-coupling of 4-chloroquinolin-2(1*H*)-one **264** [118]



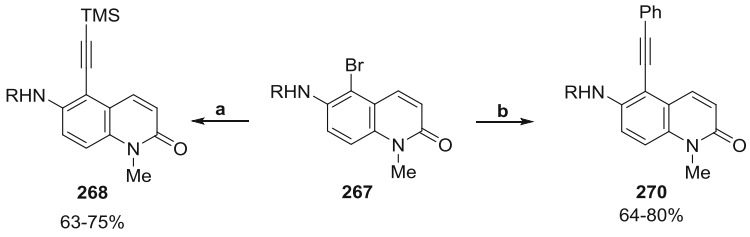
a: NBS, CH_3CN, rt, 30 min; **b:** (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), 5:3:2 DMF/THF/Et_3N, 70 ºC, sealed tube, 6-8 h; **c:** DMF, CuI (50 mol%), reflux, 1 h.

Scheme 84 Synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **269** by sequential Sonogashira coupling and cyclization reactions of 5-bromoquinolin-2(1*H*)-ones **267** with (trimethylsilyl)acetylene [119]

from commercially available quinolines [120, 121] and then brominated, and the resulting bromo derivatives **267** transformed into the required heteroannulation precursors **268** by a Sonogashira coupling with (trimethylsilyl)acetylene using $PdCl_2(PPh_3)_2$ as catalyst and CuI as the cocatalyst. The reactions were optimized by smoothly heating the reaction in a sealed tube. Heteroannulation of the acetylenic amines to give **269** was achieved by refluxing the precursors **268** in DMF in the presence of CuI.

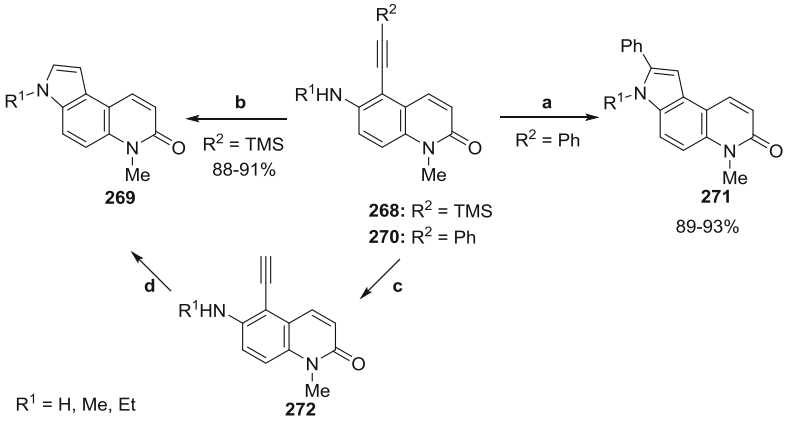
Acetylenic amines **268** and **270** were obtained by Sonogashira coupling of the corresponding 6-amino-5-bromoquinolin-2(1*H*)-one derivatives **267** with (trimethylsilyl)acetylene or phenylacetylene, respectively. Both reactions were performed in the presence of $PdCl_2(PPh_3)_2$ as catalyst and CuI as cocatalyst, although in slightly different experimental conditions (Scheme 85) [122].

Pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones were also synthesized in high yield by cycloisomerization of previously described acetylenic amines **270** using $AuCl_3$ in the absence of any silver salts or any other bases. Under these conditions acetylenic amines with electron-donating groups readily undergo cycloisomerization (Scheme 86, **a**). No cycloisomerization product was obtained with trimethylsilyl-substituted acetylenic amines **268**, even when using other solvents (toluene,



a: (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$ (4.8 mol%), CuI (11 mol%), 2:2:5 Et_3N/THF/DMF, sealed tube, 80 °C, 9 h; **b:** phenylacetylene, $PdCl_2(PPh_3)_2$ (5.7 mol%), CuI (11 mol%), 2:5 Et_3N/DMF, 120 °C, 1.5 h.

Scheme 85 Sonogashira coupling of 6-amino-5-bromoquinolin-2(1*H*)-ones **267** with phenylacetylene and (trimethylsilyl)acetylene [122]

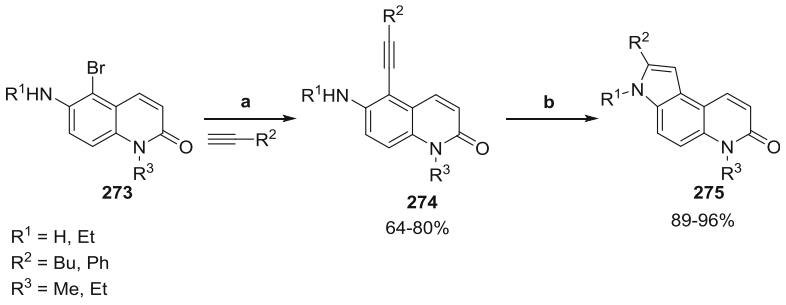


a: $AuCl_3$ (1 mol%), EtOH, 80 °C, 4-7 h; **b:** $AuCl_3$ (1 mol%), EtOH, K_2CO_3, 70 °C, sealed tube, 8.5–10 h; **c:** K_2CO_3, MeOH, 30 °C, 4 h; **d:** $AuCl_3$ (1 mol%), EtOH, 80 °C.

Scheme 86 Synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **269** and **271** by gold-catalysed cycloisomerization of acetylenic amines **268** and **270** [122]

1,4-dioxane, DMF or MeCN) and increasing the amount of catalyst to 5 mol% or the temperature, probably due to the presence of bulky trimethylsilyl group. Cyclized products **269** were only obtained in very good yield when **268** was treated with $AuCl_3$, using K_2CO_3 as base (Scheme 86, **b**). The trimethylsilyl group was initially eliminated by the reaction with K_2CO_3, and then cyclization proceeded in a one-pot transformation with the unsubstituted alkyne moiety, which was verified by the reaction of the unsubstituted alkyne **272** (Scheme 86, **c** and **d**). The time required for the cyclization of compounds **268** in these conditions is relatively long because the triple bond at the terminal position is not activated [122].

Another series of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **275** were synthesized from the intramolecular hydroamination reaction of acetylenic amines **274**, obtained from **273**, catalysed by $PdCl_2/FeCl_3$ (Scheme 87) [123]. $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ were



a: $PdCl_2(PPh_3)_2$ (5 mol%), CuI (5 mol%), 3:2 DMF/Et_3N, 80 °C, 1.5–3 h; **b:** $PdCl_2$ (1 mol%), $FeCl_3$ (5 mol%), DCE, 85 ºC, 2.5-4 h.

Scheme 87 Synthesis of pyrrolo[3,2-*f*]quinolin-7(6*H*)-ones **275** by $PdCl_2/FeCl_3$-catalysed intramolecular hydroamination of acetylenic amines **274** [123]

also tested as Pd(II) sources but found to be ineffective, unlike $PdCl_2$ that is efficient in only 1 mol%. The presence of $FeCl_3$ is necessary for this hydroamination reaction to occur and may facilitate the reoxidation of Pd(0) to Pd(II) in the catalytic cycle. This cyclization proceeded well in the presence of aromatic- and aliphatic-substituted alkynes and with both protected and unprotected amines.

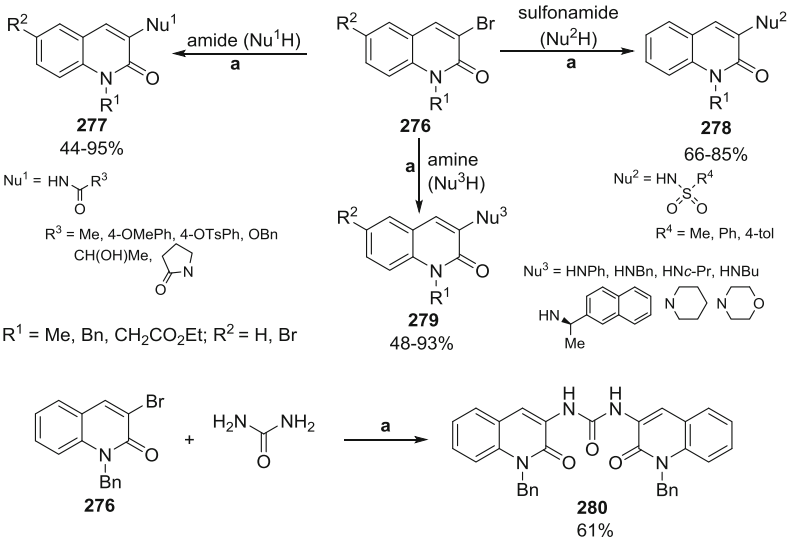
5.4 Buchwald–Hartwig Reaction

A series of 3-(*N*-substituted-amino)quinolin-2(1*H*)-ones **277–280** were synthesized in good to excellent yields by the Pd-catalysed C–N coupling reaction starting from 3-bromoquinolin-2-(1*H*)-ones **276**. Several nucleophiles, including amines, amides and benzylcarbamate, as well as the less nucleophilic alkyl- or arylsulfonamides, were effective in this transformation (Scheme 88) [124]. The C–N bond-forming reaction was also studied with urea leading to the double heteroarylated coupling product **280** in good yield (61%). In the presence of two carbon–bromine atoms of quinolin-2-(1*H*)-one **276** (R^2=Br), the coupling proceeded at the more activated C-3 position and yielded the mono-substituted product (44–48%) together with the disubstituted one (15–27%).

Later, the same authors described a Pd-catalysed coupling reaction of 3-bromo-1-methylquinolin-2(1*H*)-one **276** with indole and 5-methoxyindole affording the coupling products **282** in excellent yields (Scheme 89) [125].

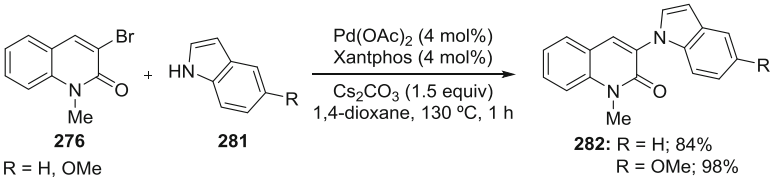
5.5 Aminocarbonylation Reaction

Quinolin-2(1*H*)-one-6-carboxamides **288**, potential gonadotropin-releasing hormone antagonists, were obtained via the Pd-catalysed aminocarbonylation reaction



a: $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), Cs_2CO_3 (2 mmol), 1,4-dioxane, 100 ºC, 10 h, sealed Schlenk tube.

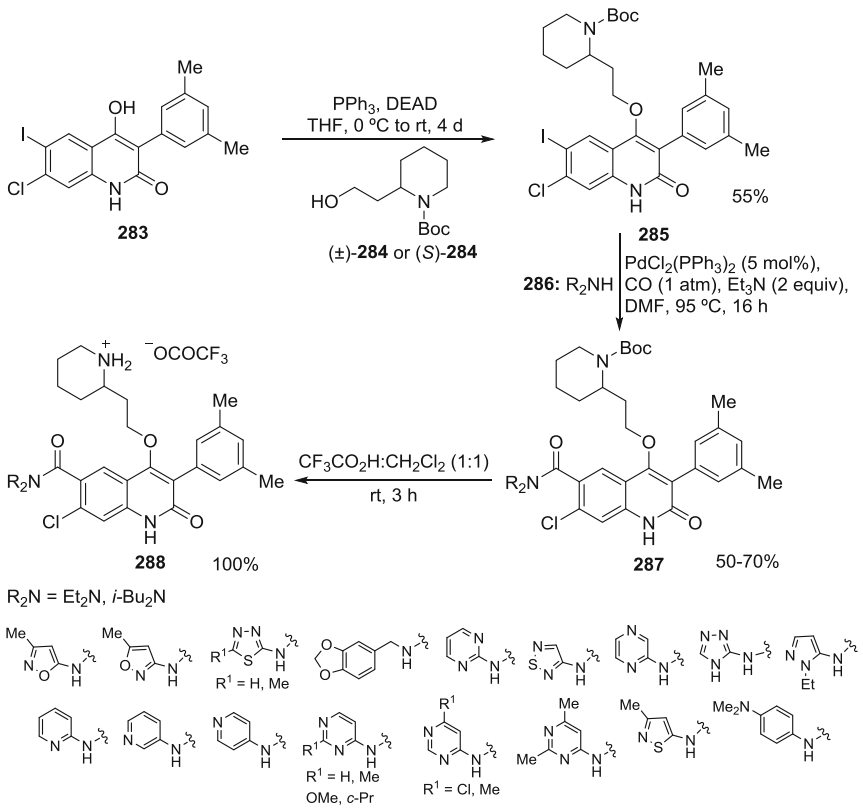
Scheme 88 Synthesis of 3-(*N*-substituted-amino)quinolin-2(1*H*)-ones **277**–**280** by Pd-catalysed C–N coupling reaction of 3-bromoquinolin-2-(1*H*)-ones **276** [124]



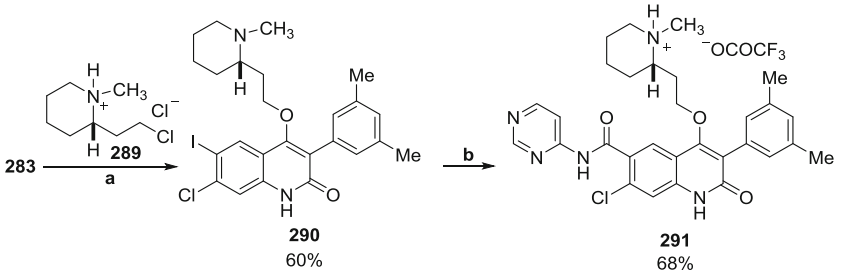
Scheme 89 Synthesis of 3-aminoquinolin-2(1*H*)-ones **282** by Pd-catalysed coupling reaction of 3-bromo-1-methylquinolin-2(1*H*)-one **276** with indoles **281** [125]

of 4-hydroxyquinolin-2(1*H*)-one **283** [126]. *O*-Alkylation of **283** with either (±)-**284** or (*S*)-**284** using the Mitsunobu protocol afforded the *O*-alkyl ethers (±)-**285** and (*S*)-**285**. Then Pd-catalysed aminocarbonylation of the iodo compound **285** with a variety of primary and secondary amines **286** led to the protected quinolin-2(1*H*)-one-6-carboxamides **287**. Removal of Boc protecting group of piperidines **287** using trifluoroacetic acid afforded the targeted amides **288** in quantitative yields (Scheme 90).

Quinolin-2(1*H*)-one-6-carboxamide **291** was also prepared by alkylation of 4-hydroxyquinolin-2(1*H*)-one **283** with (*S*)-2-(2-chloroethyl)-1-methylpiperidine **289** followed by aminocarbonylation of intermediate **290** with 4-aminopyrimidine (Scheme 91).

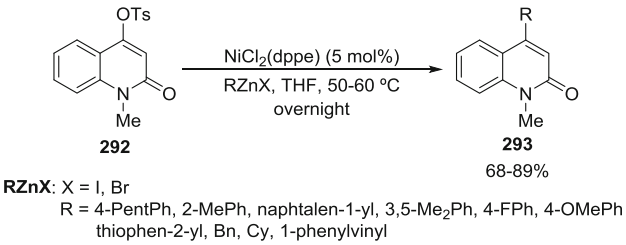


Scheme 90 Synthesis of quinolin-2(1*H*)-one-6-carboxamides **288** by Pd-catalysed aminocarbonylation of 4-hydroxyquinolin-2(1*H*)-one **283** with several amines **286** [126]



a: K_2CO_3, DMF, 80 ºC, 3 h; **b:** 4-aminopyrimidine, $PdCl_2(PPh_3)_2$ (5 mol%), CO (1 atm), Et_3N (2 equiv), DMF, 95 ºC, 16 h.

Scheme 91 Synthesis of quinolin-2(1*H*)-one-6-carboxamide **291** by Pd-catalysed aminocarbonylation of 4-hydroxyquinolin-2(1*H*)-one **283** with 4-aminopyrimidine **289** [126]



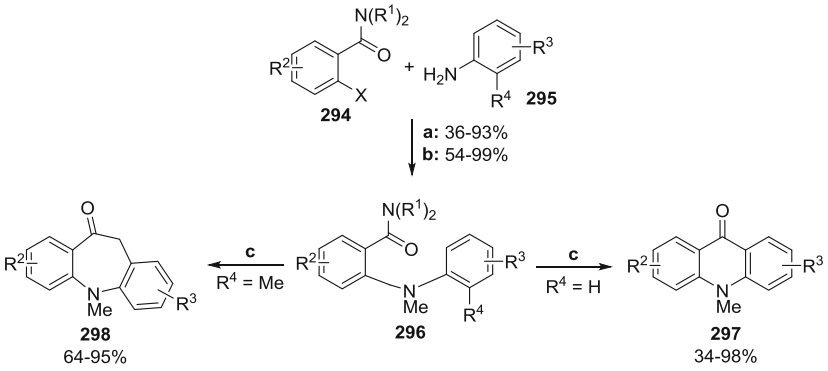
Scheme 92 Synthesis of 4-substituted quinolin-2(1*H*)-ones **293** via Ni-catalysed cross-coupling of 1-methyl-4-tosyloxyquinolin-2(1*H*)-one **292** with organozinc reagents [127]

5.6 Ni-Catalysed Cross-Coupling Reaction

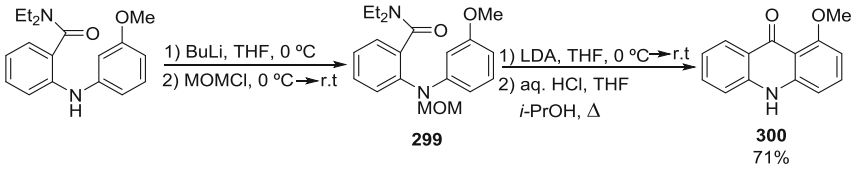
4-Substituted quinolin-2(1*H*)-ones **293** were synthesized via Ni-catalysed cross-coupling of 4-tosylate **292** with organozinc reagents as an alternative to the Suzuki–Miyaura cross-coupling reaction of 1-methyl-4-tosyloxyquinolin-2(1*H*)-one **292** and arylboronic acids that were not well succeeded and no product was detected [127]. The use of zinc reagent as substrate under Pd-catalysed conditions using different Pd catalysts [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, $Pd_2(dba)_3$] in the reaction of 4-tosylate **292** with 4-pentylphenylzinc iodide afforded quinolin-2(1*H*)-ones **293** in low yields (10–30%) even with the addition of ligand, with different solvents or temperatures. When $NiCl_2$(dppp) (5 mol%) was used as the catalyst, 71% yield of the desired product **293** (R=4-PentPh) was afforded in 12 h at 50°C. After optimization of the reaction conditions, $NiCl_2$(dppe) was identified as the best catalyst (**293**, R=4-PentPh; 84%). The method is simple, and air-stable, inexpensive tosylates are used under extremely mild conditions. Alkylzinc and electron-rich and electron-poor arylzinc reagents were suitable for this reaction and gave the desired products in good yields (Scheme 92).

6 Synthesis of Acridin-9(10*H*)-ones

An efficient and regioselective route to acridin-9(10*H*)-ones through application of a combined Buchwald–Hartwig aryl amination-directed remote metalation (DreM) protocol has been disclosed [128, 129]. Diarylamines **296** were prepared by Buchwald–Hartwig C–N cross-coupling of 2-halobenzamides **294** with anilines **295**, in good yields, as an alternative to the harsh conditions, tedious workup and purification procedures typical of Ullmann chemistry. In light of the inability to effect LDA-mediated cyclization of the unprotected diarylamines, these derivatives were *N*-methylated in excellent yields. Upon treatment with LDA, *N*-methyldiarylamines were converted to acridin-9(10*H*)-ones **297** or dibenzo[*b*,*f*]azepinones **298**, in good to excellent yields with regioselectivity depending upon the presence or absence of directed metalation groups (Scheme 93). When R^4=H, only the



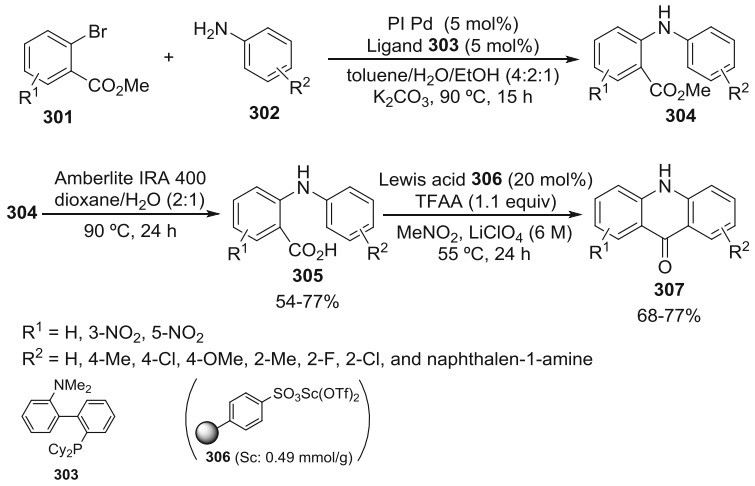
Scheme 93 Synthesis of acridin-9(10*H*)-ones **297** by a combined Buchwald–Hartwig aryl amination (DreM) [128, 129]



Scheme 94 Synthesis of *N*-unsubstituted acridin-9(10*H*)-one **300** from a MOM-protected diarylamine **299** through a DreM protocol [129]

acridin-9(10*H*)-ones **297** were obtained, while when R^4=Me, regioselectivity for dibenzo[*b*,*f*]azepinones **298** over acridin-9(10*H*)-ones **297** was quite remarkable, except when a methoxyl or a chlorine group is present in the *para*-position relatively to the methyl group (R^4=Me). This synthetic route represents a vast improvement over classical methods for acridin-9(10*H*)-one synthesis, offering significant advantages when compared to the classical Friedel–Crafts reactions.

This synthetic strategy requires the *N*-alkylation of substrates prior to LDA-mediated cyclization. To overcome the limitation of *N*-functionalization post-cyclization, the authors used the MOM-protected diarylamine **299** and applied the standard LDA conditions (Scheme 94). A smooth cyclization ensued to give the product which, upon mild acidic hydrolysis, afforded acridin-9(10*H*)-one **300** in good overall yield, thus extending the DreM approach for the construction of *N*-unsubstituted acridin-9(10*H*)-ones.



Scheme 95 Synthesis of acridin-9(10*H*)-ones **307** using polymer-supported Pd and Sc catalysts [130]

Another methodology to the synthesis of *N*-unsubstituted acridin-9(10*H*)-ones is based on a combined use of polymer-supported Pd and Sc catalysts in arylamination and intramolecular Friedel–Crafts acylation reactions, respectively (Scheme 95) [130]. The best conditions for the amination step involved the use of PI Pd [Pd $(PPh_3)_4$ immobilized onto polystyrene-based copolymers using polymer-incarcerated (PI) method] and ligand **303** in a toluene–water–ethanol solvent system and K_2CO_3 as a stoichiometric base. The obtained compounds **304** after hydrolysis underwent intramolecular Friedel–Crafts reaction in the presence of TFAA and a polymer-supported Sc catalyst in a $MeNO_2$-$LiClO_4$ solution and afforded acridin-9(10*H*)-ones **307** in good yields. The supported catalysts used can be recovered quantitatively by simple filtration and reused several times without loss of activity.

More recently the synthesis of 2,3-diarylacridin-9(10*H*)-ones **190** by electrocyclization of the Heck products (*E*,*E*)-2,3-distyrylquinolin-4(1*H*)-ones **189** was described and was already discussed in Sect. 4.1.1 [92].

7 Conclusion

We have described the extensive work in the syntheses and transformations of quinolin-2 and quinolin-4(1*H*)-ones by using metal-catalysed cross-coupling reactions. These transition metal-catalysed procedures have been developed providing increased tolerance towards functional groups, leading generally to higher reaction yields. A great number of these transformations involved Pd-catalysed reactions, although the use of copper, zinc, nickel, gold, tin, iridium, rhodium and scandium

can also be found. The Sonogashira cross-coupling transformation is one of the most typical and used metal-catalysed reactions.

Although there are a relatively interesting number of studies on the metal-catalysed cross-coupling synthesis and transformations of quinolones, this field still needs further development. For instance, homoeopathic Pd-catalysed transformations are rare (usually 1–5 mol% Pd is employed), thus opening space to further research in this area, concerning the development of Pd-catalysed cross-coupling reactions using milder conditions with lower Pd loadings using more efficient catalytic systems. Likewise the search for heterogeneous catalysed procedures that include either the formation of the desired heterocycles or their transformation to highly substituted compounds is another important research topic. Developments in these two new fields can be important to overcome some drawbacks of metal-catalysed procedures, as metal contamination of bioactive products, generally over accepted limits expressed in medicinal regulations that often preclude further industrial development of these methods, towards more environmentally friendly and economically cheaper methods.

The study on the metal-catalysed cross-coupling reactions for the synthesis of acridin-9(10*H*)-ones is almost inexistent, since only three studies have been disclosed. This means that this field presents an interesting issue for future research.

The asymmetric catalysis to obtain enantiopure quinolones is another underdeveloped topic since only four examples were found concerning the synthesis of 3,4-dihydroquinolin-2(1*H*)-ones by Pd-catalysed cyclocarbonylation or Buchwald–Hartwig reaction and Cu-catalysed cyclization.

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Synthesis and Transformations of Oxygen Heterocycles

Zoltán Novák and András Kotschy

Abstract The recent developments in the transition metal-catalyzed synthesis and transformations of such oxygen-containing heteroaromatic systems are reviewed, where the oxygen is part of a five-membered ring.

Keywords Benzofuran · Benzoxazole · Catalysis · Furan · Isoxazole · Oxadiazole · Oxazole · Transition metal

Contents

Abbreviations

Ac	Acetyl
acac	Acetylacetonate

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Ad	1-Adamantyl
BAr^F	Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
BINAM	2,2′-Bis(diphenylphosphinoamino)-1,1′-binaphthyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl
BmimBF4	1-Butyl-3-methylimidazolium tetrafluoroborate
bpy	2,2′-Bipyridyl
BQ	1,4-Benzoquinone
cod	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CuTC	Copper(I) thiophene-2-carboxylate
Cy	Cyclohexyl
Cy-DHTP	Cyclohexyl-dihydroxy-terphenylphosphine
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicycloundec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dcpe	1,2-Bis(dicyclohexylphosphino)ethane
DEA	Diethylamine
diglyme	1-Methoxy-2-(2-methoxyethoxy)ethane
DIPA	Diisopropylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
DPE-Phos	2,2′-Bis(diphenylphosphino)-diphenyl ether
dppe	1,2-Bis(diphenylphoshino)ethane
dppf	1,1′-Bis(diphenylphoshino)ferrocene
dppp	1,3-Bis(diphenylphoshino)propane
DTAC	Dodecyl trimethylammonium chloride
EDIPA	Ethyldiisopropylamine
hfacac	Hexafluoroacetylacetonate
Im	Imidazol-1-yl
IMes	1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-Bis(2′,6′-diisopropylphenyl)imidazol-2-ylidene
MonoPhos	3,4-A′(dinaphthalen-4-yl)dimethylamine
NBS	*N*-bromosuccinimide
NHC	*N*-heterocyclic carbine
NIS	*N*-iodosuccinimide
NMI	*N*-methylimidazole
NMP	*N*-methyl-2-pyrrolidone
Ph	Phenyl

Phen	1,10-Phenanthroline
PIFA	(Bis(trifluoroacetoxy)iodo)benzene
Piv	2,2-Dimethyl-propanoyl
PMP	4-Methoxyphenyl
pTSA	*p*-Toluenesulfonic acid
PyBroP	Bromotripyrrolidinophosphonium hexafluorophosphate
SDS	Sodium dodecyl sulfate
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis (tetrafluoroborate)
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
Sylphos	1,1′-Bis(1-diphenylphosphino-1-methylethyl)ferrocene
TBAB	Tetrabutylammonium bromide
TEA	Triethylamine
Tf	Trifluoromethylsulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMEDA	Tetramethylethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TMHD	2,2,6,6-Tetramethyl-3,5-heptanedionate
tmpp	Tris(2,4,6-trimethoxyphenyl)phosphine
Ts	Tosyl, 4-toluenesulfonyl
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

Oxygen-containing heterocycles are a class amply represented both in natural products and in biologically active compounds; therefore, it is not surprising that their research has been always in the forefront of interest both in basic and applied science [1, 2]. Due to the vastness of the area, this chapter is limited to the last decade's (2004–2014) developments in the transition metal-catalyzed synthesis and transformations of mono- and bicyclic compounds that contain at least a five-membered aromatic ring with an oxygen atom. For those looking for a broader coverage of the area, a significant number of monographs and review articles are available.

The discussion of the subject is dived into chapters on the basis of the number of heteroatoms in the given ring systems; thus, the first block describes the synthesis and functionalization of furans and benzofurans, which is followed by the description of the synthesis and transformations of such five-membered oxygen heterocycles that also contain another hetero atom.

2 Synthesis of Furans and Benzofurans

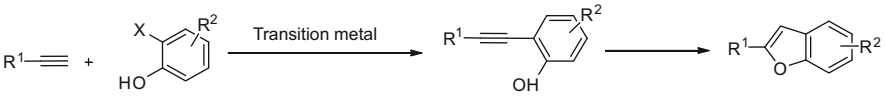
This chapter summarizes the transition metal-catalyzed approaches for the creation of the furan ring. Reactions leading to furans and benzofurans are treated separately. Within the chapters describing the synthesis of these compound classes, a further classification was made on the basis of the type of chemical transformation that results in the ring closure.

2.1 Transition Metal-Catalyzed Synthesis of Benzofurans

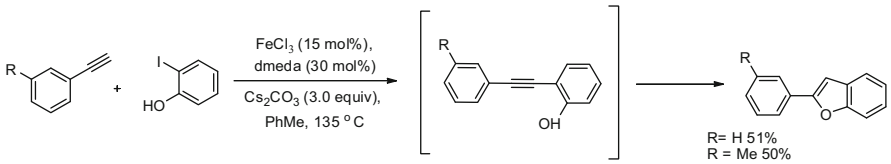
The benzofuran ring is widely abundant both in nature and in synthetic compounds; therefore, it is not surprising that several approaches have been established for its preparation. The following chapter provides an overview of the recent developments in the transition metal-catalyzed construction of the furan ring when condensed to a benzene moiety.

2.1.1 Direct Ring Closure of Halophenols Including Sonogashira-Type Reaction: The Coupling/Ring Closure Approach

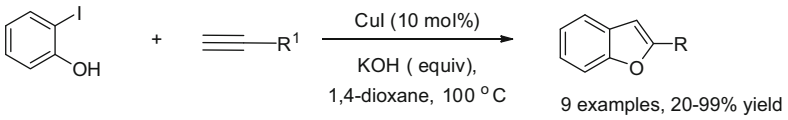
The benzofuran ring can be constructed via the utilization of Sonogashira reaction of *ortho*-halophenols and terminal acetylenes. In this chapter new variants of the transition metal-catalyzed coupling of terminal acetylenes and aryl halides and the subsequent ring closure are collected.



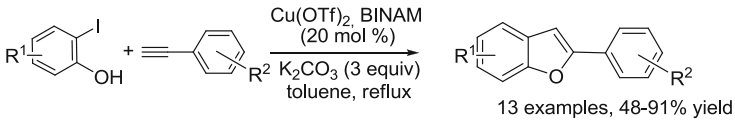
A new iron-catalyzed version of the Sonogashira reaction was developed by Bolm and coworkers [3]. The procedure utilizes simple $FeCl_3$ as catalyst in conjunction with DMEDA as ligand. The couplings of terminal acetylenes and aryl halides were achieved with 15 mol% $FeCl_3$ and 30 mol% DMEDA in toluene at 135°C in the presence of Cs_2CO_3 as base. Beyond the synthesis of simple internal acetylenes, the procedure allows the construction of benzofuran ring through the usual 5-endo-dig cyclization. With this strategy 2-phenyl benzofuran and 2-m-tolyl benzofuran were synthesized starting from the appropriate iodophenol and terminal acetylene in 51 and 50% yield, after the 72 h reaction time. Although the procedure offer a new possibility for the Sonogashira coupling by replacing palladium as catalyst, later it was demonstrated that the palladium contaminants in the other components had a significant role in the Sonogashira coupling [4].



Later Shen and coworkers used 10 mol% CuI as catalyst for the construction of benzofuran and indole rings from 2-iodophenol or aniline in 1,4-dioxane at 100°C [5]. Several alkyl and aryl acetylenes were used as coupling partners and the substituted benzofurans were synthesized in 20–99% yield. The authors demonstrated that ultrapure CuI (99.999% purity) is less efficient in the coupling due to its low palladium content. However, addition of 100 ppb palladium to CuI significantly increased the conversion.

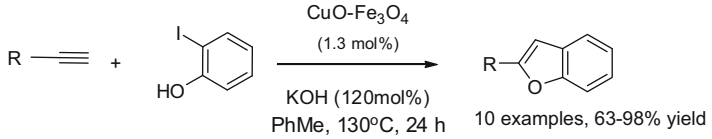


Copper triflate with *N,N*-disubstituted BINAM ligand is an efficient catalytic system for the construction of the benzofuran ring from 2-iodophenols and terminal acetylenes as it was demonstrated by Sekar [6]. In the presence of 20 mol% $Cu(OTf)_2$-BINAM catalyst in refluxing toluene, several 2-arylbenzofuran derivatives were obtained. With the utilization of substituted iodophenols, benzofurans could be isolated bearing alkyl group or halogen in position-5. Despite the relatively long reaction time (22–38 h), the desired heterocycles were obtained with good to excellent yield (48–91%). However, the possibility of palladium effect cannot be completely ignored in this case either since the procedure requires 3 equiv. of K_2CO_3, which can be a possible source of palladium contamination.

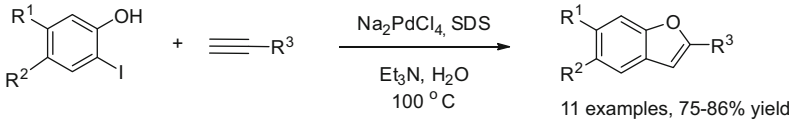


Besides the several homogeneous copper-catalyzed transformations, the benzofuran ring can also be constructed using a heterogeneous catalyst. An impregnated copper catalyst was developed and utilized by Ramon for the Sonogashira coupling of 2-iodophenols and different terminal alkynes [7]. After the coupling step the ring closure took place straightforward in a stepwise manner. The syntheses were performed in the presence of 1.3 mol% of $CuO\text{-}Fe_3O_4$ catalyst and 1.2 equiv. KOH in toluene at 130°C. After 24 h reaction time, the catalyst was simply removed with the aid of outer magnetic field and it was proved to be reusable ten times without the significant loss of activity. The methodology has good functional group tolerance considering the acetylene part. Several aryl acetylenes bearing electron-donating and electron-withdrawing groups were coupled with

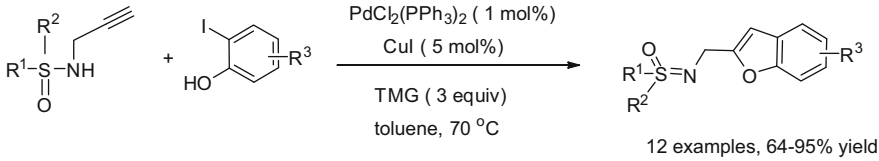
2-iodophenol and the desired benzofurans were isolated with good yield. 2-Pyridylacetylene gave the 2-pyridylbenzofuran with 93% yield and alkylacetylenes were also successfully coupled with iodophenol, with the exception of ^{t}Bu-acetylene, which did not provide the appropriate product even after 72 h reaction time.



The palladium-catalyzed Sonogashira reaction can be achieved under both homogeneous and heterogeneous catalytic conditions. However, in situ generated palladium nanoparticles are also able to catalyze the coupling reaction, which was demonstrated by Ranu and coworkers [8]. Their methodology enables the coupling of aromatic iodides with terminal acetylenes under aqueous conditions in the presence of sodium dodecyl sulfate (SDS) at rt. For the successful coupling the nanoparticles were prepared in situ from Na_2PdCl_4. The Sonogashira conditions were also used for the synthesis of the benzofuran core using a general coupling-ring closure strategy. However, in this case the coupling required higher temperature (100°C) and longer reaction time (typically 12–18 h). The functionalized 2-aryl and 2-alkylbenzofurans were obtained in 75–86% yield, which demonstrates the robustness of the procedure.

