Topics in Organometallic Chemistry 58

Syuzanna R. Harutyunyan
Editor

Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers

Springer

58
Topics in Organometallic Chemistry

Aims and Scope

The series *Topics in Organometallic Chemistry* presents critical overviews of research results in organometallic chemistry. As our understanding of organometallic structure, properties and mechanisms increases, new ways are opened for the design of organometallic compounds and reactions tailored to the needs of such diverse areas as organic synthesis, medical research, biology and materials science. Thus the scope of coverage includes a broad range of topics of pure and applied organometallic chemistry, where new breakthroughs are being achieved that are of significance to a larger scientific audience.

The individual volumes of *Topics in Organometallic Chemistry* are thematic. Review articles are generally invited by the volume editors. All chapters from Topics in Organometallic Chemistry are published OnlineFirst with an individual DOI. In references, Topics in Organometallic Chemistry is abbreviated as Top Organomet Chem and cited as a journal.

More information about this series at http://www.springer.com/series/3418

Syuzanna R. Harutyunyan
Editor

Progress in Enantioselective Cu(I)-catalyzed Formation of Stereogenic Centers

With contributions by

X. Fang · B.L. Feringa · J.-B. Gualtierotti · S.R. Harutyunyan · A. Hensel · V. Hornillos · M. Kanai · F. Lanza · K. Lawson · B. Maciá · A.V. Malkov · M. Oestreich · P. Ortiz · Y. Shimizu · C.-J. Wang · X. Wei · J.-W. Zhang

Springer

Editor
Syuzanna R. Harutyunyan
Stratingh Institute for Chemistry
University of Groningen
Groningen
The Netherlands

ISSN 1436-6002 ISSN 1616-8534 (electronic)
Topics in Organometallic Chemistry
ISBN 978-3-319-33412-7 ISBN 978-3-319-33414-1 (eBook)
DOI 10.1007/978-3-319-33414-1

Library of Congress Control Number: 2016938219

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

Ever since the discovery of the Ullmann reaction over a century ago, copper has become increasingly important in the construction of various bonds in organic synthesis. As of today, one can conclude that copper chemistry is remarkably diverse. In particular, copper(I) catalysis has found its unique place in asymmetric transformations for the synthesis of chiral molecules. Over the years, several monographs and reviews have been written that summarise the various aspects of copper chemistry. However, even today, the number of publications on copper-catalysed organic reactions keeps growing continuously, and new methodologies become available on a regular basis. This volume is not intended to provide a comprehensive review of all copper-catalysed reactions, but focuses on the most recent scientific advances in copper(I)-catalysed asymmetric synthesis. For this purpose, I have selected seven topics, most of which cover research conducted during the period 2010–2015. Several chapters deal with copper(I)-catalysed addition of organometallics to allylic substrates, β,β-disubstituted Michael acceptors and carbonyl groups. The chapters on additions of soft carbon nucleophiles and cycloaddition/cascade addition–cyclisation reactions extend the theme of carbon–carbon bond-forming reactions. Finally, copper(I)-catalysed carbon–silicon, carbon–boron and carbon–hydrogen bond-forming reactions are discussed. I am very grateful to the authors and experts in their field, who contributed to the production of this volume, and hope that it will be useful to researchers and students working in organic synthesis and catalysis.

Groningen, The Netherlands S.R. Harutyunyan

Contents

Asymmetric Allylic Substitutions Using Organometallic Reagents 1
Valentín Hornillos, Jean-Baptiste Gualtierotti, and Ben L. Feringa

Formation of Quaternary Stereocentres by Copper-Catalysed Enantioselective Conjugate Addition Reaction 41
Beatriz Maciá

1,2- Versus 1,4-Asymmetric Addition of Grignard Reagents to Carbonyl Compounds 99
Pablo Ortiz, Francesco Lanza, and Syuzanna R. Harutyunyan

Asymmetric Addition of Boron and Silicon Nucleophiles 135
Alexander Hensel and Martin Oestreich

Catalytic Asymmetric Addition Reactions of Cu(I)-Conjugated Soft Carbon Nucleophiles 169
Xiaofeng Wei, Yohei Shimizu, and Motomu Kanai

Asymmetric Cycloaddition and Cascade Addition–Cyclization Reactions 183
Xin Fang, Jia-Wei Zhang, and Chun-Jiang Wang

1,2- Versus 1,4-Asymmetric Reduction of Ketones 207
Andrei V. Malkov and Kurt Lawson

Index 221

Top Organomet Chem (2016) 58: 1–40
DOI: 10.1007/3418_2015_165

Published online: 26 February 2016

Asymmetric Allylic Substitutions Using Organometallic Reagents

Valentín Hornillos, Jean-Baptiste Gualtierotti, and Ben L. Feringa

Abstract This chapter summarises recent progress in Cu-catalysed asymmetric allylic alkylation (AAA) with organometallic compounds, including Grignard, organolithium, organoaluminium, organozinc and organozirconium reagents. New reaction conditions and chiral ligands that improve these transformations or allow to overcome previous limitations associated with chemo-, regio- and enantioselectivities will be described. Moreover, a description of new ligands and conditions for the introduction of previously elusive nucleophiles, such as highly reactive organolithium compounds, is included together with a brief mechanistic discussion. Additionally, new challenging substrates which provide densely functionalised building blocks, as well as new synthetic applications that take advantage of the terminal olefin formed in these reactions, will be described.

Keywords Allylation • Asymmetric allylic substitution • Copper catalysis • Enantioselectivity • Organometallic reagents

Contents

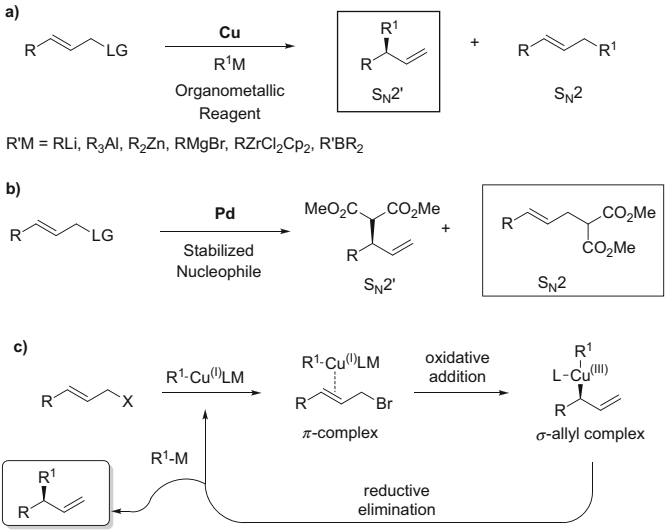
1 Introduction 2
2 Asymmetric Allylic Substitutions Using Grignard Reagents 3
3 Asymmetric Allylic Substitutions Using Organolithium Reagents 15
4 Asymmetric Allylic Substitutions Using Organoaluminium, Zinc and Zirconium Reagents 25
5 Asymmetric Allylic Substitutions on Racemic Substrates with Organometallic Reagents 30
References 34

V. Hornillos, J.-B. Gualtierotti, and B.L. Feringa (✉)
Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
e-mail: b.l.feringa@rug.nl

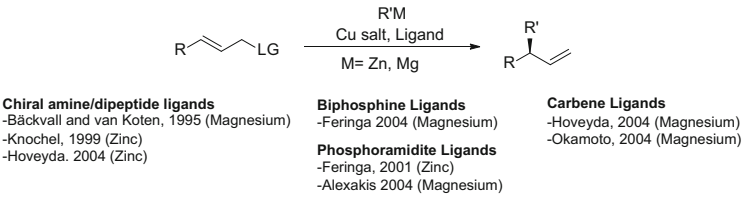
1 Introduction

Asymmetric catalysis using transition metals is a highly efficient tool for the construction of stereogenic centres with control over the absolute configuration, which is often a key factor determining the activity of pharmaceuticals [1–3]. This strategy presents various advantages such as atom economy, reduction of by-product formation, functional group tolerance and the capability to provide the desired product with high levels of selectivity. Several transition metals have proven their efficiency in catalytic asymmetric processes [4]. In particular, the use of copper provides cheaper and more readily available catalyst systems while maintaining high activity and selectivity. Among the Cu-catalysed enantioselective processes, asymmetric allylic alkylation (AAA) represents a useful and powerful methodology for the synthesis of chiral building blocks, in particular for the synthesis of pharmaceuticals and natural products [4–12]. This transformation generally leads to the S_N2'-functionalised product, through the reaction of a nucleophile and an allylic system, bearing a suitable leaving group, and provides a carbon-based stereocentre next to a terminal olefin (Scheme 1a). This alkene moiety can be further converted into a variety of functionalities while preserving the stereochemical integrity of the starting material. Cu-catalysed AAA represents a highly efficient catalytic process for the use of organometallic reagents, such as organozinc, organomagnesium, organoaluminium, organozirconium and organolithium compounds. These AAA reactions, with these "hard" C-nucleophiles, are complementary to the well-known Pd-catalysed asymmetric allylic alkylations which employs soft and stabilised nucleophiles [13–16]. These nucleophiles generally approach the Pd-allyl moiety from the less hindered side of the allyl moiety coordinated to the metal ion leading to the S_N2 product (Scheme 1b). In the case of Cu-catalysed AAA, the organometallic compound first undergoes transmetallation to a Cu (I) complex, followed by π-complex formation and subsequent oxidative addition to form a Cu (III) σ-allyl complex. This is also the enantiodiscriminating step. Finally, reductive elimination gives rise to the new C–C bond and the branched (S_N2') product (Scheme 1c) [17].

The groups of Bäckvall and Van Koten pioneered the use of hard nucleophiles in their Cu-catalysed AAA of Grignard reagents and allylic acetates [18–21]. Knochel's work [22] illustrated that bulky dialkylzinc reagents were also suitable nucleophiles, and the groups of Feringa [23, 24] and Alexakis [25] subsequently reported on the use of phosphoramidite ligands in combination with linear dialkylzinc and Grignard nucleophiles featuring excellent (up to 99% ee) selectivities. Later on, a variety of peptide-based ligands, aminoalkyl phosphites or N-heterocyclic carbene (NHC) ligands, in combination with organozinc, Grignard and organoaluminium compounds, have also been shown to be effective in the Cu-catalysed AAA of a variety of di- and trisubstituted allyl systems (Scheme 2). As several reviews have already been reported on this field [6–12], this chapter will focus on developments in Cu-catalysed AAA since 2010.



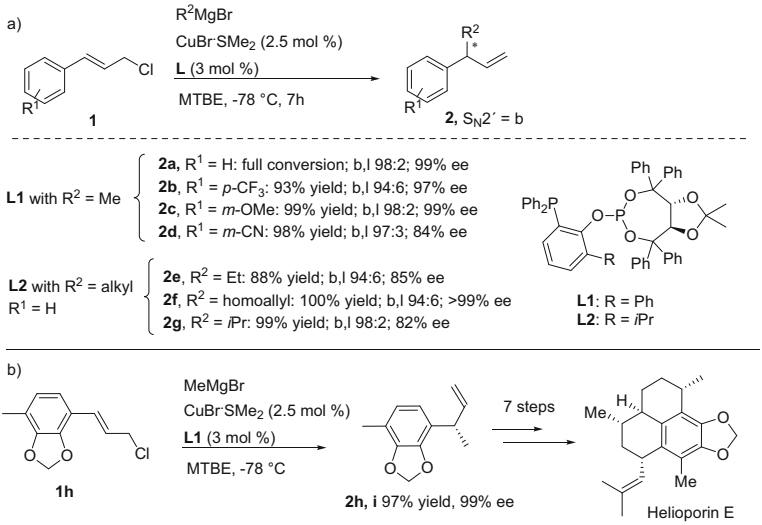
Scheme 1 (**a**) Pd- and (**b**) Cu-catalysed AAA methodologies. (**c**) General mechanism on the Cu-catalysed AAA



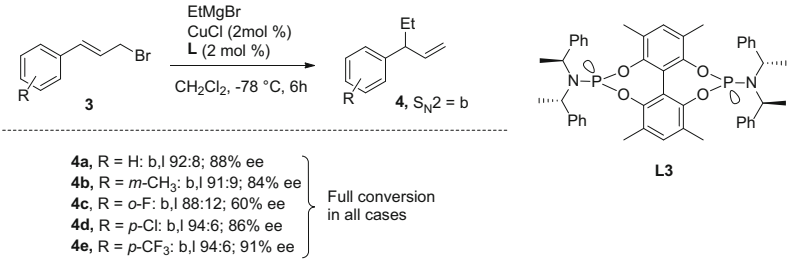
Scheme 2 Early reports on Cu-catalysed AAA methodologies

2 Asymmetric Allylic Substitutions Using Grignard Reagents

Schmalz and co-workers screened a library of modular phosphine–phosphoramidites as chiral ligands for the copper-catalysed allylic alkylation of cinnamyl chlorides **1** and Grignard reagents resulting in a broader methodology than previously reported [26]. In general, better selectivities were found for TADDOL-derived ligands in comparison with BINOL-derived ligands, and **L1** in combination with $CuBr{\cdot}SMe_2$ was found optimal for the addition of MeMgBr (Scheme 3a). The use of less coordinating ethereal solvents, in particular MTBE, yielded the highest regio- and enantioselectivities (S_N2'/S_N2 ratio up to 98:2; ee up to $> 99\%$). Modest enantioselectivities were obtained when using longer alkyl Grignard reagents although by switching to related phosphine–phosphite ligand **L2** the enantioselectivity was partially restored. The method was further employed



Scheme 3 Copper-catalysed AAA of cinnamyl chlorides with Grignard reagents employing, as chiral ligands, phosphine–phosphoramidites

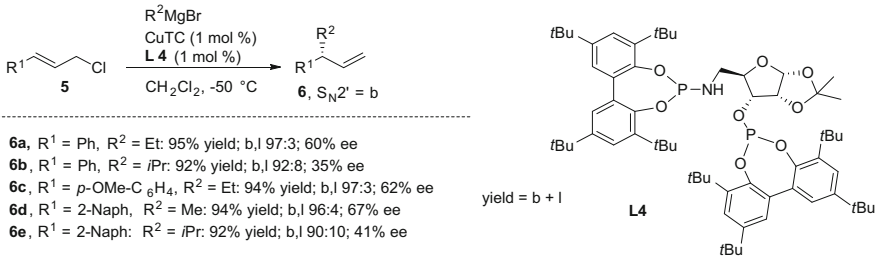


Scheme 4 Copper-catalysed AAA of cinnamyl chlorides with EtMgBr employing an atropos bridged phosphoramidite

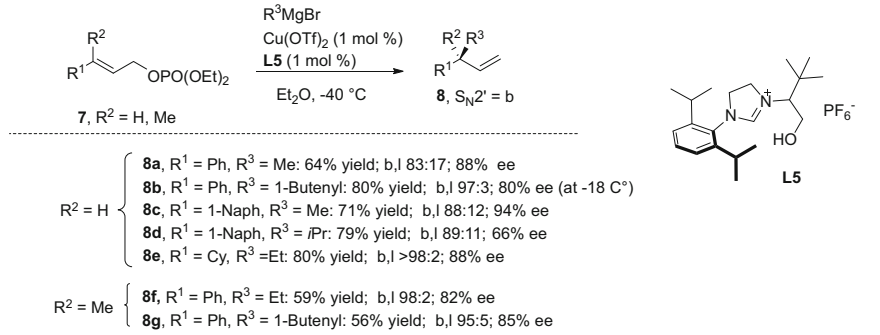
to set up the first stereogenic centre in the enantioselective total synthesis of *helioporins C* and *E*, which are marine metabolites with antiviral and cytotoxic activity (Scheme 3b) [27].

At the same time, the group of Zhang independently showed that D_2 symmetric atropos biphenyl phosphoramidites were efficient ligands for the Cu-catalysed AAA of cinnamyl bromide derivates **3** [28]. These ligands have two identical substituents linked pairwise by four bridges, which induces the axial chirality. Tetramethyl-substituted **L3** promoted the addition of EtMgBr with good regioselectivity and moderate to good enantioselectivity (Scheme 4). However, reactions with other Grignard reagents were not reported.

The group of Alexakis subsequently reported a study on the use of bidentate furanoside phosphite–phosphoramidite and diphosphoramidite ligands for the Cu-catalysed AAA of cinnamyl-type substrates [29]. A range of different cinnamyl



Scheme 5 Cu-catalysed asymmetric allylic alkylation using a furanoside phosphite–phosphoramidite as chiral ligand **L4**

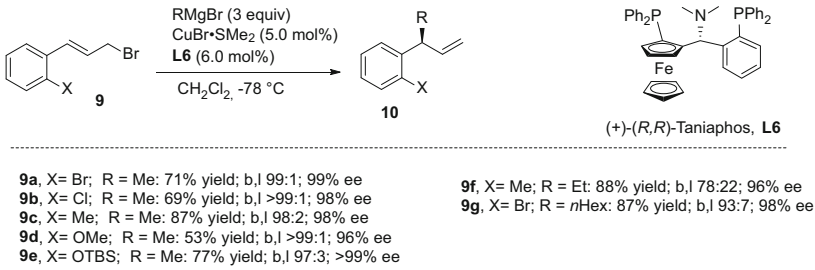


Scheme 6 Bidentate hydroxyalkyl NHC ligand for the copper-catalysed AAA

chlorides **5** and Grignard reagents could be coupled, with only 1 mol% of **L4** and CuTC as the catalyst system, with excellent regioselectivity, but modest enantioselectivity (Scheme 5).

Mauduit and co-workers investigated the use of bidentate hydroxyalkyl NHC ligands, derived from the amino acid chiral pool, in the Cu-catalysed AAA of cinnamyl phosphates **7** with alkyl Grignard reagents [30]. Using **L5** as ligand precursor, a variety of linear Grignard reagents afforded good regio- (S_N2'/S_N2 up to $> 98:2$) and enantioselectivities in the alkylation reaction, especially using MeMgBr (up to 94% ee). A practical advantage is that the Grignard reagent also deprotonates the imidazolium salt **L5**, without the necessity of using an external base or preformed copper or silver carbene complex. Diminished enantioselectivity was found in the case of secondary Grignard reagents (Scheme 6). Moreover, the reaction conditions could be extended to the formation of all-carbon quaternary stereocentres in high yields and with good levels of enantioselectivity.

The use of *ortho*-substituted cinnamyl substrates in Cu-catalysed AAA is a particularly difficult transformation, especially when the reaction is performed with MeMgBr, as an erosion on the regio- and enantioselectivity is generally observed. Feringa and co-workers demonstrated that, by employing their previously developed copper–taniaphos (**L6**) catalyst, a variety of *ortho*-substituted cinnamyl

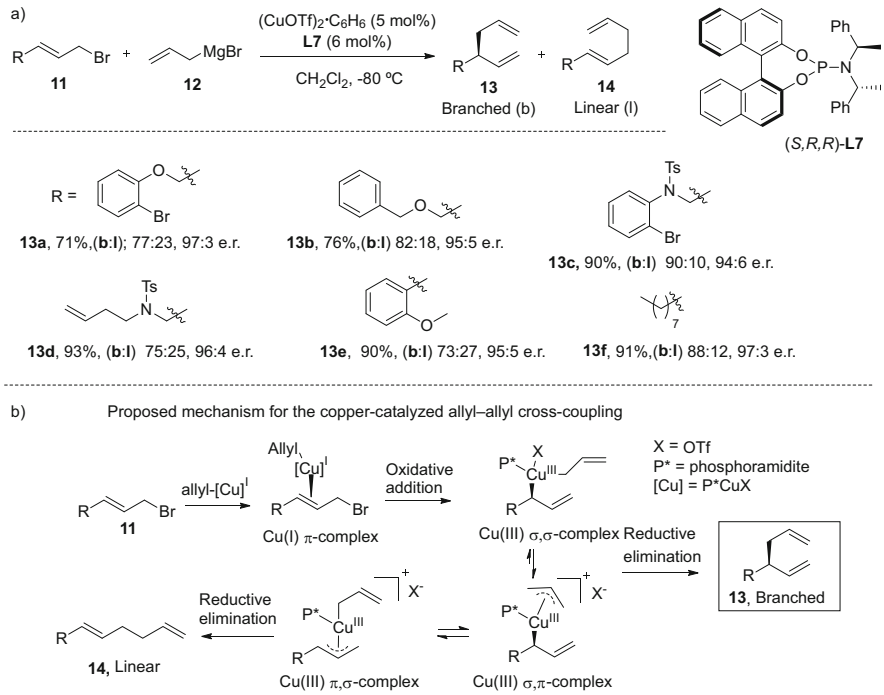


Scheme 7 Copper-catalysed AAA of *ortho*-substituted cinnamyl bromides **9** with Grignard reagents

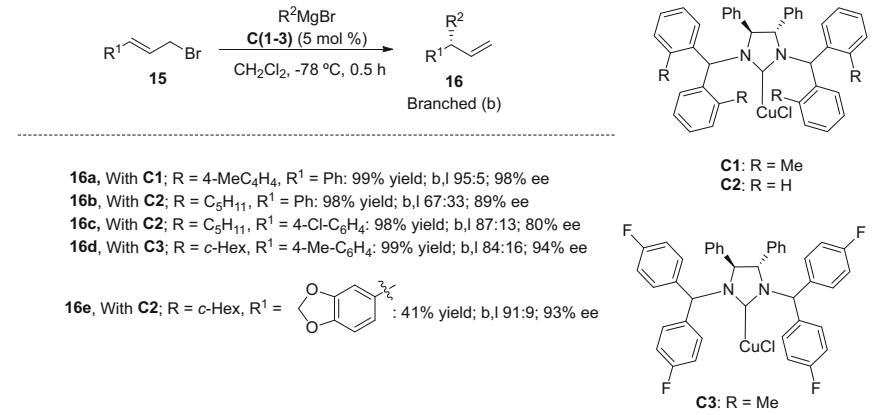
substrates **9** can participate in the alkylation reaction with alkyl Grignard reagents, affording the corresponding branched products **10** with excellent regio- and enantioselectivity (S_N2'/S_N2 up to >99:1 and up to 99% ee) [31]. A variety of *ortho* substituents including Br, Cl, CH_3, -OMe and OTBS were tolerated in the reaction with MeMgBr as well as longer alkyl Grignard reagents (EtMgBr and *n*-HexMgBr) when using *ortho* methyl- and *ortho* methoxy-cinnamyl bromide as substrates (Scheme 7).

Feringa and co-workers used (*R*,*S*,*S*)-**L7** as ligand to promote the first Cu-catalysed asymmetric allylic alkylation using an allyl Grignard reagent [32]. Although this reaction is similar to the conventional Cu-catalysed AAA with alkyl nucleophiles, the dual coordination modes of allyl metal species may have delayed the development of an effective enantioselective version of this reaction. The use of allylMgBr in the reaction with allyl bromides **11** afforded chiral 1,5-dienes **13** in good yields and high enantioselectivity (Scheme 8a). The use of non-coordinating counter anions in the copper salt precursor favours the branched substitution product **13**, with $(CuOTf)_2{\cdot}C_6H_6$ being optimal. Excellent enantioselectivities were obtained for a variety of substrates bearing different functionalities including protected alcohols, amines, alkenes or acetals. The authors proposed that the corresponding Cu^{III} σ–σ complex, which is formed after oxidative addition of an allyl-Cu**L7**OTf to an allyl bromide, is in equilibrium with a Cu^{III} σ-π intermediate. Fast reductive elimination from these intermediates would produce the branched substitution product. However, due to stabilisation caused by the η^3 bonding mode of the allyl group, isomerisation from the Cu^{III} σ-π-complex to the Cu^{III} π-σ-complex may occur, giving rise to the formation of the linear product. This proposal is further supported by the fact that for cinnamyl-type substrates, lower regioselectivity is observed. In this case, the presence of an aryl ring in the benzylic position may further stabilise the Cu^{III} σ-π-complex, favouring the above-mentioned isomerisation (Scheme 8b).

In 2011 Tomioka and co-workers expanded their previously reported Cu-catalysed asymmetric allylic arylation of aryl Grignard reagent and cinnamyl bromides [33] to the corresponding aliphatic bromides [34]. For this purpose, structural steric and electronic modifications of their chiral Cu(I)-NHC **C1** catalyst

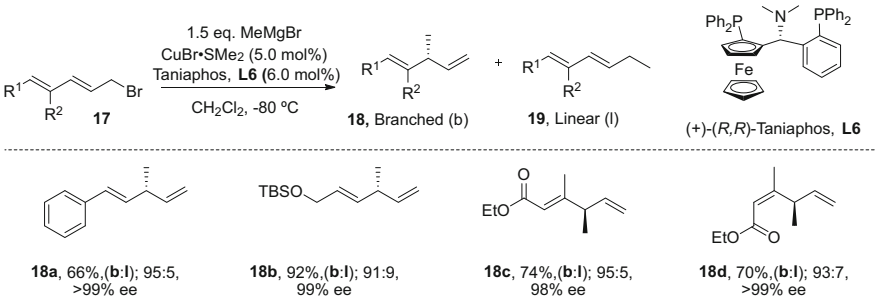


Scheme 8 Asymmetric allylic alkylation using allylMgBr

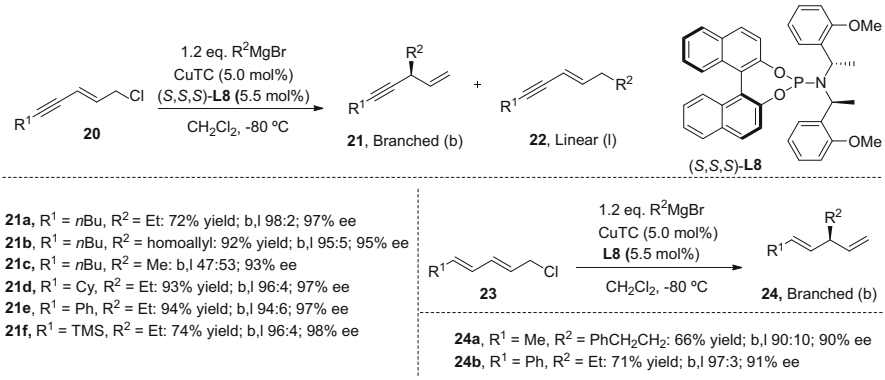


Scheme 9 Asymmetric allylic arylation of aliphatic allylic bromides

were carried out. They found that the presence of benzhydryl (**C2**) or 4,4′-difluorobenzhydryl (**C3**) groups at the N atoms of the catalyst allowed to obtain moderate to high S_N2' selectivity (S_N2'/S_N2 ratios up to 96:4) with good to excellent



Scheme 10 Synthesis of skipped dienes **18** via Cu-catalysed AAA with MeMgBr

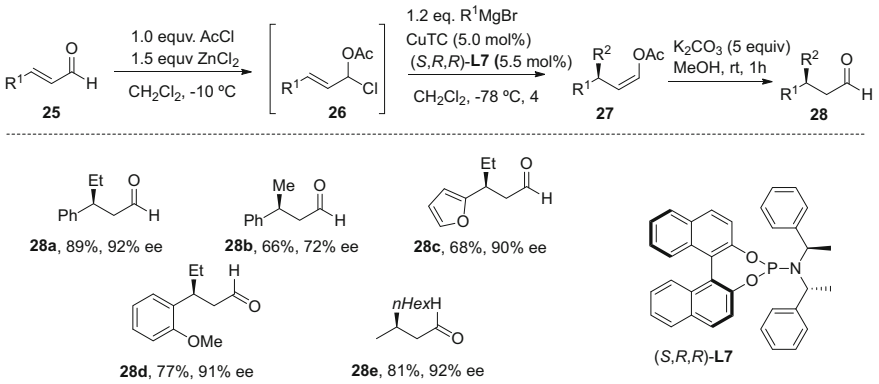


Scheme 11 Synthesis of chiral 1,4-enynes and 1,4-dienes via Cu-catalysed AAA with alkyl Grignard reagents

enantioselectivities (up to 96% ee) in the reaction of a variety of bulky or electron-poor aryl Grignard reagents and aliphatic allylic bromides **15** (Scheme 9).

Recently, Feringa and co-workers have demonstrated that chiral 1,4-dienes **18** (skipped dienes) can be prepared in excellent regio- and enantioselectivities (S_N2'/S_N2 ratio up to 97:3 and up to 96% ee) via the Cu-catalysed asymmetric allylic alkylation of prochiral diene bromides **17** with MeMgBr using Taniaphos **L6** as chiral ligand [35]. This is an important transformation as many biologically active molecules as *hennoxazole A*, *ansalactam A*, *lejimalide* and *phorbasins* present this motive in their structures. Notably, the *E*-geometry of the double bond was found crucial to obtain high regio- and enantioselectivity. However, these values are independent of the geometry of the remote double bond as similar selectivities were obtained by using a (*Z*,*E*)- or (*E*,*E*)-diene **17** (Scheme 10).

Using phosphoramidite ligand **L8** allowed Alexakis and co-workers to perform a similar transformation but employing prochiral *E*-enyne chlorides **20** as substrates [36]. A variety of alkylmagnesium bromide reagents were used as nucleophiles providing 1,4-enynes **21** in excellent regio- and enantioselectivities (S_N2'/S_N2 ratio up to 98:2 and up to >99% ee). Unlike in the Feringa report, the use of MeMgBr

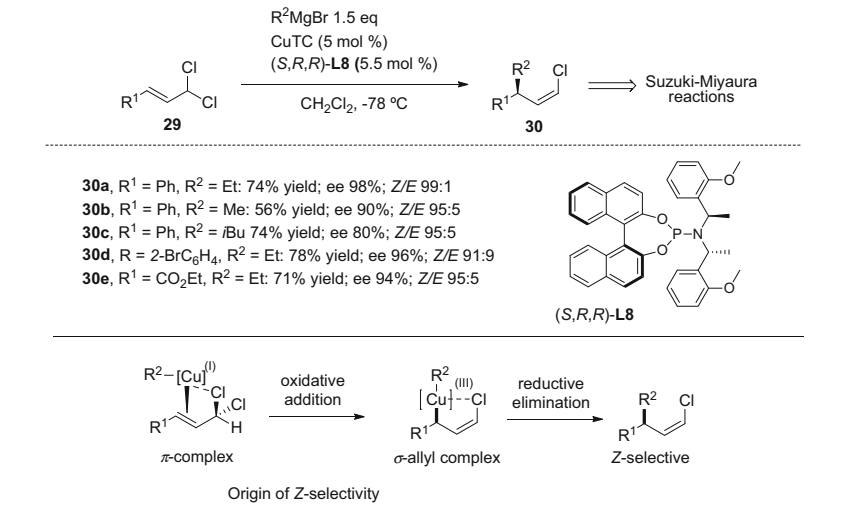


Scheme 12 Cu-catalysed enantioselective synthesis of chiral enol acetates **27** and β-substituted aldehydes **28**

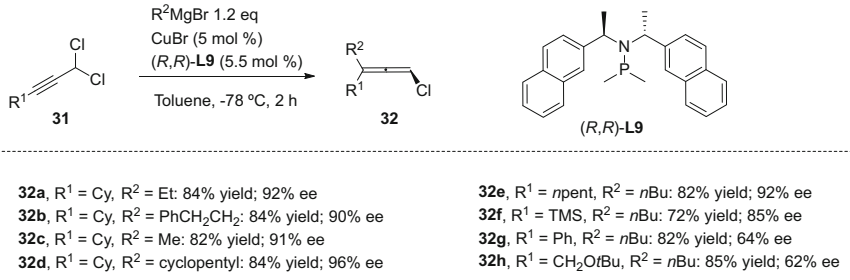
constitutes a limitation in terms of regioselectivity (S_N2'/S_N2 ratio 1:1), although the enantioselectivity was maintained (Scheme 11). This method can be considered complementary to the Cu-catalysed AAA using alkynylaluminium reagents, recently described by Hoveyda and co-workers [37], as both lead to 1,4-enynes, although with reversed polarity of the reaction partners. Similar to Feringa's observations, the selectivity of the reaction substantially decreases when the *Z* isomer was used. Additionally, the scope of the reaction was also extended to conjugated *E*,*E*-diene chlorides **23** which showed to behave similarly, affording the chiral 1,4-dienes **24** in high yield and selectivity (Scheme 11).

Asymmetric allylic alkylation reactions of geminal disubstituted allylic electrophiles have been studied by the group of Feringa. In 2010, they reported that the use of the phosphoramidite ligand (*S*,*R*,*R*)-**L7**, in the Cu-catalysed reaction between Grignard reagents and *α*-chloroallylic acetates **26**, in situ prepared from the corresponding α,β-unsaturated aldehydes **25**, affords enantiomerically enriched enol acetates **27** in a one-pot process (Scheme 12) [38]. Exposure of these products to methanolysis under basic conditions delivered the products of the formal conjugate addition to β-substituted aldehydes **28**. This reaction represents a viable alternative to the conjugate addition to enals, which is problematic due to the reactivity of the carbonyl group towards these organometallic compounds. The transformation affords excellent regio- and enantioselectivities (up to 94% ee) with a variety of primary alkyl Grignard reagents. The conventional limitation of phosphoramidites for the Cu-catalysed AAA of methyl groups is again manifested, as a decrease of regio- and enantioselectivity was observed for the use of MeMgBr.

The high *Z*-selectivity observed in the formation of the enol acetate encouraged Feringa and co-workers to investigate the substitution of allylic *gem*-dichlorides **29** (Scheme 13) [39]. The use of (*S*,*S*,*S*)-**L8** in the alkylation reaction with a variety of primary Grignard reagents affords chiral *Z*-vinyl chlorides **30** with excellent regio-, enantio- and *Z*:*E*-selectivity (99:1 *Z*:*E* ratio, ee up to 98%). The use of an ester-



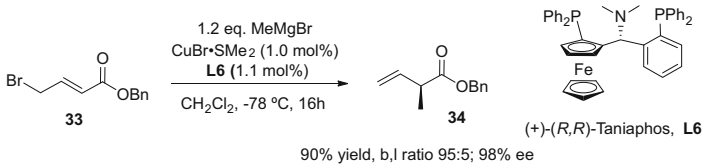
Scheme 13 Z-Selective Cu-catalysed asymmetric allylic alkylation



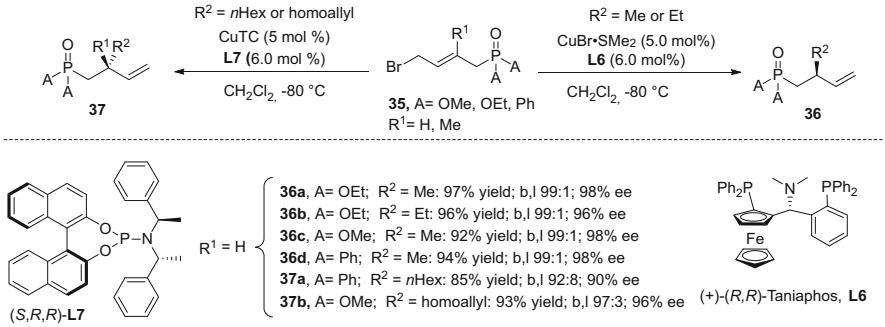
Scheme 14 Copper-catalysed asymmetric propargylic alkylation using Grignard reagents

substituted dichloride is also well tolerated, without the formation of carbonyl addition or S_N2 products. The corresponding *Z*-vinyl chlorides **30** were subsequently employed in Suzuki–Miyaura cross-coupling reactions providing a variety of chiral *Z*-alkyl- and aryl-substituted alkenes and dienes. To explain the selectivity for the (*Z*)-isomer, the authors propose that an extra coordination between the copper complex and one of the chlorides favours the formation of a (*Z*)-σ allyl complex that subsequently undergoes (*Z*)-selective reductive elimination to give the alkylated product (Scheme 13).

A similar system, but employing prochiral propargylic compounds, has been reported by Alexakis and co-workers [40]. In this case, 1,1-dichloro propargylic compounds **31** prepared from the corresponding aldehydes were reacted with a variety of primary and secondary Grignard reagents using copper-SimplePhos complex as catalyst. A variety of chiral allenes **32** were obtained with high regioselectivities and good enantioselectivities (up to 96% ee) (Scheme 14). Unlike in the copper-catalysed AAA using MeMgBr and other phosphoramidites, the



Scheme 15 Cu-catalysed AAA of halocrotonates

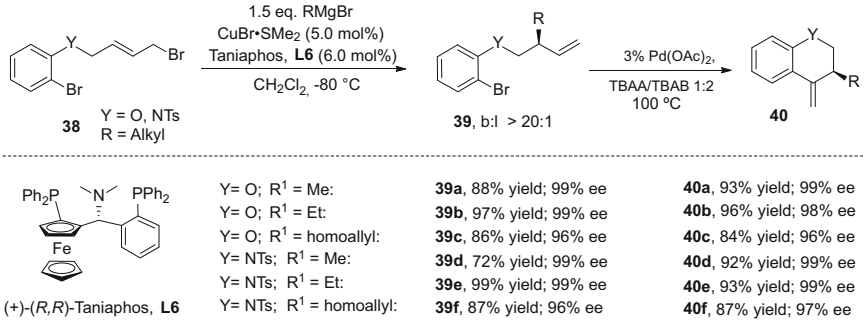


Scheme 16 Cu-catalysed AAA phosphonate and phosphine oxide allylic bromides

methyl group could be successfully introduced with good regio- and enantioselectivity. Transformation of the final products into the corresponding alkylated allenes or arylated propargylic compounds was also performed showing complete chirality transfer.

A variety of Cu-catalysed AAA reactions with allylic electrophiles, bearing synthetically useful functionalities, have been described by the group of Feringa. They first reported the enantioselective synthesis of α-methyl-substituted ester **34** via allylic alkylation of benzyl 4-bromocrotonate **33** using copper–Taniaphos **L6** as chiral ligand (Scheme 15) [41]. The corresponding products were further elaborated into chiral multifunctional building blocks including hydroxyl- or iodo-substituted lactones, without significant loss of stereochemistry.

Using the same ligand **L6**, this group also described the enantioselective copper-catalysed alkylation of phosphonate and phosphine oxide allylic bromides **35** with methyl- and ethylmagnesium bromide in good yields and high regio- and enantioselectivity (S_N2'/S_N2 up to 99:1 and up to 98% ee) (Scheme 16) [42]. However, with this ligand, the use of Grignard reagents with a longer alkyl chain afforded more moderate values. Further screening showed that phosphoramidite (*S*,*R*,*R*)-**L7**, in combination with *n*-hexyl- or homoallyl magnesium bromide, restored the selectivity towards the desired products **37** (S_N2'/S_N2 up to 97:3 and up to 96% ee). This reaction constitutes an alternative to the catalytic enantioselective conjugate addition of alkyl nucleophiles to α-β-unsaturated organophosphorus compounds, which has not been described to date. The reaction was further extended to the enantioselective synthesis of all-carbon quaternary centres although the



Scheme 17 Tandem asymmetric allylic alkylation and intramolecular Heck coupling

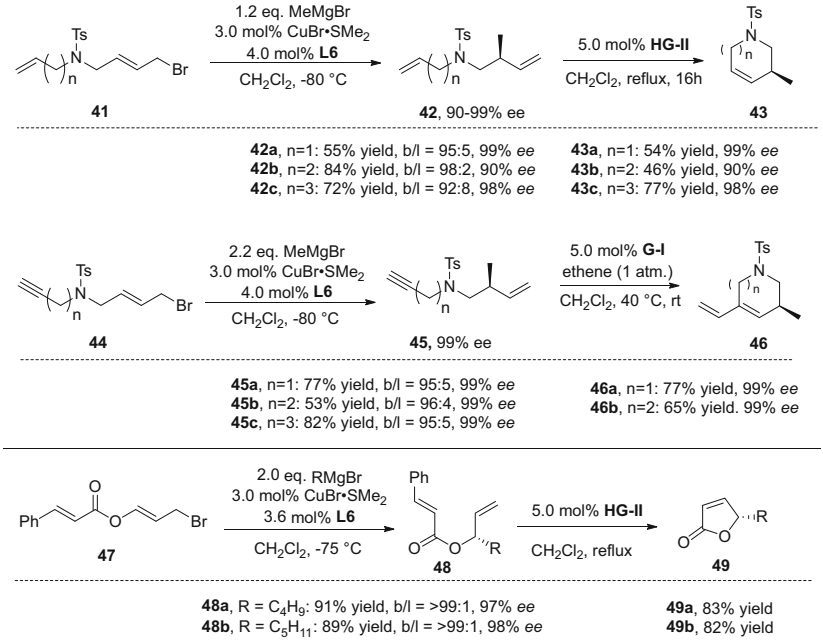
enantioselectivities were moderate (up to 60% ee). The obtained products were transformed to a variety of new phosphorus-containing chiral intermediates.

One major advantage of the allylic alkylation reactions is that it furnishes terminal olefinic groups, which represent ideal starting points for further modifications. One representative example is a tandem asymmetric allylic alkylation/intramolecular Heck reaction [43]. Copper–Taniaphos (**L6**) was used as catalyst to furnish chiral products **39** bearing a *o*-bromophenyl ether or amine in high regio- and enantioselectivity (up to 99% ee). The terminal olefin adjacent to the stereogenic centre formed was subjected to intramolecular Heck coupling, using a molten mixture of tetrabutylammonium bromide (TBAB) and tetrabutylammonium acetate (TBAA). The cyclised products **40** were obtained in excellent yields without racemisation at the stereogenic centre nor isomerisation of the exocyclic double bond (Scheme 17). The synthetic utility of these compounds was explored via the use of ring closing metathesis (RCM), stereoselective hydroborations, and reductions resulting in diverse synthetically relevant compounds.

Feringa and co-workers have shown that another interesting approach for the synthesis of N-heterocycles is combining Cu-catalysed AAA with RCM [44]. In this case, allylic bromides, substituted with a protected amine and terminal olefin (**41**) or alkyne (**42**) substituents, were alkylated with MeMgBr, and the obtained products **42** and **45** were subjected to RCM using Hoveyda–Grubbs (II) or Grubbs (I) catalysts. A collection of unsaturated piperidines, azepanes and azocanes were obtained in high yields and excellent enantioselectivities (Scheme 18, upper).

The same strategy was applied by this group for the preparation of γ-butyrolactone rings **49** [45]. In this case, the chiral olefin precursors **48** were prepared through their previously developed *hetero*-allylic asymmetric alkylation reaction [46] (*h*-AAA, where the allyl bromide contains a heteroatom at the gamma position) of allylic esters **47**, and Grignard reagents (Scheme 18, lower). The utility of this protocol was further demonstrated by converting these chiral lactones into the (−)-*whiskey* and (−)-*cognac lactone*. No loss of enantiomeric excess was observed in any of these transformations.

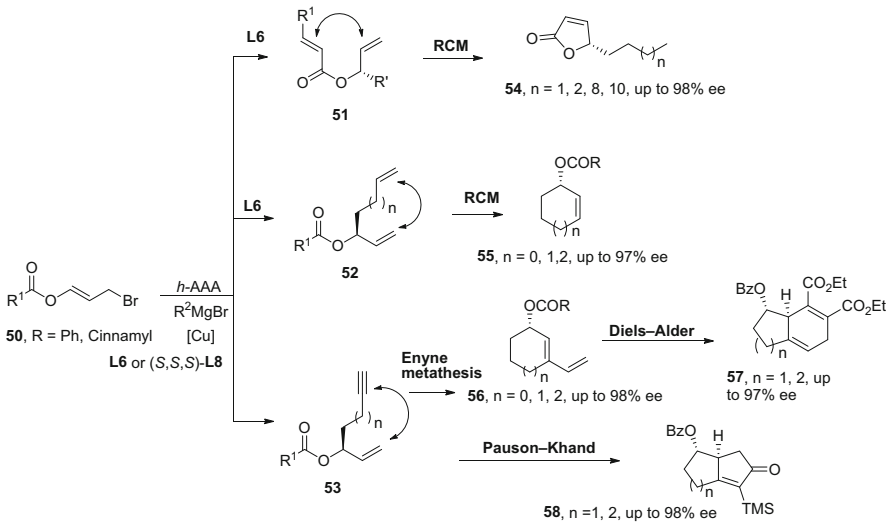
Combining the *h*-AAA reaction with RCM, the authors further reported on the preparation of a variety of chiral cyclic allylic esters **54–56** in high yields and



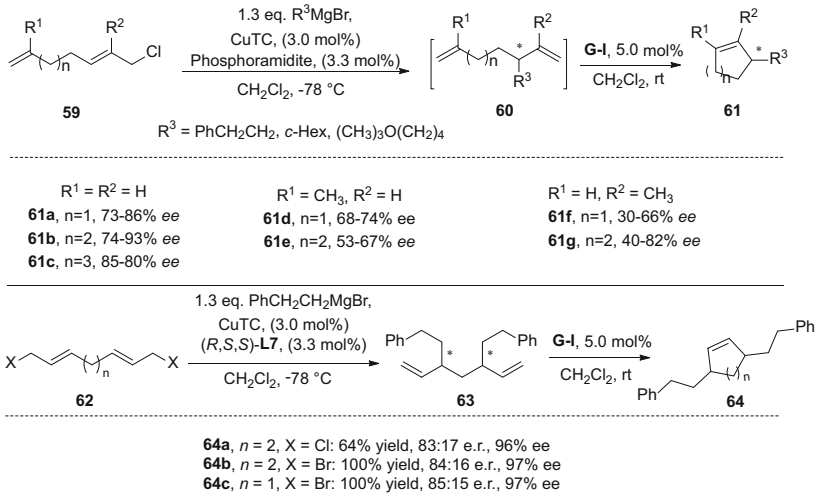
Scheme 18 Tandem asymmetric allylic alkylation/ring closing metathesis for the synthesis of N- and O-heterocycles

enantioselectivities (up to 98% ee) [47]. In addition, they also showed the diversity-oriented synthesis of different ring-fused bicyclic structures **57**, **58** through Diels–Alder reactions on 2,4-dienol esters **56** or Pauson–Khand reactions on enyne substrates **53** (Scheme 19).

Allylic alkylation in combination with RCM has also been employed by the group of Alexakis for the preparation of chiral carbocycles. In this case, ω-ethylenic allylic substrates **59** were subjected to Cu-catalysed AAA with primary and secondary Grignard reagents using phosphoramidite ligands [48, 49]. The choice of chiral ligand depends both on the length of the carbon chain between the allylic double bond and the ethylenic bond, as well as on the structure of the Grignard reagent. The subsequent RCM was performed in situ, without quenching the alkylation reaction, using Grubbs (I) catalyst. With simple unsubstituted ω-ethylenic allylic chlorides **59a-c**, five-, six- and seven-membered rings could be generated with enantioselectivities up to 86%, 93% and 85%, respectively. They also apply this strategy to similar substrates, bearing a methyl group on the terminal double bond (**59d**,**e**) or in the β-position (**59f**,**g**) of the allyl system, affording methyl-substituted five- and six-membered cycloalkenes **61d-g**, although with lower enantioselectivity (up to 82% ee). The authors anticipate metal coordination to the terminal olefin group prior to the σ-allyl complex formation to explain the variation on the enantioselectivity. Furthermore, the alkylation reaction on substrates with double allylic systems **62** was performed, which afforded compounds



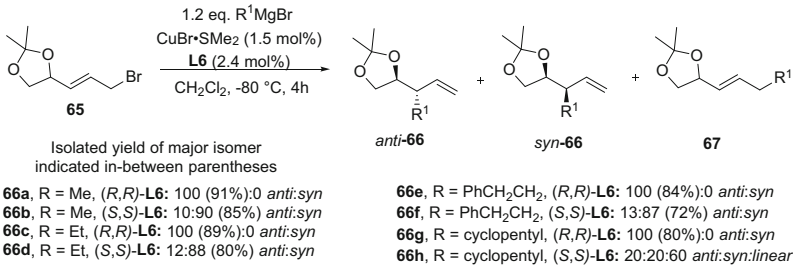
Scheme 19 Tandem asymmetric allylic alkylation/ring closing metathesis for the synthesis of chiral cyclic allylic esters and ring-fused bicyclic structures



Scheme 20 Construction of enantio-enriched carbocyclic compounds by asymmetric allylic alkylation and RCM

with two terminal vinyl groups **63** that were further subjected to intramolecular metathesis (Scheme 20).

Using both enantiomers of Taniaphos **L6** allowed Feringa and co-workers to perform the copper-catalysed AAA of δ-alkoxy-substituted allyl bromide **65** with high regio- and stereocontrol for both the *syn* and the *anti* isomers **66** [50]. When

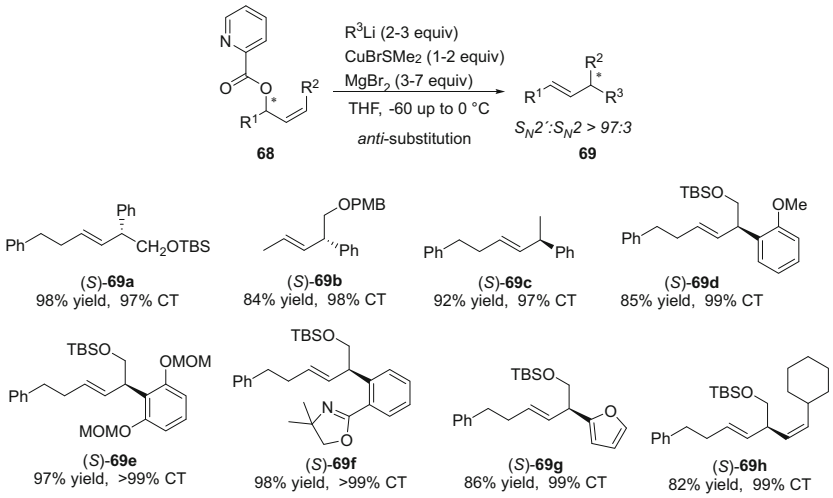


Scheme 21 Stereoselective synthesis of 1,2-hydroxyalkyl moieties **66** via Cu-catalysed AAA

allyl bromide **65**, which is readily obtained from commercial 1,2:5,6-di-*O*-isopropylidene-D-mannitol, was subjected to the reaction with MeMgBr using CuBr·SMe_2/(*R*,*R*)-Taniaphos (**L6**) as a catalyst, complete selectivity was observed towards the *anti* product **66**. The reaction with the (−)-enantiomer of the ligand led to the syn isomer with complete regioselectivity and high selectivity (*syn*/*anti* 90:10). Masking the alkoxy substituent in the dioxolane ring and performing the reaction at −80°C are key factors to control the stereoselectivity of the reaction. A variety of Grignard reagents could also be used in the allylic alkylation with high selectivities in nearly all cases (Scheme 21). However, a strong mismatch effect was observed in the case of cyclopentyl magnesium bromide.

3 Asymmetric Allylic Substitutions Using Organolithium Reagents

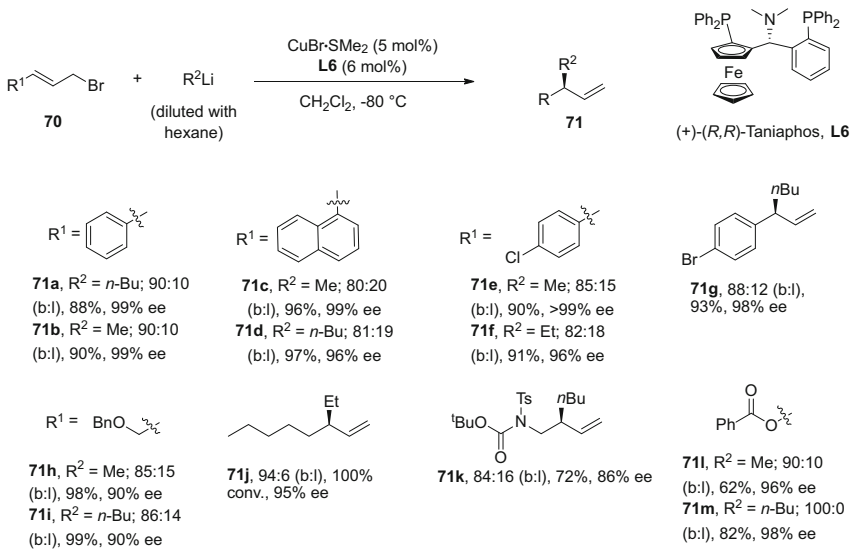
Recently, Feringa and co-workers reported for the first time the direct use of highly reactive organolithium reagents in Cu-catalysed AAA [51]. The application of these reagents in catalytic processes has been complicated due to their tendency to react spontaneously, by-passing the required involvement of the catalyst, but also due to their propensity to form aggregates in solution [52]. By the judicious choice of the chiral ligand and an exquisite control of the reaction conditions, the high reactivity of these organometallic reagents could be controlled affording the desired alkylated compounds with high stereochemical selectivity, without the presence of side products. More recently, the authors have reported novel highly efficient methodology for the palladium-catalysed direct cross-coupling of organolithium reagents with (hetero)aryl- and alkenyl(pseudo)halides under mild reaction conditions [53, 55] ([54] and references cited therein). However, a description of this palladium-based catalytic process is beyond the scope of this section. We will focus on the use of organolithium reagents in copper-catalysed asymmetric allylic substitution which includes the formation of tertiary and quaternary all-carbon stereogenic centres and their further application in the preparation of chiral building blocks for the synthesis of natural products and bioactive substances.



Scheme 22 Allylic substitution of optically active picolinates

In 2010, the group of Kobayashi described conditions for the asymmetric allylic substitution of chiral allylic picolinates **68** with aryl, alkenyl, and heteroaryl copper reagents in situ prepared from organolithium compounds and $CuBr{\cdot}SMe_2$ [56]. The reaction led to the *anti* S_N2' products **69** with high regioselectivity and chirality transfer (CT, defined by [% ee of product/% ee of starting material] $\times$ 100). The authors found that a number of experimental requirements were essential in order to obtain this high selectivity: (1) The addition of larger amounts of $MgBr_2$ with respect to Li^+ salts. (2) The use of 1–2 equivalents of $CuBr{\cdot}SMe_2$ with respect to the use of 2 equivalents of organolithium compound. (3) The geometry of the olefin in the starting material needs to be *cis*. The use of the corresponding *trans* picolinate still led to excellent selectivity although a *trans*/*cis* mixture of the olefin in the final product is obtained. Different allylic picolinates **68** were tolerated in the substitution reaction (R^1 and $R^2 = c$-Hex, $PMBOCH_2$ $TBSOCH_2$, Me, $Ph(CH_2)_2$, $PMBO(CH_2)_3$) as well as a wide variety of organolithium compounds, which were prepared by Li-halogen exchange or direct *ortho* metalation. Interestingly, *Z*- and *E*-alkenyl lithium could also be employed providing the *anti* S_N2' product with high regioselectivity and CT, with retention of the olefin geometry (Scheme 22).

In 2011, the group of Feringa reported that the use of catalytic amounts of in situ formed chiral copper complexes, generated from copper salts and chiral phosphorus-based ligands in CH_2Cl_2 as solvent, is an effective way to control the high reactivity of alkyllithium compounds allowing for an efficient and highly selective asymmetric allylic alkylation process [51]. Different factors, typically associated with the use of organolithium compounds, were required to be considered in order to achieve a highly selective and high-yielding reaction. (1) A fast lithium-leaving group exchange has to be suppressed by efficient transmetallation to the Cu complex. (2) After oxidative addition of the allylic system, a fast

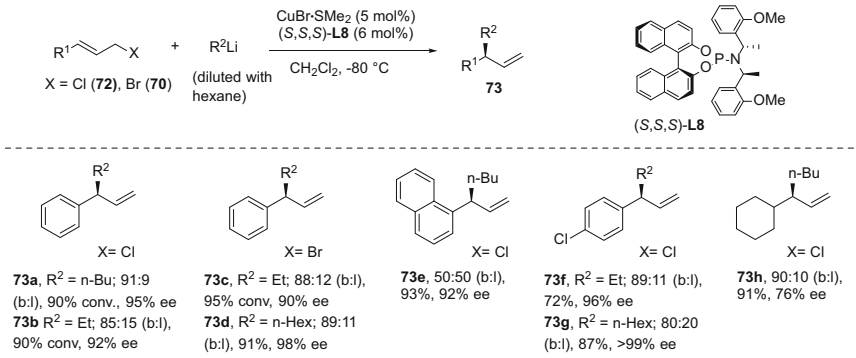


Scheme 23 Cu-catalysed AAA with alkyllithium compounds

reductive elimination from the σ-allylcopper complex, leading to the S_N2' product, should also be promoted. If the reductive elimination step is slow, the undesired linear product can be formed via isomerisation from the Cu(III) σ-complex to the Cu(III) π-allyl complex, followed by reductive elimination [17]. (3) Finally, if the substrate contains an aryl halide, lithium–halogen exchange would lead to the formation of aryl lithium species which can give a new range of undesired side products.

The study of the reaction between *n*-BuLi, the most well-known organolithium reagent, and cinnamyl bromide **70a** was chosen to establish optimised conditions for the AAA reaction. During initial experiments, the authors observed that the use of non-ethereal solvents maintains the aggregation of the organolithium species within the reaction prior to transmetallation to copper, which in turn reduces its intrinsic reactivity and thereby, as a consequence, avoids a plethora of side reactions. Among the different ferrocenyl-type chiral diphosphines ligands screened, (*R*,*R*)-(+)-Taniaphos **L6** at −80°C gave the best results affording the branch product **71** in high S_N2'/S_N2 (83:17) regioselectivity and enantioselectivity (98% ee). In order to achieve these excellent selectivities, the organolithium reagent needs to be diluted with *n*-hexane and added to a solution of the catalyst and allylic bromide in dichloromethane at −80°C. Methyllithium is an exception where toluene was used for dilution and addition, as the use of *n*-hexane as co-solvent gave solubility problems with this organolithium reagent.

Under the optimised reaction conditions, different alkyl chains in the lithium reagent were tolerated providing excellent regio- and enantioselectivities (Scheme 23). Importantly, the reaction tolerates the presence of aryl halide



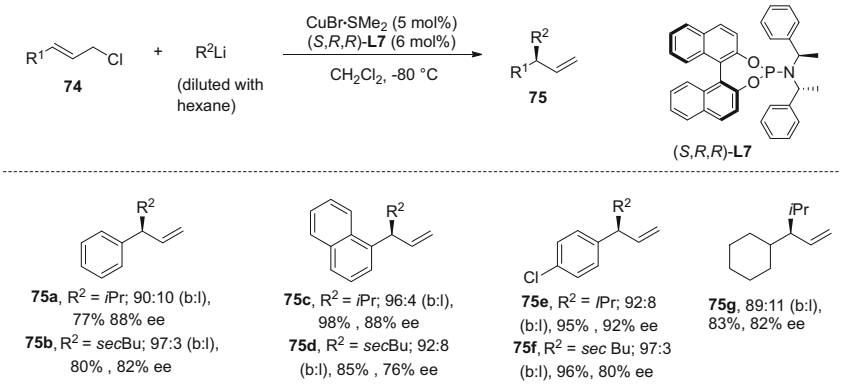
Scheme 24 Cu-(*S*,*S*,*S*)-**L8**-catalysed allylic substitution of allyl chlorides and bromides with primary organolithium reagents

substituents in the allylic system (**70e-g**), without lithium–halogen exchange observed. Sterically demanding groups including 1-naphthyl (**71c-d**) are also well tolerated providing the corresponding AAA products within high ee's (96–99%) although with lower regioselectivity.

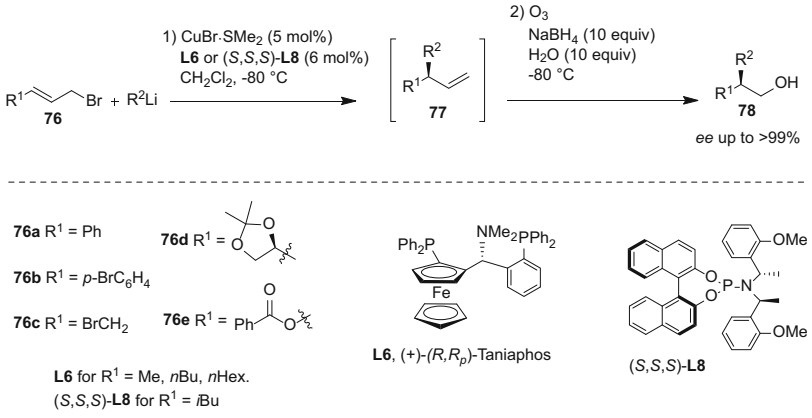
Interestingly, the reaction also tolerates various functional groups known to be sensitive to organolithium compounds. These include benzyloxy- and *N*-Boc-protected amine groups, esters and alcohols.

Unfortunately, the use of the corresponding allyl chlorides employing the optimised catalyst system (CuBr·SMe_2/(*R*,*R*)-Taniaphos, **L6**) led to disappointing selectivities for the S_N2'-alkylated products. Nonetheless, the authors further showed that it was possible to control the selectivity of the reaction, employing both allyl chlorides and bromides by switching the chiral ligand to monodentate phosphoramidite ligands [57]. Screening of these ligands (for a review on the use of phosphoramidite ligands in catalytic asymmetric transformations, see [58]) and conditions in the reaction between cinnamyl chloride **72a** and *n*-BuLi showed that by using a 1:1 mixture of CuBr·SMe_2/(*S*,*S*,*S*)-**L8** as catalyst, the desired product **73a** could be obtained with an excellent S_N2'/S_N2 ratio of 91:9 and 96% ee. Under these conditions, a variety of allyl chlorides **72** were converted into the alkylated product in excellent yield and enantiomeric ratio in nearly all cases. Additionally, the CuBr·SMe_2/(*S*,*S*,*S*)-**L8** system proved also to be very efficient with allyl bromides **70**, thus providing a complementary catalytic procedure for the previous Taniaphos-based method. As observed before, the reaction tolerates the presence of *p*-chloro cinnamyl substituents (**72f-g**), without lithium–halogen exchange. Cyclic and acyclic aliphatic substituents were also tolerated affording the corresponding product although with slightly lower ee values (Scheme 24).

The use of secondary lithium reagents constitutes a second limitation for the CuBr·SMe_2/Taniaphos system [57]. Phosphoramidites were again the most effective ligands, in combination with allyl chlorides, for this transformation, and the use of a CuBr·SMe_2/(*S*,*R*,*R*)-**L7** catalyst system was found to be optimal for the addition of *sec*-BuLi and *i*-PrLi. Interestingly, under these conditions the use of



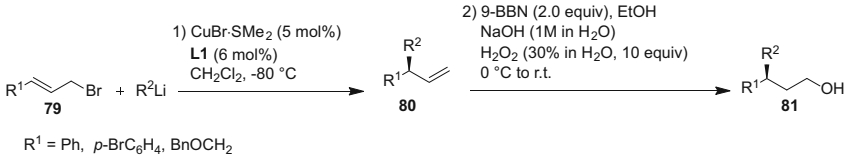
Scheme 25 **Cu/L4**-catalysed allylic substitution of allyl chlorides and bromides with secondary organolithium reagents



Scheme 26 One-pot synthesis of β-alkyl-substituted alcohols **27** through Cu-catalysed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by ozonolysis and reduction

the corresponding allyl bromides led to a decrease in selectivity as observed for the reaction between cinnamyl bromide and *sec*-BuLi (S_N2'/S_N2 79:21, 38% ee). As reported before, this catalyst system tolerates sterically hindered 1-naphthyl-substituted allyl chlorides (**75c**-**d**) or halogen-containing cinnamyl substituents (**75e**-**f**), although lower selectivity was observed for the reaction with cyclohexyl-substituted allyl chloride **75g** (Scheme 25). In general, the transfer of the *sec*-butyl chain proceeds with slightly lower enantioselectivity (up to 82% ee).

As mentioned above, one of the advantages of the AAA reaction is that it gives access to products with a carbon stereogenic centre next to a terminal olefin, which can be further functionalised. Taking advantage of this structural feature, Feringa and co-workers developed a one-pot synthesis of β- and γ-alkyl-substituted alcohols



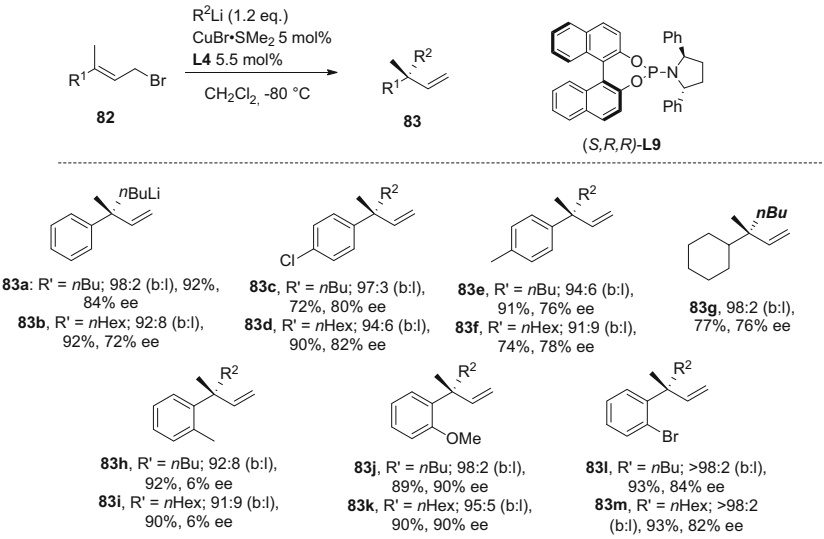
Scheme 27 Synthesis of γ-alkyl-substituted alcohols through Cu-catalysed asymmetric allylic alkylation of allyl bromides with organolithium reagents followed by a hydroboration/oxidation

(**78** and **81,** respectively) (Schemes 26 and 27) through a tandem copper-catalysed asymmetric allylic alkylation (AAA) with organolithium reagents followed by reductive ozonolysis or hydroboration/oxidation, respectively [59]. In the first case, after Cu-catalysed AAA, using **L7** or (*S*,*S*,*S*)**-L8** as ligand, and ozonolysis of the corresponding alkene **77**, the use of ten equivalents of $NaBH_4$ and ten equivalents of water was necessary to achieve full conversion of the desired β-alkyl-substituted alcohols **78**. This one-pot protocol was applied to a variety of lithium reagents such as MeLi, *n*-BuLi and *n*-HexLi and different allylic bromides counterparts, bearing aromatic (**76a**,**b**) and aliphatic substituents (**76c**,**d**), as well as an ester functionality (**76e**), generating the corresponding alcohols with excellent ee's (72–99%) and good overall yields (up to 90%) (Scheme 26).

The corresponding γ-alkylated alcohols **81** were also obtained in good yields (67–93%), without erosion of the enantiomeric excess, when the terminal olefins **80** were subjected to hydroboration/oxidation reaction using 9-BBN (Scheme 27).

To achieve catalytic enantioselective formation of all-carbon quaternary stereogenic centres, a carbon atom bound to four distinct carbon substituents is a considerable synthetic challenge in organic synthesis [60, 61]. In the case of acyclic systems, it is even more complicated due to the number of degrees of freedom associated with these structures. In the past decades, impressive progress has been made in this field, and several synthetic transformations, including enantioselective allylic substitution and conjugate additions, enantioselective alkylation, nucleophilic allylations, aldol reactions, Mannich reactions, rearrangements reactions and catalytic and enantioselective intermolecular Heck-type reactions, have been described for the construction of these highly congested structural moieties [62, 63].

As part of their research programme on the direct use of organolithium reagents in AAA, Feringa and co-workers developed methodologies for the synthesis of all-carbon quaternary stereogenic centres via copper-catalysed AAA of *E*- and *Z*-trisubstituted allyl bromides [57]. While examining the reaction between *n*-BuLi and an *E*-trisubstituted allyl bromide **82a** and after extensive screening of different phosphoramidite ligands, it was found that chiral ligand **L9** was optimal for the reaction, providing product **83a** in high regioselectivity (S_N2'/S_N2 98:2) and good enantioselectivity (84% ee, Scheme 28). Different primary alkyl organolithium reagents gave excellent regioselectivity (up to >98:2) and moderate to good enantioselectivities (ranging from 72% to 84% ee) although the use of secondary alkyllithium compounds was not shown. *p*-Methyl- and *p*-chloro-substituted

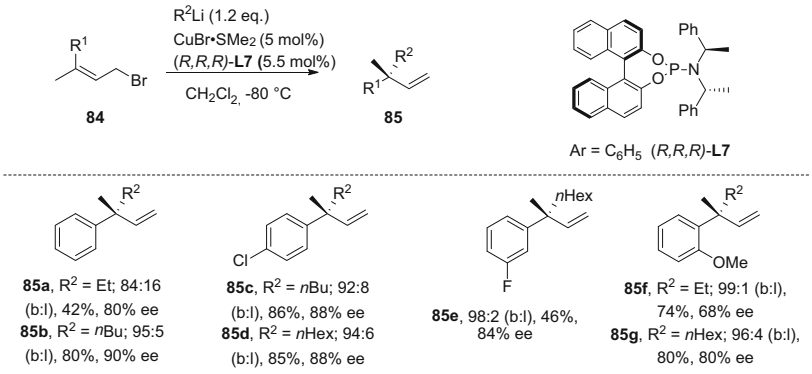


Scheme 28 Enantioselective Cu/**L15**-catalyed synthesis of quaternary carbons with organolithium reagents

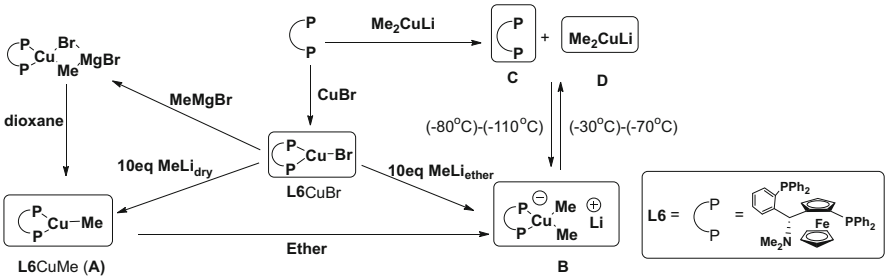
cinnamyl bromides (**82c-f**) were found to be effective electrophilic partners, as well as a cyclohexyl-substituted derivate **82g**.

Interestingly, it was observed that the nature of the *ortho* substituents at the aryl ring plays an important role in the stereochemical outcome of the AAA reaction. The use of simple methyl groups (**83h-i**) led to nearly racemic products, independently of the nature of the organolithium compound used. However, the enantioselectivity was enhanced, when the corresponding *o*-bromo- or *o*-methoxy-substituents (**83j-m**) were used instead. The authors suggest a coordination between these *ortho* substituents and the copper complex as a key parameter in the stereo-discrimination event that allows to achieve these high enantioselectivities (Scheme 28).

In a subsequent report [64], Feringa and co-workers studied the effect of the geometry of the prochiral trisubstituted allyl substrate on the stereochemical outcome of the copper-catalysed AAA with organolithium reagents. Various *Z*-trisubstituted allyl bromides **84** were examined, and it was found that phosphoramidite (*S*,*R*,*R*)-**L9** was the most effective ligand, affording the corresponding all-carbon quaternary stereogenic centres in good enantioselectivities (Scheme 29). As before (Scheme 28), different organolithium reagents including EtLi, *n*-BuLi and *n*-HexLi were tolerated providing good regio- and enantioselectivities (up to 90% ee) (Scheme 29). The substrate scope includes *p*-chloro-, *m*-chloro- and *m*-fluoro-substituted allyl bromides and does not suffer from parasitic lithium–halogen exchange. In general, slightly higher enantiomeric ratios were obtained with Z-allyl bromides **84** when using this catalytic system ($CuBr{\cdot}SMe_2$/(*R*,*R*,*R*)-**L7**) than for the previously reported *E*-allyl bromides (using $CuBr{\cdot}SMe_2$/(*S*,*R*,*R*)-**L9**) [57]. An exception is the use of *o*-methoxy-substituted allyl bromide (**84f**) where a



Scheme 29 Enantioselective Cu-(*R*,*R*,*R*)-**L7**-catalysed synthesis of quaternary carbons with organolithium reagents



Scheme 30 Copper species formed from alkylmagnesium and alkyllithium compounds in the AAA

decrease in the enantiomeric ratio was observed. In contrast with the results obtained by the groups of Hoveyda [65] and Sawamura [66] but in agreement with a previous findings of the Feringa group [42], this catalyst system led to the same enantiomer independently of the use of the E and Z geometry of the trisubstituted allyl bromide. This observation suggests lack of interaction between the copper catalyst and the leaving group of the substrate prior to the oxidative addition taking place during the catalytic cycle.

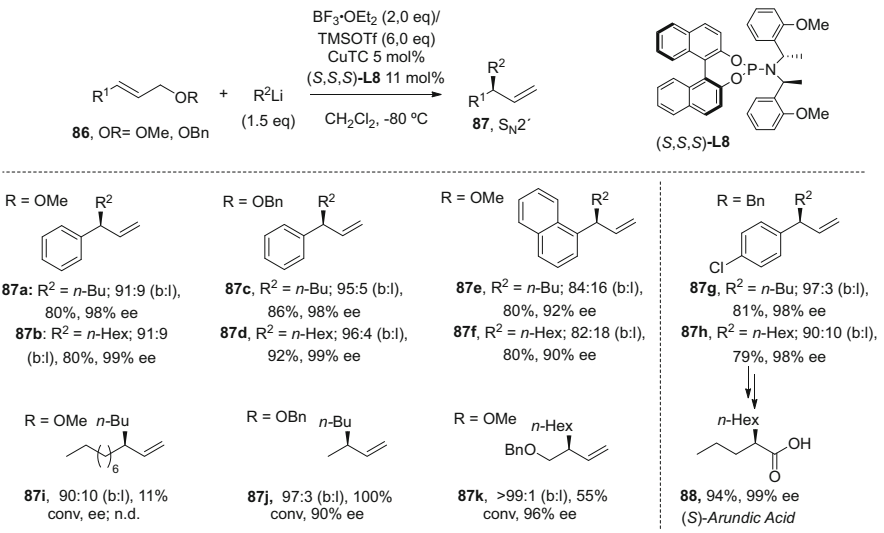
Mechanistic studies were also performed to elucidate the nature of the chiral copper complex which is responsible for the high activity and selectivity in the AAA and to elucidate the dramatic effect of the solvent on the selectivity of the reaction [51, 57]. The effect of different combinations of copper salts, solvents and quantities of MeLi over a range of temperatures by ^{1}H, ^{31}P and $^{6}Li/^{7}Li$ NMR spectroscopy was examined. Similarly to the corresponding Grignard reagents [17, 67], the authors suggested that the first step in the AAA catalytic cycle is the formation of the chiral methyl copper complex, via transmetallation between the methyllithium compound and the ligand-bound copper species (**L6**CuBr). Indeed, by employing an excess of ten equivalents of MeLi and copper complex **L6**CuBr in

CH_2Cl_2 at −80°C, the exclusive formation of **L6**CuMe was observed (complex **A**, Scheme 30). This copper species was independently confirmed via the reaction between **L6**CuBr complex and the corresponding Grignard reagent (MeMgBr or Me_2Mg) followed by removal of $MgBr_2$ by coordination with dioxane [68]. Additionally, the use of stoichiometric amounts of this copper species (**L6**CuMe, **A**) in the AAA of cinnamyl bromide led to the alkylation product with high enantiomeric excess (>98% ee).

Remarkably, lithium does not seem to have any interaction with the active catalyst, unlike with the corresponding Grignard reagents where Mg is part of the catalytically active copper species. Indeed, in the absence of Et_2O, the enantioselectivity of the reaction is independent of the nature of copper source used. When Et_2O was added to the solution, the mixture resulted in the formation of fragile bimetallic **B** that is in a temperature-dependent dynamic equilibrium with the non-ligated organo-cuprate $LiCuMe_2$ **D**. The low enantioselectivity observed (28% ee) when the organolithium compound is diluted (Et_2O) supports the existence of non-ligand-bound cuprate **D**.

Allylic halides are very useful and versatile substrates for the Cu-catalysed AAA with organometallic reagents, with many applications in the synthesis of natural product and pharmaceuticals. Nonetheless, the use of these reactive electrophilic partners could constitute a drawback when the alkylation reaction needs to be performed at the latest stages of a multistep synthesis. A possible solution would consist in the use of more robust and inert leaving groups in the allylic substrate that can initially act as a protecting group along the synthetic sequence, but when desired, it can be activated to operate as a leaving group for the asymmetric alkylation reaction. With this aim, the use of stable alkyl- and aryl-protected allylic ethers as electrophilic partners in Cu-catalysed AAA with organolithium reagents was evaluated [69].

Screening of different allylic esters and ethers in the reaction with *n*-BuLi, in the presence of different Lewis acids for the activation of the allyl ether, revealed that the use of CuTC/(*S*,*S*,*S*)-**L8**, together with a mixture of $BF_3{\cdot}OEt_2$ and TMSOTf, as optimal combination. The use of the $BF_3{\cdot}OEt_2$/TMSOTf mixture, which in situ forms the new Lewis acid BF_2OTf, was found to be indispensable to obtain high selectivity. The reaction does not proceed in the absence of $BF_3{\cdot}OEt_2$, thus allowing the ether to act as a robust protecting group. Under these conditions, similar regio- and enantioselectivities, compared to the previous results, using allyl halides were obtained. High regio- and enantioselectivities were obtained for the reaction between *n*-BuLi and *n*-HexLi with linear aliphatic and aromatic substrates **86**, including the use of hindered 1-naphthyl substituents as well as aromatic chlorides (Scheme 31). An interesting observation was made for a substrate bearing both an allylic -OMe and -OBn ether **86k**, where substitution occurred preferentially towards the -OMe group rather than the -OBn group. The synthetic utility of this novel Cu-catalysed AAA was demonstrated in the three-step asymmetric synthesis of biologically active *(S)-arundic acid* **88**, with high enantioselectivity (>99:1 e.r., Scheme 31).



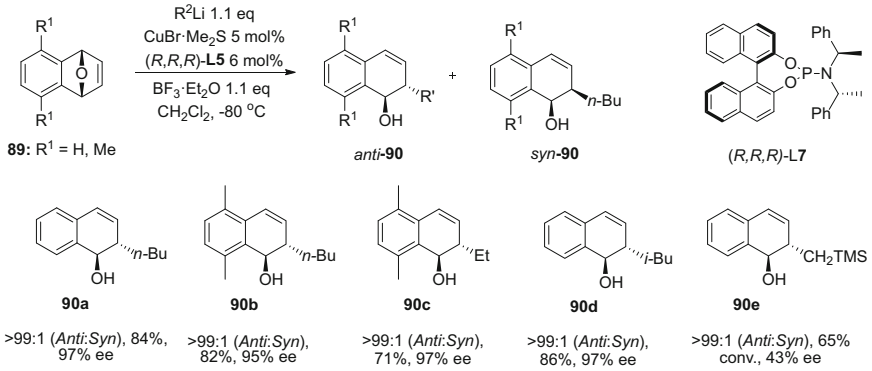
Scheme 31 Copper-catalysed AAA of acyclic allylic ethers with organolithium reagents

The catalytic enantioselective ring opening of oxabicyclic alkenes by carbon-based nucleophiles is a useful method for the simultaneous introduction of multiple stereocentres under high stereocontrol ([70] and references cited therein). Recently, several methods have been developed for ring opening of these *meso* heterobicyclic compounds employing different soft- and organometallic nucleophiles [71, 72].

In general, the use of transition-metal catalysts led to the *syn* product, as a result of the *exo* attack of the nucleophile to the oxabicyclic alkene. Of particular interest is the palladium-based methodology using organozinc reagents, developed by the group of Lautens, which proceeds with high selectivity for the *syn* diastereomer [73]. Exceptions to the formation of the *syn* ring-opened products, leading to high *anti* selectivity, have been reported using copper-based catalysts. In 2002, an unprecedented copper/phosphoramidite-catalysed enantioselective alkylative ring opening of oxabenzonorbornadiene derivatives with dialkylzinc reagents was reported by Minnaard and Feringa [74]. This transformation reaction shows a high level of *anti* stereoselectivity (up to >99:1 *anti*/*syn*). In 2003, the group of Carretero also reported conditions for the copper-catalysed *anti* stereoselective ring opening of oxabicyclic alkenes with Grignard reagents [75].