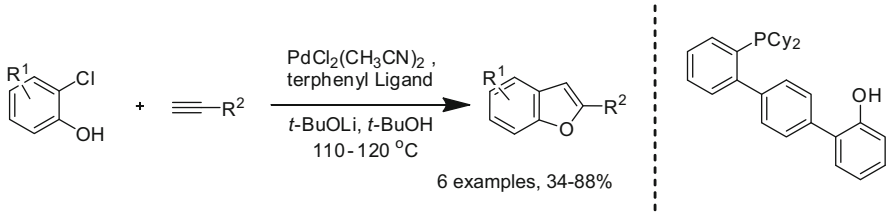


N-propargyl arylmethyl sulfoximines were also successfully coupled with 2-iodophenols under homogeneous catalytic conditions utilizing the frequently used $PdCl_2(PPh_3)_2$ catalyst (1 mol%) together with 5 mol% CuI. The reactions, developed by Bolm, were conducted in toluene at 70°C in the presence of 3 equiv. of 1,1,3,3-tetramethylguanidine (TMG) as base [9]. A versatile benzofuran library was built up with the use of differently substituted aryl sulfoximines and 2-iodophenols, and the procedure provided the products in excellent yield (64–95%).

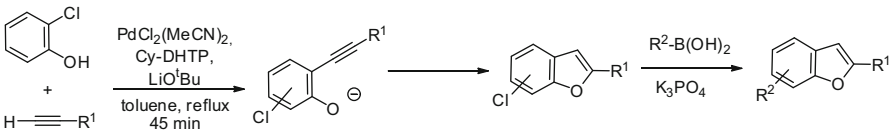


Most of the coupling-ring closure synthetic approaches for the construction of the benzofuran ring start from bromo- or iodophenols and terminal acetylenes.

Reactivity of chlorophenols is much lower due to the slower oxidative addition of the C–Cl bond to Pd. In general, aryl chlorides are less reactive in the Sonogashira reaction, and the presence of the hydroxyl group, which is required for the benzofuran formation, further deactivates the substrate for the coupling due to its strong electron donating property. Wang and Manabe described the first benzofuran synthesis from 2-chlorophenols following the common strategy [10]. The key point in their transformation is the choice of the appropriate ligand. The special bifunctional terphenyl ligand (Cy-HTP), which bears phosphano and hydroxyl groups proved to be an excellent ligand for the desired coupling and ring closure. In ^{t}BuOH at 110–120°C in the presence of ^{t}BuOLi, several benzofurans were synthesized with good yields. The additional advantage of the bifunctional ligand beyond its enhanced activity was exploited when dichlorophenols were selectively coupled with terminal acetylenes in position 2. The selectivity was ensured by the heteroaggregates of lithium phenoxides of the substrate and the ligand.

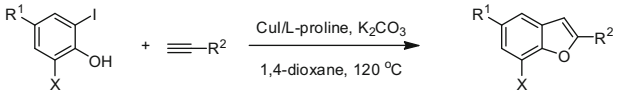


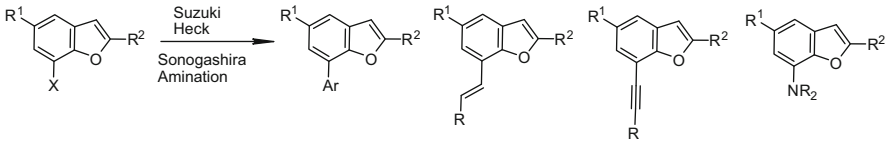
The catalytic system was improved later by Manabe with the design and utilization of dihydroxy-terphenylphosphine ligands bearing cyclohexyl groups on the phosphorous atom (Cy-DHTP) [11]. With this ligand the same transformations were performed, but the reaction time significantly decreased (from 22 h to 45 min) in the presence of Cy-DHTP. Dichlorophenols were also selectively coupled in position 2 with terminal acetylenes, and chlorobenzofurans were obtained. The chloro function offers the possibility of further functionalization via cross-coupling reactions. Taking advantage of this a one-pot sequential synthesis of disubstituted benzofurans was developed from dichlorophenols. The Cy-DHTP promoted coupling and ring closure was followed by a subsequent Suzuki coupling on the chloro function. The second coupling reaction required XPhos ligand. Utilizing this methodology several 2,4-, 2,5-, 2,6-, and 2,7-diarylated benzofurans were prepared in good to excellent yield (28–94%).



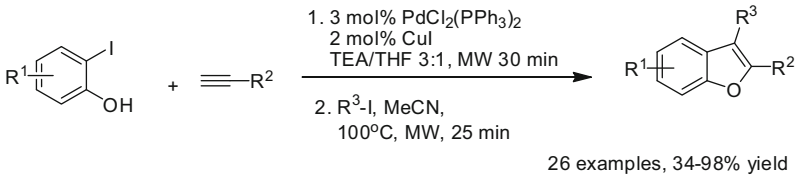
The similar sequential coupling – ring closure – coupling strategy was used by Arcadi et al. for the synthesis of 2,5,7-trisubstituted benzofurans from halophenols. Such 2-bromo- or 2-chloro-6-iodophenols were used as substrates that contained

other substituents in position 4 (Me, F, Ph, Me(CH_2)CO_2) [12]. The Sonogashira reaction with terminal acetylenes was achieved with 10 mol% CuI catalyst and 20 mol% L-proline ligand in the presence of 2 equiv. K_2CO_3 in 1,4-dioxane at 120°C in 1–8 h. The appropriate 2-aryl or 2-alkyl 7-chloro or 7-bromobenzofurans were isolated in 60–85% yield. In a separate reaction the halo function in position 7 was successfully transformed via different cross-coupling reactions. In a palladium-catalyzed Suzuki reaction, 30 different 7-arylbenzofurans were prepared in 94–99% yield. 7-Alkynylbenzofurans were also synthesized via palladium-catalyzed Sonogashira coupling (yields varied between 50 and 99%), while the efficiency of the copper-catalyzed amination of benzofurans was demonstrated with 18 examples and typical yields of the C–N bond-forming reaction were 56–99%.



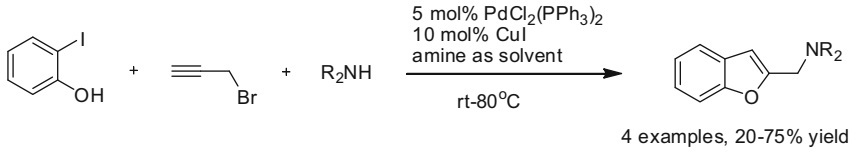


2,3-Disubstituted benzofurans were prepared by Larock from 2-iodophenols, terminal acetylenes, and aryl iodides utilizing palladium-catalyzed Sonogashira reactions with the aid of microwave irradiation [13]. The coupling between the iodophenol and the terminal acetylene was achieved with 3 mol% $PdCl_2(PPh_3)_2$ and 2 mol% CuI in TEA/THF at 25°C; then the appropriate aryl iodide and MeCN were added. The arylation of the preformed benzofuran ring in position 3 took place in 25 min at 100°C under microwave conditions. 27 examples demonstrate the usefulness of the procedure, and different aryl and heteroaryl groups were introduced into position 2 and 3 of the benzofuran ring via this sequential methodology.

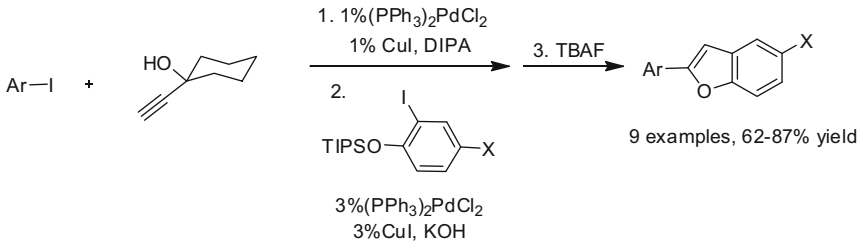


2-Aminomethyl-substituted benzofurans were prepared by Russo et al. in a one-pot three component reaction from propargyl halides, 2-iodophenols, and secondary amines [14]. The nucleophilic substitution on the propargyl halide propargyl was achieved by using the amine in excess (solvent); then the

palladium-catalyzed Sonogashira reaction took place between the iodophenol and the terminal acetylene, followed by the ring closure affording the desired benzofuran derivatives. The reaction was achieved with 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI at 80°C.



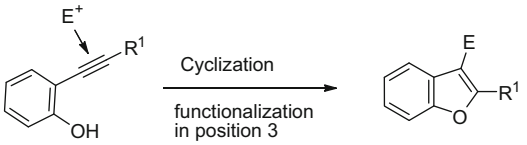
Based on Sonogashira coupling strategy, the benzofuran ring can also be constructed from three components: aryl iodides, *O*-protected 2-iodophenols, and an acetylene surrogate. For example, monoprotected acetylenes straightforwardly connect to aryl iodides under standard palladium-copper-catalyzed Sonogashira coupling conditions. Then the removal of the protecting group from the acetylene generates a new terminal acetylene ready to undergo another Sonogashira coupling. When this second Sonogashira coupling takes place with iodophenol, the benzofuran ring is formed in the traditional way. This approach was explored by Kotschy and coworkers utilizing ethynylcyclohexanol as an acetylene source [15]. The first coupling was carried out at rt in DIPA in the presence of 1 mol% $PdCl_2(PPh_3)_2$/CuI catalyst. After the completion of the coupling step, the silyl-protected iodophenol and KOH was added. The strong base removed the carbinol-protecting group from the acetylene and the second coupling took place with the iodophenol. After the addition of TBAF, the desilylation of the hydroxyl group and a subsequent ring closure occurred and the desired 2-arylbenzofurans were isolated in good yield (nine examples, 62–87%). The effectiveness of the procedure was demonstrated by the one-pot synthesis of the natural product Vignafuran.



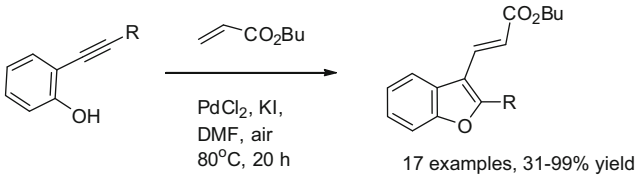
2.1.2 Electrophile-Induced Ring Closure

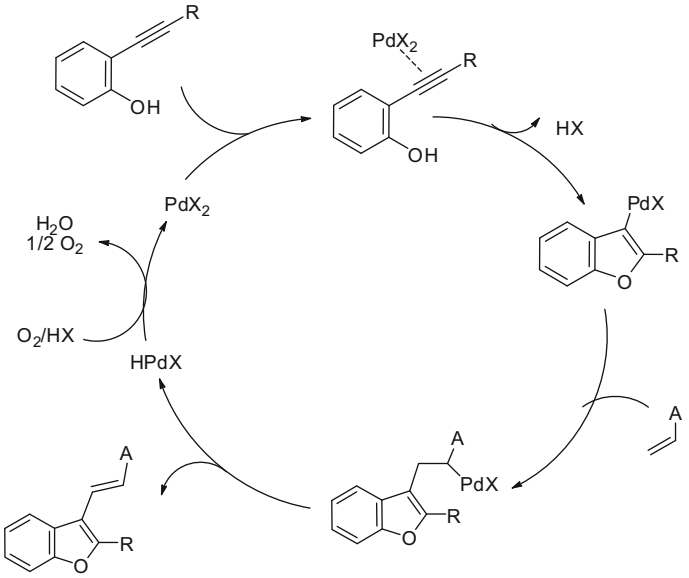
The cyclization of *ortho*-hydroxyl-aryl-acetylenes represents a powerful tool for the construction of the benzofuran core. With the aid of the coordination of transition metals to the triple bound, the nucleophilic attack of the oxygen is facilitated. Based

on this phenomenon simple 2-aryl or alkyl benzofurans can be prepared after the ring closure. However, in the last couple of years, several transition metal-catalyzed methodologies were developed for the synthesis of 2,3-disubstituted benzofurans from *ortho*-alkynylphenols.



A palladium-catalyzed cascade heterocyclization-oxidative Heck coupling was developed by Álvarez et al. for the synthesis of alkenyl-substituted benzofurans from *ortho*-ethynylphenols [16]. In the presence of palladium(II) complexes and KI, the alkynes were reacted with olefins at 80°C and the appropriate 2,3-disubstituted benzofurans were isolated in 31–91% yield.

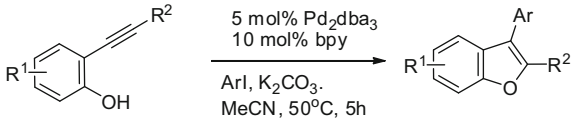




The first mechanistic step of the transformation is the coordination of the palladium(II) species to the triple bond, which induces the ring closure. The palladated benzofuran undergoes alkene insertion followed by β-hydride

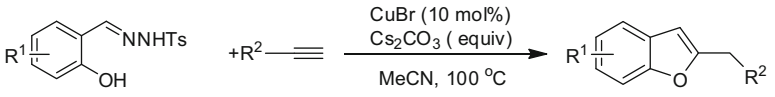
elimination providing the 2-aryl-3-alkenylbenzofuran and HPdX. The oxidative media is necessary to keep the palladium in the +2 oxidation state.

The palladium-catalyzed annulation strategy was used by Hu et al. for the synthesis of 2,3-diarylated benzofurans from *o*-alkynylphenols and aryl iodides [17]. The transformation was achieved with 5 mol% Pd_2dba_3 and 10 mol% bipyridyl ligand in MeCN at 50°C in 5 h, and the 2,3-disubstituted benzofurans were isolated in 52–87% yield. The synthetic methodology was used in the solid phase synthesis of benzofurans from on-bead iodophenols. However, for the successful annulation step 2.2 equiv. of palladium was required.



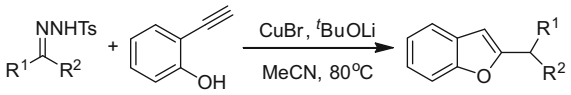
12 examples, 52-87% yield

A different approach for the construction of the benzofuran ring was developed by Wang and coworkers [18]. In their copper-catalyzed transformation, the heterocyclic system was built up from tosylhydrazones and terminal acetylenes. In the presence of base, the tosylhydrazone provides diazo derivatives and the acetylene gives copper acetylide. The reaction of these two species enables the formation of an allene intermediate which undergoes cyclization by the attack of nucleophilic OH group. The protonolysis of the alkyl cuprate intermediate provided 2-benzylbenzofurans as the product. The reactions were performed with 10 mol% CuBr catalyst in the presence of Cs_2CO_3 as base in MeCN at 100°C and the desired products were isolated in 48–91% yield after 4 h reaction time. The functional group tolerance of the transformation was demonstrated on 16 examples.



16 examples, 48-91% yield

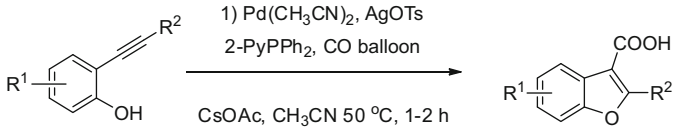
Later, the transformation was further developed by Zhou with the opposite approach regarding the key functional groups of the reactants [19]. The benzofuran synthesis was achieved efficiently with *O*-ethynyl-phenols and aromatic hydrazones with diverse substrates. In this latter approach ^tBuOLi was used as base instead of Cs_2CO_3. The formed copper acetylide reacts with the in situ generated diazo compound and afford ethynyl-copper carbene. Followed by the migratory insertion of carbene carbon and the protonation step, the allene intermediates undergo copper-promoted intramolecular cyclization to give the desired benzofuran molecules. The synthetic utility of the transformation was demonstrated with 20 examples and various benzofurans were isolated in 62–95% yield.



R^1: aryl; R^2: H, Alkyl

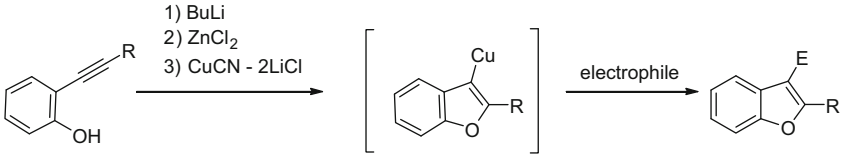
20 examples, 62-95% yield

o-Ethynylphenols are suitable substrates for the synthesis of benzo[b]furan-3-carboxylic acids using the palladium-catalyzed carboxylative annulation strategy [20]. With $Pd(MeCN)_2Cl_2$ in the presence of AgOTf and 2-$PyPPh_2$ under 1 atm CO in MeCN, the ring closure on the acetylene part takes place straightforwardly providing the desired 3-carboxylic acid derivatives in 1–2 h at 50°C. Utilizing the optimized reaction conditions, several 2-aryl- and alkyl-substituted benzofuran 3-carboxylic acid derivatives were isolated in 66–88% yield.

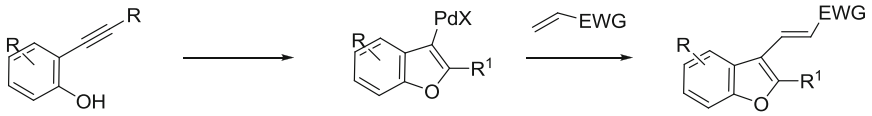


7 examples, 66-88% yield

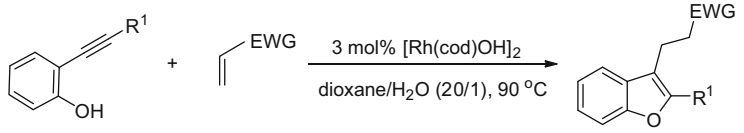
2,3-Disubstituted benzofurans can be prepared from *o*-ethynylphenols via $ZnCl_2$-assisted cyclization using BuLi as base [21]. The benzofuranyl zinc intermediates were transmetalated with copper(I) salts to form the corresponding cuprates. The organocuprates were readily reacted with several organic electrophiles such as allyl bromides, acid chlorides, enone systems, and aldehydes. Utilizing this transformation several 2,3-disubstituted benzofurans became accessible.



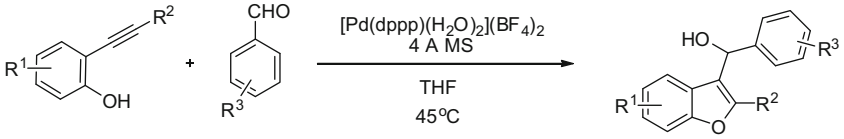
The palladium-catalyzed cyclization/coupling strategy was also utilized by Alvarez and Aurrecoechea for the synthesis of 3-ethenylbenzofurans from *o*-ethynylphenols [22]. The oxypalladation cyclization step starts with the coordination of the palladium catalyst to the triple bond, which induces the ring closure and results in the formation of a benzofuryl palladium species. Through the Heck-type coupling (insertion, β-elimination), 3-ethynylbenzofurans are formed. Utilizing the developed reaction conditions, several 2-aryl 3-alkenyl-benzufurans were prepared at 80–100°C in the presence of $PdCl_2$ and KI in DMF. The methodology provides the desired compounds in 31–91% yield.



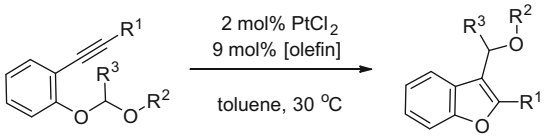
Change of the transition metal catalyst from palladium to rhodium provides 3-alkyl-substituted benzofurans in the reaction of *o*-ethynylphenols and electron deficient alkenes [23]. The cyclizations were conducted in dioxane/water (20:1) solvent mixtures at 90°C. In the presence of rhodium complexes the desired alkyl-substituted benzofurans were isolated with up to 96% yield, but in several cases the appropriate alkene derivatives also formed as side products (ca. 5%). A more detailed mechanistic study and expansion of this rhodium-catalyzed transformation was performed later by Lautens and coworkers [24].



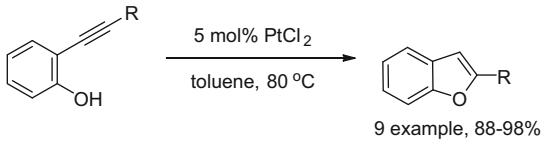
Han and Lu demonstrated that the utilization of cationic palladium species in the synthesis of 2-substituted-3-hydroxymethylbenzofurans is a powerful tool for the tandem annulation strategy [25]. The $[Pd(dppp)(H_2O)_2](BF_4)_2$ catalyst dissolved in THF enables the cyclization of 2-ethynylphenols and a subsequent functionalization in position 3 with aldehydes as electrophilic reagents. The synthetic utility of the methodology was demonstrated with 21 examples where the desired benzofurans were prepared in 37–100% yield in 2–5 h at 45°C.



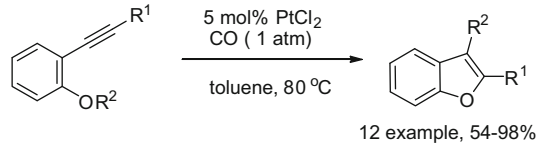
Alkynylphenyl acetals were transformed into 2,3-disubstituted benzofurans in a platinum-catalyzed ring closing reaction. The methodology developed by the Yamamoto group enables the synthesis of 2-alkyl and arylbenzofurans bearing alkyl ether function in position 3 in excellent yield (61–94%) [26]. The reaction takes place at 30°C in toluene. However, the catalyst loading is 2–100 mol% $PtCl_2$ depending on the substrates and the required reaction time varies between 1 h and 4 days. The ring closure is initiated by the coordination of the platinum to the triple bond which induces the nucleophilic attack of the oxygen. The cyclization product is the oxonium ion which is transformed trough the migration of the alkoxyalkyl group from position 2 to 3. The elimination of the platinum chloride closes the catalytic cycle and provides the desired benzofuran.



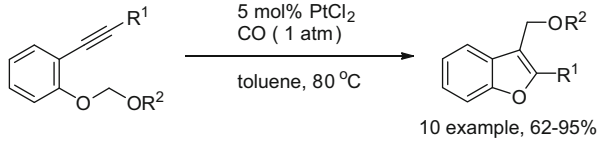
At the same time a similar strategy was used for the construction of the benzofuran ring from *ortho*-ethynylphenols and ethers by Fürstner and Davies [27]. The $PtCl_2$-catalyzed reactions of ethynylphenols provided the 2-alkyl and arylbenzofurans in good yield (88–98%) at 80°C in toluene in 1–5 h.



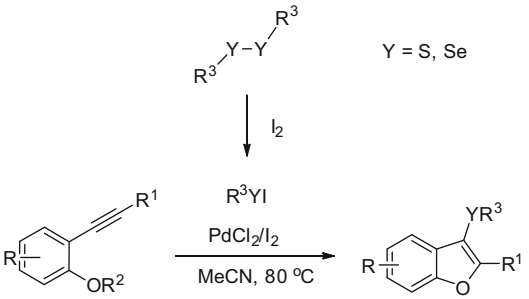
In case of the allyl ether derivatives, the ring closure is accompanied with the transfer of allyl group to position 3 from the oxygen providing 2,3-disubstituted benzofurans via intramolecular carboalkoxylation. The authors showed that the best results can be reached when the reaction was performed under CO atmosphere.



The platinum-catalyzed carboalkoxylation strategy was extended for the synthesis of 2,3-disubstituted benzofurans bearing a protected hydroxymethyl group in position 3. The alkyl migration takes place in case of MOM-, BOM-, and SEM-protected alcohols in 0.5–2 h and provides the benzofurans in excellent yield (62–95%).

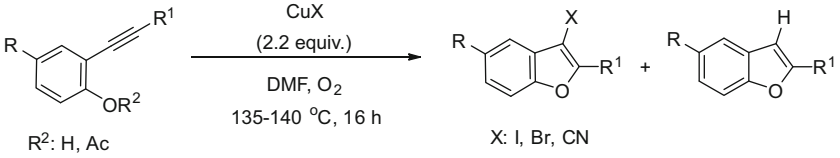


The palladium-catalyzed electrophilic annulation of 2-alkynylphenol derivatives with disulfides or diselenides enables the synthesis of 2,3-disubstituted benzofurans containing C–S or C–Se bond in position 3 [28]. The cyclization takes place in MeCN at 80°C in the presence of iodine in 36 h. The methodology provides the desired sulfides in good yield when substituted *ortho*-arylethynylanisole derivatives are subjected to ring closure, but alkylacetylenes cannot be transformed. Reactions with diselenides generally require shorter reaction time (6–18 h) for the preparation of selenobenzofurans in good yields (69–89%).

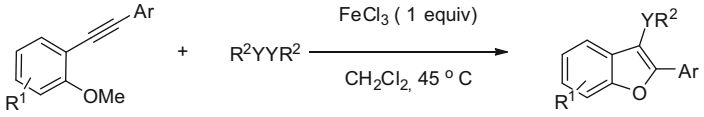


The reaction does not occur in the absence of iodine. It is suggested that the iodine reacts first with the disulfide and forms PhSI. Several synthetic methodologies exist for the iodine-mediated electrophilic cyclization for the synthesis of 3-iodobenzofurans, but in this case Li and coworkers ruled out the formation of iodobenzofuran intermediates through the absence of transformation between 3-iodobenzofuran and diphenylsulfide under the applied conditions.

Pyne developed a copper-mediated reaction for the synthesis of 3-iodo, 3-bromo, and 3-cyanobenzofurans from *ortho*-ethynylphenol derivatives [29]. The cyclization reaction was carried out in DMF at 135–140°C under oxygen atmosphere in 16 h in the presence of 2.2 equiv. of the appropriate Cu(I) salt. The copper salt delivered the incoming group to the 3 position of the benzofuran ring.

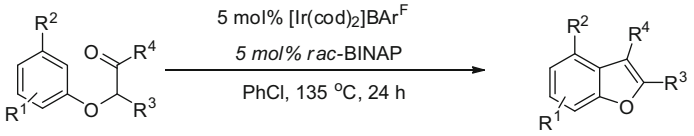


The similar cyclization-substitution strategy was developed by Zeni for the synthesis of 3-benzofuranyl-sulfides, selenides, and tellurides [30]. Although the procedure requires 1 equiv. of iron(III) salt, the desired compounds can be obtained in good yield under mild reaction conditions.



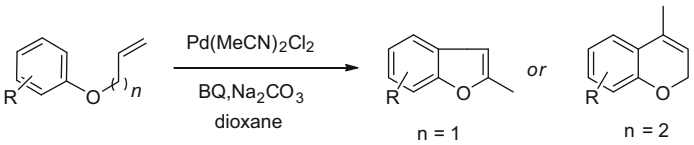
Y: Se, S, Te; R^1: H, Me; Ar: Ph, p-Me-Ph, m-CF3-Ph

The benzofuran ring can also be constructed starting from aryl ethers such as α-aryloxy-ketones and allyl phenyl ethers in transition metal-catalyzed cyclization [31]. The cyclodehydration of α-aryloxy-ketones bearing an *ortho* directing group proceeds in an iridium-catalyzed transformation. In the presence of $Ir(cod)_2BARF$ catalyst and *rac*-BINAP ligand in chlorobenzene at 135°C, the cyclization is complete in 24 h providing the multisubstituted benzofurans in good to excellent yield (82–99%).

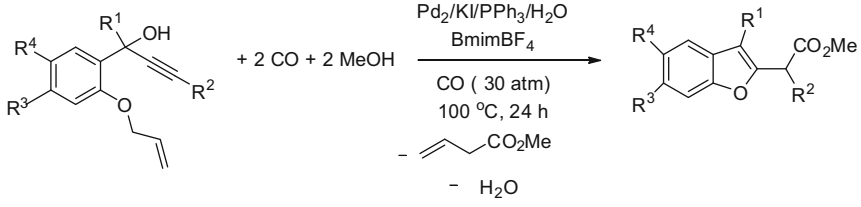


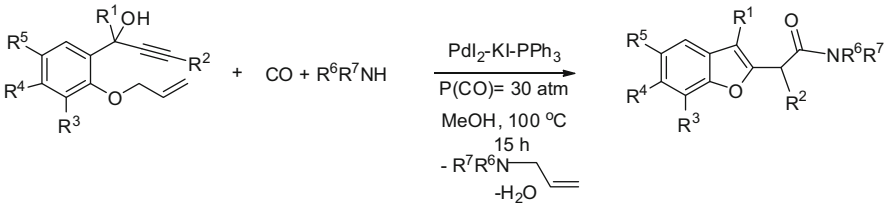
Shibata improved later his procedure and the cyclization was complete at rt in 8 h in DCE using a $Cp^*IrCl_2/AgSbF_6/Cu(OAc)_2$ catalyst system, and the appropriate benzofuran products were obtained in the same excellent yields [32].

Using the oxidative cyclization strategy, several 2-methylbenzofurans were synthesized by Youn and Eom [33] from allyl aryl ethers in the presence of $Pd(MeCN)Cl_2$ catalyst and benzoquinone oxidant in dioxane.



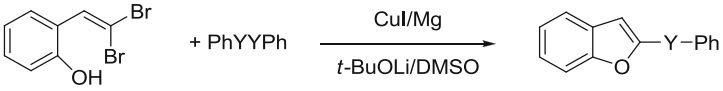
Allyl aryl ethers bearing an ynol motif in the *ortho*-position are excellent substrates for the synthesis of benzofuran 2-acetic acid esters [34] and amides [35] in deallylative carbonylation reactions. Under 30 atm CO pressure, the palladium-catalyzed coupling proceeds in the presence of alcohols or amines providing the appropriate esters or amides in good yield.



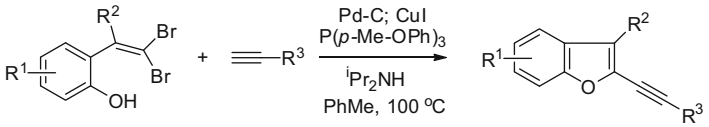


2.1.3 Synthesis of Benzofurans from Acetylene Alternatives

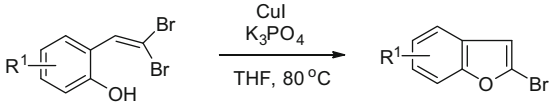
Construction of the benzofuran ring can also be achieved from 2-*gem*-dibromovinyl phenols [36]. The advantage of this strategy is that it enables the introduction of bromo, selenide, aryl, and ethynyl function into position 2 of the benzofuran ring utilizing palladium- or copper-catalyzed cross-coupling chemistry. In general the first step of the transformation is the ring closure through one of the bromines. The 2-bromobenzofuran intermediate offers further functionalization to obtain the desired products. Utilizing the procedure of Wang, 2-selenyl or sulfenylbenzofurans were prepared. Dibromovinyphenols were reacted with diaryl selenides or sulfides in the presence of t-BuLi and magnesium metal. The reaction proceeds with 10 mol% CuI in DMSO in 12 h at 110°C providing the appropriate products in 53–81% yields.



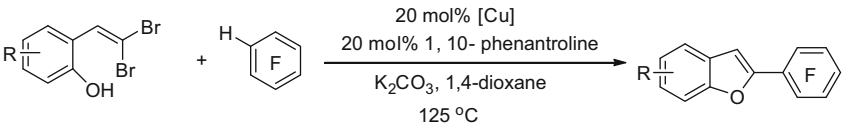
Under typical Sonogashira coupling conditions, in the presence of a Pd/C-CuI catalyst system, dibromovinylphenols smoothly react with terminal acetylenes in diisopropylamine providing 2-ethynylbenzofuran derivatives. In the procedure developed by Lautens and coworkers, both alkyl and aryl acetylenes are applicable for the coupling [37].



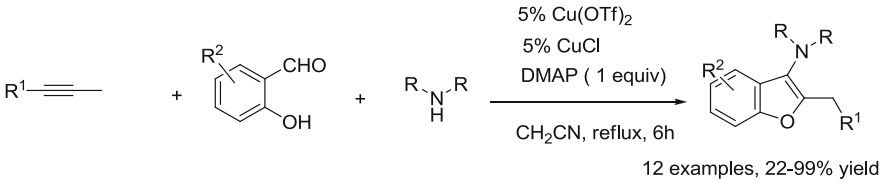
In the absence of any nucleophilic coupling partner, the transformation allows the isolation of 2-bromobenzofuran derivatives when the dibromovinyl compound is treated with 5 mol% CuI in the presence of K_3PO_4 in THF at 80°C for 6 h [38].



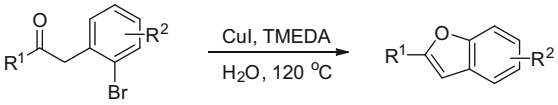
Beyond cross-coupling chemistry polyfluorinated aromatic compounds can be coupled directly via C–H functionalization to obtain 2-arylbenzofurans in the presence of CuI/phenanthroline catalyst system in dioxane at 125°C [39].



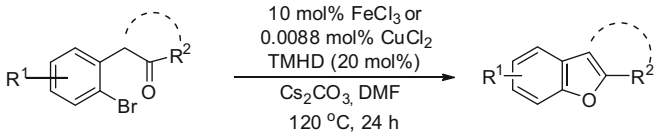
2,3-Disubstituted benzofurans were synthesized in a multicomponent reaction starting from salicylaldehyde, a secondary amine, and terminal or silyl-protected aryl acetylenes in a copper(II)-catalyzed reaction carried out in toluene or MeCN at reflux temperature [40]. The procedure enabled the synthesis of a versatile benzofuran library containing amino substituent in position 3.



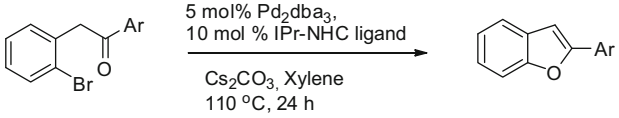
The benzofuran ring can be constructed from *o*-bromobenzyl ketones in copper- or palladium-catalyzed transformations. Domínguez and SanMartin utilized CuI/TMEDA catalyst for the ring closure under aqueous conditions [41].



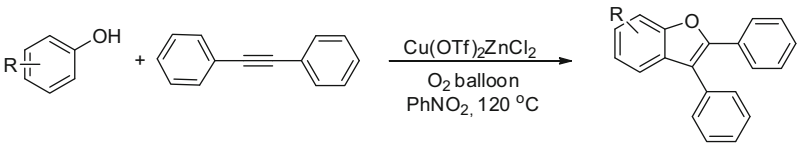
The similar transformation was developed by Bolm, using sub-mol% $CuCl_2$ beside $FeCl_3$ as catalyst in DMF. The desired 2-arylbenzofurans were isolated in good yields [42].



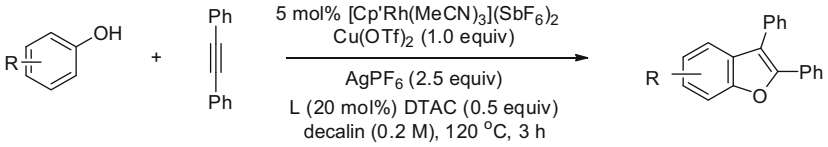
Faragó and Kotschy synthesized the desired 2-arylbenzofurans from 2-bromobenzylketones with the utilization of Pd_2dba_3 catalyst in the presence of NHC ligand [43].



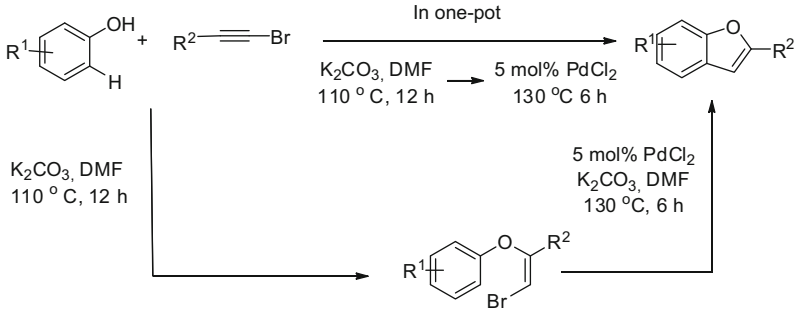
A novel methodology was developed for the construction of the benzofuran ring utilizing the transition metal-catalyzed oxidative coupling of aromatic alcohols. The coupling partner in most cases is an acetylene derivative. Jiang and coworkers developed a copper-catalyzed protocol for the construction of 2,3-disubstituted benzofurans from phenols and diaryl or aryl-alkyl acetylenes using molecular oxygen as oxidant [44]. The coupling reaction takes place in $MeNO_2$ at 120°C and the products were isolated in 72–93% yield.



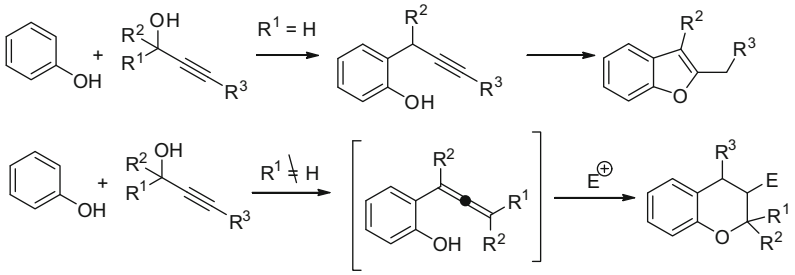
The same strategy was used by Shi and coworkers, but the transformation used a rhodium catalyst and the procedure required the addition of 1 equiv. of $Cu(OTf)_2$, 2.5 equiv. $AgPF_6$, 20 mol% acetanilide as ligand, and 50 mol% dodecyl trimethylammonium chloride as phase transfer catalyst [45].



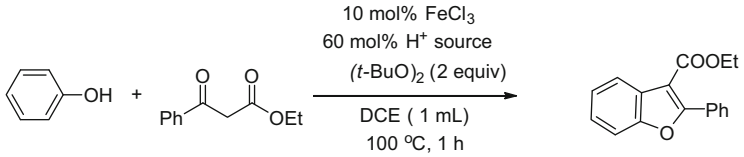
When 1-bromoacetylenes were used for this oxidative ring closure strategy, the palladium-catalyzed reaction afforded 2-aryl-substituted benzofurans from phenols at 130°C in DMF, as it was demonstrated by Wang and coworkers [46].



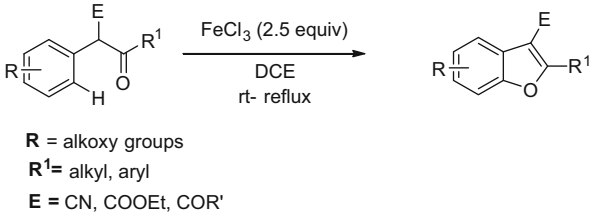
In the iron-catalyzed one-pot cascade reaction of propargylic alcohols and phenols, polysubstituted benzofurans or naphthopyrans can be prepared efficiently. The synthetic procedure developed by Han and Yuan enables the efficient synthesis of a diverse collection of oxygen heterocycles [47].



Iron(III) catalyst in the presence of di-*tert*-butylperoxide catalyzes the formation of benzofurans from phenol derivatives and β-ketoesters [48]. It was demonstrated that the reaction performed in DCE at 100°C was accelerated by water or various alcohols and Brönsted acids. The desired polysubstituted benzofuran derivatives were synthesized in 20–75% yield.



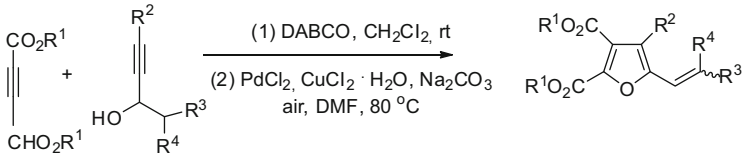
Another iron(III)-mediated oxidative approach was demonstrated by Zhao and coworkers [49]. Their procedure involves the oxidative C–O bond formation of α-aryl cyanoketones, which transformation provides 2-aryl-3-cyanobenzofurans in 50–94% yield.



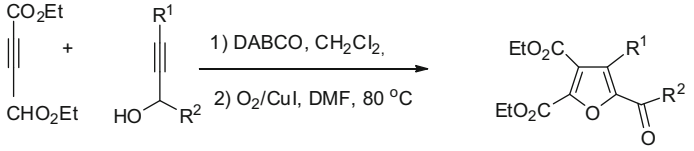
2.2 *Transition Metal-Catalyzed Synthesis of Furans*

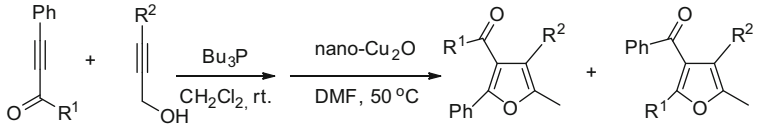
The synthesis of furan derivatives from acetylene derivatives generally takes place via the formation of propargyl vinyl ether intermediates. Several transition metal-catalyzed transformations were developed in the last couple of years for the construction of the furan ring. This synthetic strategy enables the formation of polysubstituted furan rings. In this chapter the most important methodologies are summarized.

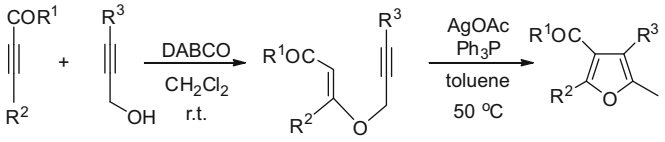
Polysubstituted furans can be synthesized in the palladium-catalyzed reaction of alkynoates and 2-yn-1-ols via the DABCO promoted propargyl vinyl ether formation in a two steps process [50]. Jiang and coworkers developed efficient conditions for the transformation and the desired tetrasubstituted furans were isolated on a broad scale in good yield (70–94%).



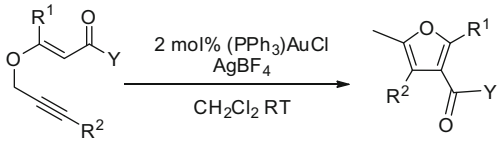
Jiang and coworkers also demonstrated that the same transformation could be achieved in a copper-catalyzed reaction. In the presence of Bu_3P or DABCO, internal acetylenes reacted smoothly with propargyl alcohols providing propargyl vinyl ethers, which underwent ring closure in the presence of nanosized Cu_2O in DMF at 50–80°C or with Ag(I) salts at 50°C in toluene [51–53].



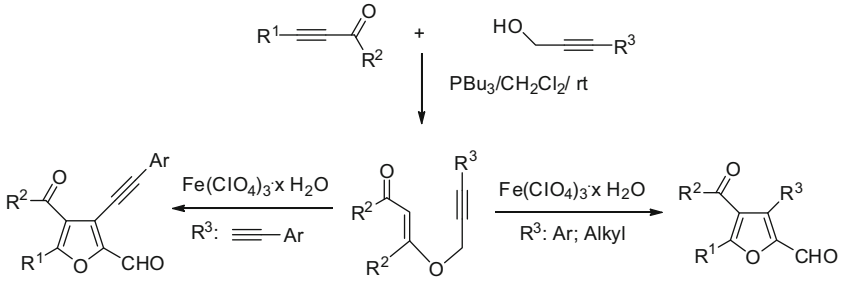




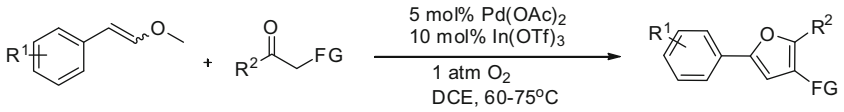
The synthesis of tetrasubstituted furans from propargyl vinyl ethers can be achieved in a gold-catalyzed transformation. Kirsch and coworkers demonstrated that the cyclization takes place straightforwardly at 23°C in DCM in the presence of 2 mol% $(PPh_3)_2AuCl$ catalyst [54].



Besides noble metal catalysis, the synthesis of tetrasubstituted furans can also be achieved from propargylic alcohols and ynones in a two-step process [55]. The formation of propargyl vinyl ethers occurs in the presence of Bu_3P in DCM. After the addition of an iron(III) salt, the ring closure provides furan-2-carbaldehydes in DMSO at 80°C in good yield (53–83%).

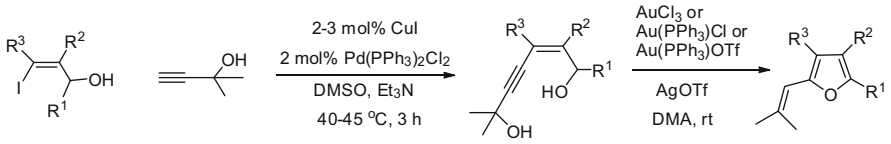


Jiang and coworkers demonstrated that the palladium-catalyzed ring closure also takes place with methyl vinyl ethers and 1,3-diketones in the presence of catalytic amount of $In(OTf)_3$ [56]. Applying the developed conditions several 2,4,5-trisubstituted furans were synthesized in DCE at 60–75°C under oxygen atmosphere.

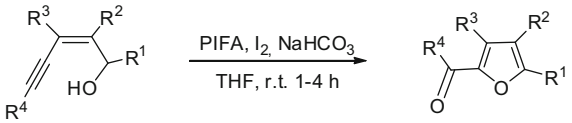


Another approach to the construction of the furan ring is based on enyne systems. Cyclization of enyneols or their equivalents (ynediols, alkynyl oxyranes), enyneones, and ethers in the presence of palladium, silver, or gold catalyst provides the furan ring generally under mild reaction condition with high efficiency.

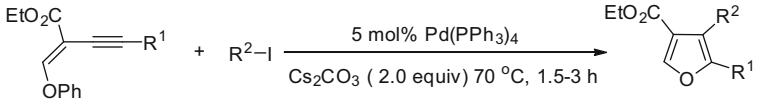
Z-enynols are excellent precursors for tetrasubstituted furans. The cyclization of the conjugated system occurs in the presence of gold catalysts such as $AuCl_3$, Au(PPh_3)Cl or Au(PPh_3)OTf [57–59]. The latter form of phosphano gold catalyst can also be generated in situ from chlorides with AgOTf. The reactions take place in DCM or DMA at rt in 1–5 h providing the desired polysubstituted furan derivatives in typically good yield (up to 94%).

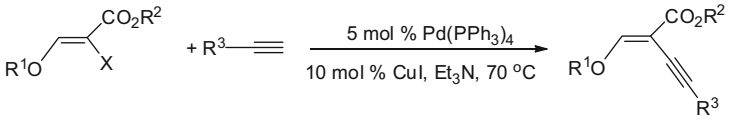


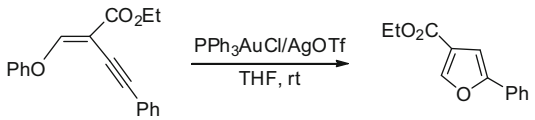
The cyclization of enyneols can also be achieved in the absence of transition metals as it was demonstrated by Liu and coworkers [60]. The synthesis of substituted furans was performed via PIFA (phenyliodine bis(trifluoroacetate))-I_2-mediated oxidative cycloisomerization of *Z*-enynols in THF. The furans were obtained 31–92% yield.



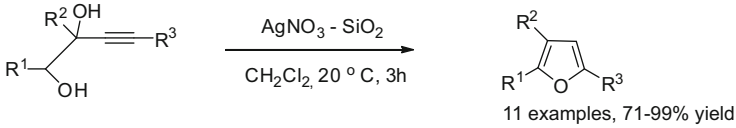
Using a similar approach trisubstituted furans can be prepared in the highly efficient palladium-catalyzed cascade reaction of aryloxy enynes. In the presence of $Pd(PPh_3)_4$ catalyst and Cs_2CO_3, the ring closure occurs at 70°C in DMF in 1.5–3 h. Trisubstituted furans [61] were isolated in 57–92% yield, while disubstituted furans [62] were obtained in 44–91% yield.



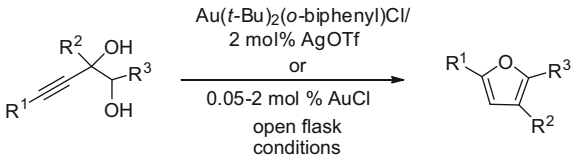




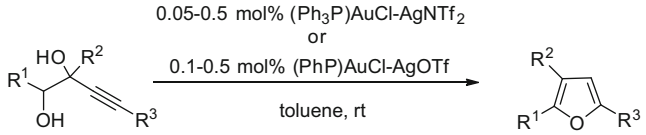
Besides *Z*-enynols 3-alkyne-1,2-diols can be easily transformed into substituted furans in transition metal-catalyzed cyclizations. In 2007, Knight and coworkers developed a heterogeneous $AgNO_3$/-SiO_2-catalyzed synthesis for trisubstituted furans [63]. The reaction takes place in DCM at 20°C in 3 h providing the appropriate furan derivatives in almost quantitative yields.



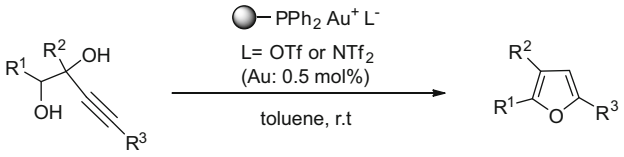
A similar gold-catalyzed cyclization strategy was developed by Aponick and coworkers [64]. For the open flask cyclization, 2 mol% Au[P(t-Bu)$_2$(*o*-biphenyl)]Cl and 2 mol% AgOTf were used as catalyst. The transformation was typically complete within 1 h at 0°C and provided the desired furans in excellent yield (75–99%).



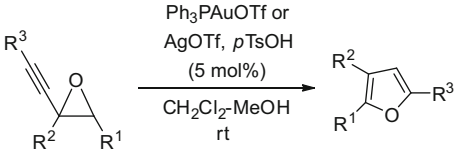
At the same time Akai and coworkers described the efficient cyclization of ethynyl-1,2-diols to furans using AuPPh$_3$Cl-AgNTf$_2$ or AuPPh$_3$Cl-AgOTf catalyst systems [65]. The advantage of the methodology is the utilization of a low amount (0.05–0.5 mol%) of catalyst, ambient temperature, and the high isolated yields.

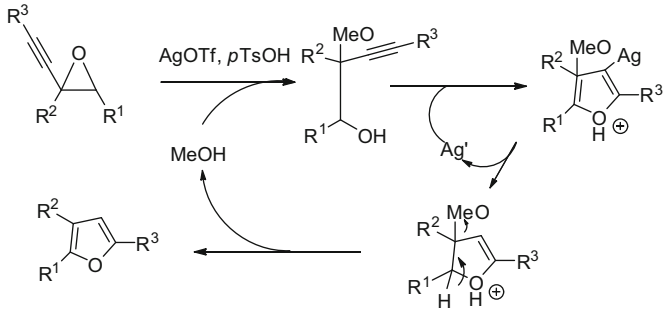


The previous examples showed that the gold-catalyzed cyclizations occur very efficiently under homogeneous catalytic conditions. The Akai research group developed a procedure for the gold-catalyzed cyclization utilizing an immobilized gold catalyst [66]. The gold center was attached to polystyrene support through a linked PPh$_3$ ligand. The polystyrene-supported phosphane ligand binds the gold catalyst quantitatively, and the subsequent anion exchange (chloride to OTf or NTf$_2$) provided efficient catalyst for the cyclization of alkynyl 1,2-diols. With the utilization of the methodology, the desired furans could be obtained with similar efficiency to the homogeneous version. The catalyst was reused several times without the loss of a significant amount of gold. The applicability of the polystyrene-supported gold catalyst in flow chemistry was also demonstrated.

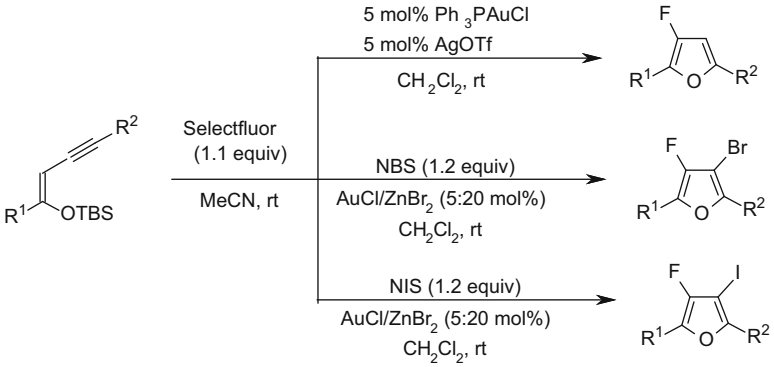


Similarly to alkynyl diols, alkynyl oxyranes can also be used in the cyclization. In the presence of silver or gold catalysts, the furan ring is constructed in an efficient manner as it was demonstrated by Pale [67, 68] and Aurrecoechea [69].

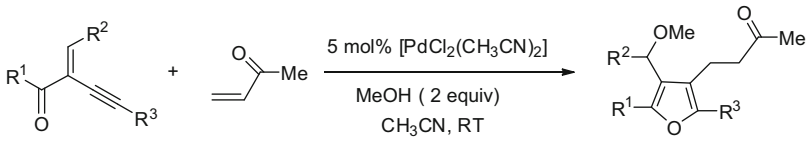




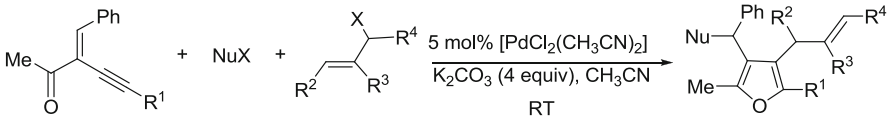
The gold-catalyzed cyclization strategy developed by Dembinski provides easy access to 2,5-substituted 3-fluorofurans. Starting from 1,4-disubstituted alkynons, silyl enol ethers were prepared for subsequent fluorination with Selectfluor. The formed fluorobutynone derivatives straightforwardly underwent gold-catalyzed cyclization in the presence of Ph_3PAuCl providing 3-fluorofurans [70, 71].



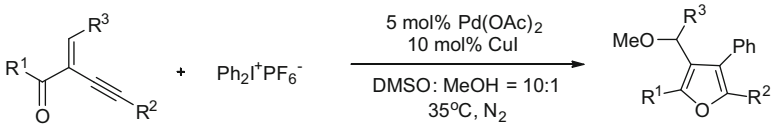
A palladium-catalyzed three component domino cyclization process was developed by Zhang and coworkers for the synthesis of tetrasubstituted furans from alkynylalkenones, vinyl ketones, and alcohols [72]. This transformation provides easy access to fully substituted furan derivatives with versatile substitution patterns.



Using allyl chloride instead of vinyl ketones, the palladium-catalyzed transformation provides 3-allyl furans in a Michael addition-cyclization-cross-coupling sequence from alkynylalkenones [73].

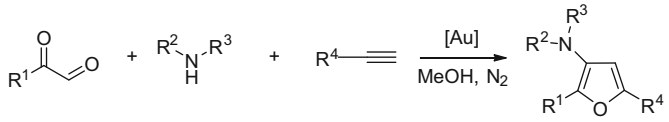


The three component approach enabled the introduction of aryl groups into position 3 when a diaryl iodonium salt was involved in the reaction as electrophile. The extension of the three component domino reaction was developed by Zhang and Li, and its efficiency was demonstrated with numerous examples [74].

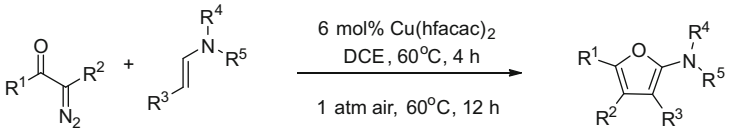


Acetylenes are widely utilized in furan syntheses. The following examples demonstrate their versatile applicability in the synthesis of tri or tetrasubstituted furan derivatives. In these transformations gold, copper, rhodium, silver, indium, and palladium catalyst are used.

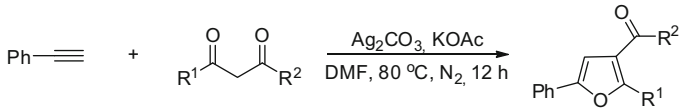
The gold-catalyzed three component cascade cyclization of phenylglyoxal derivatives, secondary amines, and terminal alkynes provides 2,5-diaryl 3-aminofurans [75]. The reaction takes place in MeOH at 60°C in the presence of 5 mol% $AuBr_3$ providing the desired furans in good yield (65–93%).



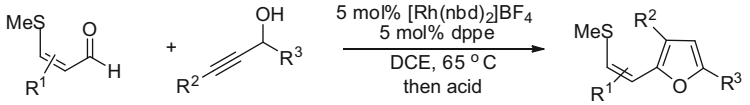
The synthesis of 2-aminofurans in the copper-catalyzed [3 + 2] cycloaddition of diazoesters and enamines was developed by Park and coworkers [76]. The tetrasubstituted furans bearing amino function in position 2 were isolated in good yield (16 examples, 52–76%) using $Cu(hfacac)_2$. The process also offers access to 2-unsubstituted furans (nine examples, 54–71%) through the elimination of amines from the 2,3-dihydrofuran intermediate in the presence of *p*-TsOH.



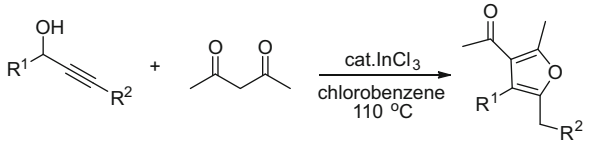
A silver-mediated oxidative C–C coupling of diketones and terminal acetylenes afforded trisubstituted benzofurans with high selectivity [77]. The transient presence of an alkynylalkenone is suggested as the result of C–C bond formation. The furan ring is formed through this intermediate in a silver-assisted cyclization step, and the diversely substituted furan derivatives (24 examples, 43–95%) were obtained in good yield.



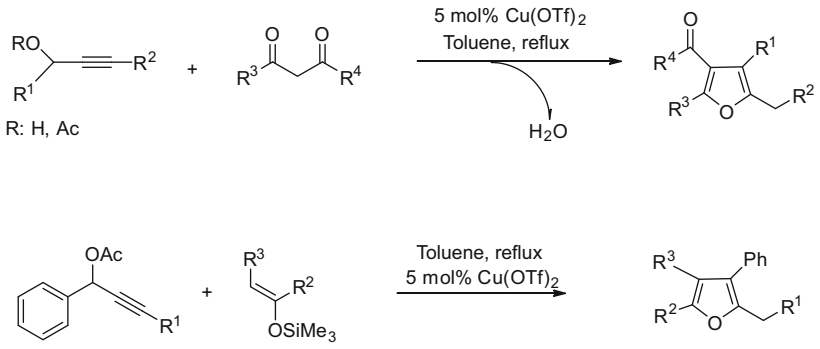
The rhodium-catalyzed hydroacylation-cyclization sequence enables the formation of furan ring from propargyl alcohols and aldehydes [78]. In the first step of the reaction, the hydroacylation occurs providing the hydroxyl enone intermediate, which cyclizes straightforwardly to the substituted furans. The methodology developed by Willis and coworkers enables the synthesis of diverse methylthioalkyl- or aryl-substituted furans in good yield (42–93%).



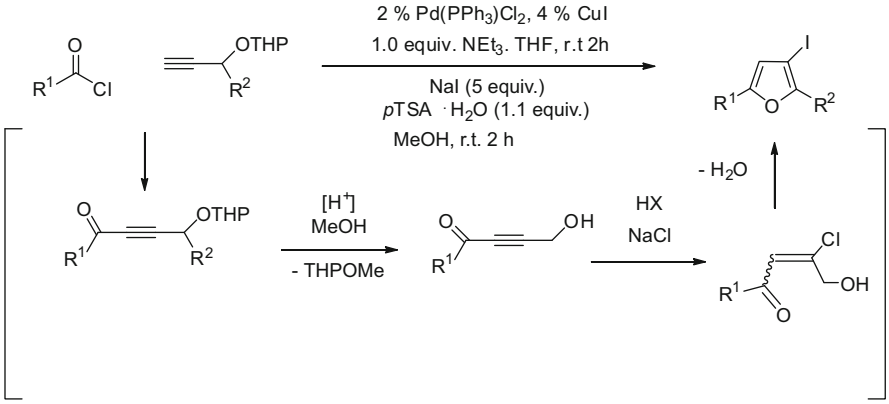
Propargylic alcohols are suitable starting materials for the construction of the furan ring in an $InCl_3$-catalyzed reaction [79]. The heterocycling ring is constructed utilizing 1,3-diketones or acetoacetates as reaction partners. The Lewis acid-catalyzed ring closure takes place in chlorobenzene at 110°C affording tetrasubstituted furans in 44–91% yield.



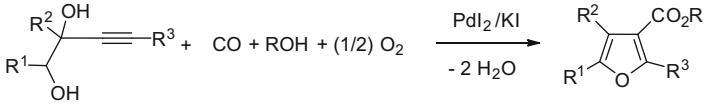
The same propargylation-cycloisomerization strategy was utilized by Zhan and coworkers in the presence of $Cu(OTf)_2$. In their work a high number of tetrasubstituted furans were synthesized from propargylic alcohols or acetates and 1,3-dicarbonyls [80] or silyl enol ethers [81].



The reaction of THP-protected propargylic alcohols with acid chlorides enables the synthesis of 3-halofurans or 3-chloro-4-iodofurans in a palladium-catalyzed one-pot three component transformation [82]. This efficient reaction provides access to iodo and chloro functionalized furans with high diversity (23 examples, 31–73% yield).

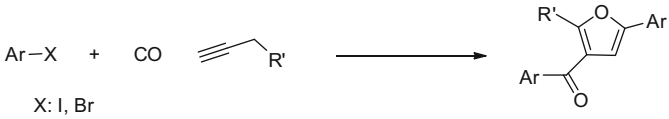


3-Yne-1,2-diol derivatives can be transformed to furan-3-carboxylic acids in alcoholic media via oxidative palladium-catalyzed cyclization under carbon monoxide atmosphere [83]. The catalytic transformation provides the tri- and tetrasubstituted furan carboxylic acid esters in good to excellent yields (21 examples, 56–93%).

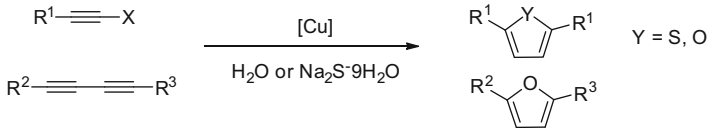


A double carbonylative process was used by Beller and coworkers for the synthesis of 3-ketofurans from aryl iodides and terminal acetylenes [84]. The carbon monoxide is the source of carbon and oxygen atoms both for the furan

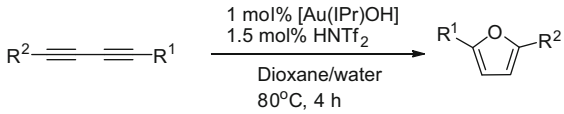
ring and the carbonyl function introduced into position 3 of the heterocycle. The synthesis was performed in the presence of 2 mol% of $Pd(OAc)_2$ and 4 mol % P(*o*-tolyl)$_3$ ligand under 10 bar CO. The synthetic utility of the methodology was demonstrated on 16 examples and the desired furans were isolated in 53–85% yield.



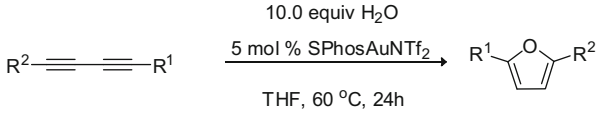
The ring closure of diynes provides 2,5-disubstituted furans where the heteroatom originates from water. Thus, 2,5-diarylfurans can be prepared from 1,4-butadiynes in copper- or gold-catalyzed ring closure. Jiang and coworkers developed a CuI-catalyzed synthesis of furans in a cyclization process [85]. It was also demonstrated that the furans (12 examples) could be obtained from 1-bromoacetylenes with high efficiency (68–93%).

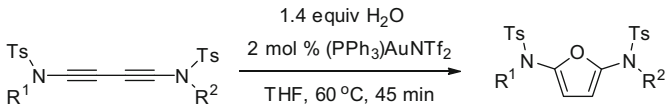


Nolan and coworkers utilized an Au-NHC complex to perform the same cyclization process to obtain 2,5-disubstituted furans (12 examples, 62–84%) [86].



Gold-phosphano complexes also catalyze the cyclization of butadiynes as it was demonstrated by Skrydstrup's group [87]. This procedure not only enables the synthesis of 2,5-diarylfurans (seven examples, 59–84%) but also 2,5-diaminofurans were prepared (four examples, 51–85%) from diamino butadiynes.





2.3 Functionalization of Furans and Benzofurans

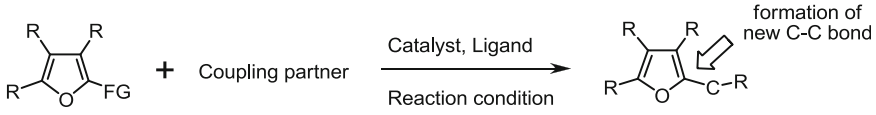
In this chapter the latest methods for the functionalization of furans and benzofurans utilizing transition metal-catalyzed transformations are summarized. There are two major synthetic approaches for the construction of a new carbon–carbon bond. First one is the traditional cross-coupling chemistry and the second one is the direct C–H functionalization of the heterocyclic ring. These two types of transformation are discussed separately. Each section is organized by the position of the incoming substituent on the furan and the benzofuran ring.

2.3.1 Cross-Coupling on Furans and Benzofurans

There are several synthetic possibilities for the functionalization of the furan ring via cross-coupling reactions. Traditional couplings such as the Heck, Sonogashira, Suzuki, Hiyama, and Negishi reactions are all well known. Palladium is the most frequently used catalyst for these transformations, which usually gives excellent yields.

Functionalization of Furans in the 2-Position via Cross-Coupling

In the recent years several new palladium-catalyzed cross-coupling reaction conditions were developed which are based on the utilization of efficient new phosphane ligands. 2-Chloro, bromo, and iodo furans are appropriate substrates for cross-coupling (Entries 1–7). Several examples show the utility of furyl organometallic species such as boronic acids (Entries 8–12), tin reagent (Entry 13), silyl (Entries 14, 15), and zinc derivatives (Entry 16) in coupling with aryl halides and tosylates. Aluminum and indium derivatives were also used for the coupling (Entries 17, 18), while desulfinylative and decarboxylative couplings were also described.



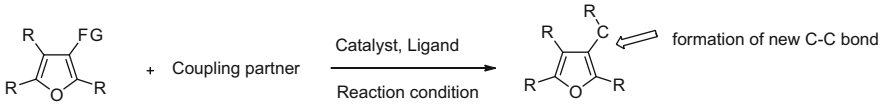
Entry	FG	Coupling partner	Catalyst, ligand	Reaction conditions	Yield	Examples	References
1	Cl	$PhB(OH)_2$	2% $Pd(OAc)_2$, 2.4% XPhos	$BuOH/H_2O$, CsOH, 25°C, 5 min–1 h	91–99%	3	Zhou [88]
2	Br	Ar-CCH	5% $PdCl_2(PPh_3)_2$, 10% CuI	THF, DEA, 20°C, 24 h	75–90%	3	Langer [89]
3	Br	$RCHCH_2$	5% $Pd(OAc)_2$, 10% SPhos or XPhos	DMF, TEA, 120°C, 36 h	78–94%	17	Langer [90]
4	Br	$CH_2CH\text{-}BF_3K$	2% $PdCl_2$, 6% PPh_3	THF/H_2O, Cs_2CO_3, 85°C, 22 h	70%	1	Brown [91]
5	Br	$RSnBu_3$	$PdCl_2$dppf	DMF, 105–110°C, 21 h	20–69%	13	Hocek [92]
6	Br	Het-H	$Pd(OAc)_2$,	DMA, KOAc, 120°C, 16 h	55–91	19	Doucet [93]
7	I	InX_2Li	4%, $Pd(dppf)Cl_2$,	NMP, 40°C, 4 h	70%	1	Knochel [94]
8	$B(OH)_2$	Ar-Cl	2% PdBiphenylamine-XPhos	THF, K_3PO_4, rt, 30 min	82–99%	3	Buchwald [95]
9	$B(OH)_2$	Ar-Cl, Ar-Br	3% $Pd(OAc)_2$, 6% DABCO,	DMF, Cs_2CO_3, 40°C, 19–21 h	90–98%	2	Xie [96]
10	$B(OH)_2$	3-Cl-Py, 2-OTs-Py, 2-Cl-thiophene, 2-OTs-thiophene	2% $Pd(OAc)_2$, 2.4% XPhos	$BuOH/H_2O$, CsOH, 25°C, 5 min–72 h	90–98%	8	Zhou [88]
11	$B(OH)_2$	Ar-Br	$PdCl_2(PPh_3)_2$,	EtOH-DME, Na_2CO_3, 60°C	29–86%	14	Debnath [97]
12	$B(OH)_2$	SO_2Cl	8% $Pd(PPh_3)_4$	THF, K_2CO_3, reflux	40	1	Vogel [98]
13	$Sn(n\text{-}Bu)_3$	Ar-Br, Ar-Cl or cyclopentenyl-Cl	Pd_2dba_3, azaphosphatrane	CsF, Dioxane, rt-110°C, 48 h	87–97%	5	Verkade [99]
14	$SiMe_2OH$	Ar-I, Ar-Br	Pd_2dba_3, $^tBu_3P$	NaH, Toluene, rt-50°C, 1–24 h	60–82%	10	Regens [100]
15	$SiMe_2OH$	Ar-I	Pd_2dba_3, $(2furyl)_3As$ or $Pd_2Cl(^tBu_3)_2$	NaH, Toluene, rt-50°C, 1–24 h	61–82%	8	Baird [101]
16	ZnBr	3-bromo-pyridine	$NiCl_2$, $(EtO)_2P(O)H$	110°C, 22 h	59	1	Knochel [102]

(continued)

Entry	FG	Coupling partner	Catalyst, ligand	Reaction conditions	Yield	Examples	References
17	$Al_{2/3}Cl$	Ar-Br, Ar-I	$Pd(tmpp)_2Cl_2$	THF:DMF 1:2, 50°C, 5–6 h	65–72%	2	Knochel [103]
18	InX_2LiX	ArI	4%, $Pd(dppf)Cl_2$,	NMP, 40°C, 4 h	73–78%	2	Knochel [94]
19	SO_2Li	Ar-Br	$PdCl_2$, PPh_3	DMF/water 170°C, 8 min, MW	65%	1	Forgione [104]
20	COOK	Ar-Br	CuI, $Pd(acac)_2$ 1,10-phenanthroline	NMP, quinoline, 190°C, 50 W, 5 min, MW	38%	1	Hartung [105]
21	COOK	Naphthyl-OTs	2.5–7.5% Cu_2O/phen, 5% $Pd(acac)_2$, 7.5% XPhos	NMP,180°C, 100 W, 2 min, MW	78	1	Goossen [106]

Functionalization of Furans in the 3-Position

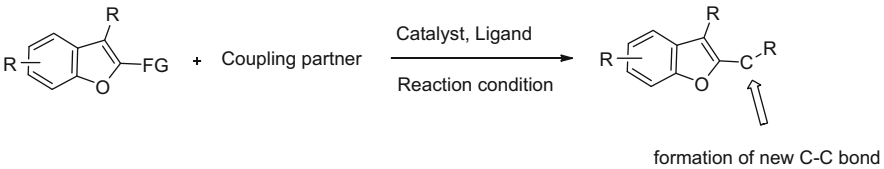
Compared to the number of transformations in position 2 of the furan ring, there are fewer examples for the cross-coupling reactions in which the functional group is introduced into position 3. 3-Bromofurans can couple with alkenes in Heck reaction (Entry 1) and with arylboronic acid (Entry 2) in Suzuki coupling. However, 3-furylboronic acid derivatives also undergo palladium-catalyzed Suzuki coupling with aryl or hetaryl halides and tosylates (Entries 3–5).



Entry	FG	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	Br	$RCHCH_2$	5% $Pd(OAc)_2$, 10% SPhos or Xphos	DMF, TEA, 120°C, 36 h	78–94%	17	Langer [90]
2	Br	Ar-$B(OH)_2$	2% PdBiphenylamine-XPhos	THF, K_3PO_4, rt, 30 min	45%	1	Buchwald [95]
3	$B(OH)_2$	Ar-Cl	2% PdBiphenylamine-XPhos	THF, K_3PO_4, rt, 30 min	80%	1	Buchwald [95]
4	$B(OH)_2$	3-Cl-Py, 2-OTs-Py, 2-Cl-thiophene, 2-OTs-thiophene	2% $Pd(OAc)_2$, 2.4% XPhos	BuOH/H_2O, CsOH, 25°C, 5 min–1 h	90–93%	4	Zhou [88]
5	$B(OH)_2$	2-Cl, 6-methoxy-pyridine	2% Pd-NHC complex	tBuOH, 30°C, 24 h	70%	1	Lough [107]

Functionalization of Benzofurans in the 2-Position

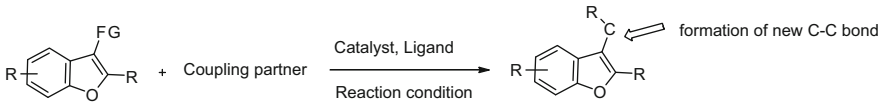
2-Bromo- and iodobenzofurans are smoothly coupled with terminal acetylenes in the presence of palladium catalysts generally with high isolated yields. 2-Benzofurylboronic acids are also applicable reagents for the Suzuki coupling as several examples demonstrate their utility in this type of cross-coupling reaction (Entries 4–8). Silanes and sulfinyl groups on the heterocyclic ring can also be transformed to aryl function in their palladium-catalyzed reaction with aryl halides (Entries 9–11).