In 2012, the group of Feringa described the use of organolithium reagents as nucleophiles for the asymmetric ring opening of oxabicyclic alkenes, with excellent *anti* selectivity and enantioselectivity [76].

Screening different reaction parameters in the asymmetric ring opening of compound **89a** with *n*-BuLi, it was found that the use of a copper/phosphoramidite (*R*,*R*,*R*)-**L7** complex, together with a Lewis acid ($BF_3 \cdot OEt_2$) at −80°C, allowed for the exclusive formation of the *anti* diastereoisomer with excellent



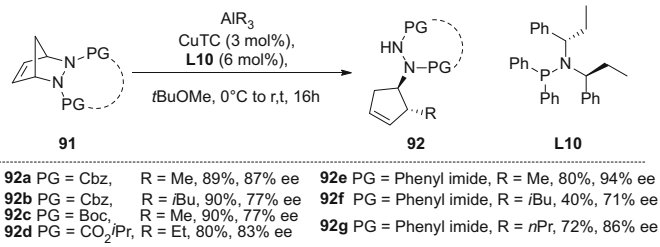
Scheme 32 Cu-catalysed asymmetric ring opening of oxabicyclic substrate **89** with organolithium reagents

enantioselectivity (97% ee). The reaction tolerates the use of primary (*n*-BuLi, *n*-HexLi, EtLi) and secondary organolithium compounds (*i*-BuLi) providing in all cases full conversion and high selectivity towards the desired *anti* products **90**. (Scheme 32). Remarkably, the bifunctionalised organolithium reagent, $TMSCH_2Li$, was used for the first time in a catalytic asymmetric process although decreased reactivity and enantioselectivity were observed (**90e**, 43% ee).

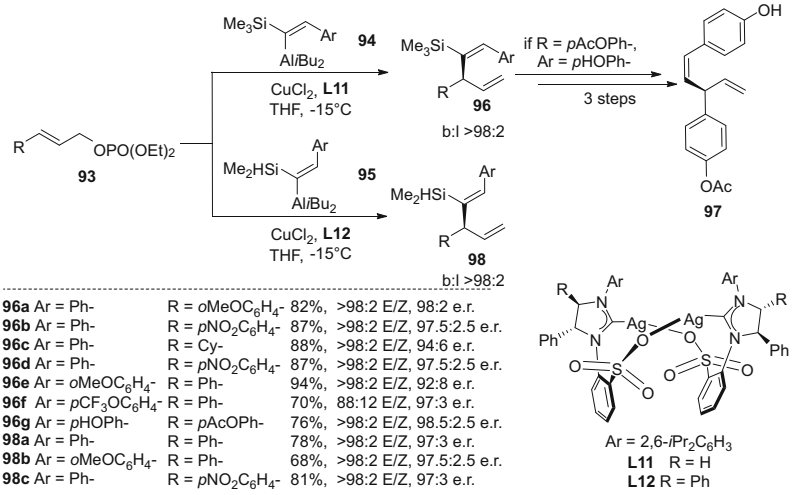
4 Asymmetric Allylic Substitutions Using Organoaluminium, Zinc and Zirconium Reagents

In 2010, Alexakis and co-workers reported the enantioselective ring opening desymmetrisation of meso-hydrazines with trialkylaluminium reagents catalysed by copper (Scheme 33) [77]. This process is proposed to follow a classical allylic substitution pathway, with the organoaluminium reagent playing an important role in the activation of the leaving group taking advantage of its Lewis acidity, in addition to being an alkyl donor. After testing several ligands, SimplePhos **L10** proved to be optimal allowing for various organoaluminium species to selectively add onto *N*-carbamate-protected meso-hydrazines **91** in good yields (up to 90%) and selectivities (94% ee). Phosphoramidites were also tested as ligands but, in some cases, cleaved to the corresponding phosphine amines, resulting in poor selectivities as a consequence.

In 2010, Hoveyda and co-workers tackled the problem of the stereo- and enantioselective synthesis of chiral 1,4-dienes, using allylic substitution, and developed an efficient *one-pot* protocol to access these valuable intermediates [78]. They showed that by reacting vinylaluminium reagents with allylic phosphates **93** in the presence of a copper–NHC catalyst **L11–12**, it was possible to obtain both geometrically and enantiomerically pure 1,4-dienes in excellent yields. This is



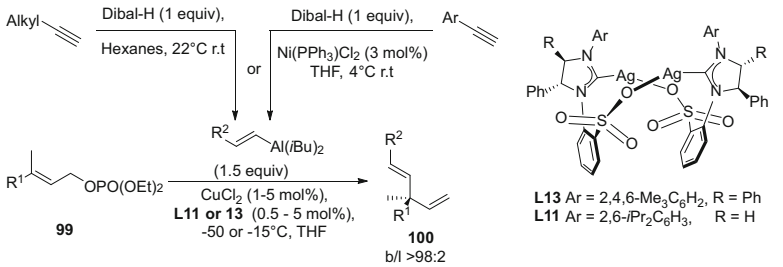
Scheme 33 Copper-catalysed ring opening of meso-hydrazines



Scheme 34 Copper-catalysed enantioselective synthesis of 1,4-dienes containing Z or E alkenes

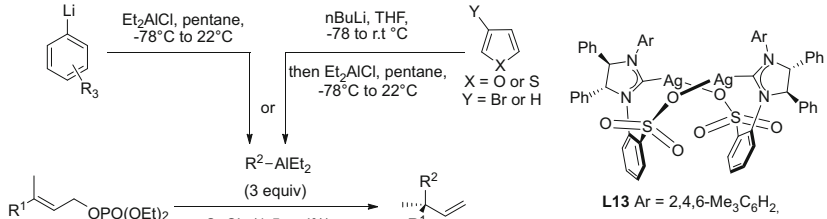
achieved by carefully controlling the *E*/*Z* geometry of the starting vinylaluminium reagent as the olefin's stereo information is transferred without erosion to the final product during this reaction (Scheme 34). Both electron-rich and electron-poor allylic phosphates perform well in combination with diverse aromatic vinyl aluminium reagents (Scheme 34, entries **96a-g, 98a-c**). Further exploring this method, they were able to achieve the first enantioselective synthesis of *nyasol* **97** (Scheme 34, upper, **96g**).

As a follow-up of the aforementioned studies, Hoveyda and co-workers then addressed one of the limitations in scope their method still had. Indeed, more sterically demanding Si-containing aryl vinyl aluminiums were incompatible with the reaction conditions. Hence, they turned their attention to alternative methods for the preparation of organoaluminiums compatible with the asymmetric allylic substitution of allylic phosphates for the formation of quaternary stereogenic centres. Firstly, they studied the enantioselective substitution of alkyl vinyl aluminiums obtained from the hydroalumination with DIBAL-H of alkyl-substituted alkynes (Scheme 35) [65]. When the proper catalyst is chosen (**L11** as chiral ligand), this



100a R^1 = Ph-	R^2 = *n*Hexyl-	82%, 93.5:6.5 e.r.	**100f** R^1 = Ph-	R^2 = *p*MeOC$_6$H$_4$-	84%, 96.5:3.5 e.r.
100b R^1 = *o*MeOC$_6$H$_4$-	R^2 = *n*Hexyl-	83%, 97.5:2.5 e.r.	**100g** R^1 = *o*BrC$_6$H$_4$-	R^2 = Ph-	91%, 98:2 e.r.
100c R^1 = *p*NO$_2$C$_6$H$_4$-	R^2 = *n*Hexyl-	91%, 94.5:5.5 e.r.	**100h** R^1 = *p*NO$_2$C$_6$H$_4$- .	R^2 = Ph-	84%, 93:7 e.r.
100d R^1 = Cy-	R^2 = *n*Hexyl-	91%, 95:5 e.r.	**100i** R^1 = Me$_2$CCH(CH$_2$)$_2$-	R^2 = *p*MeOC$_6$H$_4$-	90%, 91:9 e.r.
100e R^1 = PhMe$_2$Si-	R_2 = *t*Bu-	>98%, 91:9 e.r.	**100j** R^1 = Me$_2$CCH(CH$_2$)$_2$-	R^2 = *p*CF$_3$OC$_6$H$_4$-	79%, 87:13 e.r.

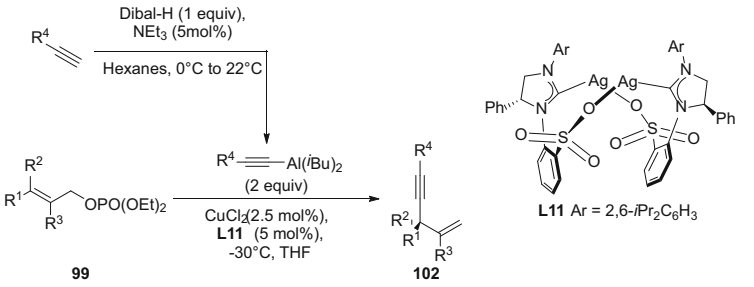
Scheme 35 Copper-catalysed enantioselective synthesis of 1,4-dienes via hydroalumination



101k R^1 = *t*BuCO$_2$-	R^2 = Ph-	98%, 91:9 e.r.	**101p** R^1 = *o*MeOC$_6$H$_4$-	R^2 = 2-furyl-	95%, >98:2 e.r.
101l R^1 = *t*BuCO$_2$-	R^2 = *p*MeOC$_6$H$_4$-	87%, 90.5:9.5 e.r.	**101q** R^1 = Ph-	R^2 = 3-furyl-	90%, 97:3 e.r.
101m R^1 = *t*BuCO$_2$-	R^2 = *p*CF$_3$OC$_6$H$_4$-	88%, 83:17 e.r.	**101r** R^1 = *o*BrOC$_6$H$_4$-	R^2 = 2-thienyl-	98%, 98:2 e.r.
101n R^1 = PhMe$_2$Si-	R^2 = Ph-	81%, 96:4 e.r.	**101s** R^1 = *p*NO$_2$C$_6$H$_4$-	R^2 = 2-thienyl-	96%, 94:6 e.r.
101o R^1 = PhMe$_2$Si-	R^2 = *p*MeOC$_6$H$_4$-	97%, 97:3 e.r.	**101t** R^1 = *o*BrC$_6$H$_4$-	R^2 = 3-thienyl-	89%, 97:3 e.r.

Scheme 36 Copper-catalysed enantioselective synthesis of diaryl bearing quaternary carbon stereogenic centres

reaction proceeds to provide good yields and high regio- and enantioselectivities with a wide range of substrates (Scheme 35, entries **100a-e**). Secondly, they focused on aryl-substituted organoaluminium reagents. These proved more challenging, as a non-negligible amount of alkynyl addition product was formed under standard conditions. This most probably results from the deprotonation of the corresponding alkyne to afford the alkynylaluminium which subsequently reacts with the allyl phosphate. This issue was solved by the addition of a catalytic amount of Ni$(PPh_3)_2Cl_2$ during the hydroalumination step, which significantly enhanced the rate of the desired reaction, thereby eliminating the formation of the by-product. This mixture, when added to the allyl phosphate in the presence of copper chloride and **L13**, gave the allylic substitution product with good yields and high regio- and enantioselectivities with a range of substrates (Scheme 35, entries **100f-j**).



R^2 = Me, R^3 = H

102a R^1 = Ph- R^4 = Ph- 98%, 95:5 e.r.
102b R^1 = $pCF_3C_6H_4$- R^4 = Ph- >98%, 92:8 e.r.
102c R^1 = $pNO_2C_6H_4$- R^4 = Ph- >98%, 92:8 e.r.
102d R^1 = $pClC_6H_4$- R^4 = Cy- >98%, 96:4 e.r..
102e R^1 = $oBrC_6H_4$- R^4 = Cyclohexenyl- >98%, >99:1 e.r.
102f R^1 = $oMeOC_6H_4$- R^4 = $oClC_6H_4$- >98%, >99:1 e.r.
102g R^1 = $tBuO_2C$- R^4 = 3-thionyl- 96%, 98:2 e.r.
102h R^1 = Me_2PhSi- R^4 = mFC_6H_4- 91%, 96:4 e.r.

R^2 = H, R^3 = -CO_2Me

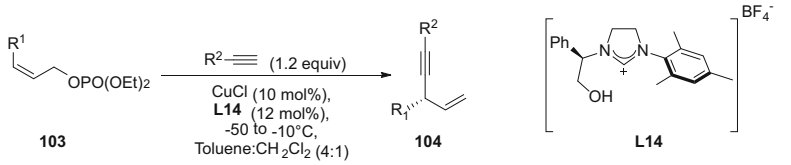
102i R^1 = $oMeOC_6H_4$- R^4 = Ph- 58%, 97:3 e.r.
102j R^1 = $pBrC_6H_4$- R^4 = Ph- 98%, 92:8 e.r.
102k R^1 = $pBrC_6H_4$- R^4 = 3-thionyl- >98%, 90:10 e.r.
102l R^1 = Ph- R^4 = Cy- 84%, 98:2 e.r.

Scheme 37 Copper-catalysed enantioselective synthesis of alkyne-substituted stereogenic centres

In parallel Hoveyda and co-workers also studied the asymmetric allylic substitution of arylaluminium species on similar allyl phosphates to generate valuable and difficult to obtain diaryl compounds bearing chiral quaternary carbon stereocentres (Scheme 36) [65, 77–79]. By reacting aryllithium species with diethylaluminium chloride, followed by direct addition to an allyl phosphate in conjunction with copper and N-heterocyclic carbene ligand **L13**, quaternary stereocentres were obtained in excellent yields and good enantiomeric ratios for both aromatic and heteroaromatic compounds.

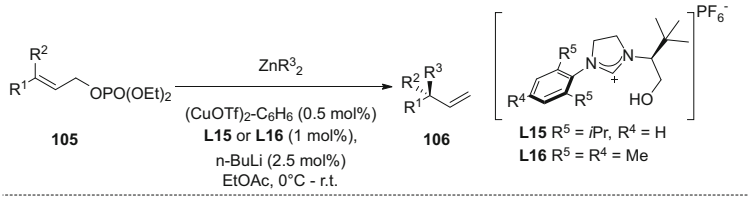
Hoveyda and co-workers also exploited the reactivity of the alkynyl aluminium compounds for the formation of alkyne-substituted stereogenic centres, which were initially observed as a by-product during their study of the synthesis of 1,4-dienes via hydroalumination (Scheme 35) [73]. By altering the previous hydroalumination protocol and adding a catalytic amount of triethylamine instead of a nickel catalyst to the reaction mixture, they could switch the selectivity of that step to give solely the alkynylaluminium intermediate. These could then be used under similar conditions to give the corresponding alkyne-substituted enantiopure quaternary stereogenic centres with various substrates (Scheme 37, entries **102a**-**h**) [37]. Subsequently it was also shown that ester-substituted allyl phosphates could also serve as substrates for this reaction (Scheme 37, entries **102i**-**l**) [80].

Recently Ohmiya and Sawamura reported a similar transformation based on in situ formed lithium acetylides [81]. With the perspective of expanding the scope of existing methods by avoiding the need for organoaluminium species, which had a strong impact on the functional group tolerance of the reaction, they investigated the possibility of using lithium acetylides obtained by deprotonation of terminal alkynes in combination with (*Z*)-allyl phosphates and a copper N-heterocyclic



104a R^1 = Et- R^2 = iPr$_3$Si- 75%, 90% ee
104b R^1 = BocO(CH$_2$)$_3$- R^2 = iPr$_3$Si- 76%, 90% ee
104c R^1 = TsO(CH$_2$)$_3$- R^2 = iPr$_3$Si- 65%, 95% ee
104d R^1 = pCNC$_6$H$_4$C(O)O(CH$_2$)$_3$- R^2 = iPr$_3$Si- 79%, 92% ee
104e R^1 = Ph(CH$_2$)$_2$- R^2 = Me$_3$Si- 73%, 74% ee
104f R^1 = Ph(CH$_2$)$_2$- R^2 = tBu- 65%, 83% ee
104g R^1 = Ph(CH$_2$)$_2$- R^2 = Ph- 64%, 65% ee
104h R^1 = Ph(CH$_2$)$_2$- R^2 = Cyclohexenyl- 85%, 70% ee

Scheme 38 Copper-catalysed enantioselective allylic alkylation of terminal alkynes



with **L15** R^2 = H
106a R^1 = Ph, R^3 = Et, 90%, 96% ee
106b R^1 = Ph, R^3 = nBu, 85%, 95% ee
106c R^1 = naph-, R^3 = Me-, 69%, >98% ee
106d R^1 = cyclohexyl-, R^3 = Et-, 82%, 93% ee

with **L16** R^2 = Me
106e R^1 = Ph, R^3 = Et, 82%, 82% ee
106f R^1 = 2-naph, R^3 = Et, 76%, 92% ee
106g R^1 = oBrC$_6$H$_4$-, R^3 = Me-, 75%, 90% ee

Scheme 39 Hydroxyalkyl NHC copper-catalysed enantioselective allylic alkylation on allylic diethyl phosphates

carbene catalytic system (Scheme 38). Mechanistical investigations showed that the presence of the coordinating phenol group on the ligand (**L14**) was crucial to obtain high enantioselectivities. First, it avoided ligand dissociation, which had proven problematic, and second it allowed for a tighter bridged transition state between the counteranion, acetylide carbon and phosphate leaving group resulting in a regio- and enantiodiscriminating step and showing higher selectivity. The geometry of the allyl double bond proved also to be crucial as (*E*)-allyl phosphates gave poor yields and enantioselectivities.

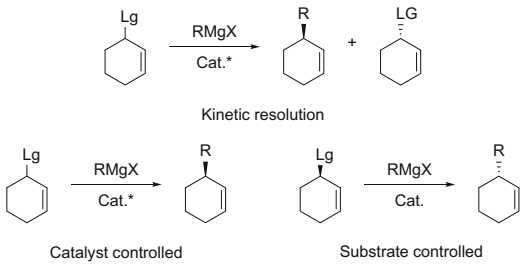
Mauduit and co-workers explored the effect of various ligands on copper-catalysed enantioselective allylic alkylation reactions and showed that chelating hydroxyalkyl NHCs were efficient ligands for the asymmetric alkylation of organozinc reagents to allylic diethyl phosphates (Scheme 39, entries **106a-d**) [82]. After a screening of their ligands towards this reaction in several solvents, it became apparent that a combination of copper(I) triflate and ligand **L15** in ethyl acetate at room temperature afforded good yields and selectivities for this transformation, even at low catalyst loadings. Subsequently the use of a novel family of NHC's was reported for the reaction between organozinc reagents and 3-methyl-

allyl phosphates to generate quaternary centres under the same conditions, with **L16** providing the best results (Scheme 39, entries **106e-g**) [83].

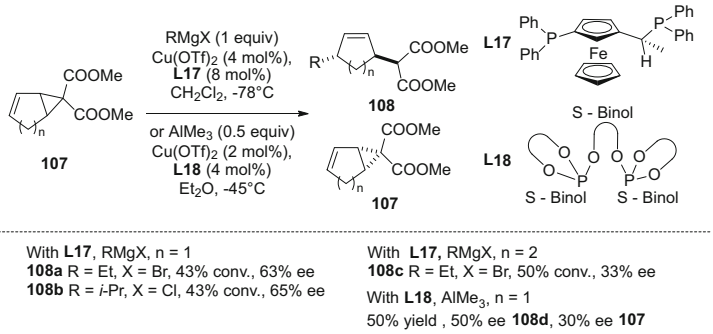
5 Asymmetric Allylic Substitutions on Racemic Substrates with Organometallic Reagents

In addition to the previously described examples of copper-catalysed asymmetric allylic alkylation on non-chiral substrates using organometallic reagents, some reports, dedicated to performing the same reaction on chiral compounds, have appeared over the past few years. Carrying out allylic substitution on this type of substrates remains a great challenge due to the additional and distinct diastereomeric interactions existing between the catalyst and each enantiomer, in comparison to non-chiral substrates. These different interactions, and therefore reactivity, have been taken as an advantage to perform kinetic resolutions on certain racemic allylic substrates [84]. However, the major limitation of simple kinetic resolution, a maximum theoretical yield of 50%, has led to a shift in focus to other, novel, mechanistic concepts which, in theory, allow for the quantitative allylic alkylation of racemic compounds [37, 65, 77–86]. These revolve around two major principles, the first involves constructing a catalytic cycle containing a step in which the chiral information in the starting substrate is erased, followed by a step in which new chiral information is introduced. This was done either by inducing rapid interconversion between the two starting enantiomers, with only one being reactive (dynamic kinetic resolution), or by developing a system which is able to pass via either a C2 symmetrical or a meso transition state (dynamic kinetic asymmetric transformation). A second approach involves establishing two enantioconvergent pathways from each enantiomer to the same product (for one of the first examples, see [87]). Reactions where the configuration of the starting substrate dictates the stereochemical outcome of the reaction, called enantiospecific allylic alkylations, are not pertinent to this chapter and will therefore not be treated here (Scheme 40) (for a review covering these, see [88]).

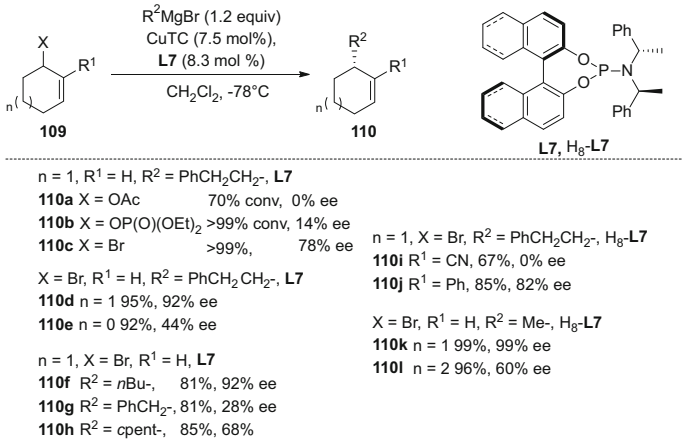
Alexakis and co-workers employed copper in conjunction with a variety of ligands to perform the kinetic resolution of cyclic alkenyl cyclopropane malonates using trimethylaluminium or alkylmagnesium reagents in moderate yields and



Scheme 40 Substrate-controlled vs. catalyst-controlled allylic alkylation on chiral substrates



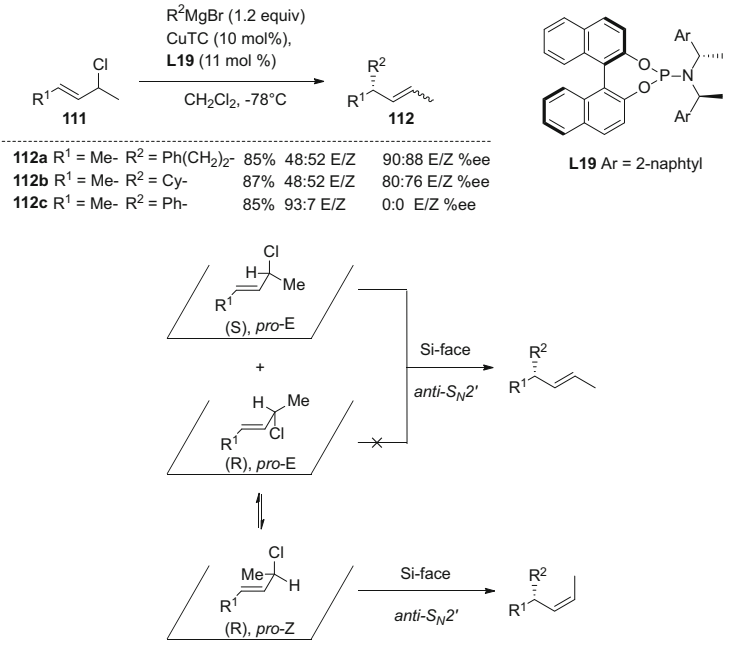
Scheme 41 Kinetic resolution of cyclic alkenyl cyclopropane malonates



Scheme 42 Copper-catalysed asymmetric allylic alkylation of racemic cyclic substrates

selectivities (Scheme 41) [89]. Of the diverse ligands tested, ferrocenyl-based **L17** gave the best overall results. Under these conditions, organozinc as well as arylmagnesium reagents failed to react.

In the same year Alexakis and co-workers also described the copper-catalysed allylic alkylation of organomagnesium reagents onto racemic cyclic substrates **109**. They based themselves on the idea that a dynamic kinetic asymmetric transformation could be employed to reach an enantiopure product starting from a mixture of both enantiomers [90]. After extensive screening, it was shown that phosphoramidite ligands gave the best results and that the outcome of the reaction was strongly dependent on both the solvent and leaving group used (Scheme 42, **110a-c**). Preliminary mechanistical investigations suggested that the outcome of the reaction was indeed governed by a dynamic kinetic asymmetric transformation. In terms of scope, a wide range of organomagnesium reagents were tested to provide good yields and moderate to good enantioselectivities (Scheme 42, **110c**, **110f-h**,

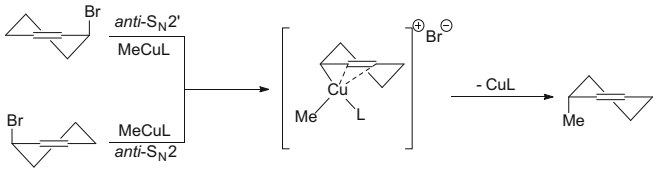


Scheme 43 Copper-catalysed asymmetric allylic alkylation of racemic substrates

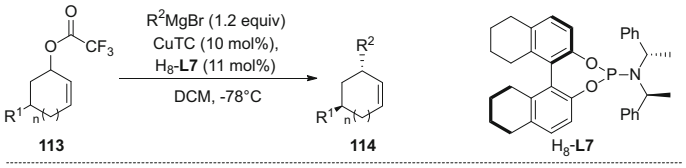
110k-l). The reaction also tolerates cyclic substrates of diverse sizes and substitution patterns, though only 3-bromocyclohexanes gave good results, while larger rings yield only moderate selectivities (Scheme 42, **110d-e**, **110i-l**).

In a follow-up study, Alexakis and co-workers investigated whether their dynamic kinetic asymmetric transformation could be applied to non-cyclic substrates [91]. Here, it was observed, after some optimisation, that (*E*)-4-chloropent-2-enes **111** smoothly reacted with an organomagnesium reagent to give a mixture of enantio-enriched E/Z-alkylated products **112** with the same absolute configuration for both isomers. Based on experimental observations, the authors postulate that the catalyst, due to substrate–ligand interactions with the vinylic methyl group ($R^1 = Me$), will react in an *anti*-fashion, specifically with the Si face of the substrate, and, hence, force one enantiomer to take a pro-Z conformation before reacting (Scheme 43). This behaviour, named stereodivergent kinetic resolution, was consistent with several alkylmagnesium species, but failed when arylmagnesiums were used.

In 2012 Alexakis and co-workers, prompted by the uncertainties remaining in their mechanistic investigations of their allylic alkylation of racemic cyclic substrates, extended their study of the mechanism of the reaction by turning to computational methods and deuterium-labelling experiments [92]. Modelling of the potential transition states, with emphasis on the interaction of each enantiomer with the ligand, pointed towards the fact that, rather than undergoing a dynamic

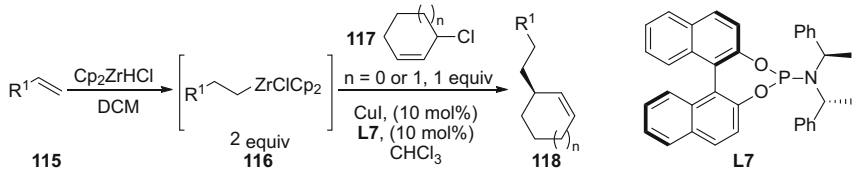


Scheme 44 Enantioconvergent pathway proposed by Alexakis and co-workers



114a n = 1, R^1 = H, R^2 = $Ph(CH_2)_2$- 85%, 97% ee
114b n = 1, R^1 = H, R^2 = *c*pent- 86%, 90% ee
114c n = 1, R^1 = Me, R^2 = $Ph(CH_2)_2$- 80%, 93% ee
114d n = 0, R^1 = H, R^2 = $Ph(CH_2)_2$- 78%, 62% ee

Scheme 45 Copper-catalysed asymmetric allylic alkylation of racemic cyclic substrates with trifluoroacetate as leaving group



118a n = 1 R^1 = *n*Bu- 56%, 95% ee
118b n = 1 R^1 = TMS- 52%, 93% ee
118c n = 1 R^1 = *o*BrC_6H_4- 87%, 87% ee
118d n = 1 R^1 = *p*$MeOC_6H_4$- 63%, 95% ee
118e n = 0 R^1 = $Ph(CH_2)_2$- 57%, 92% ee
118f n = 0 R^1 = $Br(CH_2)_9$- 42%, 92% ee

Scheme 46 Dynamic kinetic asymmetric allylic alkylation of 3-substituted cyclohexenes

kinetic resolution based on a common meso-π-allyl intermediate, the reaction proceeds via two divergent pathways for each enantiomer. One proceeds via an *anti*-S_N2' pathway, while the other involves an *anti*-S_N2 pathway due to different interactions with the ligand during approach by the metal (Scheme 44). These results are supported by deuterium-labelling experiments, which show a relatively equal partition of S_N2 and S_N2' addition products with two different reaction rates for the formation of each and are coherent with previous studies by Pineschi and Feringa [93, 94].

This allowed the optimisation of the allylic alkylation of racemic cyclic substrates with trifluoroacetate as leaving group to provide good yields and enantioselectivities (Scheme 45).

Early 2015 Fletcher and co-workers reported the use organozirconium reagents for the dynamic kinetic asymmetric allylic alkylation of racemic 3-substituted cyclohexenes (Scheme 46) [95]. By generating in situ organozirconium reagents from terminal alkenes with Schwartz's reagent (Cp_2ZrHCl) and adding these to 3-substituted cyclohexenes, in the presence of a copper/phosphoramidite (*R*,*R*,*R*)-**L7** catalytic system, the corresponding chiral 3-alkyl-substituted cyclohexenes **118** were obtained in good yields and with excellent enantioselectivities. Interestingly, the counteranion in the copper salt proved key to the transformation with copper iodine reaching significantly higher yields than copper chloride or bromide under the same conditions. NMR studies of the potential mechanism of the reaction suggest that the iodine present in the mixture, under the influence of the copper, plays a role in the racemisation of the starting material during the reaction, potentially allowing for dynamic kinetic resolution. However, the exact role of the counteranion, as well as evidence pointing towards multiple copper ligand aggregates, makes it yet unclear as to the nature of the interactions of each enantiomer with the catalyst and whether this process is a resolution or an enantioconvergent reaction. This method provided a valuable intermediate (Scheme 46, entry **118f**) for the asymmetric total synthesis of *chaulmoogric acid* and *anthelmintic in C*.

As an extension, Fletcher and co-workers evaluated their methodology towards the performance of vinylzirconium compounds under these conditions [96]. However, despite extensive optimisation of reaction conditions, only moderate enantioselectivities could be reached (up to 19:81 e.r.). Nonetheless this demonstrated the possibility of using these sp^2-hybridised reagents in the context of copper-catalysed allylic alkylation via dynamic kinetic resolution.

In conclusion, asymmetric allylic alkylation has evolved into one of the key catalytic enantioselective C–C bond formations. The use of hard organometallic reagents (i.e. organozinc, Grignard, organolithium) and copper catalysis, showing excellent chemo-, regio- and enantioselectivities, provides highly versatile synthetic methodology which is complementary to the Tsuji–Trost palladium-catalysed allylation with soft carbon nucleophiles. With a variety of protocols and chiral catalysts for both cyclic and acyclic substrates available, including those allowing the formation of all-carbon quaternary stereocentres, AAA has now gained a firm position in our synthetic repertoire.

References

1. Blaser HU, Federsel HJ (2010) Asymmetric catalysis on industrial scale. Wiley, Weinheim
2. Ojima I (2000) Catalytic asymmetric synthesis, 2nd edn. Wiley, New York
3. Jacobsen EN, Pfaltz A, Yamamoto H (1999) Comprehensive asymmetric catalysis I–III. Springer, Berlin
4. Ojima I (2013) Catalytic asymmetric synthesis. Wiley, Weinheim
5. Karlström ASE, Bäckvall JE (2002) In: Krause N (ed) Copper-Mediated Enantioselective Substitution Reactions. Modern organocopper chemistry. Wiley, Weinheim, pp 259–288

6. Yorimitsu H, Oshima K (2005) Recent progress in asymmetric allylic substitutions catalyzed by chiral copper complexes. Angew Chem Int Ed 44:4435–4439
7. Geurts K, Fletcher SP, van Zijl AW, Minnaard AJ, Feringa BL (2008) Copper catalyzed asymmetric allylic substitution reactions with organozinc and Grignard reagents. Pure Appl Chem 80:1025–1037
8. Harutyunyan SR, den Hartog T, Geurts K, Minnaard AJ, Feringa BL (2008) Catalytic asymmetric conjugate addition and allylic alkylation with Grignard reagent. Chem Rev 108:2824–2852
9. Alexakis A, Bäckvall JE, Krause N, Pamies O, Dieguez M (2008) Enantioselective copper-catalyzed conjugate addition and allylic substitution reactions. Chem Rev 108:2796–2823
10. Falciola CA, Alexakis A (2008) Copper catalyzed asymmetric allylic alkylation. Eur J Org Chem 22:3765–3780
11. Langlois JB, Alexakis A (2012) Copper-catalyzed enantioselective allylic substitution. Top Organomet Chem 38:235–268
12. Baslé O, Denicourt-Nowicki A, Crévisy C, Mauduit M (2014) In: Alexakis A, Krause N, Woodward S (eds) Copper-catalyzed asymmetric synthesis. Wiley, Weinheim
13. Trost BM, Crawey ML (2003) Asymmetric transition-metal-catalyzed allylic alkylations: applications in total synthesis. Chem Rev 103:2921–2944
14. Trost BM (2004) Asymmetric allylic alkylation, an enabling methodology. J Org Chem 69:5813–5837
15. Lu Z, Ma SM (2008) Metal-catalyzed enantioselective allylation in asymmetric synthesis. Angew Chem Int Ed 47:258–297
16. Milhau L, Guiry PJ (2012) Palladium-catalyzed enantioselective allylic substitution. Top Organomet Chem 38:95–154
17. Yoshikai N, Nakamura E (2011) Mechanisms of nucleophilic organocopper(I) reactions. Chem Rev 112:2339–2372
18. Vanklaveren M, Persson ESM, Delvillar A, Grove DM, Bäckvall JE, van Koten G (1995) Chiral arenethiolatocopper(I) catalyzed substitution reactions of acyclic allylic substrates with Grignard reagents. Tetrahedron Lett 36:3059–3062
19. Meuzelaar GJ, Karlstrom ASE, van Klaveren M, Persson ESM, del Villar A, van Koten G (2000) Asymmetric Induction in the arenethiolatocopper(I)-catalyzed substitution reaction of Grignard reagents with allylic substrates. Tetrahedron 56:2895–2903
20. Karlstrom ASE, Huerta FF, Meuzelaar GJ, Bäckvall JE (2001) Ferrocenyl thiolates as ligands in the enantioselective copper-catalyzed substitution of allylic acetates with Grignard reagents. Synlett 923–926
21. Cotton HK, Norinder J, Bäckvall JE (2006) Screening of ligands in the asymmetric metallocenethiolatocopper(I)-catalyzed allylic substitution with Grignard reagents. Tetrahedron 62:5632–5640
22. Dübner F, Knockel P (1999) Copper(I)-catalyzed enantioselective substitution of allyl chlorides with diorganozinc compounds. Angew Chem Int Ed 38:379–381
23. Malda H, van Zijl AW, Arnold LA, Feringa BL (2001) Enantioselective copper-catalyzed allylic alkylation with dialkylzincs using phosphoramidite ligands. Org Lett 3:1169–1171
24. Feringa BL, Badorrey R, Pena D, Harutyunyan SR, Minnaard AJ (2004) Copper-catalyzed asymmetric conjugate addition of Grignard reagents to cyclic enones. Proc Natl Acad Sci U S A 101:5834–5838
25. Alexakis A, Malan C, Lea L, Benhaim C, Fournioux X (2001) Enantioselective copper catalyzed S_N2' substitution with Grignard reagents. Synlett 927–930
26. Lölsberg W, Ye S, Schmalz HG (2010) Enantioselective copper catalyzed allylic alkylation of cinnamyl chlorides by Grignard reagent using chiral phosphine-phosphite ligands. Adv Synth Catal 352:2023–2031
27. Lölsberg W, Werle S, Neudörfl JM, Schmalz HG (2012) An enantioselective total synthesis of helioporins C and E. Org Lett 14:5996–5999

28. Fang F, Zhang H, Xie F, Yang G, Zhang W (2010) Highly enantioselective copper-catalyzed allylic alkylation with atropos phosphoramidites bearing a D2-symmetric biphenyl backbone. Tetrahedron 66:3593–3598
29. Magre M, Mazuela J, Diéguez M, Pàmies O, Alexakis A (2012) Furanoside phosphite-phosphoroamidite and diphosphoroamidite ligands applied to asymmetric Cu-catalyzed allylic substitution reactions. Tetrahedron Asymmetry 23:67–71
30. Magrez M, Le Guen Y, Baslé O, Crévisy C, Mauduit M (2013) Bidentate hydroxyalkyl NHC ligands for the copper-catalyzed asymmetric allylic substitution of allyl phosphates with Grignard reagents. Chem Eur J 19:1199–1203
31. Van der Molen NC, Tiemersma-Wegman TD, Fañanás-Mastral M, Feringa BL (2015) Regio- and enantioselective copper-catalyzed allylic alkylation of *ortho*-substituted cinnamyl bromides with Grignard reagents. J Org Chem 80:4981–4984
32. Hornillos V, Pérez M, Fañanás-Mastral M, Feringa BL (2013) Copper-catalyzed enantioselective allyl-allyl cross-coupling. J Am Chem Soc 135:2140–2143
33. Selim KB, Matsumoto Y, Yamada K, Tomioka K (2009) Efficient chiral N-heterocyclic carbene/copper(I)-catalyzed asymmetric allylic arylation with aryl Grignard reagents. Angew Chem Int Ed 48:8733–8735
34. Selim KB, Nakanishi H, Matsumoto Y, Yamamoto Y, Yamada K, Tomioka K (2011) Chiral N-heterocyclic carbene-copper(I)-catalyzed asymmetric allylic arylation of aliphatic allylic bromides: steric and electronic effects on γ-selectivity. J Org Chem 76:1398–1408
35. Huang Y, Fañanás-Mastral M, Minnaard AJ, Feringa BL (2013) A novel catalytic asymmetric route towards skipped dienes with a methyl-substituted central stereogenic carbon. Chem Commun 49:3309–3311
36. Li H, Alexakis A (2012) Enyne chlorides: Substrates for copper catalyzed asymmetric allylic alkylation. Angew Chem Int Ed 51:1055–1058
37. Dabrowski JA, Gao F, Hoveyda AH (2011) Enantioselective synthesis of alkyne-substituted quaternary carbon stereogenic centers through NHC−Cu-catalyzed allylic substitution reactions with $(i\mathrm{Bu})_2$(alkynyl)aluminum reagents. J Am Chem Soc 133:4778–4781
38. Fananas-Mastral M, Feringa BL (2010) Copper-catalyzed regio- and enantioselective synthesis of chiral enol acetates and beta-substituted aldehydes. J Am Chem Soc 132:13152–13153
39. Giannerini M, Fañanás-Mastral M, Feringa BL (2012) Z-selective copper-catalyzed asymmetric allylic alkylation with Grignard reagents. J Am Chem Soc 134:4108–4111
40. Li H, Müller D, Guénée L, Alexakis A (2012) Copper-catalyzed enantioselective synthesis of axially chiral allenes. Org Lett 14:5880–5883
41. Den Hartog T, Macía B, Minnaard AJ, Feringa BL (2010) Copper catalyzed asymmetric allylic alkylation of halocrotonates: efficient synthesis of versatile chiral multifunctional building blocks. Adv Synth Catal 352:999–1013
42. Hornillos V, Pérez M, Fañanás-Mastral M, Feringa BL (2013) Cu-catalyzed asymmetric allylic alkylation of phosphonates and phosphine oxides with Grignard reagents. Chem Eur J 19:5432–5441
43. Hornillos V, van Zijl AW, Feringa BL (2012) Catalytic asymmetric synthesis of chromenes and tetrahydroquinolines via sequential allylic alkylation and intramolecular Heck coupling. Chem Commun 48:3712–3714
44. Teichert JF, Zhang S, van Zijl AW, Slaa JW, Minnaard AJ, Feringa BL (2010) Asymmetric allylic alkylation in combination with ring closing metathesis for the preparation of chiral N-heterocycles. Org Lett 12:4658–4660
45. Mao B, Geurts K, Fañanás-Mastral M, van Zijl AW, Fletcher SP, Minaard AJ, Feringa BL (2011) Catalytic enantioselective synthesis of naturally occurring butenolides via hetero-allylic alkylation and ring closing metathesis. Org Lett 13:948–951
46. Geurts K, Fletcher SP, Feringa BL (2006) Copper catalyzed asymmetric synthesis of chiral allylic esters. J Am Chem Soc 128:15572–15573
47. Mao B, Fañanás-Mastral M, Lutz M, Feringa BL (2013) Diversity-oriented enantioselective synthesis of highly functionalized cyclic and bicyclic alcohols. Chem Eur J 19:761–770

48. Giacomina F, Riat D, Alexakis A (2010) *o*-Ethylenic allylic substrates as alternatives to cyclic substrates in copper- and iridium-catalyzed asymmetric allylic alkylation. Org Lett 12:1156–1159
49. Giacomina F, Alexakis A (2013) Construction of enantioenriched cyclic compounds by asymmetric allylic alkylation and ring-closing metathesis. Eur J Org Chem 29:6710–6721
50. Fañanás-Mastral M, ter Horst B, Minnaard AJ, Feringa BL (2011) Stereoselective synthesis of syn and anti 1,2-hydroxyalkyl moieties by Cu-catalyzed asymmetric allylic alkylation. Chem Commun 47:5843–5845
51. Pérez M, Fañanas-Mastral M, Bos PH, Rudolph A, Harutyunyan SR, Feringa BL (2011) Catalytic asymmetric carbon–carbon bond formation via allylic alkylations with organolithium compounds. Nat Chem 3:377–381
52. Hodgson DM (2003) Organolithiums in enantioselective synthesis. Springer, Germany
53. Giannerini M, Fañanás-Mastral M, Feringa BL (2013) Direct catalytic cross-coupling of organolithium compounds. Nat Chem 5:667–672
54. Hornillos V, Giannerini M, Vila C, Fañanás-Mastral M, Feringa BL (2015) Direct catalytic cross-coupling of alkenyllithium compounds. Chem Sci 6:1394–1398
55. Firth JD, O'Brien P (2015) Cross-coupling knows no limits: assessing the synthetic potential of the palladium-catalysed cross-coupling of organolithiums. ChemCatChem 7:395–397
56. Kiyotsuka Y, Kobayashi Y (2010) Highly efficient substitution of allylic picolinates with copper reagents derived from aryl-, alkenyl-, furyl-, and thienyl-lithiums. Tetrahedron 66:676–684
57. Fañanás-Mastral M, Pérez M, Bos PH, Rudolph A, Harutyunyan SR, Feringa BL (2012) Enantioselective synthesis of tertiary and quaternary stereogenic centers: copper/phosphoramidite-catalyzed allylic alkylation with organolithium reagents. Angew Chem Int Ed 51:1922–1925
58. Teichert JF, Feringa BL (2010) Phosphoramidites: privileged ligands in asymmetric catalysis. Angew Chem Int Ed 49:2486–2528
59. Guduguntla S, Fañanás-Mastral M, Feringa BL (2013) Synthesis of optically active β- or γ-alkyl-substituted alcohols through copper-catalyzed asymmetric allylic alkylation with organolithium reagents. J Org Chem 78:8274–8280
60. Hawner C, Alexakis A (2010) Metal-catalyzed asymmetric conjugate addition reaction: formation of quaternary stereocenter. Chem Commun 46:7295–7306
61. Trost BM, Jiang C (2006) Catalytic enantioselective construction of all-carbon quaternary stereocenters. Synthesis 369–396
62. Mei TS, Patel HH, Sigman MS (2014) Enantioselective construction of remote quaternary stereocentres. Nature 508:340–344
63. Prakash J, Marek I (2011) Enantioselective synthesis of all-carbon quaternary stereogenic centers in acyclic systems. Chem Commun 47:4593–4623
64. Fañanás-Mastral M, Vitale R, Pérez M, Feringa BL (2015) Enantioselective synthesis of all-carbon quaternary stereogenic centers via copper-catalyzed asymmetric allylic alkylation of (*Z*)-allyl bromides with organolithium reagents. Chem Eur J 21:4209–4212
65. Gao F, McGrath KP, Lee Y, Hoveyda AH (2010) Synthesis of quaternary carbon stereogenic centers through enantioselective Cu-catalyzed allylic substitutions with vinylaluminum reagents. J Am Chem Soc 132:14315–14320
66. Hojoh K, Shido Y, Ohmiya H, Sawamura M (2014) Construction of quaternary stereogenic carbon centers through copper-catalyzed enantioselective allylic cross-coupling with alkylboranes. Angew Chem Int Ed 53:4954–4958
67. Tseng CC, Paisley SD, Goering HL (1986) Alkylation of allylic derivatives. 11. Copper(I)-catalyzed cross coupling of allylic carboxylates with Grignard reagents. J Org Chem 51:2884–2891
68. Von dem Bussche-Hünnefeld JL, Seebach D (1992) Enantioselective preparation of sec. Alcohols from aldehydes and dialkyl zinc compounds, generated in situ from Grignard reagents, using substoichiometric amounts of TADDOL-titanates. Tetrahedron 48:5719–5730

69. Pérez M, Fañanás-Mastral M, Hornillos V, Rudolph A, Bos PH, Harutyunyan SR, Feringa BL (2012) Asymmetric allylic alkylation of acyclic allylic ethers with organolithium reagents. Chem Eur J 18:11880–11883
70. Zhang L, Le CM, Lautens M (2014) The Use of silyl ketene acetals and enol ethers in the catalytic enantioselective alkylative ring opening of oxa/aza bicyclic alkenes. Angew Chem Int Ed 53:5951–5954
71. Fagnou K, Lautens M (2003) Rhodium-catalyzed carbon−carbon bond forming reactions of organometallic compounds. Chem Rev 103:169–196
72. Yang D, Liang N (2014) Platinum-catalyzed anti-stereocontrolled ring-opening of oxabicyclic alkenes with Grignard reagents. Org Biomol Chem 12:2080–2086
73. Lautens M, Renaud JL, Hiebert S (2000) Palladium-catalyzed enantioselective alkylative ring opening. J Am Chem Soc 122:1804–1805
74. Bertozzi F, Pineschi M, Macchia F, Arnold LA, Minnaard AJ, Feringa BL (2002) Copper phosphoramidite catalyzed enantioselective ring-opening of oxabicyclic alkenes: remarkable reversal of stereocontrol. Org Lett 4:2703–2705
75. Gómez Arrayás R, Cabrera S, Carretero JC (2003) Copper-catalyzed anti-stereocontrolled ring opening of oxabicyclic alkenes with grignard reagents. Org Lett 5:1333–1336
76. Bos PH, Rudolph A, Perez M, Fañanas-Mastral M, Harutyunyan SR, Feringa BL (2012) Copper-catalyzed asymmetric ring opening of oxabicyclic alkenes with organolithium reagents. Chem Commun 48:1748–1750
77. Palais L, Bournaud C, Micouin L, Alexakis A (2010) Copper-catalysed ring opening of polycyclic meso-hydrazines with trialkylaluminium reagents and SimplePhos ligands. Chem Eur J 16:2567–2573
78. Akiyama K, Gao F, Hoveyda AH (2010) Stereoisomerically pure trisubstituted vinylaluminum reagents and their utility in copper-catalyzed enantioselective synthesis of 1,4-dienes containing Z or E alkenes. Angew Chem Int Ed 49:419–423
79. Gao F, Lee Y, Mandai K, Hoveyda AH (2010) Quaternary carbon stereogenic centers through copper-catalyzed enantioselective allylic substitutions with readily accessible aryl- or heteroaryllithium reagents and aluminum chlorides. Angew Chem Int Ed 49:8370–8374
80. Dabrowski JA, Haeffner F, Hoveyda AH (2013) Combining NHC–Cu and Brønsted base catalysis: enantioselective allylic substitution/conjugate additions with alkynylaluminum reagents and stereospecific isomerization of the products to trisubstituted allenes. Angew Chem Int Ed 52:7694–7699
81. Harada A, Yusuke M, Tatsunori S, Ohmiya H, Sawamura M (2014) Copper-catalyzed enantioselective allylic alkylation of terminal alkyne pronucleophiles. J Am Chem Soc 136:13932–13939
82. Jennequin T, Wencel-Delord J, Rix D, Daubignard J, Crévisy C, Mauduit M (2010) Chelating hydroxyalkyl NHC as efficient chiral ligands for room-temperature copper-catalyzed asymmetric allylic alkylation. Synlett 11:1661–1665
83. Jahier-Diallo C, Morin MST, Queval P, Rouen M, Artur I, Querard P, Toupet L, Crévisy C, Baslé O, Mauduit M (2015) Multicomponent synthesis of chiral bidentate unsymmetrical unsaturated N-heterocyclic carbenes: copper-catalyzed asymmetric C–C Bond formation. Chem Eur J 21:993–997
84. Pellissier H (2011) Organocatalyzed dynamic kinetic resolution. Adv Synth Catal 353:659–676
85. Nakano K, Kitamura M (2014) Dynamic kinetic resolution (DKR). Wiley, Weinhelm
86. Huerta FF, Minidisa ABE, Bäckvall JE (2001) Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis. Chem Soc Rev 30:321–331
87. Ito H, Kunii S, Sawamura M (2010) Direct enantio-convergent transformation of racemic substrates without racemization or symmetrisation. Nat Chem 2:972–976

88. Cherney AH, Kadunce NT, Reisman SE (2015) Enantioselective and enantiospecific transition-metal-catalyzed cross-coupling reactions of organometallic reagents to construct C–C bonds. Chem Rev 115:9587–9652
89. Ladjel C, Fuchs N, Gremaud L, Alexakis A (2010) Copper-catalysed kinetic resolution of cyclic alkenyl cyclopropane malonates with organoaluminium and grignard reagents. Synlett 02:0317–0320
90. Langlois JB, Alexakis A (2010) Copper-catalyzed asymmetric allylic alkylation of racemic cyclic substrates: application of dynamic kinetic asymmetric transformation (DYKAT). Adv Synth Catal 352:447–457
91. Langlois JB, Alexakis A (2011) Identification of a valuable kinetic process in copper-catalyzed asymmetric allylic alkylation. Angew Chem Int Ed 50:1877–1881
92. Langlois JB, Emery D, Mareda J, Alexakis A (2012) Mechanistic identification and improvement of a direct enantioconvergent transformation in copper-catalyzed asymmetric allylic alkylation. Chem Sci 3:1062–1069
93. Bertozzi F, Crotti P, Macchia F, Pineschi M, Feringa BL (2001) Highly enantioselective regiodivergent and catalytic parallel kinetic resolution. Angew Chem Int Ed 40:930–932
94. Crotti P, Di Bussolo V, Pineschi M (2011) Copper-catalyzed divergent kinetic resolution of racemic allylic substrates. Chirality 23:703–710
95. You H, Rideau E, Sidera M, Fletcher SP (2015) Non-stabilized nucleophiles in Cu-catalysed dynamic kinetic asymmetric allylic alkylation. Nature 517:351–355
96. Sidera M, Fletcher SP (2015) Cu-catalyzed asymmetric addition of sp2-hybridized zirconium nucleophiles to racemic allyl bromides. Chem Commun 51:5044–5047

Top Organomet Chem (2016) 58: 41–98
DOI: 10.1007/3418_2015_158

Published online: 6 November 2015

Formation of Quaternary Stereocentres by Copper-Catalysed Enantioselective Conjugate Addition Reaction

Beatriz Maciá

Abstract Remarkable progress in copper-catalysed enantioselective conjugate addition (ECA) reactions has been made over the past decade. This enantioselective transformation now allows the challenging formation of chiral quaternary centres by addition of different nucleophiles to trisubstituted α,β-unsaturated systems. This chapter summarises the developments in the area.

Keywords Conjugate addition · Copper catalysis · Enantioselective catalysis · Quaternary centres

Contents

1 Introduction 42
2 Formation of All Carbon Quaternary Centres by Copper-Catalysed ECA 44
2.1 Organoaluminium Reagents as Nucleophiles 44
2.2 Grignard Reagents as Nucleophiles 67
2.3 Organozinc Reagents as Nucleophiles 80
2.4 Organozirconium Reagents as Nucleophiles 84
3 Formation of Boron-Containing Quaternary Centres by Copper-Catalysed ECA 86
4 Formation of Silicon-Containing Quaternary Centres by Copper-Catalysed ECA 93
5 Perspective 95
References 96

Abbreviations

CA	Conjugate addition
CBz	Carboxybenzyl

B. Maciá (✉)
Division of Chemistry and Environmental Science, Faculty of Science and Engineering, Manchester Metropolitan University, John Dalton East, Oxford Road, M1 5GD Manchester, UK
e-mail: B.Macia-Ruiz@mmu.ac.uk

*c*Hex	Cyclohexyl
*c*Pent	Cyclopentyl
CuTC	Copper(I)-thiophene-2-carboxylate
DCM	Dichloromethane
DME	Dimethoxyethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	Dimethylsulfoxide
ECB	Enantioselective conjugate borylation
HMPA	Hexamethylphosphoramide
m-CPBA	*meta*-Chloroperoxybenzoic acid
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NHC	*N*-heterocyclic carbene
NIS	*N*-Iodosuccinimide
THF	Tetrahydrofuran
TMS	Trimethylsylil
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

1 Introduction

Quaternary stereocentres, which bear four different carbon or heteroatom substituents at the four vertices of a tetrahedron, add greatly to the three dimensionality and novelty of molecules [1]. Three-dimensional structures represent a much larger fraction of the chemical space and often have superior properties compared to flat aromatic compounds [2], since they can interact better with the target protein, which has a three-dimensional structure as well. Several recent studies have suggested that drug candidates with a larger fraction of sp^3 carbons and chiral centres have a lower rate of attrition in the clinic [3]. However, building quaternary stereocentres is challenging [4–7], which has hampered their implementation in the synthesis of medicines, agriculturals and potentially other areas such as flavouring, fragrances and materials [8]. One of the difficulties of constructing quaternary centres in a stereoselective manner is their congested nature [9]. Remarkable advances have been made during the last decade in the stereocontrolled construction of quaternary stereocentres using chemical catalysis [10, 11]. Catalytic asymmetric transformations, including Diels Alder, Heck, conjugate additions and allylic substitution reactions, allow the synthesis of quaternary stereocentres [12, 13].

Since the initial reports in the mid-1990s, metal-catalysed enantioselective conjugate addition (ECA) reactions have evolved as an important tool for the synthetic chemist to access to enantiopure molecules [14–16], such as the natural products and biologically active compounds represented in Fig. 1 [17–24].

Most of the research efforts in the field of ECA involve the use of rhodium [25], palladium [26] and copper catalysis [27]. From all these transition metals able to catalyse an ECA reaction, copper is probably the most versatile [28]. Copper is not only one of the cheapest transition metals used in asymmetric catalysis, but it is also

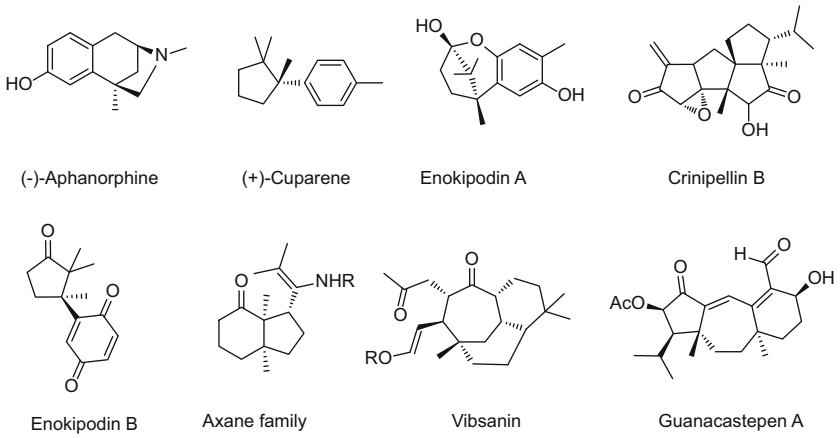


Fig. 1 Examples of natural products and biologically active compounds containing chiral quaternary centres, synthesised by copper-catalysed ECA

easily transmetalated from many organometallic reagents, such as organoaluminium, magnesium and zinc. Rhodium and palladium were initially preferred for the ECA reaction with aryl and alkenyl nucleophiles, but nowadays the copper-catalysed ECA is not restricted anymore to alkyl nucleophiles, and aryl/alkenyl counterparts give comparable levels of enantiocontrol to the other metals.

Over the past two decades, the copper-catalysed ECA of nitroalkenes and Meldrum acid derivatives and, more recently, simple cyclic and acyclic enones and other α,β-unsaturated systems, with different organometallic reagents, has emerged as a powerful approach to access chiral molecules [29–31]. Two substituents in the β-position of an α,β-unsaturated system hamper the conjugate addition of the nucleophile; however, several highly efficient copper-based catalytic systems are able to overcome this barrier and allow the synthesis of quaternary stereogenic centres with very good selectivities [32, 33], as it will be presented in the following pages of this chapter. Alternative strategies to facilitate the copper-catalysed formation of quaternary chiral centres include the activation of the β,β-disubstituted α,β-unsaturated systems (by making the β-position more electrophilic) by using Lewis acidic nucleophiles or by the implementation of additional electron-withdrawing functionalities in the substrate.

This chapter is an overview of the copper-based catalytic systems that enable the formation of chiral quaternary centres through conjugate addition reactions. The existing methodologies have been classified in three main sections, according to the nature of the nucleophile that participates in the ECA reaction. Thus, Sect. 2 covers carbon nucleophiles, including organoaluminium (Sect. 2.1), Grignard (Sect. 2.2), organozinc (Sect. 2.3) and organozirconium reagents (Sect. 2.4). Next, Sect. 3 reviews the use of organoboron reagents, to form boron-containing quaternary centres. And last, Sect. 4 presents the use of organosilicon reagents, to form silicon-containing quaternary centres.

After the ECA reaction step, the generated enolate requires protonation to generate the corresponding enol, which rapidly tautomerises to the ketone product.

Protonation is typically carried out by the addition of water, aqueous NH_4Cl or aqueous HCl. For simplicity, this step has been omitted in all schemes, and only the conditions for the ECA have been presented.

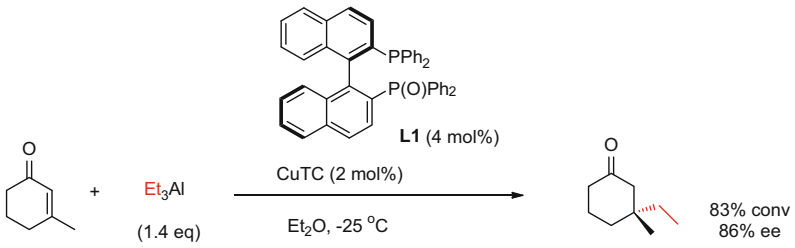
2 Formation of All Carbon Quaternary Centres by Copper-Catalysed ECA

2.1 Organoaluminium Reagents as Nucleophiles

Aluminium reagents are strong Lewis acids that can coordinate to the oxygen atom of the enone and thus render the substrate more electrophilic. For this reason, these organometallic reagents were the first to be successfully utilised for the formation of quaternary centres by reaction with a β,β-disubstituted enone. Enantioselective conjugate addition reactions with organoaluminium reagents are usually carried out in coordinating solvents such as Et_2O or THF, as this allows the cleavage of the AlR_3 dimeric species, thus increasing its reactivity.

Initial attempts at copper-catalysed conjugate addition with organoaluminium reagents and β-substituted cyclic enones utilised the hemilabile P,O-heterobidentate and axially chiral (*R*)-BINPO (**L1**, Scheme 1) [34]. The presence of a soft phosphorous centre which could bind to copper and also a hard oxygen centre that could potentially coordinate to aluminium was thought to lead to a highly organised, asymmetric transition state. Although not reaching full conversion (83%), the addition of triethylaluminium in diethyl ether at −25°C gives 86% enantiomeric excess (Scheme 1).

Phosphoramidite ligands are more efficient in the generation of stereogenic quaternary centres by copper-catalysed addition of aluminium organyls to β-substituted cyclic enones. Alexakis has demonstrated that excellent enantiomeric excesses can be achieved with catalytic amounts of **L2-3** (Fig. 2) and CuTC, for a range of commercially available nucleophiles and β-substituted cyclic enones (Schemes 2 and 3) [35, 36]. In general, 'simple' substrates give excellent conversions, isolated yields and enantioselectivities, whereas Michael acceptors such as five-membered ring systems and highly hindered substrates need carefully optimised conditions.



Scheme 1 Copper-catalysed ECA to β-substituted cyclohexenones by Alexakis [34]

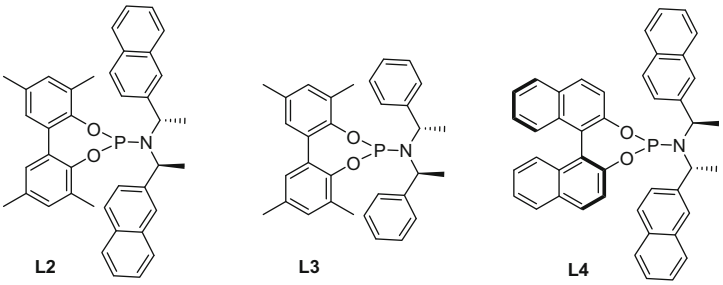
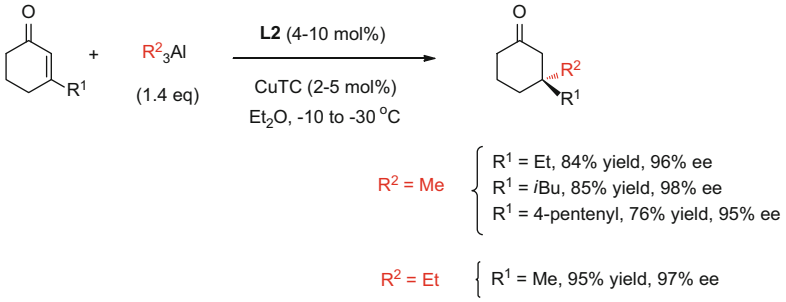
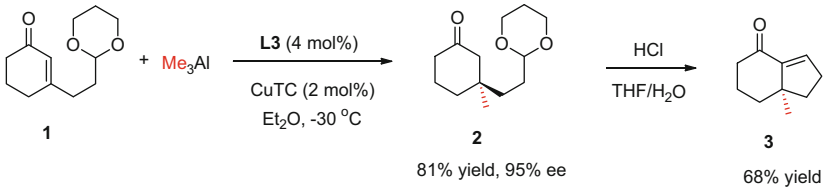


Fig. 2 Effective phosphoramidite ligands for the copper-catalysed ECA of organoaluminium reagents to enones



Scheme 2 Copper-phosphoramidite-catalysed ECA to β-substituted cyclohexenones by Alexakis [35]

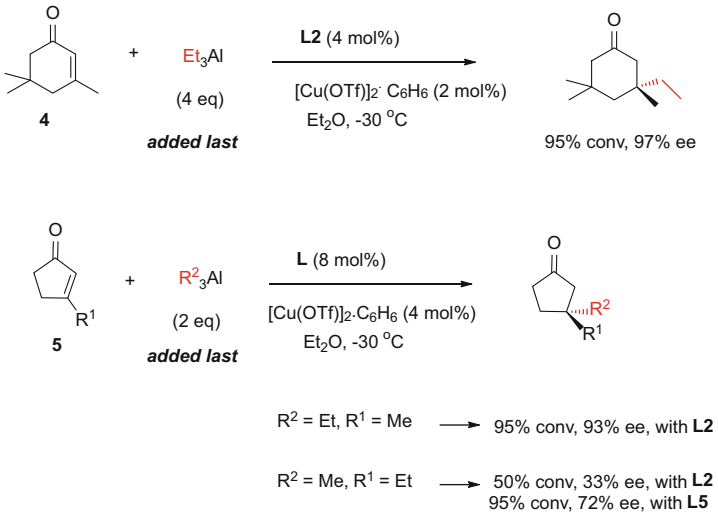


Scheme 3 Copper–phosphoramidite-catalysed ECA to functionalised β-substituted cyclohexenones by Alexakis [36]

With this catalytic system, the order of addition of the reagents is crucial for the outcome of the reaction, and better results are normally achieved when the enone is added last to the reaction mixture, after the addition of the organoaluminium reagent.

In general, both Me_3Al and Et_3Al work well with this methodology, and high yields and enantioselectivities can be achieved in the addition to β-substituted cyclohexenones, as represented by the key examples in Scheme 2 [35].

Functionalised enones are also compatible with this methodology and easily undergo stereoselective copper-catalysed conjugate addition with trimethylaluminium reagents in the presence of phosphoramidite ligand **L3**. Thus, **1** can be converted by treatment with Me_3Al into the chiral ketone **2** (95% *ee*), which can be



Scheme 4 Copper-catalysed ECA to bulky β-substituted cyclohexenones and β-substituted cyclopentenones by Alexakis [37]

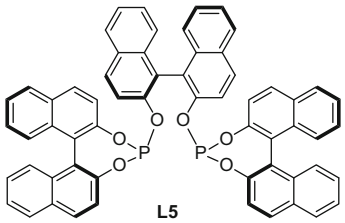
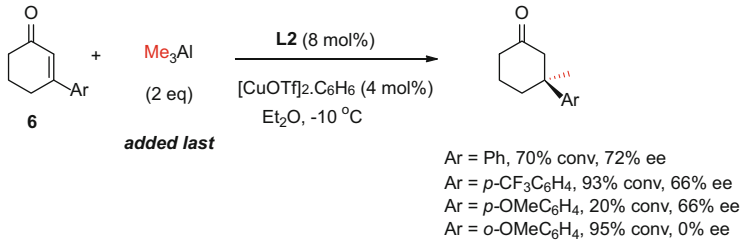


Fig. 3 Chiral diphosphite ligand for the addition of organoaluminium reagents to β-substituted cyclopentenones by Alexakis [37]

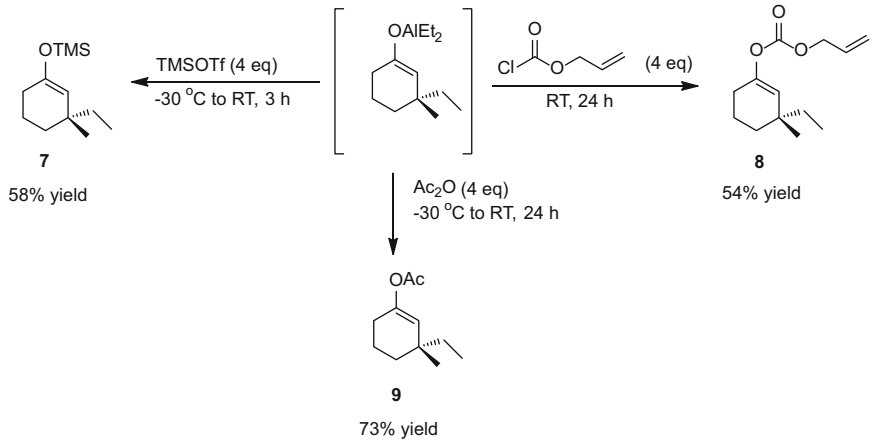
transformed into the bicyclic product **3** under acidic conditions. This method is also suitable for the generation of quaternary stereogenic centres at the β position of cyclopentanones [36]. The main limitation of this methodology is the performance of bulky nucleophiles, such as triisobutylaluminium (iBu$_3$Al), which often lead to complex reaction mixtures.

Similarly, sterically demanding substrates, such as the isophorone **4** and β-substituted cyclopentenones **5**, also proved challenging, but moderate to good enantioselectivities can be achieved when a 'reverse' addition protocol (i.e. adding the organoaluminium reagent last to the reaction mixture, after the addition of the enone, Scheme 4) is conducted. For the addition of organoaluminium reagents to β-substituted cyclopentenones **5**, the chiral diphosphite ligand **L5** (Fig. 3) provides slightly better results than the phosphoramidite ligands [37].

Phosphoramidite ligands are also able to promote the addition of organoaluminium reagents to aromatic cyclohex-2-en-1-ones **6**, using again a reverse addition protocol (Scheme 5) [36, 38]. Only moderate yields and enantioselectivities are reached for these substrates with this methodology, and detrimental



Scheme 5 Copper–phosphoramidite-catalysed ECA to β-aryl cyclohexenones by Alexakis [38]

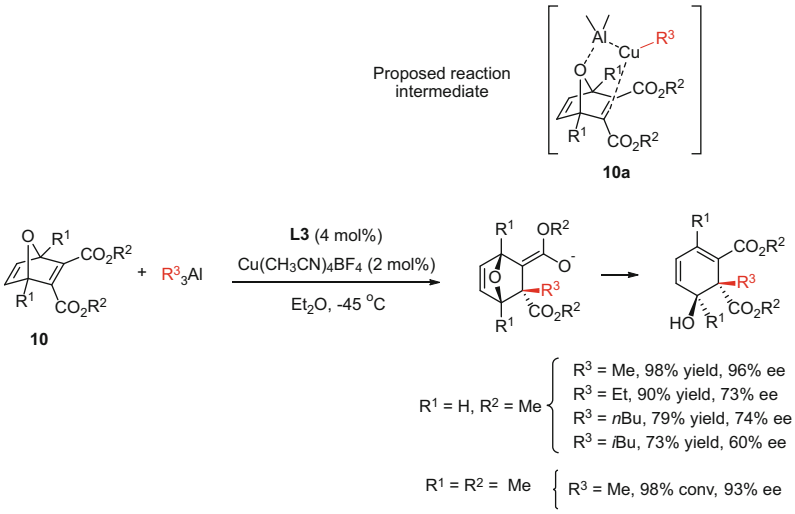


Scheme 6 In situ trapping of aluminium enolates by Alexakis [36]

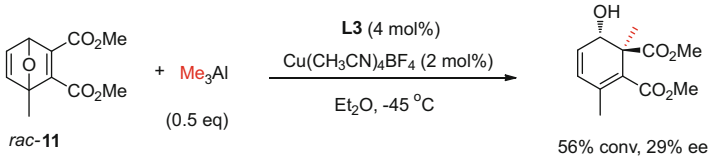
steric and electronic effects are observed. For example, the addition of Me_3Al to 3-phenyl-cyclohexenone gives 72% *ee*, whilst functionalised aromatic groups give up to 66% *ee*. If the substituent of the phenyl group is in the *ortho*-position, racemic product is obtained.

The aluminium enolates generated after ECA do not react directly with electrophiles, probably due to their high stability. However, they can be trapped in situ by silylation, carbonation and *O*-acylation in good yields (Scheme 6). These intermediates **7–9** can eventually be used in Tsuji reactions or ozonolysis, for example, to generate more elaborated adducts [36].

Trialkylaluminium reagents have been shown to undergo copper–phosphoramidite-catalysed ECA reaction with oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates **10**, with the simultaneous creation of up to two adjacent quaternary stereocentres (Scheme 7) [39]. The conjugate addition occurs from the *exo*-side, probably due to coordination by the bridging oxygen atom (see intermediate **10a**). The intermediate enolate subsequently undergoes β-elimination opening the ring. The *syn*-relative stereochemistry of the products indicates a conjugate addition/elimination mechanism rather than an allylic substitution, which would have afforded the *endo*-addition product.



Scheme 7 Copper–phosphoramidite-catalysed ECA to oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates by Alexakis [39]



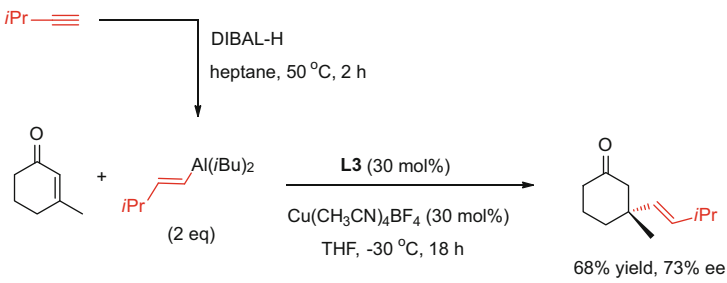
Scheme 8 Copper–phosphoramidite-catalysed ECA to racemic dimethyl 1-methyl-7-oxabicyclo [2.2.1]hepta-2,5-diene-2,3-dicarboxylate by Alexakis [39]

The best enantiomeric excesses on this type of oxabicyclic substrates are obtained with Me_3Al. The addition of Et_3Al, nPr_3Al, nBu_3Al and iBu_3Al gives good yields (70–92%) but moderate enantioselectivities (55–73%). When bulkier isopropyl esters are used, instead of methyl esters, both yield and enantioselectivity of the reaction drop (73% yield and 67% ee for the addition of Me_3Al to the isopropyl esters analogue **10** where R^1=H, R^2=*i*Pr).

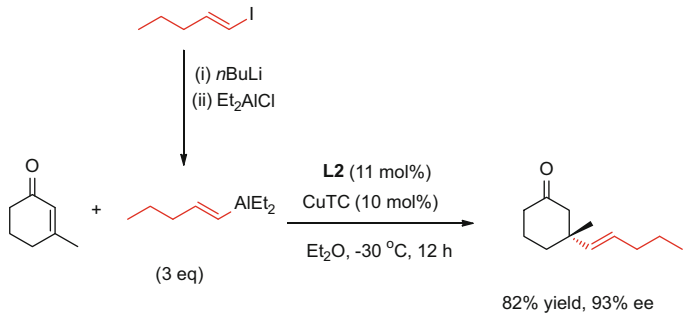
Unfortunately, this methodology does not allow kinetic resolution of racemic mixtures. When a racemic oxabicyclic substrate, such us **11**, is used with 0.5 equiv. of trimethylaluminium, only poor enantioselectivities are obtained (Scheme 8).

Phosphoramidite ligands are also suitable for the challenging enantioselective addition of alkenyl aluminium reagents to β-substituted cyclic enones [36]. Although the introduction of alkenyl groups to enones has been largely the domain of Rh catalysis [40, 41], the remarkable advances in copper-catalysed ECA have now made this transformation possible.

Alkenyl aluminium reagents can be easily generated by hydroalumination of the corresponding alkynes with DIBAL-H, under Zweifel conditions (Scheme 9)



Scheme 9 Copper–phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared via hydroalumination) to β-substituted cyclohexenones by Alexakis [36]

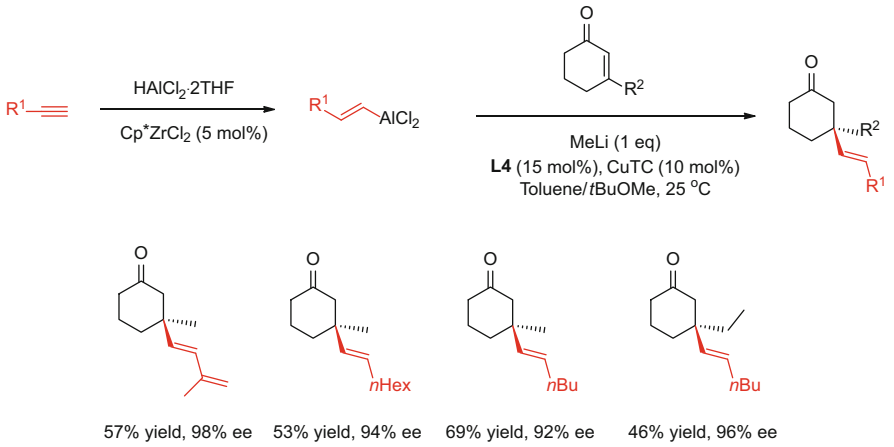


Scheme 10 Copper–phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared from iodoalkenes) to β-substituted cyclohexenones by Alexakis [32, 44]

[42]. Interestingly, the use of the 'standard' conditions (CuTC, Et_2O), optimal for the ECA of alkyl aluminium reagents with phosphoramidite ligands, only leads to the 1,2-addition–dehydration product when alkenyl aluminium reagents are used as nucleophiles. However, the use of THF as solvent suppresses the 1,2-addition by-product and allows moderate yields and enantioselectivities, albeit at catalyst loadings up to 30 mol% (Scheme 9). A possible explanation for the need of such large amounts of catalyst might be that in the hydroalumination reaction, about 6% of Al acetylide is formed by deprotonation of the corresponding terminal alkyne. These Al acetylides are known to strongly bind to copper and act as non-transferable ligands in cuprate chemistry [43].

Alkenyl aluminium reagents can be also prepared by halogen/lithium exchange from the corresponding iodoalkene, followed by transmetalation with Et_2AlCl. In this way, the formation of Al acetylides is avoided and lower catalysts loading for the ECA are allowed (Scheme 10) [32, 44].

Recently, Woodward et al. have described the synthesis of alkenylaluminium reagents from their corresponding alkynes and $HAlCl_2{\cdot}2THF$, using $Cp^*_2ZrCl_2$ as



Scheme 11 Copper–phosphoramidite-catalysed ECA of alkenyl aluminium reagents (prepared via zirconium-catalysed hydroalumination) to β-substituted cyclohexenones by Woodward [45]

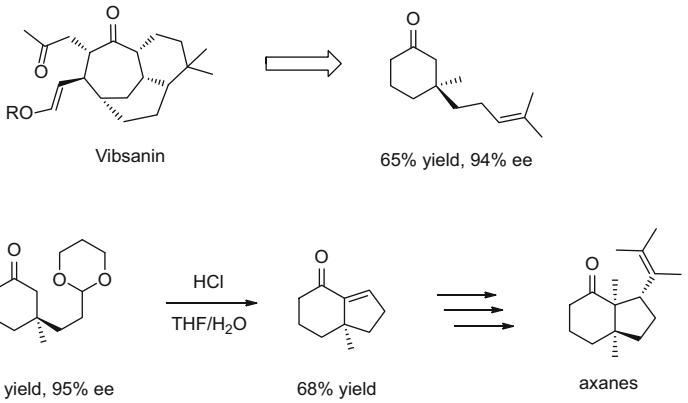
catalyst. The initially obtained aluminium species can be activated with MeLi (1 equiv.)[1] to generate the alane (*E*)-ClAlMeCH=CHR[1] which, under copper(I)–phosphoramidite catalysis with a cyclic enone, provides the corresponding 1,4-addition product with high enantioselectivity (Scheme 11) [45]. This process shows good generality for 1,4-additions to a wide variety of β-substituted cyclohexenones. The alkenyl aluminium reagents generated by this methodology are more reactive than those prepared by hydroalumination with DIBAL-H (which bear a bulky isobutyl substituent on the aluminium atom) and therefore lead to faster reactions and higher yields.

The synthetic utility of copper–phosphoramidite-catalysed conjugate additions as a means for generating quaternary stereocentres using organoaluminium reagents has been demonstrated with the synthesis of several key intermediates in natural product syntheses, as represented in Scheme 12 [36, 46].

Introduced by Alexakis et al., copper–phosphinamine systems also stand out as effective catalysts for the addition of organoaluminium reagents to cyclic enones [46, 47]. In many cases, and in particular with challenging substrates, phosphinamine ligands (Fig. 4) outperform the phosphoramidite counterparts.

For example, phosphinamine ligands are not only efficient in the addition of linear organoaluminium reagents to both bulky and non-bulky β-substituted cyclic enones (Scheme 13) but perform particularly well with β-aryl-substituted cyclic enones, giving higher yields and enantioselectivities than phosphoramidite ligands (Scheme 14 versus Scheme 5).

[1] Strangely, the use of two equivalents of MeLi gave poor processes – despite the known efficacy of $Me_2AlCH{=}CHR$ species in related processes.