Entry	FG	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	Br	Ph-CCH	2 mol% $PdCl_2(PPh_3)_2$, 7 mol % CuI	DMF, TEA, rt4-6.5 h	50–98%	3	Mao [108]
2	Br	Ar-CCH	5 mol% $PdCl_2(PPh_3)_2$ 10 mol% CuI	THF, DEA, 20°C, 24 h	75–90%	3	Langer [89]
3	I	Ar-CCH	2 mol% $PdCl_2(PPh_3)_2$, 4 mol % CuI	THF, TEA, rt, 5 h	94%	1	Barret [109]
4	$B(OH)_2$	Ar-Cl	2 mol% PdBiphenylamine-XPhos	THF, K_3PO_4, rt, 30 min	97–99%	3	Buchwald [95]
5	$B(OH)_2$	3-Cl-Py, 2-OTs-Py, 2-Cl-thiophene, 2-OTs-thiophene	2 mol% $Pd(OAc)_2$, 2.4 mol% XPhos	BuOH/H_2O, CsOH, 25°C, 5 min–4 h	90–92%	4	Zhou [88]
6	$B(OH)_2$	Ar-Br	various Pd catalysts	DME, Na_2CO_3, 80°C, 8 h	21–90%	5	Antane [110]
7	$B(OH)_2$	ArCHCH-Br	5 mol% $Pd(PPh_3)_4$	DME/water, Na_2CO_3, 90°C, 20 h	57%	1	Barret [109]
8	$B(OH)_2$	3-Br thiophene	2 mol% Pd-NHC complex	^{i}PrOH, 30°C, 24 h	85%	1	Lough [107]
9	$SiMe_2ONa$	Ar-Br	2.5.5 mol% $^{t}Bu_2Pd$	Toluene, THF or dioxane 60–70°C, 3.5–8 h	58–99%	7	Denmark [111]
10	TMS	Ar-I	$PdCl_2(PPh_3)_2$, $AgNO_3$, KF	DMSO, 100°C	43–86%	7	Mori [112]
11	SO_2Li	Ar-Br	$PdCl_2$, PPh_3	DMF/Water, 170°C, 8 min, MW	82%	1	Forgione [104]

Functionalization of Benzofurans in the 3-Position

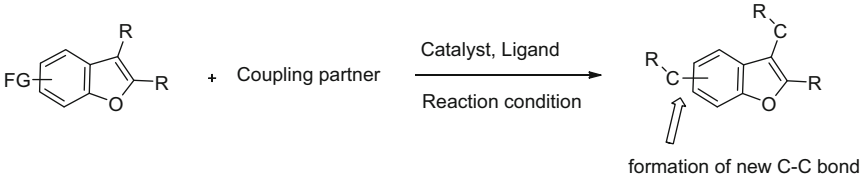
There are two procedures reported for the cross-coupling of 3-iodobenzofuran. Terminal alkynes react straightforwardly with the iodo species under standard Sonogashira conditions (Entry 1). The introduction of an alkenyl group into this position was achieved with tin reagents, and the desired 3-alkenyl-benzofurans were isolated with good yields (Entry 2).



Entry	FG	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	I	R-CCH	1% $PdCl_2(PPh_3)_2$, 2% CuI	TEA, rt–60°C, 2–24 h	40–99%	22	Zeni [113]
2	I, OTf	Bu_3Sn-alkene	$Pd(PPh_3)_4$, CuI	DMF, CsF, 40°C	56–80%	6	Wada [114]

Functionalization of Benzofurans in the 5- and 7-Position

The functionalization of the benzofuran ring in positions 5 or 7 has also been described mostly in palladium-catalyzed Suzuki coupling. 5-Bromo, 7-chloro, and 7-bromo derivatives were all coupled with arylboronic acid (Entries 1–4). The opposite approach with benzofuran-7-ylboronic acid has also provided the arylated product in reaction with an aryl bromide (Entry 5).



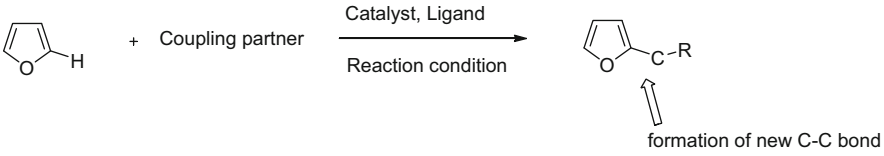
Entry	FG	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	5-Br	Ar-B $(OH)_2$	Benzothiazole based Pd complex, $PdCl_2PPh_3$	H_2O, TBAB, KOH,160°C, 250 W, 10–20 min	6.5–96 %	6	Dawood [115]
2	7-Cl	ArB $(OH)_2$	Pd_2dba_3, SPhos	1,4-dioxane, K_3PO_4, 100°C, 2–4 h	95–99%	15	Goggiamani [116]
3	7-Cl	NHR_2	Pd_2dba_3, XPhos	toluene, NaO^tBu, 80°C, 12–40 h	70–99%	4	Goggiamani [116]
4	7-Br	ArB $(OH)_2$	$Pd(PPh)_4$	DME (aq), Na_2CO_3,	81%	1	Goggiamani [116]
5	7-B $(OH)_2$	Ar-Br	$Pd(PPh)_4$		67%	1	Goggiamani [116]

2.3.2 Direct Functionalization of Furans and Benzofurans via C–H Activation

Beyond the traditional cross-coupling reactions, the direct functionalization of the furan C–H bonds is also possible. The most frequently used catalysts in this transformation are palladium based. However, there are some examples for the efficient application of rhodium, cobalt, or iridium catalysts too.

Functionalization of Furans via C–H Activation in Position 2

The direct arylation of the furan ring leads to the functionalization of the 2-position. These reactions can be performed with aryl chlorides (Entries 1–2), bromides (Entries 3–10), and iodides (Entries 11–15). The oxidative coupling with terminal olefins provides 2-alkenylated furans (Entries 16–21). The synthesis of 2-aryl or 2-hetarylfurans is also possible in palladium-catalyzed cross-dehydrogenative couplings with the utilization of aromatic and heteroaromatic systems (Entries 22–25).



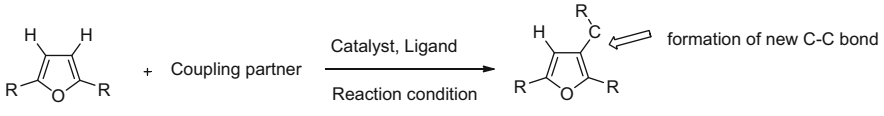
Entry	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	ArCl	$PdClNHCPCy_3$,	PivOH, DMA, K_2CO_3, 110°C, 12–15 h	41–89%	30	Lee [117]
2	ArCl	$Pd(OAc)_2$, Cy_2P-*o*-biphenyl	K_3PO_4, NMP, 100°C, 24 h	50–92%	11	Daugulis [118]
3	ArBr	$Pd(OAc)_2$, PCy_3	PivOH, K_2CO_3, DMF, 180°C, 10 min	85%	1	Kappe [119]
4	ArBr	$Pd(OAc)_2$,	DMA, KOAc, 130°C, 17 h	42–76%	13	Doucet [120]
5	ArBr	$Pd(OAc)_2$, ferrocene-based phosphane ligand	DMA, KOAc, 150°C, 16 h	38–93%	28	Doucet [121]
6	ArBr	$Pd(OAc)_2$,	DMA, KOAc, 150°C, 16 h	30–87%	24	Doucet [122]
7	ArBr	$Pd(OAc)_2$, PCy_3HBF_4,	PivOH, K_2CO_3, DMA, 100°C, 16 h	44–70%	3	Fagnou [123]
8	ArBr	$(PdCl\text{-}allyl)_2$, Tedicyp	NaOAc, DMA, 150°C, 20 h	70–88%	9	Santell [124]
9	ArBr	$PdCl(C_3H_5)$dppb	KOAc, DMA, 150°C, 16 h	63–90%	16	Doucet [125]
10	ArBr	$Pd(OAc)_2$	KOAc, DMA, 130°C, 17 h	49–91%	35	Dixneuf [126]
11	ArI	$Pd(OAc)_2$	105°C, 24 h, K_2CO_3, DMF	62–71%	2	Catellani [127]
12	ArI	RhCl(CO){P[OCH(CF3)2]3}2	150–120°C, MW, m-xylene/DME, Ag_2CO_3,	64–66%	2	Itami [128]
13	ArI	$Pd(OAc)_2$, electron deficient phosphane ligand	PivOH, K_2CO_3, Ag_2CO_3,DMA, 100°C, 16 h	43–46%	2	Fagnou [129]
14	ArI	Co-porphyrin	furan, tBuOH, KOH, 200°C, 30–60 min	52–62%	2	Chan [130]
15	ArI	$[Ir(COD)(Py)PCy_3]PF_6$	Ag_2CO_3, m-xylene, 160°C, 18 h	54–72%	3	Itami [131]
16	*N*-butyl acrylate	$Pd(OAc)_2$,	AgOAc, pyridine, 120°C, 12 h	64–90%	4	Zhang [132]
17	*N*-butyl acrylate	$Pd(OAc)_2$,	$Cu(OAc)_2$, LiOAc, DMF, 120°C, 12 h	53–67%	2	Miura [133]
18	Styrenes	$Pd(OAc)_2$,	BQ, $Cu(OAc)_2$, $EtCO_2H$, Et_2O or THF 40–60°C	50–78%	23	Muzart [134]

(continued)

Entry	Coupling partner	Catalyst	Conditions	Yield	Examples	References
19	Styrenes	$Pd(OAc)_2$,	BQ, AcOH/DMSO, rt, 24–48 h	40–79%	6	Le Bras [135]
20	Allylacetate	$Pd(OAc)_2$,	Ag_2CO_3, DMSO/Dioxane, 110°C, 15 h	60%	1	Liu [136]
21	*N*-Boc-allylamines	$Pd(OAc)_2$,	Ag_2CO_3, $Cu(OAc)_2$, DMF/DCE, 120°C, 14 h	65–83%	7	Xiao [137]
22	Ar-H	$Pd(OAc)_2$, monophos	*N*-fluoropyridinium triflate, AcOH, 100°C, 2 h	61–78%	10	Seayad [138]
23	Xanthines-H, benzimidazoles, pyridine and quinoline *N*-oxides	$Pd(OAc)_2$	$Cu(OAc)_2$, pyridine, dioxane, 120°C, 20 h	60–95%	6	You [139]
24	F_5Ph-H	$Pd(OAc)_2$	Ag_2CO_3, HOAc, DMF/DMSO, 120°C, 3 h	54–73%	2	Zhang [140]
25	HetAr-H	$(RhCp^*Cl_2)_2$, $AgSBF_6$	CsOPiv, Cu(II) (2-ethylhexanoate), t-AmylOH, 120°C, 20 h	48–84%	12	Glorious [141]

Functionalization of Furans via C–H Activation in Position 3

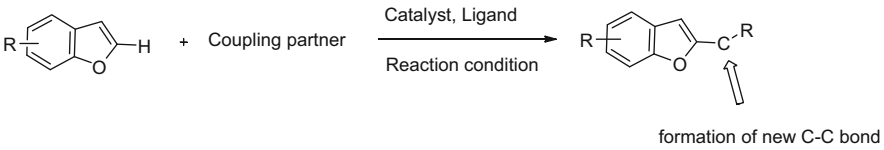
The direct arylation of the furan ring in position 3 occurs when position 2 and 5 is occupied by another functional group. Both arylation and alkenylation of the furan ring can be achieved in palladium-catalyzed oxidative coupling using aryl bromides and iodides (Entries 1, 2) or terminal alkenes (Entries 3–6).



Entry	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	Ar-Br	$(PdCl\text{-}Allyl)_2$,	DMA, KOAc, 120°C, 12 h	36–76%	18	Doucet [142]
2	ArI, ArBr	$Pd(OAc)_2$, PPh_3,	DMA, Cs_2CO_3, 120°C	62–90%!	29	Yang [143]
3	Styrenes	$Pd(OAc)_2$,	BQ, $Cu(OAc)_2$, $EtCO_2H$, Et_2O or THF 40–60°C	52–66%	6	Le Bras [134]
4	Styrenes	$Pd(OAc)_2$,	BQ, AcOH/DMSO, rt, 24–48h	40–54%	2	Le Bras [135]
5	Acrylates, styrene	$Pd(OAc)_2$	$Cu(OAc)_2$, LiCl, DMF	44–91%	12	Zhu [144]
6	*N*-Boc-allylamines	$Pd(OAc)_2$,	Ag_2CO_3, $Cu(OAc)_2$, DMF/DCE, 120°C, 14 h	80–83%	2	Xiao [137]
7	Butyl acrylate	$[Cp^*RhCl_2]_2$	$AgSbF_6$, Ag_2CO_3, diglyme, 120°C	63	1	Miura [145]

Functionalization of Benzofurans via C–H Activation in Position 2

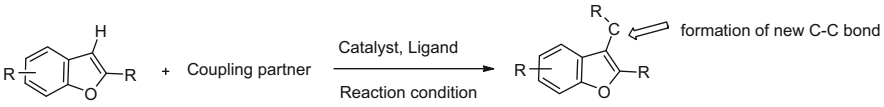
Similarly to the furan ring, direct functionalization of benzofurans is preferred in position 2. The C–H bond can be transformed in palladium-catalyzed reaction with the utilization of aryl halides (Entries 1–5), boronic acids (Entry 6), or diazonium salts (Entry 7). Alkenylation and oxidative arylation via double C–H activation are also possible on this heterocyclic ring (Entries 8–11).



Entry	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	ArCl	$Pd(OAc)_2$, Sylphos	TBAB, KOAc, DMA, 150°C, 20h	38%	1	Doucet [146]
2	ArBr	$Pd(OAc)_2$, PCy_3	PivOH, K_2CO_3, DMF, 180°C, 60 min	50%	1	Kappe [119]
3	ArBr	$Pd(OAc)_2$, PCy_3HBF_4,	PivOH, K_2CO_3, DMA, 100°C, 16 h	29%	16	Fagnou [123]
4	ArBr	$Pd(P^tBu_3)_2$,	LiOtBu, DMF, 100°C	34–47%	2	Mori [147]
5	PhI	$PdBr_2BiPy$	Ag_2CO_3, Dioxane, 120°C, 13 h	48%	1	Itami [148]
6	$ArB(OH)_2$	$Pd(OAc)_2$, bis-oxazoline ligand,	TEMPO, TFA, DMF, 80°C, 12 h	67–87%	2	Itami [149]
7	ArN_2BF_4	Pd(OAc)2	MeOH, rt-65°C	33–61%	5	Correira [150]
8	Allylacetate	$Pd(OAc)_2$,	Ag_2CO_3, DMSO/ Dioxane, 110°C, 25 h	55%	1	Liu [136]
9	F_5Ph-H	$Pd(OAc)_2$	Ag_2O, O_2, PivOH, DMF/DMSO, 120°C	87%	1	Zhang [151]
10	F_5Ph-H	$Pd(OAc)_2$	Ag_2CO_3, HOAc, DMF/DMSO, 120°C, 3 h	78%	1	Zhang [140]
11	Xanthines-H	$Pd(OAc)_2$	$Cu(OAc)_2$, pyridine, dioxane, 120°C, 20h	66%	1	You [139]

Functionalization of Benzofurans via C–H Activation in Position 3

The preferred site of C–H functionalization on benzofurans is position 2; therefore, introduction of aryl or alkenyl groups in position 3 is achievable only when position 2 is occupied by another substituent. In these substrates the general C–H activation procedures enable the introduction of substituents into position 3. For this transformation aryl bromides (Entries 1, 2) and acrylates (Entries 3–5) were used.



Entry	Coupling partner	Catalyst	Conditions	Yield	Examples	References
1	ArBr	$Pd(OAc)_2$, P(^{t}Bu)$_2$MeHBF$_4$,	PivOH, Cs_2CO_3, mesitylene, 140°C, 24 h	40–61%	2	Fagnou [152]
2	ArBr	$Pd(OAc)_2$, P(^{t}Bu)$_2$MeHBF$_4$	K_2CO_3, PicOH, mesitylene or DMA, 150°C, 16–63 h	18–98%	25	Bertounesque [153]
3	Allylacetate	$Pd(OAc)_2$,	Ag_2CO_3, DMSO-dioxane, 110°C, 25 h	55%	1	Liu [136]
4	Butyl acrylate	[Cp*$RhCl_2$]$_2$	$AgSbF_6$, Ag_2CO_3, diglyme, 120°C	78	1	Miura [145]
5	Butyl acrylate	[Ru(p-cymene) Cl_2]$_2$	$Cu(OAc)_2$, LiOAc, DMF	66%	1	Miura [154]

3 Oxygen Heterocycles with Additional Heteroatom

Oxazole, isoxazole, [1,3,4]oxadiazole, and benzoxazole are ring systems whose derivatives are abundant both in nature and in the pool of synthetic compounds. The presence of the five-membered heteroaromatic ring in these compounds is the source of a collection of diverse transformations that result in the broad variability of their substitution pattern. In parallel the hydrogen bond acceptor nature of the heteroatoms in the ring in combination with the presence of several synthetically tractable vectors make them optimal building blocks in medicinal chemistry. Therefore, it is not surprising that the synthesis and functionalization of these molecular scaffolds has been widely studied and they are also a prime target for the development of novel synthetic methodologies. The following chapter doesn't attempt to cover this broad area in an exhaustive manner. It would rather like to give the reader a taste of the diversity of chemical approaches that were developed for and used on these ring systems in the last decade.

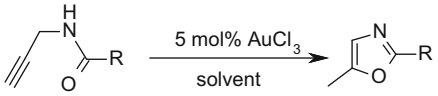
3.1 Synthesis of Oxygen Heterocycles with Additional Heteroatom

The synthesis of oxazoles, isoxazoles, oxadiazoles, and their benzologues can be achieved on several ways. This chapter is limited to those transformations, which result in the formation of the five-membered heterocyclic ring. Due to the broad range of reactions that can be applied, the selected examples are classified on the basis of the number of bonds formed.

3.1.1 Direct Ring Closure

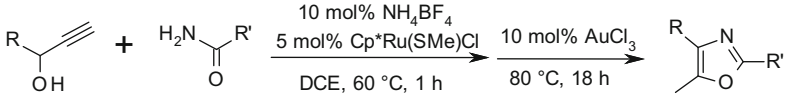
The common feature of the transformations in this chapter is the fact that the ring formation is achieved by the formation of a single bond from the appropriate linear precursor.

The transition metal-catalyzed ring closure of linear compounds containing at least two unsaturated bonds has been well established. An extension of this protocol to the synthesis of oxazoles is the gold-catalyzed cycloisomerization of propargylic amides. The process reported by Hashmi [155] yields various 2-substituted oxazoles in the presence of gold(III) chloride. The authors were also able to identify some of the intermediates in the process supporting the gold(III)-promoted electrophilic activation of the triple bond as the opening step of the sequence.



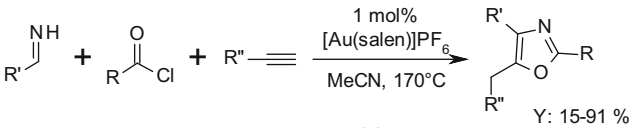
R= alkyl, alkenyl, (het)aryl Y: 48-91 %

A similar process has been reported concomitantly by Nishibayashi and Uemura [156]. The formation of the oxazole ring follows the same protocol as above but this step is preceded by the ruthenium catalyzed synthesis of the propargyl amide from the appropriate amide and propargylic alcohol derivative. The one-pot protocol gave oxazoles bearing different substituents in the 2- and 4-position.



R= alkyl, alkenyl; R'= alkyl, aryl Y: 20-88 %

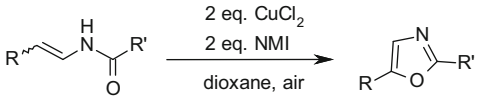
A recent three component transformation combining benzyl imines, acid chlorides, and acetylenes, reported by Strand [157], does also allow for the variation of the substituents in the 2-, 4-, and 5-position of the oxazole core. Although the process is modular, its efficiency varies with the selection of reagents, being more sensitive to the nature of the acetylene than of the acid chloride. The authors managed to bridge the gold catalyzed addition of the acetylides and imines, followed by the gold catalyzed cycloisomerization of the intermediate propargyl amides. The reaction was run at elevated temperature in a microwave reactor.



Y: 15-91 %

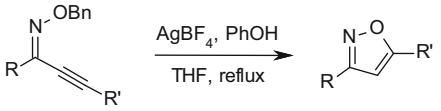
R= alkyl, aryl; R'= H, Ph, alkyl; R"= Ph, CO_2Me

An extension of the propargyl amide cycloisomerization to enamides has been reported by Stahl recently [158]. The transformation requires the use of stoichiometric amounts of copper(II) chloride that acts both as the mediator of the ring closure and oxidizes the formed intermediate to oxazole. The addition of *N*-methylimidazole that might serve as a ligand to copper was found to be beneficial for the process. The incorporation of aromatic groups into the oxazole ring is usually more efficient than that of the aliphatic analogues. The reaction works equally well with *E*- and *Z*-enamides and is believed to follow a single electron transfer mechanism.



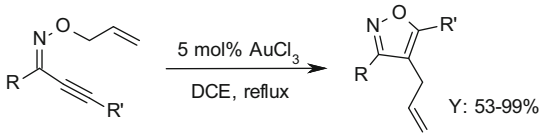
R= alkyl, aryl; R'= ^{t}Bu, aryl, styryl Y: 29-74 %

The transition metal-catalyzed synthesis of isoxazoles has also been explored. Miyata reported [159] a practical synthesis of 3,5-disubstituted isoxazoles via a silver catalyzed cyclization and subsequent protonation of alkynyl oxime ethers. The method tolerated the variation of the 3- and 5-substituents in a fairly broad range. The benzyl moiety attached to the oxime in the starting material is lost during the process.



R= H, (het)aryl, CO_2Me
R'= allyl, Ph, CO_2Me Y: 59- 81 %

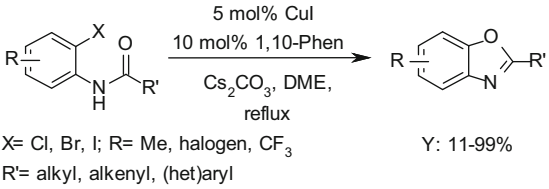
The same research group has reported the gold(III)-catalyzed rearrangement of the allyl ether analogue of the alkynyl oximes [160]. In this case the allyl group is not lost in the process, but the intermediate *O*-allylisoxazolium derivative undergoes a Claisen-type rearrangement to deliver the allyl group into the 4-position of the product.



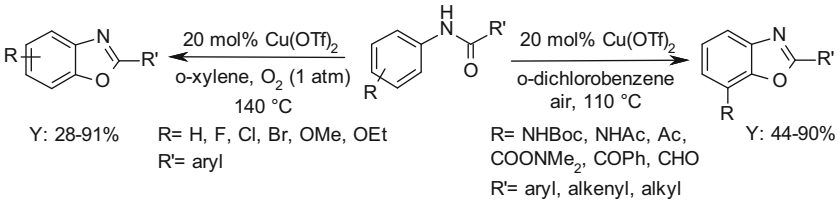
Y: 53-99%

R= Cy, (het)aryl, CO_2Me; R'= alkyl, aryl

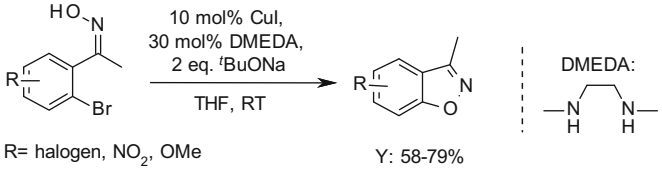
It has long been recognized that the transition metal-catalyzed carbon—heteroatom bond-forming reactions provide an easy access to heterocyclic compounds through direct ring closure. The copper-catalyzed synthesis of a collection of benzoxazole derivatives from *N*-acylated *ortho*-haloanilines has been reported by Batey [161]. The substitution of the aniline as well as the variation of the acyl moiety has been well tolerated except for some amino acid-derived amides.



The copper-catalyzed cyclization of amides into benzoxazoles can also be achieved through C–H activation as reported by Nagasawa [162]. Depending on the substitution pattern of the aniline derivative, the authors usually observed a regioselective ring formation. Although steric factors favor the formation of 5- and 6-substituted benzoxazoles, for compounds that bear a functional group capable of coordinating the copper(II) ion, the selective formation of the 7-substituted benzoxazole was observed. Through the variation of the acyl group, a wide range of substituents were introduced into the 2-position.

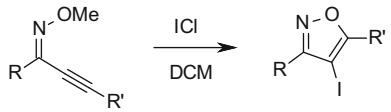


Tois reported the synthesis of 1,2-benzisoxazoles exploiting the same chemical transformation [163]. *ortho*-Bromoacetophenone oximes underwent copper-catalyzed cyclization at room temperature in the presence of a simple diamine ligand. According to the authors the key to the success is the use of *Z*-oximes to which they also devised a synthetic route.



3.1.2 Electrophile-Induced Ring Closure

Besides the transition metal-catalyzed rearrangement of alkynyl oxime ethers to isoxazoles that were described in the previous chapter, it is worth mentioning that the same compounds can also undergo electrophile-induced ring closure as reported by Larock [164]. The added value of this transformation is the incorporation of an iodine into the 4-position of the isoxazole ring that might serve as a starting point for a myriad of follow-up reactions. The ring closure works equally efficiently with a wide selection of substituents thus introducing a diverse set of 3- and 5-substituents onto the isoxazole ring.

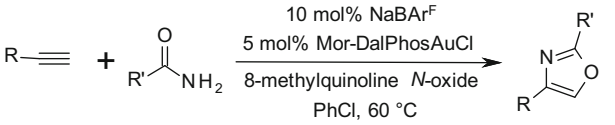


R= H, alkyl, (het)aryl
R'= alkyl, (het)aryl

Y: 55-99%

3.1.3 Simultaneous Formation of Two Ring Bonds

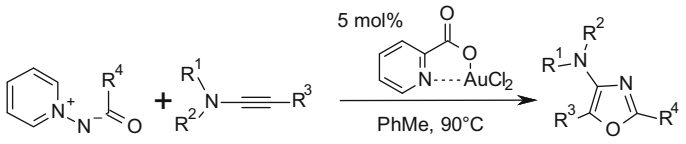
The gold(I)-catalyzed synthesis of 2,4-disubstituted oxazoles in the [3 + 2] annulation of terminal alkynes and carboxamides in the presence of an oxidizing agent has been reported by Zhang [165]. The reaction whose postulated key intermediate is an α-oxo gold carbine runs under mild conditions and the use of a bidentate *P*,*N*-ligand was crucial for its efficiency. The transformation worked equally well with (het)aryl and alkenyl carboxamides, while aliphatic carboxamides gave only poor yields.



R= alkyl, aryl; R'= alkenyl, (het)aryl

Y: 53-95%

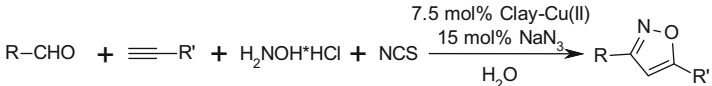
The gold(III)-catalyzed intermolecular [3 + 2] cycloaddition of conjugated *N*-ylides and *N*-alkynyl sulfonamides or cyclic carbamates were described by Davies [166]. The transformation gave the 2,5-disubstituted 4-aminooxazole derivatives with high selectivity. The reaction is not limited to ynamides since ethyl phenylethynyl ether gave the appropriate 4-ethoxyoxazole derivative albeit in a moderate yield.



R^1= acyl, sulfonyl; R^2= alkyl, Ph; R^3= alkyl, Ph
R^4= alkyl, alkenyl, (het)aryl, OMe

Y: 74-96 %

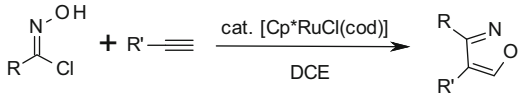
The reaction of copper(I) acetylides and nitrile oxides has been shown by Fokin [167] to yield 3,5-disubstituted isoxazoles. A simple and efficient one-pot variant of the same transformation starting from an aromatic aldehyde, a terminal alkyl or aryl acetylene, hydroxylamine, and NCS in the presence of a clay supported copper(II)/sodium azide catalyst precursor system has been reported by Vishwakarma [168].



R= Aryl; R'= Alkyl, Aryl

Y: 55-88%

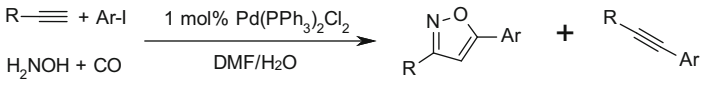
An opposite regioselectivity has been achieved by changing the catalyst to ruthenium. In the reaction of terminal aryl and alkyl acetylenes and differently substituted chlorooximes, the predominant formation of 3,4-disubstituted isoxazoles has been observed by Fokin [169]. Using internal alkynes the cyclization has also shown good selectivity: the more electronegative carbon center of the alkyne became C4 of the isoxazole ring unless a hydrogen bond donor was present that always ended up at C4.



R= alkyl, alkenyl, aryl R'= alkyl, aryl

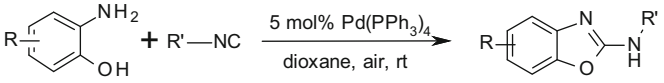
Y: 67-93%

The room temperature palladium-catalyzed carbonylative coupling of terminal alkynes and aryl iodides in the presence of hydroxylamine led to the formation of 3,5-disubstituted isoxazoles as reported by Mori [170]. The transformation ran under 1 atm of carbon monoxide and the use of an excess of hydroxylamine hydrochloride and aqueous ammonia was found to be beneficial in avoiding the main side reaction (Sonogashira coupling).



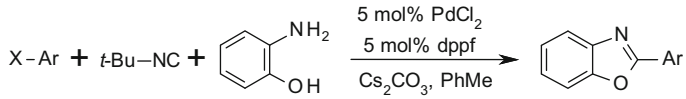
R= Ph, Ar= p-anisyl Y: 66% Y: 9%
R= p-anisyl, Ar= Ph Y: 54% Y: trace

A mild and general protocol has been reported recently by Jiang [171] for the palladium-catalyzed oxidative cyclization of *ortho*-aminophenols and isocyanides to 2-aminobenzoxazole derivatives. The transformation tolerated a broad range of substituents on the benzene ring, and alkyl and aryl isocyanides were coupled successfully. Interestingly the direction of the ring closure could be altered by the change of the catalyst and solvent and elevation of the temperature giving rise to 3-aminobenzoxazines with equally good selectivity.



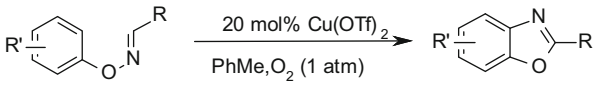
R= H, alkyl, halogen, CN, OMe, NO_2 R'= alkyl, aryl Y: 75-91%
COMe, CO_2Me, SO_2Me, $SONH_2$

The synthesis of 2-arylbenzoxazoles has been achieved by Lang [172] in the reaction of *ortho*-aminophenols, *tert*-butyl isocyanide, and aryl halides. Although seemingly analogous to the above transformation, this reaction runs in the absence of oxidizing agent and uses a significant excess of the aminophenol.



ArX= PhI, 4-$MeOC_6H_4Br$, 4-ClC_6H_4Br Y: 92-99%

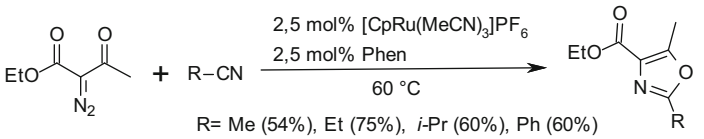
The copper(II) catalyzed oxidative rearrangement of bisaryloxime ethers to 2-arylbenzoxazoles was reported recently by Punniyamurthy [173]. The scope of the reaction is limited to *O*-aryl aldoximes and it uses molecular oxygen (1 atm) as the oxidant.



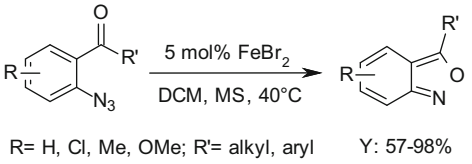
R= (het)aryl; R'= H, Me, Cl Y: 81-90%

3.1.4 Miscellaneous

α-Diazocarbonyl compounds and nitriles underwent ruthenium-catalyzed ring closure to the appropriate oxazole derivatives in acceptable yield. The transformation reported by Lacour [174] utilizes the nitrile as the solvent.



Iron(II) bromide was reported to catalyze the transformation of *ortho*-acyl arylazides into 2,1-benzisoxazoles by Driver [175]. The transformation tolerates a variety of different substituents on the benzene ring, while the carbonyl group might carry an aliphatic or aromatic substituent but not hydrogen.



3.2 *Functionalization of Oxygen Heterocycles with Additional Heteroatom*

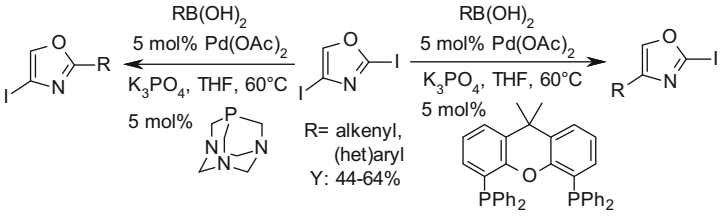
The transition metal-catalyzed functionalization of oxazoles, isoxazoles, and oxadiazoles, as well as their condensed derivatives has long been being explored due both to the inherent reactivity of these systems towards electrophilic reagents and the easy access to the appropriate halogenated azoles. As the following selection of examples demonstrates, a wide variety of substrates might be introduced onto these ring systems. This and the multitude of available transformations allow today's chemists to easily access diversely substituted ring systems in a highly selective manner. The presented reactions have been classified according to the nature of the newly formed bond.

3.2.1 Carbon–Carbon Bond Formation

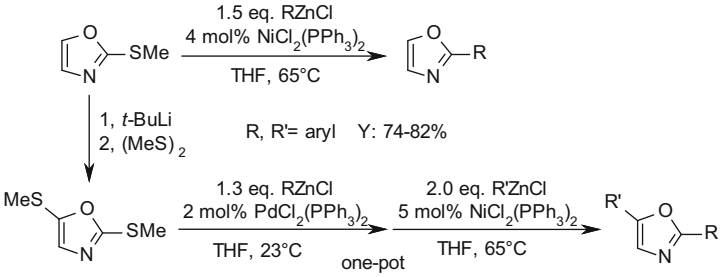
The interest for the introduction of carbon-based substituents onto the five-membered heterocyclic core in a transition metal-catalyzed process has been widely explored because of the abundance of these cores in medicinal chemistry. Besides the well-established cross-coupling reactions, of which we only present a limited selection, in the recent years a great deal of attention has been given to the functionalization of azole C–H bonds (a.k.a. C–H activation). The inherent reactivity of the five-membered heterocycles towards electron-deficient reagents as well as the selectivity of the ensuing reactions made these transformations very popular as will be demonstrated by the diversity of examples.

C–X Functionalization

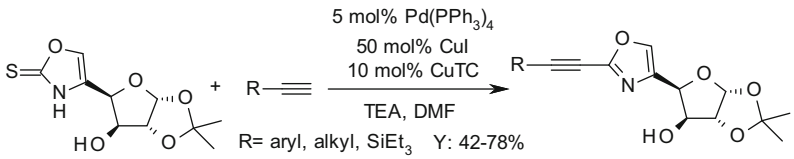
The uneven distribution of the electrons in the five-membered ring make the reactivity of the two halogens in 2,4-diiodooxazole different. Strotman and Chobanian [176] have screened a series of different palladium-based catalyst systems and found that by the proper selection of the used ligand a regioselective Suzuki coupling can be achieved in either position. When using Xantphos the traditionally more reactive 2-position was functionalized while in the presence of the phosphaadamantane-based ligand the transformation took place in the 4-position. Another advantage of these ligands is the limited formation of bis-arylated products, which allows for the sequential introduction of different substituents into the 2- and 4-position in subsequent Suzuki couplings. The conditions are applicable to the coupling of a wide variety of aryl-, heteroaryl-, cyclopropyl-, and vinylboronic acids.



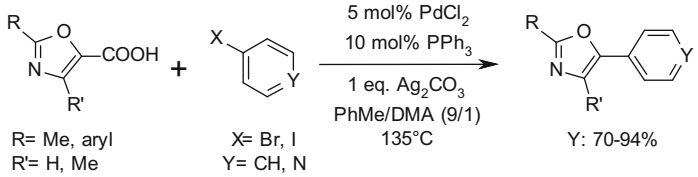
The use of methylthio derivatives in place of aryl halides in cross-coupling reactions in the presence of a copper(I) additive is a well-established protocol [177]. Stambuli reported [178] that 2-methylthiooxazoles undergo cross-coupling with a wide range of organozinc reagents in the presence of a palladium- or nickel-based catalyst system. Interestingly the addition of a copper(I) salt has blocked the coupling completely. The reaction was also extended to 2,5-bis(methylthio)-oxazole. By using a moderately active palladium-based catalyst and one equivalent of an organozinc chloride, the reaction could be stopped after the first coupling that took place in the 2-position. The change of the catalyst system to a more active nickel phosphine and the addition of another organozinc reagent initiated the cross-coupling in the 5-position and gave the desired 2,5-disubtituted oxazole derivative.