Scheme 12 Copper–phosphoramidite-catalysed ECA of organoaluminium reagents in the synthesis of some key intermediates from natural products by Alexakis [36, 46]

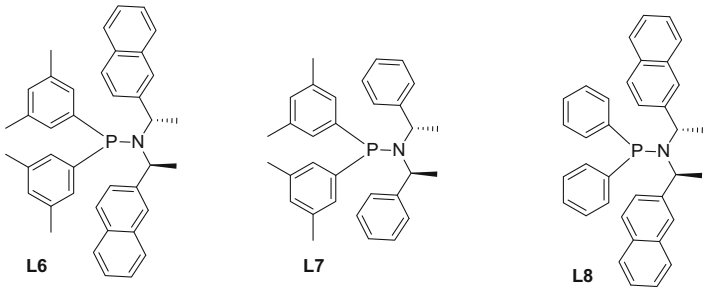
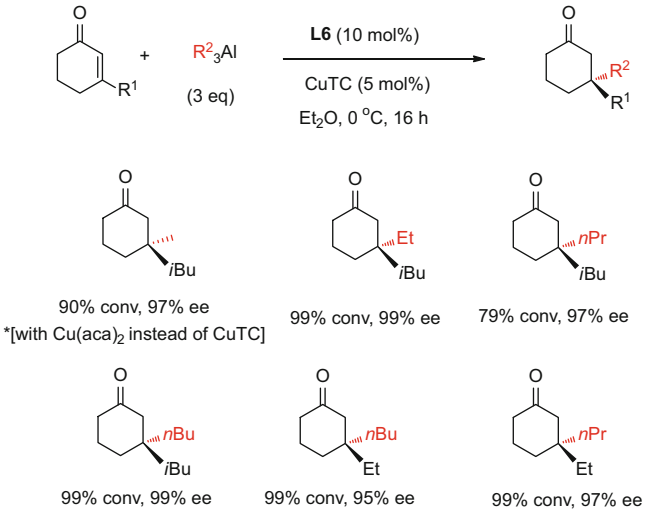


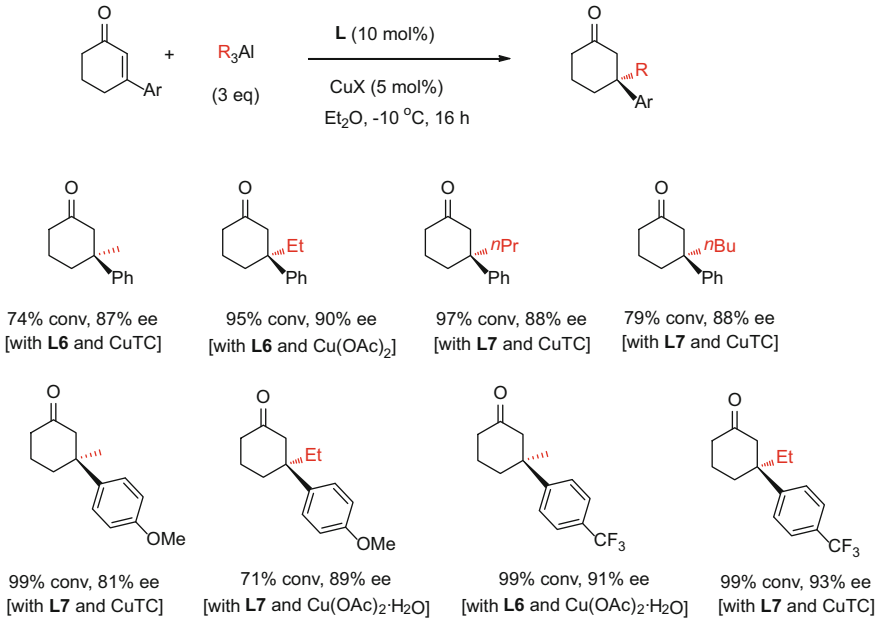
Fig. 4 Effective phosphinamine ligands for the copper-catalysed ECA of organoaluminium reagents to β,β-disubstituted enones

Regarding the challenging β-substituted cyclopenten-2-one substrates, phosphinamine ligands give moderate, comparable enantioselectivities to phosphoramidites, as shown in Scheme 15.

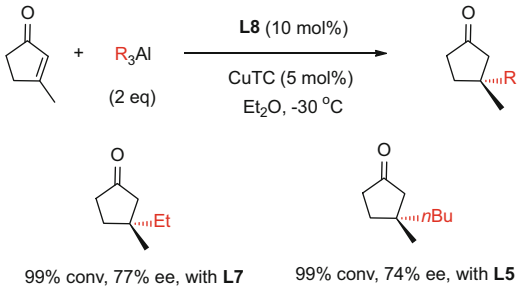
The tandem hydroalumination–ECA process to β-substituted cyclic enones with phosphinamine ligands also works very efficiently (Scheme 16) [48, 49]. The best copper source for this catalytic system is copper (II) naphthenate, which is cheaper than the CuTC used in previous methodologies and can be used as a stock solution. A wide range of alkenylaluminium reagents can be added with very good levels of enantioselectivity, including (*Z*)-nucleophiles, halogen-containing alkenes, conjugated alkenes, protected alcohols and α-substituted alkenes, which might be difficult to achieve using other organometallic species. Furthermore, this methodology allows high levels of enantioselectivity for sterically hindered substrates, although further activation with 1 equiv. of Me_3Al is required to obtain high conversion (see example in Scheme 16). Cycloheptenone substrates can be also used (see example in Scheme 16), but unfortunately, the cyclopentenone analogues give low levels of enantioselectivity with this method.



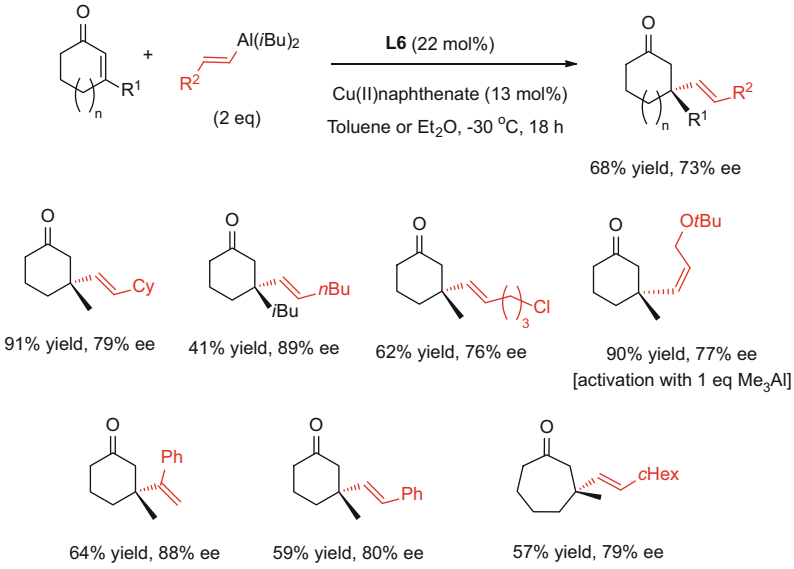
Scheme 13 Copper–phosphinamine-catalysed ECA of organoaluminium reagents to β-substituted cyclohexenones by Alexakis [46, 47]



Scheme 14 Copper-catalysed ECA of organoaluminium reagents to β-aryl cyclohexenones by Alexakis [46, 47]



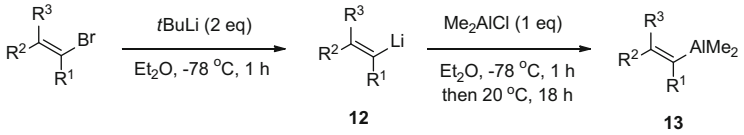
Scheme 15 Copper–phosphinamine-catalysed ECA of organoaluminium reagents to β-substituted cyclopentenones by Alexakis [46, 47]



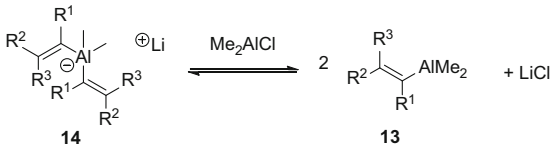
Scheme 16 Copper–phosphinamine-catalysed ECA of alkenyl aluminium reagents (prepared by hydroalumination with DIBAL-H) to β-substituted cyclic enones by Alexakis [48, 49]

It is worth mentioning that no transfer of the isobutyl group from the alkenyl aluminium reagents is observed in any case; the preferential transfer of the vinylic group occurred exclusively.

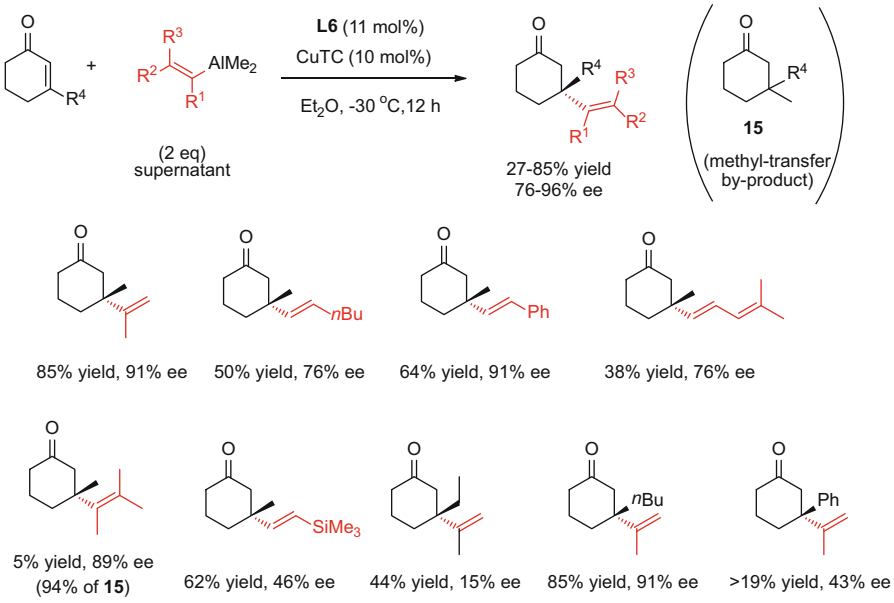
As mentioned before, the amounts of copper and ligand needed for the ECA of alkenyl aluminium reagents can be diminished if the nucleophile is prepared from the corresponding alkene halide instead of by a hydroalumination process. For example, a halogen/lithium exchange (using *t*BuLi), followed by transmetalation with dimethylaluminium chloride, provides the desired alkenyl aluminium reagent (Scheme 17) that can be used directly in the ECA reaction [49, 50]. It is important to stir the 2-alkenyl lithium **12** and the Me_2AlCl overnight, at room temperature, to cleanly obtain the desired alane **13** by allowing its equilibration from the initially formed alanate **14** (Scheme 18).



Scheme 17 Preparation of alkenyl aluminium reagents from bromoalkenes by Alexakis [49, 50]



Scheme 18 Equilibrium reaction between alkenyl organoaluminium species generated from bromoalkenes [50]



Scheme 19 Copper–phosphinamine-catalysed ECA of alkenyl aluminium reagents (prepared by Br/Li exchange) to β-substituted cyclic enones by Alexakis [49, 50]

Bromoalkenes are the preferred starting material for the generation of the corresponding nucleophile **13**, since many are commercially available or readily prepared [51–55]. Whilst the methodology is also efficient when iodoalkenes are used as the precursors for the organoaluminium reagent, a very precise temperature protocol must be followed and Et_2AlCl provides better results in the transmetalation process [32, 44].

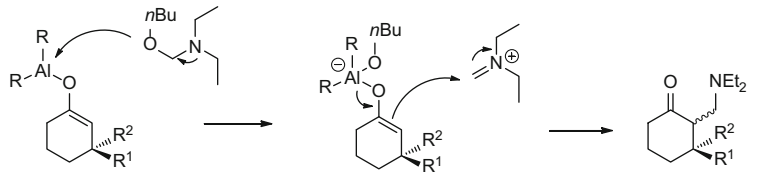
The supernatant solution of the generated alkenyl aluminium reagent **13** can be used directly in the ECA to β-substituted cyclohex-2-enones (Scheme 19), providing good yields and enantioselectivities with only 10 mol% of the Cu–

phosphinamine catalyst. The enantioselectivity of the process varies with the equivalents of organoaluminium reagent added. When decreased quantities of nucleophile **13** are used, the enantiomeric excess improves but the amount of methyl transfer also increases and more of the by-product **15** is obtained. Using more than 2.0 equiv. of **13** leads to a drop in enantioselectivity, probably due to contamination of the organoaluminium reagent with traces of lithium salts, which might perturb the structure of the chiral copper complex.

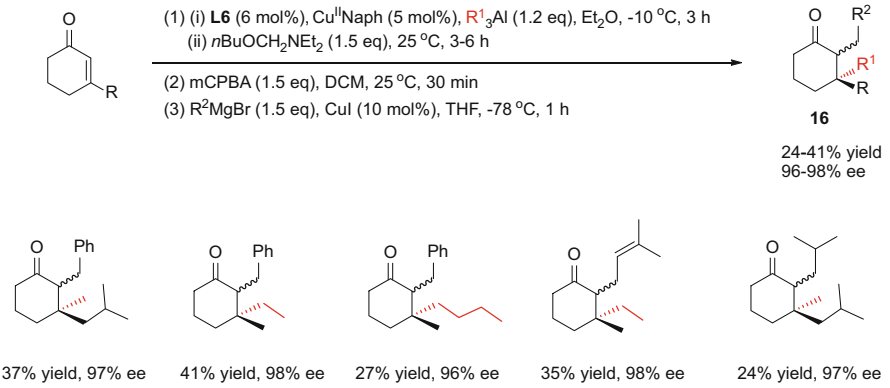
General observations and limitations on the copper–phosphinamine-catalysed CA of alkenyl aluminium reagents include:

1. Hindered alkenylaluminium reagents produce higher amounts of the methyl transfer by-product **15**.
2. Alkenylaluminium reagents where R^2=aryl group provide higher enantioselectivities than when R^2=alkyl group (see Scheme 17 and examples in Scheme 19).
3. Silyl-protected vinyl aluminiums give disappointing results (see example in Scheme 19).
4. Dimethylvinylaluminium (generated by either a bromine–lithium exchange from vinyl bromide and subsequent trapping with Me_2AlCl or by transmetalation of a vinyl Grignard reagent) gives low enantioselectivities.
5. Changing the substituent on the β-position of the cyclohexenone from methyl to ethyl, butenyl or phenyl leads to significant drops in conversion and enantioselectivity.
6. Five- and seven-membered substrates give lower enantioselectivities than cyclohexenones.
7. Conjugate addition to acyclic enones furnishes the product as racemic mixtures.

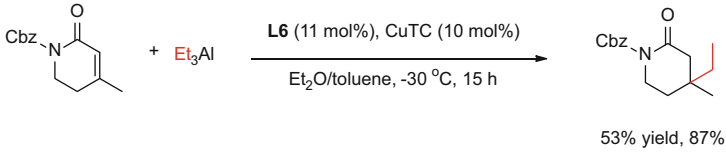
Phosphinamine ligands have also been applied to the formation of chiral and sterically congested cyclohexanone derivatives through a multistep sequence using (*n*-butoxymethyl)-diethylamine for the direct trapping of the aluminium enolate (Scheme 20) [56]. As mentioned before, aluminium enolates (and those adjacent to an all-carbon quaternary stereocentre in particular) are not very reactive towards most electrophilic species. However, when an α-aminoether is used as electrophile, the trapping process works efficiently. The (*n*-butoxymethyl)-diethylamine coordinates to the aluminium enolate, and a subsequent transfer of the *n*-butoxy group to the aluminium takes place, forming the desired electrophile, but also activating the



Scheme 20 Mechanism for the direct trapping of sterically encumbered aluminium enolates by Alexakis [56]



Scheme 21 Tandem copper–phosphinamine-catalysed ECA/direct trapping by Alexakis [56]



Scheme 22 Copper–phosphinamine-catalysed ECA of organoaluminium reagents to β-methyl-substituted δ-lactams by Alexakis [57]

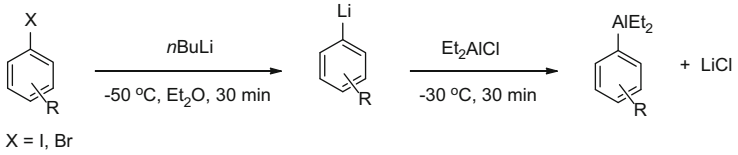
enolate in the same step. The formation of a reactive electrophile and reactive nucleophile in close proximity explains the high efficiency of this transformation.

After work-up and oxidation with m-CPBA, an elimination reaction takes place to generate a double bond. A second CA with a Grignard reagent can be then performed to provide products **16** in 27–41% overall isolated yields with good enantioselectivities (Scheme 21).

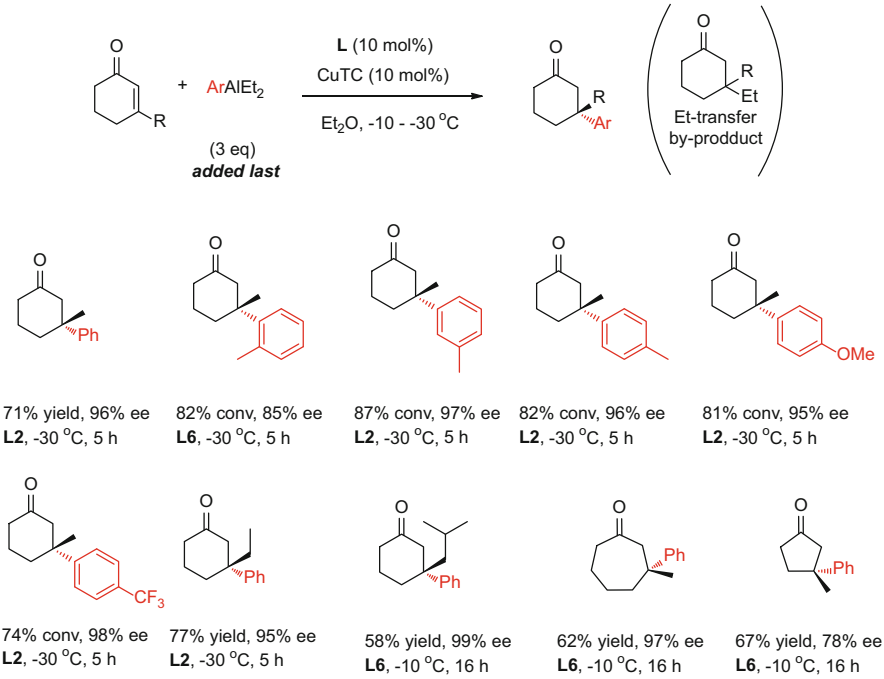
The versatile phosphinamine ligands are also suitable for the copper-catalysed ECA of organoaluminium reagents to α,β-unsaturated lactams, including β-methyl-substituted δ-lactams, whose reaction allows the formation of all-carbon quaternary stereogenic centres in moderate yields and good enantioselectivities, as exemplified in Scheme 22 [57].

Regarding the use of aryl aluminium reagents as nucleophiles in the copper-catalysed ECA, both phosphoramidites and phosphinamine ligands have demonstrated to be effective. Only one triaryl aluminium compound is commercially available (Ph_3Al), but its use as nucleophile would not be an atom-economical process. For this reason, readily available dialkyl aryl aluminium species are preferred. The preparation of these mixed aryl alkanes can easily be achieved from the corresponding aryl iodide or bromide through a halogen/Li exchange (with *n*BuLi) followed by a Li/Al transmetalation process with Et_2AlCl (Scheme 23) [44].

A suspension of an aryl aluminium reagent prepared with this method can be directly added to an enone without the need to remove the LiCl. The aryl transfer to

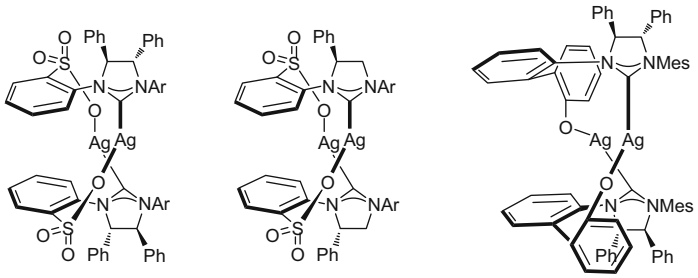


Scheme 23 Preparation of dialkyl aryl aluminium species from aryl halides by Alexakis [44]



Scheme 24 Copper–phosphinamine-catalysed ECA of aryl aluminium reagents to β-substituted cyclic enones by Alexakis [44]

the β-position of the enone is always preferred to the ethyl transfer. The addition of a wide variety of aryl organoaluminium reagents proceeds with enantioselectivities up to 99%, using 10 mol% of ligand (note that this catalyst loading is slightly higher than when alkyl organoaluminium reagents are used as nucleophiles) and 10 mol% of the copper salt with both six- and seven-membered ring cyclic enones (Scheme 24). Three equivalents of the organoaluminium reagent are needed, which must be added last to the reaction mixture, after the enone, in order to achieve good results. Reaction conditions and ligand may also need to be adapted for the more challenging, bulkier substrates. Higher temperatures and longer reaction times are usually needed in these cases in order to achieve satisfactory conversion, although, unfortunately, this leads to an increase of ethyl transfer. The main limitation of this methodology is the reduced enantioselectivity obtained with five-membered cyclic enones (see example in Scheme 24).



L9, Ar = 2,4,6-$Me_3C_6H_2$ (Mes)
L10, Ar = 2-*i*PrC_6H_5
L11, Ar = 2,4,6-*i*$Pr_3C_6H_2$ (Mes)

L12, Ar = 2,4,6-MeC_6H_2 (Mes)
L13, Ar = 2,6-EtC_6H_3
L14, Ar = 2,6-(*i*Pr)$_2C_6H_3$

L15

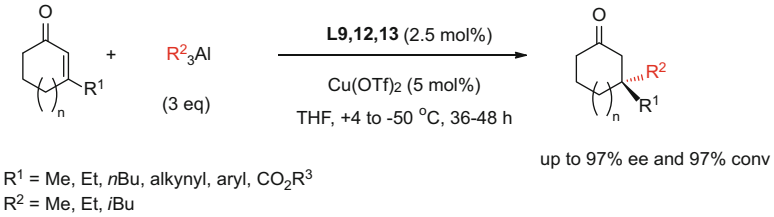
Fig. 5 Effective NHC ligands for the ECA of organoaluminium reagents to β,β-disubstituted enones

A different and very versatile class of catalysts for the addition of organoaluminium reagents to β-substituted cyclic enones are the silver-*N*-heterocyclic carbene (NHC) complexes **L9**–**14** developed by Hoveyda and co-workers (Fig. 5) [58].

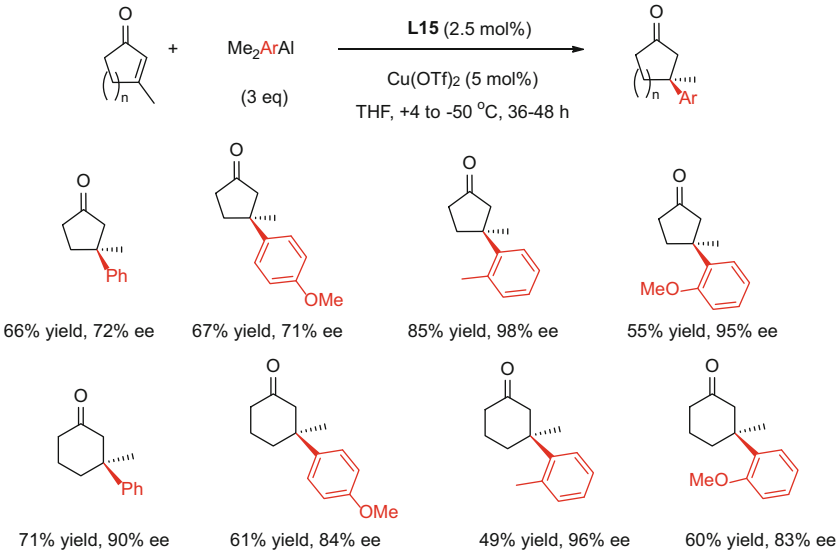
Since their discovery in 1968 by Öfele [59] and Wanzlick [60], and their first isolation in the free state by Arduengo [61] in the early 1990s, NHCs have received a growing attention as catalysts in many organic transformations [62]. These NHC ligands are likely to surpass in popularity well-known phosphorous-based ligands because of their remarkable ability to form strong bonds with metallic centres, allowing significant doping of catalytic activity in a wide range of chemical transformations, such as olefin metathesis, carbon–carbon and carbon–nitrogen cross-coupling reactions, hydrogenation and hydrosilylation reactions [63]. The electronic donating properties of NHCs are similar to those of their phosphine counterparts, but their topological features are quite different; phosphines produce a conical environment, whereas NHCs have a planar chelation site.

The copper–NHC-catalysed addition of organoaluminium reagents to cyclohexenones and cycloheptenones reported by Hoveyda [58] is, in some cases, slightly less selective than those performed in the presence of phosphoramidites or phosphinamine catalysts ($\leq$90% *ee* for the imidazolium ligands versus $\leq$99% *ee* that the phosphoramidites and phosphinamine can provide). However, NHC–Cu catalysis provides better results (up to 97% *ee* and 97% conv) when challenging cyclopentenones and bulky β-substituted cyclic enones (bearing *n*-butyl, alkynyl, aryl or an ester group as the β substituent) are used as substrates (Scheme 25).

Aryl-based aluminium reagents are also compatible with Cu–NHC catalysis. These nucleophiles can be prepared by the treatment of the corresponding aryl lithium compound (which can be easily obtained by treatment of commercially available aryl bromides with *n*BuLi) with 1 equiv. of commercially available



Scheme 25 Copper–NHC-catalysed ECA of organoaluminium reagents to β-substituted cyclohexenones by Hoveyda [58]

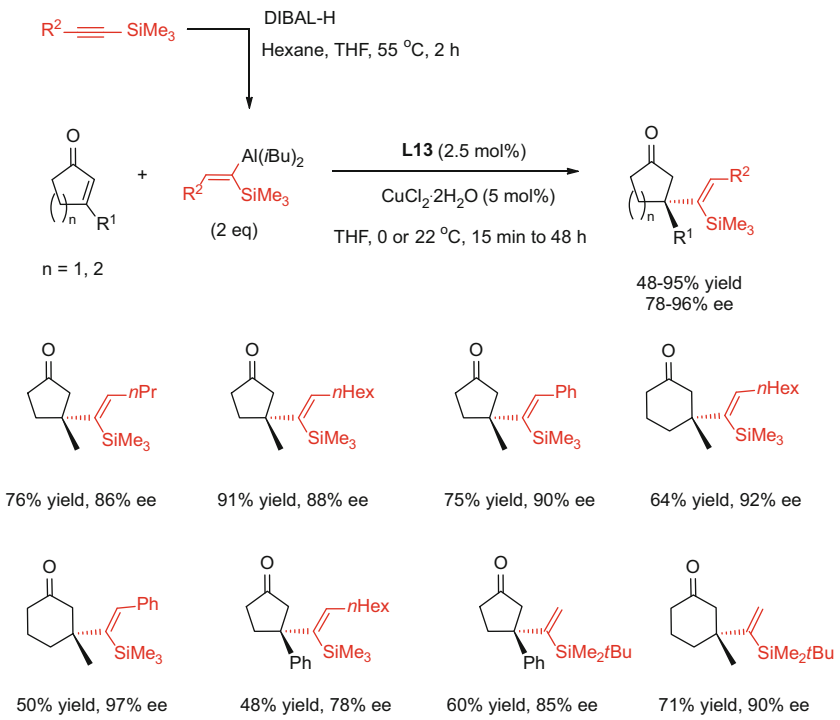


Scheme 26 Copper–NHC-catalysed ECA of aryl aluminium reagents to β-substituted cyclic enones by Hoveyda [58]

Me_2AlCl in pentane (−78 to 22 °C, 12 h).[2] The resulting solution of Me_2PhAl, containing LiCl, can be used directly – without filtration or purification – in the copper-catalysed ECA reactions of β-substituted cyclic enones (Scheme 26) and can be also stored under N_2 for more than 2 months without any noticeable diminution in efficiency.

As exemplified in Scheme 26, the reaction works well with five- and six-membered β-substituted cyclic enones, affording the desired products in up to

[2] Note that when Et_2AlCl is used as transmetalating agent (see [44]), instead of Me_2AlCl, shorter reaction times are needed for the transmetalation step (30 min at −30 °C for Et_2AlCl versus 12 h at −78 to 22 °C for Me_2AlCl).

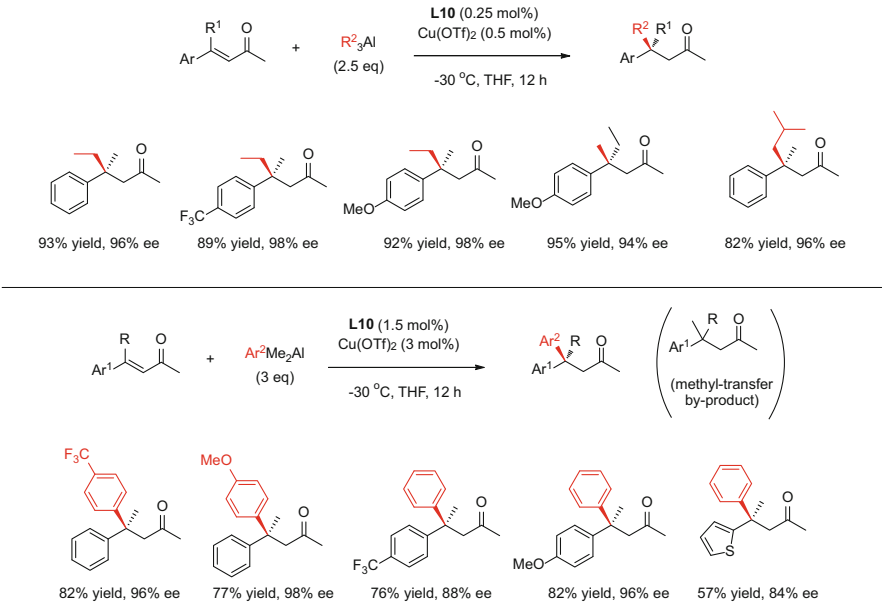


Scheme 27 Copper–NHC-catalysed ECA of alkenyl aluminium reagents (prepared by hydroalumination with DIBAL-H) to β-substituted cyclic enones by Hoveyda [64]

98% *ee*. Aryl lithium species bearing electron-donating and electron-withdrawing substituents can be used effectively, although enantioselectivities appear to be highest when the aryl unit is sterically more encumbered (i.e. carries an *ortho*-substituent); otherwise, levels below 90% *ee* are obtained. The moderate yields stated are ascribed to difficulties with the removal of biphenyl formed in the course of the transformation. Despite this, results for the five-membered rings are remarkable, considering that they are usually challenging substrates in the ECA.

The use of alkenyl aluminium reagents as nucleophiles for the copper–NHC-catalysed ECA has also been described through a tandem hydroalumination–CA process. To prevent the formation of aluminium acetylides during the hydroalumination reaction, which could perturb the chiral complex, Hoveyda and co-workers opt for the use of silyl-protected alkynes as starting material, which undergo clean *cis*-hydroalumination with DIBAL-H in coordinating solvents (Scheme 27) [64].

Although sterically congested, the resulting silicon-substituted alkenyl aluminium reagents undergo fast ECA using 1.0–5.0 mol% of a NHC–Cu complex, which is prepared from air-stable $CuCl_2 \cdot 2H_2O$ and precursor **L13**. Both cyclopentenones and cyclohexenones are suitable substrates for this methodology, and only their β-aryl-substituted derivatives lead to diminished reaction rates. The challenging cyclopentenones generally react more efficiently than cyclohexenones. Catalytic



Scheme 28 Copper–NHC-catalysed ECA of organoaluminium reagents to β,β-disubstituted linear enones by Hoveyda [65]

additions of alkenyl aluminium reagents to cycloheptenones under these reaction conditions are, however, inefficient.

As represented in the last two examples in Scheme 27, vinyl aluminium reagents bearing a more hindered silyl unit (tBuMe$_2$Si vs SiMe$_3$) also provide high enantioselectivities. The vinylsilane moiety within the products can be functionalised to afford acyl, vinyl iodide or desilylated alkenes in 67% to >98% yield and with >90% retention of the alkene's stereochemical identity [64].

The use of acyclic enones for ECA reactions is very challenging. They lack the ring strain of their cyclic counterparts, and most catalysts fail to differentiate the enantiotopic faces of the olefin. The 'privileged' silver–NHC complexes are effective, however, in combination with Cu(OTf)$_2$ [65].

A wide range of acyclic trisubstituted enones readily undergo ECA with both commercially available trialkylaluminium reagents and the in situ-generated aryl (dialkyl)aluminium reagents. Very low catalyst loadings are sufficient (0.5–3.0 mol %) and products are formed in good yields (33–95%) and exceptional enantioselectivities (80 to 99%) (Scheme 28) [65].

The main limitations of the methodology are the low reactivity observed with *ortho*-substituted aryl(dimethyl)aluminium reagents and the competing methyl transfer-derived by-product which can be detected. Conversely, the addition of alkyl aluminium reagents to bulky substrates and non-aromatic enones proceeds with very high enantioselectivity, as exemplified in Fig. 6.

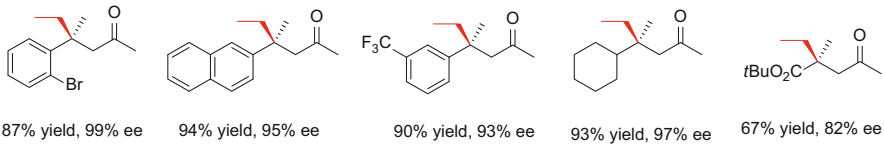
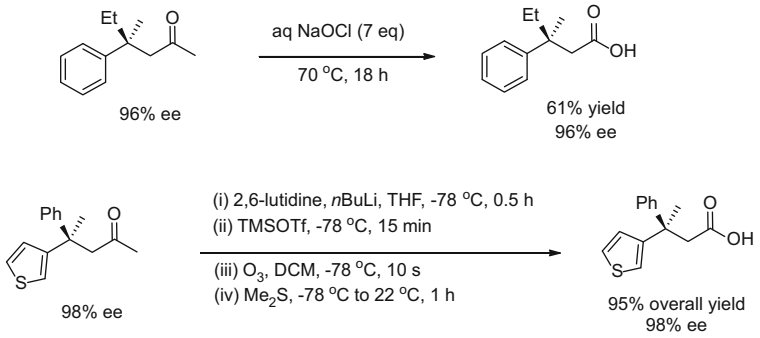


Fig. 6 Copper–NHC-catalysed ECA of organoaluminium reagents to both bulky and aliphatic β,β-disubstituted linear enones by Hoveyda [65]

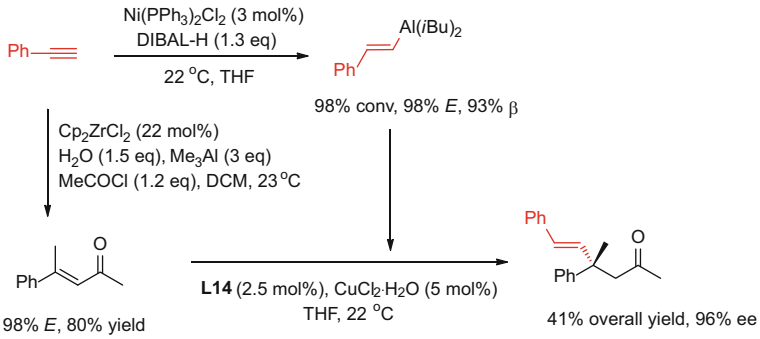


Scheme 29 Oxidation of chiral ketones to versatile carboxylic acids by Hoveyda [65]

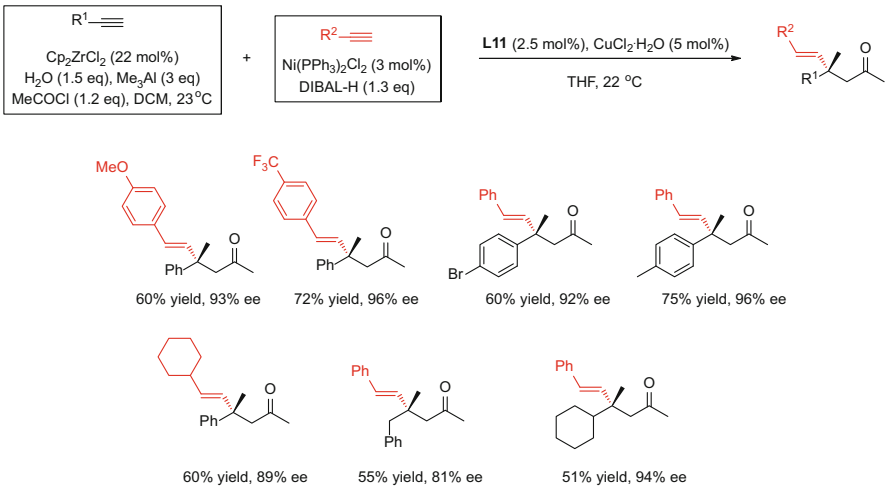
Although this methodology is not successful with acyclic carboxylic acid derivatives (e.g. Weinreb amides, *N*-acyloxazolidinones, carboxylic esters or thioesters), it is possible to reach this kind of valuable enantiomerically enriched products by a simple oxidation with commercial bleach from the corresponding ketone (Scheme 29, top). If the ketone possesses a substituent prone to oxidation, an alternative procedure, involving the formation of a silyl enol ether (which does not need isolation/purification), can be followed instead (Scheme 29, bottom).

The addition of alkenyl aluminium nucleophiles to linear β,β-disubstituted enones to give all-carbon quaternary stereogenic centres can be also achieved with consistently high yields and enantioselectivities (up to 99% *ee*) by copper–NHC-catalysed ECA, using very low catalyst loadings at room temperature (Scheme 30) [66].

In this work, Hoveyda et al. synthesise alkenyl aluminium reagents with exceptional site selectivity and/or stereoselectivity using a Ni-catalysed hydroalumination process and use them directly. Unlike the methodology previously described for β-substituted cyclic enones, silyl-substituted alkenyl aluminium species are not necessary to obtain high enantioselectivities with linear substrates. The overall process becomes highly efficient when the acyclic enone is also prepared through catalytic means, by a site- and stereoselective zirconocene-catalysed carboalumination/acylation reaction (Scheme 30). It is important to note that the acyclic enone prepared here must be purified by silica gel chromatography before the ECA reaction, to prevent loss of enantioselectivity. Thus, the addition of aryl- or heteroaryl-substituted β-alkenyl aluminium compounds to aryl- or alkyl-substituted substrates furnishes β-alkenyl ketones in moderate to good yields (24–60% after the



Scheme 30 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [66]



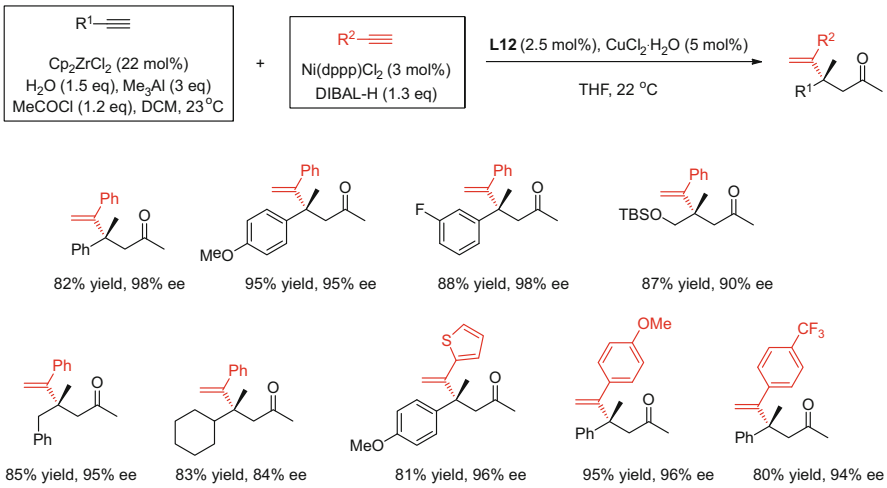
Scheme 31 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of linear alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [66]

3 steps) and high enantioselectivities (>90%), using the NHC silver complexes **L11** (Scheme 30) or **L14** (Scheme 31) as precatalyst, in combination with $CuCl_2 \cdot H_2O$.

Moreover, when the Ni-catalysed hydroalumination is carried out with Ni(dppp)Cl_2, the α-substituted alkenylaluminium reagent is obtained, which can be also used in the ECA to acyclic enones, providing good yields and enantioselectivities when a **L12**/$CuCl_2 \cdot H_2O$ mixture is used as catalyst (Scheme 32).

Linear alkyl (vs methyl) ketones and unsaturated ketoesters are also tolerated with this methodology, as exemplified in Fig. 7.

The utility of this method has been demonstrated with the enantioselective synthesis of antimicrobial Enokipodin B (Fig. 1) [66].



Scheme 32 Multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of branched alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [66]

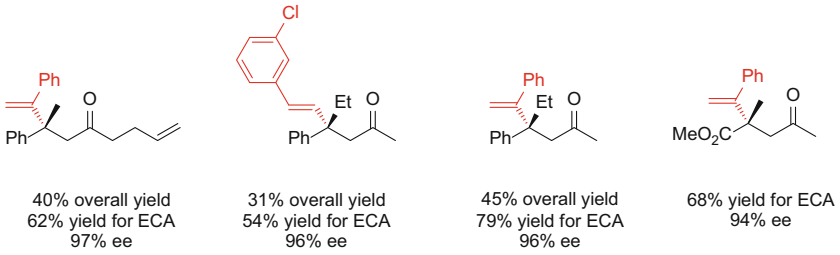


Fig. 7 Examples on the multicomponent Ni-, Zr- and Cu-catalysed strategy for ECA of alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [66]

The DFT calculations carried out to gain insight on the origins of the enantioselectivity in this process indicate that an initial conjugate addition of the (alkenyl) Cu^{I} complex followed by a reductive elimination of the (alkenyl)Cu^{III} alkyl intermediate are the key steps involved in the catalytic cycle. Complex **A** (Fig. 8) represents the lowest energy pathway, consistent with the identity of the major isomers, whilst complex **B** (Fig. 8), leading to the minor enantiomers, is about 1.6 kcal/mol higher in energy. In the latter case, simultaneous coordination of the substrate to the Lewis acidic aluminium bridge atom and copper centre dictates that the enone binds in its energetically more demanding s-*trans* conformation (vs. s-*cis* in complex **A**), introducing severe A(1,3) strain between the ketone and alkene substituents. In the absence of an aluminium bridge atom, the transition state for addition to the same face as the complex is appreciably higher in energy.

Phosphine ligands such as **L16** and **L17** (Fig. 9), based on either a SPINOL or BINOL architecture, are also suitable ligands for the copper-catalysed ECA of

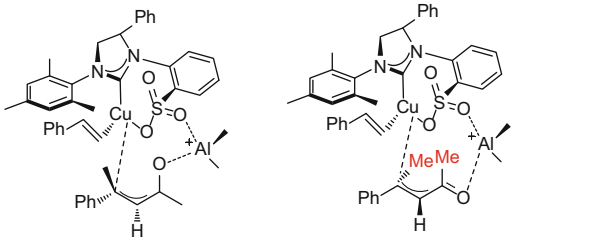


Fig. 8 Proposed transitions states for the copper–NHC-catalysed ECA or alkenyl aluminium reagents to β,β-disubstituted linear enones by Hoveyda [66]

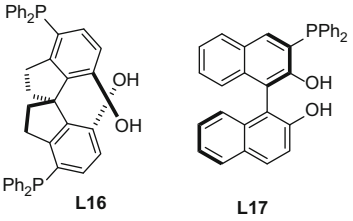
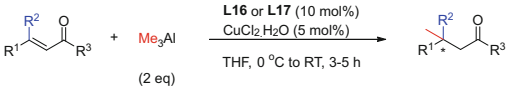
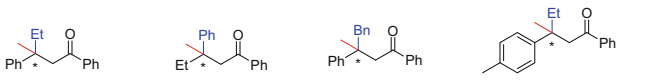
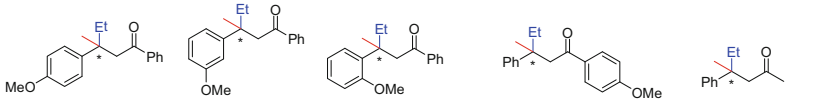


Fig. 9 Effective phosphine ligands for the ECA of organoaluminium reagents to β,β-disubstituted enones





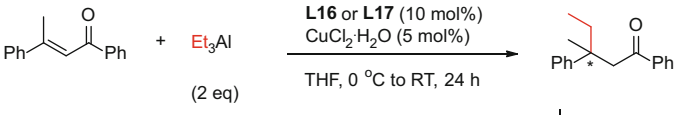
L16	98% yield, 98% ee (+)	98% yield, 35% ee (-)	80% yield, 97% ee (+)	95% yield, 98% ee (+)
L17	98% yield, 95% ee (-)	98% yield, 75% ee (-)	72% yield, 94% ee (-)	97% yield, 98% ee (-)



L16	98% yield, 98% ee (+)	93% yield, 98% ee (+)	93% yield, 94% ee (+)	97% yield, 98% ee (*R*)	97% yield, 93% ee (-)
L17	86% yield, 98% ee (-)	60% yield, 95% ee (-)	89% yield, 98% ee (-)	98% yield, 98% ee (*S*)	76% yield, 98% ee (+)

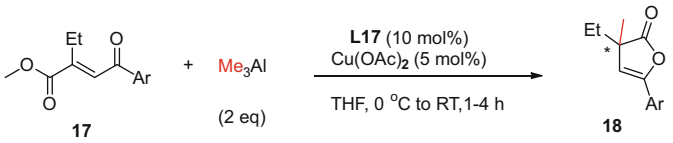
Scheme 33 Copper–phosphine-catalysed ECA of trimethylaluminium to β,β-disubstituted linear enones by Endo [67]

Me_3Al to β,β-disubstituted acyclic enones, giving the corresponding chiral quaternary carbon centres with enantioselectivities higher than 95% at room temperature (Scheme 33) [67].



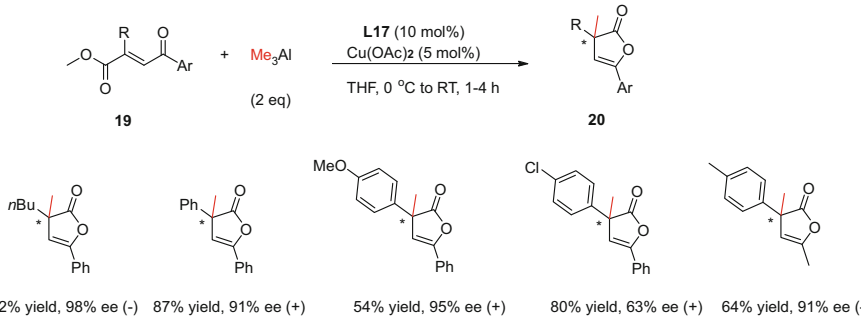
L16	53% yield, 90% ee (-)
L17	70% yield, 98% ee (+)

Scheme 34 Copper–phosphine-catalysed ECA of triethylaluminium to β,β-disubstituted linear enones by Endo [67]



Ar	Ph	*p*-FC_6H_4	*p*-$MeOC_6H_4$	*o*-$MeOC_6H_4$	2-naphthyl
yield (%)	88	94	92	92	95
ee (%)	97 (-)	98 (-)	98 (-)	98 (-)	96 (-)

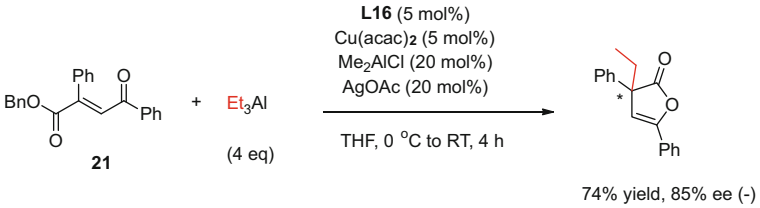
Scheme 35 Synthesis of α,α-disubstituted furanones by copper–phosphine-catalysed ECA of trimethylaluminium by Endo [68]



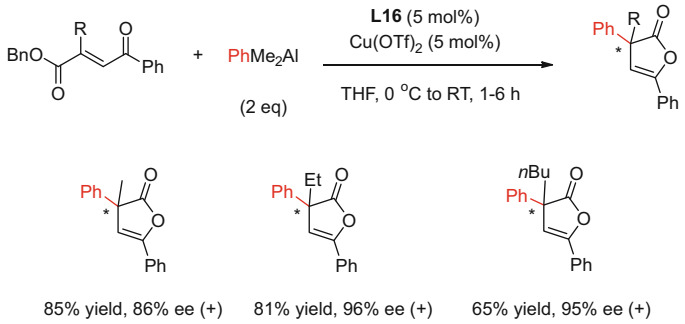
Scheme 36 Synthesis of α,α-disubstituted furanones by copper–phosphine-catalysed ECA of trimethylaluminium by Endo [68]

The addition of other alkyl aluminium reagents, such as Et_3Al, with phosphine ligands **L16** and **L17**, provides good enantioselectivities but moderate yields, due to low conversions (Scheme 34).

When unsaturated ketoesters **17** or **19** are used as substrates, the copper-catalysed addition of Me_3Al in the presence of **L17** provides, after subsequent lactonization, chiral furanones **18** and **20**, respectively, bearing quaternary stereogenic centres (Schemes 35 and 36) [68]. The optimised reaction conditions are applicable to a wide variety of benzyl ketoesters, and all products can be



Scheme 37 Benzyl ketoesters as substrates for the synthesis of α,α-disubstituted furanones by copper–phosphine-catalysed ECA of triethylaluminium by Endo [68]



Scheme 38 Aryl aluminium reagents as nucleophiles for the synthesis of α,α-disubstituted furanones by copper–phosphine-catalysed ECA by Endo [68]

obtained in high to excellent yields with high enantioselectivities. Furanones are versatile synthetic intermediates, which can be easily transformed into a variety of densely functionalised scaffolds.

Benzyl ketoesters, such as **21**, are also suitable substrates for this methodology and efficiently undergo ECA with $Cu(acac)_2$ and **L16**, when Me_2AlCl and AgOAc are used as additives (Scheme 37).

Regarding the use of aryl aluminium reagents as nucleophiles for the copper-catalysed ECA with phosphines **L16** and **L17**, the reaction does not work with Ph_3Al, but the mixed aryl alane $PhMe_2Al$ (or $PhEt_2Al$) provides good results with **L16**, as exemplified in Scheme 38.

2.2 *Grignard Reagents as Nucleophiles*

The copper-catalysed ECA of Grignard reagents has been extensively studied with a variety of phosphorous ligands [16]. Some of the interesting economical aspects of these nucleophiles, as compared to their zinc or aluminium counterparts, include the following:

1. They are more reactive (less excess needed to complete the addition).
2. They are readily accessible and highly tunable.
3. All R groups from the nucleophile are transferred to the substrate.

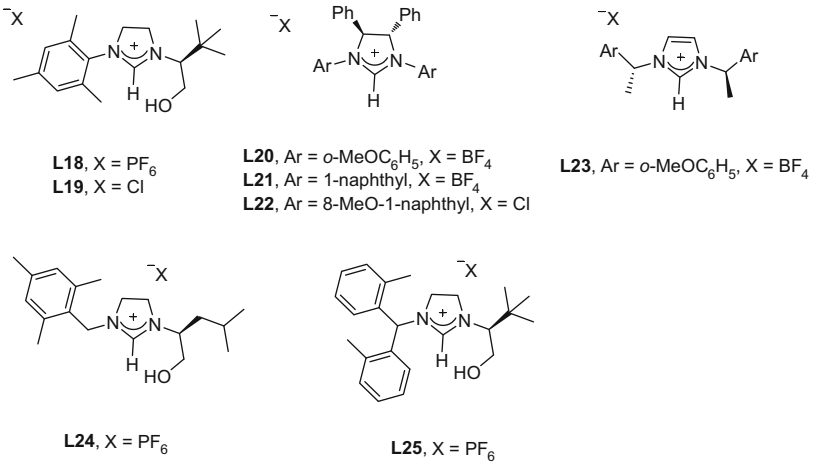


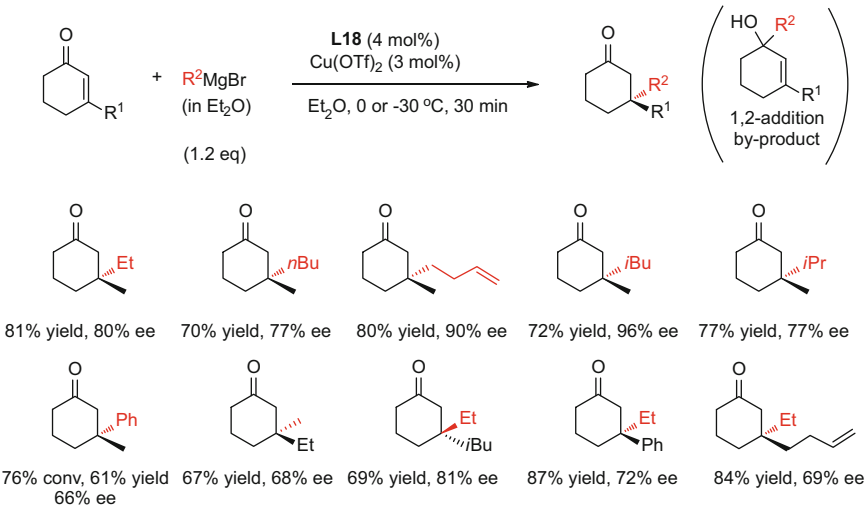
Fig. 10 Effective imidazolinium salts for the copper-catalysed ECA of Grignard reagents to β-trisubstituted enones

In 2006, Alexakis and Mauduit demonstrated that NHC ligands derived from C2-symmetric imidazolidinium salts (**L18–25**, Fig. 10) were superior to phosphoramidite and ferrocene-based ligands when used for the copper-catalysed ECA of Grignard reagents to β,β-disubstituted enones [69]. They also observed that these ligands give better results with Grignard reagents than with any other organometallic compound.

In particular, imidazolium salt **L18** (Fig. 10) shows very high efficiency for the copper-catalysed ECA of Grignard reagents to β-substituted cyclohexenones (Scheme 39) [69]. A very low catalyst loading is needed to achieve moderate to good enantioselectivity, and the reaction proceeds in 30 min, working at 0 or −30 °C. The slight excess of Grignard reagent employed is necessary for in situ deprotonation of the imidazolium salt (precatalyst) to form the NHC species. Slightly better conversions and enantioselectivities are obtained by adding the substrate last to the reaction mixture, after the addition of the Grignard reagent.

The scope of the reaction is wide, as represented in Scheme 39. Primary and secondary Grignard reagents give good to high enantioselectivities (up to 96%). The methodology is also applicable to more hindered substrates and seven-membered ring enones, as exemplified in Fig. 11. Unfortunately, the addition of aryl Grignard reagents proceeds with moderate regioselectivities (the 1,2-addition product is obtained in high percentages), and the sterically demanding *t*BuMgBr does not react, even at higher temperatures.

Although salts **L18–19** are superior and provide the best results in terms of conversions and enantiomeric excesses (with their main limitations mentioned above), other C_2-symmetric [70] and nonsymmetric [71] imidazolium salts, such as **L20–23**, are able to induce the copper-catalysed ECA of alkyl Grignard reagents to 3-methylcyclohex-2-enone in moderate to good enantioselectivities, as



Scheme 39 Copper–NHC-catalysed ECA of Grignard reagents to β-substituted cyclic enones by Alexakis [69]

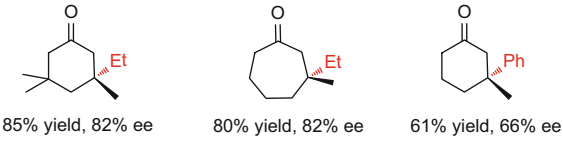
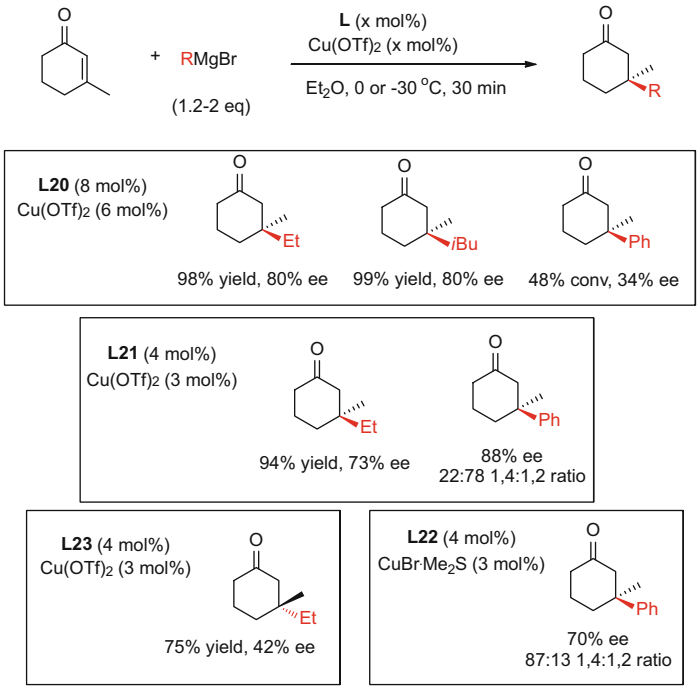


Fig. 11 Synthesis of chiral bulky cyclohexanones and cycloheptanones via copper–NHC-catalysed ECA of Grignard reagents by Alexakis [69]

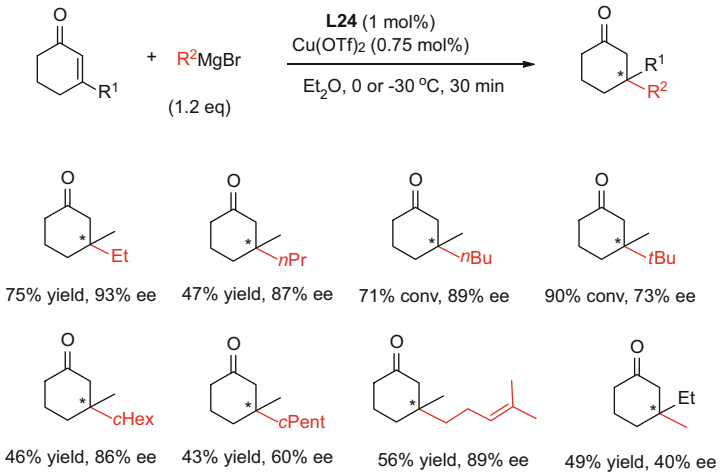
exemplified in Scheme 40. Unfortunately, none of these ligands as **L20–23** provides better results for the addition of PhMgBr or *t*BuMgBr than the hydroxyl containing ligands **L18–19**.

The imidazolium salt **L24**, bearing an additional methylene spacer to increase the flexibility on that side of the carbene and thus occupying a larger space versus **L18–19**, gives very good results for the copper-catalysed ECA of Grignard reagents to β-substituted cyclic enones (Scheme 41). The challenging five-membered ring substrates, which are out of scope for ligands **L18–19** (Scheme 42), perform well in this example [72]. Thus, the ECA of a wide variety of Grignard reagents (both primary and secondary) to β-substituted cyclic enones allows the formation of quaternary centres with high levels of regio- and enantioselectivity with only 1 mol% of **L24**. One of the main drawbacks of this methodology is the moderate results obtained when methylmagnesium bromide is used as nucleophile (40% *ee* for the addition to 3-ethylcyclohex-2-enone); this is certainly due to the well-known lack of reactivity and specific behaviour of this nucleophile.

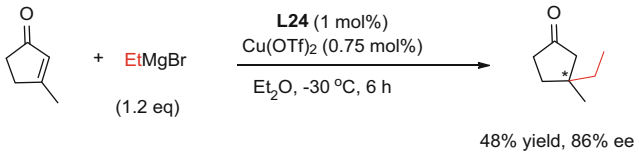
Alexakis et al. have proposed a catalytic cycle for the ECA with imidazolium ligands and Grignard reagents (Scheme 43) [72].



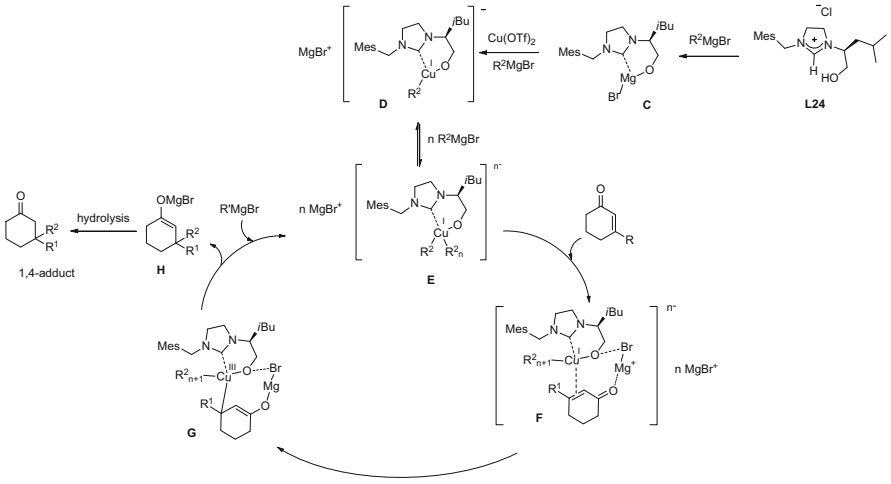
Scheme 40 Copper–NHC-catalysed ECA of Grignard reagents to β-substituted cyclic enones by Alexakis [71] and Tomioka [70]



Scheme 41 Copper–NHC-catalysed ECA of Grignard reagents to β-substituted cyclohexenones by Alexakis [72]

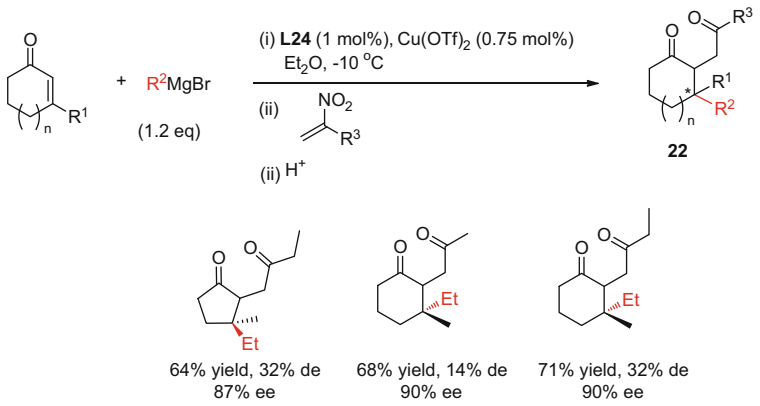


Scheme 42 Copper–NHC-catalysed ECA of Grignard reagents to β-substituted cyclopentenones by Alexakis [72]

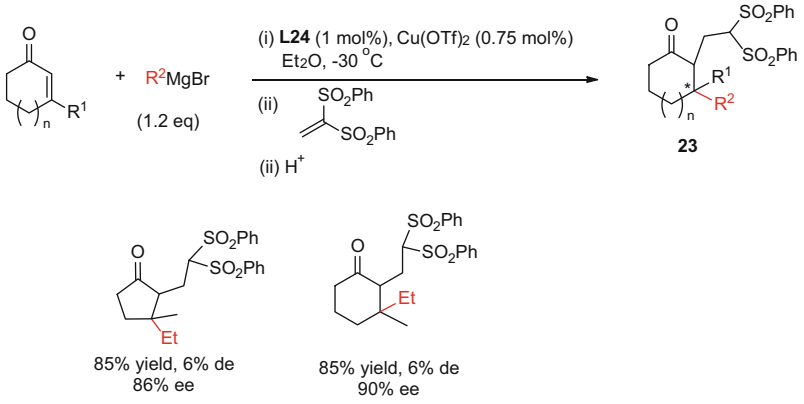


Scheme 43 Proposed catalytic cycle for the copper–NHC-catalysed ECA of Grignard reagents to cyclic enones by Alexakis [72]

Acting as a base, the Grignard reagent deprotonates first the hydroxyl group in the side chain, and then the imidazolium, leading to the NHC-coordinated alkoxymagnesium compound **C**. Copper triflate, which is reduced in situ by 1 equiv. of the Grignard reagent to give a copper(I) species, is involved in a transmetalation step to give the Cu–NHC complex, which upon addition of the Grignard reagent gives a heterocuprate **D**. In the presence of excess Grignard reagent, cuprate **D** probably forms higher-order aggregates **E** [73]. The equilibrium between heterocuprate **D** and higher-order heterocuprate **E** could be the key to understanding the following experimental fact: the slow addition of R^2MgBr generates heterocuprate **D**, which undergoes a non-enantioselective conjugate addition faster than forming the higher-order heterocuprate **E**. When the enone is added as the last component, the heterocuprate **D** has had time to equilibrate towards the highly efficient heterocuprate **E** and good enantioselectivities are obtained. The equilibrium between **D** and **E** could also be affected by the nature of the halogen present in the Grignard reagent, which explains why iodide and chloride are undesirable counterions [74]. The following steps in the catalytic cycle correspond to the classical mechanistic pathway of a copper-mediated conjugate



Scheme 44 Domino copper–NHC-catalysed ECA of Grignard reagents/CA trapping with 1-alkyl-1-nitroolefins by Alexakis [76]. All *ee*'s measured before trapping

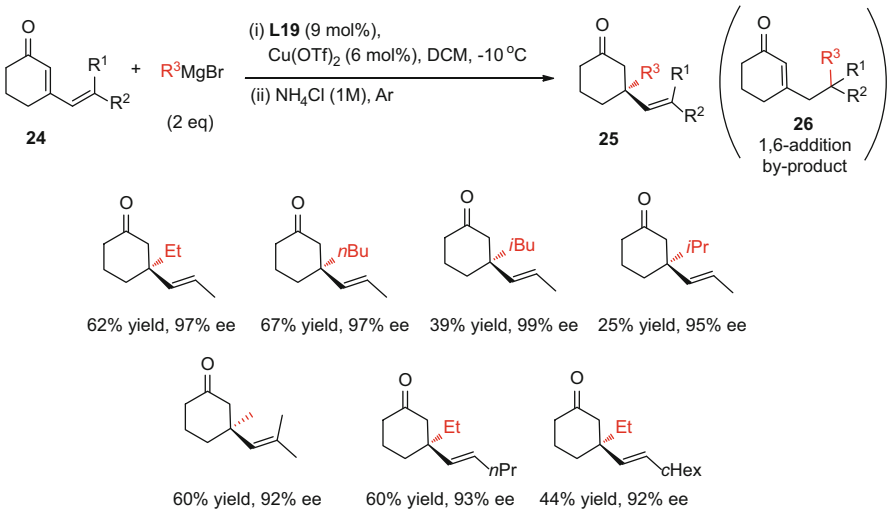


Scheme 45 Domino copper–NHC-catalysed ECA of Grignard reagents/CA trapping with vinyl disulfones by Alexakis [76]. All *ee*'s measured before trapping

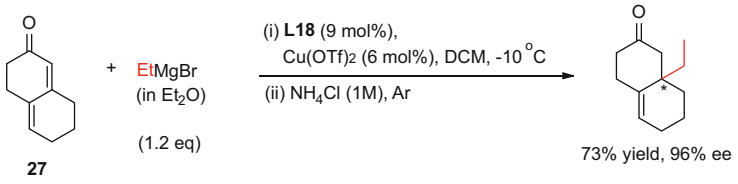
addition [75]. Thus, a reversible π complex **F** undergoes oxidative addition to a Cu^{III} intermediate **G**, which collapses by reductive elimination to give the magnesium enolate **H**.

The magnesium enolates generated by ECA using the copper–**L24** catalytic system can be easily trapped with 1-alkyl-1-nitroolefins (Scheme 44) [76]. After the trapping, an in situ Nef reaction [77] takes place, generating the corresponding 1,4-diketones **22**. These Michael adducts **22** can be then derivatised towards notable bicyclic structures, with relevance in natural products.

The same tandem procedure can be carried out using vinyl disulfones as electrophiles to provide the corresponding γ-sulfonylated ketones **23** in high yields and diastereo- and enantioselectivities (Scheme 45) [76]. Sulfone derivatives are tunable synthetic entities [78]. For example, the homolytic cleavage of disulfones



Scheme 46 Copper–NHC-catalysed ECA of Grignard reagents to conjugated dienones by Alexakis [80, 81]

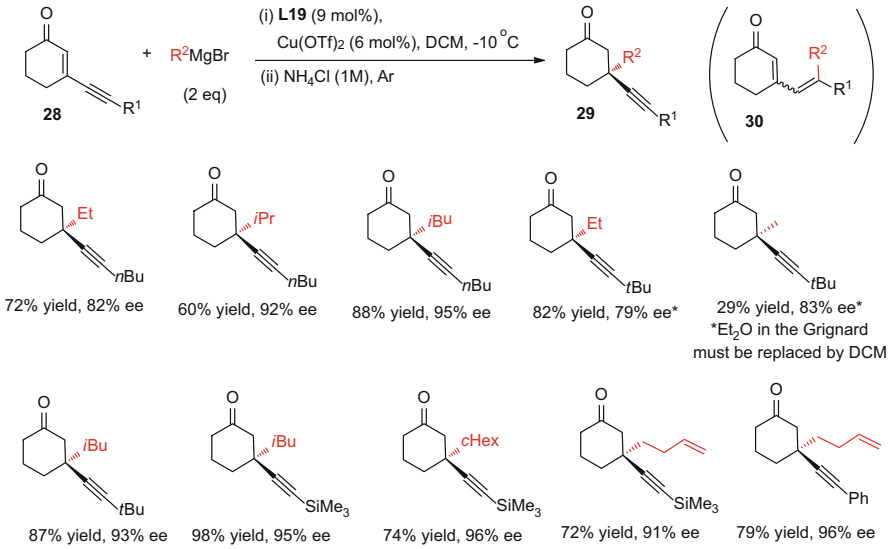


Scheme 47 Copper–NHC-catalysed ECA of ethylmagnesium bromide to the bicyclic conjugated dienone **27** by Alexakis [81]

through lithium naphthalenide or samarium iodide methodologies are well-established procedures for their corresponding derivatisation [79].

NHC ligands bearing a hydroxyl group (such as the ones derived from the imidazolium salts **L18–19**) also allow a high regio- and enantioselective CA reaction to conjugated dienones **24** (Scheme 46) [80, 81]. Primary and secondary Grignard reagents provide the corresponding 1,4-adduct **25** with greater than 95% selectivity (less than 5% of 1,6- and/or 1,2-addition regioisomers is observed) and enantioselectivity values as high as 99%. To prevent the formation of oxidative by-products, hydrochloric acid or NH_4Cl – which must be degassed with argon – are used to quench the reaction. The methodology demands the use of 2 equiv. of Grignard reagent, to compensate the reduced reactivity that these species display in DCM, the optimal solvent for this transformation. Also, the presence of Et_2O has negative effects on the regiocontrol; replacing the Et_2O Grignard solvent with DCM provides higher regioselectivity towards the desired 1,4-adducts.

Bicyclic substrates, such as **27**, also give excellent regio- and enantioselectivity in the conjugate addition reaction of EtMgBr promoted by the copper–NHC system derived from **L18** (Scheme 47).



Scheme 48 Copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [80, 84]

Unsuitable nucleophiles for this methodology are PhMgBr, which gives complex reaction mixtures, and MeMgBr, which only provides the corresponding 1,6-addition product **26** when the substituent R^1 in the dienone **24** (Scheme 46) is a hydrogen atom. The addition of MeMgBr is not always problematic; γ,δ-disubstituted dienones **24** (R^1, $R^2 \neq H$) allow the formation of the 1,4-adduct exclusively, with high enantioselectivities (92% *ee* when $R^1 = R^2 = Me$).

This regiodivergent ECA is quite intriguing. Experiments with simpler NHC's (Arduengo's carbene [82]) and Grignard reagents give exclusively the 1,6-adduct **26**. The pendant hydroxyl group in the imidazolium ligand is essential to obtain good 1,4-selectivity. Also, other ligands, such as phosphoramidites, Josiphos and BINAP derivatives, only lead to the corresponding 1,6-addition product **26** in moderated to low enantioselectivities [83].

In terms of synthetic applications, the remaining C=C double bond in the 1,4-adduct **25** allows useful transformations, affording interesting bicyclic building blocks. In addition, the corresponding magnesium enolate intermediate can be trapped with different electrophiles, allowing for the formation of useful synthons [80, 81].

This methodology also allows very good regio- and enantioselectivities when cyclic enynones such as **28** are used as substrates [80, 84]. The use of $Cu(OTf)_2$ and imidazolium ligand **L19** as catalysts in DCM leads to the unique formation of the 1,4-adduct **29** (Scheme 48). Again, this selectivity does not follow the general trend observed when extended Michael acceptors are used with phosphoramidites or phosphine ligands, which provide the 1,6-adduct **30** as the major regioisomer [58, 85].

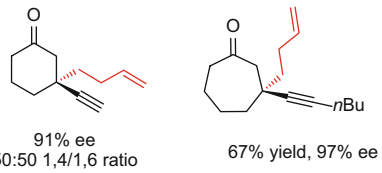
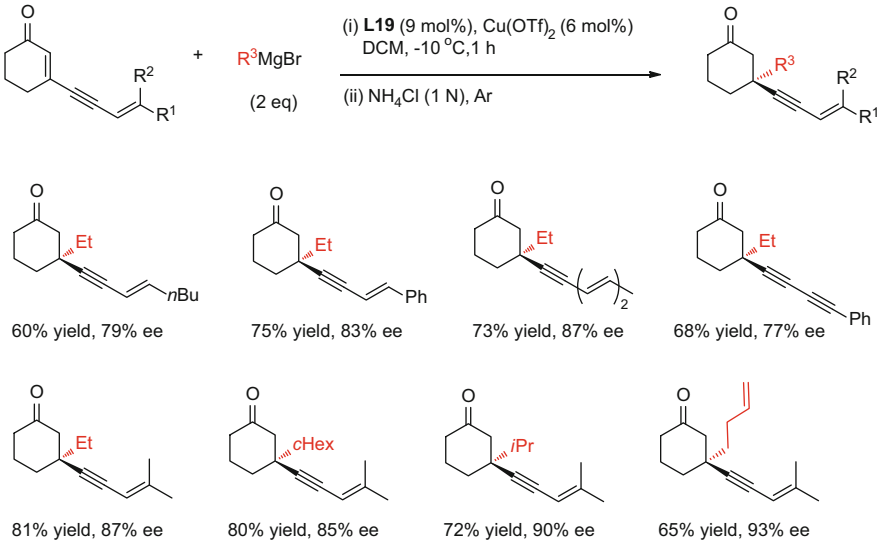


Fig. 12 Synthesis of chiral cyclohexanone bearing a terminal alkyne and chiral cycloheptanone by copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones by Alexakis [84]

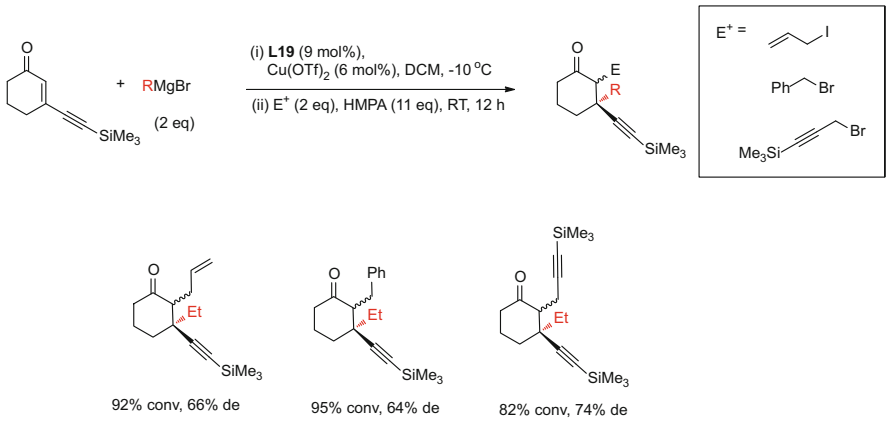


Scheme 49 Copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones that bear additional unsaturations by Alexakis [84]

The ECA to cyclic enynones provides good selectivities and enantioselectivities in most cases with ethyl, isopropyl and *n*-butyl Grignard reagents. In some cases, the Et_2O Grignard solvent has to be replaced by DCM, to avoid low 1,4-regioselectivity. The addition of MeMgBr is again problematic regarding regioselectivity; the corresponding 1,6-adduct **30** is obtained as the major isomer unless a bulky substituent is placed at the alkyne position (e.g. R^1=*t*Bu), in which case the 1,4-adduct **29** is favoured and obtained with good enantioselectivity (Scheme 48).

The scope of the methodology includes seven-membered cyclic enynones (Fig. 12), whereas the five-membered rings give complex reaction mixtures, with very poor regioselectivity control. Enynones possessing a terminal alkyne give low regioselectivity but high enantioselectivity for the 1,4-addition product, as exemplified in Fig. 12.

Challenging substrates possessing additional unsaturated units also give good to moderate results with this methodology (Scheme 49). Primary and secondary Grignard reagents add with high regio- and enantioselectivity (up to 90%). Unfortunately, MeMgBr remains problematic.



Scheme 50 Tandem copper–NHC-catalysed ECA of Grignard reagents to cyclic enynones/enolate trapping by Alexakis [84]

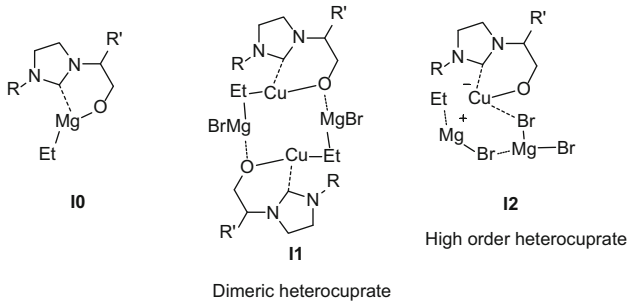
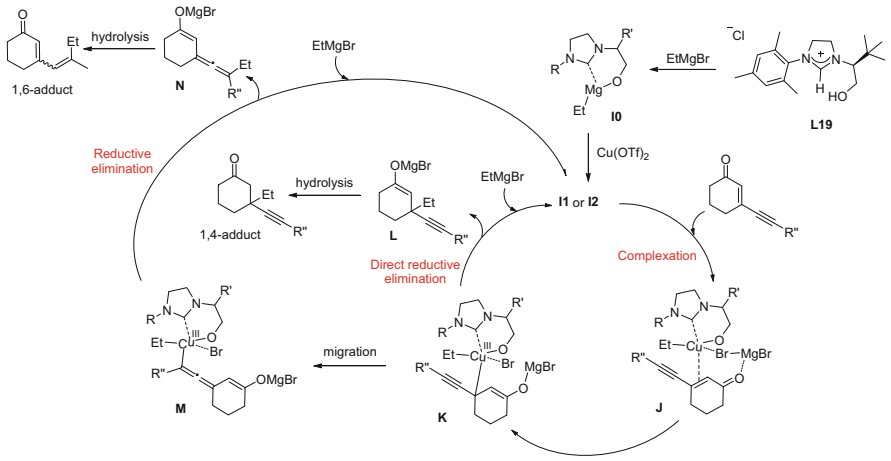


Fig. 13 Proposed carbenoid metal complexes for the copper–NHC-catalysed ECA reaction with Grignard reagents by Alexakis [84]

The catalytic system copper/**L19** gives moderate diastereoselectivities (see examples in Scheme 50) in a tandem CA electrophilic trapping process, using allyl, benzyl and propargyl halides as electrophiles.

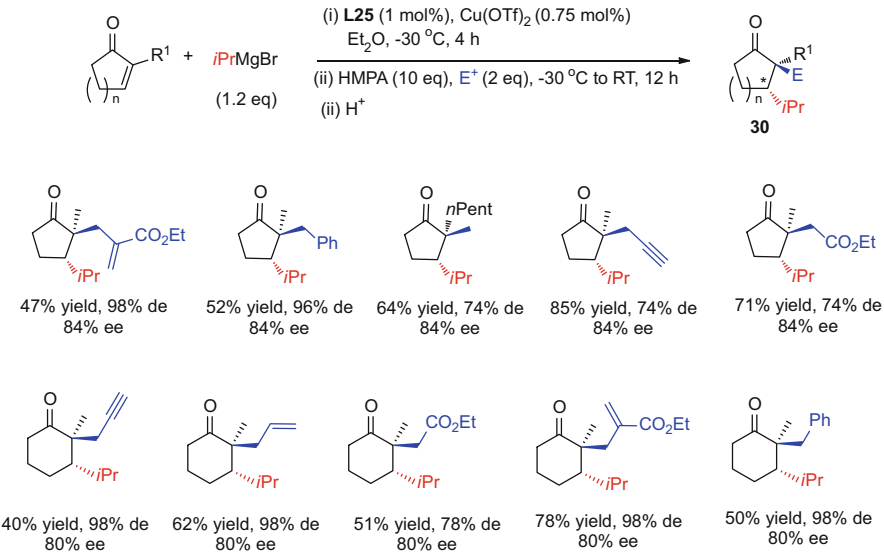
Several experimental observations have been taken into account to propose a plausible structure of the catalytic system (Fig. 13) and mechanism for the ECA reaction to polyconjugated cyclic enones (Scheme 51). Better enantioselectivities are obtained when the substrate is added last to the reaction mixture, after the addition of the Grignard reagent. This means that the hydroxy group of the NHC is deprotonated by the Grignard reagent, leading to the formation of a transient complex **I0**, followed by the formation of the heterocuprate complex. Based on the characterisation of a magnesium organocuprate complex by Davies et al. [86], Alexakis proposes the dimeric heterocuprate **I1** as the copper complex in the reaction with the polyconjugated cyclic enones. However, the large excess of Grignard reagents employed cannot exclude the presence of a high-order heterocuprate **I2**. Presumably, the addition of the dienone to complexes **I1** or **I2** leads to



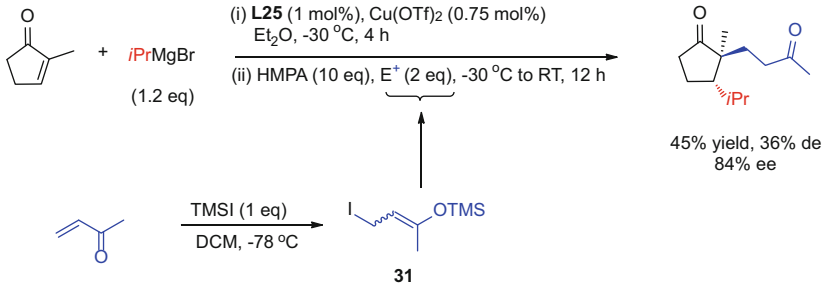
Scheme 51 Proposed catalytic cycle for the ECA reaction to polyconjugated cyclic enones by Alexakis [84]

the formation of a π complex **J** followed by the generation of a β-cuprio(III) enolate intermediate **K**. At this point, two pathways can be envisaged: complex **K** can reductively eliminate to afford the 1,4-adduct, enolate **L**, or the heterocuprate complex can migrate to the triple bond to form a new organocopper(III) intermediate **M**, followed by reductive elimination to afford the 1,6-adduct, enolate **N**. Both enolate species **M** and **N** can be transformed upon hydrolysis into the corresponding 1,4- and 1,6-adducts, respectively. In this case, the 1,4-addition trend observed with the above-discussed catalytic system implies that the 1,4-reductive elimination is faster than the migration to form complex **M**. It has been postulated that the copper complex derived from **L19** lowers the activation barrier of this 1,4-reductive elimination step and thus disfavours the migration to the 1,6-position.

The enantioselective generation of quaternary centres via copper-catalysed CA can be also achieved through a tandem ECA–enolate trapping process on α-substituted cyclic enones (Schemes 52, 53, 54, 55, 56 and 57). In this case, the quaternary centre is generated at the α-position of the carbonyl, contiguous to a β-tertiary centre. The imidazolium ligand **L25** is able to catalyse such a transformation, using Grignard reagents as nucleophiles in the presence of $Cu(OTf)_2$, giving very good enantio- and diastereoselectivities with both α-substituted cyclopentanones and cyclohexanones (Scheme 52) [87, 88]. Alkyl, propargyl, allyl and benzyl halides have been used as electrophiles, all providing ketone derivatives **30** in high diastereoselectivity and good enantioselectivity when the secondary and bulky Grignard reagent *i*PrMgBr is used as nucleophile. Primary Grignard reagents are inferior to their branched counterparts in the addition to α-substituted cyclic enones. The maximum enantioselectivities for the addition of ethylmagnesium bromide to α-substituted cyclohexenones and cyclopentenones are 80 and 60%, respectively. The reaction with MeMgBr does not proceed, due probably to the lower reactivity of this species.



Scheme 52 Tandem copper–NHC-catalysed ECA of Grignard reagents to α-substituted cyclic enone/enolate trapping by Alexakis [87, 88] (all *ee*'s measured after recrystallisation)

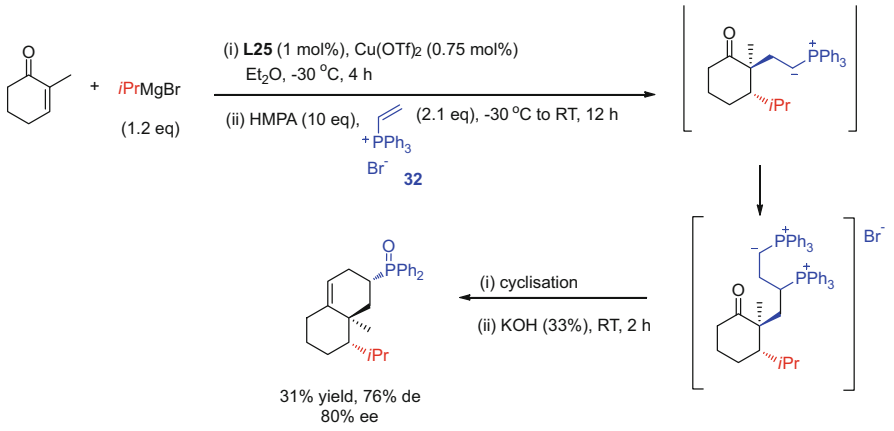


Scheme 53 Tandem copper–NHC-catalysed ECA of Grignard reagents to α-substituted cyclic enone/enolate trapping with **31** by Alexakis [88]

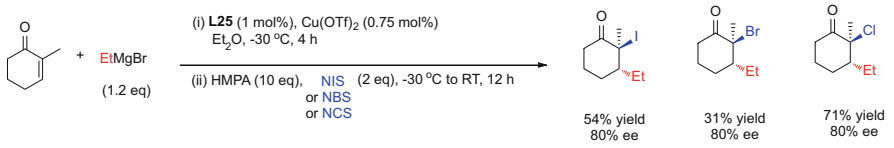
It is worth highlighting that this methodology brings a new approach to versatile terpenoid-like skeletons of bioactive natural products, and it has been applied to the formal synthesis of Crinipellin B and Guanacastepene A (Fig. 1) [87].

Other electrophiles, such as derivative **31** (Scheme 53),[3] triphenylvinylphosphonium bromide **32** (Scheme 54), *N*-halosuccinimides (Scheme 55) and tosyl cyanide (Scheme 56), have been also evaluated in this tandem ECA–enolate trapping methodology [88]. Lower regio- and enantioselectivities are obtained in these cases than when the trapping is carried out with alkyl, propargyl, allyl or benzyl halides.

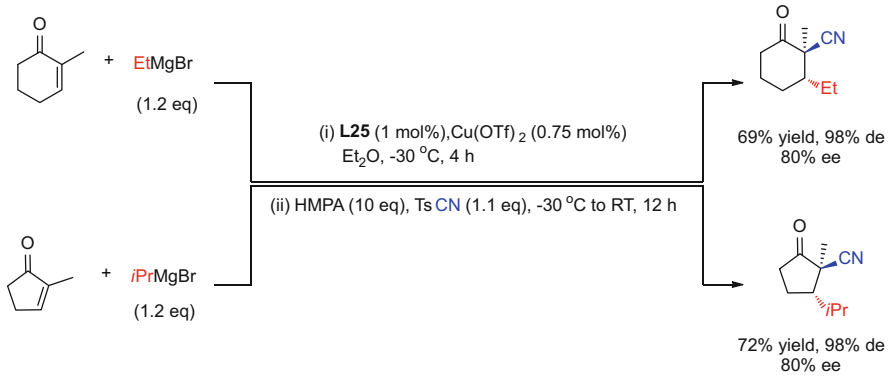
[3] The direct trapping with methylvinyl ketone (MVK) gives a complex mixture of oligomers.



Scheme 54 Tandem copper–NHC-catalysed ECA of Grignard reagents to α-substituted cyclic enone/enolate trapping with triphenylvinylphosphonium bromide **32** by Alexakis [88]

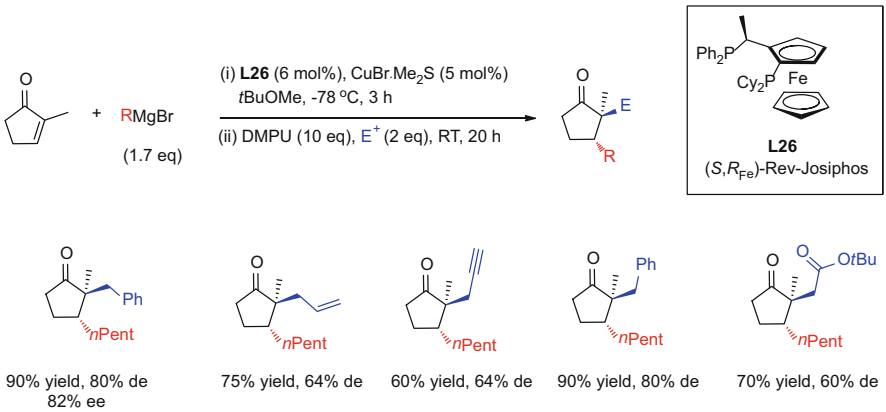


Scheme 55 Tandem copper–NHC-catalysed ECA of Grignard reagents to α-substituted cyclic enone/enolate trapping with *N*-halosuccinimides by Alexakis [88]



Scheme 56 Tandem copper–NHC-catalysed ECA of Grignard reagents to α-substituted cyclic enone/enolate trapping with tosyl cyanide by Alexakis [88]

Interestingly, a complementary methodology that allows the addition of linear Grignard reagents to α-substituted cyclic enones has been recently developed. It includes the use of copper/Rev-Josiphos (**L26**) for the ECA reaction, followed by in situ trapping of the magnesium enolate with various alkylating reagents, in the presence of DMPU. This strategy provides α-quaternary centres contiguous to β-tertiary centres with very good enantio- and diastereoselectivities, especially when cyclopentenones are used as substrates (Scheme 57) [89].



Scheme 57 Tandem copper–diphosphine-catalysed ECA of Grignard reagents to α-substituted cyclopentenones/enolate trapping by Minnaard [89]

2.3 *Organozinc Reagents as Nucleophiles*

Although zinc reagents are very popular nucleophiles in the copper-catalysed conjugate addition reaction, their relatively low reactivity makes the formation of quaternary stereocentres via addition to unactivated β,β-disubstituted enones very challenging. Nitroolefins, a class of especially reactive substrates, are, however, suitable substrates for this transformation, and their corresponding trisubstituted derivatives display good reactivity towards the addition of dialkylzinc reagents catalysed by copper and chiral peptide-based ligand **L27** (Fig. 14 and Scheme 58) [90].

One way to enhance the enantioselectivity of this transformation when dimethylzinc is used as nucleophile consists on employing (*Z*)-nitroalkenes instead as starting materials and $[(MeCN)_4Cu]PF_6$ as the copper source [91]. By using the (*Z*) isomer, the undesired nitroalkene isomerisation is minimised and the enantioselectivity of the process is enhanced dramatically, as shown in the examples in Scheme 59.

Another class of activated α,β-unsaturated compounds that is effective towards the ECA with organozinc reagents is the enone **33** (Scheme 60). The ester group at the α-position renders the substrate more electrophilic and, therefore, more prone to attack by dialkylzinc reagents. The peptide-based ligand **L28**, in combination with CuCN, successfully catalyses this process [92]. Cyclic six-membered substrates provide higher yields and enantioselectivities than the five-membered counterparts. Although variation of the α-ester is tolerated in the reaction, bulky esters lead to the highest enantioselectivities.

The doubly activated Meldrum's acid derivatives **34** also undergo copper-catalysed ECA with diorganozinc reagents, to provide all-carbon quaternary centres in moderated to good yields and enantioselectivities with phosphoramidite ligand

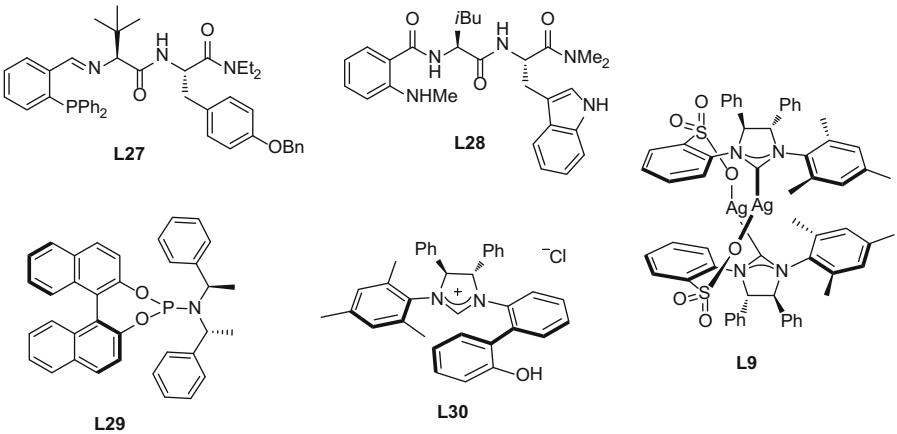
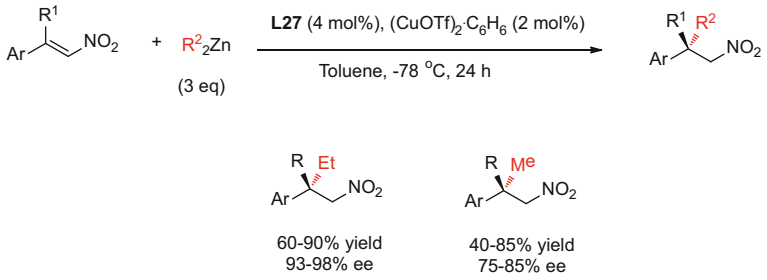
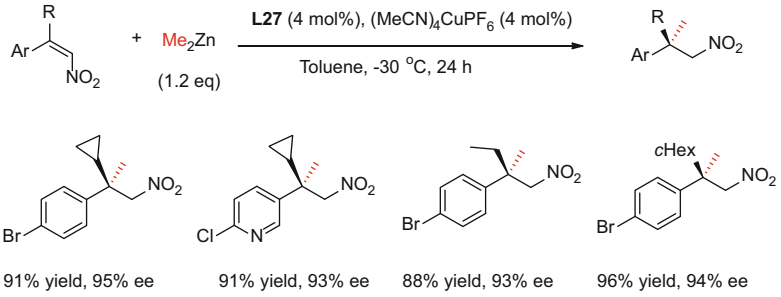


Fig. 14 Efficient ligands for the copper-catalysed ECA of organozinc reagents to β,-β-disubstituted α,β-unsaturated systems

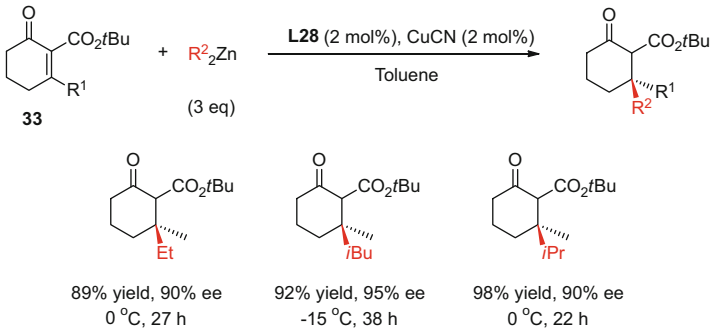


Scheme 58 Copper–peptide-catalysed ECA of organozinc reagents to β,β-disubstituted (*E*)-nitroalkenes by Hoveyda [90]

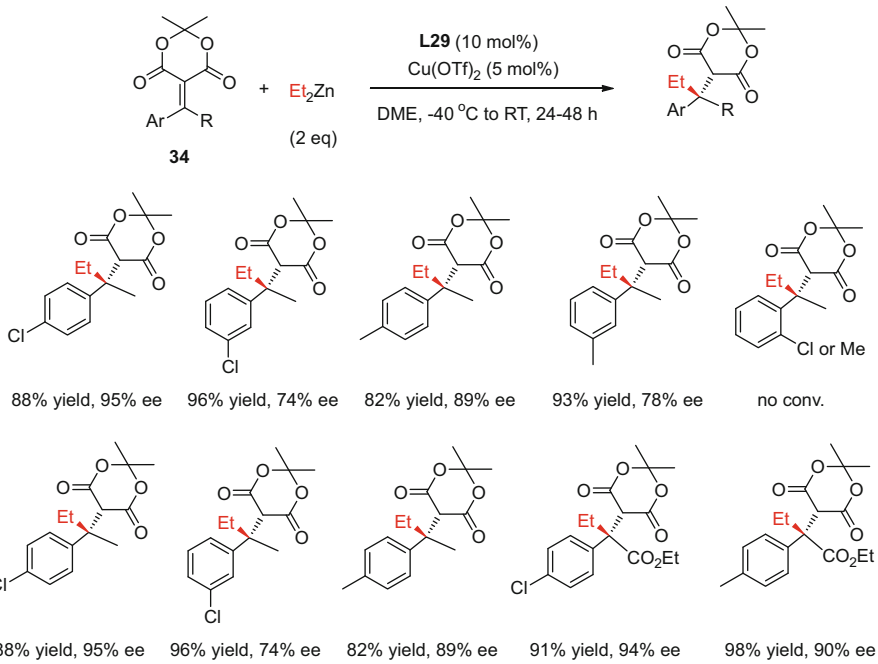


Scheme 59 Copper–peptide-catalysed ECA of organozinc reagents to β,β-disubstituted (*Z*)-nitroalkenes by Zeng [91]

L29 (Scheme 61) [93–96]. The scope of the reaction excludes *ortho*-substituted aromatic derivatives, which do not react under these conditions. The acid and ester moieties present on the all-carbon quaternary centre allow for a wide variety of



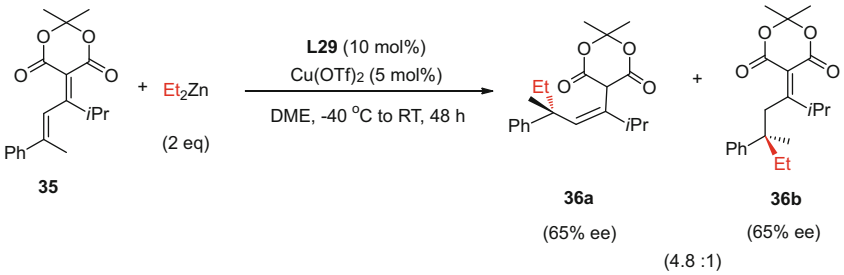
Scheme 60 Copper–peptide-catalysed ECA of organozinc reagents to activated cyclic ketoesters by Hoveyda [92]



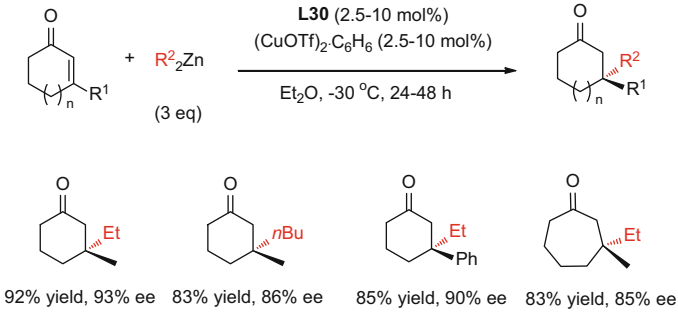
Scheme 61 Copper–phosphoramidite-catalysed ECA of organozinc reagents to Meldrum's acids derivatives by Fillion [93–96]

subsequent transformations, leading to the expedient preparation of succinimides, succinate esters and succinic acids, γ-butyrolactones and β-amino acid derivatives [94].

The formation of quaternary stereogenic centres via 1,6-conjugate addition of dialkylzinc reagents to Meldrum's acid derived acceptors has also been reported [97]. Thus, **35** reacts with Et_2Zn in the presence of $Cu(OTf)_2$ (5 mol%) and



Scheme 62 Copper–phosphoramidite-catalysed enantioselective 1,6-CA of organozinc reagents to Meldrum's acids derivatives by Fillion [97]



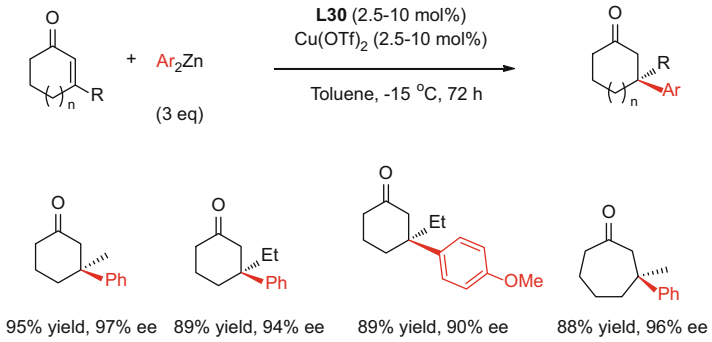
Scheme 63 Copper–NHC-catalysed ECA of dialkylzinc reagents to β-substituted cyclic enones by Hoveyda [98]

phosphoramidite ligand **L29** (10 mol%) to afford exclusively 1,6-adducts **36a** and **36b** in a 4.8:1 ratio, 81% combined isolated yield and 65% enantiomeric excess (Scheme 62). It is noteworthy that *Z*-olefin **36a** was obtained as a single isomer (determined by NOE experiments).

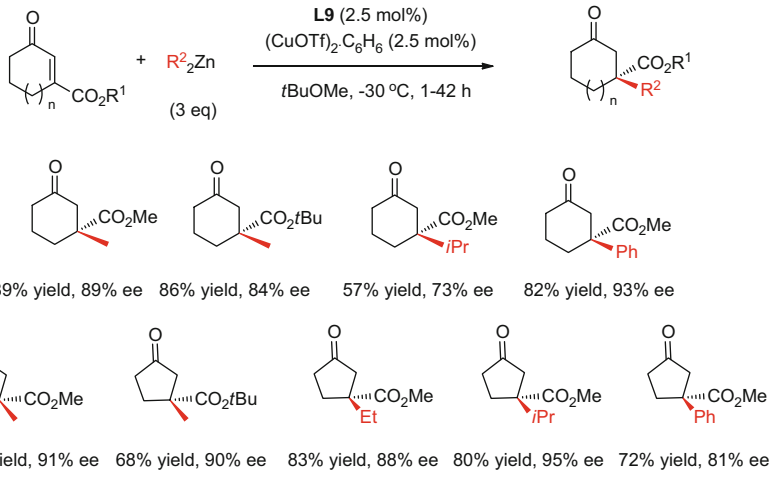
The more recent development of NHC ligands, such as those derived from the imidazolium salt **L30**, has allowed the addition of dialkylzinc (Scheme 63) and diarylzinc reagent[4] (Scheme 64) to simple unactivated β-substituted cyclic enones [98]. Very good yields and enantioselectivities are obtained with a wide variety of organozinc compounds; only the less reactive Me_2Zn does not provide any conversion.

When the β-substituent in the cyclic enone is an ester group, the enantioselective formation of the quaternary stereogenic centre is very effective using ligand **L9** (Scheme 65) [99]. The scope of this reaction includes both alkyl (including methyl) and aryl dialkylzinc reagents as nucleophiles and methyl and more sterically

[4] The generation of the diarylzinc reagents can be carried out by transmetalation from the corresponding Grignard reagent using $ZnCl_2$, requiring subsequent filtration over Celite under argon to remove the magnesium salts.



Scheme 64 Copper–NHC-catalysed ECA of diarylzinc reagents to β-substituted cyclic enones by Hoveyda [98]

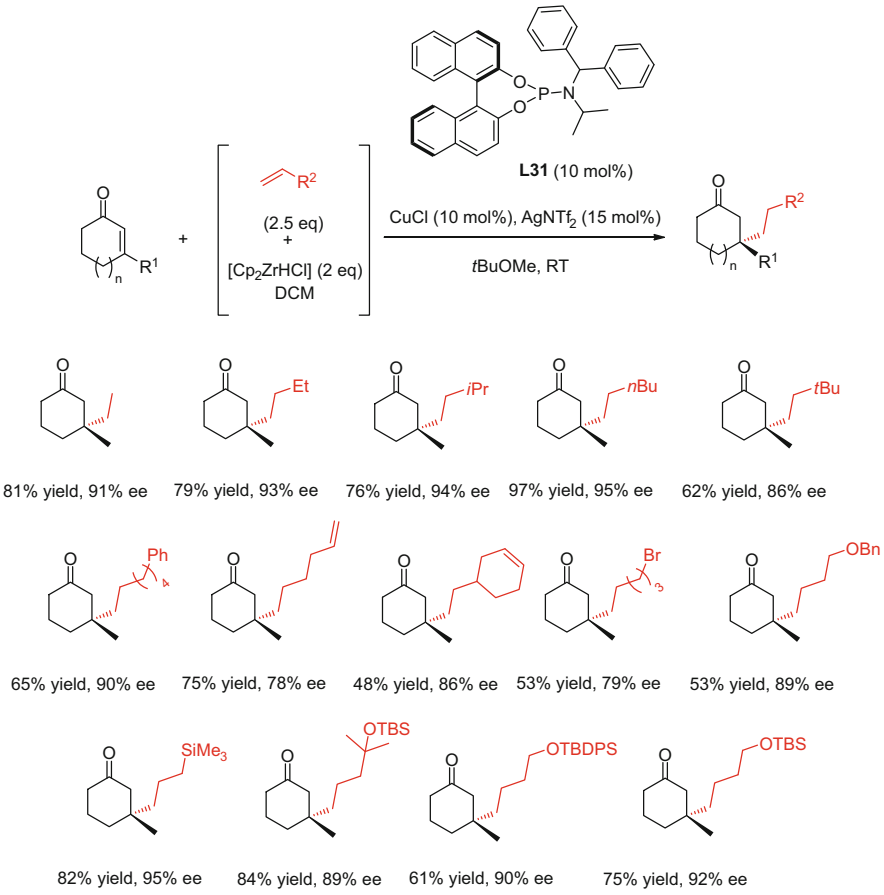


Scheme 65 Copper–NHC-catalysed ECA of dialkylzinc reagents to cyclic ketoesters by Hoveyda [99]

hindered *tert*-butyl esters as substituents in the substrates. Under the optimal conditions, cyclopentenone substrates provide higher enantiomeric purity than cyclohexenones. The enantiomerically enriched products obtained by this protocol are very versatile, since the carboxylic ester unit provides a convenient handle for further manipulations.

2.4 *Organozirconium Reagents as Nucleophiles*

Recently, Fletcher et al. have demonstrated that the formation of all-carbon quaternary centres can be carried out by copper-catalysed ECA of alkylzirconium reagents to β-substituted cyclic enones (Scheme 66) [100, 101].



Scheme 66 Copper-catalysed ECA of organozirconium reagents to β-substituted cyclic enones by Fletcher [100]

The reaction proceeds in high yields and very good enantioselectivity under mild conditions (i.e. room temperature) when phosphoramidite ligand **L31** and CuNTf (prepared in situ from CuCl and $AgNTf_2$) are used as catalyst. β-Substituted cyclohexenone and cycloheptenone substrates provide higher enantioselectivities than cyclopentenones analogues, as long as the β-substituent is not too sterically demanding (Fig. 15).

Alkylzirconium reagents are prepared in situ by hydrometalation from the corresponding alkenes [102–104] which, conceptually, act as the equivalent to premade organometallic nucleophiles. The mild reaction conditions in which the reaction takes place, together with the low reactivity that the in situ-prepared organozirconium reagents display, lead to several advantages for this methodology: (1) it allows the preparation and use of more complex nucleophiles, (2) more functional groups are compatible, and (3) alkenes are easier to handle, compared to the air- and moisture-sensitive often pyrophoric organometallic reagents.

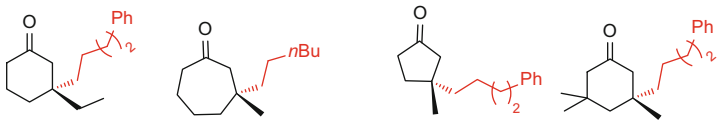


Fig. 15 Chiral ketones prepared by copper-catalysed ECA of organozirconium reagents to β-substituted cyclic enones by Fletcher [100]

3 Formation of Boron-Containing Quaternary Centres by Copper-Catalysed ECA

Chiral organoboron compounds are versatile synthetic intermediates due to the convertibility of C–B bonds to a variety of functional groups [105, 106]. Furthermore, chiral organoboron molecules exhibiting unique biological activities have been recently identified, such as potent inhibitors of the proteasome, thrombin and histone deacetylases [107]. The formation of boron-containing quaternary centres via copper-catalysed ECA of organoboron reagents to β,β-disubstituted α,-β-unsaturated systems is challenging (due both to the low reactivity and smaller steric and electronic differences between two substituents on the β-prochiral carbon of the substrate), but very impressive contributions have appeared in the literature over the past 10 years (Fig. 16).

As described by Shibasaki et al., the formation of quaternary centres via enantioselective conjugate boration (ECB) to β-substituted cyclic enones can be efficiently catalysed by the phosphine ligand **L32** and $CuPF_6{\cdot}4CH_3CN$. Commercially available bis(pinacolato)diboron [(Pin)B–B(Pin)] is the borylating reagent that provides the best results in this transformation (Scheme 67) [108]. The reaction generally proceeds with high enantioselectivity for both aromatic and aliphatic β-substituted cyclic enones, including five-, six- and seven-membered rings (Scheme 67).

This reaction is a useful platform for the synthesis of various chiral building blocks that are otherwise difficult to access, as exemplified in Scheme 68.

For acyclic β,β-disubstituted α,β-unsaturated substrates, the copper(I)–chiral diamine **L33** complex catalyses the enantioselective conjugate boration (ECB) in high yields and enantioselectivity (Scheme 69) [109]. Amine ligands have a weaker affinity for Cu(I) compared to phosphine ligands, and for this reason, there are not many efficient asymmetric reactions to date using a nucleophilic Cu(I)–chiral amine complex as a catalyst. However, in this case, very good yields and enantioselectivities are achieved under the optimised reaction conditions for a wide range of substrates, including methyl, linear and branched alkyl-substituted enones. Both aromatic and aliphatic organoboron compounds are effective. The addition of 2 equiv. of *i*PrOH as additive in the reaction allows a substantial improvement on the yield, since it promotes the conversion of the enolate intermediate to the corresponding borylated product (see mechanism of the reaction in Scheme 70).

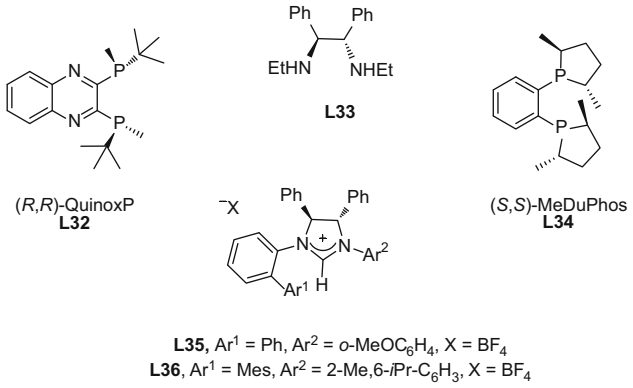
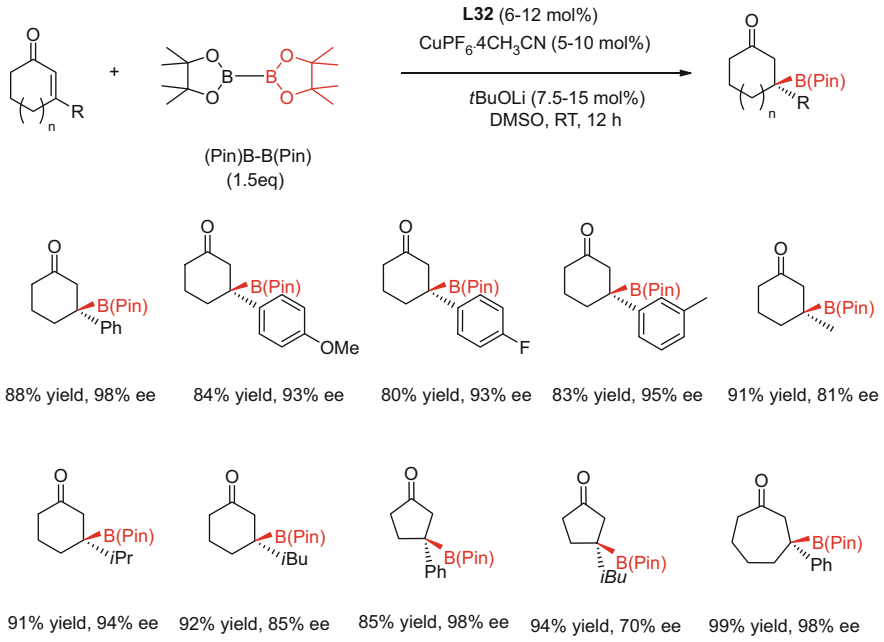
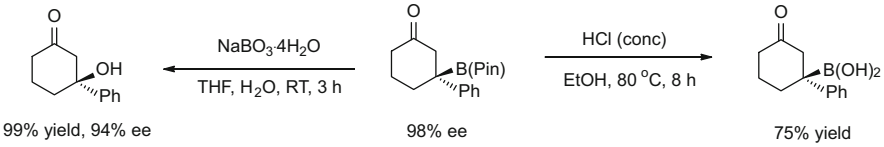


Fig. 16 Effective ligands for the enantioselective conjugate boration (ECB) to β,β-disubstituted α,β-unsaturated compounds

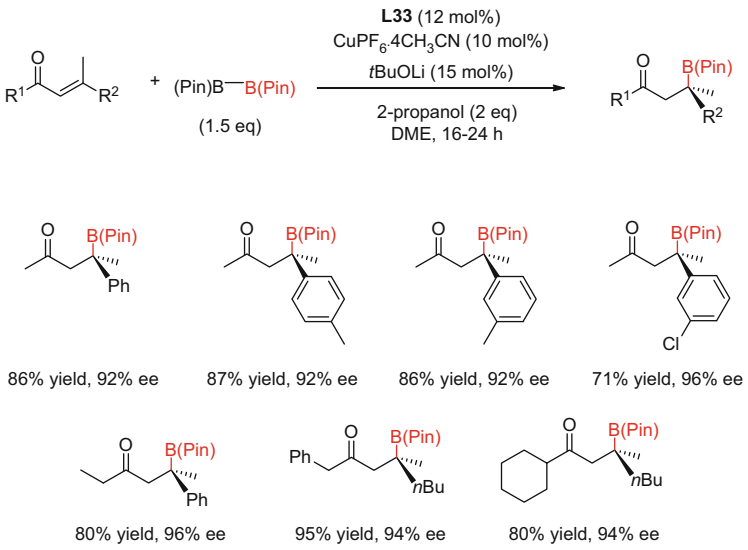


Scheme 67 Copper–phosphine-catalysed ECB of β-substituted cyclic enones by Shibasaki [108]

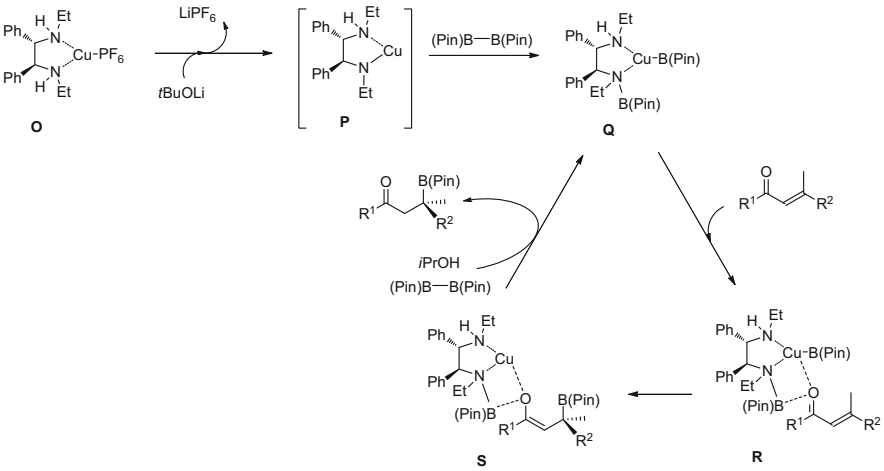
When the reaction is carried out with *t*BuOCu, in the absence of a lithium salt, yields and enantioselectivities are not affected. This indicates that the diamine coordinates to the copper atom at the enantio-differentiating step, even in the presence of the cationic lithium atom. In addition, ESI-MS experiments support the presence of complex **O** (Scheme 70). Shibasaki et al. have proposed a working hypothesis for the catalytic cycle, as shown in Scheme 70. Copper amide **P** is generated from **O** and *t*BuOLi, and next, the copper–nitrogen bond cleaves



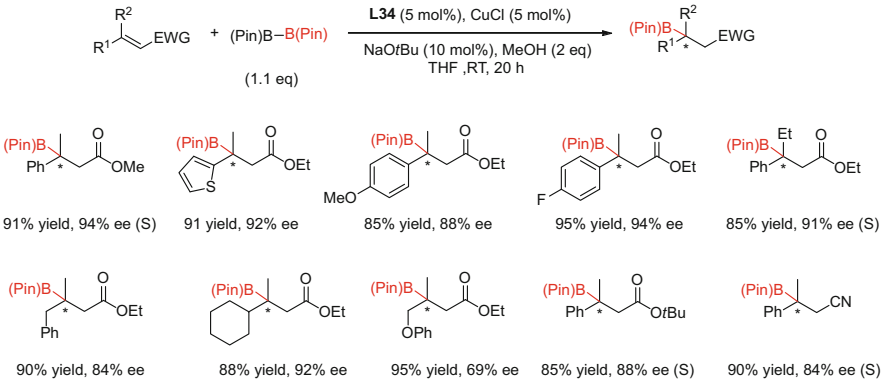
Scheme 68 Derivatisation of chiral organoboron compounds by Shibasaki [108]



Scheme 69 Copper–diamine-catalysed ECB of β,β-disubstituted enones by Shibasaki [109]



Scheme 70 Proposed mechanism for the copper–diamine-catalysed ECB of β,β-disubstituted enones by Shibasaki [109]



Scheme 71 Copper–phosphine-catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated esters by Yung [110]

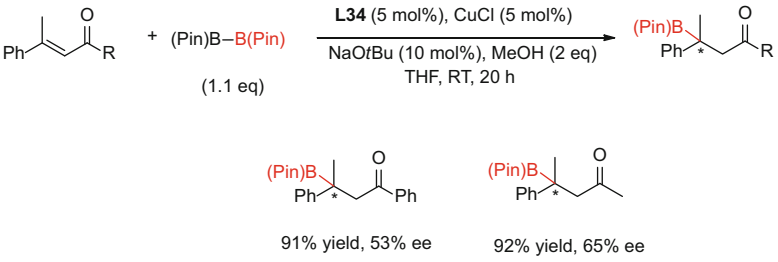
(Pin)B–B(Pin) through metathesis, generating the copper boronate complex **Q**, which contains a *N*-borylated ligand. Next, the carbonyl oxygen atom of the substrate coordinates to the Lewis acidic boron atom of the aminopinacolyl boronate part of the catalyst, generating a pre-transition state complex **R**. ECB from **R** produces boron enolate complex **S** (or a copper enolate complex, alternatively), which is protonated by 2-propanol, and reactive species **Q** is regenerated by reaction with (Pin)B–B(Pin). This proposed mechanism is in accordance with the low enantioselectivity observed when using diamine ligands without an ability to form copper amides.

Yung et al. have demonstrated that for acyclic β,β-disubstituted α,β-unsaturated esters, the phosphine ligand **L34** provides high yields and enantioselectivities in the copper-catalysed ECB reaction (Scheme 71) [110]. Again, the inclusion of proton accelerators (2 equiv. of MeOH – in contrast to the aprotic DMSO used with cyclic enones; see Scheme 67 and [110]) is necessary to promote the conversion of the enolate intermediate to the corresponding borylated product.

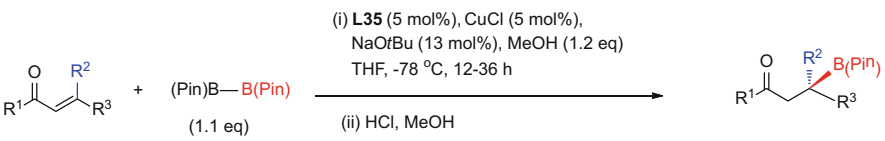
Under the optimised conditions (see Scheme 71), a wide range of β,-β-disubstituted α,β-unsaturated substrates afford the corresponding borylated products with high enantioselectivity. The electronic nature of the aromatic substituent in the β position does not affect the yield nor enantioselectivity; however, β,-β-dialkyl-substituted esters give good to modest results. Also, bulkier conjugated EWG groups such as *tert*-butyl esters or nitriles provide lower enantioselectivities.

Unfortunately, this methodology only provides moderate levels of enantiomeric excess when acyclic β,β-disubstituted α,β-unsaturated ketones are used as substrates (Scheme 72).

In contrast, the catalytic methodology reported by Hoveyda et al. allows the enantioselective synthesis of boron-substituted quaternary carbons units by copper-catalysed addition of boronate to unsaturated carboxylic esters, ketones and thioesters [111]. The transformations proceed with high yields and enantioselectivities, using bis(pinacolato)diboron as the nucleophile and the readily accessible



Scheme 72 Copper–phosphine-catalysed ECB of acyclic β,β-disubstituted enones by Yung [110]



Scheme 73 Copper–NHC-catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated systems by Hoveyda [111]

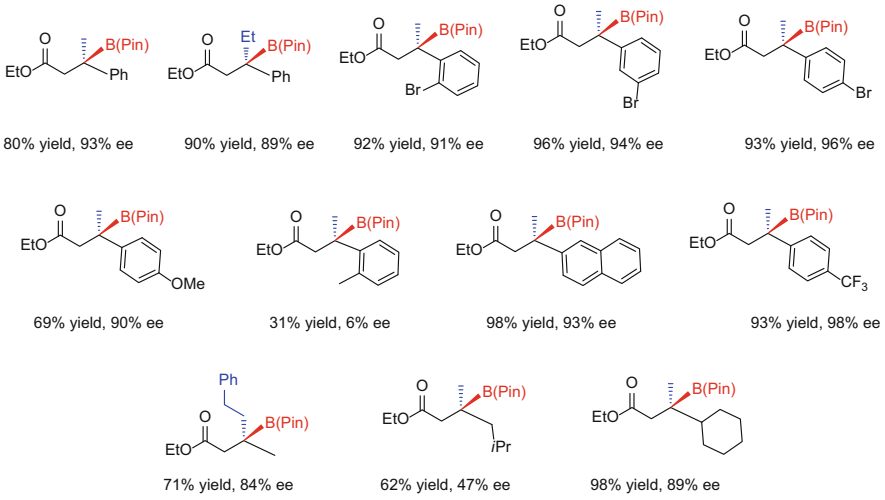


Fig. 17 Representative examples for the copper–NHC-catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated esters by Hoveyda [111]

chiral imidazolium ligand **L35** (Scheme 73). Once again, the presence of MeOH as additive in the reaction is necessary to achieve good conversions, but it does not affect the enantioselectivity of the process.

As represented in Fig. 17, β-aryl-substituted esters (R^1=OEt, R^3=aryl, Scheme 73) give, in general, very good yields and enantioselectivities, except when the β-substituent is an *o*-tolyl group, in which case the corresponding boron adduct is obtained as a near racemate. A *p*-methoxyphenyl substituent in the β-position affords the desired β-boryl ester in moderate yield, due to diminished

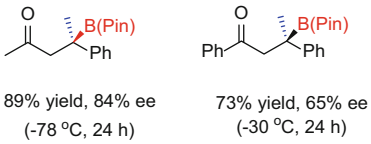


Fig. 18 Representative examples for the copper–NHC-catalysed ECB of acyclic β,β-disubstituted enones by Hoveyda [111]

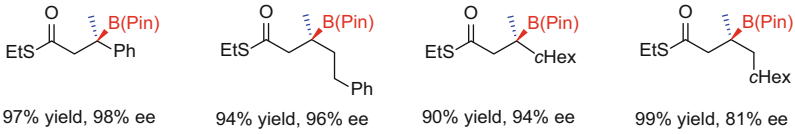


Fig. 19 Representative examples for the copper–NHC-catalysed ECB of acyclic β,β-disubstituted α,β-unsaturated thioesters by Hoveyda [111] (all reactions carried out at −50 °C for 18 h)

substrate electrophilicity. β,β-Dialkyl-substituted esters afford slightly lower yields and enantioselectivities (especially when R^3=CH_2*i*Pr) than the aromatic substrates.

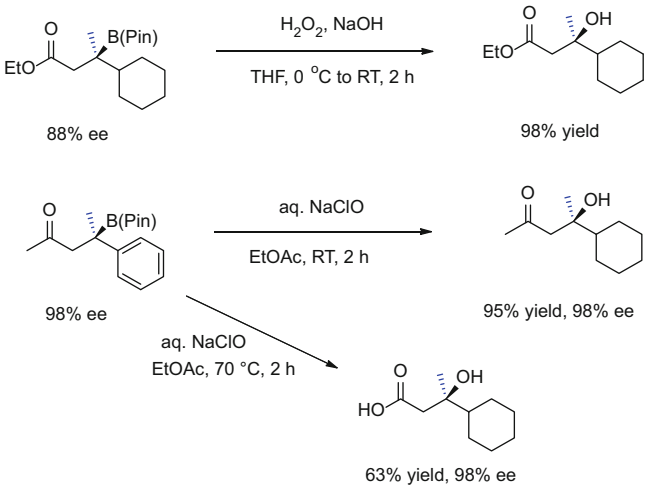
In the case of β,β-disubstituted unsaturated ketones (R^1=Me, Ph, Scheme 73), reactions are, as expected, less enantioselective than with the analogous and less reactive unsaturated esters. However, moderate to good enantioselectivities and yields are reached, taking into account the challenging nature of this type of acyclic substrates (Fig. 18).

Lastly, the methodology gives excellent yields and enantioselectivities when β,β-disubstituted unsaturated thioesters are used as substrates (R^1=SEt, Scheme 73), regardless of whether an aromatic β-substituent is present (Fig. 19). The thioester functionality allows easy conversion to the corresponding unsaturated carboxylic ester or ketones through Ag-mediated and Pd-catalysed procedures, respectively [111].

Chiral boron-containing adducts are versatile building blocks which can be derivatised easily. For example, oxidation of the C–B bond of the chiral 1,4-adduct with H_2O_2/NaOH (at 0 °C) or common household bleach (at RT) delivers the corresponding tertiary alcohols in high yield. If the bleach-assisted oxidation is carried out at 70 °C, the methyl ketone will be transformed into a carboxylic acid as well during the process (Scheme 74).

The proposed model that explains the results for the NHC–copper-catalysed boronate conjugate addition reaction is represented in Fig. 20. Complex **T** provides a rationale for the levels and trends in selectivity. Alkene coordination likely occurs such that the Cu–B bond is aligned with the substrate π*, whilst the carbonyl moiety resides proximal to the NHC's monosubstituted *N*-Ar unit (vs **U**).

Very recently, Hoveyda et al. have demonstrated that the conjugate addition of organoboron reagents to β-substituted cyclic enones, catalysed by the readily accessible imidazolium ligand **L36** and in the *absence of any transition metal*,



Scheme 74 Derivatisation of chiral organoboron compounds by Hoveyda [111]

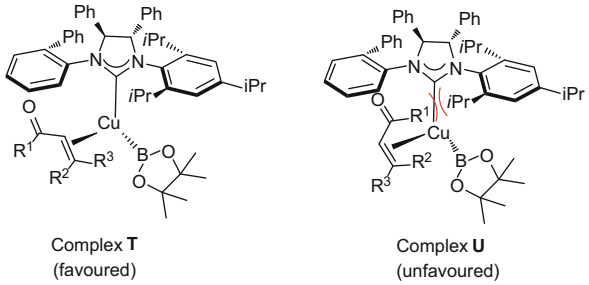


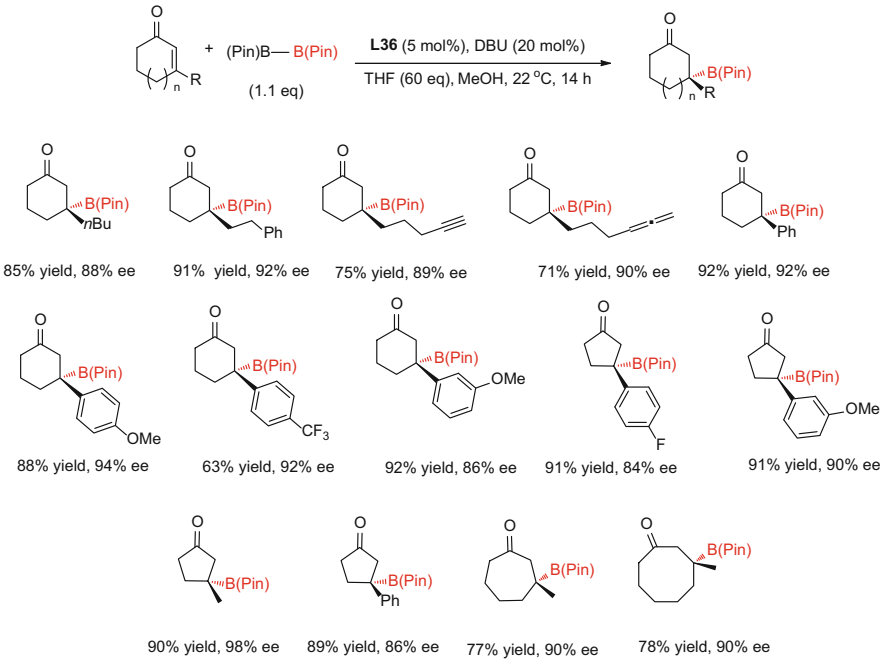
Fig. 20 Proposed transition states for the copper–NHC-catalysed ECB of acyclic β,-β-disubstituted α,β-unsaturated systems by Hoveyda [111]

gives excellent selectivities in the formation of boron-substituted quaternary carbon stereogenic centres (63–95% yield and 82 to >98% *ee*, Scheme 75) [112].

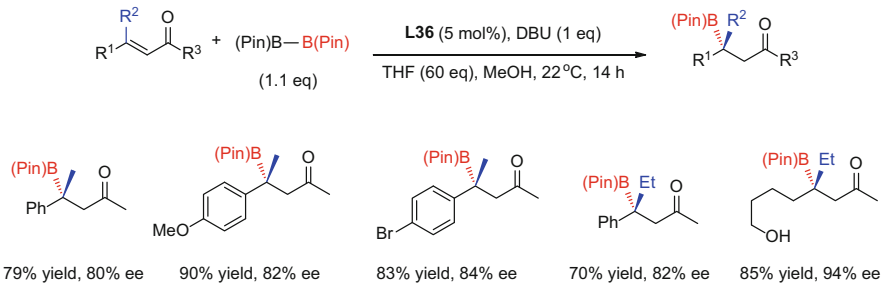
Both yields and enantioselectivities obtained with this methodology are comparable to the copper-catalysed reaction with (*R*,*R*)-QuinoxP **L32** [108]. However, when the enone is provided with β-substituents that contain multiple bonds, the reaction is more efficient with **L36** in the absence of a copper salt, probably because competitive reactions of the Cu–B(pin) complex with the alkyne or alkene moieties are avoided this way.

The imidazolium salt **L36** is also effective when acyclic, aryl- or alkyl-substituted enones are used as substrates. The corresponding linear β-boryl ketones can be obtained from 56 to 94% yield and >98% *ee* (Scheme 76).

The mechanism of these NHC-catalysed boryl conjugate addition reaction in the absence of transition metal complexes [113] will not be discussed here, as it is outside of the scope of this chapter.



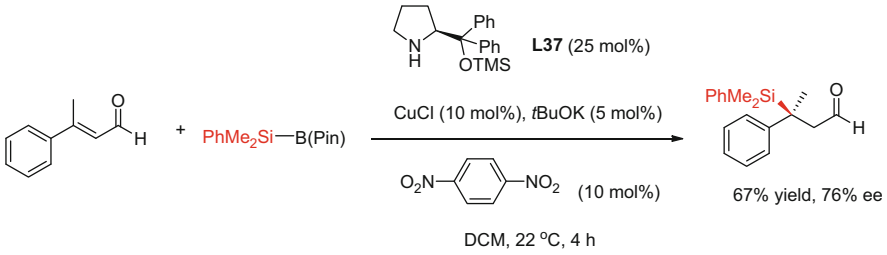
Scheme 75 Transition metal-free NHC-catalysed ECB of β-substituted cyclic enones by Hoveyda [112]



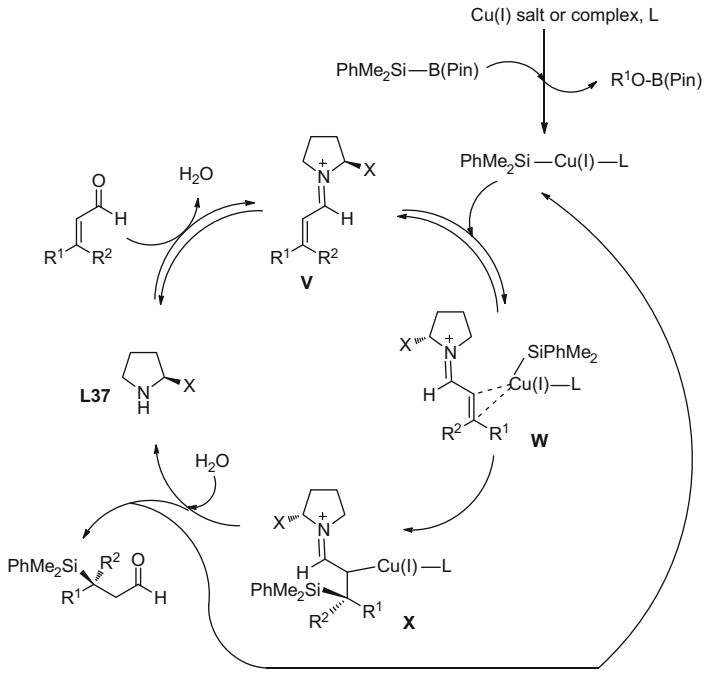
Scheme 76 Transition metal-free NHC-catalysed ECB of β,β-disubstituted linear enones by Hoveyda [112]

4 Formation of Silicon-Containing Quaternary Centres by Copper-Catalysed ECA

The development of methods for the catalytic enantioselective formation of C–Si bonds is an important challenge in organic synthesis [114]. In this context, the transition metal-catalysed enantioselective conjugate addition (ECA) of in situ-generated Si nucleophiles derived from readily available sources [e.g. Cl_2PhSi–$SiMe_3$ and Me_2PhSi–B(Pin)] to α,β-unsaturated acceptors with a substituent in the



Scheme 77 Copper- and amine-catalysed ECS of β,β,-disubstituted linear enals by Cordova [115]



Scheme 78 Proposed catalytic cycle for the ECS of enals catalysed by combination of copper and chiral amine catalysts by Hoveyda [115]

β-position is particularly attractive, as it provides direct access to synthetically useful β-silyl quaternary centres.

As described by Cordova et al., the strategy of combining transition metal-catalysed nucleophilic activation with chiral amine-catalysed iminium activation allows the enantioselective conjugate silyl addition to α,β-unsaturated aldehydes [115]. The reaction proceeds with good 1,4-selectivity and moderate enantioselectivity when β,β-disubstituted unsaturated aldehydes are used as substrates, as exemplified in Scheme 77. The silylated products are versatile adducts that can be easily converted to protected 1,3-diols and β-functionalised esters.

Supported by DFT calculations, the proposed catalytic cycle for this transformation is presented in Scheme 78. The origin of the enantioselectivity is attributed to the steric repulsion between the nucleophile and the bulky group of the catalyst.

The copper salt (or copper complex) reacts with Me_2PhSi–B(Pin) to deliver the corresponding L–Cu(I)–silane. In parallel, the chiral amine forms the iminium intermediate **V** with the α,β-unsaturated aldehyde. Next, the catalytic cycles merge and the L–Cu–silane complex stereoselectively reacts with the chiral iminium intermediate **V** via a possible intermediate **W** to form a C–Si bond in intermediate **X**. Subsequent hydrolysis of iminium ion **X** gives the corresponding β-silyl aldehyde product as well as regenerate the Cu(I)–silane and the chiral catalyst **L37** [115].

It is worth mentioning that other methodologies for the asymmetric silyl addition to α,β-unsaturated systems [116] do not allow the formation of quaternary centres.

5 Perspective

The amount of methodologies available to synthetic chemists for incorporating quaternary stereocentres in organic molecules with high enantioselectivity has substantially increased in the past decade, especially in the area of conjugate addition reactions.

Although a diverse range of chemical transformations are now available to meet this formidable challenge, there are limitations and challenges to overcome. Not only is the development of alternative catalytic methods, based on readily available and less expensive complex catalysts, highly desirable, but also other particular issues need to be addressed. For example, the formation of quaternary stereocentres in acyclic molecules or acyclic molecular fragments is still in its early stage and needs further development [117, 118]. Also, efficient methodologies are needed for the ECA to β,β-disubstituted α,β-unsaturated carboxylic acid derivatives (e.g. ester, thioesters, amides etc.); except for the ECB procedure developed by Hoveyda et al. [111], none of the reported methodologies allows the formation of chiral quaternary stereocentres on any substrate different from an enone. Lastly, and of particular interest, is the development and/or improvement of existing methodologies for the ECA of the less reactive methyl nucleophiles that provide an easy approach to methyl-substituted quaternary stereogenic centres, ubiquitous in natural products [119, 120].

The methods now available for the copper-catalysed enantioselective formation of quaternary stereocentres remove many of the previous barriers to incorporating such fragments in organic molecules. These enantiomerically enriched building blocks can be used in the synthesis of natural products, medicines and agriculturals to polymers and advanced materials. We expect an increasing number of novel compounds containing quaternary stereocentres, including new drug candidates, being designed, synthesised and evaluated in the near future.

Acknowledgements BM thanks the European Commission for a Marie Curie Career Integration Grant, the EPSRC for a First Grant and G. P. Howell for helpful comments on the manuscript.

References

1. Shibasaki M, Matsunaga S (2007) In: Christmann M, Brase S (eds) Asymmetric synthesis—the essentials, 2nd edn. Wiley-VCH, Weinheim, pp 47–51
2. Ritchie TJ, Macdonald SJF (2009) Drug Discov Today 14:1011–1020
3. Lovering F (2013) Med Chem Comm 4:515–519
4. Trost BM, Jiang C (2006) Synthesis 3:369–396
5. Fuji K (1993) Chem Rev 93:2037–2066
6. Douglas CJ, Overman LE (2004) Proc Natl Acad Sci U. S A 101:5363–5367
7. Corey EJ, Guzman-Perez A (1998) Angew Chem Int Ed 37:388–401
8. Liu Y, Han SJ, Liu W-B, Stoltz BM (2015) Acc Chem Res 48:740–751
9. Christoffers J, Mann A (2001) Angew Chem 113:4725–4732; Angew Chem Int Ed 40:4591–4597
10. Quasdorf KW, Overman LE (2014) Nature 516:181–191
11. Christoffers J, Baro A (2006) Quaternary stereocentres: challenges and solutions for organic synthesis. Wiley-VCH, Weinheim
12. Christoffers J, Baro A (2003) Angew Chem Int Ed 42:1688–1690
13. Jacobsen EN, Pfaltz A, Yamamoto H (1999) Comprehensive asymmetric catalysis. Springer, Heidelberg
14. Jerphagnon T, Pizzuti MG, Minnaard AJ, Feringa BL (2008) Chem Soc Rev 38:1039–1075
15. Alexakis A, Bäckvall J, Krause N, Pàmies O, Diéguez M (2008) Chem Rev 108:2796–2823
16. Harutyunyan S, den Hartog T, Geurts K, Minnaard AJ, Feringa BL (2008) Chem Rev 108:2824–2852
17. Futamura J, Ohba Y, Sawama Y, Ganesh K, Fujioka H, Kita Y (2003) J Org Chem 68:5917–5924
18. Yoshida M, Shoji Y, Shishido K (2009) Org Lett 11:1441–1443
19. Gallen M, Williams CM (2008) Eur J Org Chem 27:4697–4705
20. Gallen M, Williams CM (2008) Org Lett 10:713–715
21. Guevel A-C, Hart DJ (1996) J Org Chem 73:473–479
22. Heim R, Wiedemann S, Williams CM, Bernhardt PV (2005) Org Lett 7:1327–1329
23. Tilly DP, Williams CM, Bernhardt PV (2005) Org Lett 7:5155–5157
24. Schwartz BD, Tilly DP, Heim R, Wiedemann S, Williams CM, Bernhardt PV (2006) Eur J Org Chem 14:3181–3192
25. Cordova A (2010) Catalytic asymmetric conjugate reactions. Wiley-VCH, Weinheim
26. Kikushima K, Holder JC, Gatti M, Stoltz BM (2011) J Am Chem Soc 133:6902–6905
27. Müller M, Alexakis A (2012) Chem Commun 48:12037–12049
28. Alexakis A, Krause N, Woodward S (2014) Copper-catalysed asymmetric conjugate addition. In: Copper-catalysed asymmetric synthesis. Wiley-VCH, Weinheim, Chap 2, pp 33−63
29. Hayashi T, Yamasaki K (2003) Chem Rev 103:2829–2844
30. Wencel J, Mauduit M, Henon H, Kehrli S, Alexakis A (2009) Aldrichimica Acta 42:43–50
31. Hoveyda AH, Hird AW, Kacprzynski MA (2004) Chem Commun 1779−1785
32. Hawner C, Alexakis A (2010) Chem Commun 46:7295–7306
33. Alexakis A, Benhaim C (2002) Eur J Org Chem 19:3221–3236
34. Fuchs N, d'Augustin M, Humam M, Alexakis A, Taras R, Gladiali S (2005) Tetrahedron Asymmetry 16:3143–3146
35. d'Augustin M, Palais L, Alexakis A (2005) Angew Chem Int Ed 44:1376–1378
36. Vuagnoux-d'Augustin M, Alexakis A (2007) Chem–Eur J 13:9647–9662

37. Vuagnoux-d'Augustin M, Kehrli S, Alexakis A (2007) Synlett 13:2057–2060
38. Palais L, Mikhel IS, Bournaud C, Micouin L, Falciola CA, Vuagnoux-d'Augustin M, Rosset S, Bernardinelli G, Alexakis A (2007) Angew Chem Int Ed 46:7462–7465
39. Ladjel C, Fuchs N, Zhao J, Bernardinelli G, Alexakis A (2009) Eur J Org Chem 29:4949–4955
40. Takaya Y, Ogasawara M, Hayashi T (1998) With alkenyl boronic acids. J Am Chem Soc 120:5579–5580
41. Hawner C, Muller D, Gremaud L, Felouat A, Woodward S, Alexakis A (2010) With organoaluminium reagents. Angew Chem Int Ed 49:7769 –7772
42. Zweifel G, Miller JA (1984) Org React 32:375–517
43. Corey EJ, Beames DJ (1972) J Am Chem Soc 94:7210–7211
44. Hawner C, Li K, Cirriez V, Alexakis A (2008) Angew Chem 120: 8334–8337; Angew Chem Int Ed 47:8211–8214
45. Willcox D, Woodward S, Alexakis A (2014) Chem Commun 50:1655–1657
46. Palais L, Alexakis A (2009) Chem Eur J 15:10473–10485
47. Palais L, Mikhel IS, Bournaud C, Micouin L, Falciola CA, Vuagnoux-d'Augustin M, Rosset S, Bernardinelli G, Alexakis A (2007) Angew Chem 119:7606–7609
48. Müller D, Tissot M, Alexakis A (2011) Org Lett 13:3040–3043
49. Müller D, Alexakis A (2013) Chem Eur J 19:15226–15239
50. Müller D, Hawner C, Tissot M, Palais L, Alexakis A (2010) Synlett 11:1694–1698
51. Zweifel G, Whitney CC (1967) J Am Chem Soc 89:2753–2754
52. Das JP, Roy S (2002) J Org Chem 67:7861–7864
53. Ramirez F, Desai NB, McKelvie N (1962) J Am Chem Soc 84:1745–1747
54. Abbas S, Hayes CJ, Worden S (2000) Tetrahedron Lett 41:3215–3219
55. Dolby LJ, Wilkins DC, Frey TG (1966) J Org Chem 31:1110–1116
56. Bleschke C, Tissot M, Müller D, Alexakis A (2013) Org Lett 15:2152–2155
57. Cottet P, Müller D, Alexakis A (2013) Org Lett 15:828–831
58. May TL, Brown MK, Hoveyda AH (2008) Angew Chem Int Ed 47:7358–7362
59. Öfele K (1968) J Organomet Chem 12:42–43
60. Wanzlick H-W, Schönherr H-J (1968) Angew Chem Int Ed Engl 7:141–142
61. Arduengo AJ III, Harlow RL, Kline M (1991) A stable crystalline carbine. J Am Chem Soc 113:361–363
62. Nolan SP (2005) N-Heterocyclic carbenes in synthesis. Weinheim, Wiley-VHC
63. Glorius F (2007) N-Heterocyclic carbenes in transition metal catalysis. Topics in organometallic chemistry series, vol 21. Springer, Berlin
64. May TL, Dabrowski JA, Hoveyda HA (2011) J Am Chem Soc 133:736–739. And correction article: May TL, Dabrowski JA, Hoveyda HA (2014) J Am Chem Soc 136:10544–10544
65. Dabrowski JA, Villaume MT, Hoveyda AH (2013) Angew Chem Int Ed 52:8156–8159
66. McGrath KP, Hoveyda AH (2014) Angew Chem 126:1941; Angew Chem Int Ed53:1910–1914
67. Endo K, Hamada D, Yakeishi S, Shibata T (2013) Angew Chem Int Ed 52:606–610
68. Endo K, Yakeishi S, Takayama R, Shibata T (2014) Chem Eur J 20:8893–8897
69. Martin D, Kehrli S, d'Augustin M, Clavier H, Mauduit M, Alexakis A (2006) J Am Chem Soc 128:8416–8417
70. Matsumoto Y, Yamada K, Tomioka K (2008) J Org Chem 73:4578–4581
71. Kehrli S, Martin D, Rix D, Mauduit M, Alexakis A (2010) Chem Eur J 16:9890–9904
72. Germain N, Magrez M, Kehrli S, Mauduit M, Alexakis A (2012) Eur J Org Chem 27:5301–5306
73. Lipshutz BH, Wilhelm RS, Kozlowski JA (1984) Tetrahedron 40:5005–5038
74. Alexakis A, Marek I, Mangeney P, Normant JF (1990) J Am Chem Soc 112:8042–8047
75. Yoshikai N, Nakamura E (2012) Chem Rev 112:2339–2372
76. Germain N, Schlaefli D, Chellat M, Rosset S, Alexakis A (2014) Org Lett 16:2006–2009
77. Tissot M, Alexakis A (2013) Chem Eur J 19:11352–11363
78. Yu JR, Cho HS, Falck JR (1993) J Org Chem 58:5892–5894
79. Chandrasekhar S, Yu J, Falck J, Mioskowski C (1994) Tetrahedron Lett 35:5437–5440

80. Henon H, Mauduit M, Alexakis A (2008) Angew Chem Int Ed 47:9122–9124; Angew Chem 120:9262–9264
81. Tissot M, Poggiali D, Henon H, Müller D, Guénée L, Mauduit M, Alexakis A (2012) Chem Eur J 18:8731–8747
82. Arduengo AJ III, Harlow MK (1991) J Am Chem Soc 113:361–363
83. den Hartog T, Harutyunyan SR, Font D, Minnaard AJ, Feringa BL (2007) Angew Chem Int Ed 47:398–401
84. Tissot M, Pérez-Hernández A, Müller D, Mauduit M, Alexakis A (2011) Org Lett 13:1524–1527
85. Krause N, Thorand S (1999) Inorg Chim Acta 296:1–11
86. Bomparola R, Davies RP, Hornauer S, White AJP (2008) Angew Chem 120:5896–5899; Angew Chem Int Ed 47:5812–5815
87. Germain N, Guénée L, Mauduit M, Alexakis A (2014) Org Lett 16:118–121
88. Germain N, Alexakis A (2015) Chem Eur J 21:8597–8606
89. Calvo BC, Madduri AVR, Harutyunyan SR, Minnaard AJ (2014) Adv Synth Catal 356:2061–2069
90. Wu J, Mampreian DM, Hoveyda AH (2005) J Am Chem Soc 127:4584–4585
91. Zeng X, Gao JJ, Song JJ, Ma S, Desrosiers J-N, Mulder JA, Rodriguez S, Herbage MA, Haddad N, Qu B, Fandrick KR, Grinberg N, Lee H, Wei X, Yee NK, Senanayake CH (2014) Angew Chem Int Ed 53:12153–12157
92. Hird AW, Hoveyda AJ (2005) J Am Chem Soc 127:14988–14989
93. Wilsily A, Fillion E (2006) J Am Chem Soc 128:2774–2775
94. Dumas AM, Fillion E (2010) Acc Chem Res 43:440–454
95. Wilsily A, Fillion E (2009) J Org Chem 74:8583–8594
96. Wilsily A, Fillion E (2008) Org Lett 10:2801–2804
97. Fillion E, Wilsily A, Liao E-T (2006) Tetrahedron: Asymmetry 17:2957–2959
98. Lee K-L, Brown MK, Hird AW, Hoveyda AH (2006) J Am Chem Soc 128:7182–7184
99. Brown MK, May TL, Baxter CA, Hoveyda AH (2007) Angew Chem 119:1115–1118; Angew Chem Int Ed 46:1097–1100
100. Sidera M, Roth PMC, Maksymowicz RM, Fletcher SP (2013) Angew Chem Int Ed 52:7995–7999
101. Roth PMC, Sidera M, Maksymowicz RM, Fletcher SP (2014) Nat Protocols 9:104–111
102. Schwartz J, Labinger JA (1976) Angew Chem Int Ed Engl 15:333–340
103. Maksymowicz RM, Roth PMC, Fletcher SP (2012) Nat Chem 4:649–654
104. Maksymowicz RM, Bissette AJ, Fletcher SP (2015) Chem Eur J 21:5668–5678
105. Davidson M, Hughes AK, Marder TB, Wade K (2000) Contemporary boron chemistry. RSC, Cambridge
106. Matteson DS (1995) Stereodirected synthesis with organoboranes. Springer, Berlin
107. Molander GA, Canturk B (2009) Angew Chem 121:9404 – 9425; Angew Chem Int Ed 48:9240–9261
108. Chen IH, Yin L, Itano W, Kanai M, Shibasaki M (2009) J Am Chem Soc 131:11664–11665
109. Chen I-H, Kanai M, Shibasaki M (2012) Org Lett 12:4098–4101
110. Feng X, Yun J (2010) Chem Eur J 16:13609–13612
111. O'Brien JO, Lee K-S, Hoveyda AH (2010) J Am Chem Soc 132:10630–10633
112. Radomkit S, Hoveyda AH (2014) Angew Chem Int Ed 53:3387–3391
113. Wu H, Garcia JM, Haeffner F, Radomkit S, Zhugralin AR, Hoveyda AH (2015) J Am Chem Soc 137:10585–10602
114. Suginome M, Ito Y (2000) Chem Rev 100:3221–3256
115. Ibrahem I, Santoro S, Himo F, Cordova A (2011) Adv Synth Catal 353:245–252
116. Hoveyda K, Lee S, Hoveyda AH (2010) J Am Chem Soc 132:2898–2900
117. Das JP, Marek I (2011) Chem Commun 47:4593–4623
118. Thaler T, Knochel P (2009) Angew Chem Int Ed 48:645–648
119. Brown MK, Hoveyda AH (2008) J Am Chem Soc 130:12904–12906
120. Mendoza A, Ishihara Y, Baran PS (2012) Nat Chem 4:21–25

Top Organomet Chem (2016) 58: 99–134
DOI: 10.1007/3418_2015_164

Published online: 29 January 2016

1,2- Versus 1,4-Asymmetric Addition of Grignard Reagents to Carbonyl Compounds

Pablo Ortiz, Francesco Lanza, and Syuzanna R. Harutyunyan

Abstract The first copper(I)-catalysed conjugate addition of Grignard reagents to α,β-unsaturated carbonyl compounds was reported in 1941. Impressive developments have been made since then, with catalytic asymmetric additions representing the most remarkable achievement. The recent discovery that copper(I) is able to catalyse the asymmetric 1,2-addition of Grignard reagents to α,β-unsaturated, as well as aromatic ketones, was a true revelation. Recent progress in copper(I)-catalysed addition of Grignard reagents is reviewed throughout this chapter, comparing and contrasting the well-established 1,4-selectivity of Cu(I)-ligand complexes with the newly introduced 1,2-selectivity. Mechanistic insights towards the better understanding of the regiodivergence are also discussed.

Keywords 1,2-Addition • 1,4-Addition • Asymmetric catalysis • Copper • Grignard reagents

Contents

1 Introduction 100
2 Chemo-, Regio- and Stereocontrolled Additions of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds 101
3 Paradigm Shift: From Copper(I)-Catalysed 1,4- to 1,2-Addition 109
4 Catalytic Asymmetric Alkylation of Ketones Using Grignard Reagents 116
5 Mechanistic Discussion 119
5.1 Copper(I)-Catalysed 1,4-Addition 119
5.2 Copper(I)-Catalysed 1,2-Addition 125
References 130

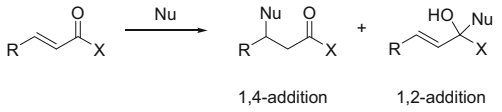
P. Ortiz, F. Lanza, and S.R. Harutyunyan (✉)
Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
e-mail: s.harutyunyan@rug.nl

1 Introduction

Catalytic enantioselective addition of carbon nucleophiles to electron-deficient conjugated systems is undoubtedly among the most powerful tools in organic synthesis, with a C–C bond and at least one stereogenic centre formed [1–5]. Its origin can be traced back to 1883, when the uncatalysed 1,4-addition of diethyl sodiomalonate to diethyl ethylidenemalonate was reported [6]. When addition to α,β-unsaturated carbonyl compounds is considered (Scheme 1), the soft (organic) nucleophiles generally attack the β-carbon (1,4-addition or conjugate addition) while the hard organometallic nucleophiles add to the carbonyl moiety (1,2-addition or direct addition).

This was the state of the art until 1941, when Kharash and Tawney reported the conjugate addition of an organomagnesium reagent (Grignard reagent) to an α,β-unsaturated ketone [7]. The use of a catalytic amount of a copper(I) salt enabled the control of regioselectivity towards conjugate addition (CA). This discovery led, over the following seventy years, to the establishment of copper(I)-based catalysis as the primary tool to achieve 1,4-selectivity in addition reactions of a wide range of organometallic reagents. Following these achievements, early synthetic efforts were directed towards the control of the stereoselectivity, initially making use of chiral substrates, chiral auxiliaries or stoichiometric chiral ligands. Over the last two decades, copper(I)-based chiral catalysts have become essential for catalytic asymmetric conjugate addition (ACA) of hard organometallics to α,β-unsaturated carbonyl compounds. Better performing chiral ligands were introduced, which allowed the addition to increasingly challenging α,β-unsaturated carbonyl substrates, including those leading to quaternary stereocenters [3–5, 8, 9]. Moreover, the current scope of CA has been expanded to a wide range of organometallic reagents, in approximate order of reactivity: $R_2Zn < R_3Al < RMgX$.

Thus, during the 70 years since the pioneering work of Kharash and Tawney in 1941, copper(I)-based reagents and catalysts have become a mainstay in 1,4-additions, in which the 1,2-additions were effectively avoided. A fundamental paradigm change came about in 2012, when the first example of copper(I)-catalysed 1,2-addition of Grignard reagents was reported [10]. In a way, it was coming back to the starting point, where the intrinsic reactivity of an organometallic reagent directs it towards the carbonyl moiety. However, the return to the origin was at a higher level: thanks to the copper(I)/chiral ligand catalytic system the addition to α,β-unsaturated ketones was possible not only with high 1,2-selectivity but also with excellent enantioselectivity. Further research in this field proved that Cu(I)-



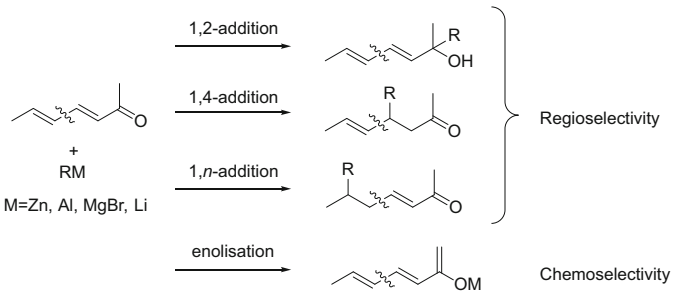
Scheme 1 1,4- versus 1,2-selectivity in addition of nucleophiles to α,β-unsaturated carbonyl compounds

based chiral catalysts are also effective in asymmetric alkylations (direct additions) of other classes of enolisable ketones using highly reactive Grignard reagents. This methodology allowed access to chiral tertiary alcohols with excellent yields and enantiomeric ratios [11].

As of today, copper(I)-catalysed ACA of organometallic reagents to α,β-unsaturated carbonyl compounds has been thoroughly reviewed [3–5, 8, 9, 12, 13]. Therefore, the aim of this chapter is not to provide another comprehensive review on this topic but to give a concise overview of copper(I)-catalysed ACA methodologies and to contrast them with more detailed examples of the recently discovered copper(I)-catalysed asymmetric 1,2-additions and direct alkylations of ketones using Grignard reagents. Furthermore, mechanistic support for both methodologies is discussed.