In a unique transformation reported by Tatibouet [179] a sugar-coupled oxazolinethione was alkynylated. The key to the process is the copper-mediated activation of the C–S bond of oxazole through its thiol tautomeric form. The process worked equally well with a series of acetylene derivatives and could also be extended to oxazolidinethiones.



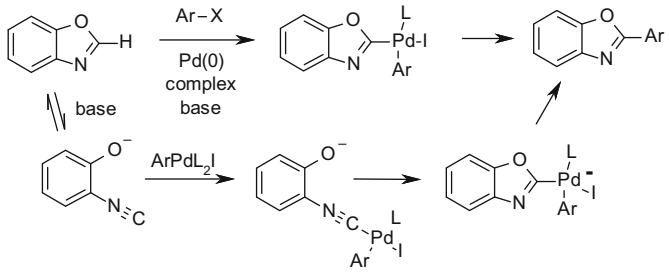
The decarboxylative cross-coupling reaction of aryl halides and aryl carboxylic acids has attracted significant attention since the groundbreaking work of Goossen [180]. The palladium-catalyzed cross-coupling of oxazole 5-carboxylic acids and a variety of aryl and hetaryl halides was reported by Greaney [181]. The success of the reaction requires the addition of an equivalent amount of silver carbonate.



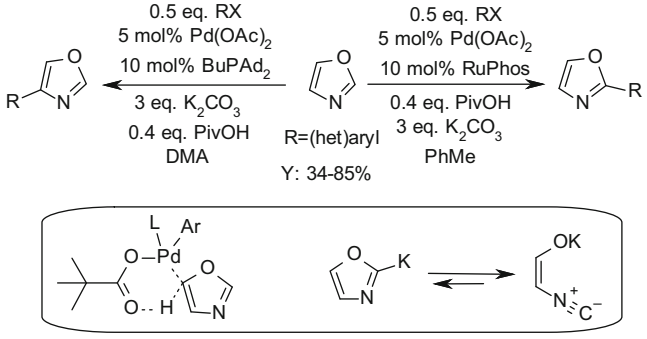
C–H Activation

Traditionally transition metal-catalyzed cross-coupling reactions utilize an aryl halides and an organometallic reagent as coupling partners. With the better understanding of their mechanism and the drive to develop transformations that have a decreased ecological footprint, the search intensified for such cross-coupling reactions where one or both reacting bonds are replaced by a C–H bond (a.k.a. C–H activation). The five-membered heteroaromatic systems proved to be an excellent reagent class for such transformations due to the increased electron density of the heteroaromatic ring [182]. One of the most utilized transformations of this class is the palladium-catalyzed coupling of an aryl halide with a five-membered heteroaromatic ring, an example of which is shown below. The commonly implicated mechanism features the electrophilic attack of the arylpalladium halide on the heteroaromatic ring giving rise to a bis-arylpalladium complex. An alternate mechanism has been proposed for the arylation of benzoxazoles by Zhuravlev [183] where the opening step is the base-promoted ring opening of the azole ring that in a ligand substitution-ring closure sequence leads to the formation of the shown

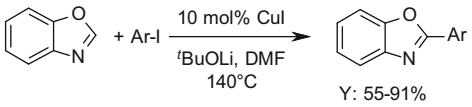
bis-arylpalladate complex. The concluding step in each case is the reductive elimination of the product and regeneration of the active catalyst.



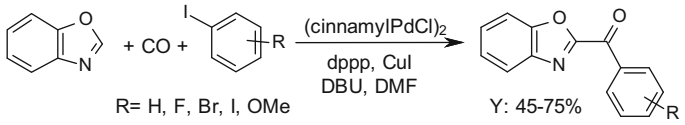
Studying the palladium-catalyzed coupling of aryl halides and oxazole under different conditions Strotman and Chobanian [184] established complementary conditions for the direct arylation of oxazole with very high regioselectivity both at the 2- and 5-position. The scope of reagents covered a wide range of aryl and heteroaryl bromides, chlorides, iodides, and triflates. Using polar solvents and *n*-butyl diadamantylphosphine as ligand, C-5 arylation is preferred, whereas switching to nonpolar solvents and RuPhos C-2 arylation became preferred. The authors reason that in C-5 selective reactions, the second palladium-carbon bond is formed in a concerted metalation-deprotonation reaction proposed by Fagnou [185], while in C-2 selective reactions the deprotonated form of the oxazole or its ring-opened analogue might react with the monoarylpalladium complex.



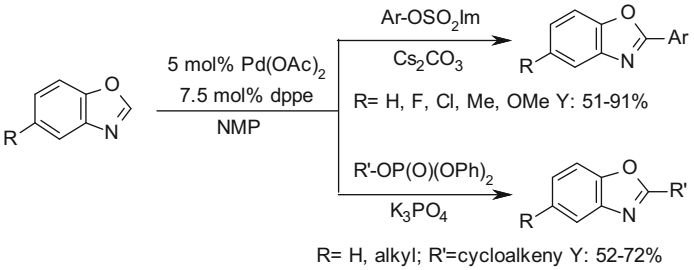
The copper-catalyzed arylation of benzoxazole by aryl iodides in the presence of lithium *tert*-butoxide has been reported by Daugulis [186]. The coupling takes place selectively in the 2-position and works well for sterically hindered aromatic moieties such as the mesitylene group. Preliminary mechanistic studies using deuterated substrates ruled out the presence of a benzyne-like mechanism. A rhodium-catalyzed variant of this reaction has been reported by Bergman and Ellman [187] in 2004, while Santelli [188] described the similar palladium-catalyzed arylation of 3,5-dimethylisoxazole in the 4-position using a wide variety of aryl bromides.



Analogously to other cross-coupling reactions conducting the arylation of benzoxazole with aryl iodides in the presence of carbon monoxide, Beller [189] achieved the synthesis of 2-aroyl-benzoxazoles. The transformation required the use of a palladium catalyst system and copper(I) iodide as an additive.

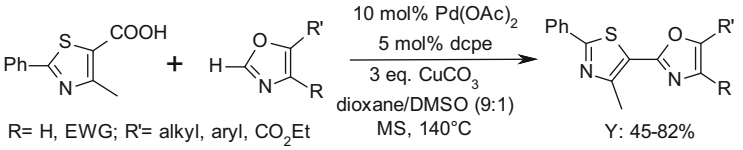


The apparent ease of arylation of oxazoles in the 2-position through C–H activation has led to a widespread effort to extend the scope of arylating agents. Using moisture stable aryl sulfamates Ackermann [190] established an efficient palladium-catalyzed protocol for the 2-arylation of benzoxazoles. The same catalyst system worked equally well with cycloalkenyl and benzyl phosphates expanding the scope of substituents to the benzyl moiety.

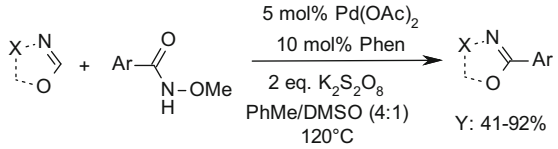


Another alternate to the use of aryl halides is the use of carboxylic acid derivatives. Greaney [191] has successfully coupled azolyl carboxylic acids with oxazole derivatives in the presence of a palladium catalyst. The use of an electron rich and bulky bidentate ligand was crucial to the selective coupling. The reaction uses an excess of copper(II) carbonate as base and oxidant and probably proceeds through an azolylcopper complex. The use of silver carbonate has led to a similar outcome.

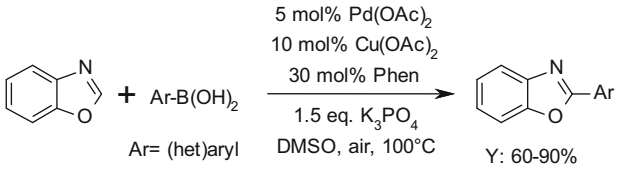
Switching the catalyst from palladium to nickel, Yamaguchi and Itami [192] has successfully extended the scope of the coupling to aryl carboxylic acid phenyl esters. Under these conditions the copper(II) salt could be replaced by potassium phosphate. The coupling worked equally well with 5- and 6-membered heteroaromatic esters as well as carbocyclic analogues.



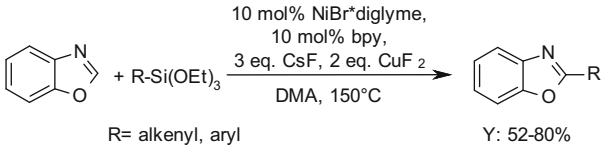
A highly chemo- and regioselective deamidative arylation of oxazoles, oxadiazoles, and benzoxazoles with arylamides has been reported by Wang [193]. The palladium-catalyzed reaction proceeds smoothly to generate the corresponding products in good yields via a tandem decarbonylation–C–H activation.



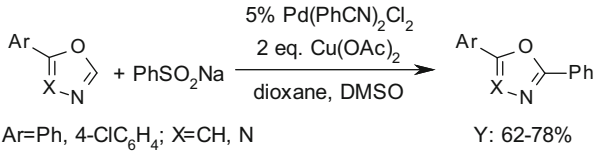
The use of arylboronic acids in the palladium-/copper-catalyzed arylation of benzoxazole has been reported by Liu [194]. The oxidative couplings were run under air and enabled the introduction of benzene derivatives and pyridine into the 2-position. A subsequent communication by Xu, Yu, and Wang [195] describes the analogous coupling of arylboronic esters, using copper as catalyst and molecular oxygen as the oxidant. Besides a similar substrate scope for the arylation of benzoxazoles, the authors were also successful in arylating oxazole and its 5-aryl derivatives.



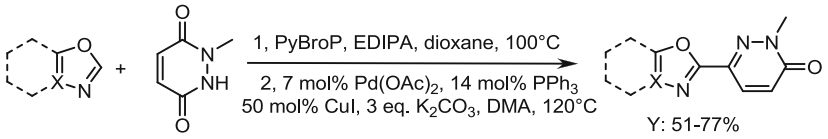
A further extension of the scope of arylating agent has been reported by Miura [196] who coupled aryl and alkenyl triethoxysilanes with oxazole and benzoxazole derivatives in the presence of a nickel-based catalyst system and stoichiometric amounts of cesium fluoride and copper(II) fluoride. In a similar experiment Ofial [197] coupled successfully oxazole and benzoxazoles with trialkoxy(aryl)silanes using palladium(II) acetate as catalyst and copper(II) acetate and silver fluoride as additives. The reaction was successfully extended to allyltriphenylstannane that gave the 2-arylazoles in good (65–76%) yield.



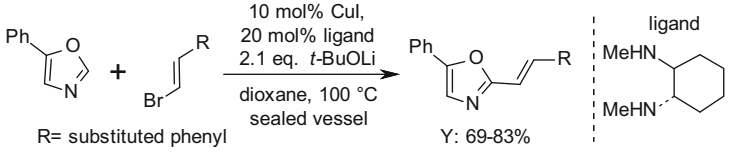
The palladium-catalyzed direct desulfitative C-arylation of the 2-position of benzoxazole with arenesulfonyl chlorides has been reported by Chen [198]. The procedure tolerates a wide range of functional groups on the arylsulfonyl chlorides. Copper salt and air were used as oxidant. In an analogous coupling You [199] used the easily available, air-stable, and easy to handle sodium sulfinates as the coupling partner. Oxazole, oxadiazole, and benzoxazole were arylated with similar yields. Using the stable and easily accessible arylsulfonyl hydrazides with a palladium catalyst and copper(II) acetate as oxidant, Li and Wan [200] arylated differently substituted oxazoles and benzoxazoles in the 2-position in a similar fashion.



The direct arylation of benzoxazoles and 2-phenyloxadiazole in cross-coupling with tautomerizable heterocycles has been reported by van der Eycken [201]. The reaction proceeds through a PyBroP-mediated and Pd/Cu-catalyzed sequential C–O/C–H activation. The methodology worked equally well for 1,2-, 1,3-, and 1,4-diazines.

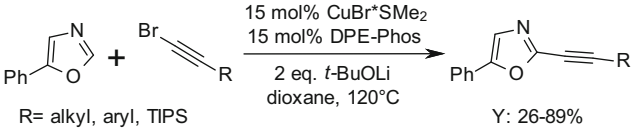


The functionalization of azole derivatives through C–H activation is not limited to arylation reactions. Piguel [202] has reported the copper-catalyzed alkenylation of oxazoles and benzoxazole with bromoalkenes in a regio- and stereoselective process.

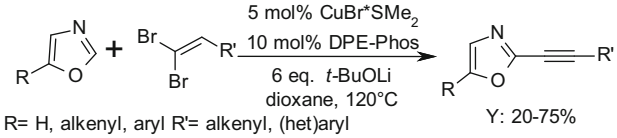


The alkynylation of oxazole and benzoxazole using bromoacetylene derivatives has been reported by Miura. The nickel-catalyzed coupling worked well for several

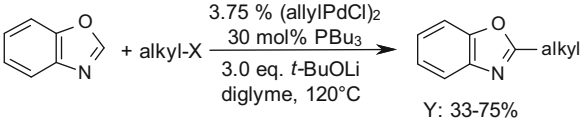
substrates, but in certain cases the addition of copper(I) iodide as co-catalyst was required to achieve good yield [203]. The analogous copper(I)-catalyzed alkynylation of oxazole, benzoxazole, and oxadiazole derivatives with bromoalkynes was reported concomitantly by Piguel [204].



The copper-catalyzed direct alkynylation of azoles can also be achieved using 1,1-dibromo-1-alkenes as electrophiles as described by Piguel [205]. The reactive bromoacetylene is presumably generated by the added strong base in the opening step of the process. The scope of the process was similar to that of the above-described copper-catalyzed alkynylation, which might not be too surprising since the two transformations share the same catalyst system and only the amount of added base differs significantly. Ackermann [206] described an analogous palladium-catalyzed transformation using 1,1-dichloroalkenes as reagent.

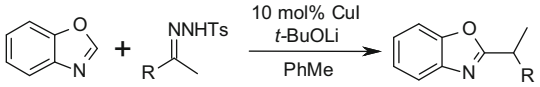


The alkylation of azoles through C–H activation has also been described. Miura and Hirano [207] reported an efficient palladium and nickel catalyst systems for the direct alkylation of oxazoles and benzoxazoles with alkyl bromides and chlorides. Interestingly for more complex reagents (e.g., 6-bromohexene), the outcome of the reaction depended on the catalyst used. Miura [208] has also described the direct benzylation of azoles with benzyl carbonates in the presence of a palladium catalyst system that affords the corresponding diarylmethanes in good yield. In addition, the same palladium catalyst enables the benzylation of the product on its C(sp^3)-H bond with a second benzyl carbonate without employing any external base.



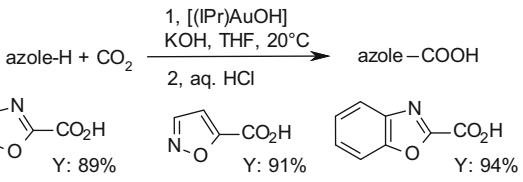
The use of tosylhydrazones of acetophenon and cyclohexenone derivatives as alkylating agent in a copper-catalyzed and base-mediated process has been reported by Wang [209]. The process leads to the direct benzylation or allylation of oxazole and benzoxazoles. An extension of this process reported by Miura and Hirano [210]

utilizes a nickel-based catalyst and works equally well with tosylhydrazones bearing non-activated alkyl groups.



R= Ph (80%), 4-MeOC6H4 (58%), 4-CF3C6H4 (76%)

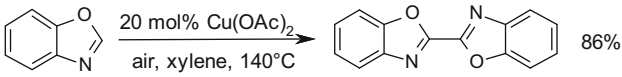
A unique example of the functionalization of azoles through C–H activation is the gold-catalyzed carboxylation of azoles with carbon dioxide. The procedure described by Nolan [211] employs gold(I)-carbene complexes as catalyst, a slight overpressure (1.5 bar) of carbon dioxide, and works equally well on oxazole, isoxazole (activation of 5-position), and benzoxazole. A similar copper-carbene complex-catalyzed transformation has been reported by Hou [212] who converted the carboxylate intermediates without isolation to the corresponding esters using different alkylating agents.



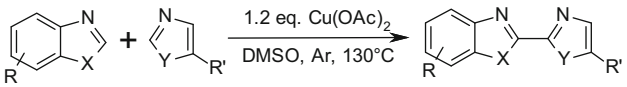
Double C–H Activation

In theory under oxidative conditions azoles and other reagents could be coupled in a double C–H activation, resulting in the formation of water as by-product. Although such a transformation would be quite appealing from the atom economy and environmental point of view its widespread application is limited mostly by the difficulty of fine tuning the conditions to achieve the selective activation of the desired C–H bonds.

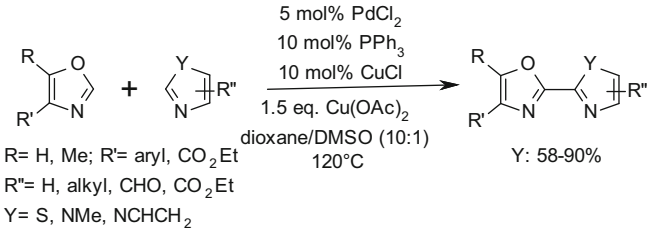
These difficulties are not present in the oxidative homocoupling of azoles that was reported by Qian and Bao [213]. Benzoxazoles and oxadiazole were found to dimerize through their 2-position in the presence of a copper catalyst and air as oxidant to give the respective bisazoles in good yield. Attempts to extend this catalyst system to the heterocoupling of azoles led to mixtures with little deviation from statistic product distribution.



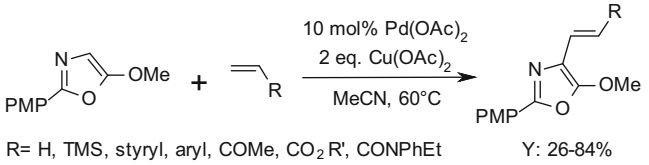
In a recent publication Xu, Yu, and Wang [214] claimed that stoichiometric copper(II) acetate in dimethyl sulfoxide under argon mediates the selective cross-coupling of different azoles in high yield and with excellent chemoselectivity. The transformation was sensitive to the applied reaction conditions and the presence of the acetate ions was also crucial for the successful coupling. They reported that the process worked well with a broad scope of azoles.



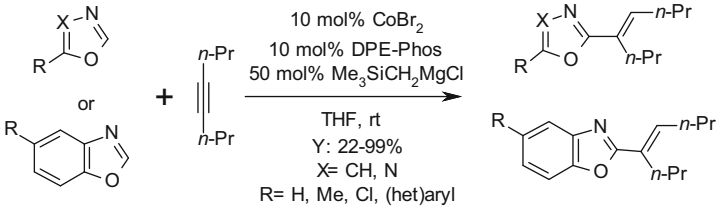
Similarly, outstanding selectivity was observed by You [215] in the coupling of oxazole derivatives with thiazoles and imidazoles. The reaction required the presence of a palladium catalyst, a copper co-catalyst, and analogously to the above-reported results, stoichiometric amounts of copper(II) acetate. In this paper the authors have also identified and quantified the formation of the homocoupled by-products.



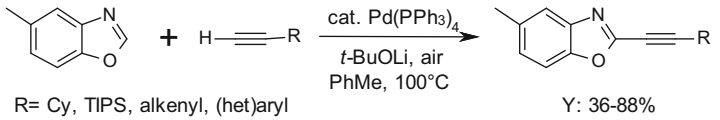
The palladium-catalyzed oxidative olefination of oxazoles at the 4-position through C–H bond activation has been reported by Antilla [216]. The transformation requires the presence of copper(II) acetate as oxidizing agent and the broad scope of applicable terminal olefins includes vinylstannanes, vinylsilanes, acrylamides, and butadiene derivatives alike. The formed products were also transformed into functionalized amino alcohol and homophenylalanine derivatives.



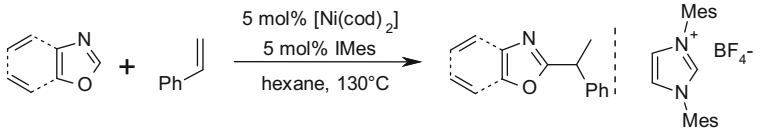
The alkenylation of the 2-position of oxazoles, oxadiazoles, and benzoxazoles can also be achieved in the cobalt-catalyzed addition of these azoles to internal alkynes as reported by Yoshikai [217]. The use of a bidentate phosphine ligand at least half equivalent of a Grignard reagent were necessary to achieve good yields.



The oxidative coupling of benzoxazoles and terminal acetylene derivatives was reported by Chang [218]. The coupling required the use of the conventional tetrakis (triphenylphosphino)palladium catalyst and air as oxidant. It is interesting to note that no copper salt was added to the reaction. The reaction was also extended to 4-aryloxazoles.



In a recent paper describing the nickel-catalyzed hydroheteroarylation of vinylarenes, Nakao and Hiyama [219] reported the phenethylation of oxazole and benzoxazole with styrene. The reaction that ran at elevated temperature gave the respective products in 41 and 97% yield.

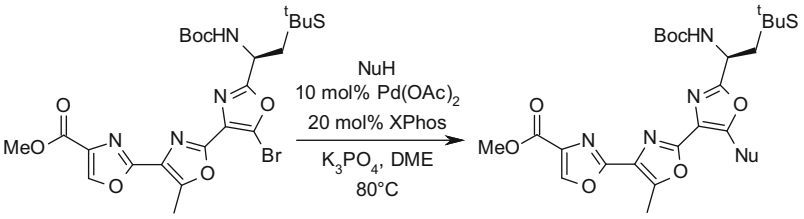


3.2.2 Carbon–Heteroatom Bond Formation

Heterocyclic compounds bearing heteroatom-based substituents have always been a primary target for organic synthesis. In case of 2-substituted oxazoles and benzoxazoles, their synthesis is frequently achieved through direct ring closure reactions. The marked reactivity of azoles towards electrophiles makes their nitro and halogen derivatives easily accessible too. The chemical pathways to transform these intermediates into the desired amine-, alcohol-, or thiol-substituted derivatives without the use of a transition metal catalyst, apart from heterogeneous hydrogenation reactions that is not discussed here, are also known. The following chapter collects representative examples for the transition metal-catalyzed introduction of heteroatom-based substituents onto the five-membered heterocyclic ring.

C–X Functionalization

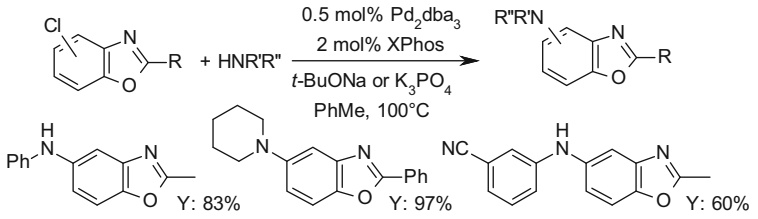
The palladium- and copper-catalyzed conversion of haloarenes to their amino- or alkoxy-substituted derivatives is well established. Contrary to its widespread use for benzene derivatives and azines, the number of relevant examples for azoles is limited. 5-Bromooxazoles were reported by Doi and Takahashi [220] to undergo Buchwald-Hartwig coupling with different amines and a phenol. The expected products were isolated in acceptable yield. In case of octylamine the amidation of the pendant ester group was also observed (not shown for clarity). Spencer [221] published a similar transformation that was used in the generation of a small library of oxazole derivatives.



NuH= octyl amine, morpholine, piperidine, 4-MeO-phenol Y: 43-70%

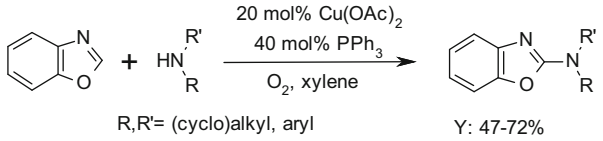
The literature of the transition metal-catalyzed amination of 4-halooxazoles is even scarcer. Boger [222] reported an example of the copper-catalyzed conversion of a 4-iodooxazole derivative to the methoxy analogue, while a recent patent application disclosed [223] the palladium-catalyzed sulfonamidation of 4-iodooxazoles.

The palladium-catalyzed amination of 6-chlorobenzoxazoles was reported by Buchwald [224]. The reaction proceeded smoothly both with anilines and piperidine in the presence of XPhos as ligand. For the efficient coupling of 3-cyanoaniline, the authors had to change the applied base from sodium *tert*-butoxide to potassium phosphate.

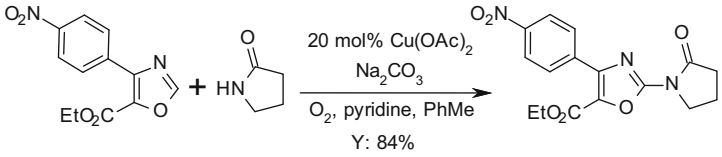


C–H Activation

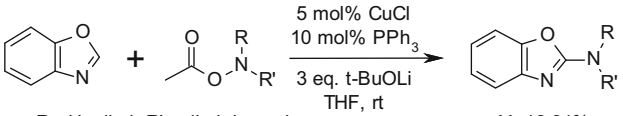
The direct functionalization of azoles with nucleophiles in a C–H, Nu–H activation is of great synthetic interest. Since the keen participation of these heteroaromatic rings in coupling reactions including a C–H activation is well documented, it is not surprising that the analogous transition metal-catalyzed introduction of nucleophiles has also been studied recently by several groups. The copper(II)-catalyzed amination of benzoxazole reported by Mori [225] proceeds readily at elevated temperature under ambient pressure of oxygen. The introduction of diphenylamine, *N*-methylaniline, and piperidine was equally efficient (66–72% yields), while the yield using diethylamine was slightly inferior (47%).



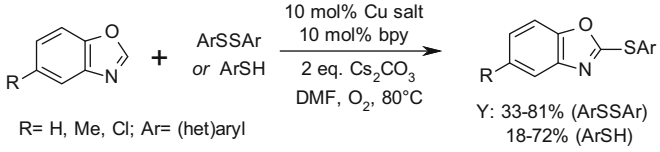
The copper(II) catalyst system is also able to catalyze the acylamination of oxazole as reported by Schreiber [226]. Pyrrolidinone reacted readily with a substituted oxazole derivative in the presence of oxygen. It is interesting to note that the analogous transformation of benzoxazole with *o*-trifluoromethylbenzamide required the use of a stoichiometric amount of copper(II) acetate. Although mechanistically distinct we should also mention the silver(I)-mediated amination of benzoxazoles in the 2-position using either amines or their formamide equivalents as reagent. The reaction was reported by Chang [227] to work well with a broad scope of amines and formamides but not on similar ring systems such as oxazole.



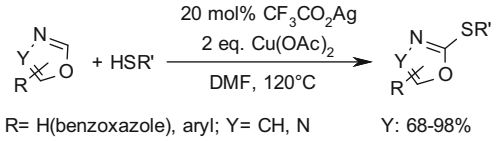
An interesting variant of the amination of benzoxazoles in the 2-position through C–H activation was reported by Yotphan [228] who used *O*-benzoyl hydroxylamine derivatives as amine source in a copper(I)-catalyzed reaction. A variety of secondary amines were introduced onto the benzoxazole core efficiently, while the use of *N*-monoalkyl derivatives proceeded only with poor yield. An example of the amination of 2-phenyl-oxadiazole was also reported.



The cross-coupling reaction of benzoxazole with aryl thiols and diaryl disulfides was reported by Fukuzawa [229]. In the presence of a copper-bipyridine catalyst and oxygen, the corresponding aryl benzoxazolyl sulfides were isolated in moderate to good yields. The coupling reaction proceeded equally well in the presence of selected copper(I) and copper(II) salts indicating the rapid oxidation of the former under the applied conditions. The oxidation of the aryl thiols to the diaryl disulfides under the applied conditions is also likely.



In the presence of a Lewis acid (typically silver trifluoroacetate) and a stoichiometric amount of copper(II) acetate oxazole, oxadiazole and benzoxazole derivatives reacted with butyl mercaptan to give the 2-butylthio derivatives in good yield [230]. Switching the silver catalyst to silver fluoride and the solvent to dimethyl sulfoxide, the methylthiolation was observed implying the dual role of the solvent.



Summary, Conclusions, Outlook

In the previous chapters we collected a bouquet of transition metal-catalyzed transformations that are useful for the synthesis and derivatization of five-membered oxygen-containing heterocycles. The richness and diversity of this collection, and the newly developed methodologies in particular, mean that this area of chemistry will remain a burgeoning field in the near future. We firmly believe that the vast capabilities of the outlined chemical transformations will continue to drive the use of these ring systems in applied science, in medicinal chemistry in particular, while their increasing presence in applied science in turn will further fuel basic research in organic synthesis.

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Transition Metal-Catalyzed Coupling Reactions in Library Synthesis

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Abstract It has been widely recognized that the global pharmaceutical and agrochemical industries are currently experiencing a dynamic change. To increase productivity and efficiency, agro and drug companies have been striving to make improvements in every aspect of the R&D. Consequently, new technologies providing novel chemical cores currently are of great demand at all major companies.

Furthermore, high-throughput screening requires the synthesis of larger and more diverse sets of compounds. High-throughput synthesis of heterocyclic compound libraries utilizes various combinatorial strategies including direct scaffold decoration, linear convergent, and divergent approaches.

Biphenyl frameworks (including heteroaromatic moieties) are found in many biologically active products and thus can be considered as a privileged motif in medicinal chemistry.

The emergence of transition metal-catalyzed coupling reactions readily facilitated library/scaffold diversification with the easy incorporation of aromatic/heteroaromatic rings into various chemotypes that are preferentially directed towards hydrophobic cavities of protein targets. Typically, carbon–halogen bonds are utilized for a variety of transition metal (mostly palladium)-catalyzed reactions, including Suzuki–Miyaura, Sonogashira, Buchwald–Hartwig, Stille, Negishi, and Heck couplings. Most recently, direct C–H activation/arylation protocols were also reported for direct derivatization of heterocyclic cores.

On the other hand, cross-coupling reactions were also implemented into domino and cascade reactions to enable multiple bond-forming and bond-cleaving events in a single synthetic operation yielding efficiently novel ring systems.

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Keywords Catalysis • Cross-coupling • Library synthesis • Palladium metal

Contents

Abbreviations

BEMP	2-*Tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCM	Dichloromethane, methylene chloride
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DIC	*N*,*N*'-Diisopropylcarbodiimide
DIPEA	*N*,*N*-Diisopropylethylamine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
dppf	1,1′- Bis(diphenylphosphino) ferrocene
DVB	Divinylbenzene
Fmoc	Fluorenylmethyloxycarbonyl
HMBA	10-[(3-Hydroxy-4-methoxybenzylidene)]-9(10*H*)-anthracenome
HOBt	Hydroxybenzotriazole
mCPBA	*Meta*-chloroperbenzoic acid
MeCN	Acetonitrile
MIDA	*N*-Methyliminodiacetic acid
MTBE	Methyl *tert*-butyl ether
MWI	Microwave irradiation
NBS	*N*-Bromosuccinic imide
NEM	*N*-Ethylmorpholine
NIS	*N*-Iodosuccinic imide

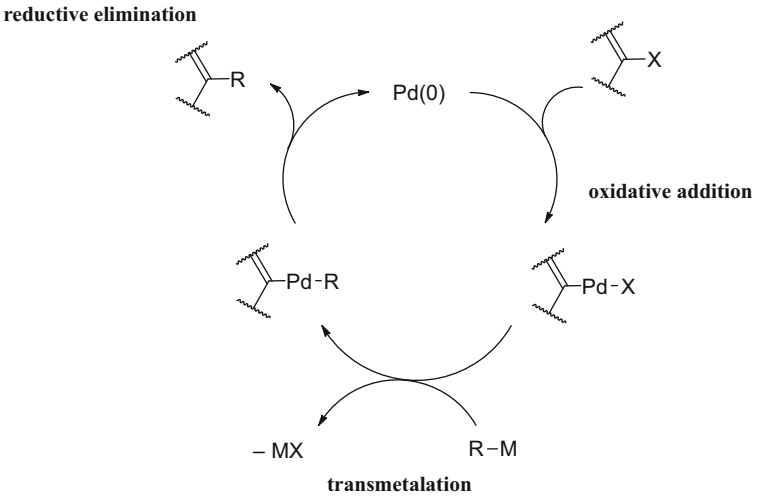
NMP	*N*-Methylpyrrolidone
POPd	Dihydrogendichlorobis(di-*tert*-butylphosphinito-*k*P)palladate(−2)
PS	Polystyrene
PTSA	4-Toluenesulfonic acid
rt	Room temperature
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TBAB	Tetrabutylammonium bromide
TBAC	Tetrabutylammonium chloride
TBAI	Tetrabutylammonium iodide
TBS	*Tert*-butyl dimethyl
TBTU	*N*,*N*,*N*′,*N*′-Tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TosMIC	Toluenesulfonylmethyl isocyanide
TPP	Triphenylphosphine
Ts	Tosyl, 4-methylsulfonyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

1 Introduction

This chapter is dedicated to demonstrate how palladium-catalyzed cross-coupling reactions paved the way for efficient library synthesis and became a privileged tool for today's chemists in designing novel scaffolds (including highly conjugated and biaromatic systems) and building diversity.

Before palladium, copper was the choice of metal for carbon–carbon bond-forming reactions albeit palladium became more popular in the course of their development. Since the early discoveries of palladium-catalyzed carbon–carbon bond-forming reactions like the Suzuki–Miyaura, Heck, Negishi, Sonogashira, and Stille coupling, substantial effort has been invested into this field to develop a wide range of versatile and useful chemistries in order to gain access to valuable fine chemicals, intermediates, and drug candidates. Undoubtedly, the highest recognition of this endeavor was the Nobel Prize in Chemistry 2010 awarded jointly to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki "for palladium-catalyzed cross-couplings in organic synthesis" [1].

As a result of decades of fundamental research and the deeper understanding of this type of chemistry, nowadays, palladium-catalyzed cross-couplings became suitable not only for scaffold and target (overall library) synthesis but also to be incorporated into multicomponent [2, 3] and domino [4, 5] processes, as well, that greatly increased diversity and step economy. Today, classical palladium-mediated C–C bond-forming "name" reactions are standard instruments in the toolkit of



Scheme 1 General catalytic cycle for palladium catalyzed C–C bond formation (stereochemistry and ligands omitted)

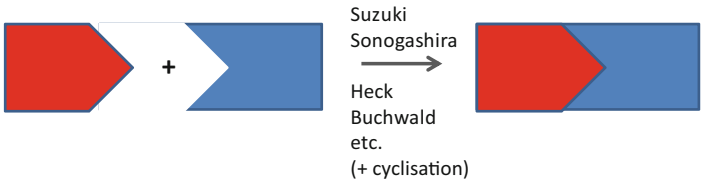
bench chemists all around the globe, and the well-known catalytic cycle [6] (Scheme 1) of these types of reactions is indispensable from every chemistry textbook.

It is important to note that these chemical transformations are still under continuous development. As outstanding examples, they proved to be particularly suitable for microwave-assisted transformations [7] and most recently in continuous-flow methodologies [8] development, as well.

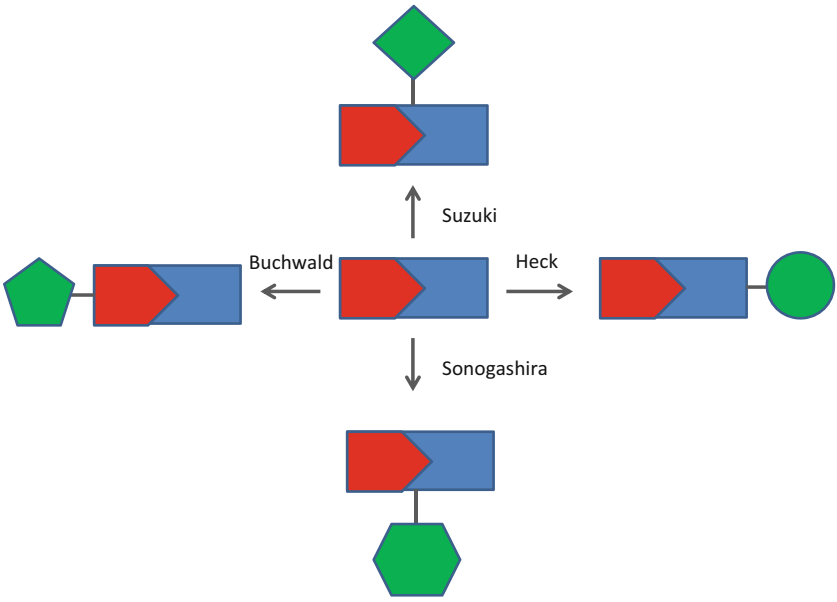
Contiguous research is ongoing towards the synthesis of new phosphine ligands [9] and circumstances also to improve catalyst activity, thus improving selectivity and yields while decreasing catalyst loading, reaction temperature, reaction time, and overall cost.