2 Chemo-, Regio- and Stereocontrolled Additions of Grignard Reagents to α,β-Unsaturated Carbonyl Compounds

A key challenge in the use of organometallic reagents in addition reactions to α,β-unsaturated carbonyl compounds is the regioselectivity, i.e. 1,4- versus 1,2-addition, as well as 1,*n*-addition (conjugated) when extended conjugated systems are considered. The tendency of hard nucleophiles, such as organozinc, organoaluminium, organomagnesium and organolithium reagents, is to give a mixture of 1,2- and 1,4-addition products with a preference for the former (Scheme 2). When Grignard or organolithium reagents are the organometallics in question, an additional challenge that must be taken into account is the chemoselectivity: these highly reactive organometallic reagents can act not only as powerful nucleophiles but can also enolise the corresponding conjugated ketones due to their high basicity (Scheme 2). Moreover, stereocontrol is also a major problem in catalytic reactions, due to the extreme reactivity profile of Grignard



Scheme 2 Regio- and chemoselectivities in the addition of organometallic reagents to α,β-unsaturated carbonyl compounds

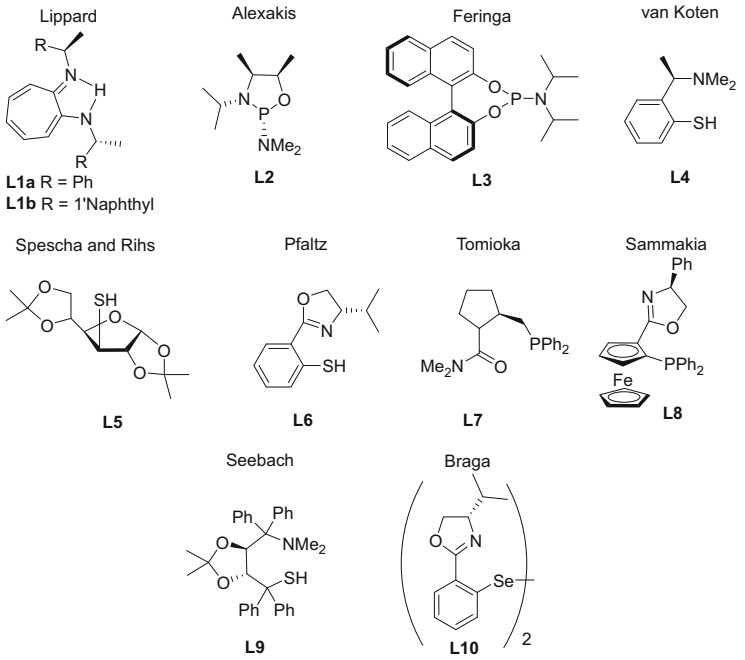
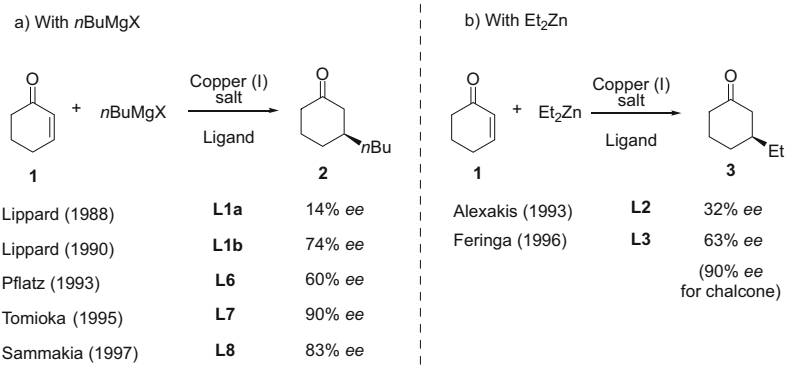


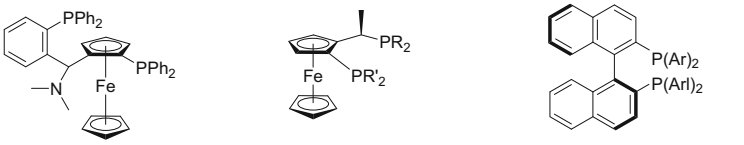
Fig. 1 Selected examples of representative ligand families used in the ACA of Et_2Zn and Grignard reagents to enones before 2004

reagents, thus making it difficult for chiral catalysts to outcompete uncatalysed reactions leading to racemic products.

Due to the challenges outlined above, methodologies for copper(I)-catalysed ACA of organolithium reagents are lacking, and for highly enantioselective catalytic ACA of Grignard reagents, they were not available until recently. In 1988 Lippard reported the first catalytic ACA of a Grignard reagent to cyclohexenone **1** using chiral copper(I)/tropinone **L1a** complex with low enantioselectivity, only 14% *ee* (Fig. 1 and Scheme 3) [14]. Nevertheless, higher enantioselectivities, up to 74%, could be obtained by modifying the conditions and using the bulkier **L1b** ligand [15]. Subsequently, the use of less reactive organozinc reagents allowed the development of a highly enantioselective copper(I)-catalysed CA of these compounds and, thus, the replacement of Grignard reagents. In 1993, Alexakis reported the first copper(I)-catalysed asymmetric conjugate addition of organozinc reagents using chiral trivalent phosphorus ligand **L2** (Fig. 1) [16]. However, it was not until the introduction of phosphoramidite ligand **L3** in combination with a copper(I) salt by Feringa et al. in 1996 that up to 90% *ee* was achieved in CA of organozinc reagents (Scheme 3) [17]. Modification of this class of ligands allowed a year later to perform the first catalytic ACA of organozinc reagents with complete stereocontrol [18]. Since then, organozinc reagents have been the most popular organometallics for the ACA reactions due to their low reactivity and,



Scheme 3 Selected representative examples of the early work of catalytic ACA of Grignard reagents (*left*) and Et_2Zn (*right*) to enones



L11 Taniaphos

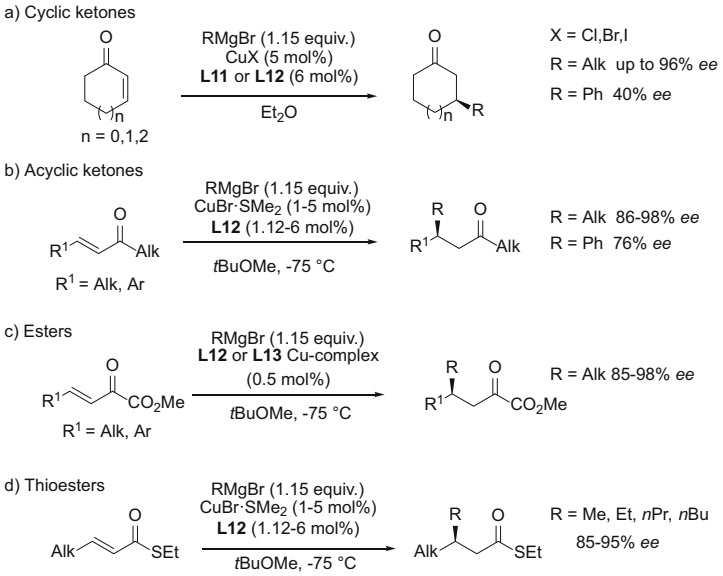
L12 R = Cy, R' = Ph Josiphos
L13 R = Ph, R' = Cy rev-Josiphos

L14 Ar = Ph, BINAP
L15 Ar = Tolyl, Tol-BINAP

Fig. 2 Chiral diphosphine ligands used in the ACA of Grignard reagents to α,β-unsaturated carbonyl compounds

consequently, fewer problems with uncatalysed blank reaction. Developments in the catalytic ACA of the highly reactive and basic Grignard reagents, on the other hand, were much slower. After the first report of Lippard in 1988, a number of publications appeared in which appreciable levels of enantioselectivity were reached in copper(I)-catalysed CA of Grignard reagents with structurally diverse chiral ligands (Fig. 1). Between 1991 and 1993, pioneered by van Koten [19, 20], several groups introduced thiolate-based chiral ligands (Fig. 1, **L4–L6**) for copper (I)-catalysed additions of Grignard reagents [21, 22]. Prior to 2004, many other chiral ligands were developed (Fig. 1, **L7–L10**) [23–26], but the highest enantioselectivity (90% *ee*) for the 1,4-addition to cyclohexenone was reported in 1995 by Tomioka using 32 mol% of chiral amidophosphine ligand **L7** (Scheme 3) [23].

It was not until 2004 that catalytic highly regio-, chemo- and stereoselective CA of Grignard reagents was achieved by Feringa et al. [27]. The key to this success was the use of bidentate diphosphine ligands (Fig. 2). All previously reported chiral ligands for catalytic ACAs of Grignard reagents incorporate a P, S or Se atom in combination with N or O in order to bind selectively the Cu and Mg atoms (Fig. 1). In this case, however, the reactivity of the Grignard reagents was harnessed by introducing a catalytic system based on copper(I) salt and chiral ferrocenyl diphosphine ligands (**L11–L13**, Fig. 2). This was a major advance in the field, as

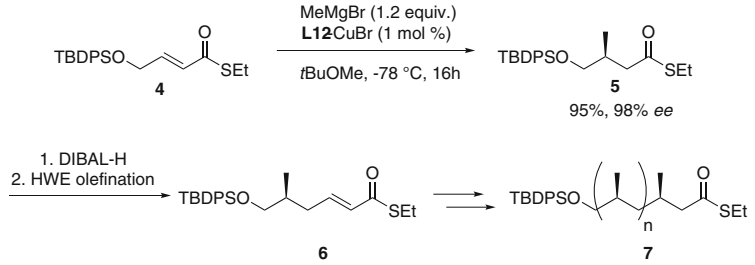


Scheme 4 Overview of the Cu/ferrocenyl diphosphine ligand-catalysed ACA of Grignard reagents to α,β-unsaturated (**a**) cyclic ketones, (**b**) acyclic ketones, (**c**) esters and (**d**) thioesters, developed by Feringa et al.

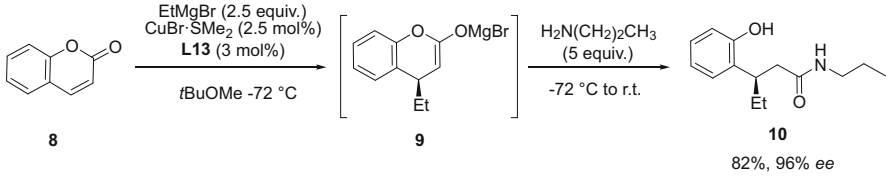
it made the readily available Grignard reagents uniquely powerful, since their reactivity could be capitalised on while controlling the selectivity. Addition of a variety of linear Grignard reagents to cyclic enones could be achieved with up to 99% of regio- and 96% of stereoselectivity using 5 mol% of the Taniaphos **L11**/CuX catalyst system (Scheme 4a). On the other hand, Josiphos ligand **L12** proved to be the best for addition of branched Grignard reagents. The scope was further expanded to stereochemically more challenging substrates such as acyclic conjugated ketones (Scheme 4b) [28]. For this class of substrates, once again ferrocenyl diphosphine ligands proved to be efficient, with Josiphos **L12** being the most suitable. Enantioselectivities of 86–98% and yields in excess of 97% for the 1,4-addition product were obtained, using linear Grignard reagents and acyclic α,β-unsaturated ketones (enones).

The methodology using a copper(I) salt and ligands **L12** and **L13** was also applied in the addition to α,β-unsaturated esters (enoates) (Scheme 4c). It was shown that excellent yields and enantioselectivities of up to 98% can be obtained with a wide range of substituted esters and aliphatic linear Grignard reagents [29]. An alternative catalytic system, namely, CuI/Tol-BINAP **L15** (Fig. 2), was developed by Wang et al. for the addition of Grignard reagents to α,β-unsaturated esters [30].

Due to the relatively low reactivity of MeMgBr, its addition to conjugated esters provided mainly starting material. To overcome this problem, Feringa



Scheme 5 The ACA of MeMgBr to α,β-unsaturated thioesters in the synthesis of the deoxypropionate motif present in many natural products



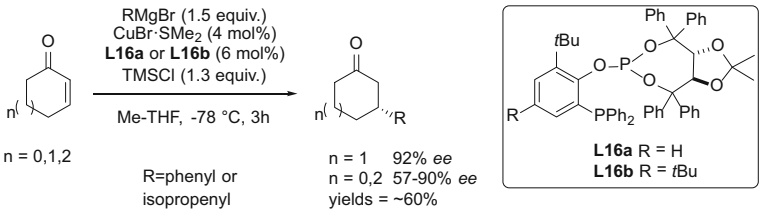
Scheme 6 The ACA of EtMgBr to coumarins and subsequent ring opening of the enolate **9** with an amine

et al. performed the addition of MeMgBr to more reactive conjugated thioesters (Scheme 4d). Excellent yields and *ee*'s were obtained for a range of α,β-unsaturated thioesters using the Cu(I) salt/Josiphos catalyst system [31]. Applying the copper (I)-catalysed methodology of ACA of MeMgBr to α,β-unsaturated thioesters, the group of Minnaard accomplished the total synthesis of a number of natural products bearing the deoxypropionate motif, such as some glycolipids present in the envelope of *Mycobacterium tuberculosis* [32–34], the anti-angiogenic (−)-Borrelidin [35], the actin binding (−)-Doliculide [36] and the apoptosis inducer(−)-Rasfonin [37].

The procedure involves copper(I)-catalysed conjugate addition of MeMgBr to an α,β-unsaturated thioester **4,** followed by reduction to the corresponding aldehyde and subsequent olefination to elongate the chain. This yields a new α,β-unsaturated thioester **6**, which, in turn, can be subjected to the next catalytic reaction (Scheme 5).

During the development of the catalytic ACA of Grignard reagents, simple substrates such as cyclohexenone were typically employed. Over the last years, on the other hand, new substrates were introduced in order to deliver more useful products, such as building blocks or intermediates in drugs [38]. Moreover, further transformation of the chiral enolate product obtained upon addition of Grignard reagent has been explored to increase the degree of functionalisation [39]. Thus, the catalytic ACA of Grignard reagents was extended to coumarins (Scheme 6) [40].

Unactivated coumarins such as **8** do not react with organozinc reagents. On the contrary, addition of the more reactive Grignard reagent leads to the corresponding



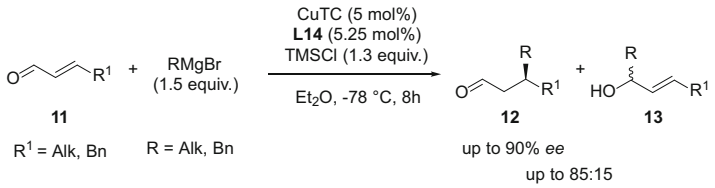
Scheme 7 ACA of phenyl and isopropenyl magnesium bromide to cyclic enones by Schmalz et al.

lactones in very good yields and enantioselectivities. The resulting chiral lactones are important synthetic intermediates by themselves, but reacting the enolate **9** in situ with an amine procured the amide **10**. This represents a formal catalytic asymmetric conjugate addition to amides, which is not yet directly achievable due to the lower reactivity of amide substrates. The same strategy was applied to linear α,β-unsaturated esters, and a wide range of chiral amides could be obtained [41]. Chromones [42], isomers of coumarins as well as structurally related pyranones [43] were also subjected to similar reaction conditions to obtain the 1,4-addition products in good yields and enantioselectivities.

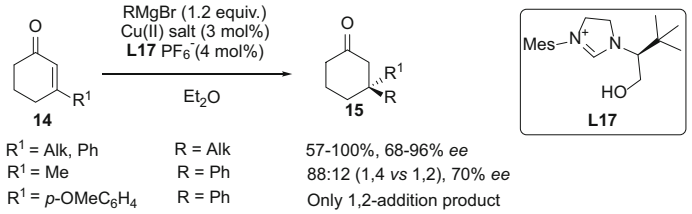
At this point, it is useful to list the general observations on the copper(I)/chiral diphosphine-catalysed ACA of Grignard reagents: (1) a wide substrate range (including α,β-unsaturated cyclic and acyclic ketones, lactones, acyclic esters, thioesters, chromones, coumarins and pyranones) can be used, furnishing the corresponding chiral CA addition products with high enantio-, regio- and chemoselectivities; (2) linear Grignard reagents add with better stereoselectivity than α- or β-branched ones; (3) the best catalytic systems include Taniaphos/CuCl, Josiphos/CuBr·SMe_2, rev-Josiphos/CuBr·SMe_2 and Tol-BINAP/CuI (Fig. 2); (4) to obtain the best results in terms of reactivity and selectivities, 1.5–5% of chiral catalyst loading is required; (5) chiral ferrocenyl-based ligands (Josiphos and Taniaphos) can be recovered in the form of Cu-complex and reused many times; (6) the best solvents for catalytic ACA of Grignard reagents are *t*BuOMe, Et_2O or CH_2Cl_2, depending on the catalytic system or substrate used; and (7) the methodology can be applied efficiently for the total synthesis of natural products.

Despite these remarkable accomplishments of the catalytic ACA of Grignard reagents, several challenges still remain, including the addition of alkenyl, aryl, allyl and α-branched Grignard reagents [28, 44, 45]. In 2008–2011, Schmalz et al. used the TADDOL-derived chiral phosphine–phosphite ligands **L16a/L16b** to perform the addition of aryl (phenyl) and alkenyl (isopropenyl) Grignard reagents to five-, six- and seven-member cyclic enones (Scheme 7) [46, 47]. Very good enantio- and regioselectivities, although with relatively low yields (~60%), were obtained, using the somewhat unusual 2-Me-THF as a solvent.

Another reaction that was elusive until recently is the addition to conjugated enals. The challenge of using these substrates in catalytic ACA is the fast uncatalysed 1,4-addition and even more the uncatalysed 1,2-addition, both



Scheme 8 ACA of Grignard reagents to conjugated enals reported by Alexakis et al.

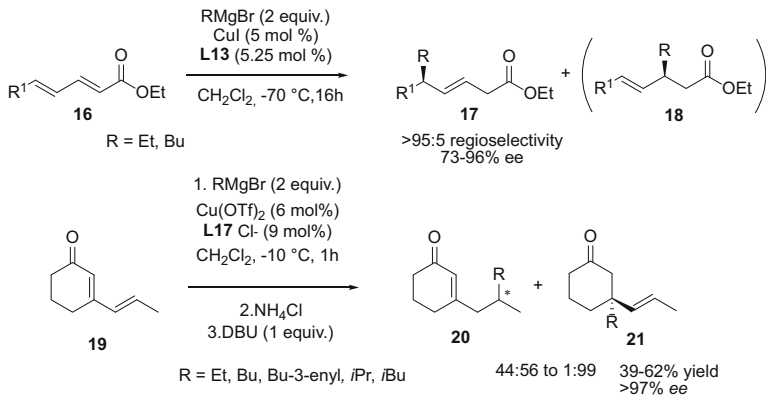


Scheme 9 Chiral quaternary stereocentres generated by ACA of Grignard reagents to trisubstituted cyclohexenone by Alexakis et al.

formidable competitors. In 2010 Alexakis reported that a copper(I)/BINAP **L14**-based catalytic system in the presence of TMSCl can promote enantioselective 1,4-addition to α,β-unsaturated aldehydes **11** with moderate to good 1,4-regioselectivities and 70% to 90% enantioselectivities (Scheme 8) [48]. Even though the additive enhanced the 1,4-addition, the overall yields were only around 50%, due to the considerable amount of 1,2-addition product **13** formed.

So far the discussion has been limited to catalytic ACA of Grignard reagents to generate tertiary stereocenters. The construction of quaternary stereocenters is one of the major challenges in asymmetric synthesis, in general. In this context, Alexakis et al. explored the addition of Grignard reagents to 3-substituted cyclic enones **14** (Scheme 9) [45, 49]. They achieved it by a novel approach, which relies on the use of chiral *N*-heterocyclic carbene (NHC) ligand **L17** in combination with Cu(II) salt. This catalytic system promotes the addition of primary and secondary Grignard reagents with good to high enantioselectivities (up to 96%). The addition of aryl Grignard reagents was difficult, and only with PhMgBr the regioselectivity for 1,4-addition product was higher than for the 1,2-addition adduct. Later, Tomioka also reported the ACA of alkyl Grignard to trisubstituted cyclohexenone, catalysed by a C2-symmetric chiral NHC ligand [44].

The final challenge to be discussed in this section is the ACA of Grignard reagents to α,β,γ,δ-unsaturated carbonyl compounds with extended conjugated systems. Due to the presence of an extra electrophilic site (double bond) and the possibility of forming regioisomers, polyconjugated carbonyl compounds pose an additional issue for regioselectivity: apart from a possible attack of the nucleophile in the 1,4- and 1,2-positions, there is a preference for addition to the terminal double



Scheme 10 Regiocontrol in the ACA of Grignard reagents to α,β,γ,δ-unsaturated carbonyl compounds: selective 1,6-ACA (*upper*) and selective 1,4-ACA (*lower*)

bond, the 1,6-addition [50]. Nakamura's mechanistic studies of conjugate addition of lithium organocuprates showed that reaction thermodynamics favours 1,6- over 1,4-addition [51]. Initial attempts to carry out addition of EtMgBr to the dienoate **16** in the presence of copper(I) salt resulted in poor selectivity: a 66:34 ratio favouring the 1,4-addition product. Interestingly, using the Cu(I) salt/**L13** catalyst system used before to promote the 1,4-ACA of Grignard reagents led selectively to the 1,6-ACA product **17**, thus indicating a clear preference for 1,6- over 1,4-addition (Scheme 10, upper) [52].

To revert the natural trend and direct the nucleophile towards 1,4-addition, Alexakis employed the NHC ligand **L17** [53]. Interestingly, if organozinc or organoaluminium compounds were used instead of Grignard reagents, 1,6-selectivity was observed in the addition to compound **19** (Scheme 10, lower). Equally crucial was the choice of ligand, as phosphoramidites, BINAP **L14**, Josiphos **L12** and simpler NHC ligands (Arduengo carbene) gave exclusively the 1,6-addition product **20**. The use of **L17**, containing a chelating hydroxyl group, was essential to afford the 1,4-adduct **21**. This is the least favoured regioisomer, and the difficulty is further increased by the fact that a quaternary stereocentre is being formed instead of a tertiary one (Scheme 10, lower). The scope was further extended to cyclic enynones [54], trienones and other polyconjugated systems [55]. In all cases, the behaviour was similar, and the products, containing a quaternary stereocentre, were isolated in good yields and excellent enantioselectivities.

These last examples show how the natural tendency can be overcome by careful selection of ligands and reaction conditions. Nonetheless, either those directing to 1,6- or to 1,4-addition take advantage of copper's soft character to guide the organometallic (in this case Grignard) reagent towards an alkene. If there is any 1,2-addition product formed, it is the result of the blank (uncatalysed) reaction. This is the opposite of the topic of the next section: the deliberate 1,2-addition using copper(I) catalysis.

3 Paradigm Shift: From Copper(I)-Catalysed 1,4- to 1,2-Addition

Chiral tertiary alcohols are widely present in naturally occurring biologically active molecules. Moreover, they are an important motif in numerous drugs and are useful synthetic building blocks (Fig. 3) [56, 57]. While a host of methods can be employed for the formation of chiral *secondary* alcohols [58–61], the synthesis of chiral *tertiary* alcohols is much more challenging because it relies exclusively on carbon–carbon bond formation [62, 63]. For example, catalytic asymmetric hydrogenation [64] is often used for the synthesis of chiral secondary alcohols, but it is not applicable for the formation of chiral molecules with quaternary stereocenters. The catalytic asymmetric addition of organometallic reagents to ketones is the synthetically most efficient approach to access chiral tertiary alcohols via the simultaneous formation of a C–C bond and a tetrasubstituted stereogenic centre. However, this approach is particularly challenging due to the low reactivity of ketones towards nucleophilic attack and the difficulty presented to chiral catalysts in differentiating between the two prochiral faces where the substituents on the ketone are similar [63, 65].

A range of organometallics, including Grignard reagents, are available to organic chemists for addition to ketones. However, catalytic asymmetric addition of organomagnesium reagents (RMgX) to ketones is not straightforward due to difficulties in controlling their extreme reactivity profile. The higher reactivity, useful to counteract the lower reactivity of ketones, has a downside: the uncatalysed (and thus racemic) reaction. Moreover, organomagnesium reagents themselves are strong bases, adding the risk of enolisation of the corresponding ketones that have hydrogens in α-position. In addition, alkyl Grignard reagents saturated in the β-position bear the risk of reducing the carbonyl substrate via β-hydride transfer [66–69]. The first attempts to obtain chiral tertiary alcohols by addition of Grignard reagents to ketones required at least one equivalent of a chiral auxiliary. Thus, in Seebach's report in 1992, the Grignard reagent was made chiral by the use of an equimolar amount of TADDOL [70]. The high reactivity of the Grignard reagents discouraged researchers into making this reaction catalytic, instead establishing organozinc (R_2Zn) compounds as the reagents of choice for these transformations,

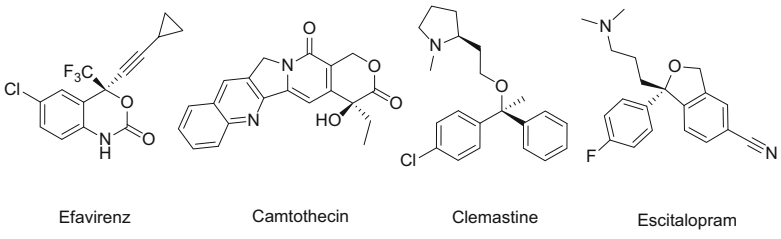
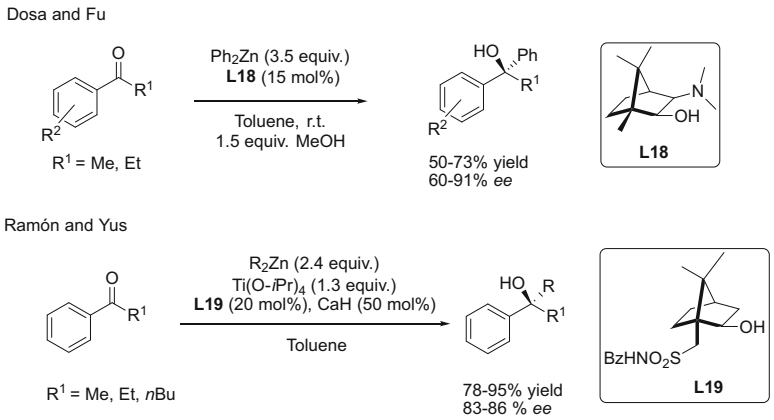


Fig. 3 Examples of marketed drugs and biologically active compounds bearing chiral tertiary alcohols



Scheme 11 Pioneering works on catalytic asymmetric addition of organozinc reagents to ketones to obtain chiral tertiary alcohols

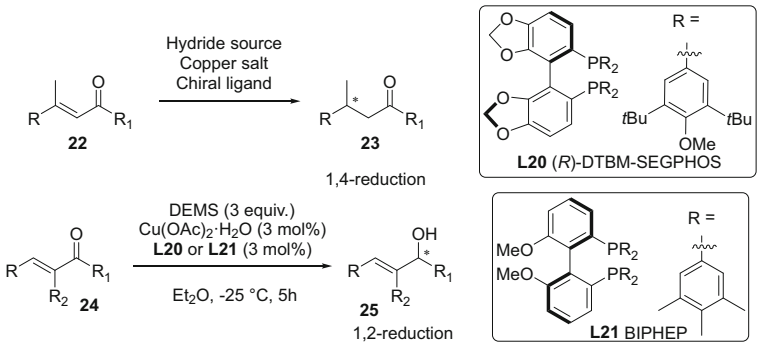
despite their cost, structural limitations and the fact that they transfer only one of the alkyl groups.

Along these lines, pioneering work was done in 1998 by Dosa and Fu for diphenylzinc and Ramón and Yus for dialkylzinc asymmetric addition to ketones (Scheme 11) [71, 72]. For the latter, the lower reactivity of dialkyl compared to diarylzinc reagents was compensated by the use of a superstoichiometric amount of titanium isopropoxide additive. In situ formation of organotitanium species is postulated, which has an intermediate reactivity between the highly reactive organomagnesium and the less reactive organozinc reagents [59, 73]. This has been intentionally pursued, either by direct addition of organotitanium reagents [74–76] or by in situ formation from the parent organometallics (organoaluminium [77, 78] and organomagnesium [79, 80]). While the direct use of Grignard reagents would allow environmentally benign, atom- and cost-efficient reaction processes, the only example of their catalytic asymmetric addition to ketones was reported by Yus and Maciá in 2012, using aryl Grignard reagents with superstoichiometric amounts of titanium tetraisopropoxide [79].

All of these protocols (based on Zn, Al or Mg) require the use of excess organometallics and superstoichiometric amounts of titanium tetraisopropoxide additive.[1] Thus, they are catalytic in the chiral ligand but not in the metal.

A fully catalytic system for the enantioselective addition of Grignard reagents was known for the 1,4-addition to α,β-unsaturated ketones and involved copper(I)-based complexes as catalysts. Since it was thought that the nature of copper was to promote the opposite regioselectivity (1,4-addition), the implementation of such a

[1] In one case, it was possible to carry out the reaction using 60 mol% of titanium tetraisopropoxide $Ti(OiPr)_4$ [81], and in another case it was reported that $Ti(OiPr)_4$-free 1,2-addition to aromatic ketones is possible when a threefold excess of organozinc reagent is used [82].



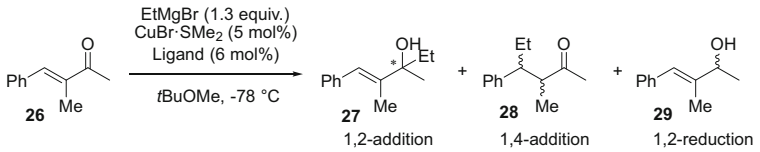
Scheme 12 Copper(I)-catalysed enantioselective 1,4-reduction and recently developed 1,2-reduction by Lipshutz et al.

system for 1,2-addition seemed counterintuitive. There was, however, some evidence that this could be achieved. For instance, copper(I)-catalysed enantioselective addition of nucleophiles to aldehydes and activated ketones was known from Shibasaki's work, involving stabilised [83] as well as non-stabilised nucleophiles. In this regard, they could perform the alkenylation and phenylation of ketones with both organosilanes [84] and organoboranes [85]. Cu(I)F-DTMB-SEGPHOS complex was transmetalated using these organometallics in order to generate the actual nucleophile.

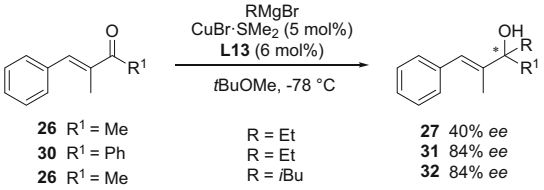
A more recent example, and closer to the system under discussion, is the copper (I)-catalysed enantioselective 1,2-reduction of α,β-unsaturated ketones investigated by Lipshutz et al. Analogously to the copper(I)-catalysed 1,4-ACA of organometallics discussed in the first section, hydrosilylation of α,β-unsaturated ketones **22**, employing chiral CuH complexes, benefits from the inherent tendency of Cu(I) to coordinate to the C-C double bond and renders 1,4-addition as the thermodynamically preferred mode of action (Scheme 12) [86]. This preference was rationalised by the Cu(I)-olefin interaction, which is of soft–soft character. Lipshutz et al. discovered in 2010 that α,β-unsaturated ketones **24**, with an α-substituent, undergo the reduction in the 1,2-position, namely, the carbonyl group is reduced instead of the conjugated double bond (Scheme 12) [86]. Importantly, in the presence of a chiral ligand, the reduction proceeds enantioselectively. DTMB-SEGHPHOS **L20** and BIPHEP **L21** gave the best results (80–90% *ee*), although, interestingly, a ferrocenyl-type ligand also catalysed the reaction.

From a chemical point of view, the 1,2-reduction of the enone involves nucleophilic attack of a hydride to the carbonyl moiety. In theory, nucleophiles other than hydride (e.g. carbon nucleophiles) could also be added to the carbonyl under copper (I) catalysis. This was achieved by the groups of Harutyunyan and Minnaard using Grignard reagents [10].

In the presence of a catalytic amount of copper(I) salt in the reaction, the addition of EtMgBr to α,β-unsaturated ketone **26** resulted in a mixture of 1,2- (25%) and 1,4-addition (21%) products, as well as carbonyl reduction (9%) and



Scheme 13 Products resulting from the Cu(I)/diphosphine ligand-catalysed addition of Grignard reagent (EtMgBr) to α,β-unsaturated ketones

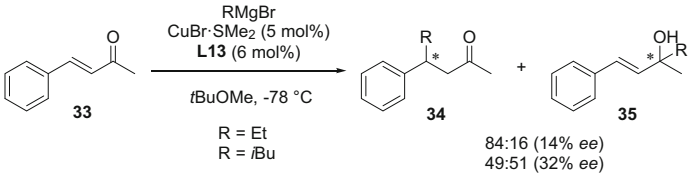


Scheme 14 Effect of the steric bulk of Grignard reagents on the enantioselectivity of addition reaction to α-substituted enones

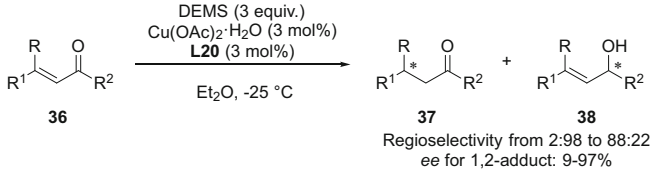
45% of unreacted ketone (Scheme 13). Interestingly, the presence of a diphosphine ligand dramatically changed the panorama. All diphosphine ligands tested increased the reactivity (full conversion was obtained) and directed the regioselectivity towards the 1,2-adduct **27** (>82%). DTBM-SEGPHOS **L20**, which worked well for copper(I)-catalysed 1,2-reduction, promoted 1,2-addition of Grignard reagent as well, albeit with a complete lack of stereoselectivity. An analogous situation was observed when Tol-Binap **L15** and ferrocenyl-based diphosphine ligands Taniaphos **L11** and Josiphos **L12** were employed as chiral ligands, in combination with a Cu(I) salt. Exceptionally, addition of EtMgBr proceeded with 40% of enantioselectivity when rev-Josiphos **L13** was used.

Increasing the steric bulk next to the carbonyl moiety by replacing Me with Ph (R^1 in Scheme 14) enhanced the enantiodiscrimination, leading to the addition product **31** with 84% *ee*. Strong enhancement in the reaction enantioselectivity was also observed when moving from linear to β-branched Grignard reagents. The addition of *i*BuMgBr to conjugated enone **26** furnished the corresponding alcohol **32** with an *ee* of 84% (Scheme 14).

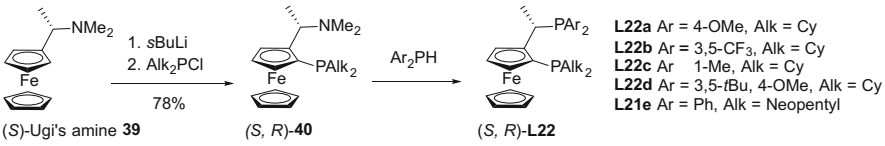
The α-substitution in the substrate was found to be essential for both the 1,2-regioselectivity and the enantioselectivity of the reaction. The addition of EtMgBr to α-H-substituted enone **33** led to only 16% of the 1,2-addition product **35** with only 14% *ee*. The sterically hindered *i*BuMgBr improved both the regioselectivity for the 1,2-adduct to 51% and the *ee* to 32% (Scheme 15). From the outcome of these experiments, one can conclude that the steric hindrance in the substrate and the bulkiness of the Grignard reagent are crucial for increasing both the enantio- and the regioselectivity.



Scheme 15 Copper(I)-catalysed addition of Grignard reagents to α-H-substituted enone **33**



Scheme 16 Copper-catalysed asymmetric reduction of β,β-disubstituted enones

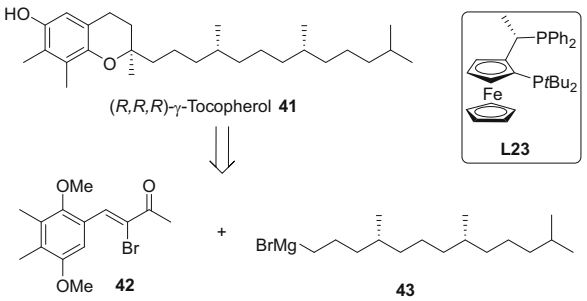


Scheme 17 Chiral ferrocenyl diphosphine ligands synthesised and applied in 1,2- and 1,4-additions by Harutyunyan and Minnaard

These results are in accordance with Lipshutz's observations in the 1,2-reduction of β,β-disubstituted enones **36** (without α-substituent), where moderate 1,2-regioselectivity and highly variable *ee*'s were obtained (Scheme 16) [87]. Intriguingly, in this case, ferrocenyl-based ligands catalysed the 1,4-addition (not shown), while DTBM-SEGPHOS lead to 1,2-addition.

To overcome some of the limitations of the methodology, namely, the requirement of β-branched Grignard reagents and the presence of a substituent on the α-position of the substrate, Harutyunyan et al. envisioned catalyst tuning. Several ferrocenyl ligands **L22a–d**, with different steric and electronic environments around the phosphorus atoms, were synthesised (Scheme 17) [88]. Unfortunately, the new ligands were unable to improve markedly the enantioselectivity of the addition of linear Grignard reagents to α-substituted enones when compared to the initial results obtained with rev-Josiphos **L13** ligand. However, it was found that for the 1,2-addition to α-H-substituted enone **33**, the **L22d** with bulky *tert*-butyl and electron-donating methoxy groups on the aromatic ring provided higher regio- (43% vs. 29%) and enantioselectivities (54% vs. 28%) compared to rev-Josiphos **L13**.

Minnaard et al. applied the Cu(I)/ferrocenyl ligand-catalysed 1,2-Grignard addition methodology in the key step of the synthesis of (*R,R,R*)-γ-tocopherol **41** (Scheme 18) [89]. They found that in this case the enantioselectivity of 42%,

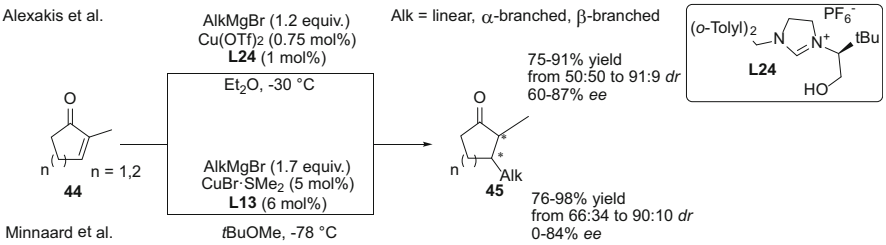


Scheme 18 Cu(I)-catalysed 1,2-asymmetric addition of Grignard reagent **43** in the key step of the synthesis of (*R*,*R*,*R*)-γ-tocopherol **41**

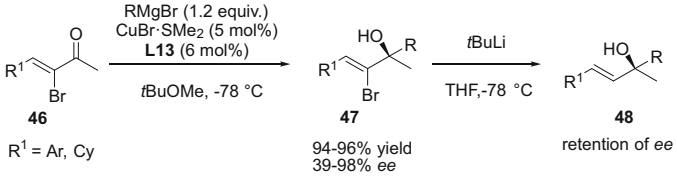
obtained in the addition of **43** to **42** under the standard catalytic conditions using rev-Joshiphos **L13**, could be improved to 73% using ferrocenyl ligand **L23**, with sterically demanding *tert*-butyl groups at the phosphine atom. Encouraged by this result, the synthesis of other bulky analogues was attempted, with the aim of further increasing the enantioselectivity. Unfortunately, the coupling of R_2PCl (R=$EtMe_2C$, Et_3C, $iPrMe_2C$ and adamantyl) with the ortho-lithiated ferrocene **39** failed, and only **L21e** could be synthesised (Scheme 17). Regrettably, it did not raise the *ee* of the product.

The observed ligand specificity for 1,2-addition reactions is remarkable. Numerous ferrocenyl ligands including rev-Josiphos are able to give high *ee*'s for the 1,4-ACA, while only very few are suitable for the 1,2-addition reaction. Experience shows that for 1,2-addition, rev-Josiphos-type ligands (which have the opposite arrangement to Josiphos-type ligands, with a dialkyl phosphine on the ferrocene and a diaryl phosphine ethyl branch) give the highest enantioselectivities. This typical structural framework seems to be necessary for success. Having said that, it might be that other ligand families are able to catalyse this transformation effectively. Still untested in this regard are chiral NHC ligands, which are also potent catalysts for 1,4-ACA [44, 45, 49, 90].

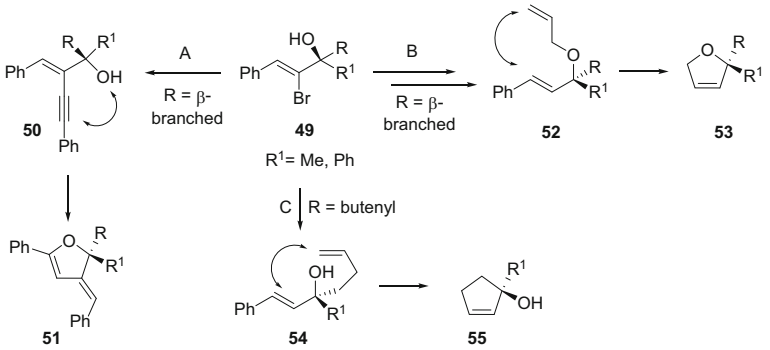
The 1,2-addition of Grignard reagents to enones seems to be a *rara avis*, as it works only with a specific type of ligand (rev-Josiphos) and substrate (α-substituted enones). Moreover, the latter needs to be linear. It is noteworthy that with cyclic α-substituted enones, the catalytic addition is directed exclusively towards the 1,4-position. This was shown by two independent studies, one employing the carbene ligand **L24** [90] and the other rev-Josiphos **L13** (Scheme 19) [91]. Remarkably, the same conditions that furnished the 1,2-addition product for acyclic enone substrates (rev-Josiphos **L13,** Cu(I) salt, *t*BuOMe), led to highly regioselective 1,4-addition when using α-methyl cyclohexenone and pentenone. One can conclude that, regardless of the catalyst, the α-substituent and the double bond configuration of the enone are important factors for 1,2- and 1,4-selectivity. More specifically, it seems that *s-cis* enones *allow* 1,2-, while *s-trans* enones favour 1,4-addition. To date, the requirement of a substituent in the α-position in order to get high values of regio- and enantioselectivities has not been overcome. Nevertheless, an indirect approach was reported, involving the catalytic asymmetric 1,2-addition of Grignard



Scheme 19 Cu(I)-catalysed addition of Grignard reagents to cyclic α-substituted enones leading to 1,4-adduct



Scheme 20 Cu/rev-Josiphos-catalysed addition of Grignard reagents to α-Br-substituted enones followed by debromination



Scheme 21 Synthesis of chiral dihydrofurans and cyclopentenols by Cu/rev-Josiphos-catalysed 1,2-addition of Grignard reagents to α-Br-substituted enones

reagents to α-bromo-substituted enones **46**, followed by debromination (Scheme 20) [92].

The α-Br-substituted allylic alcohol is not merely an extra step in the synthesis of non-α-substituted tertiary allylic alcohols. It is also interesting, in its own right, for conversion into a variety of highly functionalised chiral building blocks, namely, dihydrofurans and cyclopentenols, as shown by Minnaard et al. (Scheme 21) [93]. α-Bromo-substituted chiral allylic alcohols **49** were obtained in 86–98% *ee* when β-branched Grignard reagents were used. They could be converted into

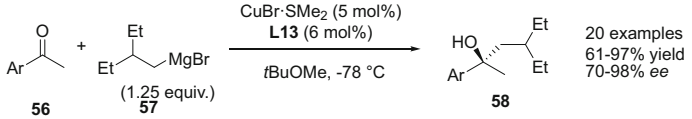
dihydrofurans **51** in two steps: the enyne **50** formed by the Sonogashira reaction was subjected to the base-induced intramolecular hydroalkoxylations to yield the final product (route A). Alternatively, the debrominated 1,2-addition product can be allylated to form 1,6-diene **52**, followed by ring-closing olefin metathesis to form chiral dihydrofurans **53** with a double bond at the 3,4-position (route B).

Finally, route C affords chiral allylic cyclopentenols **55** via the 1,2-addition of butenyl magnesium bromide to enone **49**, followed by debromination and metathesis reaction. However, the moderate enantioselectivities (44–52% *ee*) inherent to the use of linear Grignard reagents are a drawback of this last route.

4 Catalytic Asymmetric Alkylation of Ketones Using Grignard Reagents

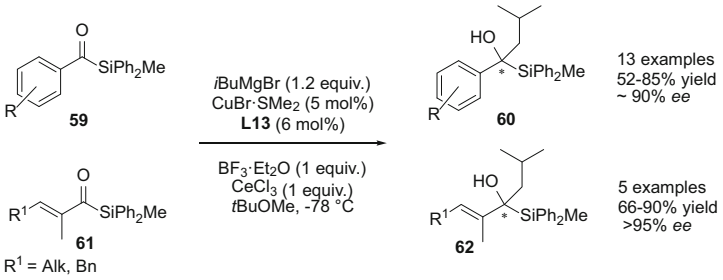
Following their interest in the synthesis of chiral tertiary alcohols, the Minnaard and Harutyunyan groups extended the previously developed catalytic 1,2-addition methodology to alkylations of enolisable aryl alkyl ketones **56** (Scheme 22) [11]. Compared to enones, the problem of regioselectivity is eliminated in this case. However, addition of Grignard reagents to aryl alkyl ketones often exhibits issues with chemoselectivity, namely, the risk of enolisation and reduction via β-hydrogen transfer from the corresponding Grignard reagent. The catalytic system based on Cu(I)/rev-Josiphos **L13** proved to be powerful for this transformation as well, outcompeting the undesired enolisation, the reduction and the uncatalysed addition reactions. Good to excellent enantioselectivities and yields were obtained in the addition of β-branched 2-ethylbutylmagnesium bromide **57** to a large variety of acetophenone derivatives **56**. The same trend found earlier for the addition to enones was seen again for aryl alkyl ketones: β-branched Grignard reagents are required in order to obtain products with good enantioselectivities, while linear Grignard reagents lead typically to products with moderate *ee*. Aryl Grignard reagents led to racemic products, whereas MeMgBr did not react.

Due to the increasing interest in silasubstitution [94–97], Harutyunyan et al. applied the same catalytic system to the addition of Grignard reagents to acylsilanes **63** with the aim of developing catalytic asymmetric synthesis of tertiary silylated alcohols (Scheme 23). Introduction of a silicon group has become a growing practice in medicinal chemistry over the last years. The presence of silicon in drugs slightly modifies the properties of the original compound, with low toxicity risk and favourable metabolic profile. Several methodologies make it possible to



56 57 58

Scheme 22 Cu/rev-Josiphos-catalysed 1,2-addition of **57** to aryl methyl ketones



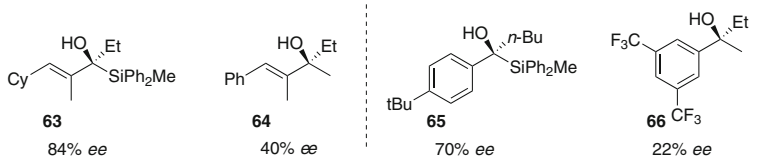
Scheme 23 Cu/rev-Josiphos-catalysed 1,2-addition of *iso*-butylmagnesium bromide to acylsilanes

obtain enantiopure secondary silylated alcohols, but few of them are catalytic. Marek et al. could obtain the tertiary counterparts by catalytic asymmetric alkynylation [98], but the alkylation remained unachievable until this research was carried out by Harutyunyan et al. [99].

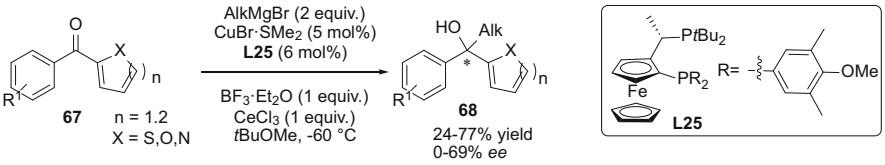
Perhaps contrary to expectations, replacing the alkyl group by a silyl group in an aryl alkyl ketone has a high impact on the reactivity. Applying the reaction conditions for the addition to aryl alkyl ketones to acylsilane **59** (R=H), an addition to reduction ratio of 1:2 was obtained while preserving a high enantioselectivity of the addition product **60**. Screening of various parameters (ligands, solvents, temperatures and substituents in the silyl moiety) did not provide enhanced addition to reduction ratios. Notably, the use of Lewis acids compatible with Grignard reagents did improve the results, and a 1:1 mixture of $BF_3 \cdot Et_2O/CeCl_3$ was found to be the most beneficial: the addition to reduction ratio improved to 5:1, while the enantioselectivity of the addition product remained 95:5. The substrate scope was again wide.

The majority of the substituents in the aromatic ring were tolerated, and good yields and enantioselectivities, mostly in the range of 90%, were obtained. Remarkably, the substrate scope also included α,β-unsaturated acylsilanes **61**, in which the competing 1,4-addition product was not observed, and the corresponding tertiary silylated allylic alcohols were obtained in good yields and *ee*'s.

Once again, the addition of β-branched Grignard reagents gave rise to the products with good yields and excellent *ee*'s. It is worth to note that, for the first time with this catalytic system, high enantioselectivities were obtained with linear Grignard reagents. Significantly, 84% *ee* was obtained when ethyl and *n*butyl magnesium bromide were added to the α,β-unsaturated acylsilane **61** (R^1=Cy). In contrast, the addition to the related α,β-unsaturated enone **26** gave rise to the tertiary alcohol **64** with much lower enantiodiscrimination (Scheme 24, left). Similarly, the addition of *n*BuMgBr (no data for EtMgBr) to silyl ketones yielded the product **65** with 70% *ee*, while the corresponding alcohol **66**, derived from the aryl ketone, was only 22% enriched in one enantiomer (Scheme 24, right). The bulkiness of the silyl group might be the reason for the enhanced enantioselectivity.



Scheme 24 Influence of the silicon group on the enantioselectivity of the addition of linear Grignards



Scheme 25 Asymmetric alkylation of aryl heteroaryl ketones by Harutyunyan et al.

The use of the Lewis acid mixture deserves a few more lines, considering that it is an unprecedented catalytic system. The reduction of ketones has been postulated to be the result of the activation of the carbonyl moiety through coordination with the magnesium atom of the Grignard reagent, followed by β-hydride transfer from the Grignard reagent [66–69]. In this scenario, Lewis acids are expected to prevent the coordination of the magnesium to the oxygen of the C=O, therefore minimising the reduction and allowing the catalytic pathway. While according to the authors the Lewis acid mixture ($BF_3 \cdot Et_2O/CeCl_3$) has this effect, the organisation at a molecular level that allows this is not clear, due to the presence of two Lewis acids. In theory, transmetalation of the Grignard reagent to form organocerium reagents can be envisioned. To test this hypothesis, the authors prepared and used the organocerium reagent directly, but only the reduction product was obtained. Consequently, this hypothesis was discarded. It is also conceivable that the mixture of Lewis acids leads to the formation of a new Lewis acid, more efficient for this catalytic system. Coordination of the Lewis acid to the copper catalyst, especially in the case of BF_3, is an option, albeit a speculative one [100]. This interesting though still not well-understood effect will be discussed further in the section dedicated to mechanistic studies.

The combination of $BF_3 \cdot Et_2O/CeCl_3$ Lewis acids was also applied in later work dealing with the addition of Grignard reagents to aryl heteroaryl ketones **67** (Scheme 25) [101]. The resulting tertiary aryl heteroaryl methanols **68** are the core structure of many marketed drugs, therefore making their synthesis of high interest. So far, catalytic asymmetric methodologies have focused on the addition of aryl nucleophiles to aryl alkyl ketones. In this case, the two substituents in the ketone are dissimilar enough to permit enantiodiscrimination by the chiral catalyst. For the very same reason, the catalytic asymmetric addition of carbon nucleophiles to diaryl ketones is particularly challenging [102].

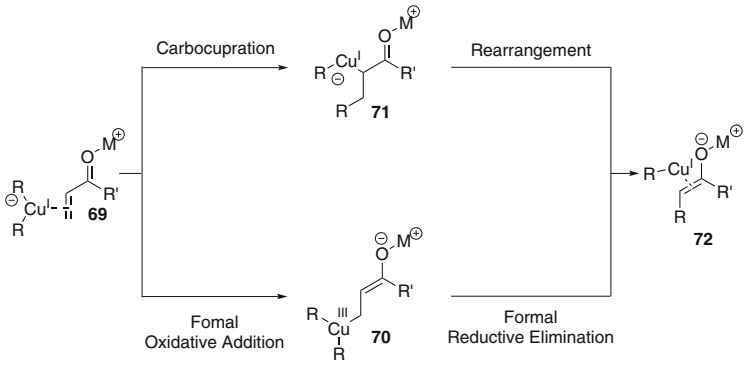
As mentioned earlier, the Lewis acid mixture was necessary in this system as well, in order to counteract the reduction pathway. Here the Lewis acid effect was even more pronounced: in its absence only the reduction product was observed. Remarkably, rev-Josiphos, which had been successful for the previous class of ketones, led to a mixture of addition and reduction products, and, what is more intriguing, the addition product was racemic. After ligand screening, the authors were able to identify ligand **L25** that allowed them to obtain the product of addition of *i*BuMgBr to 2-benzoylthiophene in 69% *ee*. Interestingly, **L25** does not have a rev-Josiphos type of arrangement of the phosphine substituents, but that of the Josiphos. In spite of this, some of the trends typically observed for 1,2-addition were repeated here: β-branched Grignard reagents led to products with *ee*'s higher than those obtained with linear ones. However, in this case, even β-branched *i*BuMgBr led to low/moderate enantioselectivities when added to different aryl heteroaryl and diheteroaryl ketones. It is noteworthy that all the substrates had (at least) one heteroatom and the results in terms of enantioselectivity were generally better if this was sulphur. This might be indicative of an additional coordination of the sulphur atom with the copper catalyst.

To conclude, the recently developed 1,2-addition of Grignard reagents to enones and ketones delivers chiral tertiary alcohols in good to excellent yields and enantioselectivities. However, it is a more specific system than 1,4-ACA, with only a few combinations of chiral catalysts and conditions allowing the desired outcome. Besides, the highest enantioselectivities in addition reactions to enones, aryl alkyl, aryl heteroaryl and diheteroaryl ketones are typically obtained with β-branched Grignard reagents. The only class of substrates that also provides high enantioselectivity with linear Grignard reagents are the acylsilanes. Apart from the challenge of the addition of linear Grignard reagents, no catalytic enantioselective 1,2-addition of aryl and alkenyl Grignard reagents has been developed yet. So far, only the diasteroselective version is available [103]. Regarding the substrate scope, highly enantioselective alkylation of diarylketones is still a remaining issue. Analogously, the addition to the even more challenging dialkyl ketones has not been achieved so far [11]. Considering that the presented methodologies are relatively recent, these feats might be accomplished in the near future.

5 Mechanistic Discussion

5.1 Copper(I)-Catalysed 1,4-Addition

Our current mechanistic understanding of copper(I)-catalysed 1,4-ACA is derived from the cumulative experimental data obtained from the studies carried out with the stoichiometric (uncatalysed) addition of lithium organocuprates [104, 105]. This approach is based on the assumption that each catalytic event in copper(I)-catalysed reactions can be considered as a single addition reaction of an

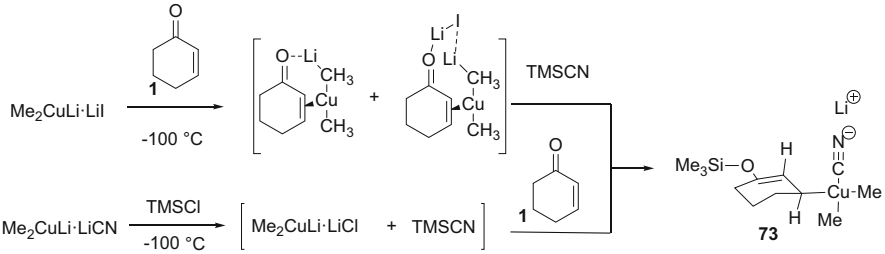


Scheme 26 Proposed mechanistic pathways for CA of organocuprates to α,β-unsaturated carbonyl compounds

organocuprate (formed upon transmetalation of copper(I) salt with a corresponding organometallic reagent) to an equimolar amount of a carbonyl compound. Two different pathways were considered originally for CA addition of organocuprates (Scheme 26).

Complex **69**, formed via π-complexation of an organocuprate with an unsaturated carbonyl compound, is the common starting point in both pathways (Scheme 26). π-Complexation is followed by either (1) a formal oxidative addition to the β-carbon of the carbonyl compound to afford σ-complex **70** (Cu(III)-intermediate) that after a reductive elimination step affords the π-adduct **72** or (2) a carbocupration reaction affording compound **71** that upon rearrangement leads to π-adduct **72** [105–108].

Historically there has been a long-standing debate over the existence of these intermediates, and their involvement in CA was supported primarily by computational studies [104]. Ullenius et al. conducted the first NMR spectroscopic study towards the detection of a π-complex in 1985 for CA of a Gilman reagent (Me_2CuLi, lithium dimethylcuprate) to enoates [109, 110]. The indication for the π-complex formation was an upfield shift, observed for the conjugated C–C double bond in the ^{13}C-NMR spectra. Since this original report, an increasing body of experimental data has appeared, bringing new insight into the nature of this intermediate. Ogle et al. carried out low-temperature rapid injection NMR (RI-NMR) in order to detect the formation of π-complexes between classical Gilman reagents and various α,β-unsaturated esters, ketones and nitriles [111]. Using RI-NMR, they were able to collect data a few instants after the beginning of the reaction, allowing the observation of the reactive intermediate involved in the transformation. Diagnostic chemical shifts for the formation of the π-complex in the ^{13}C-NMR spectra were related to signals of the α-C and β-C of the double bond and the carbon of carbonyl. The effect of a Cu-coordination with the double bond was reflected in a remarkable upfield shift of the ^{13}C-NMR for all the three carbons.



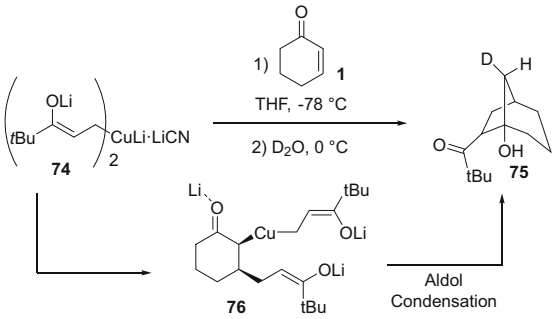
Scheme 27 Synthetic pathways for the formation of Cu(III)-intermediate **73**

Conversely, the σ-complex remained elusive for a longer time, even though House proposed its formation in CA reactions already in 1976, via an oxidative addition of an organocuprate to the β-carbon of an α,β-unsaturated carbonyl compound [112]. Exploiting the RI-NMR technique, Ogle et al. were able to observe and characterise the elusive Cu(III)-intermediate in the CA addition of Gilman reagents to cyclohexenone **1** for the first time in 2007 [113]. This outstanding achievement was possible thanks to the synthesis of the lithium cyanobis(methyl) (3-trimethylsiloxycyclohex-2-en-1-yl)cuprate(III) **73** (Scheme 27), in which the substituents play an important role in the stabilisation of such a complex, as was predicted by Snyder in 1995 based on DFT calculations [114].

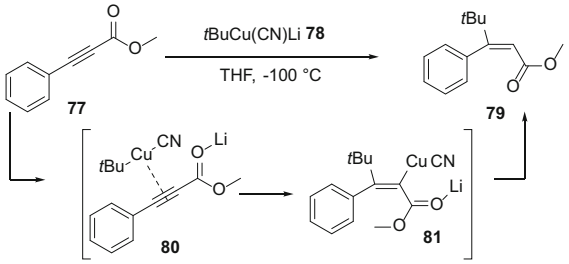
The Cu(III)-intermediate **73** was prepared by injecting a THF-d_8 solution of the reagents directly in an NMR tube at −100°C. This special setting also allowed the clear observation of the π-complex precursor of species **73**. For this intermediate, a square planar geometry was hypothesised, supported by computational studies [115]. In the ^{13}C-NMR spectrum of species **73**, two methyl peaks appear at 12.43 and 25.31 ppms, which significantly shifted downfield compared to the typical values of the same Me groups in the corresponding cuprate or in the π-complex. Based on different NMR-techniques, the peaks at 12.43 and 25.31 ppms were assigned to the methyl group in the *trans*- and *cis*-positions, respectively, with respect to the ring. Also the α-C of the enone showed a change in the chemical shift, caused by a rehybridisation from sp^2 to sp^3, moving from 130.12 ppm in cyclohexenone to 116.28 ppm in complex **73**. This remarkable work triggered a growing interest in the study of Cu(III)-species. Subsequently, various Cu(III)-species were found to be formed not only in CA reactions but also in S_N2 and S_N2' allylic substitutions, thus highlighting the importance of Cu(III)-species in copper-promoted carbon–carbon bond formation [116–119].

While several NMR spectroscopic studies have established the involvement of π- and σ-complexes in CA of organocuprates, little evidence was obtained for the carbocupration pathway until the early 2000s, when experimental evidence supporting a carbocuprate-like intermediate was reported. Reacting cyclohexenone **1** with customised homocuprate **74** bearing an enolate moiety in its structure afforded bicyclic alcohol **75** as major product (Scheme 28) [120]. The formation of **75** is more consistent with a mechanism involving carbocupration intermediate

Scheme 28 Experimental observation for carbocuration mechanism in CA of organocuprate **74** to cyclohexenone **1**



Scheme 29 Reaction between methyl phenylpropiolate **77** and *t*BuCu(CN)Li **78**

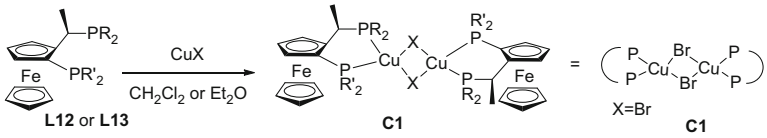


76 than with a pathway that involves a formal oxidative addition of **74** to **1** with subsequent formation of corresponding Cu(III)-species.

On the other hand, it was possible to observe vinyl copper species derived from carbocupration reactions, when an α,β-unsaturated carbonyl compound bearing an alkynyl moiety underwent addition to a Lipshutz-type organocuprate [121, 122]. Krause et al. were the first to show NMR spectroscopic evidence of such intermediates during their studies of the reaction between methyl phenylpropiolate **77** and *t*BuCu(CN)Li **78** (Scheme 29) [123].

After addition of the substrate to a pre-cooled THF solution of organocuprate **78**, new intermediate species **80** was detected (Scheme 29). For these intermediates, downfield shifts for both α-C and β-C were observed. This effect was attributed to the rehybridisation from sp to sp^2 due to the coordination of the cuprate to the triple bond. For the carbonyl carbon, a downfield shift was observed as well, consistent with it being coordinated with a lithium cation. Increasing the temperature resulted in the appearance of the signals of the starting material implying a reversible nature of the formation of the copper complex. When the temperature was raised to −70°C, new adduct **81** was formed. A downfield shift of +37.7 ppm indicated a σ-bonded copper species. Furthermore, the Z configuration of the final product **79** (Scheme 29) suggested that its precursor was obtained through a stereoselective *syn*-addition to the triple bond.

On the basis of the presented experimental and theoretical studies on the CA of organocuprates, a mechanism involving an oxidative addition-reductive elimination pathway has been postulated as the most likely one. This mechanism was also



Scheme 30 Spectroscopic evidence for the formation of dinuclear copper complexes

extended to the copper(I)-catalysed ACA of organometallics; however, relatively few supporting mechanistic studies have been reported. Moreover, there was no general agreement regarding the rate-determining step of the reaction. Noyori, Kitamura and co-workers proposed a catalytic cycle for the Cu/sulfonamide-catalysed 1,4-addition of diethylzinc to cyclohexenone. Kinetic data and $^{13}C/^{12}C$ isotope effect studies pointed to a concerted mechanism [124]. Another study by Gennari et al. on Cu(I)/Schiff base ligand-catalysed ACA of dialkylzincs revealed the oxidative addition of a Cu-complex to cyclohexenone as the rate-limiting step [125]. In contrast, Schrader et al. proposed the reductive elimination to be the rate-limiting step in Cu(I)/phosphorus ligand-catalysed CA [126].

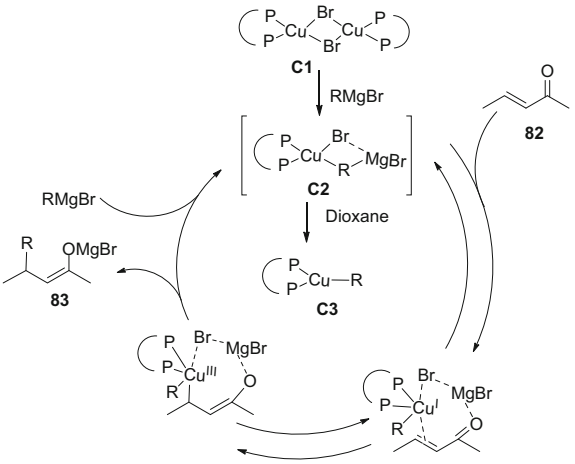
All studies related to the mechanism of the Cu(I)-catalysed ACA of organometallics postulate the transmetalation between the organometallic compounds and the copper species as the first step in the catalytic cycle, but only few studies attempted to characterise the transmetalated copper intermediates derived from the addition of organometallics.

Harutyunyan et al. investigated the formation of the chiral Cu(I)-diphosphine complexes, as part of a comprehensive mechanistic study on the Cu(I)-catalysed ACA of Grignard reagents to α,β-unsaturated carbonyl compounds [127]. Based on NMR, ESI-MS, IR, electrochemistry and X-ray crystallography measurements, they concluded that halide-bridged dinuclear copper complexes **C1** (Scheme 30) are formed and persist in the solvents typically used for the ACA (Et_2O, *t*BuOMe and CH_2Cl_2).

The copper-halide complexes are precursors to the catalytically active species generated upon addition of the Grignard reagents. To determine their structure, detailed ^{31}P- and ^{1}H-NMR spectroscopic studies were carried out at −60°C. On the basis of these experiments, it was inferred that the monomeric complex **C2**, relevant for catalysis, is formed from complex **C1** and the Grignard reagent (MeMgBr) (Scheme 31).

Kinetic results indicated that the rate of the reaction is dependent on all the reacting components and is of first order in the copper catalyst. Based on spectroscopic as well as kinetic studies, the following catalytic cycle was proposed (Scheme 31). The first step is initiated by the formation of the catalytically active monomeric complex **C2** through transmetalation of dimeric precatalyst **C1** with the Grignard reagent. The next step is the reversible formation of π-complex between **C2** and the enone (enoate), with an additional interaction of Mg with the oxygen atom of the carbonyl moiety. This step is followed by an intramolecular rearrangement of the π-complex to a σ-complex (Cu(III)-intermediate) via an

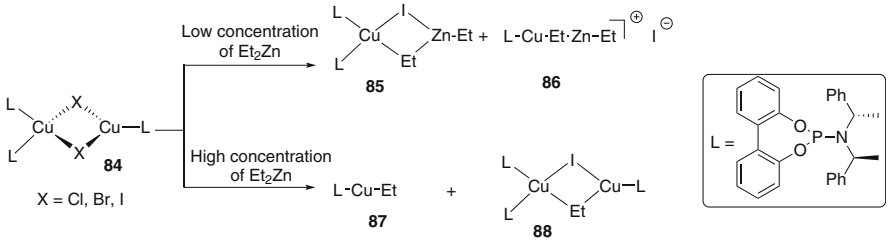
Scheme 31 Proposed catalytic cycle for copper (I)-catalysed ACA of Grignard reagents



oxidative addition to the β-carbon of the substrate. Based on the *cis–trans* isomerisation observed for enoates, it was suggested that the σ- and π-complexes are in fast equilibrium. The reductive elimination from the Cu(III)-intermediate is the last and rate-determining step, and the chiral diphosphine ligand is thought to stabilise the σ-complex by π-backbonding [128]. The dependence of the reaction rate on the Grignard reagents suggests that they are involved in the rate-limiting step. Simultaneously with the formation of the enolate product **83** via transfer of the R group from the copper to the β-carbon of the enone, the Grignard reagent acts to displace the product enolate from the Cu(III)-intermediate by adding to the latter, and thus reforming the catalytically active complex **C2** directly. Mg^{2+} and Br^- are essential for achieving high levels of stereo- and regioselectivity, since they are required for the formation of complex **C2**. The removal of the magnesium ion by addition of dioxane led to the formation of species **C3** (also formed when Me_2Mg or MeLi were used instead of MeMgBr) and a poor catalytic activity. Bromide also had to be present in the reaction, regardless of its source (coming from copper salt or Grignard reagent); otherwise, complex **C2** was not formed.

Detailed NMR studies on the nature of copper (I)/phosphine-based ligand complexes and their behaviour in transmetalation conditions have been conducted also by Gschwind et al. [129–132]. To study the transmetalation process, different organozinc reagents were tested, with Et_2Zn giving the best results [133]. Upon addition of Et_2Zn to a solution of copper complex in CD_2Cl_2, it was possible to detect an upfield shift of the peaks of the pre-catalytic complex in ^{31}P-NMR (Scheme 32).

A series of new signals, showing scalar coupling transfer between the ethyl group and the phosphorous ligand, appeared in the ^{1}H-, ^{31}P-HMBC spectrum. These signals were assigned to three monomeric transmetalated copper species and to one binuclear copper complex with mixed trigonal/tetrahedral geometry (Scheme 32). The same study also found that species **85** and **86** are formed preferentially in the presence of relatively low concentrations of organozinc



Scheme 32 Transmetalation of the pre-catalytic complex **84** with Et_2Zn

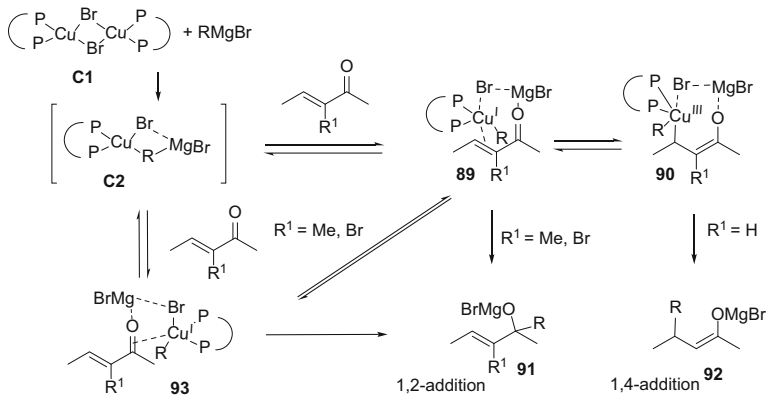
reagent, whereas complexes **87** and **88** are the most abundant species when a large amount of organozinc reagent is present in solution. Thus, considering the typical conditions in which copper-catalysed addition reactions of organometallic reagents to carbonyl compounds are carried out, one of the latter species is most probably involved in the catalytic cycle.

To summarise, all the experimental data obtained until now support a mechanism of CA in which the organocuprate (stoichiometric reagent or formed in catalytic conditions) adds to the α,β-unsaturated carbonyl compounds to first form a π-complex. Upon formal oxidative addition, the Cu(III)-intermediate is formed, followed by reductive elimination and subsequent formation of the CA product enolate. The alternative mechanism through carbocupration might become predominant only when using an acetylenic or a carbonyl substrate with specific structure and electronic properties.

5.2 Copper(I)-Catalysed 1,2-Addition

From a mechanistic point of view, the reason why some copper catalysts, similar to those used for 1,4-addition, prefer 1,2-addition is not well understood. Neither the copper(I)-catalysed 1,2-addition of Grignard reagents to enones nor the alkylations of acylsilanes, aryl alkyl and aryl heteroaryl ketones described in the previous sections can be rationalised with the existing mechanistic understanding of organocuprate chemistry involving Cu(I)/Cu(III)-intermediates. There are two necessary conditions to direct the nucleophile to the 1,2-position of an enone in the presence of Cu(I)-catalyst, namely, the need of an α-substituent in the α,β-unsaturated carbonyl compound and the s-*cis* relationship between the carbonyl moiety and the β-substituent around the double bond. As emphasised before, Cu(I)-species prefer to form a π-complex with a C=C bond, of soft character, rather than with a C=O bond, which is rather hard. This is further backed up by theoretical calculations [104].

Based on its similarity to the copper(I)-catalysed 1,4-ACA, for which the mechanistic picture is known, Harutyunyan et al. initially proposed a similar pathway for 1,2-additions of Grignard reagents to enones [10]. In particular, they

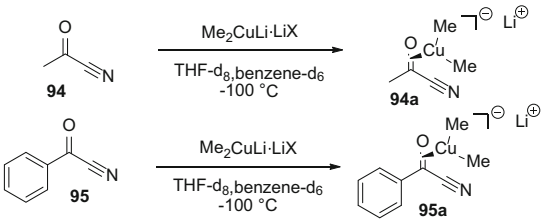


Scheme 33 Proposed mechanisms for Cu(I)-catalysed 1,2-addition of Grignard reagents

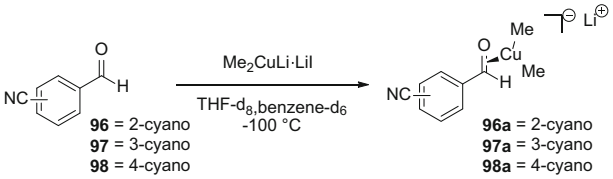
reasoned that the copper complex, upon transmetalation with the Grignard reagent, reversibly forms a π-complex **89** with the enone (Scheme 33). It was suggested that this step is followed by an oxidative addition to form σ-complex **90** and that the equilibrium constant between the π- and the σ-complex would depend on the stability of the Cu(III)-intermediate. The presence of an α-substituent in the enone might destabilise the Cu(III)-species and prevent its accumulation, thus hampering 1,4-addition and instead leading to 1,2-addition adduct **91** directly from the π-complex. Nonetheless, further research on the alkylation of aryl alkyl ketones led the authors to postulate a new mechanism, according to which the α-substituent in the enone destabilises not only the formation of σ-complex **90** but also that of the π-complex **89** with a conjugated double bond. Therefore, the transmetalated copper complex forms a new π-complex **93** directly, with the carbonyl moiety of the enone (or aryl alkyl ketone). This coordination mode provides double activation of the substrate via a pseudo-chair transition state: Lewis acid activation of the carbonyl moiety through the Mg^{2+} and activation of the carbonyl double bond by copper. The formation of the π-complex **93** is followed by an alkylation step to form the product alkoxide **91** (Scheme 33).[2]

The first experimental evidence supporting the viability of π-complex formation between organocopper species and the carbonyl moiety was serendipitously provided by Bertz and Ogle [134]. During an attempt to observe π-complex formation in the reaction between Gilman reagent and a CN triple bond with RI-NMR technique, using pyruvonitrile **94** as substrate, a new species **94a** was detected. Subjecting compound **95** (Scheme 34) to the same reaction conditions led to similar results. A two-bond coupling between the carbonyl carbon and the methyl group on the copper was found, which together with a marked upfield change in the chemical

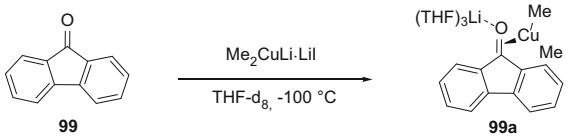
[2] Nakamura et al. predicted an intermediate similar to that of **91**, based on theoretical calculations carried out for the addition of organocuprates to acyl chlorides [104].



Scheme 34 Formation of copper-carbonyl π-complex from compounds **94** and **95**



Scheme 35 Formation of carbonyl π-complex between cyanobenzaldehyde and Gilman reagent

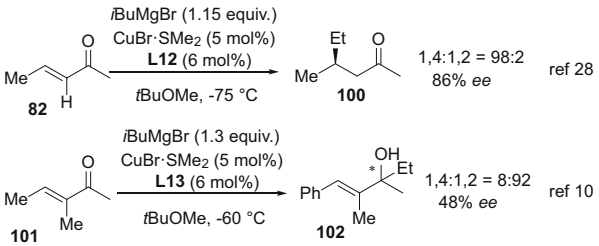


Scheme 36 Carbonyl π-complex of Gilman reagent with fluorenone **99**

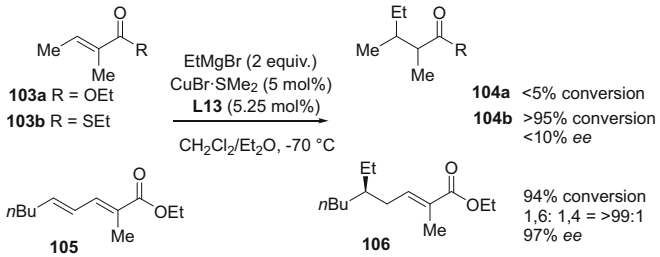
shift of the carbonyl carbon in ^{13}C-NMR supported the formation of a π-complex between the cuprate and the carbonyl moiety.

Finally, 2D NMR experiments (^{1}H-/^{13}C-HMBC) confirmed the results obtained with 1D NMR, showing a coupling between the carbonyl carbon with the methyl group bound to the copper. Subsequently, aldehydes and ketones were investigated as substrates [135], providing further information on the nature of the copper π-complex with the carbonyl moiety and corroborating the initial hypothesis proposed by Harutyunyan et al. Some representative examples of all compounds studied are shown in Scheme 35.

For all the aldehydes tested, warming up the reaction mixture resulted in the appearance of new peaks, belonging to the corresponding 1,2-addition product, simultaneously with the disappearance of the cuprate signals. When aromatic ketones and 1,3-diketones or keto-esters were tested, formation of the corresponding π-complexes was detected, albeit with on average lower conversion and stability with respect to the aldehydes. The only exceptions were acetophenone and benzophenone, for which no π-complex was detected. Fluorenone **99**, in contrast, formed a remarkably stable complex **99a** (Scheme 36) that was also characterised for the first time by X-ray diffraction [136].



Scheme 37 Cu(I)-catalysed addition of Grignard reagent to non-α-substituted-α,β-unsaturated ketone (*upper*) and α-substituted-α,β-unsaturated ketones (*lower*)

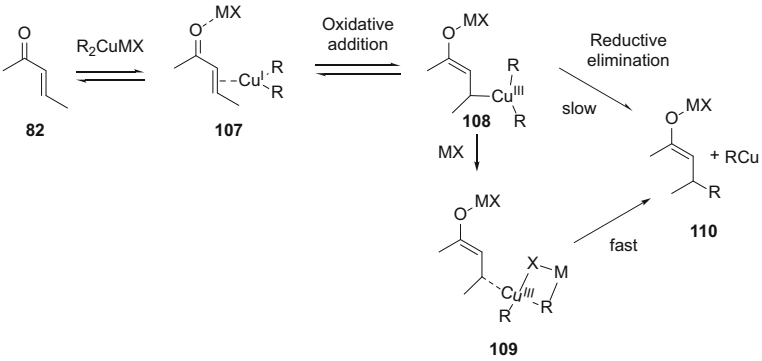


Scheme 38 Copper(I)-catalysed 1,4- and 1,6-addition of Grignard reagent to α-substituted-α,β- and α,β,γ,δ-unsaturated esters

The experimental data collected so far indicate cuprate-carbonyl π-complex as a viable intermediate in the 1,2-addition of organocuprate to carbonyl compounds. Thus, the π-complex **93** and the transition state proposed by Harutyunyan et al. for their copper-catalysed asymmetric alkylations of ketones seems to be viable as well. With respect to α-substituted α,β-unsaturated carbonyl compounds, the picture is less clear, warranting further investigations (Scheme 33). The principal problems that need to be addressed are (1) the difference in stability of the intermediates (olefin-copper π-complex and Cu(III)-species) formed either using non-α- or α-substituted α,β-unsaturated ketones and (2) the effective status of the equilibrium (if there is any) between the olefin-copper and the carbonyl-copper π-complexes formed either using non-α- or α-substituted α,β-unsaturated ketones.

Whatever the mechanism, it is clear that the presence or absence of the substituent in the α-position is crucial for the desired outcome of the reaction. Under analogous reaction conditions, the non-substituted enone **82** and α-Me enone **101** furnish the two different regioisomers, the 1,4- and 1,2-addition products respectively (Scheme 37).

Furthermore, in the 1,4-addition to ester **103a**, the α-Me substituent was deleterious and the conversion was less than 5% (Scheme 38). The more reactive thioesters **103b** allowed greater conversion, but the product **104b** was almost racemic [137]. Remarkably, if an additional unsaturation was present in the enone, as in **105**, the 1,6-addition product **106** was obtained with similar yield



Scheme 39 Lewis acid (MX) acceleration of the reductive elimination proposed by Nakamura et al.

and regioselectivity and even higher enantioselectivity than with the non-α-substituted enone (Scheme 10, upper, vide supra).

The solvent also plays a critical role in the addition reaction. The ethereal solvents work well for both 1,4- and 1,2-additions. The bulkiness of the solvent seems to have a positive effect on the outcome, as results with *t*BuOMe are better (both in terms of regio- and enantioselectivities) than with diethyl ether [10, 127]. Interestingly, THF is detrimental in both cases, giving nearly racemic products. As for non-ethereal solvents, 1,4-ACA is more tolerant, with both CH_2Cl_2 and toluene providing good results. In contrast, 1,2-addition does not tolerate CH_2Cl_2, leading in this case to extensive reduction product and low *ee* for the addition product. Calculations carried out by Nakamura showed that for CA of a cuprate, solvent coordination attenuates the Lewis acidity of the lithium atoms that are attached to the carbonyl oxygen [138]. The higher polarity of CH_2Cl_2 compared to ethereal solvents could attenuate the Lewis acidity of Mg^{2+}, making the addition difficult and therefore facilitating the reduction.

The mixture of Lewis acids introduced in recent works by Harutyunyan et al. [99, 101] further complicates an already unclear scenario. Apart from the ferrocenyl ligand, copper salt, Grignard reagent and ketone present in the reaction mixture, the two extra species to be considered are $CeCl_3$ and $BF_3 \cdot Et_2O$. The latter is known to promote the conjugate addition [139, 140]. Several hypotheses were raised to explain this phenomenon, the most obvious being the Lewis acid activation of the carbonyl moiety. Nakamura found, using computational studies, that a Lewis acid forms a complex with the Cu(III)-species and promotes its reductive elimination [100]. As said before, the same group had demonstrated before that this last step is the rate-determining one [128]. According to these authors, $BF_3 \cdot Et_2O$ intercepts the intermediate **108** and accelerates the C–C bond formation through intermediate **109** (Scheme 39). Furthermore, they suggested that the introduction of a ligand might have a positive effect. They proposed that a ligand bearing a soft donor moiety (i.e. phosphorus) would be coordinated to copper, while a hard donor atom (i.e. nitrogen) would interact with the Lewis acid. In the case of 1,2-addition

to ketones, as stated above, Lewis acids have been postulated (and used) to avoid the magnesium coordination with the carbonyl and thus prevent the reduction via β-hydride elimination. Cerium chloride is known to promote the addition by coordination to the C=O [141], and $BF_3 \cdot Et_2O$ could act analogously. Moreover, the formation of a mixed Lewis acid cannot be discarded, nor the coordination of $BF_3 \cdot Et_2O$ with the catalyst, as suggested by Nakamura [100].

In conclusion, the mechanism of the copper(I)-catalysed 1,4-ACA or the related 1,*n*-ACA additions is quite well established, thanks to the thorough studies carried out with stoichiometric organocuprates. On the other hand, there is an almost complete lack of mechanistic information for the copper(I)-catalysed alkylation of ketones using Grignard reagents. This is in accordance with the development level of these two regiodivergent reactions. Cu(I)-catalysed 1,4-ACA is a mature methodology, which has been widely studied and used, while Cu(I)-catalysed alkylation of ketones has only very recently irrupted in the catalysis arena. Therefore, it is likely that most innovation in the copper-catalysed addition to ketones and aldehydes will come from this new methodology, and it might even expand towards other related substrates, such as ketimines. Further developments and mechanistic studies should be expected to emerge in the coming years.

References

1. Tomioka K (2004) conjugate addition of organometals to activated olefinics. In: Jacobsen EN, Pfaltz A, Yamamoto H (eds) Comprehensive asymmetric catalysis, supplement 2. Springer-Verlag, Berlin, Heidelberg, p 109
2. Tomioka K, Nagaoka Y (1999) Conjugate addition of organometallic reagents. In: Jacobsen EN, Pfaltz A, Yamamoto H (eds) Comprehensive asymmetric catalysis. Springer-Verlag, Berlin, p 1105
3. Harutyunyan SR, den Hartog T, Geurts K, Minnaard AJ, Feringa BL (2008) Chem Rev 108:2824–2852
4. Alexakis A, Bäckvall JE, Krause N, Pàmies O, Diéguez M (2008) Chem Rev 108:2796–2823
5. Jerphagnon T, Pizzuti MG, Minnaard AJ, Feringa BL (2009) Chem Soc Rev 38:1039–1075
6. Komnenos T (1883) Justus Liebigs Ann Chem 218:145–167
7. Kharasch MS, Tawney PO (1941) J Am Chem Soc 63:2308–2316
8. López F, Minnaard AJ, Feringa BL (2007) Acc Chem Res 40:179–188
9. Hawner C, Alexakis A (2010) Chem Commun 46:7295–7306
10. Madduri AVR, Minnaard AJ, Harutyunyan SR (2012) Chem Commun 48:1478–1480
11. Madduri AVR, Harutyunyan SR, Minnaard AJ (2012) Angew Chem Int Ed 51:3164–3167
12. Tissot M, Li H, Alexakis A (2014) Copper-catalyzed asymmetric conjugate addition and allylic substitution of organometallic reagents to extended multiple-bond systems. In: Alexakis A, Krause N, Woodward S (eds) Copper catalyzed asymmetric synthesis. Wiley-VCH, Weinheim, pp 69–84
13. Alexakis A, Krause N, Woodward S (2014) Copper-catalyzed asymmetric conjugate addition. In: Alexakis A, Krause N, Woodward S (eds) Copper catalyzed asymmetric synthesis. Wiley-VCH, Weinheim, pp 33–68
14. Villacorta GM, Rao CP, Lippard SJ (1988) J Am Chem Soc 110:3175–3182
15. Ahn KH, Klassen RB, Lippard SJ (1990) Organometallics 9:3178–3181
16. Alexakis A, Frutos J, Mangeney P (1993) Tetrahedron Asymmetry 4:2427–2430

17. de Vries AHM, Meetsma A, Feringa BL (1996) Angew Chem Int Ed Engl 35:2374–2376
18. Feringa BL, Pineschi M, Arnold LA, Imbos R, de Vries AHM (1997) Angew Chem Int Ed Engl 36:2620–2623
19. Lambert F, Knotter DM, Janssen MD, van Klaveren M, Boersma J, van Koten G (1991) Tetrahedron Asymmetry 2:1097–1100
20. Knotter DM, Grove DM, Smeets WJJ, Spek AL, Van Koten G (1992) J Am Chem Soc 114:3400–3410
21. Zhou Q-L, Pfaltz A (1993) Tetrahedron Lett 34:7725–7728
22. Spescha M, Rihs G (1993) Helv Chim Acta 76:1219–1230
23. Kanai M, Tomioka K (1995) Tetrahedron Lett 36:4275–4278
24. Stangeland EL, Sammakia T (1997) Tetrahedron 53:16503–16510
25. Seebach D, Jaeschke G, Pichota A, Audergon L (1997) Helv Chim Acta 80:2515–2519
26. Braga AL, Silva SJN, Lüdtke DS, Drekener RL, Silveira CC, Rocha JBT, Wessjohann LA (2002) Tetrahedron Lett 43:7329–7331
27. Feringa BL, Badorrey R, Peña D, Harutyunyan SR, Minnaard AJ (2004) Proc Natl Acad Sci USA 101:5834–5838
28. López F, Harutyunyan SR, Minnaard AJ, Feringa BL (2004) Copper-catalyzed enantioselective. J Am Chem Soc 126:12784–12785
29. López F, Harutyunyan SR, Meetsma A, Minnaard AJ, Feringa BL (2005) Angew Chem Int Ed 44:2752–2756
30. Wang S-Y, Loh T-P (2009) Chem Commun 46:8694–8703
31. Des Mazery R, Pullez M, López F, Harutyunyan SR, Minnaard AJ, Feringa BL (2005) J Am Chem Soc 127:9966–9967
32. Barroso S, Castelli R, Baggelaar MP, Geerdink D, ter Horst B, Casas-Arce E, Overkleeft HS, van der Marel GA, Codée JDC, Minnaard AJ (2012) Angew Chem Int Ed 51:11774–11777
33. Geerdink D, ter Horst B, Lepore M, Mori L, Puzo G, Hirsch AKH, Gilleron M, de Libero G, Minnaard AJ (2013) Chem Sci 4:709–716
34. Barroso S, Geerdink D, ter Horst B, Casas-Arce E, Minnaard AJ (2013) Eur J Org Chem 4642–4654
35. Madduri AVR, Minnaard AJ (2010) Chem Eur J 16:11726–11731
36. Matcha K, Madduri AVR, Roy S, Ziegler S, Waldmann H, Hirsch AKH, Minnaard AJ (2012) ChemBioChem 13:2537–2548
37. Huang Y, Minnaard AJ, Feringa BL (2012) Org Biomol Chem 10:29–31
38. Rudolph A, Bos PH, Meetsma A, Minnaard AJ, Feringa BL (2011) Angew Chem Int Ed 50:5834–5838
39. den Hartog T, Rudolph A, Maciá B, Minnaard AJ, Feringa BL (2010) J Am Chem Soc 132:14349–14351
40. Teichert JF, Feringa BL (2011) Chem Commun 47:2679–2681
41. Schoonen AK, Fernández-Ibáñez MÁ, Fañanás-Mastral M, Teichert JF, Feringa BL (2013) Org Biomol Chem 12:36–41
42. Vila C, Hornillos V, Fañanás-Mastral M, Feringa BL (2013) Chem Commun 49:5933–5935
43. Mao B, Fañanás-Mastral M, Feringa BL (2013) Org Lett 15:286–289
44. Matsumoto Y, Yamada K, Tomioka K (2008) J Org Chem 73:4578–4581
45. Martin D, Kehrli S, d'Augustin M, Clavier H, Mauduit M, Alexakis A (2006) J Am Chem Soc 128:8416–8417
46. Robert T, Velder J, Schmalz H-G (2008) Angew Chem Int Ed 47:7718–7721
47. Naeemi Q, Robert T, Kranz DP, Velder J, Schmalz H-G (2011) Tetrahedron Asymmetry 22:887–892
48. Palais L, Babel L, Quintard A, Belot S, Alexakis A (2010) Org Lett 12:1988–1991
49. Kehrli S, Martin D, Rix D, Mauduit M, Alexakis A (2010) Chem Eur J 16:9890–9904
50. Krause N, Thorand S (1999) Inorganica Chim Acta 296:1–11
51. Yoshikai N, Yamashita T, Nakamura E (2006) Chem Asian J 1:322–330

52. den Hartog T, Harutyunyan SR, Font D, Minnaard AJ, Feringa BL (2008) Angew Chem Int Ed 47:398–401
53. Hénon H, Mauduit M, Alexakis A (2008) Angew Chem Int Ed 47:9122–9124
54. Tissot M, Pérez Hernández A, Müller D, Mauduit M, Alexakis A (2011) Org Lett 13:1524–1527
55. Tissot M, Poggiali D, Hénon H, Müller D, Guénée L, Mauduit M, Alexakis A (2012) Chem Eur J 18:8731–8747
56. Madduri AVR, Harutyunyan SR, Minnaard AJ (2013) Drug Discov Today Technol 10:e21–e27
57. Ameen D (2013) Snape TJ 4:893–907
58. Noyori R, Kitamura M (1991) Angew Chem Int Ed Engl 30:49–69
59. Walsh PJ (2003) Acc Chem Res 36:739–749
60. Pu L, Yu H-B (2001) Chem Rev 101:757–824
61. Luderer MR, Bailey WF, Luderer MR, Fair JD, Dancer RJ, Sommer MB (2009) Tetrahedron Asymmetry 20:981–998
62. Hatano M, Ishihara K (2008) Synthesis 2008:1647–1675
63. Shibasaki M, Kanai M (2008) Chem Rev 108:2853–2873
64. de Vries JG, Elsevier CJ (eds) (2007) Handbook of homogeneous hydrogenation. Wiley-VCH, Weinheim
65. Riant O, Hannedouche J (2007) Org Biomol Chem 5:873–888
66. Hatano M, Suzuki S, Ishihara K (2006) J Am Chem Soc 128:9998–9999
67. Hatano M, Suzuki S, Ishihara K (2010) Synlett 2010:321–324
68. Hatano M, Matsumura T, Ishihara K (2005) Org Lett 7:573–576
69. Giacomelli G, Lardicci L, Santi R (1974) J Org Chem 39:2736–2740
70. Weber B, Seebach D (1992) Angew Chem Int Ed Engl 31:84–86
71. Dosa PI, Fu GC (1998) J Am Chem Soc 120:445–446
72. Ramón DJ, Yus M (1998) Tetrahedron Lett 39:1239–1242
73. Yus M, Ramón DJ, Prieto O (2003) Tetrahedron Asymmetry 14:1103–1114
74. Li Q, Gau H-M (2011) Chirality 23:929–939
75. Zhou S, Chen C-R, Gau H-M (2010) Org Lett 12:48–51
76. Wu K-H, Zhou S, Chen C-A, Yang M-C, Chiang R-T, Chen C-R, Gau H-M (2011) Chem Commun 47:11668–11670
77. Chen C-A, Wu K-H, Gau H-M (2007) Angew Chem 119:5469–5472
78. Biradar DB, Gau H-M (2009) Org Lett 11:499–502
79. Fernández-Mateos E, Maciá B, Yus M (2014) Eur J Org Chem 6519–6526
80. Muramatsu Y, Harada T (2008) Angew Chem Int Ed 47:1088–1090
81. Li H, García C, Walsh PJ (2004) Proc Natl Acad Sci USA 101:5425–5427
82. Hatano M, Miyamoto T, Ishihara K (2007) Org Lett 9:4535–4538
83. Oisaki K, Zhao D, Kanai M, Shibasaki M (2006) J Am Chem Soc 128:7164–7165
84. Tomita D, Wada R, Kanai M, Shibasaki M (2005) J Am Chem Soc 127:4138–4139
85. Tomita D, Kanai M, Shibasaki M (2006) Chem Asian J 1:161–166
86. Moser R, Bošković ŽV, Crowe CS, Lipshutz BH (2010) J Am Chem Soc 132:7852–7853
87. Voigtritter KR, Isley NA, Moser R, Aue DH, Lipshutz BH (2012) Tetrahedron 68:3410–3416
88. Oost R, Rong J, Minnaard AJ, Harutyunyan SR (2014) Catal Sci Technol 4:1997–2005
89. Wu Z, Harutyunyan SR, Minnaard AJ (2014) Chem Eur J 20:14250–14255
90. Germain N, Guénée L, Mauduit M, Alexakis A (2014) Org Lett 16:118–121
91. Calvo BC, Madduri AVR, Harutyunyan SR, Minnaard AJ (2014) Adv Synth Catal 356:2061–2069
92. Madduri AVR, Minnaard AJ, Harutyunyan SR (2012) Org Biomol Chem 10:2878–2884
93. Wu Z, Madduri AVR, Harutyunyan SR, Minnaard AJ (2014) Eur J Org Chem 575–582
94. Mortensen M, Husmann R, Veri E, Bolm C (2009) Chem Soc Rev 38:1002–1010
95. Franz AK, Wilson SO (2013) J Med Chem 56:388–405
96. Bains W, Tacke R (2003) Curr Opin Drug Discov Devel 6:526–543

97. Gately S, West R (2007) Drug Dev Res 68:156–163
98. Smirnov P, Mathew J, Nijs A, Katan E, Karni M, Bolm C, Apeloig Y, Marek I (2013) Angew Chem Int Ed 52:13717–13721
99. Rong J, Oost R, Desmarchelier A, Minnaard AJ, Harutyunyan SR (2015) Angew Chem Int Ed 54:3038–3042
100. Nakamura E, Yamanaka M, Mori S (2000) J Am Chem Soc 122:1826–1827
101. Ortiz P, del Hoyo AM, Harutyunyan SR (2014) Eur J Org Chem 72–76
102. Fernández-Ibáñez MÁ, Maciá B, Minnaard AJ, Feringa BL (2008) Chem Commun 2571–2573
103. Nakakita T, Miura M, Toriyama M, Motohashi S, Barybin MV (2014) Tetrahedron Lett 55:1090–1092
104. Yoshikai N, Nakamura E (2012) Chem Rev 112:2339–2372
105. Woodward S (2000) Chem Soc Rev 29:393–401
106. Alexakis A, Benhaim C, Rosset S, Humam M (2002) J Am Chem Soc 124:5262–5263
107. Arnold LA, Imbos R, Mandoli A, de Vries AHM, Naasz R, Feringa BL (2000) Tetrahedron 56:2865–2878
108. Berlan J, Besace Y (1986) Tetrahedron 42:4767–4776
109. Hallnemo G, Olsson T, Ullenius C (1985) J Organomet Chem 282:133–144
110. Christenson B, Olsson T, Ullenius C (1989) Tetrahedron 45:523–534
111. Bertz SH, Cope SK, Hardin RA, Murphy MD, Ogle CA, Smith DT, Thomas AA, Whaley TN (2012) Organometallics 31:7827–7838
112. House HO (1976) Acc Chem Res 9:59–67
113. Bertz SH, Cope S, Murphy M, Ogle CA, Taylor BJ (2007) J Am Chem Soc 129:7208–7209
114. Snyder JP (1995) J Am Chem Soc 117:11025–11026
115. Hu H, Snyder JP (2007) J Am Chem Soc 129:7210–7211
116. Gärtner T, Henze W, Gschwind RM (2007) J Am Chem Soc 129:11362–11363
117. Bartholomew ER, Bertz SH, Cope S, Murphy M, Ogle CA (2008) J Am Chem Soc 130:11244–11245
118. Bertz SH, Murphy MD, Ogle CA, Thomas AA (2010) Chem Commun 46:1255–1256
119. Bartholomew ER, Bertz SH, Cope SK, Murphy MD, Ogle CA, Thomas AA (2010) Chem Commun 46:1253–1254
120. Ryu I, Nakahira H, Ikebe M, Sonoda N, Yamato S, Komatsu M (2000) J Am Chem Soc 122:1219–1220
121. Lipshutz BH, Wilhelm RS, Floyd DM (1981) J Am Chem Soc 103:7672–7674
122. Lipshutz BH, Sharma S, Ellsworth EL (1990) J Am Chem Soc 112:4032–4034
123. Nilsson K, Ullenius C, Krause N (1996) J Am Chem Soc 118:4194–4195
124. Kitamura M, Miki T, Nakano K, Noyori R (2000) Bull Chem Soc Jpn 73:999–1014
125. Gallo E, Ragaini F, Bilello L, Cenini S, Gennari C, Piarulli U (2004) J Organomet Chem 689:2169–2176
126. Pfretzschner T, Kleemann L, Janza B, Harms K, Schrader T (2004) Chem Eur J 10:6048–6057
127. Harutyunyan SR, López F, Browne WR, Correa A, Peña D, Badorrey R, Meetsma A, Minnaard AJ, Feringa BL (2006) J Am Chem Soc 128:9103–9118
128. Mori S, Nakamura E (1999) Chem Eur J 5:1534–1543
129. Zhang H, Gschwind RM (2006) Angew Chem Int Ed 45:6391–6394
130. Zhang H, Gschwind RM (2007) Chem Eur J 13:6691–6700
131. Schober K, Zhang H, Gschwind RM (2008) J Am Chem Soc 130:12310–12317
132. Gschwind RM (2008) Chem Rev 108:3029–3053
133. von Rekowski F, Koch C, Gschwind RM (2014) J Am Chem Soc 136:11389–11395
134. Bertz SH, Hardin RA, Murphy MD, Ogle CA (2013) Chem Commun 49:3010–3012
135. Bertz SH, Hardin RA, Ogle CA (2013) J Am Chem Soc 135:9656–9658
136. Bertz SH, Hardin RA, Heavey TJ, Ogle CA (2013) Angew Chem Int Ed 52:10250–10252

137. den Hartog T, Huang Y, Fañanás-Mastral M, Meuwese A, Rudolph A, Pérez M, Minnaard AJ, Feringa BL (2015) ACS Catal 5:560–574
138. Yamanaka M, Nakamura E (2001) Organometallics 20:5675–5681
139. Yamamoto Y, Maruyama K (1978) J Am Chem Soc 100:3240–3241
140. Yamamoto Y, Yamamoto S, Yatagai H, Ishihara Y, Maruyama K (1982) J Org Chem 47:119–126
141. Imamoto T, Takiyama N, Nakamura K, Hatajima T, Kamiya Y (1989) J Am Chem Soc 111:4392–4398

Top Organomet Chem (2016) 58: 135–168
DOI: 10.1007/3418_2015_156

Published online: 18 October 2015

Asymmetric Addition of Boron and Silicon Nucleophiles

Alexander Hensel and Martin Oestreich

Abstract The recent progress in catalytic asymmetric carbon–boron and carbon–silicon bond formation catalyzed by chiral copper(I) complexes is tremendous. Within less than a decade, the majority of fundamental bond-forming reactions in this arena, that is, conjugate addition, 1,2-addition and allylic substitution, were accomplished. These enantioselective transformations had been either elusive or not even known before. This chapter summarizes these fascinating developments together with a brief mechanistic discussion as these copper(I) catalyses share transmetalation of interelement bonds such as B–B and Si–B as a common feature.

Keywords Asymmetric catalysis · Borylation · Copper · σ-bond metathesis · Silylation · Transmetalation

Contents

1 Introduction 136
2 Conjugate Addition 137
2.1 1,4-Addition of Boron Nucleophiles to α,β-Unsaturated Acceptors 137
2.2 1,4-Addition of Silicon Nucleophiles to α,β-Unsaturated Acceptors 142
2.3 1,6-Addition of Boron Nucleophiles to α,β,γ,δ-Unsaturated Acceptors 145
2.4 1,6-Addition of Silicon Nucleophiles to α,β,γ,δ-Unsaturated Acceptors 145
3 1,2-Addition 147
3.1 1,2-Addition of Boron Nucleophiles to Carbonyls and Carbonyl-Derived Acceptors 147
3.2 1,2-Addition of Silicon Nucleophiles to Carbonyls or Carbonyl-Derived Acceptors 148
4 Allylic Substitution 151
4.1 Allylic Substitution with Boron Nucleophiles and Competing Cyclopropane Formation 151

A. Hensel and M. Oestreich (✉)
Institut für Chemie, Technische Universität Berlin, Straße des 17. Juni 115, 10623 Berlin, Germany
e-mail: martin.oestreich@tu-berlin.de

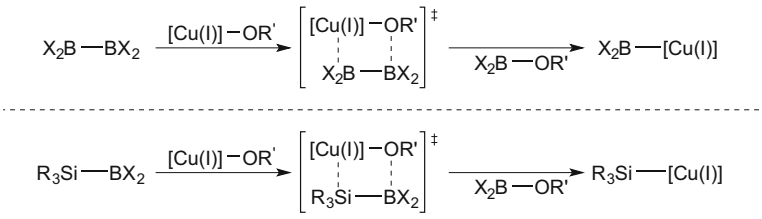
4.2 Allylic Substitution with Silicon Nucleophiles 155
4.3 Direct Enantioconvergent Transformation of Racemic Allylic Acceptors 157
5 Addition Across 1,3-Dienes 158
6 Domino Reactions 159
7 Synthesis of 1,1-Diboron Compounds 163
8 Desymmetrization of Prochiral Compounds
by Copper(I)-Catalyzed Borylation or Silylation Reactions 163
References 165

1 Introduction

Hydrocarbons containing main-group elements such as boron, silicon, and tin are ubiquitous building blocks for the synthesis of complex molecules. Transition-metal-catalyzed cross-coupling reactions of carbon–main-group element linkages as well as their transformation into more valuable functional groups are powerful tools of modern synthetic chemistry.

Often-used main-group elements are boron and silicon. An efficient way of incorporating these elements into carbon skeletons is the activation of boron–boron and silicon–boron bonds, respectively, to release main-group element nucleophiles [1–5]. The activation mechanism is believed to be the same for both pronucleophiles. Transmetalation of a boron–boron and, likewise, silicon–boron bond through σ-bond metathesis across a copper(I)–oxygen bond forms either a boron or silicon nucleophile coordinated to copper(I) (Scheme 1) [6]. Established catalysts are phosphine–copper(I) and *N*-heterocyclic carbene–copper(I) [NHC–copper(I)] complexes, usually generated in situ by combination of a copper(I) salt, a base (usually an alkoxide), and the phosphine ligand or the NHC precursor (typically an azolium salt). Chiral ligands of this type open the door to asymmetric catalysis.

This transmetalation approach together with the use of chiral ligands has made possible several fundamental enantioselective carbon–boron and carbon–silicon bond-forming reactions. The present chapter begins with asymmetric copper(I)-catalyzed conjugate additions of nucleophilic boron [7], featuring a summary of known phosphine–copper(I) and NHC–copper(I) catalysts that were successfully applied to this transformation. The related conjugate addition of silicon nucleophiles is subsequently discussed [8]. Then, regioselective 1,6-additions of these main-group elements to α,β,γ,δ-unsaturated carbonyls are presented.



Scheme 1 Activation of interelement linkages by transmetalation through σ-bond metathesis of copper(I)–oxygen complexes

The 1,2-addition of nucleophilic boron and silicon to C = O and C = N acceptors is summarized in subsequent sections.

The direct access to α-chiral allylic boronates and silanes [9] from linear precursors by copper(I)-catalyzed asymmetric allylic displacement with boron and silicon nucleophiles is another major focus of this chapter. A separate section is devoted to direct enantioconvergent transformations of racemic allylic acceptors.

The chapter closes with the application of several of these asymmetric carbon–main-group element bond formations to domino as well as desymmetrization reactions [10, 11].

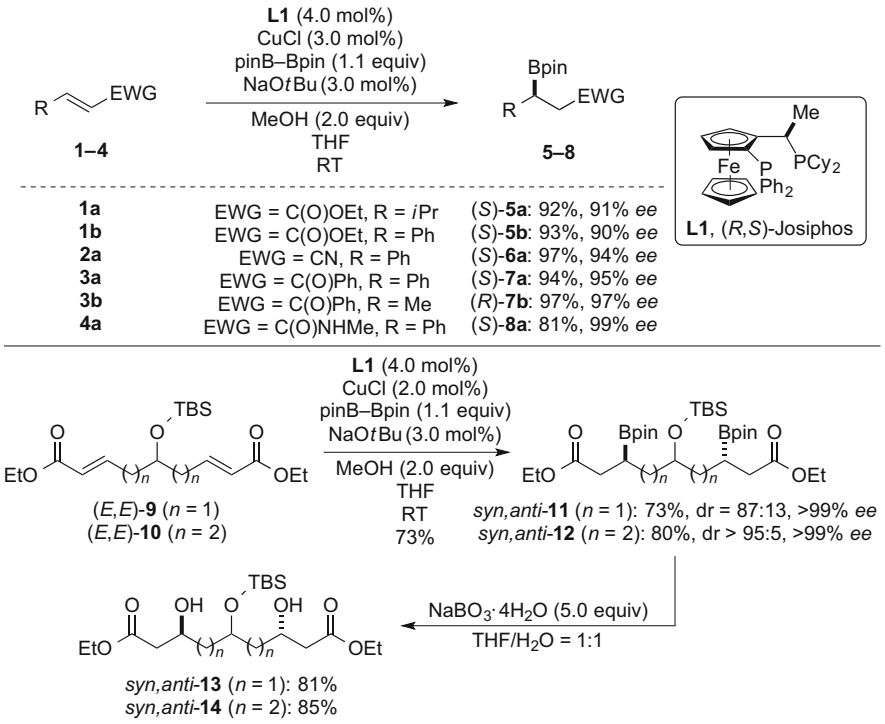
2 Conjugate Addition

2.1 1,4-Addition of Boron Nucleophiles to α,β-Unsaturated Acceptors

Yun and co-workers showed that (*R*,*S*)-Josiphos (**L1**, Scheme 2, upper) is an excellent chiral ligand in copper(I) catalysis for the activation of bis(pinacolato) diboron (pinB–Bpin) to release a boron nucleophile that adds enantioselectively to various α,β-unsaturated esters and nitriles [12]. With **L1**, CuCl, and NaO*t*Bu as the catalyst system and MeOH as an essential additive, simple β-alkyl- and β-aryl-substituted esters yielded the β-borylated compounds with high levels of enantioselectivity [(*S*)-**5a** and (*S*)-**5b**)]. However, *ortho* or *meta* substitution of the aryl ring was detrimental to enantioinduction (not shown), and the enantioselectivity collapsed when using heteroaromatic compounds as starting materials (not shown). The ester group did not influence the enantioselectivity: Enantiomeric excesses comparable to those found for ethyl esters **1a** and **1b** were obtained with the methyl ester (89% *ee*) or the bulkier *tert*-butyl ester (89% *ee*) of cinnamic acid (not shown). Nitriles, e.g., **2a**, were generally superior to esters in terms of enantioselectivity regardless of the substitution pattern on the aromatic ring. By changing the ratio between **L1**, CuCl, and NaO*t*Bu, the same group accomplished the β-borylation of α,β-unsaturated ketones [(*S*)-**7a** and (*R*)-**7b**] [13] and amides [(*S*)-**8a**] [14].

The protocol developed by the Yun group was later used in the two-directional desymmetrization of prochiral bis(α,β-unsaturated) acceptors by Hartmann and Oestreich (Scheme 2, lower) [15]. The reaction of prochiral acceptors (*E*,*E*)-**9** and (*E*,*E*)-**10** in the presence of (*R*,*S*)-Josiphos furnished diborylated *syn*,*anti*-**11** and *syn*,*anti*-**12** with perfect enantiocontrol (>99% *ee* for both) but moderate diastereoselectivity in one case (dr = 87:13 and dr > 95:5). Straightforward oxidative degradation of the carbon–boron bonds yielded the stereodefined 1,3,5,- and 1,4,7-triols *syn*,*anti*-**13** and *syn*,*anti*-**14**.

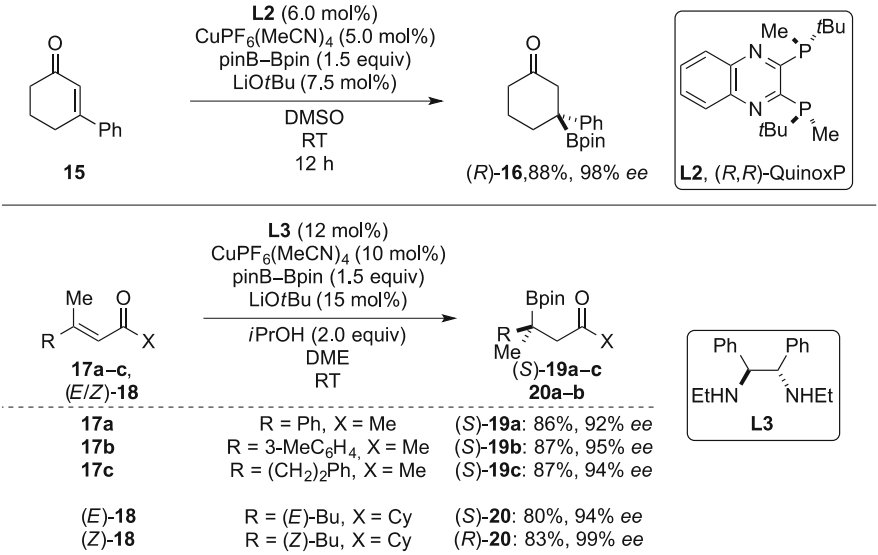
While the boryl transfer onto cyclic substrates was accomplished by a change of ligand (Taniaphos) with the established setup (not shown) [16], γ,γ-disubstituted



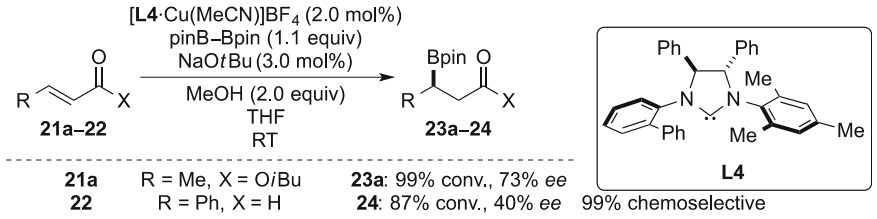
Scheme 2 Copper(I)-catalyzed enantioselective conjugate addition of boron nucleophiles to different α,β-unsaturated acceptors by Yun (*upper*) and its application to the two-directional desymmetrization of prochiral bis(α,β-unsaturated) acceptors by Oestreich (*lower*)

acceptors with a neopentylic β-carbon atom as well as β,β-disubstituted systems failed to react with these copper(I)–ligand combinations.

Shibasaki and co-workers used (*R*,*R*)-QuinoxP as ligand (**L2**, Scheme 3, upper) to promote the enantioselective conjugate addition of nucleophilic boron to β-substituted cyclic alkenes such as cyclohexenone **15**, thereby constructing boron-substituted quaternary carbon atoms [(*R*)-**16**, 98% *ee*] [17]. The in situ formation of $LiPF_6$, generated from $CuPF_6$ and Li*O*t*Bu, is believed to increase the electrophilicity of **15** by acting as a *Lewis* acid; this avoids at the same time a protic additive. It was the same group that presented a simple diphenylethylenediamine ligand for the enantioselective borylation of acyclic β-methyl-substituted, α,β-unsaturated ketones with additional substitution in the β-position (**L3**, Scheme 3, lower) [18]. In this case, the use of a protic additive (*i*PrOH) is crucial for achieving high yields. Both β-aryl- and β-alkyl-substituted enones (**17a–c** and **18**), including challenging β,β-dialkyl-substituted enones (**17c** and **18**), afforded the corresponding adducts in high yields and with excellent enantioselectivities [(*S*)-**19a–c** and **20**]. Adducts derived from different alkene diastereomers [(*E*)-**18** versus (*Z*)-**18**] showed comparable yields and levels of enantioselectivity but with opposite absolute configuration [(*E*)-**18** → (*S*)-**20** versus (*Z*)-**18a** → (*R*)-**20**].



Scheme 3 Borylation of trisubstituted cyclic and acyclic electron-deficient alkenes by Shibasaki

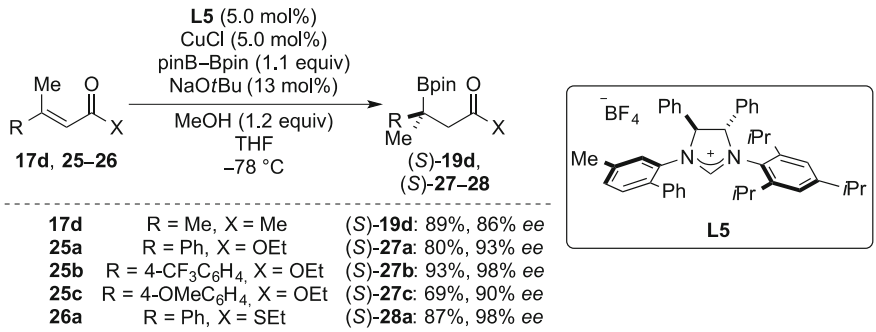


Scheme 4 Chemoselective NHC–copper(I)-catalyzed conjugate addition of boron nucleophiles to esters and aldehydes by Fernández

In addition to phosphorus- and nitrogen-containing ligands, the group of Fernández introduced chiral *N*-heterocyclic carbenes (NHCs) to the field of asymmetric conjugate borylation reactions (Scheme 4) [19]. Aside from α,β-unsaturated esters (e.g., **21**), this catalyst converts challenging α,β-unsaturated aldehydes (e.g., **22**) chemoselectively into the corresponding β-borylated adducts (1,4- versus 1,2-addition); the levels of enantioinduction are moderate though (73% *ee* for **21** → **23** and 40% *ee* for **22** → **24**). In fact, the reaction outcome was highly dependent on the ester moiety (*i*Bu: 73% *ee* versus Me: 48% *ee*, not shown).[1,2]

[1] For an analysis of the stereochemical outcome using phosphine-type ligands, see [20].

[2] For related relevant work, see: α,β-unsaturated ketimines/NHC–copper(I) catalysts [21], α,β-unsaturated imines/phosphoramidite–copper(I) catalyst [22], in situ-formed α,β-unsaturated aldimines/phosphine–copper(I) catalysts [23], and α,β-unsaturated esters/NHC–copper(I) catalysts [24, 25].



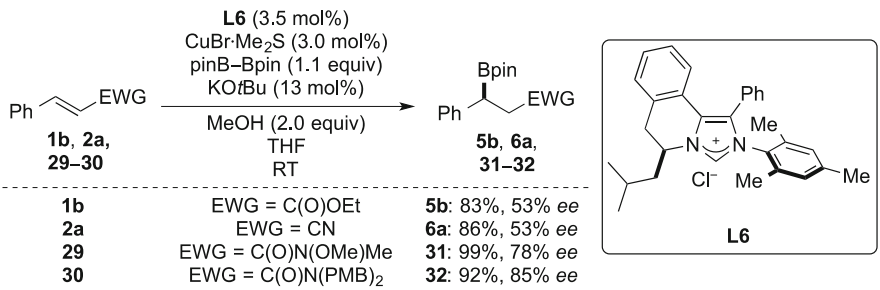
Scheme 5 NHC–copper(I)-catalyzed 1,4-addition of nucleophilic boron to various β,β-disubstituted acyclic α,β-unsaturated acceptors by Hoveyda

Parallel to the work of Shibasaki on phosphine–copper(I) complexes, the group of Hoveyda used an NHC ligand motif for the conjugate addition of boron nucleophiles to β,β-disubstituted acceptors (Scheme 5) [26]. In terms of stereocontrol, C_1-symmetric imidazolium salts (e.g., **L5**) are generally more effective than their C_2-symmetric analogs (not shown). This is also in accordance with observations made by Fernández and co-workers [19]. Additionally, structural modification of C_1-symmetric NHCs is easier than that of symmetric derivatives. The in situ-generated NHC–copper(I) complex of **L5** and CuCl transformed acyclic α,β-unsaturated carbonyls into β-borylated adducts in high yields and with good levels of enantioselection (Scheme 5). While enantiomeric excesses were high for β-aryl-substituted α,β-unsaturated esters [**25a–b** → (*S*)-**27a–b**] {**25c** was less reactive but the enantiomeric excess was still good [**25c** → (*S*)-**27c**]}, enone-derived adducts were generally isolated with moderate enantioselectivity [e.g., **17d** → (*S*)-**19d**]. Thioesters underwent the conjugate addition with excellent enantioselectivity [**26a** → (*S*)-**28a**]. Not only aromatic but also alkyl substituents in β-position were tolerated albeit yielding lower enantiocontrol (not shown).[3]

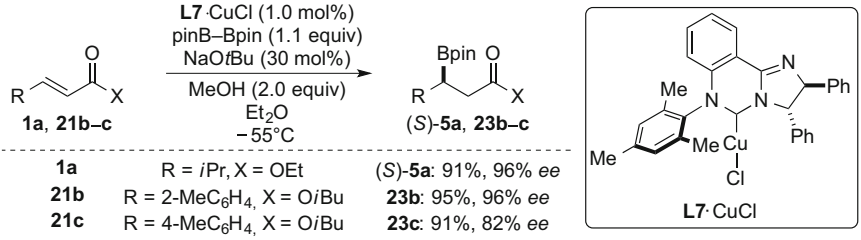
Hong and co-workers tested imidazolium salt **L6** as an NHC precursor in the copper(I)-catalyzed conjugate borylation of various activated alkenes (Scheme 6) [28]. Esters and nitriles were no suitable substrate classes for this system, giving just moderate enantiomeric excesses (**1b** → **5b**, **2a** → **6a**), whereas enantioselectivities of amide-derived borylated adducts were improved compared to the work of Yun [14]. Enantiocontrol was good for the synthetically useful β-borylated Weinreb amide **31** and even better for *N*,*N*-dialkylated amide **32**. Changing the double bond geometry from *E* to *Z* led to decreased yield and selectivity (95%, 86% *ee* for *E* versus 80%, 66% *ee* for *Z*, not shown).

McQuade and co-workers introduced a preformed 6-membered NHC–copper(I) complex **L7**·CuCl and demonstrated its potential in 1,4-addition of boron nucleophiles to typical α,β-unsaturated ester moieties (Scheme 7) [29]. The catalyst is

[3] For the 1,4-addition to α,β-unsaturated sulfones, see [27].



Scheme 6 NHC–copper(I)-catalyzed borylation of α,β-unsaturated amides by Hong

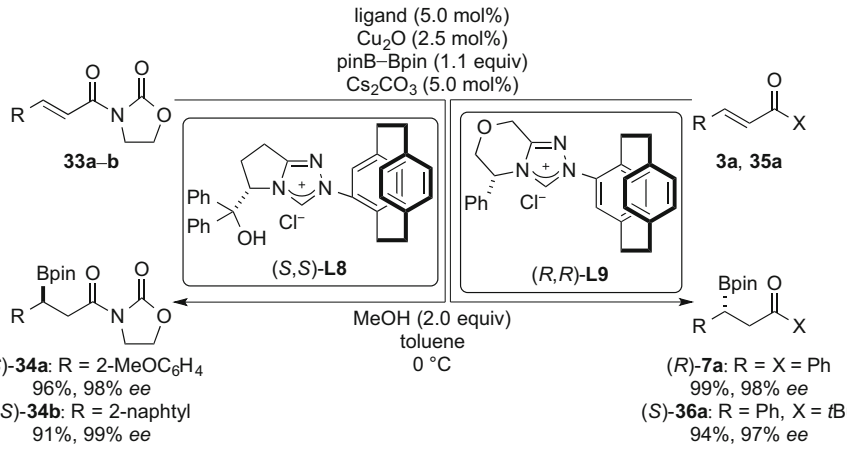


Scheme 7 Conjugate borylation catalyzed by a chiral preformed 6-membered NHC–copper(I) complex introduced by McQuade

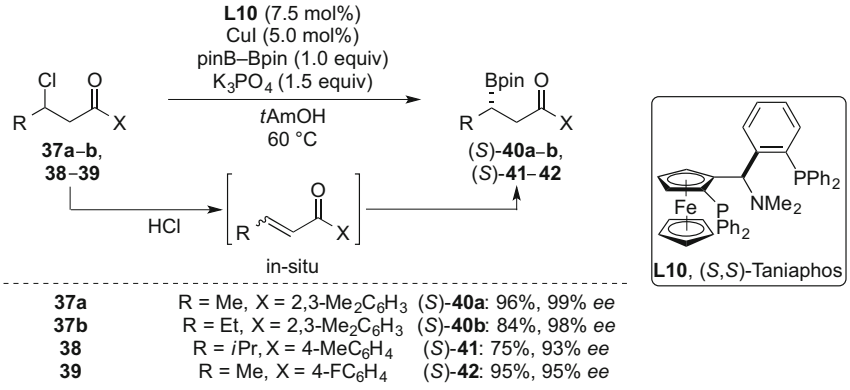
bench-stable and showed good reactivity, even at catalyst loadings as low as 0.01 mol%. The ester group attached to the alkene had little influence on the stereochemical outcome, and alkyl- [e.g., **1a** → (*S*)-**5a**] as well as aryl-substituted (e.g., **21b–c** → **23b–c**) carboxyls underwent the 1,4-addition with high levels of enantiocontrol.

The group of Song took advantage of planar and central chirality in the bicyclic triazolium precursor **L8** derived from [2.2]paracyclophane. The catalyst generated from **L8** provided β-borylated *N*-acyloxazolidinones in exceptionally high enantioselectivities [**33a–b** → (*S*)-**34a–b**, Scheme 8, left] [30]. The tunability of the triazolium backbone allowed for broad variation of this ligand motif. The same group synthesized triazolium salt **L9** and applied it to β-borylation of α,β-unsaturated ketones (Scheme 8, right) [31]. Various enones were transformed into the corresponding β-borylated adducts in excellent yields and with superb enantiomeric excesses [cf. **3a** → (*R*)-**7a**]. Also, sterically hindered *tert*-butyl ketone (*S*)-**36a** was obtained with 97% *ee*.

In 2015, the group of Yu combined the in situ generation of α,β-unsaturated acceptors [32] with the established protocol for the asymmetric conjugate borylation introduced by Yun and co-workers (Scheme 9) [13]. Base-mediated (K_3PO_4) β-elimination of HCl releases enones that are directly transformed into the desired β-borylated ketones using CuI and (*S*,*S*)-Taniaphos **L10**. Representative aryl ketones yielded the corresponding boronates with excellent enantiomeric excesses, regardless of the length and branching of the alkyl chain in the



Scheme 8 Synthesis of β-borylated N-acyloxazolidinones and ketones with paracyclophane-derived NHC–copper(I) catalysts introduced by Song

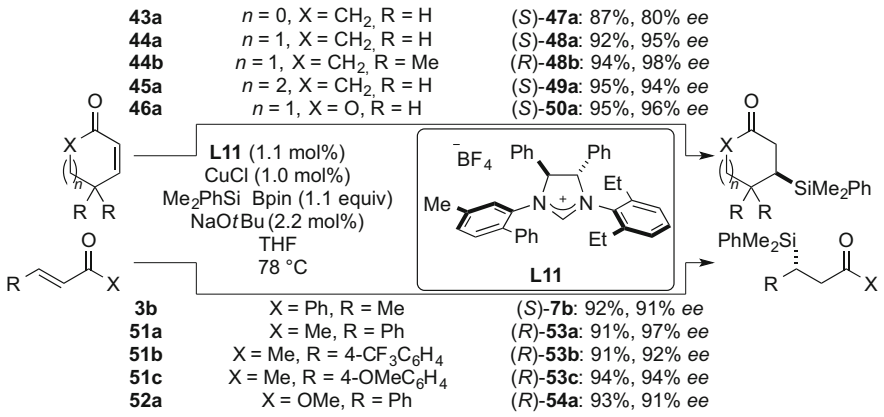


Scheme 9 Borylation of in situ-generated α,β-unsaturated acceptors by Yu

β-position [(*S*)-**40a**, 96%, 99% *ee* for R = Me versus (*S*)-**40b**, 84%, 98% *ee* for R = Et versus (*S*)-**41**, 75%, 93% *ee* for R = *i*Pr] or the substituent on the aryl X group at the carbonyl carbon atom [(*S*)-**41**, 75%, 93% *ee* for 4-Me in X versus 4-F: (*S*)-**41**, 95%, 95% *ee* for 4-F in X].

2.2 *1,4-Addition of Silicon Nucleophiles to α,β-Unsaturated Acceptors*

Lee and Hoveyda used the activation of the interelement linkage in Me_2PhSi–Bpin [33, 34] by chiral NHC–copper(I) complexes to accomplish the enantioselective

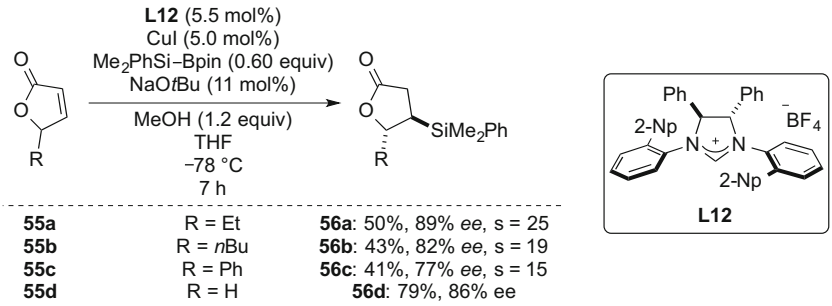


Scheme 10 Copper(I)-catalyzed enantioselective silylation of cyclic and acyclic ketones and esters by Hoveyda

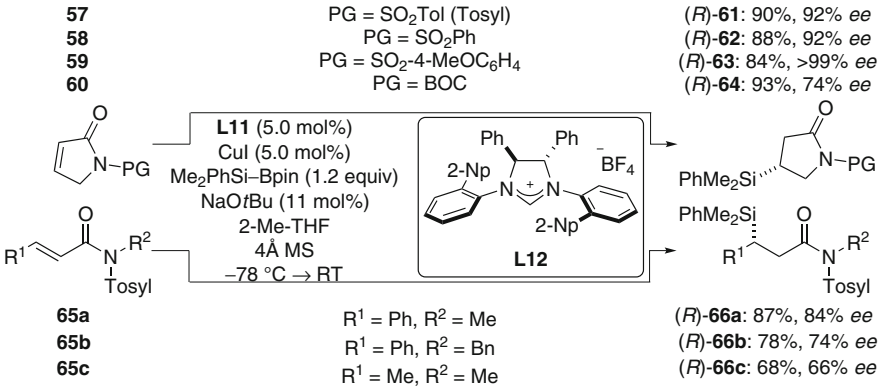
conjugate addition of silicon nucleophiles to α,β-unsaturated carbonyls and carboxyls (Scheme 10) [35]. Kleeberg clarified its mechanism by a combined spectroscopic and crystallographic analysis [36]. The active catalyst, formed in situ from CuCl, NaO*t*Bu, and C_1-symmetric chiral imidazolium salt **L11**, generates a silicon nucleophile that without any difficulty adds to representative 5-, 6-, and 7-membered cyclic enones [**43a** → (*S*)-**47a**, **44a** → (*S*)-**48a**, **44b** → (*R*)-**48b**, **45a** → (*S*)-**49a**] or a δ-lactone [**46a** → (*S*)-**50a**]. Chemical yields and enantioselectivities are generally good. Even a sterically congested δ,δ-disubstituted acceptor underwent the 1,4-addition with high enantioselectivity [**44b** → (*R*)-**48b**]. With the same catalytic system, acyclic α,β-unsaturated carbonyls [**3b** → (*S*)-**7b** and **51a–c** → (*R*)-**53a–c**] as well as carboxyls [**52a** → (*R*)-**54a**] were converted into the β-silylated adducts in high yields and with superb enantioselectivities. The electronic nature of the aryl group in β-position had no measurable influence on the selectivities. As in NHC–copper(I)-catalyzed conjugate borylation reactions, C_1-symmetric NHCs outcompeted cognate C_2-symmetric derivatives in terms of enantioselectivity.

Procter and co-workers employed chiral C_2-symmetric NHC-precursor **L12** [37] for asymmetric carbon–silicon bond formation, also applying it to kinetic resolution (Scheme 11) [38]. Conjugate silyl transfer onto 5-substituted butenolides **55a–c** furnished the corresponding enantiomerically enriched *anti*-4,5-disubstituted lactones **56a–c** in acceptable yields. Furthermore, the scope of this 1,4-addition was extended to lactones of different ring sizes (not shown). It is worthy of note that the parent lactone that had failed to react with Hoveyda's setup was obtained with good enantiomeric excess (**55d** → **56d**).

The same group accomplished the enantioselective silyl transfer to α,β-unsaturated lactams and acyclic amides with the same chiral NHC–copper(I) catalyst that is formed from **L12** (Scheme 12, upper) [39]. γ-Butyrolactams having



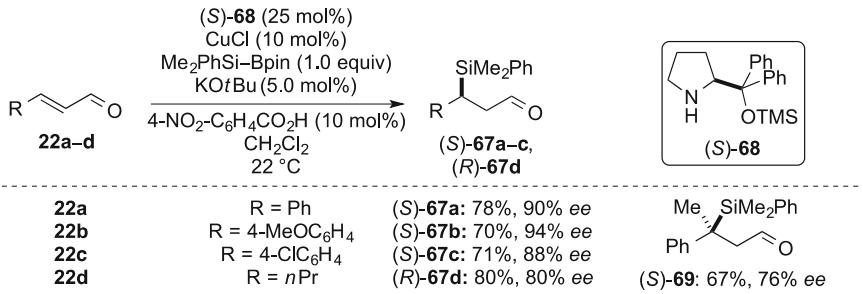
Scheme 11 Kinetic resolution of 5-substituted butenolides by conjugate silylation by Procter



Scheme 12 Enantioselective silyl transfer onto α,β-unsaturated lactams and acyclic amides by Procter

different arylsulfonyl groups attached to the nitrogen atom were efficiently converted into the corresponding β-silylated adducts [**57**–**60** → (*R*)-**61**–**64**]. Less activating substituents such as the *tert*-butyloxycarbonyl protecting group (**60**, BOC) decreased the level of enantioselection. Larger rings were also detrimental (not shown). The identical setup was applied to linear *N*-tosyl-protected α,β-unsaturated amides to afford aryl- and alkyl-substituted β-silyl amides with moderate enantioselectivity [**65a**–**c** → (*R*)-**66a**–**c**, Scheme 12, lower].

A sophisticated chemoselective 1,4-addition of silicon nucleophiles to α,β-unsaturated aldehydes (1,2- versus 1,4-addition) was disclosed by the groups of Ibrahem and Córdova, merging copper(I)-catalyzed silicon–boron bond activation with iminium ion catalysis (Scheme 13) [40]. Proline derivative (*S*)-**68** induced good to high levels of enantiocontrol in reactions of enals with either aromatic [**22a**–**c** → (*S*)-**67a**–**c**] or aliphatic substituents [**22d** → (*R*)-**67d**] in the β-position. The chemoselectivity was excellent throughout. Moreover, β,β-disubstituted substrates were also converted chemoselectively with acceptable 76% *ee* [(*S*)-**69**].



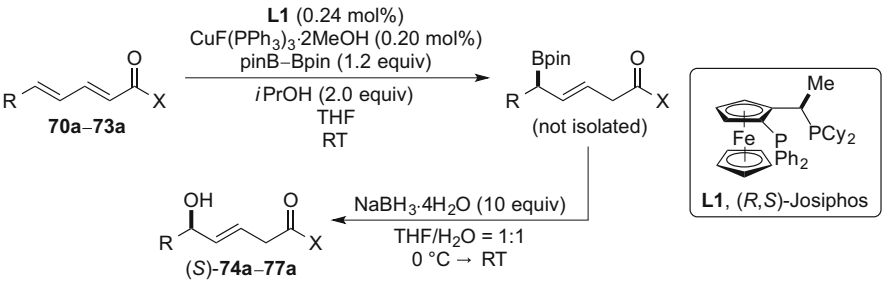
Scheme 13 Merging achiral copper(I) and chiral amine catalysts for the chemo- and enantioselective 1,4-addition to α,β-unsaturated aldehydes by Ibrahem and Córdova

2.3 *1,6-Addition of Boron Nucleophiles to α,β,γ,δ-Unsaturated Acceptors*

Lam and co-workers extended the established copper(I)-catalyzed 1,4-addition of boron nucleophiles to α,β,γ,δ-unsaturated carbonyls and carboxyls (Scheme 14) [41]. This is a noteworthy accomplishment since the 1,6-addition was seen exclusively without the requirement for a substituent in the β-position to block the attack of the nucleophile (1,4- versus 1,6-addition). Again, the Josiphos ligand **L1** was used together with a copper(I) salt to incorporate the Bpin group into various unsaturated acceptors **70a**–**73a** in an asymmetric fashion. Allylic alcohols were isolated with excellent enantioselectivities after standard oxidation with $NaBO_3 \cdot 4H_2O$ [**70a**–**73a** → (*S*)-**74a**–**77a**]. The level of enantioinduction was generally high for carboxyl compounds [**70a**–**71a** → (*S*)-**74a**–**75a**] as well as aryl- [**72a** → (*S*)-**76a**] and alkyl-substituted [**73a** → (*S*)-**77a**] carbonyl compounds. The use of the latter led to decreased yields, while enantiomeric excesses remained high. However, a cyclopropyl group in the δ-position led to predominant formation of the 1,4-adduct (not shown).

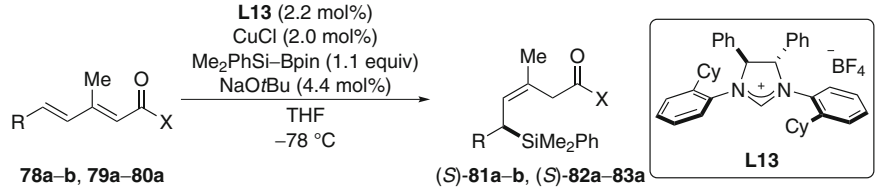
2.4 *1,6-Addition of Silicon Nucleophiles to α,β,γ,δ-Unsaturated Acceptors*

Using C_2-symmetric NHC analogs **L13** and **L14** (Scheme 15) allowed Hoveyda and co-workers to perform the chemoselective silyl transfer onto α,β,γ,δ-unsaturated carbonyl and carboxyl compounds [42]. Linear unsaturated ketones **78a**–**b**, ester **79a**, and thioester **80a** were transformed into the corresponding allylic silanes [**78a**–**b** → (*S*)-**81a**–**b**, **79a** → (*S*)-**82a**, and **80a** → (*S*)-**83a**, Scheme 15, upper). With **L13** as ligand, the δ-addition proceeded with high *Z*-selectivity and

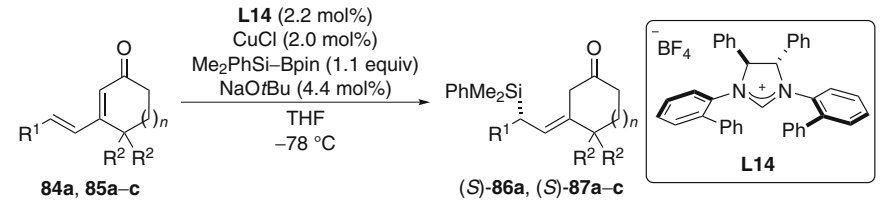


70a	R = Me, X = OBn	(*S*)-**74a**: 91%, 95% *ee*
71a	R = TBDPSO, X = OEt	(*S*)-**75a**: 75%, 95% *ee*
72a	R = Me, X = Ph	(*S*)-**76a**: 68%, 95% *ee*
73a	R = TBDPSO, X = Me	(*S*)-**77a**: 61%, 96% *ee*

Scheme 14 Copper(I)-catalyzed chemoselective 1,6-borylation of acyclic α,β,γ,δ-unsaturated acceptors by Lam



78a	X = Me, R = Ph	(*S*)-**81a**: 81%, *Z*:*E* = 93:7, >99% *ee*
78b	X = Me, R = *n*Pr	(*S*)-**81b**: 85%, *Z*:*E* = 89:11, >99% *ee*
79a	X = OMe, R = Ph	(*S*)-**82a**: 73%, *Z*:*E* > 98:2, >99% *ee*
80a	X = SEt, R = Ph	(*S*)-**83a**: 69%, *Z*:*E* > 98:2, 99% *ee*



84a	n = 0, R^1 = Ph, R^2 = H	(*S*)-**86a**: 85%, *Z*:*E* = 78:12, 90% *ee*
85a	n = 1, R^1 = Ph, R^2 = H	(*S*)-**87a**: 91%, *Z*:*E* = 95:5, 96% *ee*
85b	n = 1, R^1 = Cy, R^2 = H	(*S*)-**87b**: 92%, *Z*:*E* = 95:5, 96% *ee*
85c	n = 1, R^1 = Ph, R^2 = Me	(*S*)-**87c**: 95%, *Z*:*E* > 98:2, 92% *ee*

Scheme 15 NHC–copper(I)-catalyzed enantioselective silyl transfer onto acyclic and cyclic α,β,γ,δ-unsaturated acceptors by Hoveyda

enantiocontrol in good yields as long as a methyl group blocked the β-position. Extension of this protocol to 5- (e.g., **84a**) and 6-membered (e.g., **85a–c**) cyclic dienones using **L14** broadened the scope, furnishing new α-chiral allylic silanes through conjugate addition [(*S*)-**86a** and (*S*)-**87a–c**, Scheme 15, lower].

3 1,2-Addition

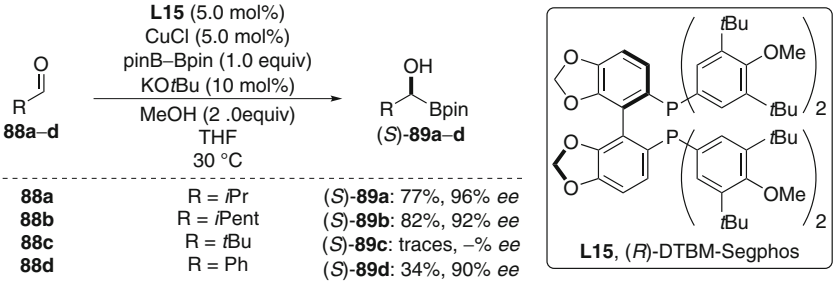
While the list of protocols for conjugate addition of boron and silicon nucleophiles to various acceptors is long, methods for the enantioselective 1,2-addition to carbon–heteroatom double bonds are still rare.

3.1 1,2-Addition of Boron Nucleophiles to Carbonyls and Carbonyl-Derived Acceptors

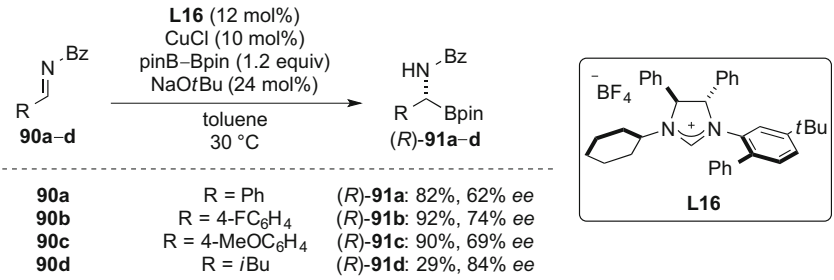
The group of Ito recently presented the catalytic enantioselective borylation of carbon–oxygen double bonds (Scheme 16) [43]. It was a combination of CuCl, DTBM-Segphos **L15**, and KO*t*Bu together with MeOH that enabled asymmetric borylation of different alkyl aldehydes with excellent enantioselectivities [**88a–b** → (*S*)-**89a–b**]. *tert*-Butyl-substituted **88c** did not yield **89c** due to steric hindrance. Benzaldehyde showed excellent enantiomeric excess, but the isolated yield was rather low [**88d** → (*S*)-**89d**]. The need for MeOH as protic additive was also addressed. Experiments with aldehydes bearing an α- [e.g., (*R*)-citronellal] or β-stereogenic center clearly showed that stereoinduction is controlled by the catalyst and not by the substrate (not shown).

Although diastereoselective methods using a chiral auxillary attached to the imine nitrogen atom had been known for a while, catalyst-controlled systems for the borylation of aldimines were elusive [44, 45].

Starting from Hoveyda's C_1-symmetric NHC precursors [26], Tian, Lin, and co-workers developed *N*,*N*′-alkyl/aryl-substituted imidazolium salt **L16** that, in combination with CuCl and NaO*t*Bu, enables the catalyst-controlled synthesis of enantioenriched α-boryl amines from benzoyl-protected aldimines (Scheme 17) [46]. Even if the levels of enantiocontrol were just moderate for aryl-substituted



Scheme 16 Copper(I)-catalyzed addition of nucleophilic silicon to aldehydes by Ito



Scheme 17 NHC–copper(I)-catalyzed addition of nucleophilic boron to aldimines by Tian and Lin

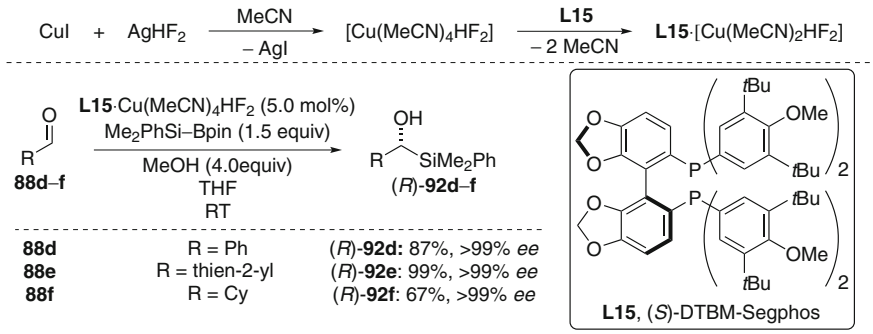
aldimines [**90a–c** → (*R*)-**91a–c**], this report is certainly seminal in the sense that it demonstrates the feasibility of the asymmetric variant. The enantioselectivity was slightly higher for alkyl-substituted substrates yet yields were poor [e.g., **90d** → (*R*)-**91d**].[4]

3.2 1,2-Addition of Silicon Nucleophiles to Carbonyls or Carbonyl-Derived Acceptors

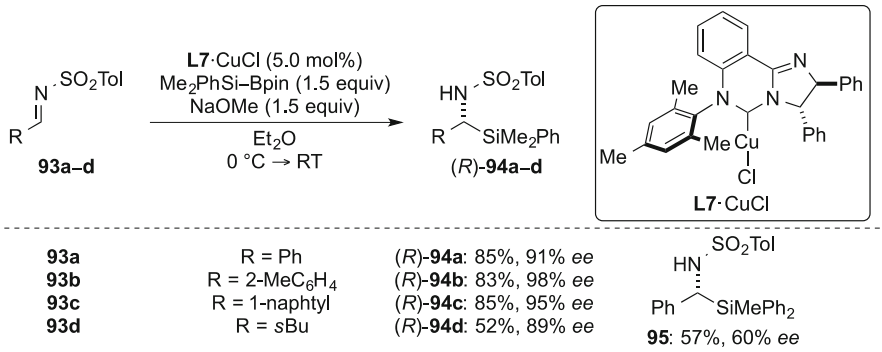
Riant and co-workers introduced an unconventional diphosphine copper(I) bifluoride complex with the sterically demanding DTBM-Segphos ligand **L15** {**L15**·[Cu(MeCN)$_2$HF$_2$], Scheme 18, upper} that allows for the enantioselective addition of silicon nucleophiles to aldehydes (Scheme 18, lower) [48]. The bifluoride anion (FHF^-) is believed to activate the silicon–boron linkage by attacking the more *Lewis*-acidic boron atom, thereby increasing the nucleophilicity of the silicon atom. As a result, an alkoxide base is not needed, and this is different from the usually assumed transmetalation of the silicon–boron bond by a copper(I)–alkoxide. Representative aromatic aldehydes afforded chiral α-silyl alcohols in good yields and with excellent enantioselectivities, both not affected by the substitution pattern and the electronic nature of the substituents on the aromatic ring [**88d** → (*R*)-**92d** and **88e** → **92e**]. Aliphatic aldehydes were also transformed with excellent enantiomeric excesses but in lower chemical yields [**88f** → (*R*)-**92f**].

Oestreich and co-workers elaborated the 1,2-addition of silicon nucleophiles to aldehyde-derived imines (Scheme 19) [49]. As in the case of the related procedure for allylic substitution (Sect. 4.2), preformed chiral 6-membered NHC–copper(I)

[4] For a metal-free protocol using a chiral phosphine as catalyst, see [47].



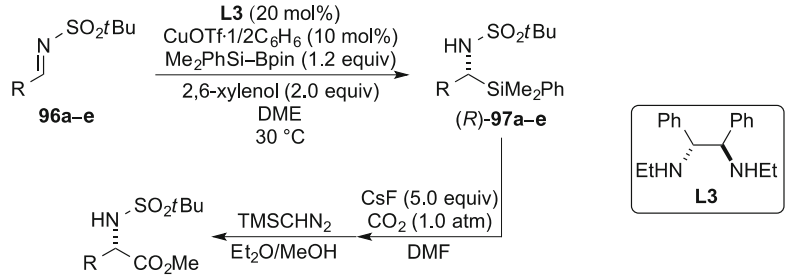
Scheme 18 Enantioselective copper(I)-catalyzed 1,2-addition of nucleophilic silicon to aldehydes by Riant



Scheme 19 Enantioselective 1,2-addition of nucleophilic silicon to aldimines using a preformed chiral 6-membered NHC–copper(I) complex by Oestreich

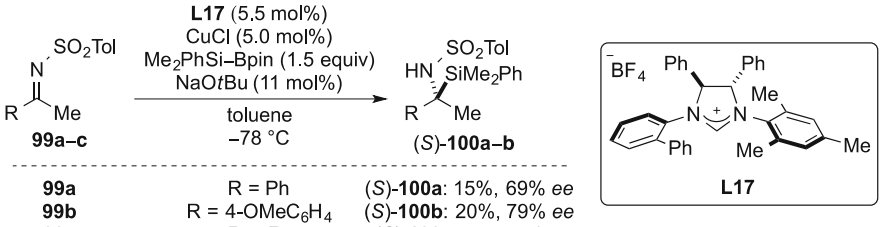
complex **L7**·CuCl [29] was used to activate the silicon–boron reagent. Among the electron-withdrawing groups attached to the imine nitrogen atom, phosphoryl- (not shown) and tosyl-protecting groups yielded the highest enantiocontrol in the transformation to the corresponding α-silyl amine [**93a–c** → (*R*)-**94a–c**, Scheme 19]. Alkyl-substituted aldimines reacted with good enantioselectivity but with decreased yield [**93d** → (*R*)-**94d**]. Aside from Me_2PhSi–Bpin, another silylboronic ester was tested, installing the $MePh_2Si$ group at the imine carbon atom (**95**).

Different from the work of Oestreich and co-workers, the Sato group prepared chiral α-silyl amines with the aid of the simple diphenylethylenediamine ligand **L3** (Scheme 20) [50]. **L3** had already been used in conjugate borylation by the Shibasaki group [18]. Although levels of enantiomeric excess were somewhat lower than those obtained with Oestreich's protocol, a broad range of aldimines was converted successfully [**96a–d** → (*R*)-**97a–d**]. Furthermore, the obtained



96a	R = Ph	(*R*)-**97a**: 91%, 86% *ee*	(*S*)-**98a**: 91%, 85% *ee*
96b	R = 4-FC_6H_4	(*R*)-**97b**: 99%, 86% *ee*	(*S*)-**98b**: 82%, 85% *ee*
96c	R = 4-MeC_6H_4	(*R*)-**97c**: 94%, 87% *ee*	(*S*)-**98c**: 89%, 86% *ee*
96d	R = 2-MeC_6H_4	(*R*)-**97d**: 100%, 95% *ee*	

Scheme 20 Enantioselective silylation of *N*-sulfonylimines and stereoselective carboxylation of α-silyl amines by Sato



99a	R = Ph	(*S*)-**100a**: 15%, 69% *ee*
99b	R = 4-$OMeC_6H_4$	(*S*)-**100b**: 20%, 79% *ee*
99c	R = *i*Pr	(*S*)-**100c**: no reaction

Scheme 21 Enantioselective addition of nucleophilic silicon to ketone-derived imines by He

α-silyl amines were activated with CsF to react with CO_2 enantioselectively, furnishing α-amino acids with retention of the configuration [(*R*)-**97a–c** → (*S*)-**98a–c**, determined after subsequent esterification with $TMSCHN_2$; two-time recrystallization of **97a–c** prior to carboxylation further increased the enantiomeric excesses to as high as >99% *ee*].

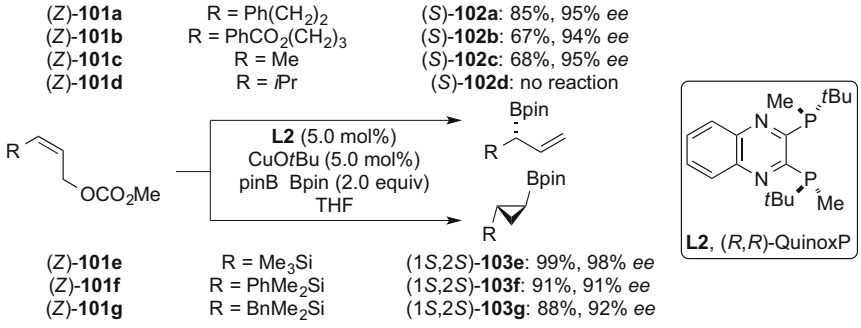
Following the examples of the groups of Oestreich and Sato, He and co-workers used one of Hoveyda's chiral NHC–copper(I) systems with **L17** (Scheme 21) [26] to achieve the 1,2-silylation of imines [51]. Aside from representative aldimines (not shown), challenging alkyl-/aryl-substituted ketimines afforded the desired enantiomerically enriched α-silylated adducts [**99a–b** → (*S*)-**100a–b**; dialkyl-substituted ketimines such as **99c** did not react]. Despite low chemical yields and moderate enantiomeric excesses of the resulting α-silyl amines, He's contribution certainly expanded the previous substrate scope.

4 Allylic Substitution

4.1 Allylic Substitution with Boron Nucleophiles and Competing Cyclopropane Formation

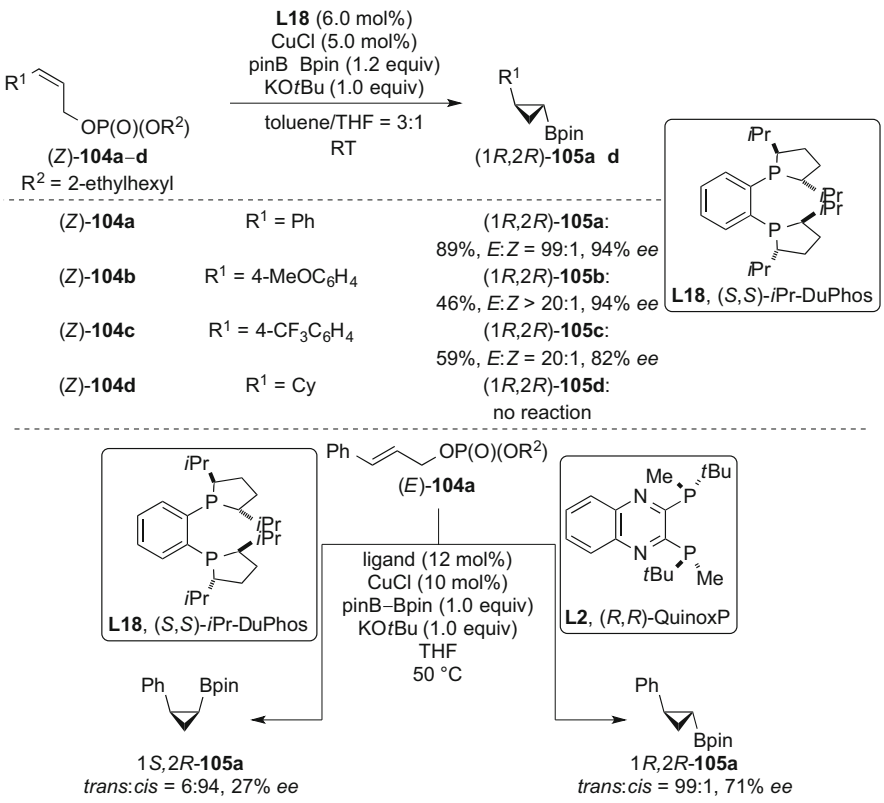
In 2007, α-chiral allylic boronates were synthesized for the first time by direct copper(I)-catalyzed allylic displacement with nucleophilic boron reagents. The Sawamura group used the σ-bond metathesis of pinB–Bpin across the copper–oxygen bond to release a boron nucleophile that reacts with alkyl-substituted allylic carbonates exclusively in an S_N2' fashion (Scheme 22, upper) [52].[5] With (*R*,*R*)-QuinoxP (**L2**) as chiral ligand, various α-chiral allylic boronates were obtained in high yields with perfect regiocontrol and excellent enantiomeric excesses [(*Z*)-**101a–c** → (*S*)-**102a–c**]. Only sterically demanding isopropyl-substituted allylic carbonate (*Z*)-**101d** did not react. The group also demonstrated the need for *Z*-configured alkenes; acceptors with *E*-geometry led to decreased levels of enantioselectivity [(*E*)-**101a** → (*R*)-**102a**: 97%, 44% *ee*, not shown].

The same group learned that if a silicon group is attached to the γ-position with respect to the carbonate leaving group, enantioenriched bifunctional cyclopropanes are obtained under otherwise identical conditions (Scheme 22, lower) [54]. The cyclopropane formation is explained through a reversal of regioselectivity in the borylation step due to an interaction of the silicon–carbon bond with the resulting carbon–copper bond in the borylated intermediate (α-silicon effect, not shown). By this, various triorganosilyl-substituted allylic carbonates were transformed into the corresponding *trans*-silyl-substituted cyclopropylboronates [(*Z*)-**101e–g** → (1*S*,2*S*)-**103e–g**]. The synthetical value of these compounds was further illustrated



Scheme 22 Copper(I)-catalyzed allylic substitution of carbonates with boron nucleophiles by Sawamura

[5] For a racemic version with chirality transfer from an enantiopure starting material, see [53].

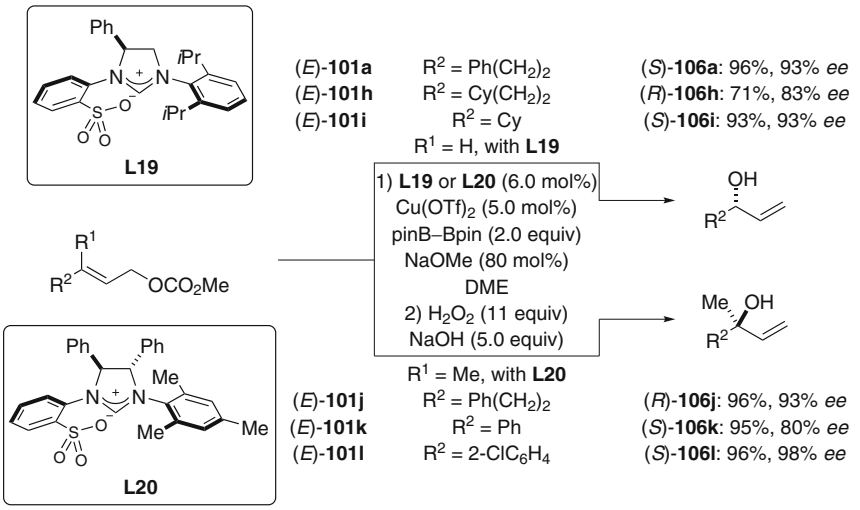


Scheme 23 Copper(I)-catalyzed enantioselective formation of trans- and cis-cyclopropylboronates by Sawamura and Ito

by subjecting cyclopropane (1*S*,2*S*)-**103g** to *Suzuki–Miyaura* coupling(s) followed by *Tamao* oxidation (not shown).

This inverted regioselectivity was also seen with aryl groups attached to bulky allylic phosphates, again producing *trans*-substituted cyclopropylboronates (Scheme 23, upper) [55]. According to the aforementioned mechanistic assumption, substrates bearing electron-rich aryl groups [(*Z*)-**104a–b** → (1*R*,2*R*)-**105a–b**, Scheme 23, upper] were transformed with high levels of diastereo- and enantioselectivity, while electron-deficient aryl groups led to lower selectivity [e.g., (*Z*)-**104c** → (1*R*,2*R*)-**105c**]. Cyclohexyl-substituted phosphate (*Z*)-**104d** did not react. Furthermore, Sawamura, Ito, and co-workers discovered a remarkable ligand-dependent switch in diastereoselectivity for phenyl-substituted allylic phosphates with *E*-geometry: *i*Pr-DuPhos **L18** leads to *cis* and QuinoxP **L2** to *trans* relative configuration (Scheme 23, lower).