There is no doubt that research in this field will continue on, as state-of-the-art methodologies are currently under close investigation in order to meet the requirements of tomorrow's research regulations and environmental criteria. These innovative fields involve reactions run in/on water [10–12], the application of polymer-supported reagents and heterogeneous palladium catalysts [13, 14], and even the use of preformed "ready-to-use" catalyst-incorporated tablets [15]. Besides technology expansion, chemical development of palladium-mediated carbon–carbon bond formation is still an area of high interest nowadays. Direct C–H activation [16, 17] and oxidative palladium-catalyzed C–C bond formation [18, 19] are leading examples of this exciting field without being exhaustive.

Assorted examples that display best the utilization of palladium-catalyzed cross-coupling reactions in library design and synthesis with a focus on carbon–carbon bond-forming reactions from broadly the past decade are presented within this chapter.



Scheme 2 Scaffold synthesis with the involvement of cross-coupling reactions



Scheme 3 Scaffold decoration and library diversification with cross-coupling reactions

2 General Synthetic Strategies

There are two main different types of synthetic strategies:

a. Scaffold synthesis with the involvement of cross-coupling reactions (Scheme 2)
b. Scaffold decoration and library diversification with cross-coupling reactions (Scheme 3)

Technically, both scaffold synthesis and decoration could be done in solid and solution phases. In solution phase solid-supported reagents and catalysts could also be used. Numerous solid-phase syntheses are reported for Suzuki–Miyaura (Entries 1 [20], 2 [21], 3 [22], 4 [23], 5 [24]) and for Sonogashira couplings (Entry 39 [25]). Stille coupling-induced ring closure on solid support was described (Entry 43 [26]) together with solution phase scaffold decoration.

Additionally, fluorous liquid–liquid phase reactions are also employed making use of the advantages of the easy separation and purification. In Entries 27 [27] and 28 [28], the fluorous tag was employed as the leaving group in Suzuki–Miyaura and in Negishi couplings (Entry 40 [29]).

There are many instances where scaffold synthesis, as well as scaffold decoration, employs cross-coupling reactions. Sonogashira reaction is particularly popular in scaffold synthesis since the inserted triple bond can be used in subsequent cyclization reactions in many ways. (Entries 58 [30], 59 [31], 60 [32], 62 [33], 63 [34]).

Suzuki–Miyaura coupling is generally performed on aromatic systems. However, there are two examples where only partially unsaturated rings are subjected to C–C coupling (Entries 22 [35], 32 [36]).

In a one-pot cross-coupling and amination reaction, aryl and unsaturated boronates were used in Entry 12 [37] at high temperatures (160°C) under MW heating. The ring halogen reacted with the boronates, while the aliphatic chloride was replaced with various amines; thus, two diversity elements were introduced selectively in one reaction. In this reaction the desired compounds were purified with scavengers using a "catch-to-release" technique.

Two identical aromatic groups can be introduced in double scaffold decoration if two identical halogens are present in the precursor structure (Entry 30 [38]). However, one-pot sequential double scaffold decoration was applied in Entry 24 [39] with different aromatic species making use of the different reactivity of the I and Br leaving groups or similarly triflate and Br (Entry 53 [40]). In another example ("sandwich sequence"), selective introduction of a bromine leaving group is followed by the first Suzuki coupling and facilitated the second Suzuki coupling (Entry 30 [38]).

Sequential Suzuki coupling was also reported leading to a chain of tiophenes (Entry 3 [22]) or thienylpyridyl garlands (Entry 16 [41]). Large majority of the synthetic targets are N- or N,O-/N,S/heterocyclic ring systems. The heterocyclic rings are either condensed ring systems or contain a chain of isolated rings (e.g., Entry: 16 [41]). Few examples lack any heteroatoms (Entries 12 [37], 13 [42], 58 [30]). Apart from some *O*-heterocycles (Entries 1 [20], 3 [22], 4 [23], 26 [43], 31 [44], 33 [45], 39 [25], 43 [26], 45 [46], 46 [47], 47 [48], 52 [49]), few S-heterocycles are reported (Entries 1 [20], 3 [22], 48 [50], 49 [51]).

Normally, the preformed scaffold contains the halogen or pseudohalogen (e.g., triflate) leaving group in the reaction. In one reported case a "reversed strategy" was used (Entry 9 [52]), namely, the triazole motif of the scaffold was converted to a boronate ester and reacted with various aryl bromides. The striking advantage of this strategy is that aryl halides are available on the market more readily and in higher numbers compared with boronates. Moreover, aryl halides are generally more reasonably priced.

In an interesting reaction sequence chromones were subjected to Suzuki coupling which was followed by subsequent ring opening and closure to pyrimidine ring (Entry: 57 [53]).

Multicomponent or tandem scaffold synthesis was reported in Entry 35 [54], which includes Heck reaction and tin-induced ring closure leading to dihydroindenoisoquinoline.

Only two examples were reported when Negishi coupling was employed in scaffold synthesis (Entries 40 [29], 41 [55]).

When a certain spatial distance is set between the aryl fragments, intramolecular direct CH activation is possible without using activating groups like boronates to induce coupling leading to fused ring systems (Entry 42 [56]).

The intermediate scaffolds having the proper leaving groups I, Br, or the pseudo halide triflates are suitable for conversion to decorated scaffolds with Suzuki–Miyaura, Negishi, Sonogashira, Heck, and Pd-catalyzed carbonylation reactions. There are several examples where many of these cross-coupling reactions were used for increasing the diversity around the scaffold or core structure (Entries 15 [57], 43 [26], 44 [58], 45 [46], 46 [47], 47 [48], 48 [50], 49 [51], 50 [59], 51 [60], 52 [49], 53 [40], 54 [61], 55 [62], 56 [63]).

Finally, there are so-called domino or tandem transformations that combine two cross-coupling reactions in one pot. In Entry 58 [30] intramolecular Heck reaction and Suzuki couplings lead to indenes. In this case, the scaffold synthesis and decoration take place in one single step and pot. Similarly, Sonogashira reaction followed by intramolecular ring closure leading to an indolizine library (Entry 59 [31]), pyrrolopyridazines (Entry 60 [32]), indoles (Entry 62 [33]), and quinolinones (Entry 63 [34]) has been reported. In Entry 61 [64] and Entry 34 [65], Heck reaction was followed by an aza-Michael-type ring closure.

Tandem Suzuki–Miyaura coupling–cyclization is reported in Entry 64 [66]. In Entry 65 [67] two scaffold fragments possessing diversity elements were merged in a Suzuki–Miyaura coupling, which was followed by intramolecular lactamization.

2.1 Components in the Suzuki Coupling

Since the Suzuki–Miyaura coupling is the most frequently used C–C bond-forming reaction in library synthesis, this subsection is primarily focused on the main factors of this type of cross-coupling reaction. There are four key components of the Suzuki coupling: boronates, Pd catalysts, organophosphine ligands, and inorganic salts or bases.

Boronates are typically used as boronic acids ($RB(OH)_2$), boronate esters ($RB(OR')_2$, and organoboranes (R_3B). Besides the common boronates, pinacol boronate is employed in Entry 10 [68]. Organotrifluoroborates are used in Entry 8 [69] that are tolerant to air and moisture and easy to handle and purify. An example of solid-supported boronate reagent (Fig. 1) is reported in Entry 6 [70]. This boronate is a variant of the MIDA boronate [71] (trivalent *N*-methyliminodiacetic acid (MIDA) ligand).

Regarding the Pd catalysts there are many variations employed (Fig. 2.): $Pd(PPh_3)_4$; $Pd(PPh_3)Cl_2$; $Pd_3(OAc)_6$ (Entry 13 [42]), the trimeric form of $Pd(OAc)_2$;

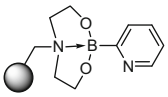


Fig. 1 Solid-supported boronate reagent for Suzuki coupling

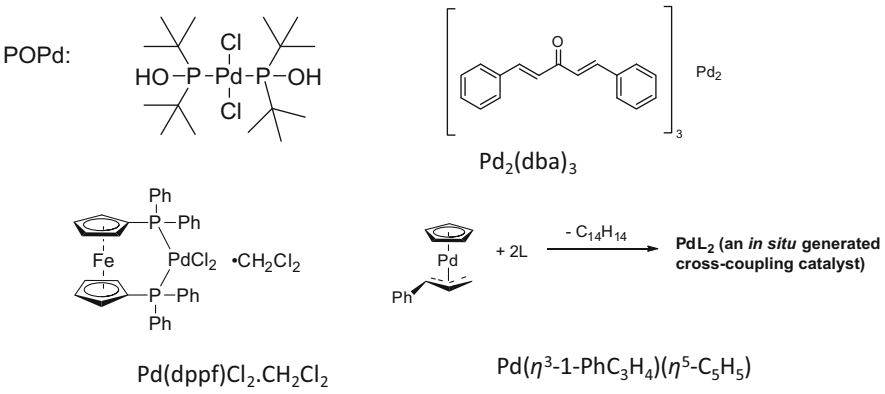


Fig. 2 Palladium catalysts

POPd (Entry 17 [72]); $Pd_2(dba)_3$, (tris(dibenzylideneacetone)dipalladium(0)] (Entry 14 [73]); and $Pd(dppf)Cl_2•CH_2Cl_2$ [1,1′-Bis(diphenylphosphino)ferrocene] dichloro-palladium(II)] (Entries 18 [74], 27 [27], 28 [28], 65 [67]).

Heat- and air-stable compound $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ [75] reacts rapidly with a wide variety of tertiary phosphines (L) to produce near-quantitative yields of the corresponding Pd(0) compounds PdL_2. This moiety is believed to be the active species in many often-used cross-coupling catalyst systems including $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $PdCl_2$, and $Pd(OAc)_2$.

Polymer-supported PS-$Pd(PPh_3)_4$ is used in Entries 11 [76], 32 [36] under MW heating.

Organophosphine ligands increase the activity and stability of the Pd catalysts reducing its loading; therefore, many different forms were reported (Fig. 3): *DavePhos* (Suzuki, Entry 8 [69]; Buchwald, Entry 36 [77]); *SPhos* (Entries 13 [42], 55 [62], 64 [66]); *XPhos* (Buchwald: Entry 37 [78]); *Xantphos* (Buchwald: Entry 38 [79]); *dppf* (direct CH activation: Entry 42 [56]; palladium-catalyzed aminocarbonylation, Entry 47 [48]); *BINA*P (Buchwald: Entry 52 [49]); and *dimethoxy-triphenylphosphine* (Heck: Entry 53 [40]).

Inorganic salts are generally applied as bases in the Suzuki reaction to facilitate transmetallation [80] – CsF, KF, Cs, Na and K carbonates, bicarbonates, phosphates and hydroxides – while TEA is often used as an acid scavenging base (e.g., Entry 32 [36]). In the Sonogashira reaction, copper salts are typically used to activate the alkyne partner beside the Pd catalyst (CuI, e.g., in Entry 39 [25]).

Cross-coupling reactions often require high reaction temperature. Microwave-assisted rate acceleration is used in Entries 8 [69], 11 [76], 12 [37], 18 [74], 19 [81], 20 [82], 23 [83], 27 [27], 28 [28], 31 [44], and 55 [62] for Suzuki–Miyaura

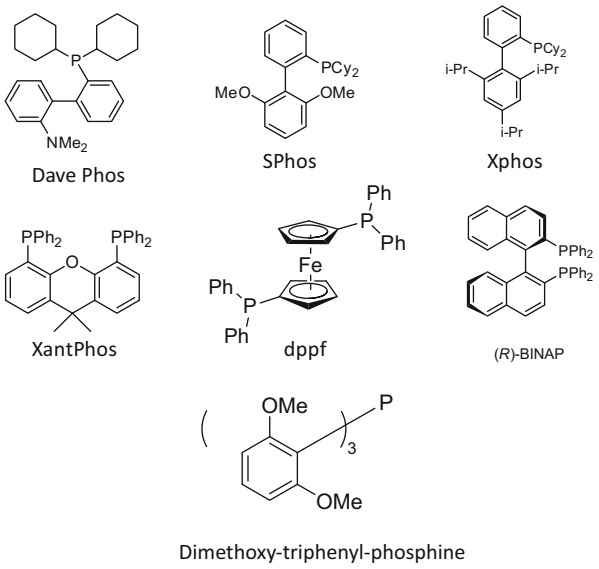


Fig. 3 Organophosphine ligands

couplings, in Entry 33 [45] for Heck couplings, and in Entry 38 [79] for Buchwald–Hartwig couplings.

Nevertheless, the choice of solvent is an important factor in transition metal-catalyzed cross-couplings. While as an exception, the Suzuki reaction tolerates water as the reaction medium, other cross-coupling reactions often require the rigorous exclusion of even moisture. Typical reaction media for palladium-catalyzed coupling reactions are toluene, THF, dioxane, and DMF, although unique transformations can be run under solvent-free conditions.

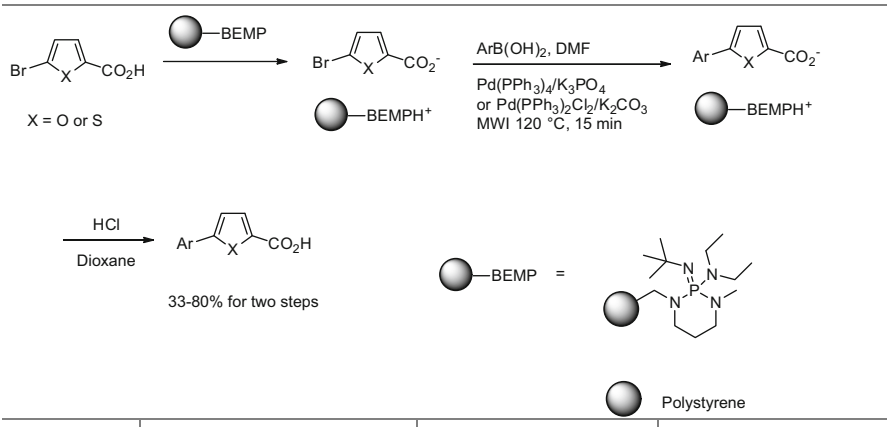
3 Reaction Summaries

3.1 Suzuki Coupling

3.1.1 Solid-Phase Synthesis

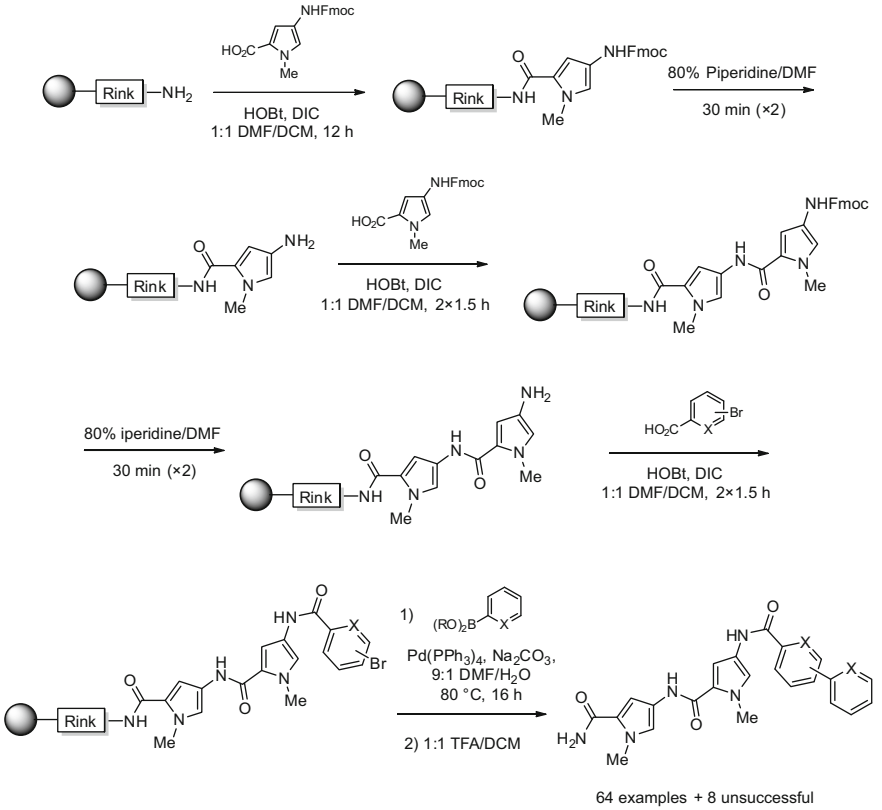
One-Ring Systems

Entry 1



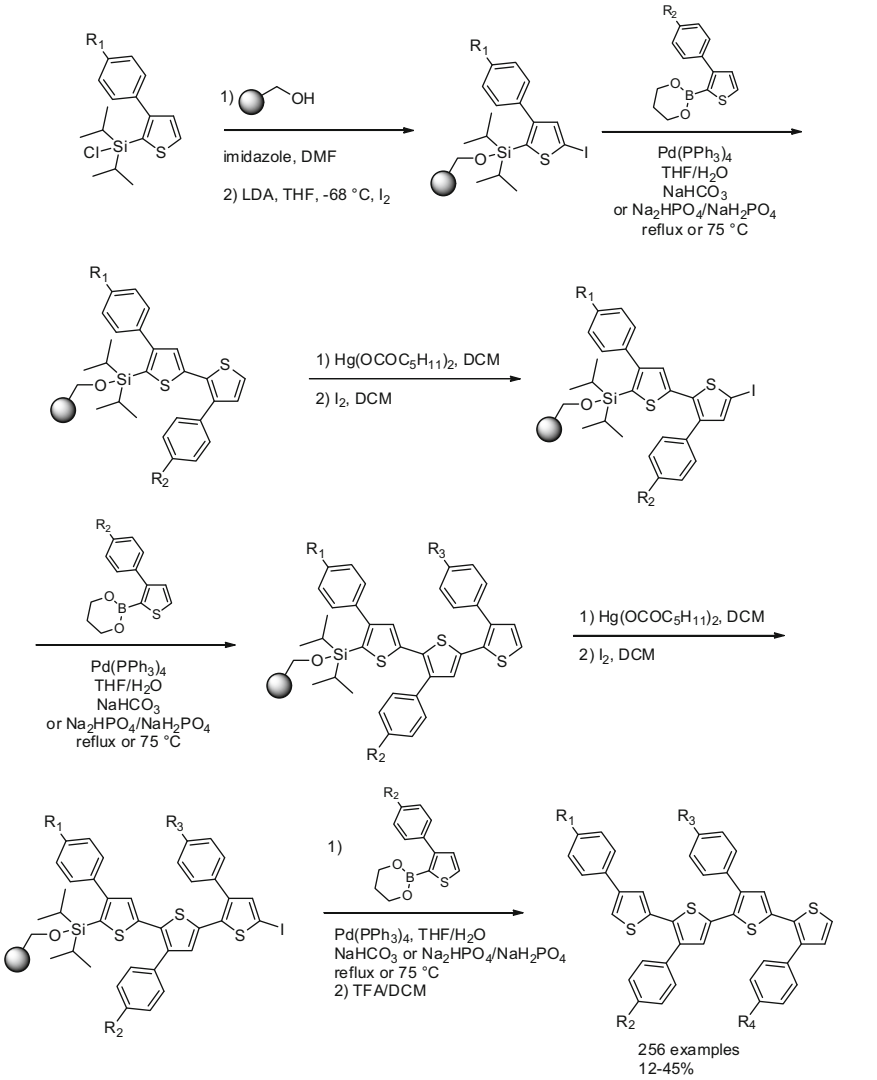
Core: Furan, thiophene	Library size: 33 examples (2×19, 6 unsuccessful)	Key step: scaffold synthesis and decoration	Method: solid phase – ionic immobilization
Yields: 33–80%	Biology: methionine aminopeptidase inhibitors	Comments:	[20]

Entry 2



Core: distamycin analogs	Library size: 72 examples	Key step: scaffold decoration (last step)	Method: solid phase – Rink Amide Linker (RAM) SynPhase lantern
Yields: n/d	Biology: n/d	Comments:	[21]

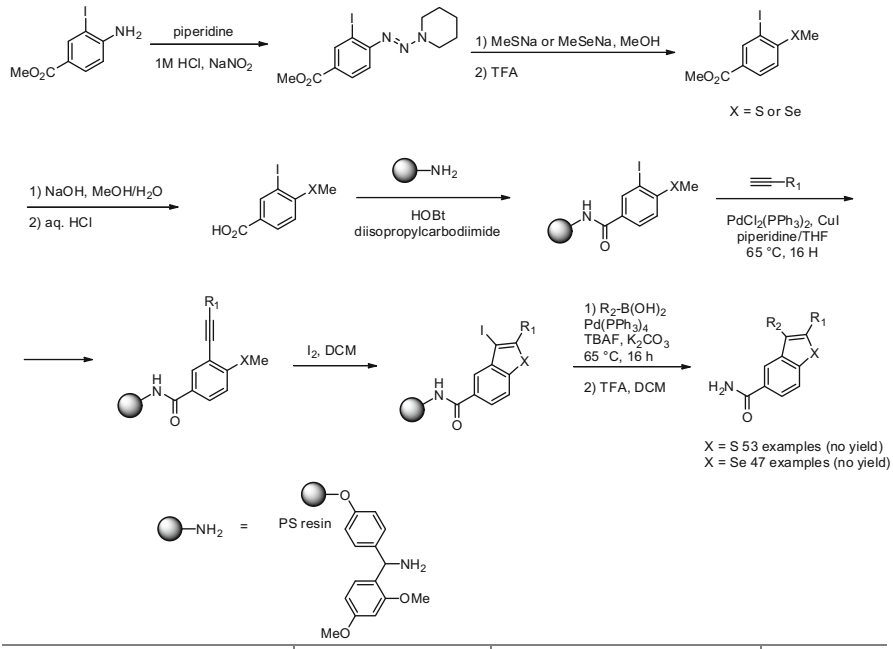
Entry 3



Core: quarter (3-arylthiophene)	Library size: 256 examples	Key step: scaffold decoration (last step)	Method: solid phase
Yields: 12–45%	Biology: n/d	Comments: sequential Suzuki coupling, organic electron transport materials	[22]

Two-Ring Systems

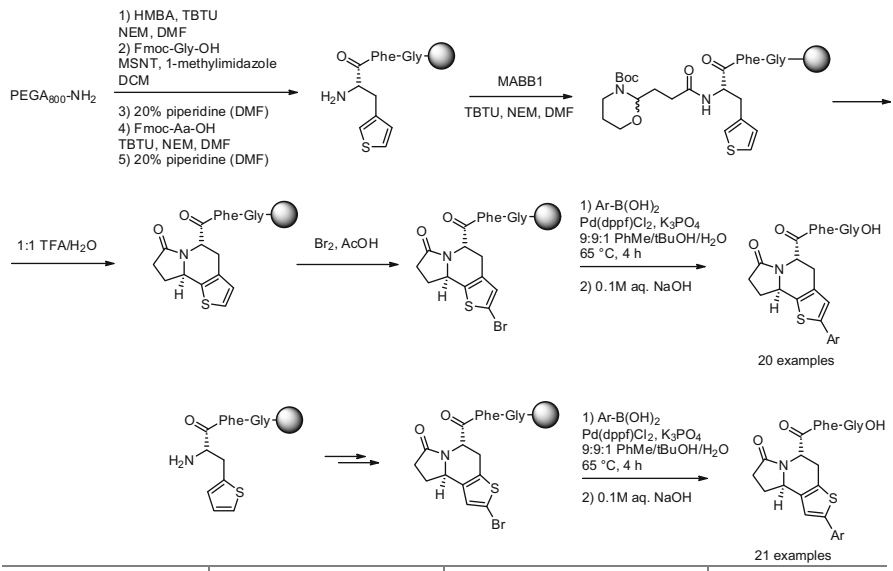
Entry 4



Core: benzo[*b*]thiophene, benzo[*b*]selenophene	Library size: 53 + 47 examples	Key step: scaffold synthesis and decoration	Method: solid phase
Yields: n/d	Biology: n/d	Comments:	[23]

Three-Ring Systems

Entry 5

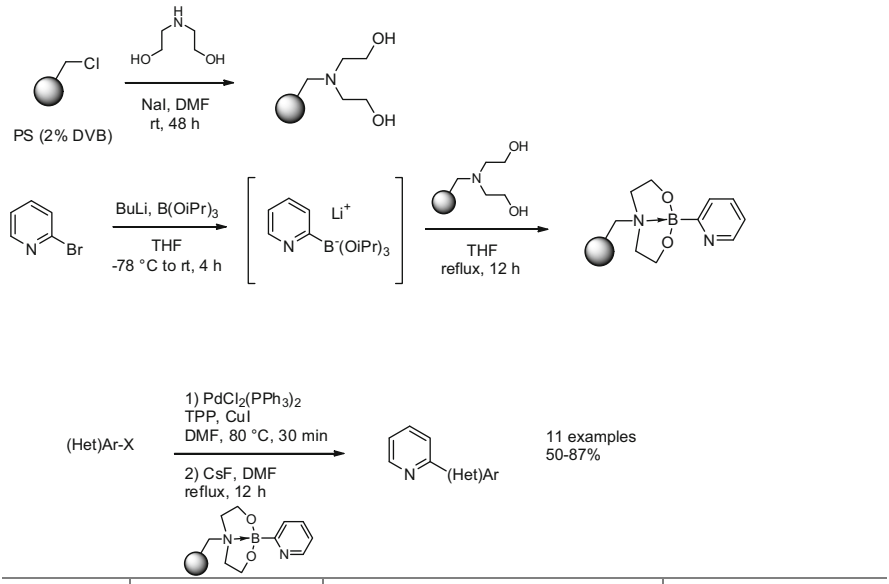


Core: thienoindolizine	Library size: 41 examples	Key step: scaffold decoration	Method: solid phase
Yields: n/d	Biology: n/d	Comments:	[24]

3.1.2 Solution Phase

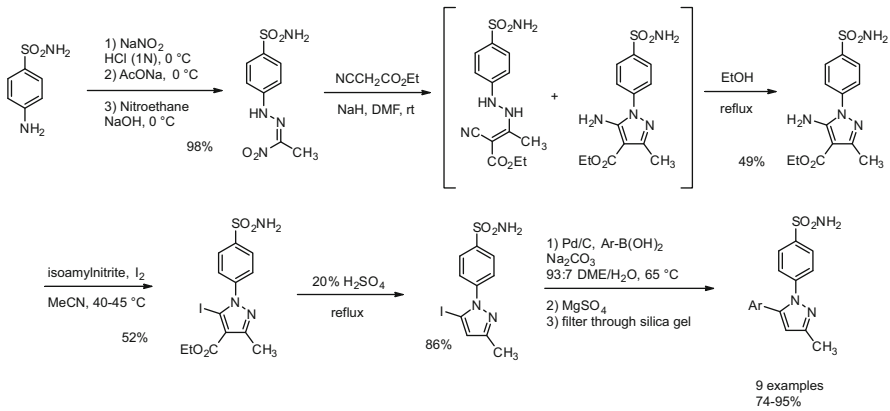
One-Ring Systems

Entry 6



Core: pyridine	Library size: 11 examples	Key step: scaffold decoration	Method: solid-supported reagent
Yields: 50–87%	Biology: n/d	Comments: methodology for 2-pyridylboronates	[70]

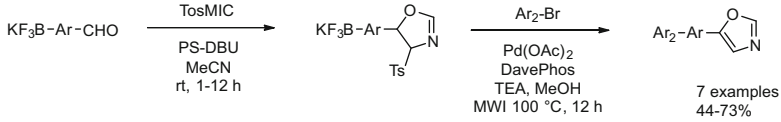
Entry 7



(continued)

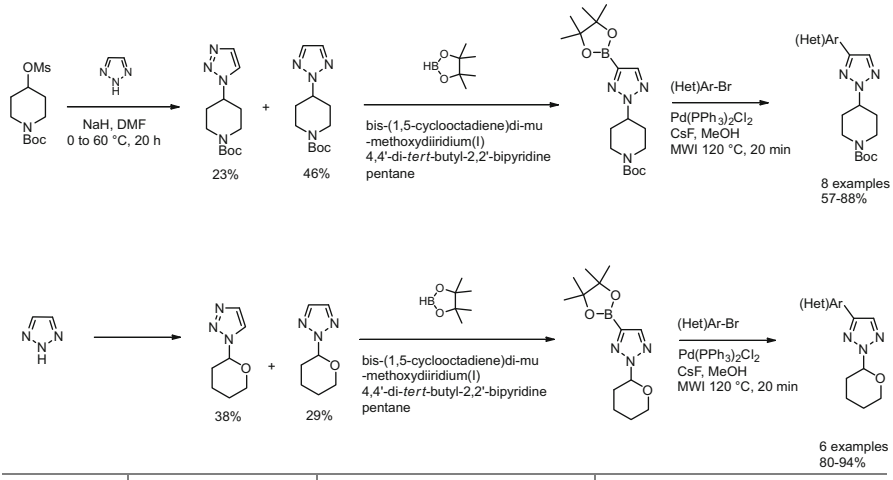
Core: pyrazole	Library size: 9 examples	Key step: scaffold decoration	Method: solution phase
Yields: 74–95%	Biology: COX-2 inhibitor	Comments:	[84]

Entry 8



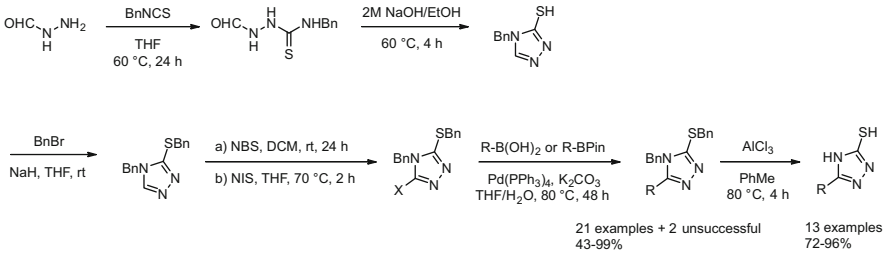
Core: oxazole	Library size: 7 examples	Key step: scaffold decoration	Method: solution phase
Yields: 44–73%	Biology: n/d	Comments:	[69]

Entry 9



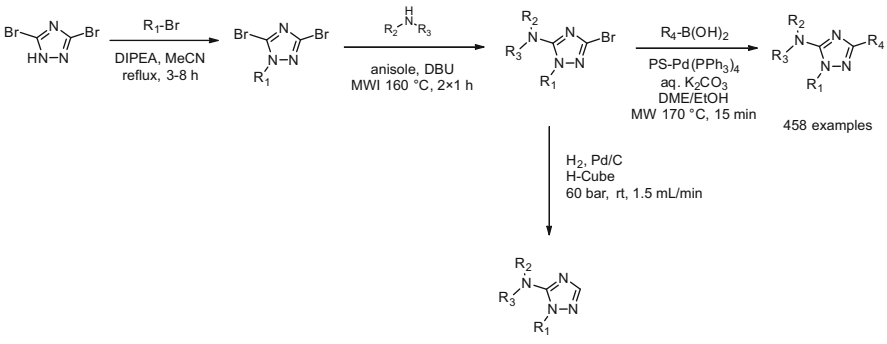
Core: triazole	Library size: 14 examples	Key step: scaffold decoration (last step)	Method: solution phase – reversed strategy!
Yields: 57–94%	Biology: n/d	Comments:	[52]

Entry 10



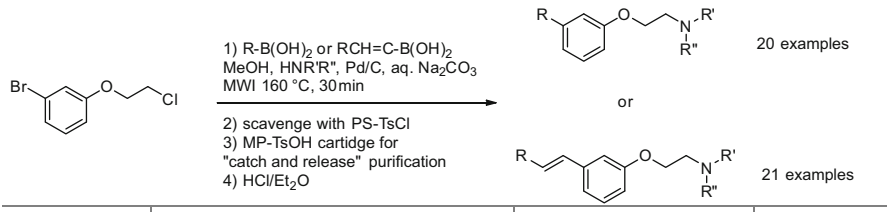
Core: triazole	Library size: 23 + 13	Key step: scaffold decoration (last step)	Method: solution phase
Yields: 43–99%, 72–96%	Biology: n/d	Comments:	[68]

Entry 11



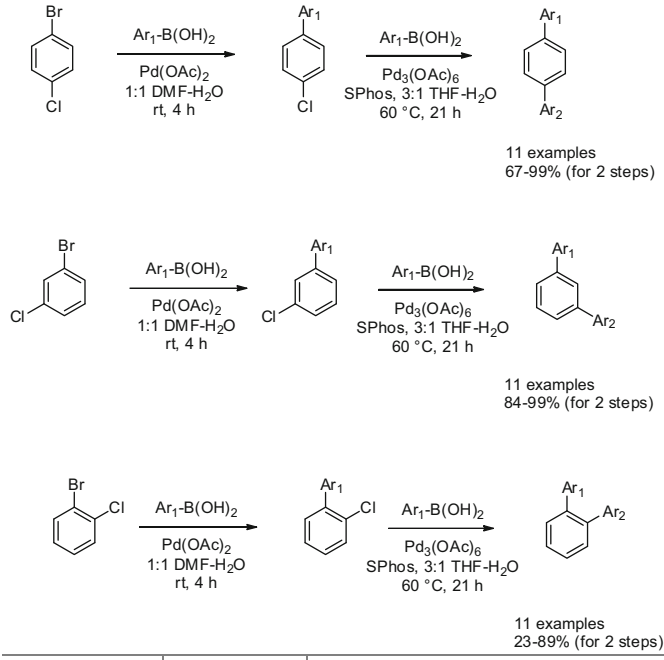
Core: triazole	Library size: 458 + 192 examples	Key step: scaffold decoration	Method: solution phase with solid-supported catalyst
Yields: n/d	Biology: n/d	Comments: flow hydrogenation	[76]

Entry 12



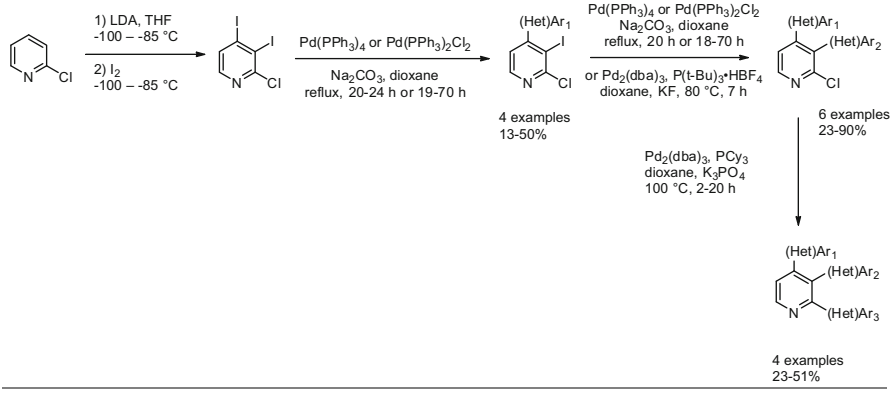
Core: biaryl and styrene	Library size: 41 examples	Key step: scaffold decoration	Method: solution phase
Yields: n/d	Biology: acetylcholine receptor agonists and antagonists nAChR	Comments: scavengers, catch and release	[37]

Entry 13



Core: *o-*,*m-*, *and* *p*-terphenyls	Library size: 33 examples	Key step: scaffold decoration (last step)	Method: solid phase
Yields: 23–99%	Biology: n/d	Comments: potential photochemical properties used in organic electroluminescent (OEL) devices	[42]

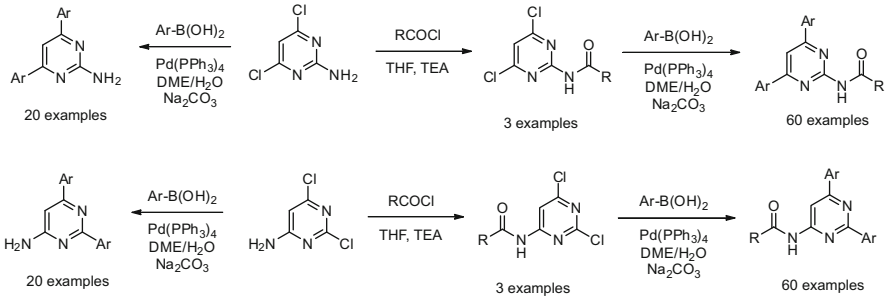
Entry 14



(continued)

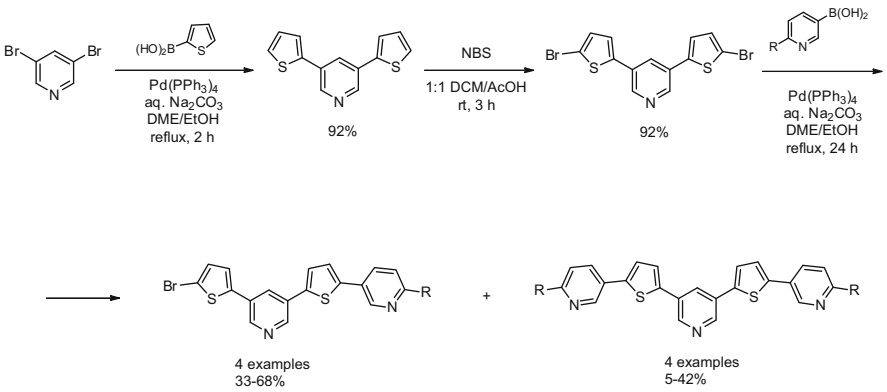
Core: Pyridine	Library size: 14 examples	Key step: scaffold decoration	Method: solution phase
Yields: 13–90%	Biology: n/d	Comments: sequential diarylation	[73]

Entry 15



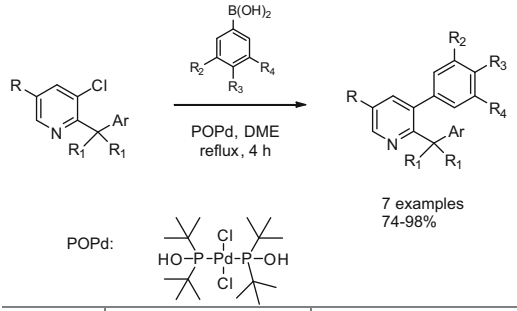
Core: pyrimidine	Library size: 160 examples	Key step: scaffold decoration	Method: solution phase
Yields: 59–94%	Biology: A3 adenosine receptor antagonist	Comments:	[57]

Entry 16



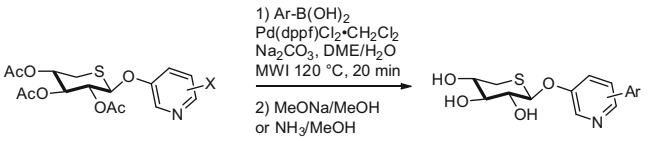
Core: thienylpyridyl garlands	Library size: 8 examples	Key step: scaffold decoration	Method: solution phase
Yields: 5–68%	Biology: non-peptidic alpha helix mimetics with potential PPI inhibitors	Comments: mono- and bisarylation	[41]

Entry 17



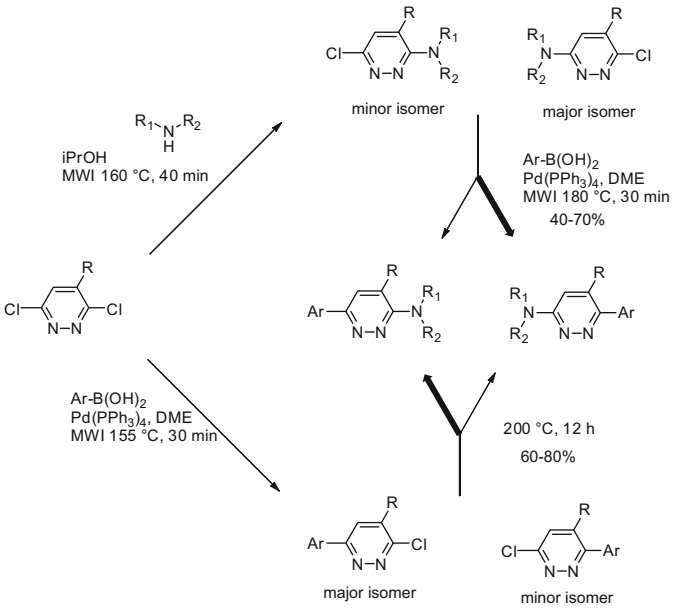
Core: pyridine	Library size: 7 examples	Key step: scaffold decoration	Method: solution phase
Yields: 74–98%	Biology: potential COX-2 inhibitors	Comments: methodology for sterically hindered pyridyl halides/air-stable catalyst POPd	[72]

Entry 18



Core: 5-thio-xylopyranoside	Library size: 23 examples	Key step: scaffold decoration	Method: solution phase
Yields: 28–92%	Biology: antithrombotic effect	Comments:	[74]

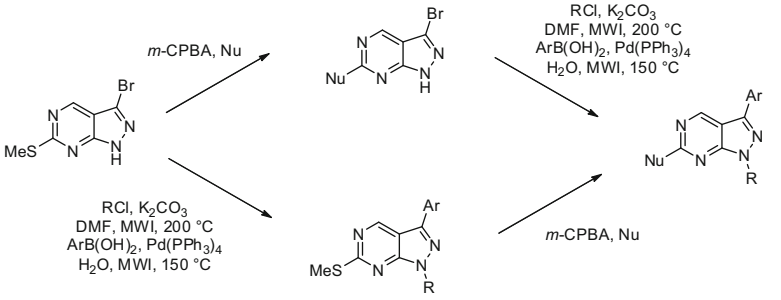
Entry 19



Core: pyridazine	Library size: two sublibraries as mixtures – $4 \times 5 \times 3 = 60$	Key step: scaffold decoration	Method: solution phase
Yields: 40–70%, 60–80%	Biology: n/d	Comments: sequential amination and Suzuki coupling (mixture synthesis)	[81]

Two-Ring Systems

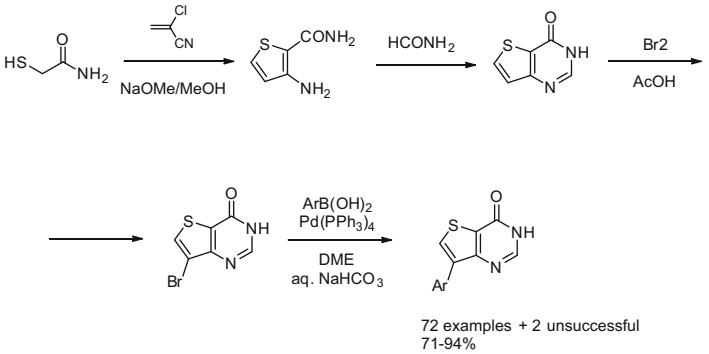
Entry 20



(continued)

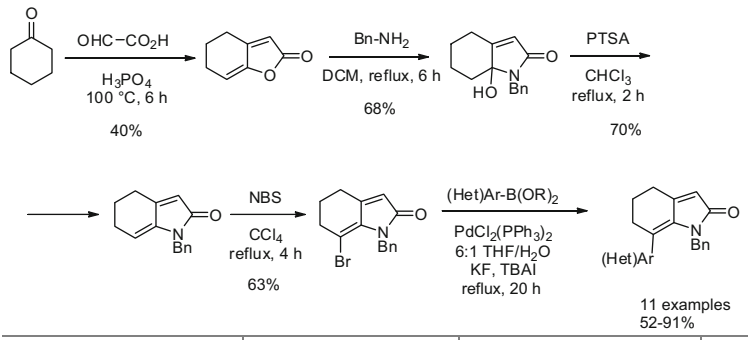
Core: pyrazolopyrimidine	Library size: 29 examples	Key step: scaffold synthesis in three steps – 14 upper route + 15 lower route	Method: solution phase
Yields: 51–93%, (60–86%)	Biology: n/d	Comments:	[82]

Entry 21



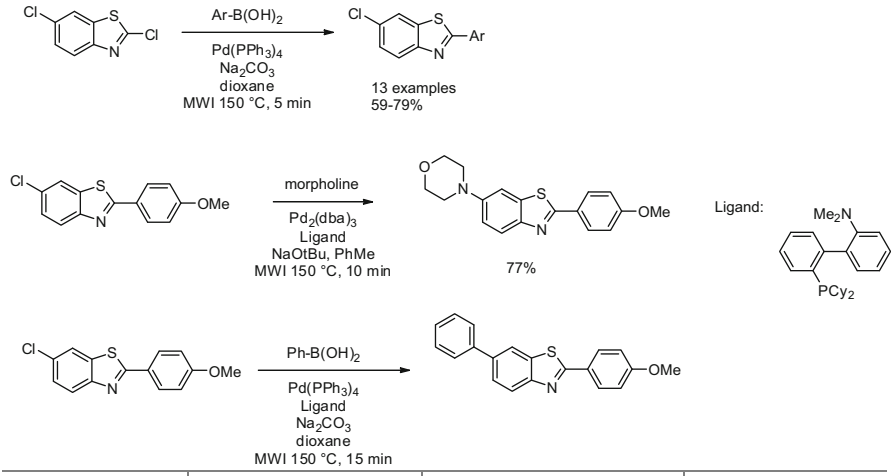
Core: thienopyrimidine	Library size: 72 examples + 2 unsuccessful	Key step: scaffold decoration (last step)	Method: solution phase
Yields: 71–94%	Biology: n/d	Comments:	[85]

Entry 22



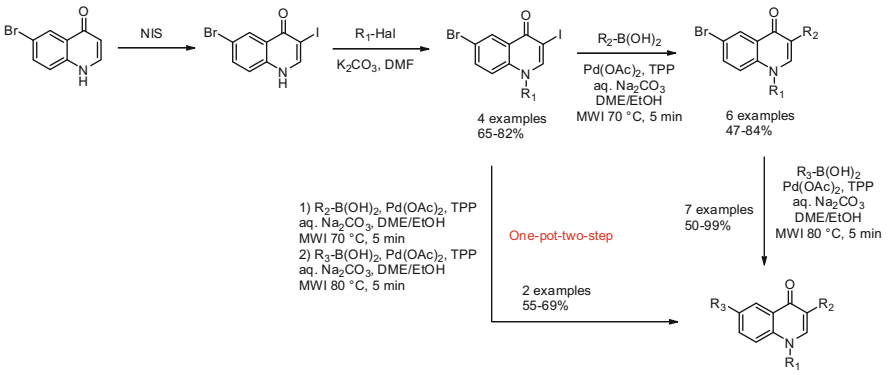
Core: 5,6-dihydroindol-2-one	Library size: 11 examples	Key step: scaffold decoration	Method: solution phase
Yields: 52–91%	Biology: n/d	Comments:	[35]

Entry 23



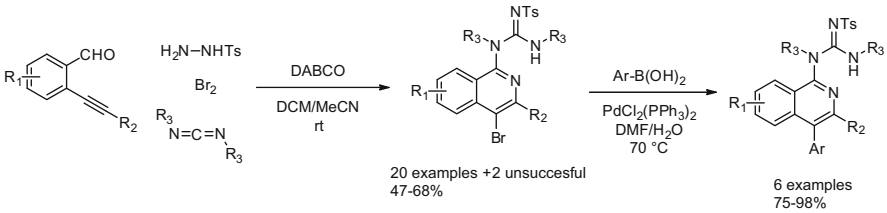
Core: benzothiazole	Library size: 13 examples	Key step: scaffold decoration	Method: solution phase
Yields: 59–79%	Biology: n/d	Comments:	[83]

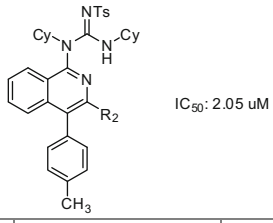
Entry 24



Core: quinolinone	Library size: 13 examples	Key step: scaffold decoration	Method solution phase
Yields: 47–99%	Biology: n/d	Comments: One-pot sequential double scaffold decoration	[39]

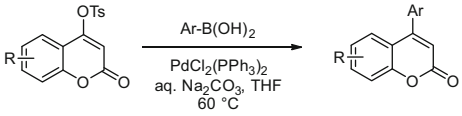
Entry 25





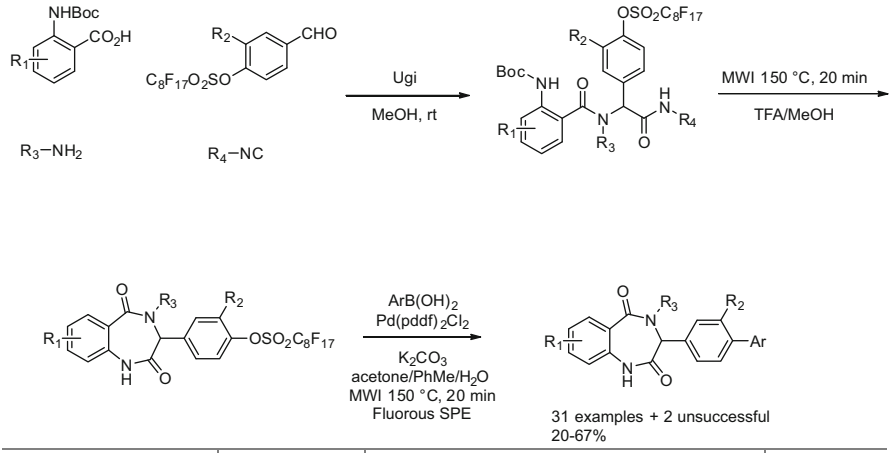
Core: isoquinoline	Library size: 6 examples	Key step: scaffold decoration	Method: solution phase
Yields: 75–98%	Biology: protein tyrosine phosphatase 1B (PTP1B)	Comments:	[86]

Entry 26



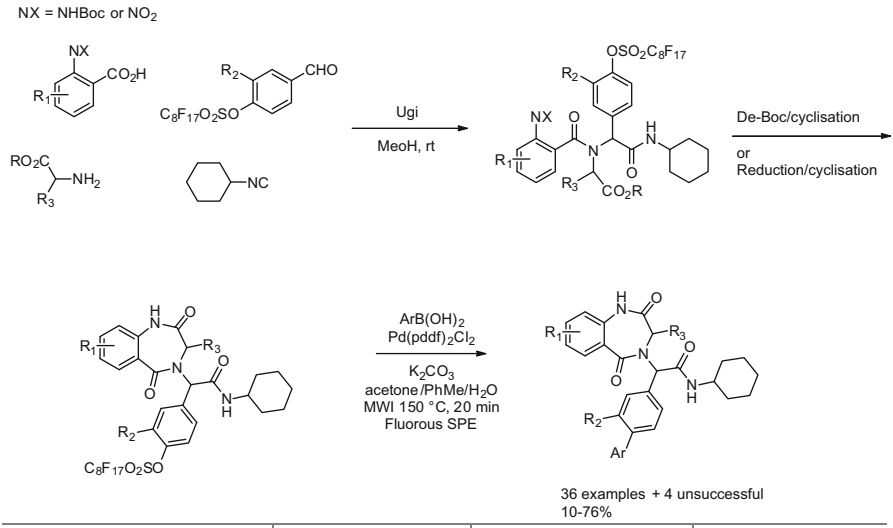
Core: cumarine	Library size: 11 examples	Key step: scaffold decoration	Method: solution phase
Yields: 51–91%	Biology: n/d	Comments:	[43]

Entry 27



Core: benzodiazepinedione	Library size: 31 examples	Key step: scaffold decoration	Method: fluorous synthesis
Yields: 20–67%	Biology: n/d	Comments: cyclohexyl and methyl 2-isocyanoacetate as convertible isonitriles	[27]

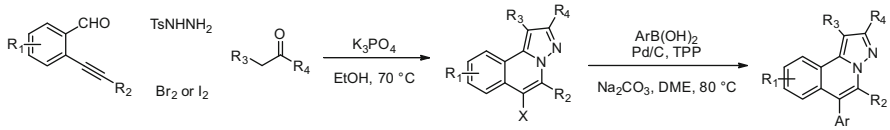
Entry 28



Core: benzodiazepinedione 2	Library size: 36 examples	Key step: scaffold decoration	Method: fluorous synthesis
Yields: 10–76% (generally 20–40%)	Biology: n/d	Comments:	[28]

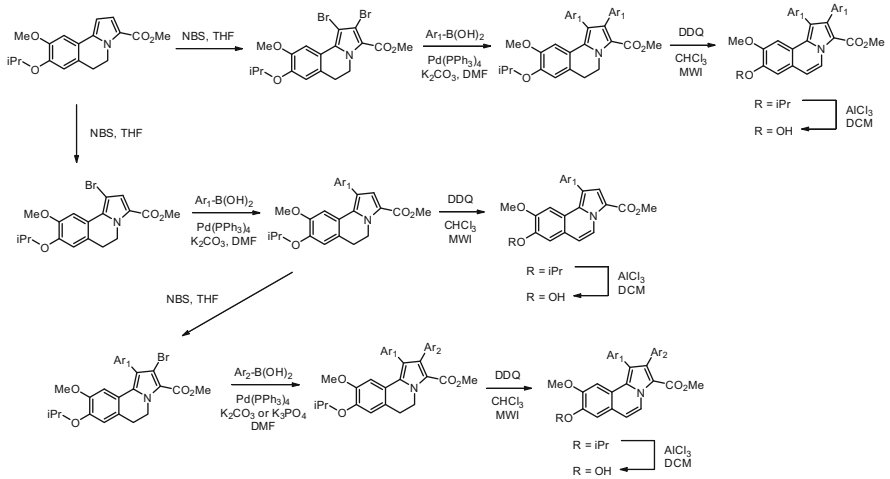
Three-Ring Systems

Entry 29



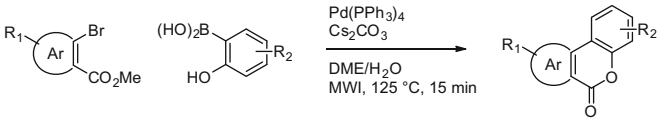
Core: pyrazole-isoquinoline	Library size: 7 examples	Key step: scaffold decoration	Method: solution phase
Yields: 76–99%	Biology: n/d	Comments:	[87]

Entry 30



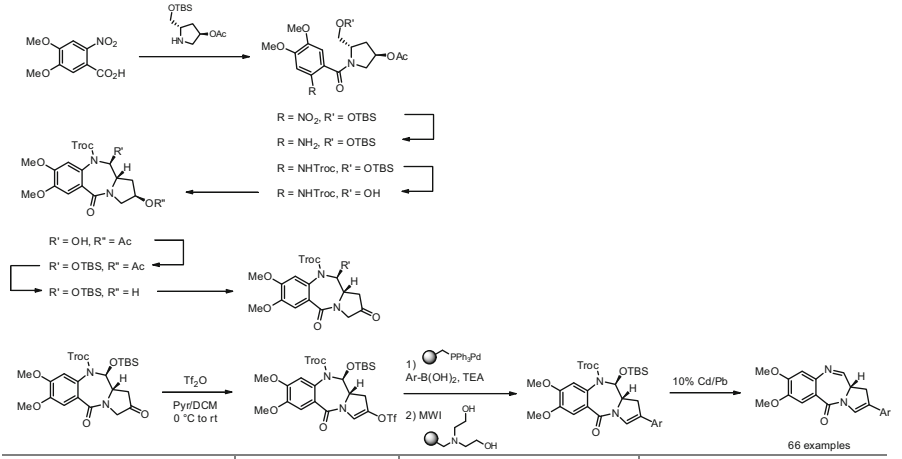
Core: pyrroloisoquinoline	Library size: 45 examples; 9 sublibraries	Key step: scaffold decoration	Method: solution phase
Yields: n/d	Biology: cytotoxicity data given	Comments: double and sequential scaffold decorations, Lamellarin D analogs	[38]

Entry 31



Core: dibenzopyranones	Library size: 32 examples	Key step: scaffold synthesis	Method: solution phase
Yields: 68–98%	Biology: n/d	Comments:	[44]

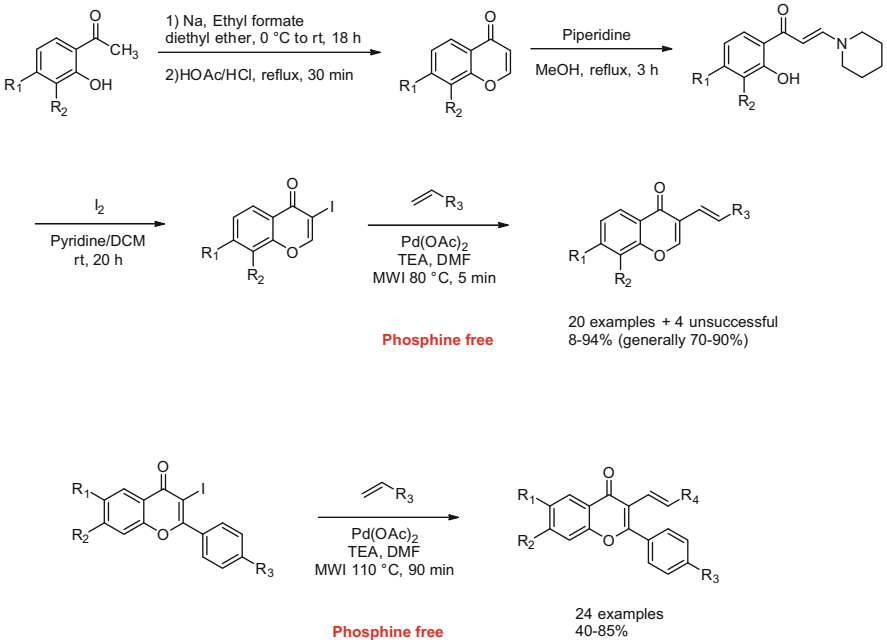
Entry 32



Core: pyrrolobenzodiazepine	Library size: 66 examples	Key step: scaffold decoration (last step)	Method: solution phase, solid-supported Pd
Yields: 4–57%	Biology: n/d	Comments:	[36]

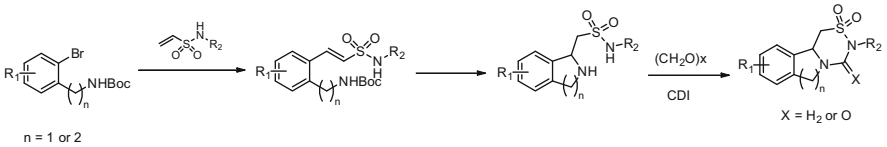
3.2 Heck Reaction

Entry 33



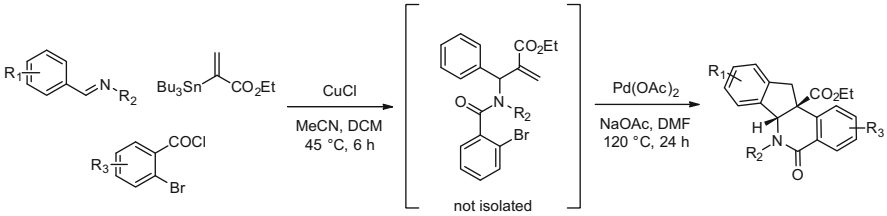
Core: chromanone, flavone	Library size: 24 + 24 examples	Key step: scaffold decoration	Method: solution phase
Yields: 8–94%, 40–85%	Biology: n/d	Comments: phosphine-free Heck	[45]

Entry 34



Core: tetrahydroisoquinoline and dihydroisoindoline containing tricyclic sultams	Library size: 120 members (40 + 40 + 40)	Key step: scaffold synthesis	Method: solution phase
Yields: 50–99%, 53–99%, 35–99%, 22–88%	Biology: n/d	Comments:	[65]

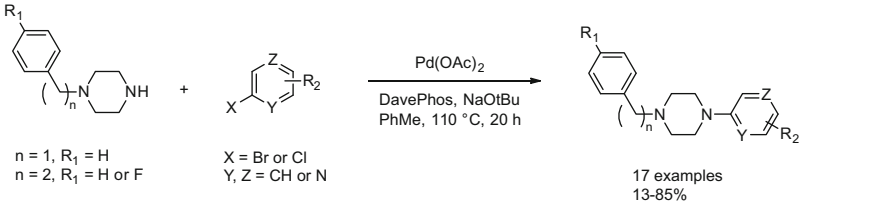
Entry 35



Core: dihydroindenoisoquinoline	Library size: 111 members	Key step: scaffold synthesis	Method: solution phase
Yields: 6–71% for two steps (generally 20–30%)	Biology: n/d	Comments: multicomponent or tandem scaffold synthesis (Heck, and tin-induced ring closure)	[54]

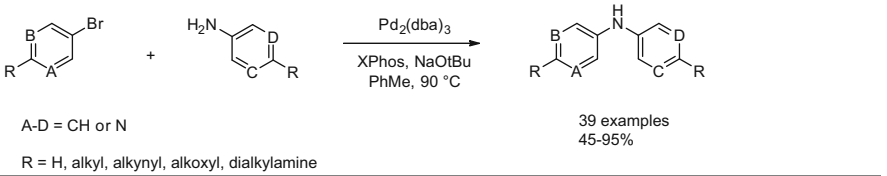
3.3 Buchwald–Hartwig Amination

Entry 36



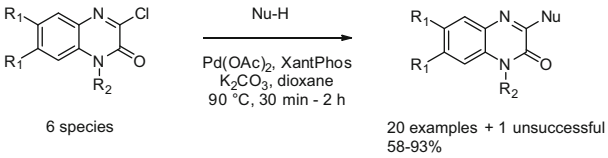
Core: piperazine	Library size: 17 examples	Key step: scaffold decoration	Method: solution phase
Yields: 13–85%	Biology: potential 5-HT2a	Comments: Ligand = DavePhos	[77]

Entry 37



Core: bis-(het) arylamine	Library size: 39 examples	Key step: scaffold decoration (last step)	Method: solution phase
Yields: 45–95%	Biology: n/d	Comments: in situ generated Pd catalyst $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$	[78]

Entry 38

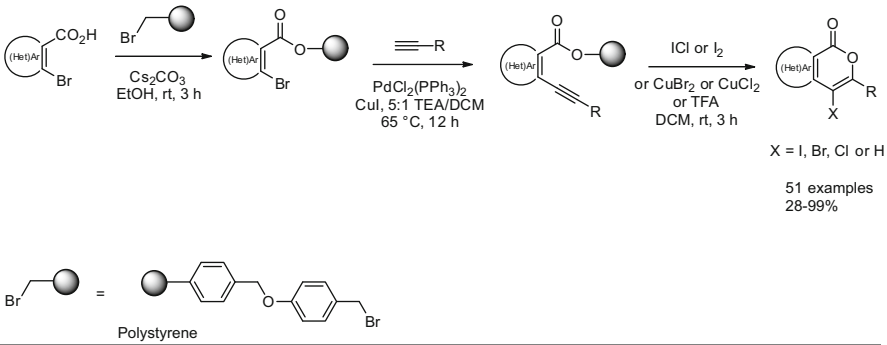


Nu-H: amides, lactames, carbamates, weak amine nucleophiles

Core: quinoxalinone	Library size: 21 examples	Key step: scaffold decoration	Method: solution phase
Yields: 58–93%	Biology: cannabinoid CB2 receptor agonist	Comments:	[79]

3.4 Sonogashira Reaction

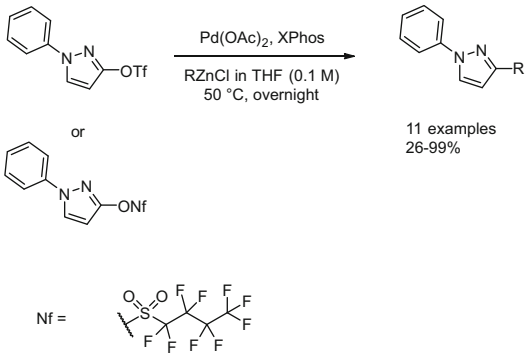
Entry 39



Core: isocoumarines and heterocyclic derivatives	Library size: 51 examples	Key step: scaffold synthesis	Method: solid phase
Yields: 28–99%	Biology: n/d	Comments:	[25]

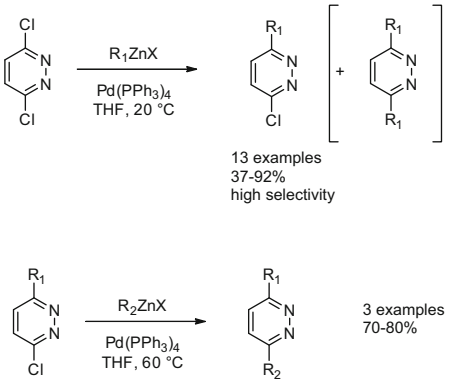
3.5 Negishi Coupling

Entry 40



Core: pyrazole	Library size: 11 examples	Key step: scaffold decoration suitable for library synthesis	Method: fluorous synthesis
Yields: 26–99%	Biology: n/d	Comments: fluorous tag was used as a leaving group	[29]

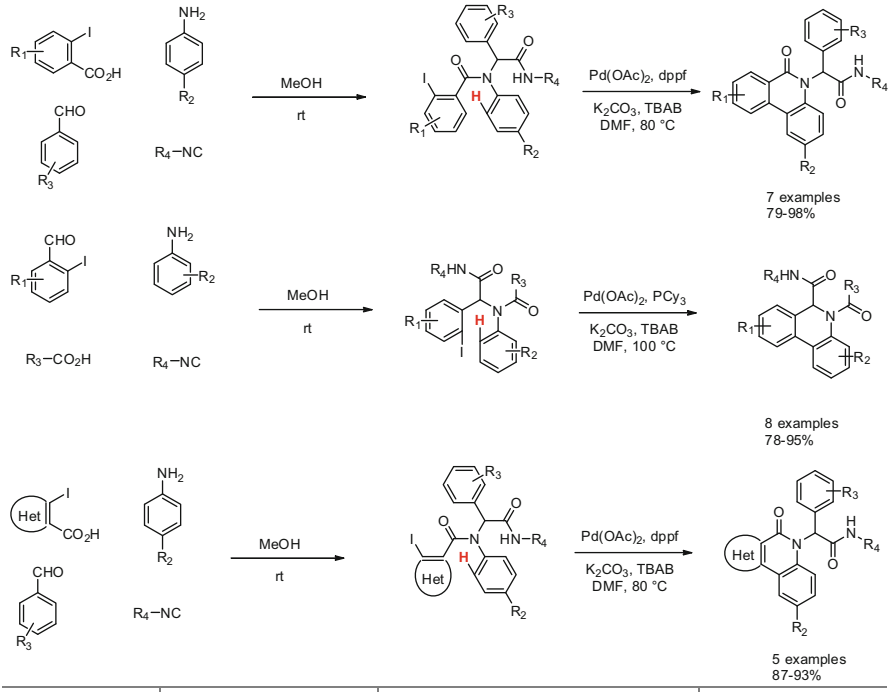
Entry 41



Core: pyridazine	Library size: 13 examples	Key step: scaffold synthesis suitable for library synthesis	Method: solid phase
Yields: 37–92%	Biology: n/d	Comments:	[55]

3.6 Direct CH Activation

Entry 42

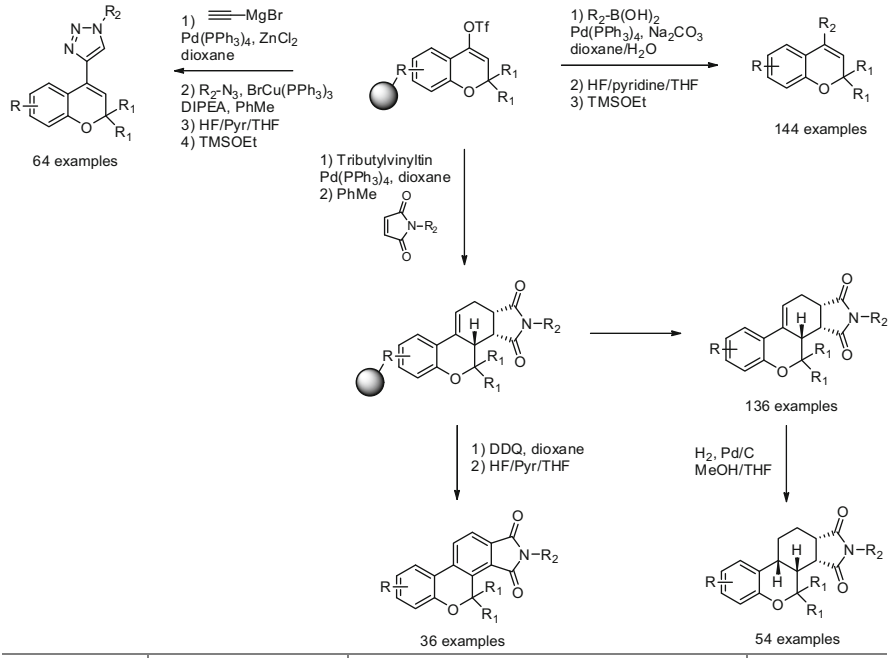


Core: quinolinone	Library size: 20 examples	Key step: scaffold decoration (last step)	Method: solution phase
Yields: 78–98%	Biology: n/d	Comments: Direct CH activation	[56]

3.7 *Multiple Cross-Couplings*

3.7.1 Solid Phase

Entry 43

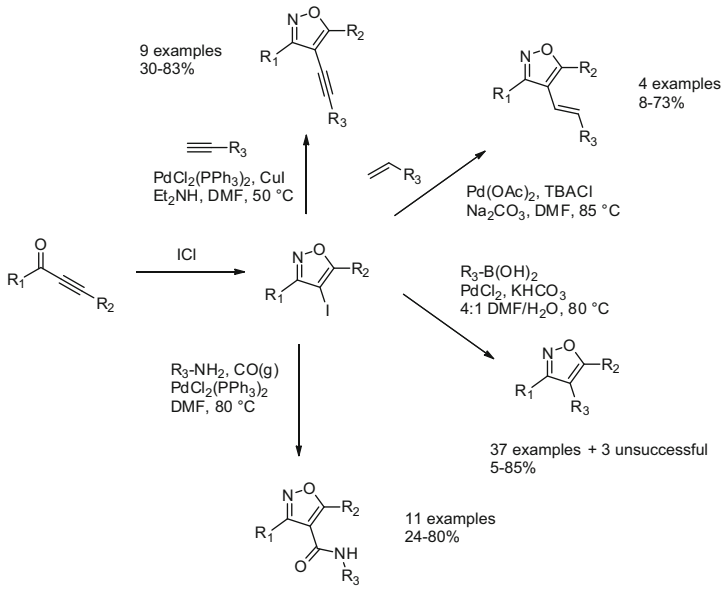


Core: benzopyrane	Library size: 424 examples	Key step: scaffold decoration	Method: solid phase
Yields: n/d	Biology: n/d	Comments: multiple cross-coupling Suzuki, Stille, Negishi	[26]

3.7.2 Solution Phase

One-Ring Systems

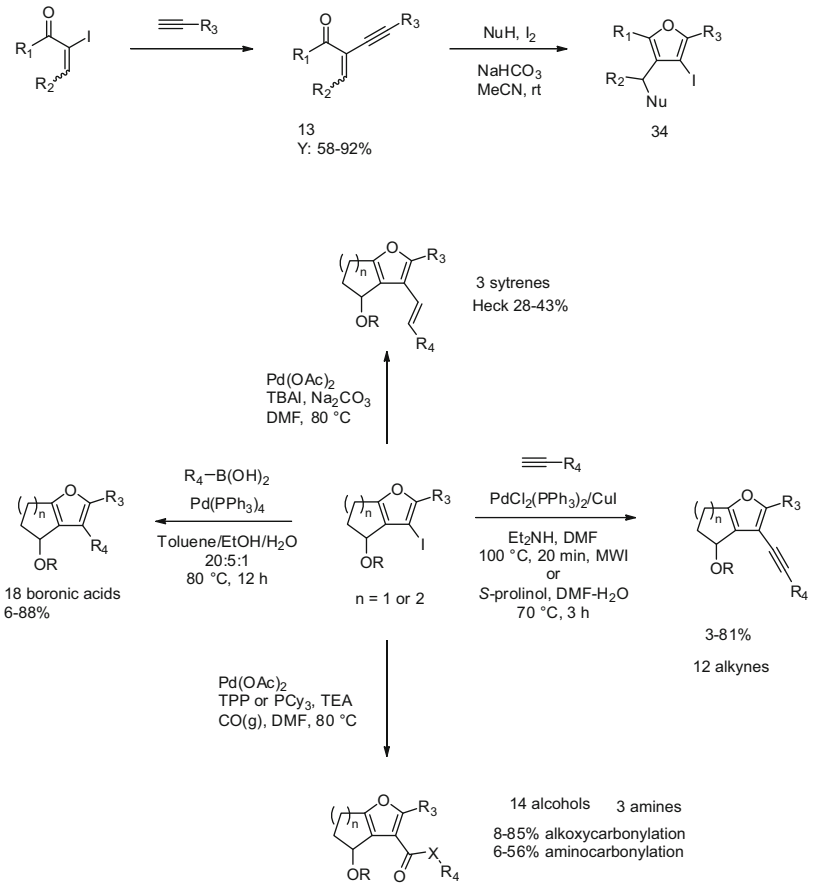
Entry 44



Core: isoxazole	Library size: 64 examples	Key step: scaffold decoration	Method: solution phase
Yields: 8–85%	Biology: n/d	Comments: multiple cross-coupling Suzuki, Sonogashira, Heck, Pd-catalyzed aminocarbonylation	[58]