Guzman-Martinez and Hoveyda introduced bidentate sulfonate-containing NHC–copper(I) complexes **L19** and **L20** (Scheme 24) for allylic displacements with boron nucleophiles followed by subsequent oxidation to the corresponding

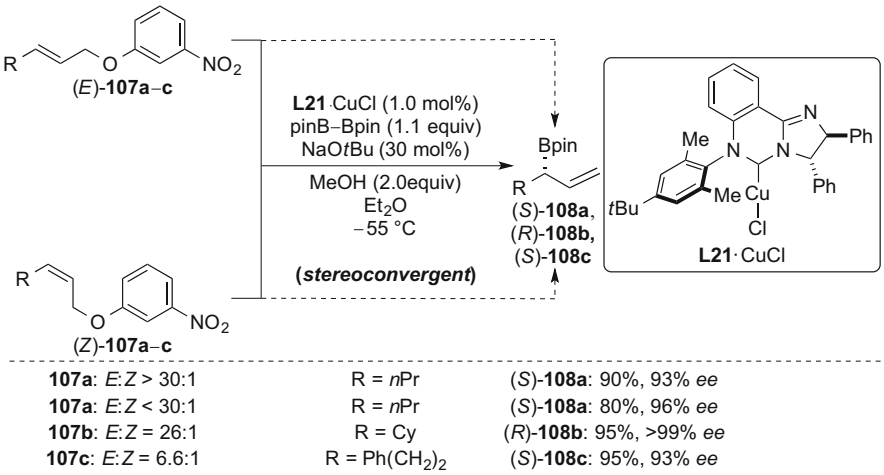


Scheme 24 NHC–copper(I)-catalyzed allylic displacement with boron nucleophiles and subsequent oxidation by Hoveyda

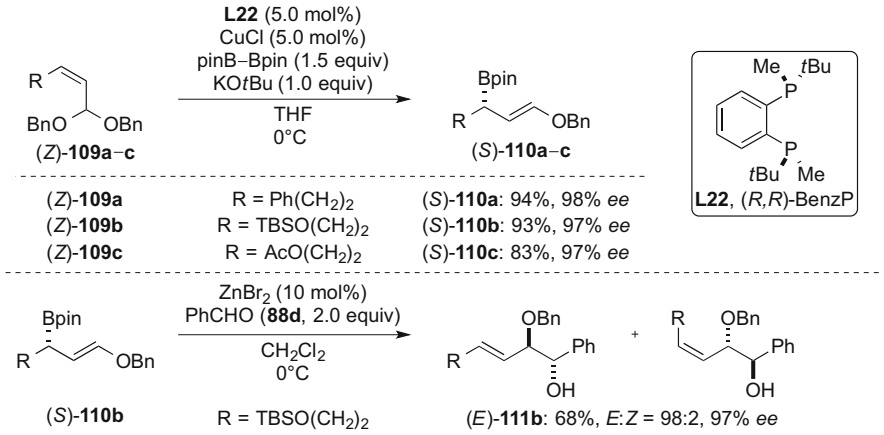
allylic alcohols [56]. With these ligands, the enantioselective allylic substitution of allylic carbonates having *E* configuration became possible [(*E*)-**101a** → (*S*)-**106a**, 96%, 93% *ee*, Scheme 24, upper; (*Z*)-**101a** → (*R*)-**106a**, 94%, 90% *ee*, opposite enantiomer, not shown]. Further examples include (*E*)-**101h** → (*R*)-**106h** and (*E*)-**101i** → (*S*)-**106i**]. More challenging trisubstituted substrates decorated with an additional alkyl [(*E*)-**101j**] or aryl group [(*E*)-**101k–l**] at the alkene terminus afforded allylic boronates with stereogenic quaternary carbon atoms [(*E*)-**101j** → (*R*)-**106j** and (*E*)-**101k–l** → (*S*)-**106k–l**, Scheme 24, lower]. It must be noted that the catalyst is generated from a copper(II) salt, and the authors believe that an excess of the boron reagent reduces copper(II) to catalytically active copper(I) through an unknown mechanism.

The stereochemical outcome, i.e., the absolute configuration of the allylic boronate, is dependent on the double bond geometry of the starting material in Sawamura's and Hoveyda's work: *E*- and *Z*-configured allylic acceptors led to opposite enantiomers. Conversely, McQuade's group presented a stereoconvergent S_N2' reaction using their preformed chiral 6-membered NHC–copper(I) complex **L21**·CuCl (Scheme 25) [57]. Using rather uncommon allyl aryl ethers with an electron-withdrawing nitro group in the *meta* position [(*E*/*Z*)-**107a–c**], these authors elaborated an enantioselective preparation of allylic boronates.[6] *E*- and *Z*-configured alkenes transformed into the same enantiomer [(*E*)-**107a** → (*S*)-**108a** ← (*Z*)-**107a**], making isomeric mixtures suitable for this allylic substitution [**107b** (*E*/*Z* = 26:1) → (*R*)-**108b** and **107c** (*E*/*Z* = 6.6:1) → (*S*)-**108c**].

[6] For the use of related NHC–copper(I) complex **L7**·CuCl in the enantioselective 1,4-addition of nucleophilic boron, see Sect. 2.1, Scheme 7 [29].



Scheme 25 Stereoconvergent allylic substitution with preformed NHC–copper(I) complex by McQuade



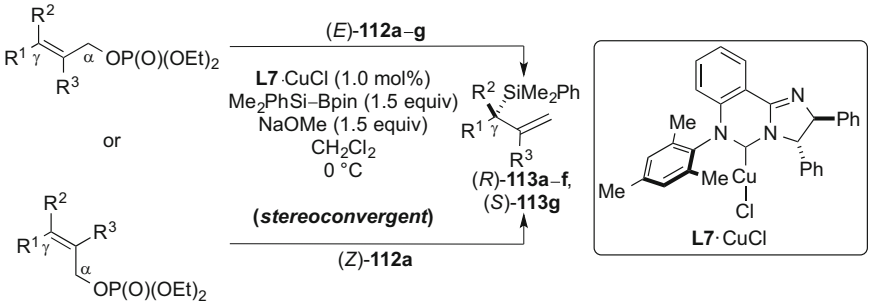
Scheme 26 Enantioselective synthesis of α-chiral (*E*)-(γ-alkoxyallyl)boronates by Ito

Ito and co-workers recently presented a particularly intriguing allylic ether displacement that provides an enantioselective access to synthetically useful *anti*-1,2-diol motifs (Scheme 26) [58]. After copper(I)-catalyzed asymmetric γ-selective displacement of one of the ether groups in the allylic acetals by the boron nucleophile [(*Z*)-**109a–c** → (*S*)-**110a–c** with **L22** as ligand, Scheme 26, upper], aldehyde allylation with the obtained α-chiral (*E*,*S*)-(γ-alkoxyallyl)boronates furnished *anti*-1,2-diols [(*S*)-**110b** → (*E*)-**111b**, Scheme 26, lower]. The stereochemical outcome of the allylation step is controlled by the stereogenicity of the borylated carbon atom.

4.2 Allylic Substitution with Silicon Nucleophiles

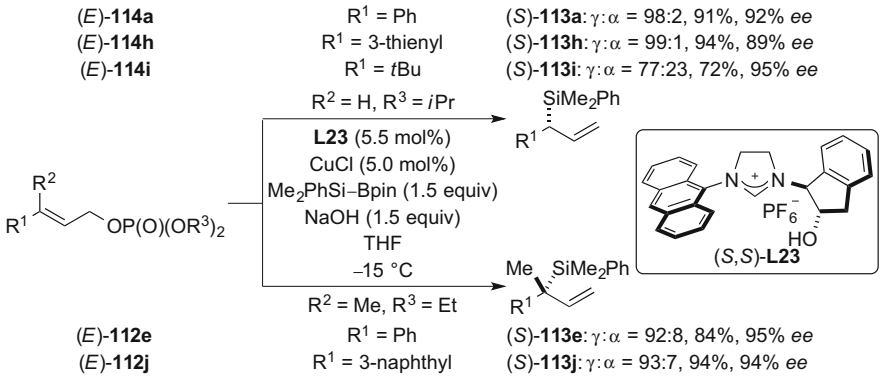
It was Oestreich and co-workers who identified a catalytic system that enables the direct synthesis of α-chiral allylic silanes through nucleophilic allylic displacement with a silicon nucleophile. These authors finally succeeded in solving this long-standing challenge by using McQuade's preformed chiral 6-membered NHC–copper(I) complex **L7**·CuCl (Scheme 27) [59]. Phosphate turned out to be the best leaving group. Aryl- [(*E*)-**112a–e**] and alkyl-substituted [(*E*)-**112f–g**] allylic phosphates with *E* configuration yielded the desired α-chiral allylic silanes enantioselectively with high preference for S_N2' over S_N2 substitution (γ versus α) [(*E*)-**112a–f** → (*R*)-**113a–f** and (*E*)-**112g** → (*S*)-**113g**, Scheme 27]. Methyl substituents in either β- [(*E*)-**112d**] or γ-position [(*E*)-**112e**] [60] ruined both, the regiocontrol and the enantioselectivity, while the latter revealed to be less sensitive to γ-methylation [(*E*)-**112d** → (*R*)-**113d**: γ:α = 65:35, 78% *ee*, (*E*)-**112e** → (*R*)-**113e**: γ:α = 73:27, 96% *ee*]. Transformation of δ-hydroxy allylic phosphate (*E*)-**112f** into otherwise difficult to access (*R*)-**113f** showcases the synthetic value of this protocol. As with the protocol for allylic substitution of nucleophilic boron by the McQuade group [57], changing the alkene isomer to (*Z*)-**112a** slightly decreased the enantiomeric excess but did not alter the absolute configuration of the allylic silane.

Independent from the work of Oestreich and co-workers, the group of Shintani and Hayashi presented another example of NHC–copper(I)-catalyzed asymmetric allylic substitution of allylic phosphates by nucleophilic silicon (Scheme 28) [61]. The NHC precursor **L23** in combination with CuCl and NaOH as base allowed for the enantioselective preparation of several α-chiral allylic silanes. The choice of base is crucial as alkoxides had a negative effect on the regioselectivity (not



(*E*)-**112a**	R^1 = Ph, R^2 = R^3 = H	(*R*)-**113a**: γ:α = 97:3, 82%, 96% *ee*
(*Z*)-**112a**	R^1 = Ph, R^2 = R^3 = H	(*R*)-**113a**: γ:α = 97:3, 88%, 91% ee
(*E*)-**112b**	R^1 = 2-MeOC_6H_4, R^2 = R^3 = H	(*R*)-**113b**: γ:α = 96:4, 92%, 95% *ee*
(*E*)-**112c**	R^1 = 4-$CF_3C_6H_4$, R^2 = R^3 = H	(*R*)-**113c**: γ:α = 97:3, 93%, 93% *ee*
(*E*)-**112d**	R^1 = Ph, R^2 = H, R^3 = Me	(*R*)-**113d**: γ:α = 65:35, 25%, 78% *ee*
(*E*)-**112e**	R^1 = Ph, R^2 = Me, R^3 = H	(*R*)-**113e**: γ:α = 73:27, 93%, 96% *ee*
(*E*)-**112f**	R^1 = CH_2OTBS, R^2 = R^3 = H	(*R*)-**113f**: γ:α = 96:4, 73%, 88% *ee*
(*E*)-**112g**	R^1 = *i*Pr, R^2 = R^3 = H	(*S*)-**113g**: γ:α = 97:3, 91%, 97% *ee*

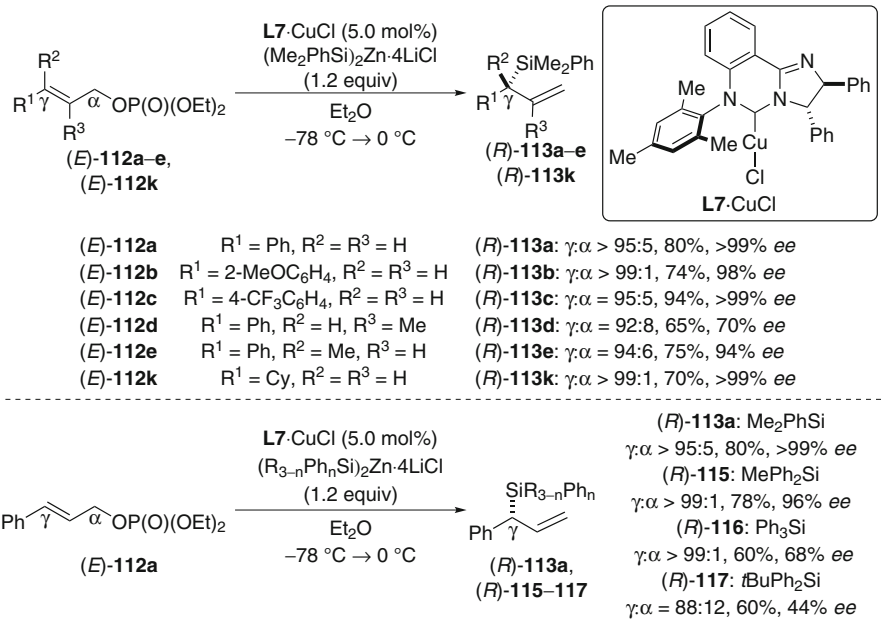
Scheme 27 Stereoconvergent NHC–copper(I)-catalyzed enantioselective silylation of allylic phosphates by Oestreich



Scheme 28 Copper(I)-catalyzed asymmetric allylic silylation of allylic phosphates by Shintani and Hayashi

shown), while NaOH led to superb regiocontrol. A broad scope of γ-monosubstituted allylic phosphates were transformed enantioselectively into the corresponding allylic silanes [(*E*)-**114a** → (*S*)-**113a**, (*E*)-**114h–i** → (*S*)-**113h–i**, Scheme 28, upper]. This study included *tert*-butyl-substituted (*E*)-**114i** that had been reported to react in an S_N2-fashion under Oestreich's setup [59]. γ,γ-Disubstituted substrates bearing a methyl group in γ-position yielded the desired allylic silanes with good levels of regio- and enantiocontrol [(*E*)-**112e** → (*S*)-**113e**, (*E*)-**112j** → (*S*)-**113j**, Scheme 28, lower]. It is worthy of note that a seemingly minor variation of the leaving group from diisopropyl to diethyl phosphate improved the regioselectivity in the case of a methyl group in the γ-position. When *Z*-isomers were used, the enantiomeric excess decreased, and the opposite enantiomer formed (not shown).

Changing the silicon pronucleophile from the silicon–boron reagent to soft bis(triorganosilyl) zinc reagents [62, 63] allowed Hensel and Oestreich to employ easy accessible cuprate-type silicon nucleophiles for the regio- and enantioselective incorporation of different silyl groups into allylic phosphates and chlorides, again arriving at highly enantioenriched α-chiral allylic silanes (Scheme 29) [64–68]. The levels of regio- and enantiocontrol were excellent regardless of the substitution pattern of the allylic acceptor [(*E*)-**112a–e** → (*R*)-**113a–e**, Scheme 29, upper]. It was only β-methyl-substituted (*E*)-**112d** that showed diminished enantiomeric excess yet still good regioselectivity [(*E*)-**112d** → (*R*)-**113d**]. As a consequence of the simplicity of the reagent preparation, various silyl groups could be used in this asymmetric allylic displacement (Scheme 29, lower). In a general sense, the enantioselectivity and to a lesser extent the regioselectivity decreased with the steric demand of the silyl group [Me_2PhSi in (*R*)-**113a** versus $MePh_2Si$ in (*R*)-**115** versus Ph_3Si in (*R*)-**116** versus *t*$BuPh_2Si$ in (*R*)-**117**]. *Z*-configured (*Z*)-**112a** afforded (*R*)-**113a** with poor regio- and enantioselectivity but same absolute configuration as (*E*)-**112a** [(*Z*)-**112a** → (*R*)-**113a**, 60%, γ:α = 88:12, 64% *ee*, not shown].

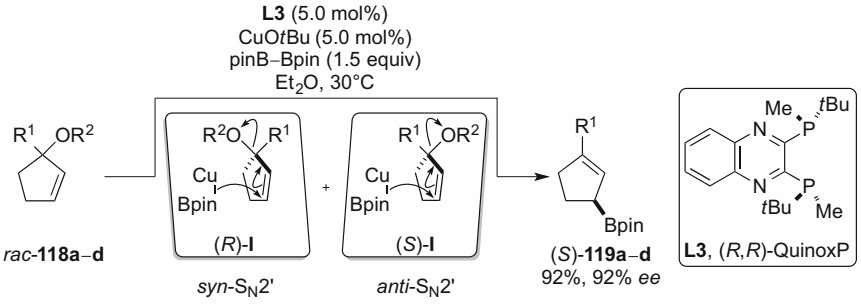


Scheme 29 Asymmetric catalysis with silicon-based cuprates by Oestreich

4.3 Direct Enantioconvergent Transformation of Racemic Allylic Acceptors

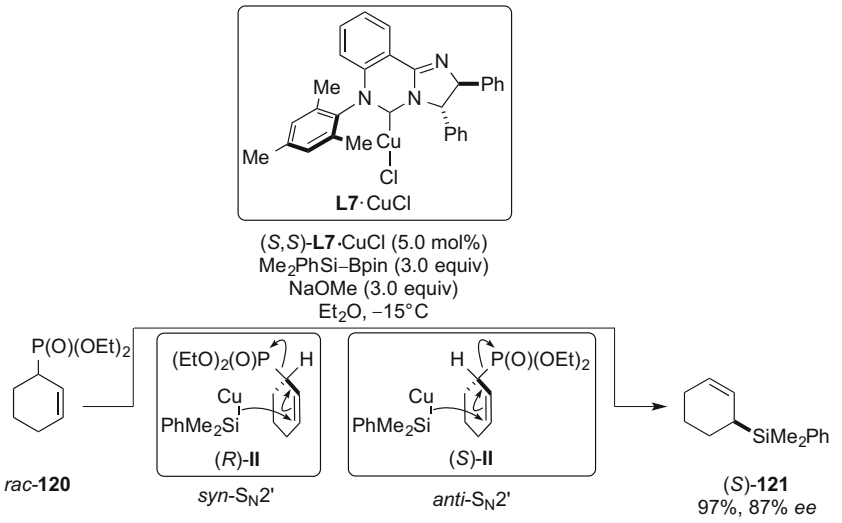
The potential of Ito's and Sawamura's asymmetric allylic displacement is further highlighted by an intriguing *direct enantioconvergent transformation* of racemic cyclic allylic acceptors (Scheme 30) [69]. A single catalytic system transforms both enantiomers of the racemic starting material **118** into the same enantiomer of **119** by two different reaction pathways. The copper(I)–boron reagent reacts in a *syn*-S_N2'-fashion with one enantiomer [(*R*)-**118** → (*R*)-**I** → (S)-**119**] and in an *anti*-S_N2'-fashion with the other enantiomer [(*S*)-**119** → (*S*)-**I** → (S)-**119**] of various allylic ethers and carbonates (carbonates not shown), yielding the corresponding allylic boronates in high yields and with good enantiocontrol [*rac*-**118a–d** → (*S*)-**119a–d**].

Recently, Delvos and Oestreich presented the related enantioconvergent silylation of a racemic cyclic allylic phosphate to arrive at an enantioenriched cyclic allylic silane (Scheme 31) [70]. A comprehensive experimental analysis revealed that preformed chiral 6-membered NHC–copper(I) complex **L7**·CuCl adopts two different courses depending on the absolute configuration of the starting material. The (*R*)-configured phosphate (*R*)-**120** reacts through a *syn*-S_N2' pathway [(*R*)-**120** → (*R*)-**II** → (*S*)-**121**], whereas the (*S*)-configured enantiomer (*S*)-**120** follows an *anti*-S_N2' mechanism [(*S*)-**120** → (*S*)-**II** → (*S*)-**121**].



rac-**118a**	R^1 = H, R^2 = Bn	(*S*)-**119a**: 91%, 93% *ee*
rac-**118b**	R^1 = Me, R^2 = Bn	(*S*)-**119b**: 80%, 98% *ee*
rac-**118c**	R^1 = $Ph(CH_2)_2$, R^2 = Me	(*S*)-**119c**: 85%, 97% *ee*
rac-**118d**	R^1 = H, R^2 = CO_2Me	(*S*)-**119d**: 84%, 91% *ee*

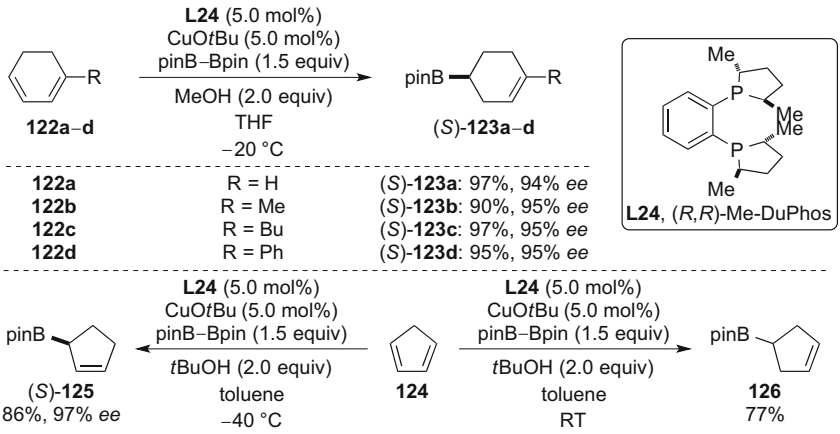
Scheme 30 Enantioconvergent allylic displacement with nucleophilic boron by Ito and Sawamura



Scheme 31 Enantioconvergent silylation of a cyclic allylic phosphate by Oestreich

5 Addition Across 1,3-Dienes

Using Me-DuPhos (**L24**, Scheme 32, upper), Ito, Sawamura, and co-workers accomplished an asymmetric borylation of 1,3-dienes to yield homoallylic boronates (*S*)-**122a–d** [71] (for related domino processes using enynes, see Sect. 6, Scheme 36 [87]). Not only parent cyclohexa-1,3-diene (**122a**) but also alkyl- and aryl-substituted congeners **122b–d** afforded homoallylic boronates in

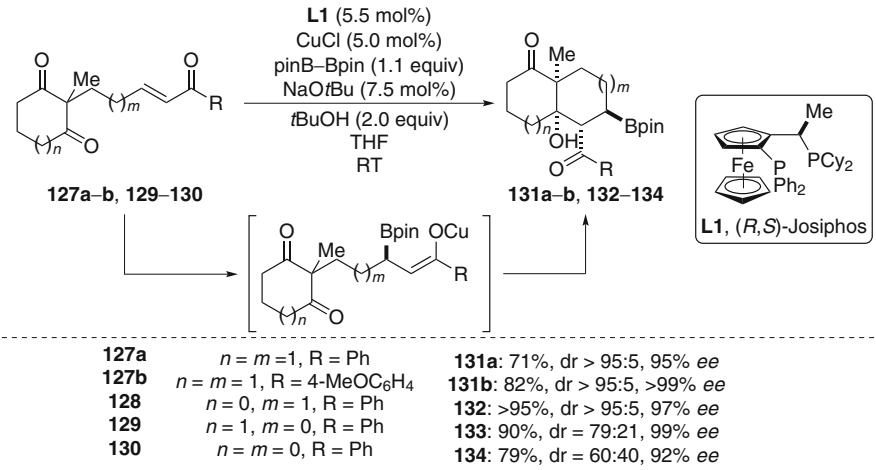


Scheme 32 Copper(I)-catalyzed asymmetric monoborylation of cyclic 1,3-dienes by Sawamura and Ito

high yields and with superb regio- (homoallylic versus allylic boronates, not shown) and enantioselectivities [**122a–d** → (*S*)-**123a–d**]. The influence of the reaction temperature was studied with cyclopenta-1,3-diene (**124**). Decreasing the temperature to −40°C and using *t*BuOH in toluene led to a switch in selectivity, favoring formation of allylic boronate (*S*)-**125** (Scheme 32, lower, left), while performing the borylation at room temperature still gave the homoallylic boronate **126**, yet in racemic form (Scheme 32, lower, right). This dichotomy is explained by thermodynamic control, that is, by a rapid isomerization of the kinetically formed allyl–copper(I) complex. Slow protonation by bulky *t*BuOH affords the homoallylic boronates (not shown).

6 Domino Reactions

The combination of the asymmetric copper(I)-catalyzed conjugate borylation and an intramolecular trapping of the resulting copper(I)–enolate was accomplished by Lam and co-workers (Scheme 33) [72]. This elegant example of a domino process resulted in the construction of one carbon–boron bond and one carbon–carbon bond with formation of four stereogenic centers, two of which quaternary! With a modification of Yun's procedure (Sect. 2.1, Scheme 2 [12]), a range of enones underwent borylative aldol cyclization with high diastereomeric ratios and enantiomeric excesses. While both were high for 6-membered rings (**127a–b** → **131a–b** and **128** → **132**), the diastereoselectivity decreased for smaller ring sizes, while the enantiomeric excess of the major diastereomer remained high (**131a**: dr > 95:5, 95% *ee* versus **133**: dr = 79:21, 99% *ee* versus **134**: dr = 60:40, 92% *ee*).



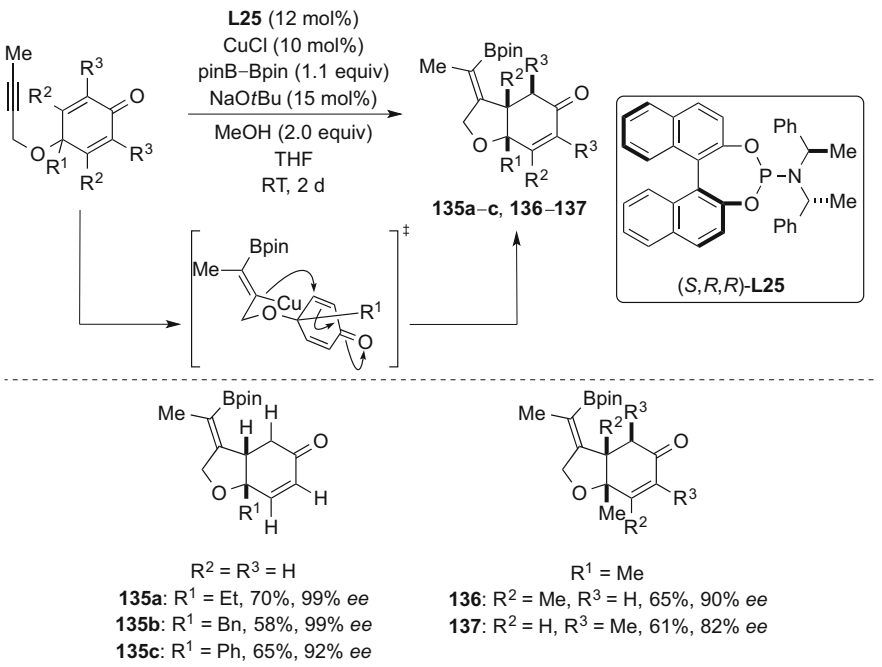
Scheme 33 Copper(I)-catalyzed enantioselective borylative aldol cyclization of enone diones by Lam

Tian, Lin, and co-workers designed an asymmetric copper(I)-catalyzed domino borylative cyclization of 1,6-enynes to construct enantioenriched, densely functionalized *cis*-hydrobenzofuran frameworks (**135a–c**, **136–137**, Scheme 34) [73]. Phosphoramidite ligand **L25** serves as a chiral ligand. The regioselective β-borylation of the alkyne functionality was achieved by steric demand of the R^1 group and/or by oxygen coordination to the propargylic ether unit.[7] The borylated vinylic copper(I) intermediate (Scheme 34, without R^2 and R^3 for clarity, middle) immediately underwent the desymmetrizing enantioselective conjugate addition to the cyclohexadienone with *syn*-diastereoselectivity.

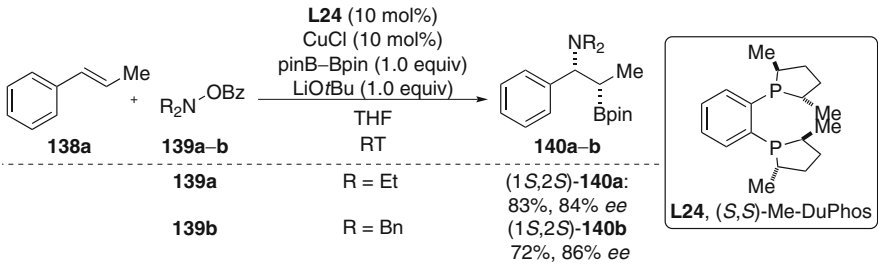
The group of Hirano and Miura presented a copper(I)-catalyzed aminoboration of styrene derivatives (Scheme 35) [86]. The phosphine–copper(I) complex generated from CuCl, **L24**, and LiO*t*Bu enabled the asymmetric borylation of styrene **138a**, and the obtained copper(I) intermediate was trapped with a nitrogen electrophile bearing benzoate as leaving group. The net result is a *syn*-aminoboration with decent enantioselectivities (**138a** + **139a–b** → (1*S*,2*S*)-**140a–b**).

The Hoveyda group recently described a highly diastereo- and enantioselective multicomponent reaction involving borylation of 1,3-enynes and aldehyde addition of the resulting propargyl/allenyl–copper(I) intermediate (Scheme 36) [87]. The sequence commences with the chemo-, site-, and enantioselective borylation of the terminal alkene in **141**. The bisphosphine–copper(I) catalyst is generated from CuCl, NaO*t*Bu, and **L26** (Scheme 36, lower middle). DFT calculations support the formation of an energetically favored trisubstituted allenyl–copper(I) complex (Scheme 36, lower right). This adds subsequently site- and diastereoselectively to

[7] For copper(I)-catalyzed addition of nucleophilic boron across C–C triple bonds, see [74–78]. For copper(I)-catalyzed addition of nucleophilic silicon across C–C triple bonds, see [79–85].



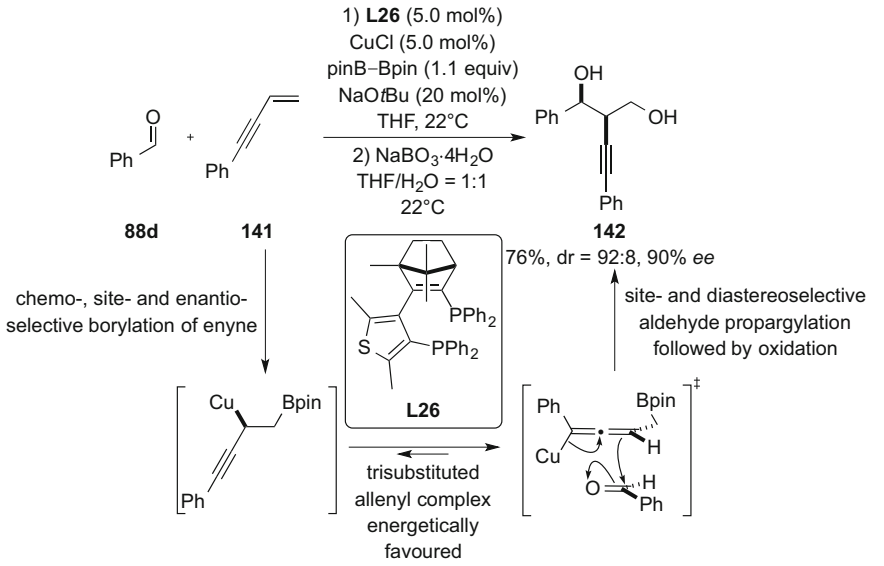
Scheme 34 Copper(I)-catalyzed desymmetrizing cyclization of cyclohexadienone-containing 1,6-enynes initiated by alkyne borylation by Tian and Lin



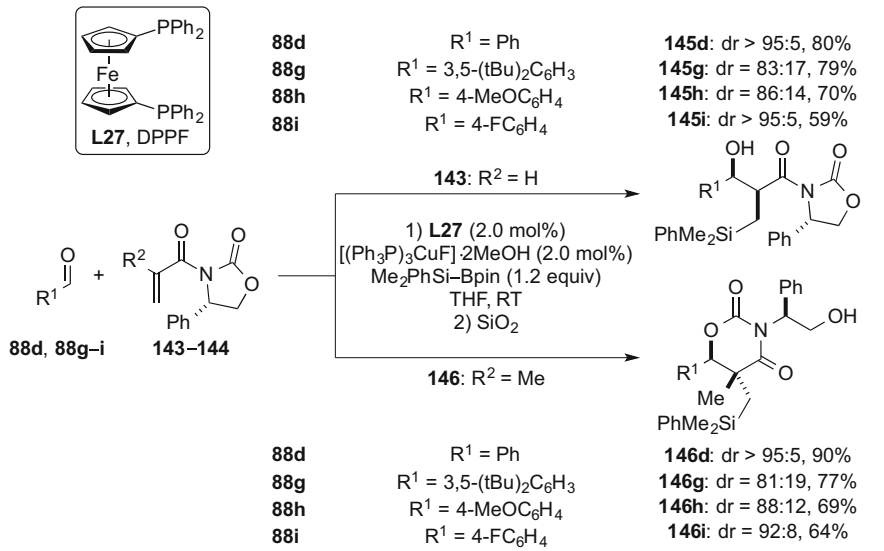
Scheme 35 Copper(I)–phosphine-catalyzed aminoboration of styrenes by Miura

an aldehyde (e.g., **88d**) and yields **142**. Experimental investigations showed that catalyst control is operative when chiral aldehydes are used as substrates (not shown).

A few years ago, Riant and co-workers had already presented a fine example of a copper(I)-catalyzed domino silylative aldol reaction. The stereochemical outcome was controlled by the use of a chiral oxazolidinone auxiliary attached to a *Michael* acceptor (Scheme 37) [88]. The copper(I)–enolate formed by the conjugate silylation of acryloyloxazolidinone **143** was trapped with different aldehydes to yield aldol structures **145d** and **145g–i** diastereoselectively (Scheme 37, upper).



Scheme 36 Diastereo- and enantioselective copper(I)-catalyzed domino reaction of pinB–Bpin with 1,3-enynes and aldehydes by Hoveyda



Scheme 37 Domino silylative aldol reactions by Riant

When methacryloyloxazolidinone **144** was subjected to the same procedure, an intramolecular ring opening of the oxazolidinone was observed, leading to rearranged **146d** and **146g–i** with good diastereoselectively (Scheme 37, lower).

7 Synthesis of 1,1-Diboron Compounds

During the investigation of the copper(I)-catalyzed hydroboration of various styrene derivatives with pinacolborane (H–Bpin) [89], Yun and co-workers found that the established catalyst generated from CuCl, NaO*t*Bu, and the phosphine ligand DTBM-Segphos **L15** would promote this hydroboration with excellent α-selectivity and high enantiocontrol (**138a–c** → (*S*)-**147a–c**, Scheme 38, upper). With styrenes already decorated with a Bdan group (dan = 1,8-naphthalenediaminato) in the β-position, the regioselectivity was reversed to β, making the highly selective synthesis of 1,1-diborylalkanes feasible (**148a–d** → (*S*)-**149a–d**, Scheme 38, lower) [90].[8]

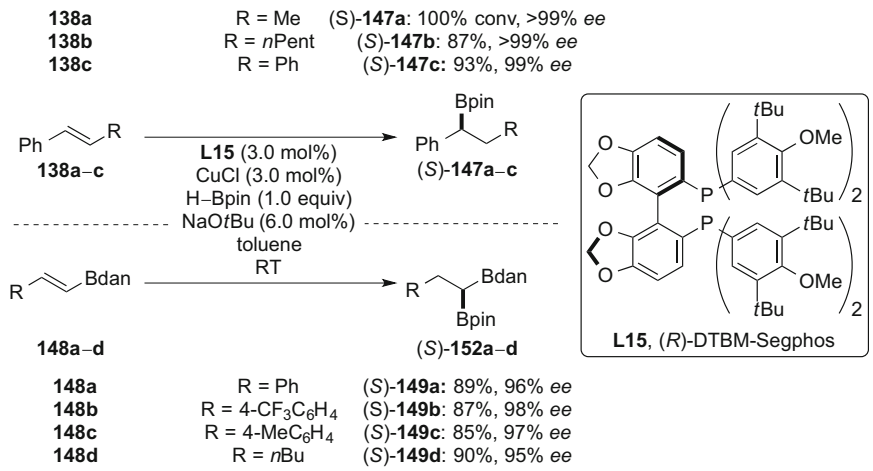
8 Desymmetrization of Prochiral Compounds by Copper(I)-Catalyzed Borylation or Silylation Reactions

The group of Ito and Sawamura also demonstrated the versatility of their allylic borylation methodology in a desymmetrization (Scheme 39) [92]. The allylic boronate obtained from the copper(I)-catalyzed asymmetric borylation of *meso*-configured **150** was directly reacted with aliphatic (**88a**) and aromatic (**88d** and **88h**) aldehydes in the same pot (Scheme 39, middle). Both the allylic displacement and the aldehyde allylation are highly stereoselective, and the overall sequence sets three stereocenters with excellent enantio- and diastereoselectivity (**88a** → **151a**, **88d** → **151d**, **88h** → **151h**).

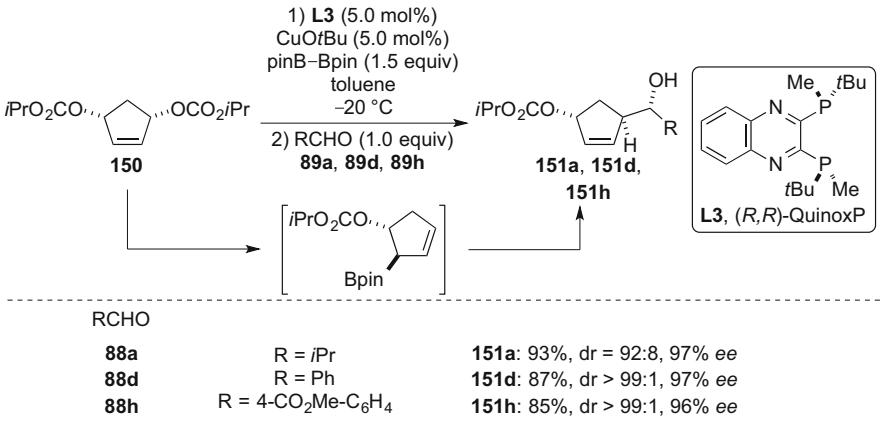
The above allylic substitution/aldehyde allylation process establishes another allylic carbonate available for another round of exactly the same sequence. For this, an achiral copper(I)–xantphos catalyst was used to yield densely functionalized, highly enantioenriched cyclopentanes with excellent levels of diastereoselection (not shown). It is worthy of mention that the initial enantioselective borylation step proceeds through an *anti*-S_N2'-type substitution, whereas the subsequent diastereoselective displacement is a *syn*-S_N2'-type borylation.

Another desymmetrization reaction was introduced by the Tortosa group that relies on the high reactivity of cyclopropenes (Scheme 40) [93]. Strained alkenes

[8] The group of Hall used enantiopure β,β-diboron-substituted esters in stereospecific and chemoselective *Suzuki–Miyaura* cross-coupling reactions (not shown) [91].

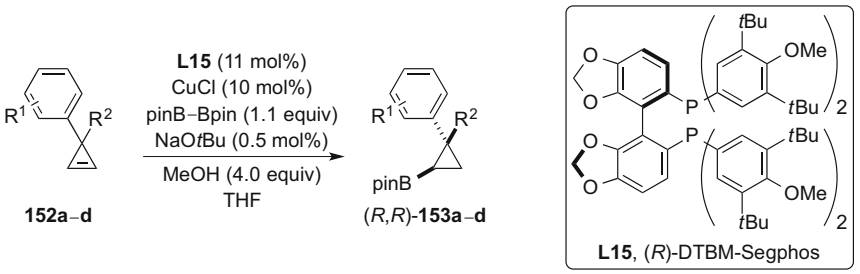


Scheme 38 Regio- and enantioselective copper(I)-catalyzed hydroboration of different styrene derivatives by Yun, arriving at orthogonally gem-diborylated $C(sp^3)$ carbon atoms



Scheme 39 Desymmetrization by copper(I)-catalyzed asymmetric borylation of a meso-configured cyclic allylic dicarbonate by Ito and Sawamura

152a–d react with the copper(I)-based boron nucleophile with high diastereo- and enantioselectivity to yield cyclopropylboronates (*R*,*R*)-**153a–d** with two stereogenic centers, one of which quaternary. Cyclopropenes bearing either electron-rich (**152a–b**) or electron-deficient (**152c**) aryl groups reacted equally well. Using sterically hindered isopropyl-substituted cyclopropene **152d** furnished **153d** with lower diastereoselectivity but high enantiomeric excess.



152a	R^1 = H, R^2 = Me	(*R*,*R*)-**153a**: 74%, dr = 97:3, 90% *ee*
152b	R^1 = 4-OMe, R^2 = Me	(*R*,*R*)-**153b**: 62%, dr = 97:3, 88% *ee*
152c	R^1 = 3-CF_3, R^2 = Me	(*R*,*R*)-**153c**: 43%, dr ≥ 98:2, 84% *ee*
152d	R^1 = H, R^2 = *i*Pr	(*R*,*R*)-**153d**: 54%, dr = 81:19, 92% *ee*

Scheme 40 Diastereo- and enantioselective desymmetrization of cyclopropenes by Tortosa

Acknowledgments M.O. thanks the Einstein Foundation (Berlin) for an endowed professorship.

References

1. Semba K, Fujihara T, Terao J, Tsuji Y (2015) Tetrahedron 71:2183–2197
2. Sawamura M, Ito H (2014) Carbon–boron and carbon–silicon bond formation. In: Alexakis A, Krause N, Woodward S (eds) Copper-catalyzed asymmetric synthesis. Wiley, Weinheim, pp 157–177
3. Oestreich M, Hartmann E, Mewald M (2013) Chem Rev 113:404–441
4. Cid J, Gulyás H, Carbó JJ, Fernández E (2012) Chem Soc Rev 41:3558–3570
5. Suginome M, Ohmura T (2011) Transition metal-catalyzed element–boryl additions to unsaturated organic compounds. In: Hall DG (ed) Boronic acids: preparation and applications in organic synthesis, medicine and materials. Wiley, Weinheim, pp 171–212
6. Hartmann E, Oestreich M (2011) Chim Oggi 29:34–37
7. Calow ADJ, Whiting A (2012) Org Biomol Chem 10:5485–5497
8. Hartmann E, Vyas DJ, Oestreich M (2011) Chem Commun 47:7917–7932
9. Delvos LB, Oestreich M (2013) Chim Oggi 31:74–77
10. Takaya J, Iwasawa N (2012) ACS Catal 2:1993–2006
11. Parra A, López A, Díaz-Tendero S, Amenós L, Ruano JLG, Tortosa M (2014) Synlett 26: 494–500
12. Lee J-E, Yun J (2008) Angew Chem Int Ed 47:145–147
13. Sim H-S, Feng X, Yun J (2009) Chem Eur J 15:1939–1943
14. Chea H, Sim H-S, Yun J (2009) Adv Synth Catal 351:855–858
15. Hartmann E, Oestreich M (2012) Org Lett 14:2406–2409
16. Feng X, Yun J (2009) Chem Commun 6577–6579
17. Chen I-H, Yin L, Itano W, Kanai M, Shibasaki M (2009) J Am Chem Soc 131:11664–11665
18. Chen I-H, Kanai M, Shibasaki M (2012) Org Lett 12:4098–4101
19. Lillo V, Prieto A, Bonet A, Dias-Requejo MM, Ramirez J, Perez JP, Fernandez E (2009) Organometallics 28:659–662
20. Fleming WJ, Müller-Bunz H, Lillo V, Fernández E, Guiry PJ (2009) Org Biomol Chem 7: 2520–2524
21. Solé C, Whiting A, Gulyás H, Fernández E (2011) Adv Synth Catal 353:376–384

22. Solé C, Bonet A, de Vries AHM, de Vries JG, Lefort L, Gulyás H, Fernández E (2012) Organometallics 31:7855–7861
23. Calow ADJ, Batsanov AS, Pujol A, Solè C, Fernández E (2013) Org Lett 15:4810–4813
24. Zhang J-L, Chen L-A, Xu R-B, Wang C-F, Ruan Y-P, Wang A-E, Huang P-Q (2013) Tetrahedron Asymmetry 24:492–498
25. Huang L, Cao Y, Zhao M, Tang Z, Sun Z (2014) Org Biomol Chem 12:6554−6556
26. O'Brien JM, Lee K-S, Hoveyda AH (2010) J Am Chem Soc 132:10630–10633
27. Moure AL, Arrayás RG, Cerretero JC (2011) Chem Commun 47:6701–6703
28. Hirsch-Weil D, Abboud KA, Hong S (2010) Chem Commun 46:7525–7527
29. Park JK, Lackey HH, Rexford MD, Kovnur K, Shatruk M, McQuade DT (2010) Org Lett 12: 5008–5011
30. Zhao L, Ma Y, Duan W, He F, Chen J, Song C (2012) Org Lett 14:5780–5783
31. Zhao L, Ma Y, He F, Duan W, Chen J, Song C (2013) J Org Chem 78:1677–1681
32. Jiang Q, Guo T, Yu Z (2015) ChemCatChem 7:660–665
33. Suginome M, Matsuda T, Ito H (2000) Organometallics 19:4647–4649
34. Ohmura T, Suginome M (2009) Bull Chem Soc Jpn 82:29–49
35. Lee K-S, Hoveyda AH (2010) J Am Chem Soc 132:2898–2900
36. Plotzitzka J, Kleeberg C (2014) Organometallics 33:6915–6926
37. Harb HY, Collins KD, Altur JVG, Bowker S, Campbell L, Procter DJ (2010) Org Lett 12: 5446–5449
38. Pace V, Rae JP, Harb HY, Procter DJ (2013) Chem Commun 49:5150–5152
39. Pace V, Rae JP, Procter DJ (2014) Org Lett 16:476–479
40. Ibrahem I, Santoro S, Himo F, Córdova A (2011) Adv Synth Catal 353:245–252
41. Luo Y, Roy ID, Madec AGE, Lam HW (2014) Angew Chem Int Ed 53:4186–4190
42. Lee K-S, Wu H, Haeffner F, Hoveyda AH (2012) Organometallics 31:7823–7826
43. Kubota K, Yamamoto E, Ito H (2015) J Am Chem Soc 137:420–424
44. Beene MA, An C, Ellman JA (2008) J Am Chem Soc 130:3769–3771
45. Wen K, Wang H, Chen J, Zhang H, Cui X, Wei C, Fan E, Sun Z (2013) J Org Chem 78: 4305–4309
46. Zhang S-S, Zhao Y-S, Tian P, Lin G-Q (2013) Synlett 24:437–442
47. Solé C, Gulyas H, Fernández E (2012) Chem Commun 48:3769–3774
48. Cirriez V, Rasson C, Hermant T, Petrignet J, Alvarez JD, Robeyns K, Riant O (2013) Angew Chem Int Ed 52:1785–1788
49. Hensel A, Nagura K, Delvos LB, Oestreich M (2014) Angew Chem Int Ed 53:4964–4967
50. Mita T, Sugawara M, Saito K, Sato Y (2014) Org Lett 16:3028–3031
51. Zhao C, Jiang C, Wang J, Wu C, Zhang Q-W, He W (2014) Asian J Org Chem 3:851–855
52. Ito H, Ito S, Sakai Y, Matsuura K, Sawamura M (2007) J Am Chem Soc 129:14856–14857
53. Ito H, Kawakami C, Sawamura M (2005) J Am Chem Soc 127:16034–16035
54. Ito H, Kosaka Y, Nonoyama K, Sakai Y, Sawamura M (2008) Angew Chem Int Ed 47: 7424–7427
55. Zhong C, Kunii S, Kosaka Y, Sawamura M, Ito H (2010) J Am Chem Soc 132:11440–11442
56. Guzman-Martinez A, Hoveyda AH (2010) J Am Chem Soc 132:10634–10637
57. Park JK, Lackey HH, Ondrusek BA, McQuade DT (2011) J Am Chem Soc 133:2410–2413
58. Yamamoto E, Takenouchi Y, Ozaki T, Miya T, Ito H (2014) J Am Chem Soc 136: 16515–16521
59. Delvos LB, Vyas DJ, Oestreich M (2013) Angew Chem Int Ed 52:4650–4653
60. Delvos LB, Hensel A, Oestreich M (2014) Synthesis 46:2957–2964
61. Takeda M, Shintani R, Hayashi T (2013) J Org Chem 78:5007–5017
62. Morizawa Y, Oda H, Oshima K, Nozaki H (1984) Tetrahedron Lett 25:1163–1166
63. Weickgenannt A, Oestreich M (2010) Chem Eur J 16:402–412
64. Oestreich M, Auer G (2005) Adv Synth Catal 347:637–640
65. Schmidtmann ES, Oestreich M (2006) Chem Commun 3643–3645
66. Vyas DJ, Oestreich M (2010) Chem Commun 46:568–570

67. Hazra CK, Oestreich M (2012) Org Lett 14:4010–4013
68. Hensel A, Oestreich M (2015) Chem Eur J 21:9062–9065
69. Ito H, Kunii S, Sawamura M (2010) Nat Chem 2:972–976
70. Delvos LB, Oestreich M (2015) Synthesis 47:924–933
71. Sasaki Y, Zhong C, Sawamura M, Ito H (2010) J Am Chem Soc 132:1226–1227
72. Burns AR, González JS, Lam HW (2012) Angew Chem Int Ed 51:10827–10831
73. Liu P, Fukui Y, Tian P, He Z-T, Sun CY, Wu N-Y, Lin G-Q (2013) J Am Chem Soc 135: 11700–11703
74. Lee J-E, Kwon J, Yun J (2008) Chem Commun 733–734
75. Lee Y, Jang H, Hoveyda AH (2009) J Am Chem Soc 131:18234–18235
76. Kim HR, Jung IG, Yoo K, Jang K, Lee ES, Yun J, Son SU (2010) Chem Commun 46:758–760
77. Kim HR, Yun J (2011) Chem Commun 47:2943–2945
78. Jung HY, Yun J (2012) Org Lett 14:2606–2609
79. Wang P, Yeo X-L, Loh T-P (2011) J Am Chem Soc 133:1254–1256
80. Meng F, Jang H, Hoveyda AH (2013) Chem Eur J 19:3204–3214
81. Hazra CK, Fopp C, Oestreich M (2014) Chem Asian J 9:3005–3010
82. Vercruysse S, Cornelissen L, Nahra F, Collard L, Riant O (2014) Chem Eur J 20:1834–1838
83. Calderone JA, Santos WL (2014) Angew Chem Int Ed 53:4154–4158
84. Linstadt RTH, Peterson CA, Lippincott DJ, Jette CI, Lipschutz BH (2014) Angew Chem Int Ed 53:4159–4163
85. Xu Y-H, Wu L-H, Wang J, Loh T-P (2014) Chem Commun 50:7195–7197
86. Matsuda N, Hirano K, Satoh T, Miura M (2013) J Am Chem Soc 135:4934–4937
87. Meng F, Haeffner F, Hoveyda AH (2014) J Am Chem Soc 136:11304–11307
88. Welle A, Petrignet J, Tinant B, Wouters J, Riant O (2010) Chem Eur J 16:10980–10983
89. Noh D, Yoon SK, Won J, Lee JY, Yun J (2011) Chem Asian J 6:1967–1969
90. Feng X, Jeon H, Yun J (2013) Angew Chem Int Ed 52:3989–3992
91. Lee JCH, McDonald R, Hall DG (2011) Nat Chem 3:894–899
92. Ito H, Okura T, Matsuura K, Sawamura M (2010) Angew Chem Int Ed 49:560–563
93. Parra A, Amenós L, Guisán-Ceinos M, López A, Ruano JLG, Tortosa M (2014) J Am Chem Soc 136:15833–15836

Top Organomet Chem (2016) 58: 169–182
DOI: 10.1007/3418_2015_163

Published online: 2 December 2015

Catalytic Asymmetric Addition Reactions of Cu(I)-Conjugated Soft Carbon Nucleophiles

Xiaofeng Wei, Yohei Shimizu, and Motomu Kanai

Abstract Copper is a ubiquitous element on the earth. Copper catalysts promote a wide variety of reaction types by acting as a Lewis acid, a π acid, a Brønsted base, or an electron mediator. These features make copper catalysts particularly attractive in modern organic chemistry. In this review, we discuss examples of recent copper (I)-catalyzed asymmetric C–C bond-forming reactions *via* the addition of soft copper(I)-conjugated carbon nucleophiles to carbonyl electrophiles. Specifically, we focus on the unique orthogonal reactivity of soft copper(I)-conjugated carbon nucleophiles to hard protic functional groups, which would allow for protecting group-minimized molecular synthesis.

Keywords Asymmetric • Catalyst • Copper • Protecting group-minimized • Soft carbon nucleophile

Contents

1 Introduction 170
2 HSAB (Hard and Soft Acid and Base) Theory 170
3 Hard Anion-Conjugated Soft Metal Catalysis (HASM) 172
4 Copper(I)-Catalyzed Chemoselective and Asymmetric C–C Bond-Forming Reactions in the Presence of Protic Functional Groups 173

X. Wei and Y. Shimizu
Graduate School of Pharmaceutical Sciences, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

M. Kanai (✉)
Graduate School of Pharmaceutical Sciences, the University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

JST-ERATO, Kanai Life Science Catalysis Project, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
e-mail: kanai@mol.f.u-tokyo.ac.jp

4.1 Copper(I)-Catalyzed Asymmetric Addition of Enolates and Their Equivalents . . . 173
4.2 Copper(I)-Catalyzed Nucleocupration of Allenes Followed by Asymmetric Addition . . . 178
5 Conclusion . . . 180
References . . . 181

1 Introduction

Asymmetric catalysis is indispensable for the synthesis of a plethora of enantiomerically enriched compounds [1–3]. Taking current high demands for environmentally benign molecular synthesis into account, asymmetric catalysis bestowed with high atom [4] and step economy [5] is desirable, especially for industrial-scale applications. A number of catalytic asymmetric C–C bond-forming reactions have been developed using pre-activated reagents, such as enolsilyl ethers and allylboronates. In those reactions, however, pre-activation steps are required in addition to target bond-forming steps. Furthermore, stoichiometric amounts of side products, such as salts and silicon- or boron-containing wastes, are produced in the pre-activation and the C–C bond-forming steps. Protecting groups are another necessary evil in organic synthesis. The use of protecting groups allows for secured molecular conversions, but atom and step economy of the overall molecular synthesis decreases. From the viewpoint of green chemistry, the development of catalytic asymmetric C–C bond-forming reactions without pre-activations [6–8] or protecting groups [9] is of great importance.

In this review, we discuss recent, selected examples of Cu(I)-catalyzed asymmetric C–C bond-forming reactions in the presence of unprotected protic functional groups. We believe that this scope setting is best suited for the appealing, unique characteristics of Cu(I)-conjugated chiral and soft carbon nucleophiles, which will be useful for developing an ideal molecular synthesis with high step and atom economy. We describe two types of generation methods for Cu(I)-conjugated carbon nucleophiles along this direction, namely, copper enolate formation via deprotonation and organocopper formation via nucleocupration of C=C double bonds (Sects. 4.1 and 4.2). Due to the editorial policy of this book, we do not intend a comprehensive review, but rather we focus on presenting basic concepts underlying the catalysis developments (Sects. 2 and 3).

2 HSAB (Hard and Soft Acid and Base) Theory

In the 1960s, Ralph G. Pearson introduced hard and soft acid and base (HSAB) theory [10, 11]. The HSAB concept is widely applied in chemistry for explaining characteristics of compounds, reaction mechanisms, and reaction pathways. In the initial studies, Lewis acids and Lewis bases were classified as hard or soft (Table 1).

Table 1 Classification of Lewis acids and Lewis bases into hard and soft groups

Hard		Soft
Acid	H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+, Tl^+, Hg^+, Cs^+
	Be^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Mn^{2+}	Pd^{2+}, Cd^{2+}, Pt^{2+}, Hg^{2+}, CH_3Hg^+
	Al^{3+}, Sc^{3+}, Ga^{3+}, In^{3+}, La^{3+}	Tl^{3+}, Au^{3+}, Te^{4+}, Pt^{4+}
	Cr^{3+}, Co^{3+}, Fe^{3+}, As^{3+}, Ce^{3+}	$Tl(CH_3)_3$, BH_3, $Co(CN)_5^{2-}$
	Si^{4+}, Ti^{4+}, Zr^{4+}, Th^{4+}, Pu^{4+}	RS^+, RSe^+, RTe^+
	Ce^{4+}, Ge^{4+}, VO^{2+}	I^+, Br^+, HO^+, RO^+
	VO_2^+, $(CH_3)_2Sn^{2+}$	I_2, Br_2, ICN, etc.
	$BeMe_2$, BF_3, BCl_3, $B(OR)_3$	Trinitrobenzene, etc.
	$Al(CH_3)_3$, $Ga(CH_3)_3$, $In(CH_3)_3$, AlH_3	Chloranil, Quinones, etc.
	RPO_2^+, $ROPO_2^+$	Tetracyanoethylene, etc.
	RSO^{2+}, $ROSO_2^+$, SO_3	M^0 (metal atoms)
	I^{7+}, I^{5+}, Cl^{7+}, Cr^{6+}, Se^{6+}	Bulk metals
	RCO^+, CO_2, NC^+	
	HX (hydrogen bonding molecules)	
Borderline: Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pd^{2+}, Sn^{2+}, Sb^{3+}, Bi^{3+}, Rh^{3+}, Ir^{3+}, NO^+, Ru^{2+}, Os^{2+}, R_3C^+, $B(CH_3)_3$		
Base	H_2O, HO^-, F^-, CH_3COO^-, PO_4^{3-}	R_2S, RSH, RS^-, I^-, SCN^-, $S_2O_3^{2-}$
	SO_4^{2-}, Cl^-, CO_3^{2-}, ClO_4^-, NO_3^-	R_3P, R_3As, $(RO)_3P$, CN^-, RNC, CO
	ROH, RO^-, R_2O	C_2H_4, C_6H_6
	NH_3, RNH_2, N_2H_4	H^-, R^-
Borderline: $C_6H_5NH_2$, C_5H_5N, N_3^-, Br^-, NO_3^-, SO_3^{2-}, N_2		

Hard acids are characterized as small size, high oxidation states with great positive charges, and the absence of polarizable outer electrons. On the other hand, soft acids have large size, small or zero positive charges, and polarizable outer electrons. Hard bases are classified as donor atoms with great electronegativity and low polarizability, while soft bases have the opposing properties with small electronegativity and high polarizability.

Since acid–base reactions are versatile, descriptions of their fundamental principles are highly important. Pearson's principle of HSAB can be stated as: hard acids prefer to bond with hard bases, and soft acids prefer to bond with soft bases. The large difference in electronegativity between hard acids and hard bases gives rise to strong ionic interactions, while soft acids and soft bases generate strong covalent interactions due to small HOMO–LUMO gaps. The mismatched interactions between hard acids and soft bases and between soft acids and hard bases are, however, polar covalent and less stable.

As a typical example, the HSAB theory qualitatively explains the reaction pathways of soft organocuprate nucleophiles and hard Grignard reagents in 1,4- and 1,2-addition reactions to cyclohexenone (**2**), respectively (Fig. 1). Soft organocuprate nucleophiles generally prefer 1,4-addition to **2** at the soft alkene moiety, affording product **1**, rather than 1,2-addition to the hard carbonyl group. Meanwhile, hard Grignard reagents attack the hard carbonyl group to give 1,2-addition product **3**.

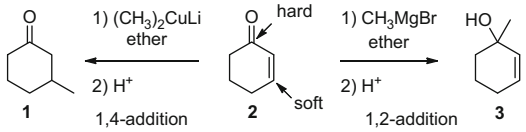


Fig. 1 1,4- vs.1,2-Addition of organometallic reagents to cyclohexenone

3 Hard Anion-Conjugated Soft Metal Catalysis (HASM)

Using the hard–soft mismatched characteristics of hard anion (X)-conjugated soft Cu(I) salts (CuX: X=F, OR), our group has identified general methods to catalytically generate a variety of reactive carbon nucleophiles for asymmetric addition to carbonyl groups and imines (Fig. 2) [12, 13]. We named the basic concept underlying these reactions as hard anion-conjugated soft metal catalysis (HASM). The soft–soft Lewis acid–Lewis base interaction between Cu(I) and the π electrons of a carbon *pre*-nucleophile (*C*-Nuc–M) polarizes the C–M bond of the *pre*-nucleophile, thus promoting the transfer of the hard anion X of the catalyst to the hard M of the *pre*-nucleophile, which are interacting with each other with a hard–hard interaction (Fig. 2, **4**). The soft carbon nucleophile (*C*-Nuc) is then transferred to the soft Cu(I), generating a Cu(I)-conjugated carbon nucleophile (Cu–*C*-Nuc) and MX, containing soft–soft and hard–hard interactions, respectively. In other words, by taking advantage of the soft–hard mismatched characteristics of catalyst CuX, the nucleophile activation process becomes thermodynamically favorable.

Introduction of chiral phosphine ligands to CuX catalysts makes various catalytic asymmetric reactions possible. Using this basic concept, we have achieved catalytic asymmetric addition reactions of allylsilicones [14], allylboronates [15–18], alkenylsilicones [19], alkenylboronates [20], arylsilicones [15], arylboronates [19, 21] and ketene silylacetals [22, 23] activated through transmetalation, ester enolates generated through conjugate reduction [24, 25] or alkylation [26] of α,β-unsaturated esters, nitriles activated through decarboxylation from cyanocarboxylic acids [27] or deprotonation [28, 29], and alkynyl groups activated through deprotonation [30]. These results demonstrate that HASM can be a general concept for catalytic activation of nucleophiles from stable molecules. In the following sections, we describe that chiral Cu(I)-conjugated carbon nucleophiles, generated by the HASM concept, act as soft nucleophiles and chemoselectively react with carbon electrophiles, even in the presence of protic functional groups.

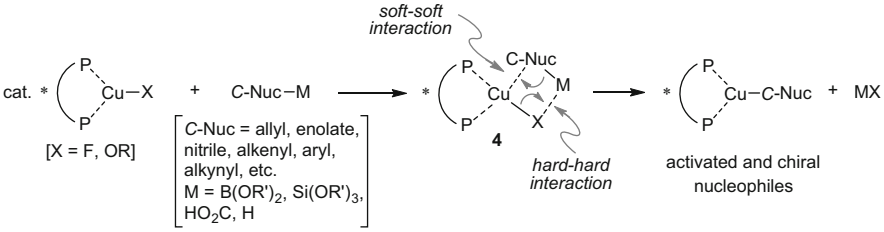


Fig. 2 General concept for nucleophile activation through hard anion-conjugated soft metal catalysis (HASM)

4 Copper(I)-Catalyzed Chemoselective and Asymmetric C–C Bond-Forming Reactions in the Presence of Protic Functional Groups

4.1 Copper(I)-Catalyzed Asymmetric Addition of Enolates and Their Equivalents

Shibasaki and Kanai developed a catalytic enantioselective nitrile aldol reaction using CuO*t*-Bu–DTBM-SEGPHOS complex as a catalyst (Fig. 3) [27] (for other reports of direct catalytic nitrile aldol reactions, see [31, 32]). Despite moderate enantioselectivity, it is noteworthy that chemoselective generation of an enolate equivalent (copper ketene imide **6** in Fig. 4) is possible from acetonitrile in the presence of aldehydes containing more acidic α-protons. The pK_a values of α-protons of acetonitrile and aliphatic aldehydes are 31.3 and ca. 23 (in DMSO), respectively. Key for the selective deprotonation from acetonitrile is the chemoselective interaction between soft Cu(I) and soft nitrile, which selectively acidifies α-protons of acetonitrile (Fig. 4, **5**).

A proposed catalytic cycle is shown in Fig. 4. The chiral Brønsted base CuO*t*-Bu catalyst generates in situ from CuOTf and KO*t*-Bu. This is a convenient method for the formation of CuO*t*-Bu catalyst on demand, because CuO*t*-Bu [33] is not very stable and storable for a long period. We have confirmed that the side product, KOTf, does not affect the results, because salt-free CuO*t*-Bu [33] catalyst produced comparable results to the catalyst generated from CuOTf and KO*t*-Bu. After chemoselective deprotonation from acetonitrile through **5**, chiral copper ketene imide nucleophile **6** is generated, which reacts with an aldehyde and produces copper alkoxide **7**. Intermediate **7** contains a soft–hard mismatch and thus is catalytically active. Copper alkoxide**7** deprotonates acetonitrile to regenerate active nucleophile **6** while forming the product. The C–C bond formation proceeds in the presence of alcohol products, because the active nucleophile generation is reversible under the reaction conditions and also soft copper ketene imide **6** prefers the attack to the soft aldehyde carbon rather than the attack to the hard alcohol proton at least to some extent.

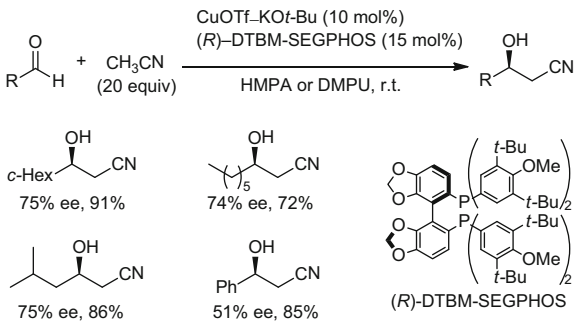


Fig. 3 Copper(I)-catalyzed asymmetric addition of acetonitrile to aldehydes

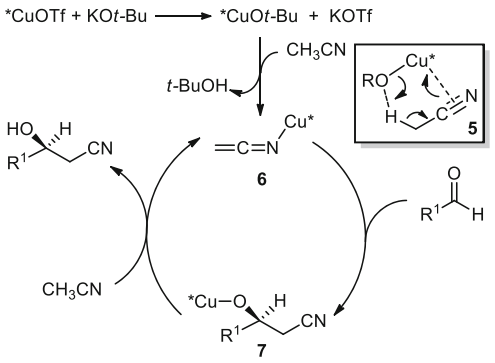


Fig. 4 Proposed catalytic cycle of copper(I)-catalyzed asymmetric addition of nitriles to aldehydes

On the basis of this finding, Shibasaki's group developed a series of asymmetric reactions using soft copper(I) Brønsted base catalysts and a wide variety of *pre*-nucleophiles (thioamides [34–43], isocyanide [44, 45], unsaturated butyrolactones [46, 47], nitroalkanes [48], allyl cyanide [49, 50], and α-trifluoromethylacetamide [51]) *via* proton transfer strategy (Fig. 5).

Dihydropyranones **9** are synthetically useful chiral building blocks for drug lead compounds. Our group reported a catalytic asymmetric synthesis of **9** from ynones **8** and aldehydes through sequential copper(I)-catalyzed asymmetric direct aldol reaction and silver(I)-catalyzed oxy-Michael reaction (Fig. 6) [52]. The addition of trifluoroethanol in a (sub)stoichiometric amount (40–200 mol%) is crucial for high yield in the aldol reaction step. The catalytic asymmetric C–C bond formation in the presence of a relatively acidic alcohol additive (pK_a of trifluoroethanol = 23.5 in DMSO, cf. pK_a of α-C–H of acetophenone = 24.7 in DMSO) is noteworthy, and this is again due to both reversible enolate formation under the reaction conditions and the nature of soft Cu(I) enolates. The additive stabilizes the aldol products, probably by reducing the basicity of the reaction media; the use of 40 mol% additive is enough for the reactions with aliphatic aldehydes (R^1 = aliphatic groups), affording relatively stable aldol products, while for aromatic aldehydes (R^1 = aromatic groups), the aldol products are less stable, and a superstoichiometric amount of additive is necessary for a high product yield. After the asymmetric aldol reaction, AgOTf-catalyzed oxy-Michael reaction produced enantiomerically enriched dihydropyranones **9**.

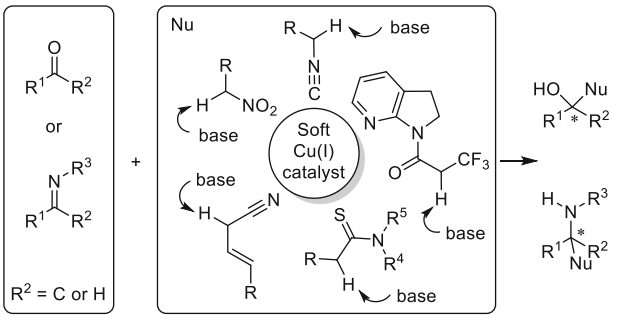


Fig. 5 Representative examples for Cu(I)-catalyzed asymmetric addition reactions through nucleophile generation via deprotonation, affording products containing protic functional groups

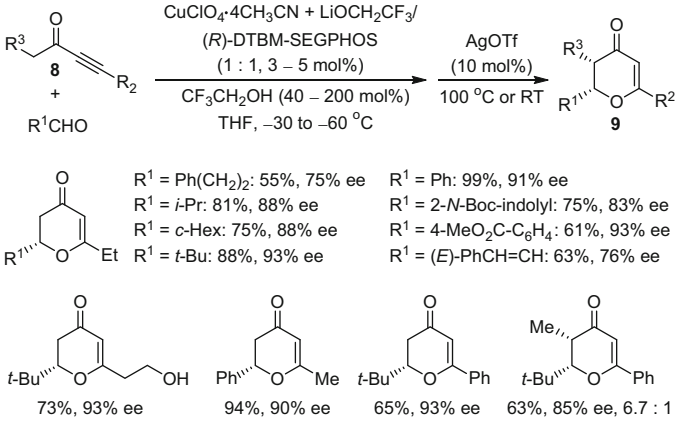


Fig. 6 Catalytic asymmetric dihydropyranone synthesis through copper(I)-catalyzed asymmetric aldol reaction and subsequent silver(I)-catalyzed oxy-Michael reaction

A plausible catalytic cycle for the direct asymmetric aldol reaction is shown in Fig. 7. Key to the success of the reaction is chemoselective enolate formation of ynones **8** in the presence of enolizable aldehydes, which is mediated by soft–soft interaction **10** between the ynone moiety and the copper catalyst. This interaction selectively acidifies the α-protons of ynones. The aldol addition of chiral Cu (I) enolate **12** to an aldehyde affords copper aldolate **13**. The soft–soft interaction between the Cu(I) atom and the π electrons of the alkyne moiety in **13** would help suppress the undesired retro-aldol reaction due to the existence of additional coordination. Nevertheless, facile protonation of unstable **13** and formation of aldol product **14** is crucial, rationalizing the inquiry of (sub)stoichiometric amounts of trifluoroethanol. Protonation of **13** regenerates the copper alkoxide catalyst.

Among protic species, water is the most problematic for Cu(I)-conjugated Brønsted base catalysts due to the instability of Cu(I)OH. Cu(I)OH is considered to decompose into insoluble and polymeric Cu_2O by dehydration [53]. In 2012, our group developed an enantioselective condensation between ketones and cyclic

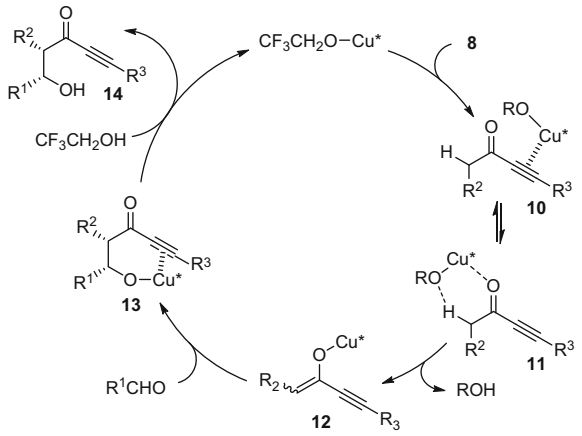


Fig. 7 Proposed catalytic cycle of copper(I)-catalyzed asymmetric aldol reaction of aldehydes and ynones

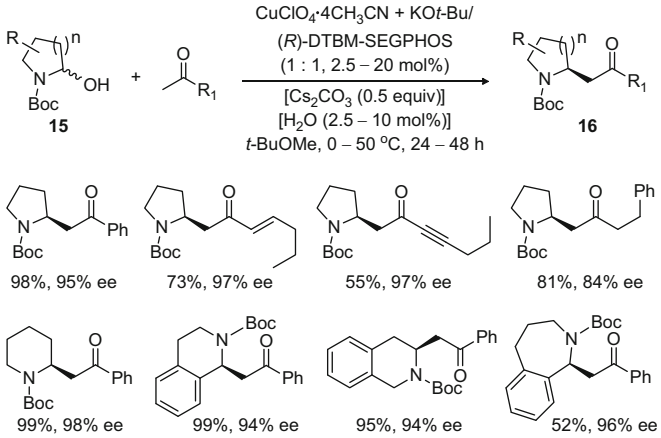


Fig. 8 Copper(I)-catalyzed enantioselective condensation of ketones and cyclic hemiaminals

hemiaminals **15** using copper(I) catalyst (Fig. 8) [54]. Products **16** are important intermediates in biosynthesis of various pyrrolidine and piperidine alkaloids and thus are versatile chiral building blocks in alkaloid synthesis. Despite their synthetic versatility, however, there was no practical catalytic enantioselective synthesis of **16** prior to our report. The Cu(I)-catalyzed enantioselective reaction is of broad substrate generality, covering aliphatic and aromatic ketones for the donor substrates and five-, six-, and seven-membered cyclic hemiaminals for the acceptor substrates (Fig. 8). Additive Cs_2CO_3 improved the yield, especially in the case of six-membered hemiaminals, possibly by increasing the concentration of reactive aldehyde form **17** derived from **15** (see below). Although water is generated during the reaction progress, the addition of catalytic amounts of water at the beginning slightly improved the enantioselectivity.

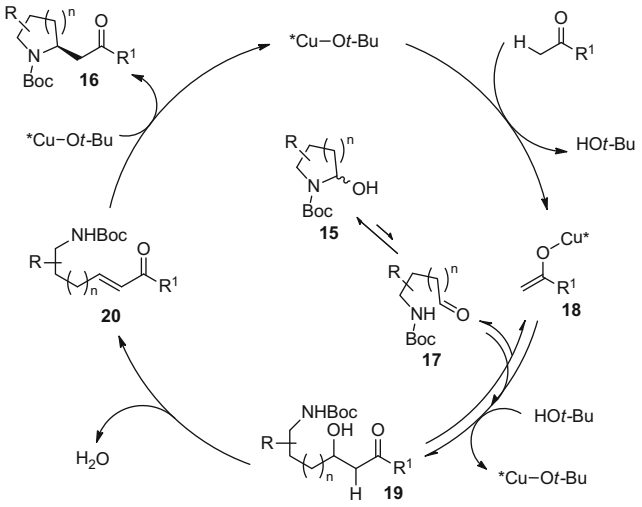


Fig. 9 Proposed catalytic cycle for copper(I)-catalyzed enantioselective condensation of ketones and cyclic hemiaminals

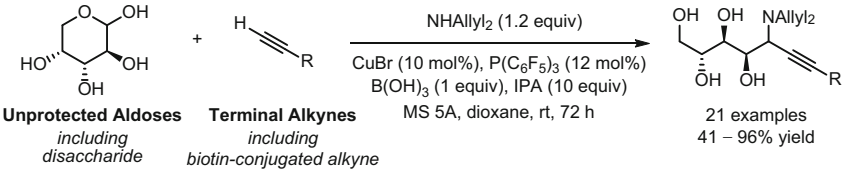


Fig. 10 Copper(I)-catalyzed anomeric aminoalkynylation of unprotected aldoses

The catalytic cycle is proposed as shown in Fig. 9. The reaction process includes (1) base-promoted facilitation of the equilibrium between hemiaminal **15** and aldehyde **17**; (2) chemoselective deprotonation of donor ketones by the Cu (I) alkoxide catalyst to generate Cu(I) enolate **18**, likely due to the large relative concentration difference between donor ketones and aldehyde **17**; (3) aldol reaction between enolate **18** and **17** to produce **19**; (4) Cu(I) alkoxide-catalyzed dehydration of **19** to generate enone **20**; and (5) Cu(I) alkoxide-catalyzed enantioselective intramolecular aza-Michael addition to give enantiomerically enriched product **16**. The Cu(I) catalyst plays multiple roles in this catalytic cycle. The proposed catalytic cycle is supported by subjecting isolated intermediates **19** and **20** to the reaction conditions, respectively, both producing **16** with comparable enantioselectivity to the reaction starting from **15**. Keys to the success of this reaction are again the reversible enolate formation and the nature of soft copper(I) enolates acting as a carbon nucleophile, even in the presence of the hard hydroxy groups of the substrates and water added or generated in the reaction.

We have developed a Cu(I)-catalyzed anomeric aminoalkynylation of unprotected sugars (Fig. 10) [55]. We do not describe this reaction in detail here, because this is not a catalyst-controlled asymmetric reaction (e.g., Cu(I)-catalyzed

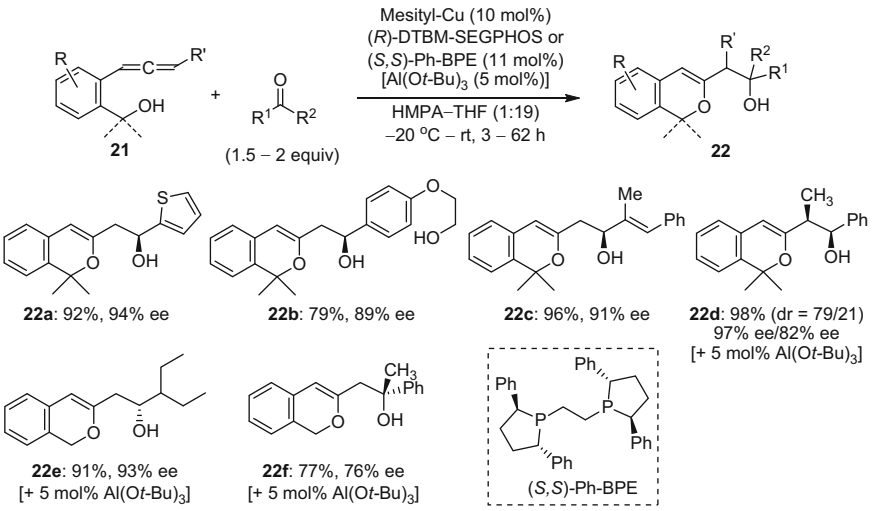


Fig. 11 Consecutive copper(I)-catalyzed oxycupration followed by asymmetric addition of carbonyl compounds for isochromene synthesis

enantioselective additions of alkynes, see [56–61]). Nevertheless, the result is noteworthy because it demonstrates that the soft copper-conjugated carbon nucleophiles (copper alkynides) can react with carbon electrophiles (iminium species generated from sugars and diallylamine) containing multiple hydroxy groups.

4.2 Copper(I)-Catalyzed Nucleocupration of Allenes Followed by Asymmetric Addition

In the examples mentioned above, the generation of reactive Cu(I)-conjugated carbon nucleophiles through deprotonation of *pre*-nucleophiles is a reversible process. Therefore, although the characteristics of the Cu(I)-conjugated soft nucleophiles should play an important role in chemoselective C–C bond formations compared to protonation, it is not critical for the reactions described in Sect. 4.1. In the case when generation of Cu(I)-conjugated carbon nucleophiles is irreversible, however, extremely high chemoselectivity is an essential requirement. To challenge this issue, our group studied an intramolecular oxycupration approach [62] for the catalytic generation of organocopper species from allenyl alcohol **21**. The thus generated organocopper species were subsequently applied to asymmetric addition to aldehydes and a ketone in a one-pot procedure (Fig. 11) [63]. Key for the success of this reaction relies on the chemoselective and enantioselective addition of the intermediate organocopper species to carbonyl compounds in the presence of stoichiometric hydroxy groups of the starting allenyl alcohols. The product isochromenes are useful synthetic intermediates for many drug lead compounds.