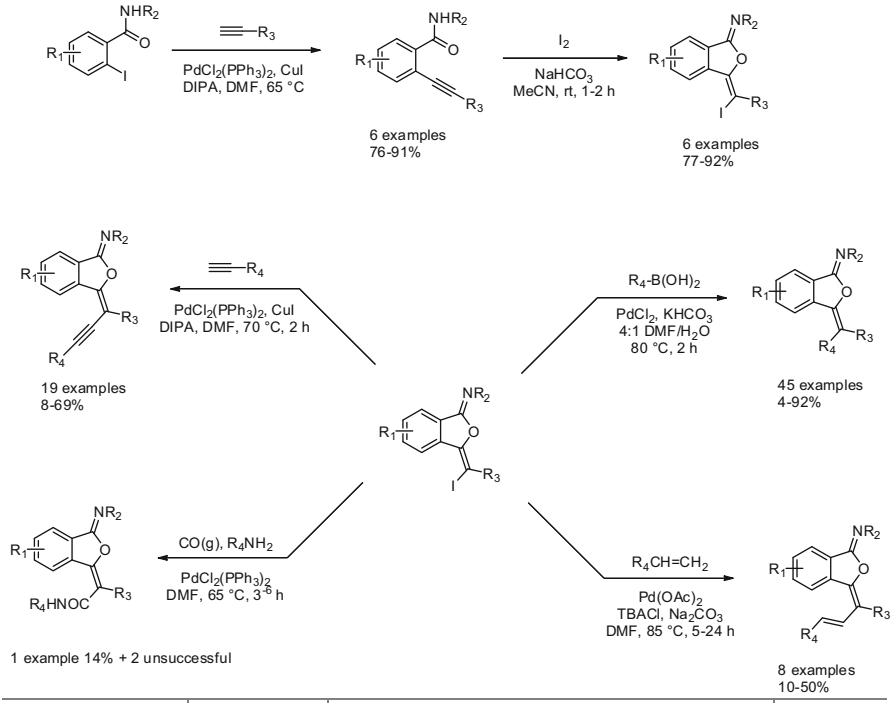
Two-Ring Systems

Entry 45



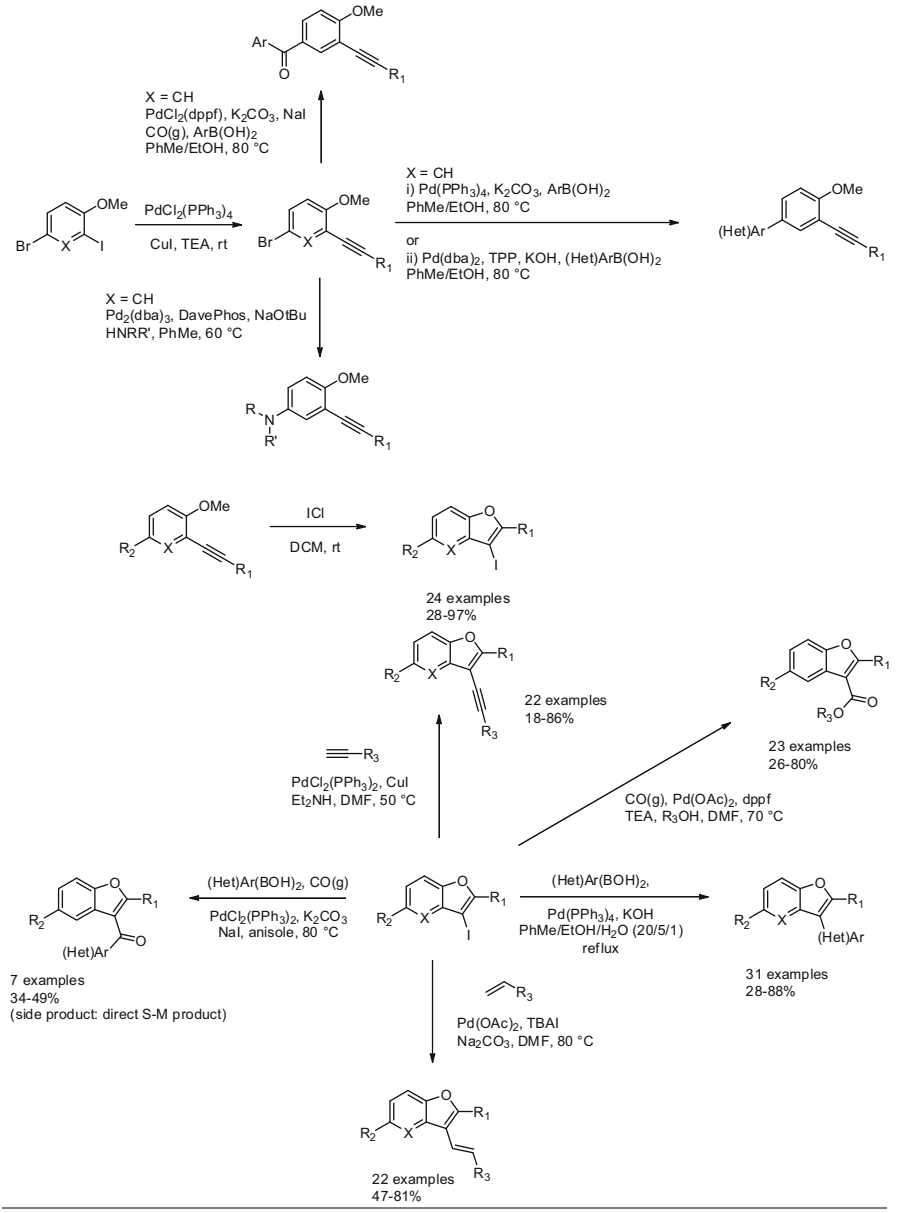
Core: furane	Library size: 163 examples, 46 (Suzuki) +53 (Sonogashira) +3 (Heck) +6 (amides) +55 (esters)	Key step: scaffold decoration	Method: solution phase
Yields: 6–88%	Biology: n/d	Comments: multiple type cross-couplings Suzuki, Sonogashira, Heck	[46]

Entry 46



Core: cyclic imidate, isobenzofurane	Library size: 75 examples	Key step: scaffold decoration	Method: solution phase
Yields: 4–92%	Biology: n/d	Comments: multiple type cross-couplings Suzuki, Sonogashira, Heck, Pd-amino carbonylation	[47]

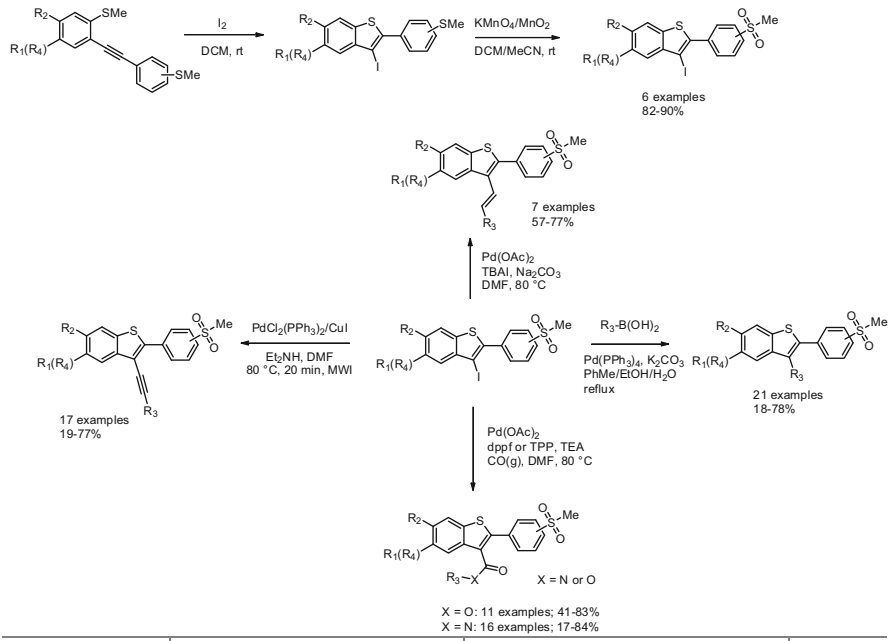
Entry 47



(continued)

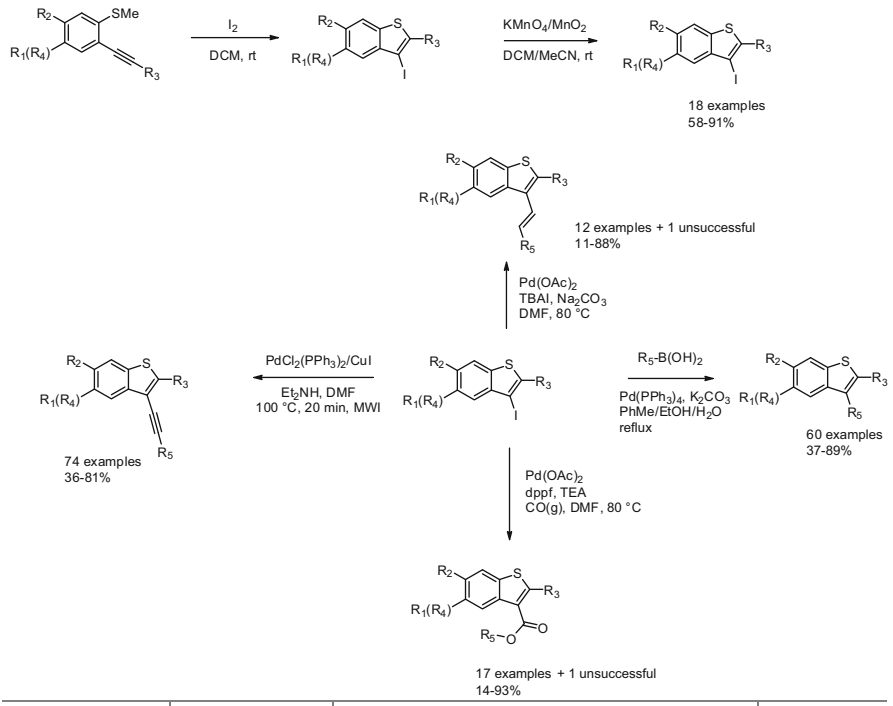
Core: benzofurane	Library size: 121 examples	Key step: scaffold synthesis and decoration	Method: solution phase
Yields: 18–88%	Biology: n/d	Comments: scaffold synthesis (Sonogashira); multiple cross-coupling Suzuki, Suzuki carbonylation., Sonogashira, Heck, Pd-catalyzed alkoxycarbonylation	[48]

Entry 48



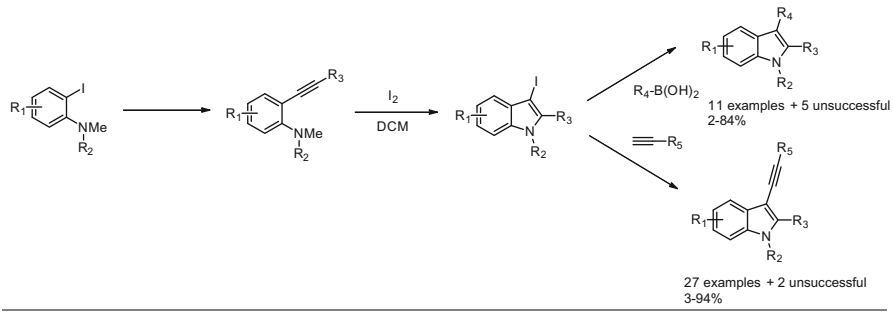
Core: benzothiophene	Library size: 72 examples – 21 (Suzuki) + 17 (Sonogashira) + 7 (Heck) + 11 (alkoxycarbonylation) + 16 (aminocarbonylation)	Key step: scaffold decoration	Method: solution phase
Yields: n/d	Biology: n/d	Comments: multiple cross-coupling Suzuki, Sonogashira, Heck, Pd-cat. amino- and alkoxycarbonylation	[50]

Entry 49



Core: benzothiophene	Library size: 165 examples	Key step: scaffold decoration	Method: solution phase
Yields: n/d	Biology: n/d	Comments: multiple cross-coupling Suzuki, Sonogashira, Heck, Pd-catalyzed alkoxycarbonylation	[51]

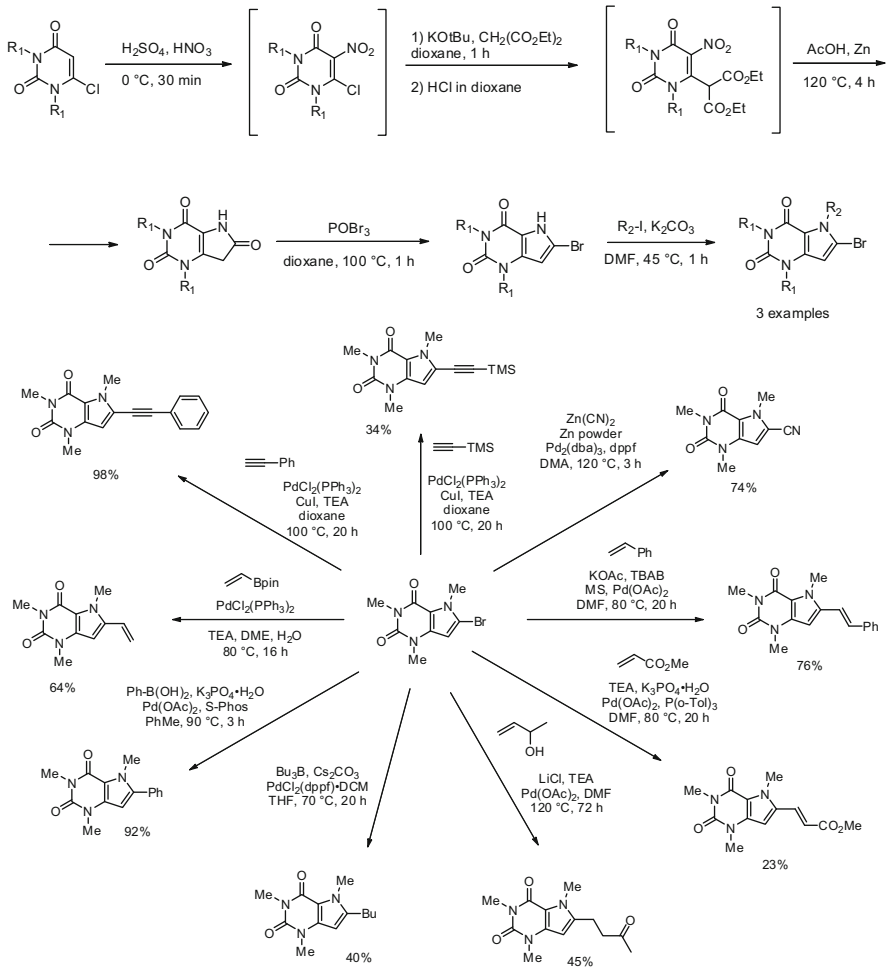
Entry 50



(continued)

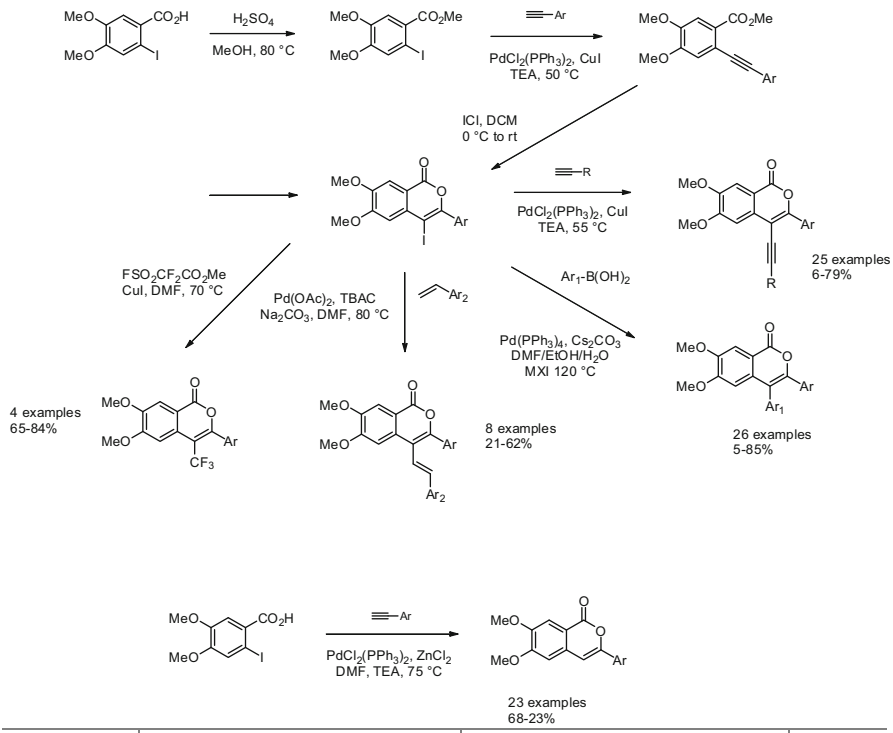
Core: indole	Library size: 38 examples (11 Suzuki + 27 Sonogashira)	Key step: scaffold synthesis and decoration	Method: solution phase – few solid-phase examples also discussed
Yields: 2–84%, 3–94%	Biology: n/d	Comments: multiple cross-coupling Suzuki, Sonogashira	[59]

Entry 51



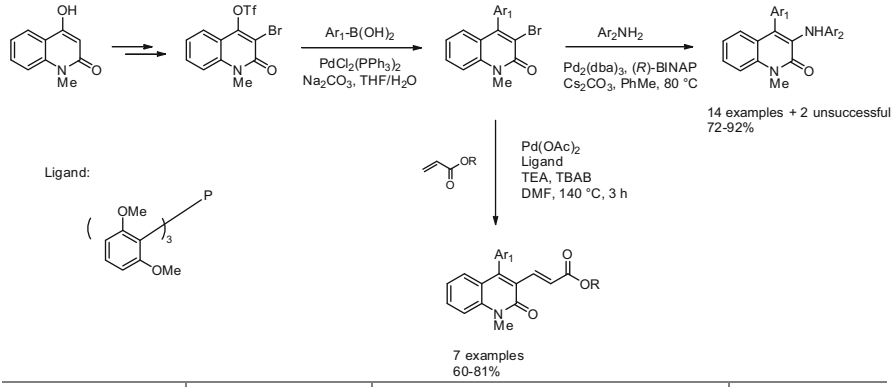
Core: 9-deazaxanthine	Library size: 9 examples	Key step: scaffold decoration	Method: solution phase
Yields: 23–98%	Biology: n/d	Comments: multiple cross-coupling Suzuki, Sonogashira, Heck, etc.	[60]

Entry 52



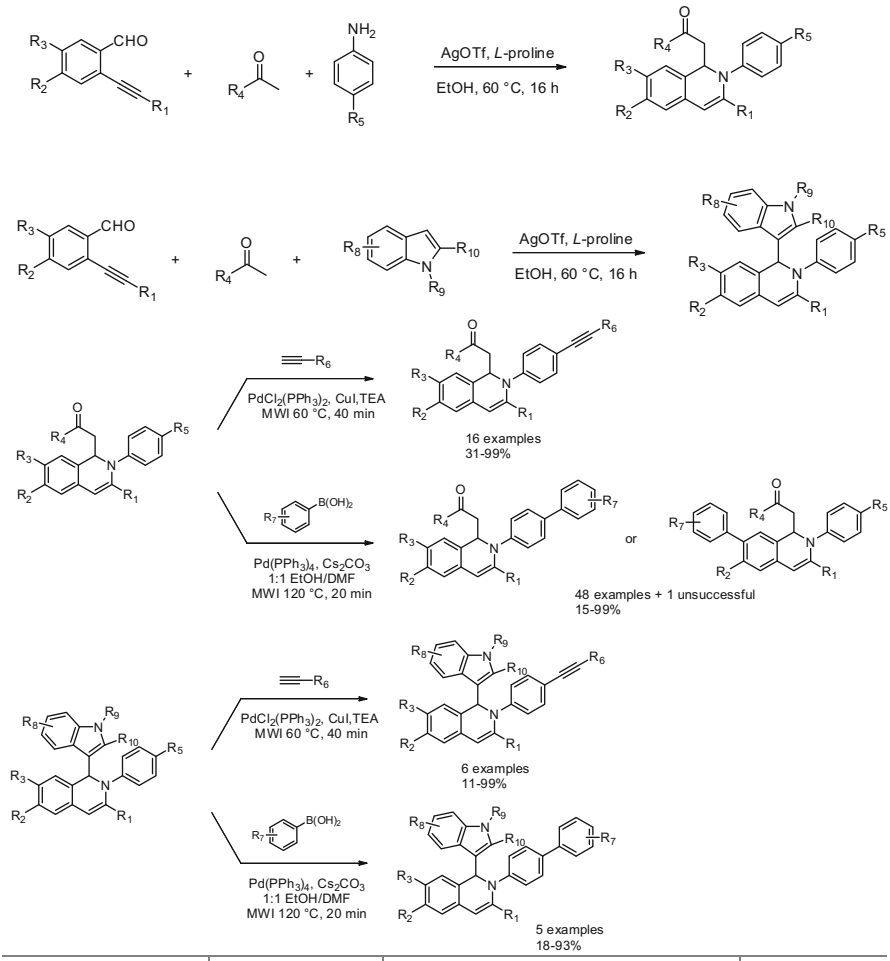
Core: isocoumarin	Library size: 82 examples – 26 (Suzuki) + 25 (Sonogashira) + 8 (Heck) + 23 (isocoumarin)	Key step: scaffold synthesis and decoration	Method: solution phase
Yields: n/d	Biology: n/d	Comments: scaffold synthesis (Sonogashira); multiple coupling Suzuki, Sonogashira, Heck	[49]

Entry 53



Core: quinoline	Library size: 23 examples	Key step: sequential double scaffold decoration	Method: solution phase
Yields: 60–81%, 72–92%	Biology: n/d	Comments: multiple cross-coupling Buchwald, Heck	[40]

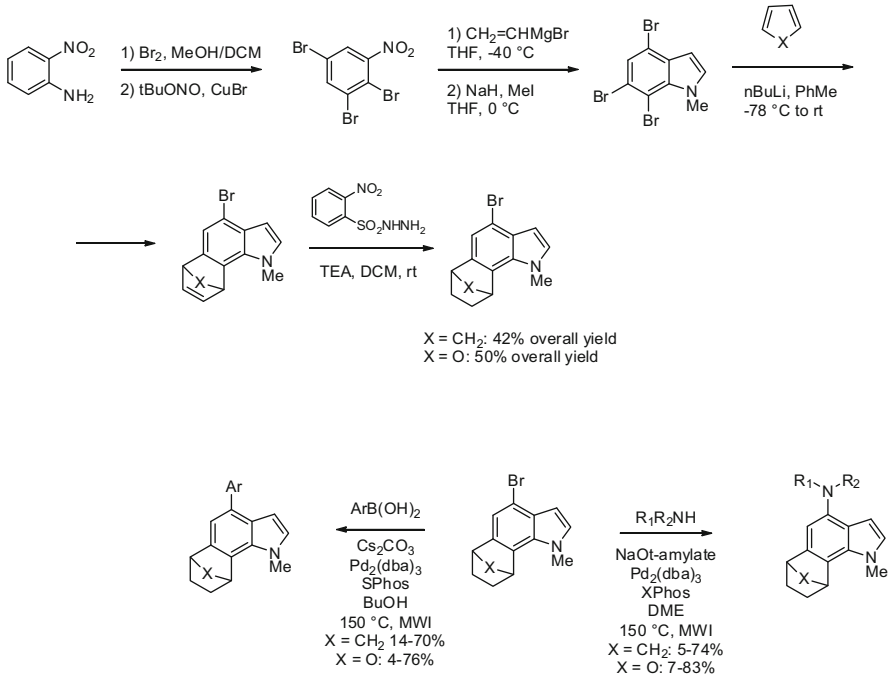
Entry 54



Core: dihydroisoquinoline	Library size: 75 examples	Key step: scaffold decoration	Method: solution phase
Yields: 11–99%	Biology: n/d	Comments: multiple cross-coupling: Suzuki, Sonogashira	[61]

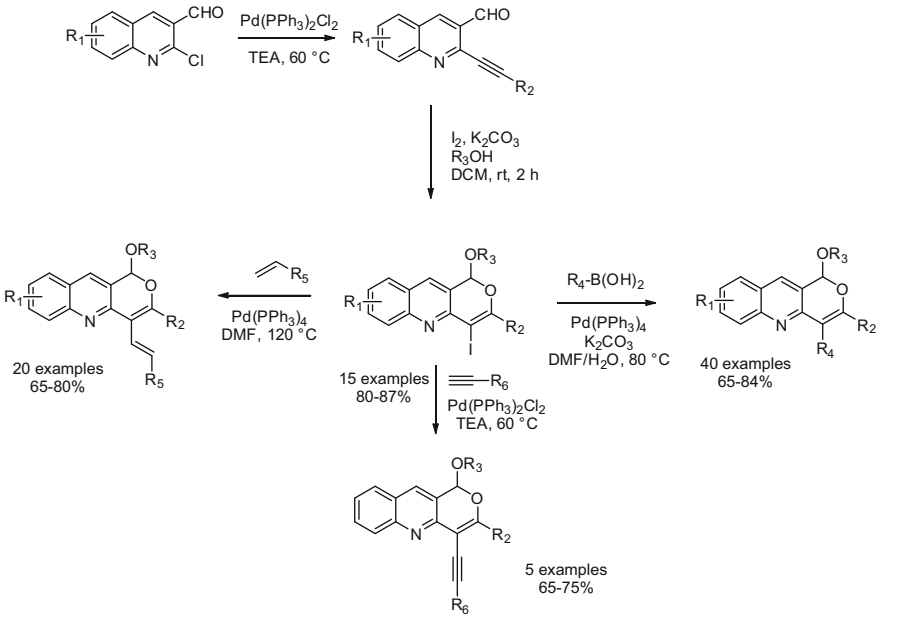
Three-Ring Systems

Entry 55



Core: indole-based NPL	Library size: 93 examples – 51 Suzuki, 42 Buchwald	Key step: scaffold decoration	Method: solution phase
Yields: 4–76%, 5–83%	Biology: n/d	Comments: multiple type cross-couplings – Suzuki, Buchwald–Hartwig	[62]

Entry 56

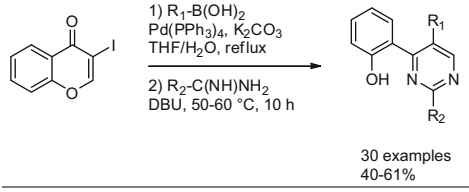


Core: pyranoquinolines	Library size: 65 examples – 40 Suzuki, 20 Heck, 5 Sonogashira	Key step: scaffold synthesis and decoration	Method: solution phase
Yields: 65–84%, 65–80%, 65–75%	Biology: n/d	Comments: scaffold synthesis (Sonogashira); multiple type cross-couplings – Suzuki, Heck, Sonogashira	[63]

3.8 Domino–Tandem Cross-Coupling Reactions

3.8.1 One-Ring Systems

Entry 57

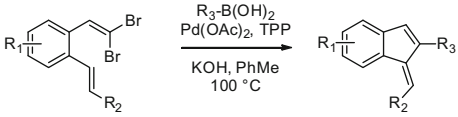


(continued)

Core: pyrimidine	Library size: 30 examples	Key step: scaffold synthesis	Method: solution phase
Yields: 40–61%	Biology: human hepatocellular carcinoma BEL-7402 cells	Comments: two-step one-pot Suzuki–cyclization	[53]

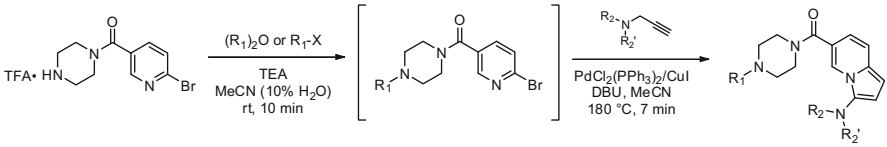
3.8.2 Two-Ring Systems

Entry 58



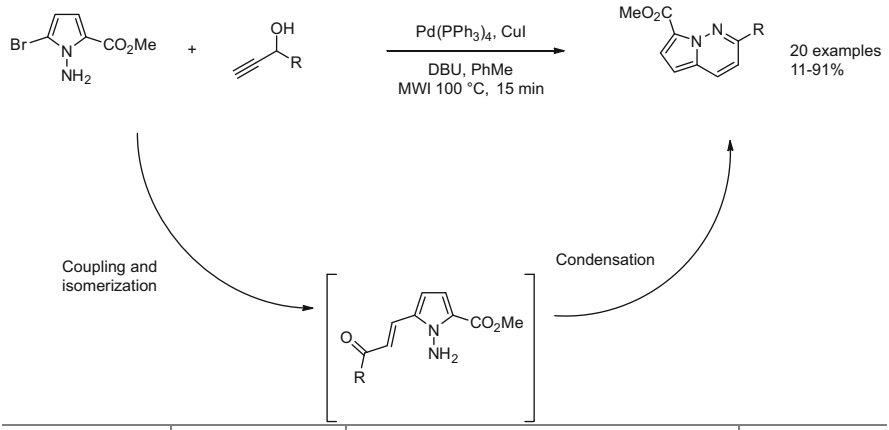
Core: indene	Library size: 20 examples	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 67–98%	Biology: n/d	Comments: tandem Suzuki–Heck	[30]

Entry 59



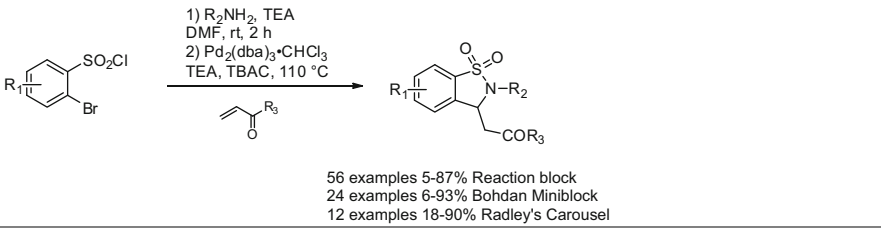
Core: Indolizine	Library size: 25 members (5 × 5)	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 28–78%	Biology: n/d	Comments: tandem Sonogashira–cycloisomerization, flow chemistry	[31]

Entry 60



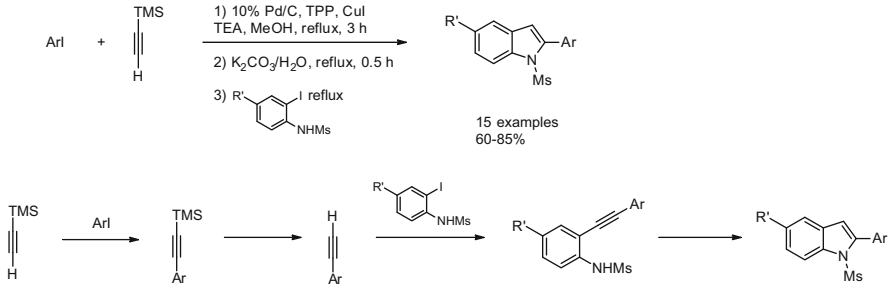
Core: pyrrolo-pyridazine	Library size: 20 examples	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 11–91%	Biology: n/d	Comments: Sonogashira coupling–isomerization–condensation	[32]

Entry 61



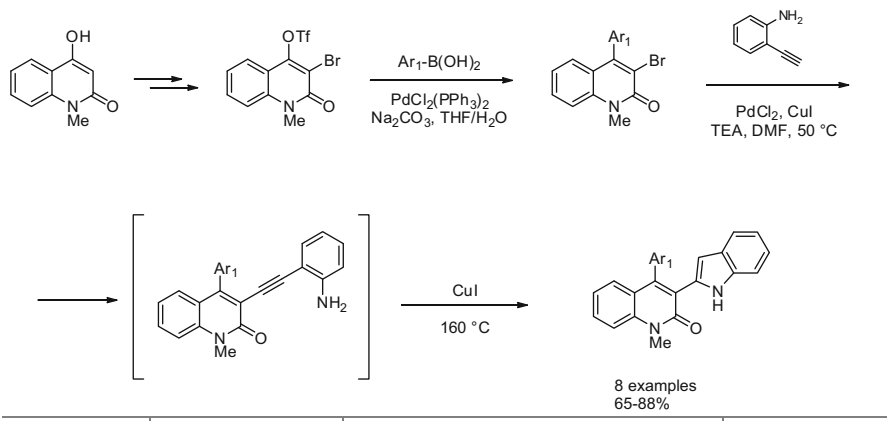
Core: sultam; 1,1-dioxido-1,2-benzisothiazoline	Library size: 92 examples	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 5–93%	Biology: n/d	Comments: tandem Heck–aza-Michael	[64]

Entry 62



Core: indole	Library size: 15 examples	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 60–85%	Biology: SIRT1	Comments: Sonogashira–desilylation–Sonogashira–cyclization	[33]

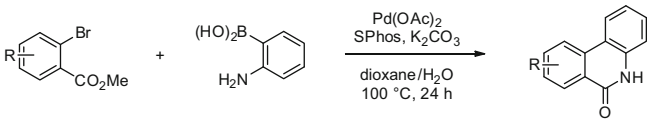
Entry 63



Core: quinolinone	Library size: 8 examples	Key step: one-pot scaffold synthesis and decoration	Method: solution phase
Yields: 65–88%	Biology: n/d	Comments: Suzuki, Sonogashira, cyclization	[34]

3.8.3 Three-Ring Systems

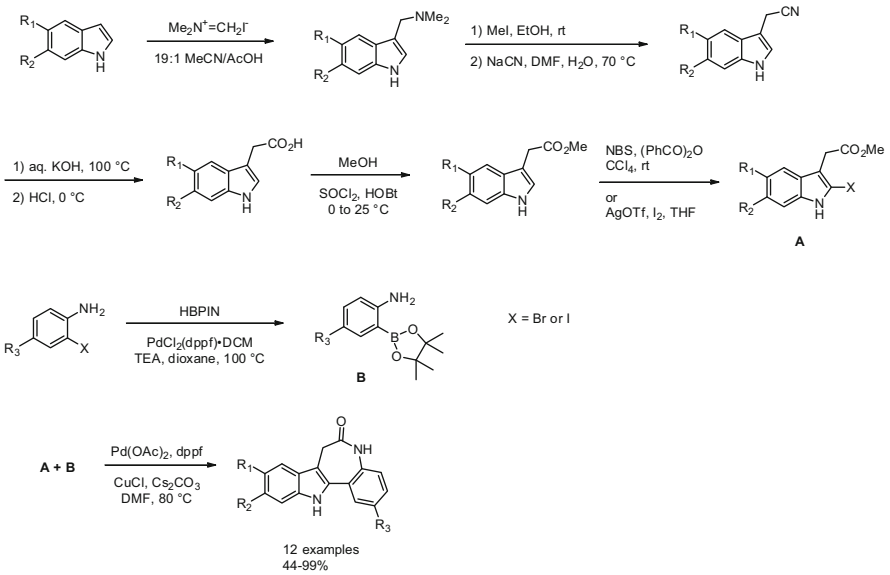
Entry 64



Core: phenanthridinone	Library size: 10 examples	Key step: one-pot scaffold synthesis and decoration	Method: solid phase
Yields: 65–96%	Biology: n/d	Comments: tandem Suzuki–cyclization	[66]

3.8.4 Four-Ring Systems

Entry 65



Core: dihydroindolo-benzazepinone (paullone)	Library size: 12 examples	Key step: one-pot scaffold synthesis, joining two diversity holding fragments	Method: solution phase
Yields: 44–99%	Biology: SIRT1 inhibitors	Comments: tandem Suzuki–intramolecular amide formation	[67]

Conclusion

In the last decade cross-coupling reactions became a standard laboratory technique in library synthesis. In the meantime biphenyl frameworks (including heteroaromatic ring systems) have extensively been reported in many biologically active products and have been considered as a privileged motif in medicinal chemistry [88]; thus, the importance of the cross-coupling reactions was further justified.

While there are some examples for solid-phase synthesis, mostly solution phase parallel synthesis is employed including the application of solid-supported reagents and fluorous two-phase reactions. Suzuki–Miyaura coupling is the most widely used C–C coupling reaction, while Sonogashira reaction is favorably used in scaffold synthesis followed by ring closure involving alkynes. Apart from the Suzuki and Sonogashira coupling, additional Pd-catalyzed reactions (Heck, Negishi, Buchwald–Hartwig amination, etc.) were used to increase the diversity around the core structure. Typically such diversity enhancement can be realized through C–C and C–N single bonds (Suzuki–Miyaura and Buchwald–Hartwig amination), double bonds (Heck), triple bonds (Sonogashira), etc. In summary, these techniques greatly increase the toolbox of the organic and medicinal chemists and contribute to afford novel chemotypes for the early phase of drug discovery.

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