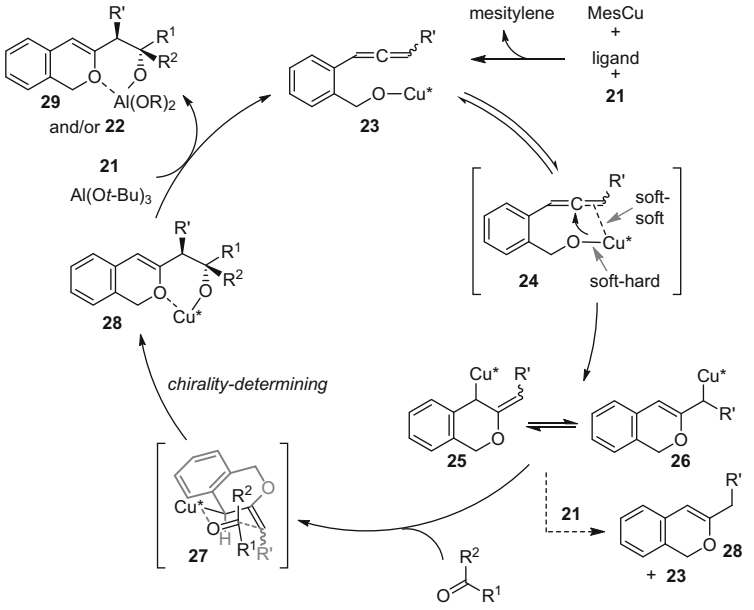


Fig. 12 Proposed catalytic cycle of the consecutive copper(I)-catalyzed oxycupration followed by asymmetric addition

Two different chiral bidentate phosphines, DTBM-SEGPHOS and Ph-BPE, are used as ligands for the copper catalysts, depending on the substrates: for substrates **21a**–**21d** containing a tertiary alcohol moiety, where oxycupration is facilitated by the Thorpe–Ingold effect, Ph-BPE is the best ligand, while for substrates with a primary alcohol moiety such as **21e**, DTBM-SEGPHOS is the best. The addition of Al(O*t*-Bu)$_3$ as a Lewis acid cocatalyst improves the yield, especially for the reactions with aliphatic aldehydes, without changing the enantioselectivity. In the case when racemic allenyl alcohol **21d** (R′=CH$_3$) was used as a substrate, product **22d** was obtained with high yield and enantioselectivity, indicating that the reaction is stereoconvergent.

The catalytic cycle is proposed in Fig. 12. First, copper alkoxide **23** is generated *via* deprotonation of the hydroxy group of **21** by the mesitylcopper (MesCu) catalyst. Then, intramolecular oxycupration of the allene moiety generates organocopper species **25** and **26**, existing in equilibrium. This step is promoted by soft–soft interaction between the Cu(I) atom and the π electrons of the allene moiety, as well as the soft–hard mismatch of the Cu(I) alkoxide (HASM, **24**). Addition of the thus generated organocopper **25** to carbonyl compounds would proceed through a six-membered transition state shown as **27** to give enantiomerically (and diastereomerically) enriched copper alkoxide **28**. We did not observe the regioisomer products derived from **26**, with the C–C bond formation at the benzylic position. The soft characteristics of organocopper species **25** and **26** are critically important in this addition step. If protonation of **25**/**26** by

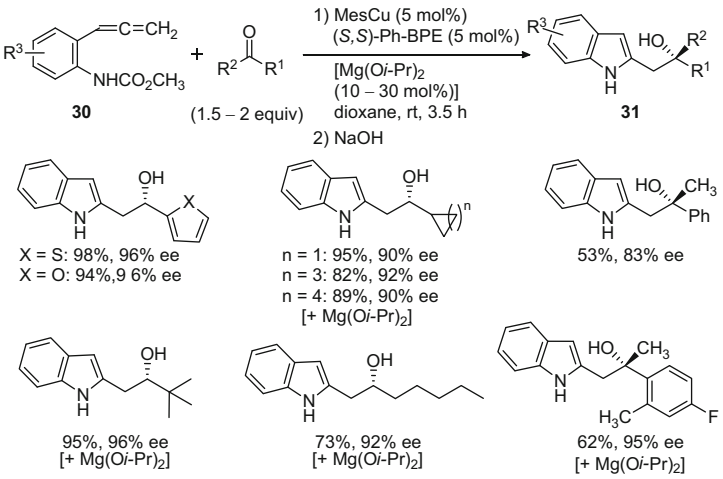


Fig. 13 Consecutive copper(I)-catalyzed amidocupration followed by asymmetric addition of carbonyl compounds for indole synthesis

stoichiometric amounts of **21** takes place instead of the C–C bond formation, cyclized **28** generates as a dead-end by-product. Since this protonation pathway is irreversible, **25/26** must exhibit high chemoselectivity for the C–C bond formation. The chirality of the substrate **21d** when R′=CH_3 is lost during the equilibrium between **25** and **26**, resulting in the observed stereoconvergent reaction of **21d**. Ligand exchange between **28** and **21** yields product **22** and catalytically active copper alkoxide **23**. This ligand exchange should be the rate-determining step. The Al(O*t*-Bu)$_3$ cocatalyst would accelerate this step through the formation of the thermodynamically favorable aluminum chelate **29** from copper chelate **28**. This hypothesis is consistent with the experimental results that enantioselectivity is not affected by the addition of Al(O*t*-Bu)$_3$, because the aluminum additive works after the enantioselectivity is determined in this catalytic cycle.

This strategy was extended to the synthesis of enantiomerically enriched 2-(2-hydroxyethyl)indole derivatives starting from allenylanilides [64] through a consecutive amidocupration, followed by enantioselective addition of the resulting nucleophilic organocopper species to aldehydes and ketones (Fig. 13). Mg(O*i*-Pr)$_2$, instead of Al(O*t*-Bu)$_3$, is a better cocatalyst in this case. Products are again versatile chiral building blocks for various drug lead compounds.

5 Conclusion

This review describes recent progress in asymmetric addition reactions of soft Cu (I)-conjugated carbon nucleophiles in the presence of protic functional groups, mainly focusing on chemoselectivity. Protic functional groups of amides, hydroxy

groups, and even H_2O are compatible in the copper(I)-catalyzed asymmetric reactions. Such characteristics of copper(I)-catalyzed asymmetric C–C bond-forming reactions will give rise to various opportunities for the application to late-stage structural optimization of drug lead compounds and protecting group-minimized synthesis of multifunctional complex molecules. Representative challenges in this field are (1) improving the external ligand-controlled enantioselectivity and diastereoselectivity, especially when the substrate contains multiple chiral centers with polar functional groups, such as polysaccharides and peptides, and (2) developing novel catalytic generation methods for copper nucleophiles, enabling high atom and step economy.

References

1. Walsh PJ, Kozlowski MC (2009) Fundamentals of asymmetric catalysis. University Science Books, Sausalito
2. Corey EJ, Kürti L (2010) Enantioselective chemical synthesis. Direct Book Publishing, Dallas
3. Zhou Q-L (2011) Privileged chiral ligands and catalysts. Wiley-VCH, Weinheim, Germany
4. Trost BM (1991) Science 254:1471
5. Wender PA, Miller BL (2009) Nature 460:197
6. Dunn PJ, Hii KK, Krische MJ, Williams MT (2012) Sustainable catalyst: challenges and practices for the pharmaceutical and fine chemical industries. Wiley, New Jersey, USA
7. Trost BM, Brindle CS (2010) Chem Soc Rev 39:1600
8. Kumagai N, Shibasaki M (2011) Angew Chem Int Ed 50:4760
9. I. S. Young, P. S. Baran (2009) Nat Chem 1:193
10. Pearson RG (1963) J Am Chem Soc 85:3533
11. Pearson RG (1966) Science 151:172
12. Shibasaki M, Kanai M (2008) Chem Rev 108:2853
13. Kanai M, Matsunaga S, Oisaki K, Shimizu Y (2013) J Synth Org Chem Japan 71:433
14. Yamasaki S, Fujii K, Wada R, Kanai M, Shibasaki M (2002) J Am Chem Soc 124:6536
15. Wada R, Oisaki K, Kanai M, Shibasaki M (2004) J Am Chem Soc 126:8910
16. Wada R, Shibuguchi T, Makino S, Oisaki K, Kanai M, Shibasaki M (2006) J Am Chem Soc 2006:7687
17. Kanai M, Wada R, Shibuguchi T, Shibasaki M (2008) Pure Appl Chem 80:1055
18. Shi S-L, Xu L-W, Oisaki K, Kanai M, Shibasaki M (2010) J Am Chem Soc 132:6638
19. Tomita D, Wada R, Kanai M, Shibasaki M (2005) J Am Chem Soc 127:4138
20. Tomita D, Kanai M, Shibasaki M (2006) Chem Asian J 1:161
21. Tomita D, Yamatsugu K, Kanai M, Shibasaki M (2009) J Am Chem Soc 131:6946
22. Oisaki K, Suto Y, Kanai M, Shibasaki M (2003) J Am Chem Soc 125:5644
23. Oisaki K, Zhao D, Kanai M, Shibasaki M (2006) J Am Chem Soc 128:7164
24. Zhao D, Oisaki K, Kanai M, Shibasaki M (2006) J Am Chem Soc 128:14440
25. Du Y, Xu W, Shimizu Y, Kanai M, Shibasaki M (2008) J Am Chem Soc 130:16146
26. Oisaki K, Zhao D, Kanai M, Shibasaki M (2007) J Am Chem Soc 129:7439
27. Yin L, Kanai M, Shibasaki M (2009) J Am Chem Soc 131:9610
28. Suto Y, Tsuji R, Kanai M, Shibasaki M (2005) Org Lett 7:3757
29. Suto Y, Kumagai N, Matsunaga S, Kanai M, Shibasaki M (2003) Org Lett 5:3147
30. Motoki R, Kanai M, Shibasaki M (2007) Org Lett 9:2997
31. Chakraborty S, Pater Y, Krause J, Guan H-R (2013) Angew Chem Int Ed 52:7523
32. Sureshkumar D, Ganesh V, Kumagai N, Shibasaki M (2014) Chem Eur J 20:15723
33. Tsuda T, Hashimoto T, Saegusa T (1972) J Am Chem Soc 94:658

34. Majumdar N, Saito A, Yin L, Kumagai N, Shibasaki M (2015) Org Lett 17:3362
35. Alagiri K, Lin S, Kumagai N, Shibasaki M (2014) Org Lett 16:5301
36. Matsuzawa A, Opie CR, Kumagai N, Shibasaki M (2014) Chem Eur J 20:68
37. Kawato Y, Chaudhary S, Kumagai N, Shibasaki M (2013) Chem Eur J 19:3802
38. Gopinath P, Watanabe T, Shibasaki M (2012) J Org Chem 77:9260
39. Sureshkumar D, Kawato Y, Iwata M, Kumagai N, Shibasaki M (2012) Org Lett 14:3018
40. Suzuki Y, Iwata M, Yazaki R, Kumagai N, Shibasaki M (2012) J Org Chem 77:4496
41. Suzuki Y, Yazaki R, Kumagai N, Shibasaki M (2011) Chem Eur J 17:11998
42. Iwata M, Yazaki R, Chen I, Sureshkumar D, Kumagai N, Shibasaki M (2011) J Am Chem Soc 133:5554
43. Iwata M, Yazaki R, Kumagai N, Shibasaki M (2010) Tetrahedron Asymmetry 21:1688
44. Takemura K, Kumagai N, Shibasaki M (2015) Eur J Org Chem 2015:3026
45. Saito A, Kumagai N, Shibasaki M (2014) Tetrahedron Lett 55:3167
46. Yin L, Takada H, Lin S, Kumagai N, Shibasaki M (2014) Angew Chem Int Ed 53:5327
47. Yin L, Takada H, Kumagai N, Shibasaki M (2013) Angew Chem Int Ed 52:7310
48. Ogawa T, Mouri S, Yazaki R, Kumagai N, Shibasaki M (2012) Org Lett 14:110
49. Yanagida Y, Yazaki R, Kumagai N, Shibasaki M (2011) Angew Chem Int Ed 50:7910
50. Yazaki R, Kumagai N, Shibasaki M (2010) J Am Chem Soc 132:5522
51. Yin L, Brewitz L, Kumagai N, Shibasaki M (2014) J Am Chem Soc 136:17958
52. Shi S-L, Kanai M, Shibasaki M (2012) Angew Chem Int Ed 51:3932
53. Korzhavyi PA, Soroka IL, Isaev EI, Lilja C, Johansson B (2012) Proc Natl Acad Sci USA 109:686
54. Shi S-L, Wei X-F, Shimizu Y, Kanai M (2012) J Am Chem Soc 134:17019
55. Kimura Y, Ito S, Shimizu Y, Kanai M (2013) Org Lett 15:4130
56. Lin W, Cao T, Fan W, Han Y, Kuang J, Luo H, Miao B, Tang X, Yu Q, Yuan W, Zhang J, Zhu C, Ma S (2014) Angew Chem Int Ed 53:277
57. Ishii T, Watanabe R, Moriya T, Ohmiya H, Mori S, Sawamura M (2013) Chem Eur J 19:13547
58. Maity P, Srinivas HD, Watson MP (2011) J Am Chem Soc 133:17142
59. Hashimoto T, Omote M, Maruoka K (2011) Angew Chem Int Ed 50:8952
60. Yazaki R, Kumagai N, Shibasaki M (2010) J Am Chem Soc 132:10275
61. Gommermann N, Koradin C, Polborn K, Knochel P (2003) Angew Chem Int Ed 42:5763
62. Shimizu Y, Kanai M (2014) Tetrahedron Lett 460:197
63. Kawai J, Chikkade PK, Shimizu Y, Kanai M (2013) Angew Chem Int Ed 52:7177
64. Chikkade PK, Shimizu Y, Kanai M (2014) Chem Sci 5:1585

Top Organomet Chem (2016) 58: 183–206
DOI: 10.1007/3418_2015_160

Published online: 7 November 2015

Asymmetric Cycloaddition and Cascade Addition–Cyclization Reactions

Xin Fang, Jia-Wei Zhang, and Chun-Jiang Wang

Abstract The copper(I) catalysis has found a wide range of applications in the field of organic chemistry, due to its ability to promote various organic reactions and more notably in enantioselective transformations. Cu(I)-catalyzed asymmetric cycloaddition and cascade addition–cyclization reactions have proven to be one of the most efficient approaches for the stereoselective construction of diverse biologically important heterocycles. In this chapter, we will discuss the recent developments that have been reported in this area since 2010.

Keywords Asymmetric cycloaddition • Cascade addition–cyclization • Copper (I) catalysis

Contents

1 Introduction 184
2 Cu(I)-Catalyzed Asymmetric Cycloaddition Reactions 184
2.1 Asymmetric [3+2] Cycloadditions 184
2.2 Asymmetric [3+3] and [3+6] Cycloadditions 196
2.3 Asymmetric [2+2], [4+1], and [4+2] Cycloadditions 199
2.4 Asymmetric Azide–Alkyne Cycloadditions 200
3 Cu(I)-Catalyzed Asymmetric Cascade Addition–Cyclization Reactions 201
4 Conclusion 203
References 203

X. Fang, J.-W. Zhang, and C.-J. Wang (✉)
College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, China
e-mail: cjwang@whu.edu.cn

1 Introduction

Copper(I) catalysis has demonstrated its long-held reputation in asymmetric synthesis over the past decade. The moderate Lewis acidity and coordination property of Cu(I) salts make it a versatile metal center in various metal–ligand complex systems and thereby have broad applications in the area of organic chemistry, especially in the asymmetric catalysis field. This chapter summarizes the recent developments of Cu(I)-catalyzed asymmetric cycloaddition and cascade addition–cyclization reactions since 2010. A wide range of asymmetric transformations catalyzed by chiral Cu(I) complexes are discussed, such as the 1,3-dipolar cycloadditions, including [3+2], [3+3], and [3+6] cycloadditions. Other cycloadditions and cascade addition–cyclization reactions are also discussed.

2 Cu(I)-Catalyzed Asymmetric Cycloaddition Reactions

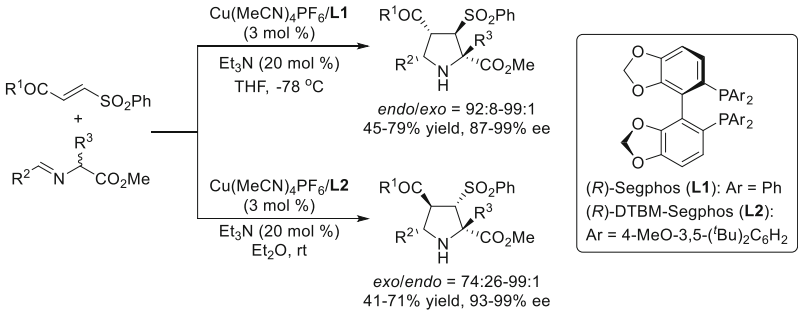
Asymmetric 1,3-dipolar cycloaddition (1,3-DC) reaction is an important strategy for the construction of highly substituted chiral heterocycles [1–3], which are the core structural elements prevalent in many natural products, pharmaceuticals, and organocatalysts [4–6]. Considerable attention has been paid to azomethine ylide-involved 1,3-DC in last several years, and the substrate scope has largely been expanded [7, 8].

2.1 Asymmetric [3+2] Cycloadditions

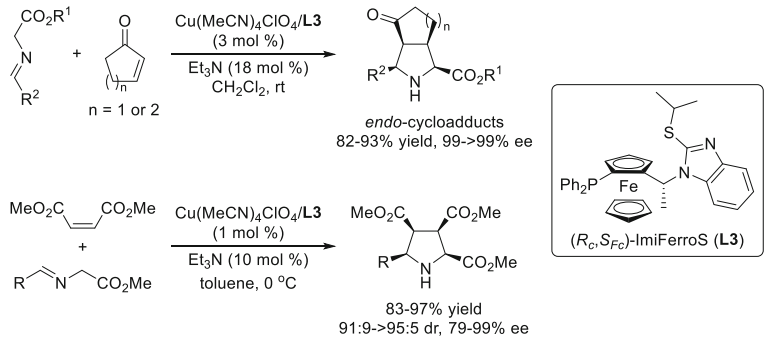
The asymmetric [3+2] cycloaddition reaction is one of the most efficient and expedient methods to prepare optically active highly functionalized five-membered heterocycles with pyrrolidine scaffold, a structural motif that is useful in medicinal chemistry. In recent 5 years, continuing reports in this field have been presented.

2.1.1 [3+2] Cycloadditions of Azomethine Ylides with Electron-Deficient Alkenes

In 2010, Carretero and co-workers described the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with (*E*)-β-phenylsulfonylenones (Scheme 1) [9]. In the presence of chiral Cu(I)–SEGPHOS catalysts, high reactivity, selectivity, and broad substrate scope were observed. Interestingly, a reversal from *endo*- to *exo*-diastereoselectivity occurred when SEGPHOS or DTBM-SEGPHOS was employed as the ligand, respectively. This work expanded the scope of [3+2]



Scheme 1 Asymmetric [3+2] cycloaddition of azomethine ylides with (*E*)-β-phenylsulfonylenones

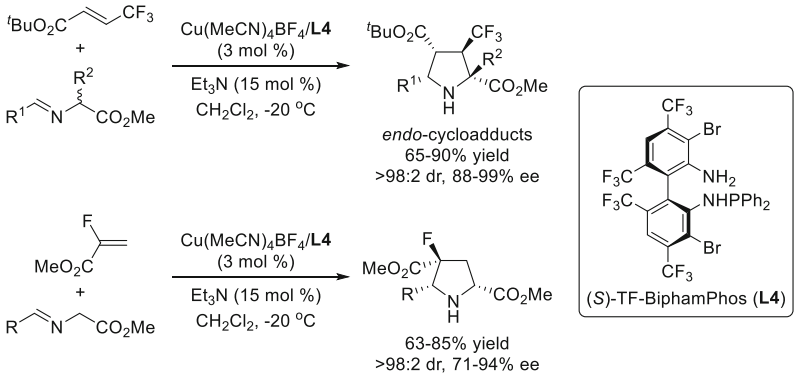


Scheme 2 Asymmetric [3+2] cycloaddition of azomethine ylides with cyclic enones and dimethyl maleate

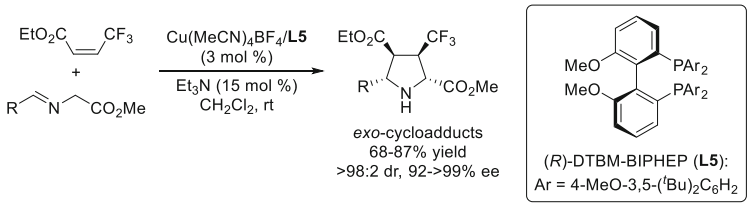
cycloaddition of azomethine ylides with sulfonyl-substituted olefins as novel dipolarophiles.

Hu and co-workers developed a new family of chiral ferrocenyl P,S-ligands, which were successfully applied in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with cyclic enones (Scheme 2) [10]. A Cu(MeCN)$_4$ClO$_4$/ImiFerroS complex catalyzed the cycloaddition to give very high *endo*-selectivity for the cycloadducts, and the products were obtained in perfect enantioselectivities (normally 99% *ee*). Most recently, Hu's group also disclosed the highly efficient asymmetric [3+2] cycloaddition of azomethine ylides with dimethyl maleate using this catalytic system, giving the cycloadducts in high *endo*-selectivities and good to excellent enantioselectivities (Scheme 2) [11].

In 2011, Wang and co-workers successfully realized the catalytic asymmetric [3+2] cycloaddition of azomethine ylides with *trans*-4,4,4-trifluorocrotonate (Scheme 3) [12]. The Cu(MeCN)$_4$BF$_4$/TF-BiphamPhos catalytic system exhibited excellent performance in catalyzing this reaction, affording trifluoromethylated pyrrolidines in high yield with excellent diastereo- and enantioselectivity. Highly efficient epimerization of the kinetically favored *endo*-cycloadducts obtained from *cis*-4,4,4-



Scheme 3 Asymmetric [3+2] cycloaddition of azomethine ylides with *trans*-4,4,4-trifluorocrotonate and methyl α-fluoroacrylate

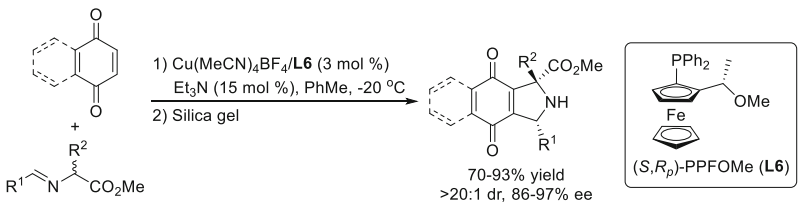


Scheme 4 Asymmetric [3+2] cycloaddition of azomethine ylides with *cis*-4,4,4-trifluorocrotonate

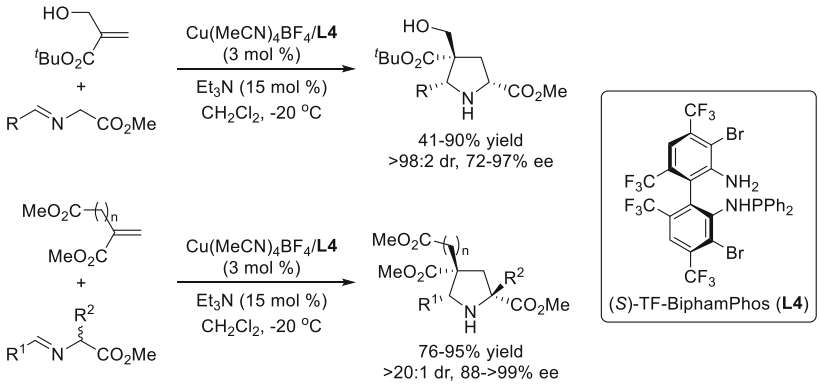
trifluorocrotonate into the thermodynamically favored *exo*-cycloadducts was revealed as well. This catalytic system was also applied to the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with methyl α-fluoroacrylate for the construction of optically active fluorinated pyrrolidine derivatives bearing one unique fluorinated quaternary and two tertiary stereogenic centers in good yields with excellent diastereoselectivities and good to high enantioselectivities (Scheme 3) [13].

Later on, Wang and co-workers reported the asymmetric *exo*-selective 1,3-dipolar cycloaddition of azomethine ylides with *cis*-4,4,4-trifluorocrotonate, providing a direct and facile access to highly substituted *exo*-pyrrolidines bearing a unique trifluoromethyl group in high yield with excellent enantioselectivity catalyzed by the $Cu(MeCN)_4BF_4$/DTBM-BIPHEP complex (Scheme 4) [14]. An appropriate combination of a bulky and electron-donating bisphosphine ligand DTBM-BIPHEP with copper(I) salt led to excellent stereoselectivity control.

Wang's group further disclosed a highly efficient Cu(I)/(S,Rp)-PPFOMe-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with quinone derivatives followed by silica gel-promoted oxidation in a one-pot reaction protocol, giving enantioenriched isoindolines bearing a quaternary and a tertiary stereogenic center in good yield with excellent stereoselectivity (Scheme 5) [15].



Scheme 5 Asymmetric [3+2] cycloaddition/oxidation of azomethine ylides with quinones

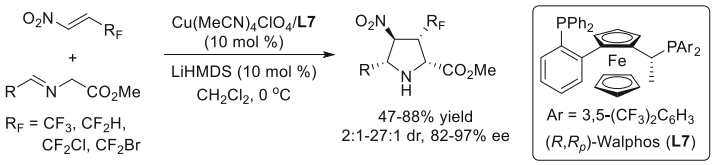


Scheme 6 Asymmetric [3+2] cycloaddition of azomethine ylides with Morita–Baylis–Hillman adduct, dimethyl itaconate, and 2-methyleneglutarate

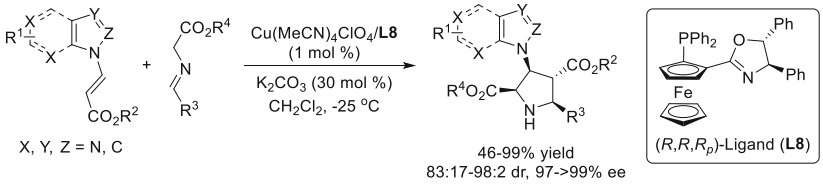
Wang and co-workers also developed the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with readily accessible Morita–Baylis–Hillman adduct as the dipolarophile catalyzed by Cu(I)/TF-BiphamPhos complex, which provides a facile access to a new kind of highly substituted pyrrolidine derivatives bearing a unique quaternary and two tertiary stereogenic centers in excellent diastereoselectivity and up to 97% ee (Scheme 6) [16]. Recently, the asymmetric [3+2] cycloaddition employing dimethyl itaconate and 2-methyleneglutarate as dipolarophiles was also realized with this catalytic system (Scheme 6) [17].

Hou and co-workers disclosed the asymmetric 1,3-dipolar cycloaddition reaction of azomethine ylides with fluoromethyl-substituted nitroalkenes using $Cu(MeCN)_4ClO_4$/Walphos as the catalyst, affording the corresponding optically active 3-(fluoromethyl)-4-nitroproline derivatives in good yield with excellent *exo*-selectivity and enantiocontrol (Scheme 7) [18].

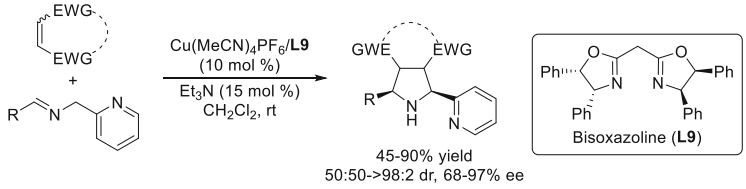
Guo and co-workers reported a highly enantioselective 1,3-dipolar cycloaddition of azomethine ylides with β-nucleobase-substituted acrylates as dipolarophiles using 1 mol% of a chiral Cu(I) complex, which provides the first rapid and divergent access to various enantioenriched azacyclic nucleoside analogues in high yields with excellent *exo*-selectivities and enantioselectivities (Scheme 8) [19]. In addition, other β-heteroarylacrylates such as pyrimidine-, benzimidazole-, imidazole-, benzotriazole-, and indole-substituted acrylates are also suitable



Scheme 7 Asymmetric [3+2] cycloaddition of azomethine ylides with fluoromethyl-substituted nitroalkenes



Scheme 8 Asymmetric [3+2] cycloaddition of azomethine ylides with β-nucleobase-substituted acrylates

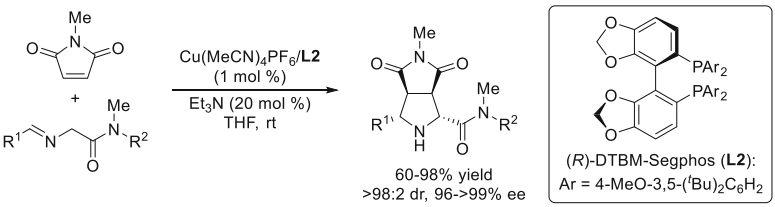


Scheme 9 Asymmetric [3+2] cycloaddition of *N*-(2-pyridylmethyl)imines with activated olefins

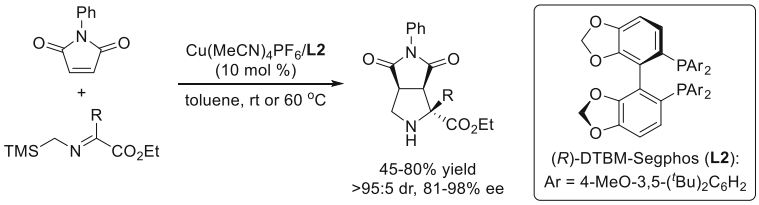
dipolarophiles for this catalytic system, giving the corresponding pyrrolidines with excellent enantioselectivity.

Prompted by the racemic example of thermal 1,3-dipolar cycloaddition of *N*-(2-pyridylmethyl)imines reported by Grigg [20], Carretero and co-workers described that *N*-(2-pyridylmethyl)imines can be used as efficient azomethine precursors in catalytic asymmetric [3+2] cycloadditions (Scheme 9) [21]. Employing Cu(I)/bisoxazoline as a chiral catalyst system, high levels of enantioselectivity (up to 97% *ee*) and moderate to high *exo*-selectivity have been accomplished for a broad scope of substituted dipolarophiles, such as maleimides, fumarates, fumaronitrile, enones, and nitroalkenes. The resulting 2-pyridyl pyrrolidines hold a great potential as chiral *N*,*N*-ligands and organocatalysts.

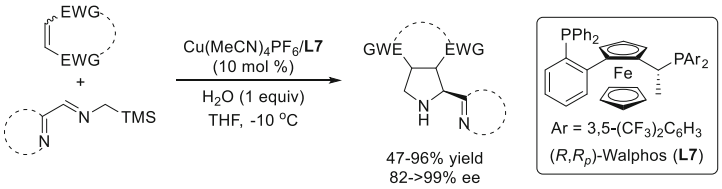
Carretero's group further developed a highly *exo*-diastereoselective and enantioselective catalytic asymmetric protocol for the [3+2] cycloaddition of α-iminoamides by using Cu(I)/DTBM-SEGPHOS complexes as catalyst system, providing a variety of 2-amido pyrrolidines, including Weinreb-type amides, with excellent levels of enantiocontrol (Scheme 10) [22]. Other activated alkenes, such



Scheme 10 Asymmetric [3+2] cycloaddition of α-iminoamides with *N*-methylmaleimide



Scheme 11 Asymmetric [3+2] cycloaddition of α-silylimines with *N*-phenylmaleimide

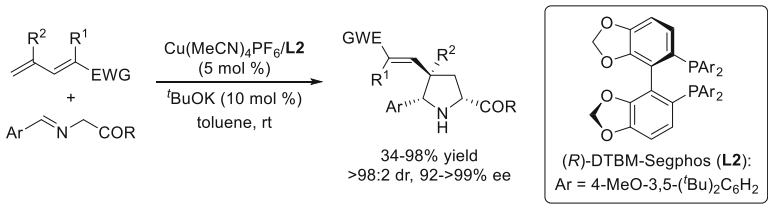


Scheme 12 Asymmetric [3+2] cycloaddition of heteroarylsilylimines with activated alkenes

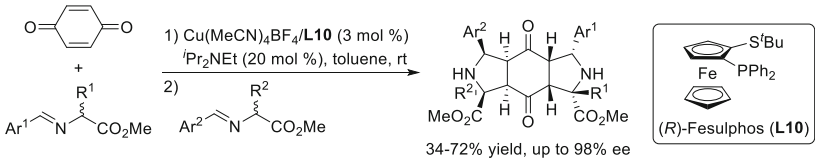
as acrylates, phenyl vinyl sulfone, (*E*)-β-nitrostyrene, *trans*-chalcone, dimethyl fumarate, and dimethyl maleate, were also used as dipolarophiles in this reaction.

Later on, Carretero and co-workers reported the first enantioselective procedure for the Cu(I)-catalyzed 1,3-dipolar cycloaddition involving α-silylimines as azomethine precursors to provide a variety of 5-unsubstituted α-quaternary proline derivatives in good yields with excellent levels of diastereoselectivity and enantiocontrol (Scheme 11) [23]. The use of the bulky DTBM-SEGPHOS ligand proved to be crucial for obtaining this high enantioselectivity. Moreover, α,-β-unsaturated sulfones could also be employed as dipolarophiles in this catalytic system.

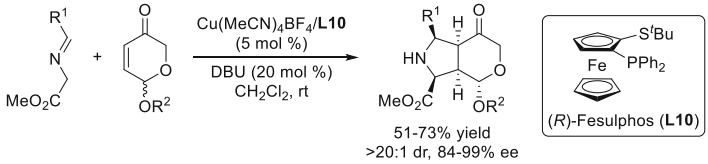
Recently, Carretero's group developed an efficient and practical procedure for the direct asymmetric synthesis of α-heteroarylpyrrolidines via [3+2] cycloaddition between heteroarylsilylimines and activated alkenes (Scheme 12) [24]. By use of $Cu(MeCN)_4PF_6$/Walphos as catalytic system, high levels of enantioselectivity and moderate to high diastereoselectivity have been achieved with a broad variety of



Scheme 13 Asymmetric [3+2] cycloaddition of azomethine ylides with acyclic 1,3-dienes



Scheme 14 Asymmetric double [3+2] cycloaddition of azomethine ylides with 1,4-benzoquinone



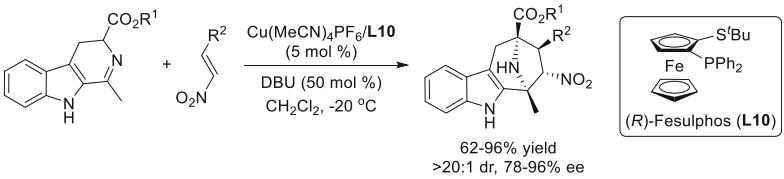
Scheme 15 Asymmetric [3+2] cycloaddition of azomethine ylides with 2*H*-pyran-3(6*H*)-ones

azomethine precursors and dipolarophiles including maleimides, maleates, fumarates, nitroalkenes, and vinyl sulfones.

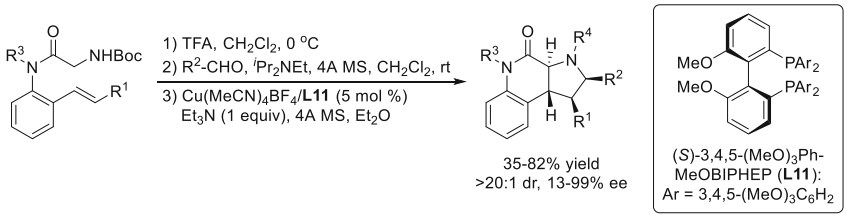
Most recently, Carretero and co-workers described the first example of the Cu (I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with acyclic activated 1,3-dienes (Scheme 13) [25]. This cycloaddition occurs selectively at the terminal C=C bond of the dienes, and the *exo*-adducts could be obtained with high diastereocontrol and excellent enantioselectivity.

In 2012, Waldmann and co-workers successfully developed the Cu(I)/Fesulphos-catalyzed double 1,3-dipolar cycloaddition of two different azomethine ylides with 1,4-benzoquinone as dipolarophile to construct stereochemically and structurally complex molecules that forms four carbon–carbon bonds and sets eight stereocenters with high regio-, diastereo- and enantioselectivity in a one-pot tandem reaction (Scheme 14) [26].

Later on, Waldmann's group described a novel highly enantioselective method for the synthesis of an iridoid-inspired compound collection by the kinetic resolution of racemic 2*H*-pyran-3(6*H*)-one derivatives by means of an asymmetric [3+2] cycloaddition with azomethine ylides using this catalytic system (Scheme 15) [27]. The desired products were formed efficiently with high stereoselectivity and led to the discovery of a new class of inhibitors of the Wnt and hedgehog signaling pathways.



Scheme 16 Asymmetric [3+2] cycloaddition of 1,3-fused cyclic azomethine ylides with nitroalkenes

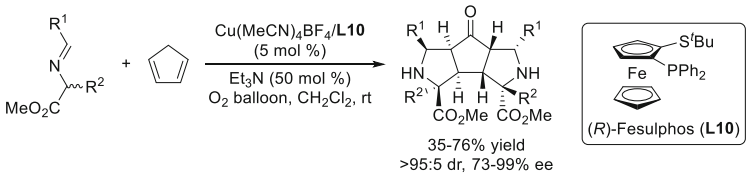


Scheme 17 Asymmetric intramolecular [3+2] cycloaddition with azomethine ylides

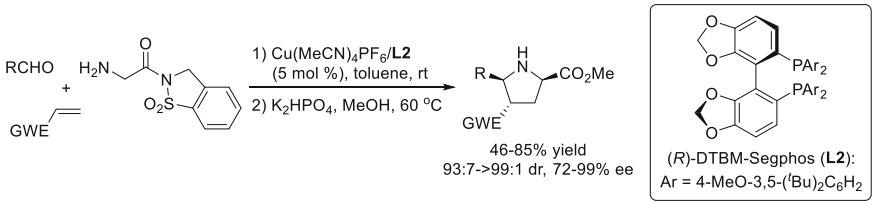
Shortly after, Waldmann and co-workers reported the first efficient Cu(I)-catalyzed highly diastereoselective and enantioselective[3+2] cycloaddition reaction of S-shaped 1,3-fused cyclic azomethine ylides with nitroalkenes, providing an unprecedented and general access to functionalized tropane scaffolds bearing quaternary and tertiary stereocenters in a stereoselective manner (Scheme 16) [28]. Furthermore, subjecting a collection of these tropane derivatives to a cell-based screen revealed a novel class of hedgehog signaling inhibitors.

Catalytic asymmetric intermolecular 1,3-dipolar cycloadditions are powerful approaches for the construction of heterocycles. In contrast, intramolecular 1,3-dipolar cycloadditions have rarely succumbed to enantioselective catalysis [29–31]. Recently, Waldmann's group developed a highly enantioselective synthesis of natural-product-inspired pyrrolidino-piperidine scaffold via an intramolecular 1,3-dipolar cycloaddition with azomethine ylides, affording a wide scope of the desired cycloadducts bearing four tertiary stereogenic centers with up to 99% *ee* (Scheme 17) [32]. Combining the catalytic asymmetric intramolecular 1,3-dipolar cycloaddition with a subsequent stereoselective intermolecular 1,3-dipolar cycloaddition gave annulated piperidino-pyrrolizidine derivatives with seven contiguous stereogenic centers in a one-pot procedure.

Most recently, Waldmann and co-workers disclosed a cascade transformation to allow the highly diastereo- and enantioselective synthesis of structurally complex 5,5,5-tricyclic products with eight stereocenters, which initiated by copper-catalyzed aerobic oxidation of cyclopentadiene to cyclopentadienone followed by catalytic asymmetric double 1,3-dipolar cycloaddition with azomethine ylides (Scheme 18) [33].



Scheme 18 Asymmetric aerobic oxidation/double [3+2] cycloaddition of azomethine ylides with cyclopentadiene



Scheme 19 Asymmetric three-component [3+2] cycloaddition of aldehydes, glycylsultam, and activated alkenes

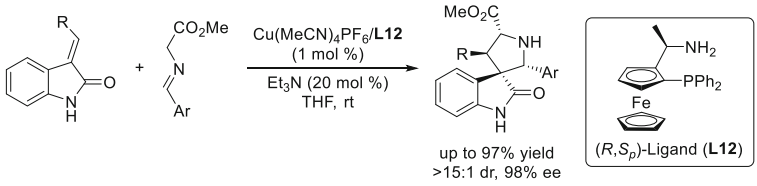
Garner and co-workers reported a catalytic asymmetric version of the *exo*-selective three-component 1,3-dipolar cycloaddition of aldehydes, glycylsultam, and electron-deficient alkenes, which can be performed using a wide variety of enolizable aliphatic aldehydes and dipolarophiles producing functionalized pyrrolidines with good to excellent enantioselectivity (Scheme 19) [34].

2.1.2 [3+2] Cycloadditions of Azomethine Ylides to Construct Spiropyrrolidines

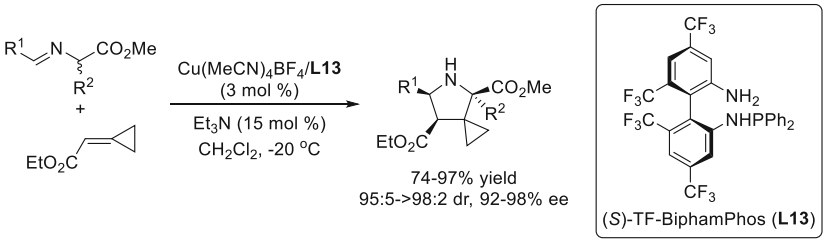
The efficient construction of spiro quaternary stereogenic carbon centers is challenging and intriguing [35], and the spirocyclic pyrrolidine skeleton owns potential application for drug discovery. In this context, recent advances in catalytic asymmetric [3+2] cycloadditions to construct optically active spiropyrrolidines will be discussed.

Waldmann and co-workers described the first highly enantioselective synthesis of biologically relevant natural-product-inspired 3,3′-pyrrolidinyl spirooxindoles (Scheme 20) [36, 37]. This transformation takes place by means of an asymmetric Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with substituted 3-methylene-2-oxindoles and efficiently gives access to spirocycles with an all-carbon quaternary spirocenter and three tertiary stereocenters in a single reaction step using low catalyst loading. Almost concurrently, Wang's group reported a similar cycloaddition with AgOAc/TF-BiphamPhos complex as the catalyst with good yield, high diastereoselectivity, and moderate enantioselectivity [38].

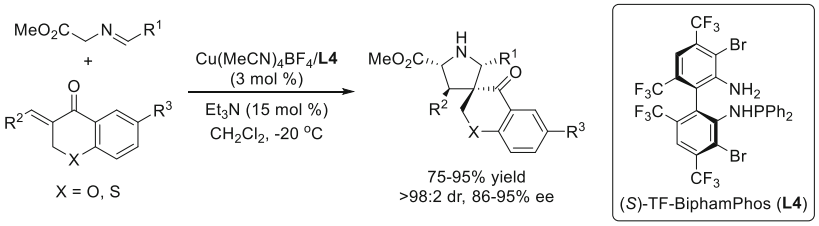
Wang and co-workers developed a general methodology for the direct and facile access to various highly functionalized 5-aza-spiro[2,4]heptane derivatives, a



Scheme 20 Asymmetric [3+2] cycloaddition of azomethine ylides with 3-alkylidene oxindoles [36]



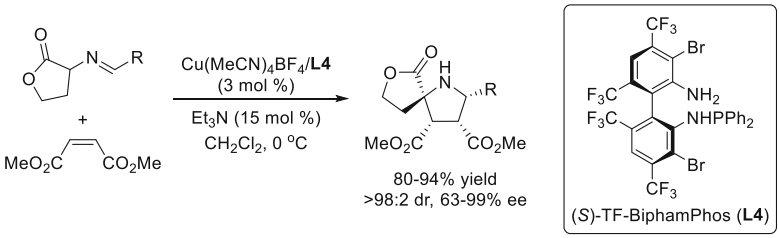
Scheme 21 Asymmetric [3+2] cycloaddition of azomethine ylides with ethyl 2-cyclopropylideneacetate [39]



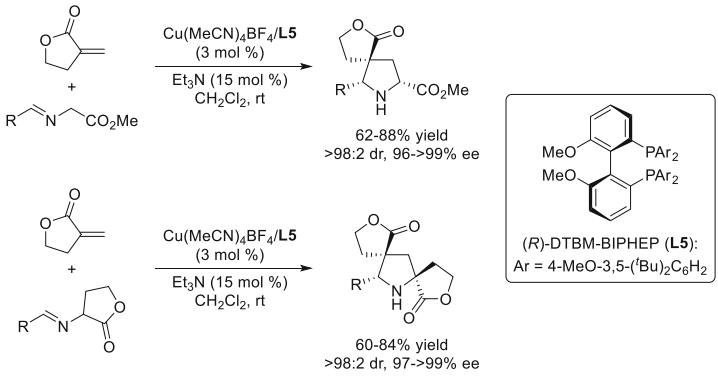
Scheme 22 Asymmetric [3+2] cycloaddition of azomethine ylides with 3-alkylidene-4-chromanones

valuable structural motif for drug discovery, in high yield with excellent levels of diastereo- and enantioselectivity via the Cu(I)/TF-BiphamPhos-catalyzed asymmetric *endo*-selective 1,3-dipolar cycloaddition of azomethine ylides with ethyl 2-cyclopropylidene acetate (Scheme 21) [39, 40]. Recently, they further employed a Cu(I)/DTBM-BIPHEP complex as the catalyst and obtained the *exo*-cycloadducts with different stereoselectivities [41].

In the same year, Wang's group reported the highly enantioselective Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with 3-alkylidene-4-chromanones, which provides a facile construction of various enantioenriched spirocyclic [4-chromanone-3,3′-pyrrolidine] derivatives featuring one unique spiro quaternary stereogenic center and three tertiary stereogenic centers (Scheme 22) [42].



Scheme 23 Asymmetric [3+2] cycloaddition of cyclic aldimino esters with dimethyl maleate



Scheme 24 Asymmetric [3+2] cycloaddition of azomethine ylides with α-methylene-γ-butyrolactone

Wang and co-workers further broadened the application of Cu(I)/TF-BiphamPhos catalyst system to the first catalytic asymmetric 1,3-dipolar cycloaddition of homoserine lactone-derived cyclic aldimino esters with dimethyl maleate for the highly efficient synthesis of biologically active spiro-[butyrolactone-pyrrolidines] containing both a γ-lactone and pyrrolidine moiety (Scheme 23) [43]. A key feature of this method is that the lactone ring in the generated spirocycles is provided by the dipole, rather than by the dipolarophile.

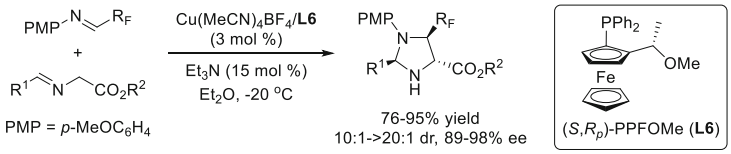
Subsequently, Wang's group presented an unprecedented asymmetric *exo*-selective 1,3-dipolar cycloaddition reaction of azomethine ylides with α-methylene-γ-butyrolactone under the catalysis of a Cu(I)/DTBM-BIPHEP complex, providing an expedient and straightforward access to a series of enantiomerically enriched spiro-[butyrolactone-pyrrolidine] derivatives bearing one to two spiro quaternary stereogenic centers with excellent levels of stereocontrol (Scheme 24) [44].

2.1.3 Other [3+2] Cycloadditions

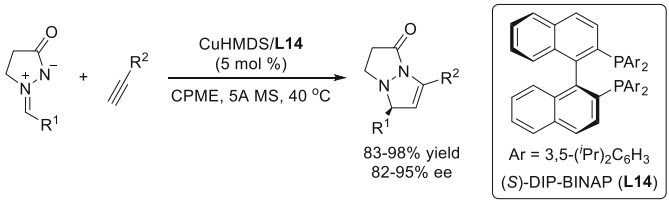
Wang and co-workers developed an elegant catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with low reactive fluorinated imines as the dipolarophiles catalyzed by $Cu(MeCN)_4BF_4$/PPFOMe complex for the synthesis of 2,4-*trans*-fluorinated imidazolidines (Scheme 25) [45]. This catalytic system exhibited high reactivity, excellent stereoselectivity, and broad substrate scope.

Kobayashi and co-workers successfully achieved the asymmetric 1,3-dipolar cycloaddition reaction of azomethine imines with terminal alkynes catalyzed by CuHMDS and DIP-BINAP ligand to provide *N*,*N*-bicyclic pyrazolidinone derivatives in high yields with exclusive regioselectivity and excellent enantioselectivity (Scheme 26) [46]. Mechanistic studies elucidated a stepwise reaction pathway and revealed that the steric character of the ligand determines the regioselectivity. Arai and co-workers applied chiral bis(imidazolidine)pyridine-CuOAc complex to the [3+2]cycloaddition of azomethine imines with propiolates for the construction of bicyclic pyrazolo[1,2-a]pyrazolone derivatives with up to 74% *ee* [47].

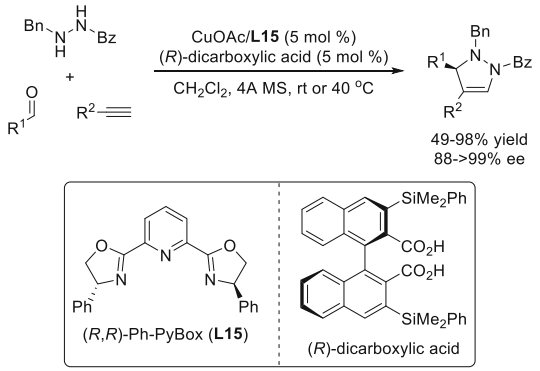
Maruoka and co-workers reported the first catalytic asymmetric three-component 1,3-dipolar cycloaddition of terminal alkynes with acyclic azomethine imines generated in situ from the corresponding aldehydes and hydrazides, which was realized using CuOAc/Ph-pybox and axially chiral dicarboxylic acid cocatalysts (Scheme 27) [48]. This transformation has a broad tolerance with regard to the substrates, affording diverse chiral 3,4-disubstituted pyrazolines with high enantioselectivities. The role of the axially chiral dicarboxylic acid is to generate the protonated acyclic azomethine imine, which then reacts with chiral Cu-acetylide.



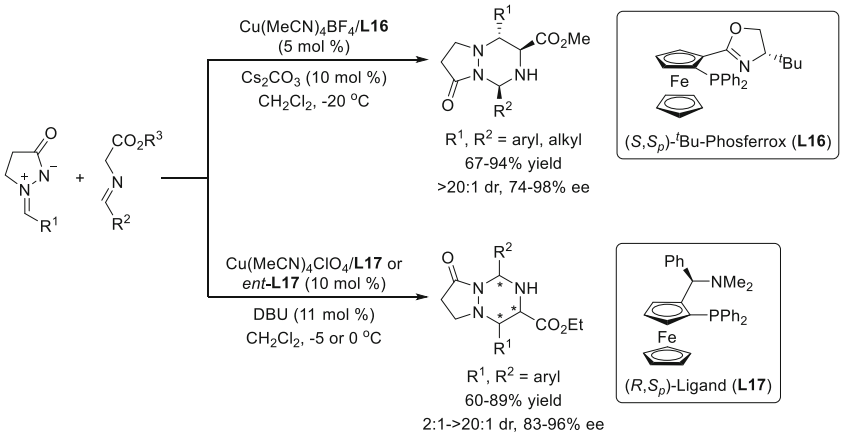
Scheme 25 Asymmetric [3+2] cycloaddition of azomethine ylides with fluorinated imines



Scheme 26 Asymmetric [3+2] cycloaddition of azomethine imines with terminal alkynes



Scheme 27 Asymmetric three-component [3+2] cycloaddition of aldehydes, hydrazides, and terminal alkynes

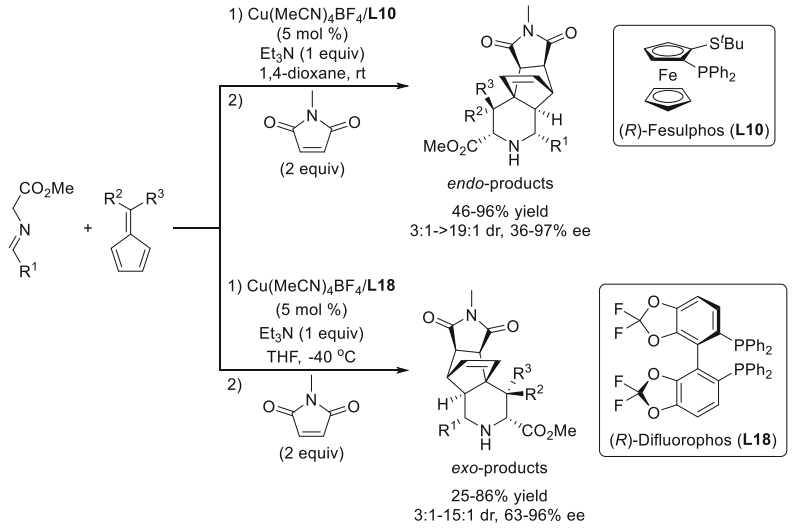


Scheme 28 Asymmetric [3+3] cycloaddition of azomethine ylides with azomethine imines

2.2 Asymmetric [3+3] and [3+6] Cycloadditions

The higher-order cycloaddition of azomethine ylides has emerged as a powerful and efficient tool for the convergent enantioselective synthesis of various medium-sized heterocycles from simple precursors. As a consequence, much attention has been paid into this research area in recent years.

In 2013, Wang and co-workers presented the first highly diastereo- and enantioselective [3+3] cycloaddition of azomethine ylides with azomethine imines employing Cu(I)/^{t}Bu-Phosferrox complex as the catalyst (Scheme 28) [49]. A wide range of azomethine ylides and azomethine imines, including those derived from aliphatic aldehydes, underwent this reaction to furnish the biologically active 1,2,4-



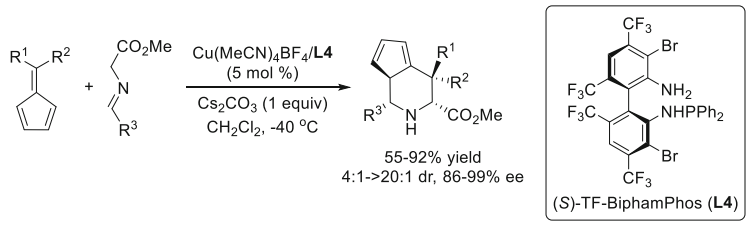
Scheme 29 Asymmetric one-pot [3+6] cycloaddition/Diels–Alder reaction of azomethine ylides with fulvenes

triazinane derivatives having a hexahydropyridazine skeleton in generally high yield with excellent stereocontrol. Almost at the same time, Guo, Hu, and co-workers reported a similar protocol under the catalysis of a copper complex with a chiral ferrocenyl P,N-ligand to provide the desired cycloadducts with high diastereo- and enantioselectivities (Scheme 28) [50].

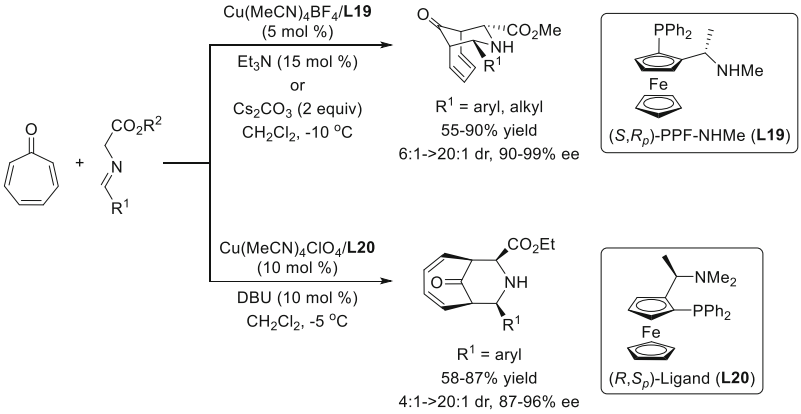
Waldmann and co-workers reported the first Cu(I)-catalyzed asymmetric [3+6] cycloaddition of azomethine ylides with fulvenes to provide piperidine derivatives having four stereocenters with high regio- and enantioselectivity and demonstrated that the enantioselective [3+6] cycloaddition can be combined with a [4+2] cycloaddition in one pot to yield complex annulated piperidines with eight stereocenters (Scheme 29) [51]. Later on, the same group developed an *exo*-selective [3+6] cycloaddition approach for the highly enantioselective preparation of polysubstituted piperidines by using (*R*)-difluorophos as a chiral ligand (Scheme 29) [52]. This methodology was applied in a one-pot [3+6]/[4+2] dicycloaddition to construct stereochemically and structurally rich polycyclic compounds from simple starting materials.

Contemporaneously with Waldmann's group, Wang and co-workers described a novel asymmetric [3+6] cycloaddition of azomethine ylides with various readily available fulvenes catalyzed by Cu(I)/TF-BiphamPhos for the synthesis of highly substituted piperidines in good yields with excellent stereocontrol and broad substrate scope (Scheme 30) [53]. Subsequent transformations allow facile access to enantioenriched fused polycyclic piperidine derivatives without loss of diastereo- and enantioselectivity.

In 2014, Wang's group reported the first Cu(I)-catalyzed [3+6] cycloaddition of azomethine ylides with tropone as a 6π dipolarophile by the use of a chiral



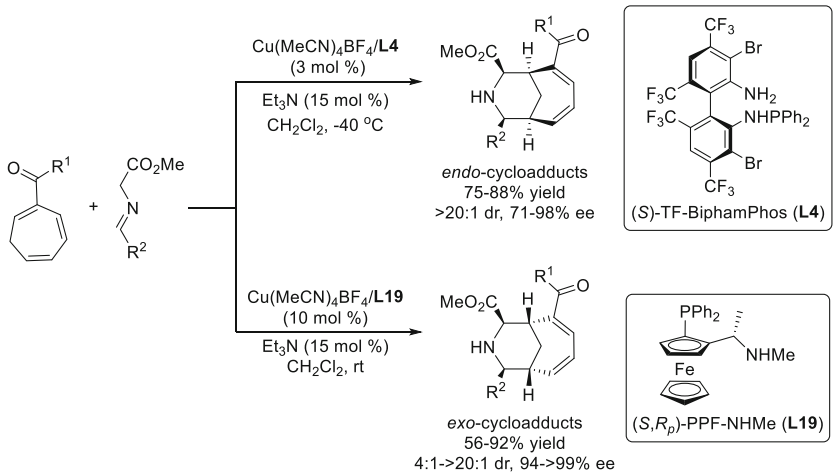
Scheme 30 Asymmetric [3+6] cycloaddition of azomethine ylides with fulvenes



Scheme 31 Asymmetric [3+6] cycloaddition of azomethine ylides with tropone

ferrocenyl phosphine ligand, affording piperidine-fused bicyclic heterocycles (bridged azabicyclo[4.3.1]decadiene derivatives),which are potential scaffolds to synthesize natural products and biologically important molecules, in good yields with high levels of diastereo- and enantioselectivities under mild reaction conditions (Scheme 31) [54]. To accommodate aliphatic imino esters bearing a less acidic α-hydrogen, Cs_2CO_3 was employed as a base instead of Et_3N. Almost simultaneously, Guo's group documented the same type of cycloaddition with a similar catalytic system (Scheme 31) [55].

Subsequently, Wang and co-workers developed an unprecedented substrate-controlled asymmetric [3+6] cycloaddition of azomethine ylides employing 2-acyl cycloheptatrienes without nonbenzenoid aromatic characteristic as the fine-tunable 6π components catalyzed by Cu(I)/TF-BiphamPhos for the first time (Scheme 32) [56]. A variety of enantioenriched heterocycles bearing a bridged piperidine moiety were obtained in good yield with exclusive regioselectivity and excellent stereoselectivity. The 2-acyl group of the cycloheptatrienes plays a significant role in determining the annulation preferentially through [3+6] pathway. Most recently, the same group realized a highly *exo*-selective [3+6] cycloaddition of azomethine ylides with 2-acylcycloheptatrienes with a Cu(I)/PPF-NHMe



Scheme 32 Asymmetric [3+6] cycloaddition of azomethine ylides with 2-acylcycloheptatrienes

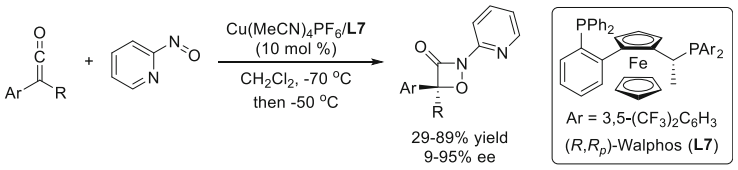
complex as the catalyst, producing a diverse range of bridged piperidines bearing multiple stereogenic centers and functionalities with excellent stereocontrol (Scheme 32) [57]. Theoretical calculations indicated a stepwise mechanism, and the remarkable feature of this annulation, different from the above *endo*-selective cycloaddition, is that all of the larger substituent groups occupy the axial positions in the six-membered chair-like conformation of the piperidine ring.

2.3 *Asymmetric [2+2], [4+1], and [4+2] Cycloadditions*

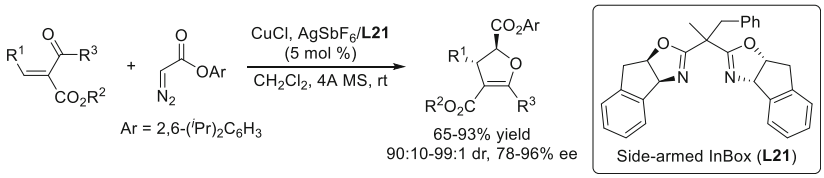
In the field of metal-catalyzed asymmetric cycloadditions, [2+2] cycloaddition seems to be relatively rare due to the ring strain force of the products. In 2010, Studer and co-workers presented the first Cu(I)/Walphos-catalyzed enantioselective [2+2] cycloaddition of 2-nitrosopyridine with various ketenes to afford synthetically valuable 1,2-oxazetidine-3-ones with good enantioselectivity (Scheme 33) [58]. Density function theory (DFT) calculations give evidence that the reaction occurs via a concerted pathway.

Tang and co-workers developed a highly efficient protocol to construct chiral tetrasubstituted 2,3-dihydrofuran derivatives in good yield with high stereoselectivity via Cu(I)/side-armed inbox-catalyzed asymmetric [4+1] cycloaddition of α-benzylidene-β-ketoesters with a diazo 2,6-diisopropylphenyl ester (Scheme 34) [59].

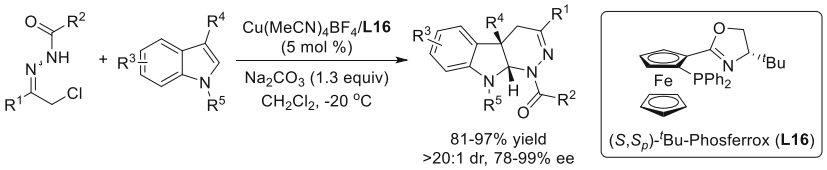
Recently, Wang and co-workers reported the first asymmetric inverse-electron-demand aza-Diels–Alder reaction of indoles with in situ formed azoalkenes catalyzed by a Cu(I)/^{t}Bu-Phosferrox complex (Scheme 35) [60]. The current methodology provides an expedient access to highly functionalized [2,3]-fused indoline



Scheme 33 Asymmetric [2+2] cycloaddition of 2-nitrosopyridine with ketenes



Scheme 34 Asymmetric [4+1] cycloaddition of α-benzylidene-β-ketoesters with a diazo 2,6-diisopropylphenyl ester

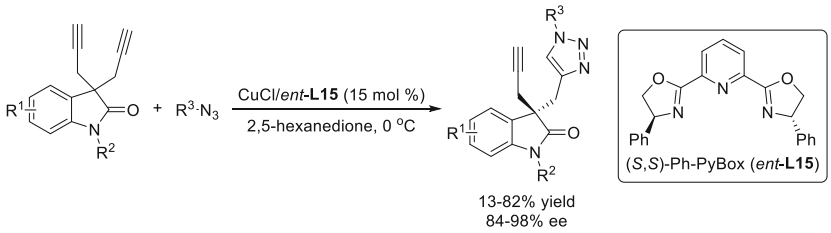


Scheme 35 Asymmetric [4+2] inverse-electron-demand aza-Diels–Alder reaction of indoles with azoalkenes

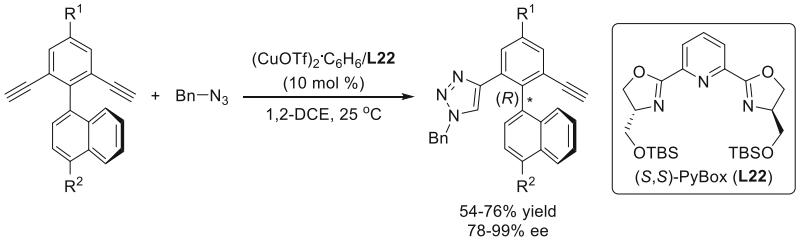
tetrahydropyridazine heterocycles bearing contiguous quaternary and tertiary stereogenic centers in good yields with excellent regio-, diastereo-, and enantioselectivity.

2.4 Asymmetric Azide–Alkyne Cycloadditions

Among the 1,3-dipolar cycloaddition reactions, click chemistry is an efficient method for the construction of triazole derivatives by the cycloaddition of azides and acetylenes. Zhou and co-workers disclosed the asymmetric Cu(I)-catalyzed azide–alkyne cycloaddition via desymmetrization of oxindole-based 1,6-heptadiynes to furnish optically active quaternary oxindoles bearing a 1,2,3-triazole moiety, which are interesting targets for medicinal chemistry (Scheme 36) [61]. This reaction also features an unprecedented highly enantioselective intermolecular desymmetrization of dialkynes, which demonstrates the great potential of this strategy in the construction of stereocenters with an alkyne group.



Scheme 36 Asymmetric azide–alkyne cycloaddition via desymmetrization of oxindole-based 1,6-heptadiynes



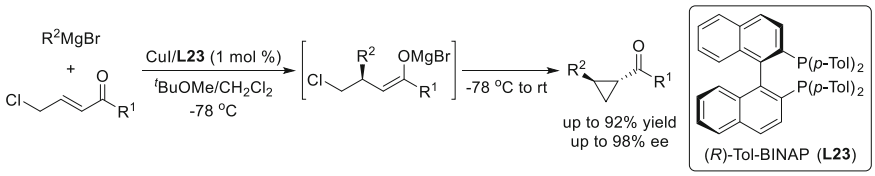
Scheme 37 Asymmetric azide–alkyne cycloaddition of dialkynes bearing prochiral biaryl groups

Later on, Uozumi and co-workers developed a highly enantioposition-selective Cu(I)-catalyzed azide–alkyne cycloaddition of benzyl azide with dialkynes bearing prochiral biaryl groups, which provides a novel and efficient protocol to obtain 1,2,3-triazole derivatives bearing axially chiral biaryl groups with high enantioselectivities (Scheme 37) [62].

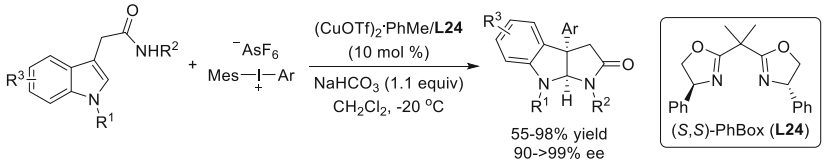
3 Cu(I)-Catalyzed Asymmetric Cascade Addition–Cyclization Reactions

Feringa and co-workers reported a new enantioselective Cu(I)/Tol-BINAP-catalyzed tandem conjugate addition–enolate trapping reaction of Grignard reagents with 4-chloro-α,β-unsaturated esters, thioesters, and ketones to yield *trans*-1-alkyl-2-substituted cyclopropanes in up to 92% yield and up to 98% *ee* (Scheme 38) [63]. The versatility of this methodology is demonstrated by the formation of key intermediates for the formal syntheses of cascarillic acid and grenadamide.

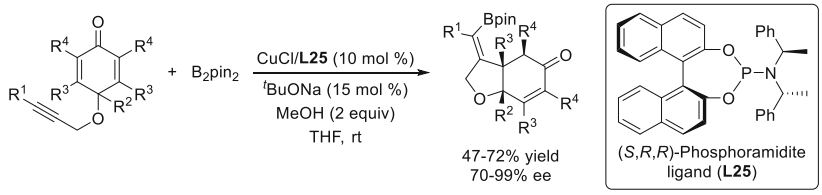
MacMillan and co-workers developed a novel catalytic asymmetric cascade arylation–cyclization reaction of indole-based nucleophiles with diaryliodonium salts using Cu(I)-bisoxazoline catalysis under mild conditions (Scheme 39) [64]. This transformation provides a new and direct strategy for the rapid and highly enantioselective construction of diverse C(3)-aryl pyrroloindoline



Scheme 38 Asymmetric tandem conjugate addition–intramolecular enolate trapping reaction



Scheme 39 Asymmetric cascade arylation–cyclization reaction

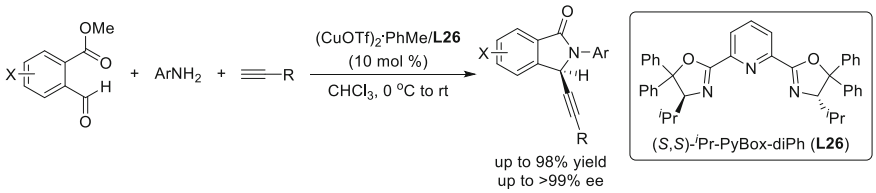


Scheme 40 Asymmetric tandem β-borylation–conjugate addition reaction

architectures, an important alkaloid structural motif that is commonly found in bioactive natural products and medicinal agents.

Lin and co-workers achieved the first Cu(I)-catalyzed asymmetric borylative cyclization reaction of cyclohexadienone-containing 1,6-enynes with bis (pinacolato)diboron (B_2pin_2) via a tandem process: selective β-borylation of propargylic ether and subsequent enantioselective conjugate addition to cyclohexadienone (Scheme 40) [65]. This reaction proceeds with excellent regio- and enantioselectivity to afford an enantioenriched *cis*-hydrobenzofuran framework with alkenylboronate and enone functional groups, which extends the realm of Cu-catalyzed asymmetric tandem reactions using B_2pin_2. In addition, the resulting bicyclic products could be transformed into other structurally useful bridged and tricyclic ring compounds.

Recently, Singh and co-workers reported an unprecedented Cu(I)/pybox-diPh-catalyzed highly enantioselective cascade alkynylation–lactamization reaction of readily available *o*-formyl methyl benzoates, aromatic amines, and terminal alkynes (Scheme 41) [66]. This protocol provides a straightforward and efficient approach to a wide range of enantiomerically enriched isoindolinones in good yield with an exceptionally high level of enantioselectivity. The methodology was further extended to the synthesis of synthetically important tetrahydroisoquinoline scaffolds in a two-step sequence with remarkable selectivity.



Scheme 41 Asymmetric cascade alkynylation–lactamization reaction

4 Conclusion

The utilization of copper(I) catalysis in asymmetric transformations is universal due to the special valence electron, Lewis acidity, and coordination characteristic of the metal. Copper salts are easily available, cost-efficient, and nontoxic. Copper(I)-catalyzed asymmetric cycloaddition and cascade addition–cyclization reactions are straightforward methodologies for the stereoselective construction of various biologically and medicinally important heterocyclic compounds. In the past 5 years, main endeavors have been paid into catalytic asymmetric [3+2] cycloadditions; other types of cycloaddition protocols are relatively less developed. The examples described in this chapter clearly demonstrate the potential of chiral Cu(I) complexes in the synthesis of enantioenriched heterocycles. Further studies may lie in the diversification of catalytic system, reaction type, and catalysis mode. Research in this field is still challenging and highly desirable, and it would be expected that more discoveries will come in the near future.

References

1. Padwa A (1984) 1,3-Dipolar cycloaddition chemistry. Wiley, New York
2. Gothelf KV, Jørgensen KA (1998) Chem Rev 98:863
3. Pandey G, Banerjee P, Gadre SR (2006) Chem Rev 106:4484
4. Padwa A, Pearson WH (2003) Synthetic applications of 1,3-dipolar cycloaddition chemistry towards heterocycles and natural products. Wiley, New York
5. Pyne SG, Davis AS, Gates NJ, Nicole J, Hartley JP, Lindsay KB, Machan T, Tang M (2004) Synlett 2004:2670
6. Pellissier H (2007) Tetrahedron 63:3235
7. Adrio J, Carretero JC (2014) Chem Commun 50:12434
8. Hashimoto T, Maruoka K (2015) Chem Rev 115:5366
9. Robles-Machín R, González-Esguevillas M, Adrio J, Carretero JC (2010) J Org Chem 75:233
10. Zhang C, Yu SB, Hu XP, Wang DY, Zheng Z (2010) Org Lett 12:5542
11. Han FZ, Yu SB, Zhang C, Hu XP (2015) Tetrahedron. doi:10.1016/j.tet.2015.01.003
12. Li QH, Tong MC, Li J, Wang CJ (2011) Chem Commun 47:11110
13. Yan DC, Li QH, Wang CJ (2012) Chin J Chem 30:2714
14. Li QH, Xue ZY, Tao HY, Wang CJ (2012) Tetrahedron Lett 53:3650
15. He ZL, Liu TL, Tao HY, Wang CJ (2012) Org Lett 14:6230
16. Teng HL, Huang H, Tao HY, Wang CJ (2011) Chem Commun 47:5494

17. Tao HY, He ZL, Wang CJ (2014) RSC Adv 4:16899
18. Li Q, Ding CH, Li XH, Weissensteiner W, Hou XL (2012) Synthesis 44:265
19. Yang QL, Xie MS, Xia C, Sun HL, Zhang DJ, Huang KX, Guo Z, Qu GR, Guo HM (2014) Chem Commun 50:14809
20. Grigg R, Donegan G, Gunaratne HQN, Kennedy DA, Malone JF, Sridharan V, Thianatanagul S (1989) Tetrahedron 45:1723
21. Padilla S, Tejero R, Adrio J, Cattetero JC (2010) Org Lett 12:5608
22. González-Esguevillas M, Adrio J, Carretero JC (2012) Chem Commun 48:2149
23. Hernández-Toribio J, Padilla S, Adrio J, Carretero JC (2012) Angew Chem Int Ed 51:8854
24. Pascual-Escudero A, González-Esguevillas M, Padilla S, Adrio J, Carretero JC (2014) Org Lett 16:2228
25. González-Esguevillas M, Pascual-Escudero A, Adrio J, Carretero JC (2015) Chem Eur J 21:4561
26. Potowski M, Schüermann M, Preut H, Antonchick AP, Waldmann H (2012) Nat Chem Biol 8:428
27. Takayama H, Jia ZJ, Kremer L, Bauer JO, Strohmann C, Ziegler S, Antonchick AP, Waldmann H (2013) Angew Chem Int Ed 52:12404
28. Narayan R, Bauer JO, Strohmann C, Antonchick AP, Waldmann H (2013) Angew Chem Int Ed 52:12892
29. Kobayashi S, Shimizu H, Yamashita Y, Ishitani H, Kobayashi J (2002) J Am Chem Soc 124:13678
30. Stohler R, Wahl F, Pfaltz A (2005) Synthesis 2005:1431
31. Li N, Song J, Tu XF, Liu B, Chen XH, Gong LZ (2010) Org Biomol Chem 8:2016
32. Vidadala SR, Golz C, Strohmann C, Daniliuc CG, Waldmann H (2015) Angew Chem Int Ed 54:651
33. Potowski M, Merten C, Antonchick AP, Waldmann H (2015) Chem Eur J 21:4913
34. Joseph R, Murray C, Garner P (2014) Org Lett 16:1550
35. Christoffers J, Baro A (2005) Quaternary stereocenters: challenges and solutions for organic synthesis. Wiley, Weinheim
36. Antonchick AP, Gerding-Reimers C, Catarinella M, Schürmann M, Preut H, Ziegler S, Rauh D, Waldmann H (2010) Nat Chem 2:735
37. Antonchick AP, Schuster H, Bruss H, Schürmann M, Preut H, Rauh D, Waldmann H (2011) Tetrahedron 67:10195
38. Liu TL, Xue ZY, Tao HY, Wang CJ (2011) Org Biomol Chem 9:1980
39. Liu TL, He ZL, Tao HY, Wang CJ (2011) Chem Commun 47:2616
40. Liu T, Li Q, He Z, Zhang J, Wang C (2015) Chin J Catal 36:68
41. Li Q, Huang R, Wang C (2014) Acta Chim Sin 72:830
42. Liu TL, He ZL, Wang CJ (2011) Chem Commun 47:9600
43. Liu TL, He ZL, Tao HY, Wang CJ (2012) Chem Eur J 18:8042
44. Li QH, Liu TL, Wei L, Zhou X, Tao HY, Wang CJ (2013) Chem Commun 49:9642
45. Li QH, Wei L, Chen X, Wang CJ (2013) Chem Commun 49:6277
46. Imaizumi T, Yamashita Y, Kobayashi S (2012) J Am Chem Soc 134:20049
47. Arai T, Ogino Y (2012) Molecules 17:6170
48. Hashimoto T, Takiguchi Y, Maruoka K (2013) J Am Chem Soc 135:11473
49. Tong MC, Chen X, Tao HY, Wang CJ (2013) Angew Chem Int Ed 52:12377
50. Guo H, Liu H, Zhu FL, Na R, Jiang H, Wu Y, Zhang L, Li Z, Yu H, Wang B, Xiao Y, Hu XP, Wang M (2013) Angew Chem Int Ed 52:12641
51. Potowski M, Bauer JO, Strohmann C, Antonchick AP, Waldmann H (2012) Angew Chem Int Ed 51:9512
52. Potowski M, Antonchick AP, Waldmann H (2013) Chem Commun 49:7800
53. He ZL, Teng HL, Wang CJ (2013) Angew Chem Int Ed 52:2934 (Part of this research work was first presented at the Chiral China 2012 Symposium in Lanzhou, China (August 17–19, 2012))

54. Teng HL, Yao L, Wang CJ (2014) J Am Chem Soc 136:4075
55. Liu H, Wu Y, Zhao Y, Li Z, Zhang L, Yang W, Jiang H, Jing C, Yu H, Wang B, Xiao Y, Guo H (2014) J Am Chem Soc 136:2625
56. Li QH, Wei L, Wang CJ (2014) J Am Chem Soc 136:8685
57. He ZL, Sheong FK, Li QH, Lin Z, Wang CJ (2015) Org Lett 17:1365
58. Chatterjee I, Jana CK, Steinmetz M, Grimme S, Studer A (2010) Adv Synth Catal 352:945
59. Zhou JL, Wang LJ, Xu H, Sun XL, Tang Y (2013) ACS Catal 3:685
60. Tong MC, Chen X, Li J, Huang R, Tao H, Wang CJ (2014) Angew Chem Int Ed 53:4680
61. Zhou F, Tan C, Tang J, Zhang YY, Gao WM, Wu HH, Yu YH, Zhou J (2013) J Am Chem Soc 135:10994
62. Osako T, Uozumi Y (2014) Org Lett 16:5866
63. Hartog T, Rudolph A, Maciá B, Minnaard AJ, Feringa BL (2010) J Am Chem Soc 132:14349
64. Zhu S, MacMillan DWC (2012) J Am Chem Soc 134:10815
65. Liu P, Fukui Y, Tian P, He ZT, Sun CY, Wu NY, Lin GQ (2013) J Am Chem Soc 135:11700
66. Bisai V, Suneja A, Singh VK (2014) Angew Chem Int Ed 53:10737

Top Organomet Chem (2016) 58: 207–220
DOI: 10.1007/3418_2015_157

Published online: 17 October 2015

1,2- Versus 1,4-Asymmetric Reduction of Ketones

Andrei V. Malkov and Kurt Lawson

Abstract Reduction of α,β-unsaturated ketones generally can give rise to a variety of products, of which chiral allylic alcohols (1,2-reduction) and saturated ketones (1,4-reduction) are the most useful from the synthetic point of view. With the appropriate substitution pattern these processes generate new stereogenic centres, where copper hydride coordinated to chiral ligand provided useful level of enantioselectivity. Attractiveness of the catalytic systems based on Cu(I) owes it to their high catalytic activity, low cost and ability to employ hydrogen or ubiquitous hydrosilanes as stoichiometric reducing reagents. This overview is focused on the efforts directed at developing and refining practical methods to tackle the issues of regio- and enantioselectivity with a particular focus on selective 1,2- and 1,4-manifolds, it mostly covers research published in 2010–2015 referring to earlier works for maintaining continuity.

Keywords Asymmetric catalysis • Carbonyl compounds • Copper • Enantioselectivity • Regioselectivity • Silanes

Contents

1 Introduction 208
2 Asymmetric 1,2- Versus 1,4-Reduction of Ketones 209
3 Asymmetric 1,2-Reduction of Ketones 213
4 Conclusions 218
References 218

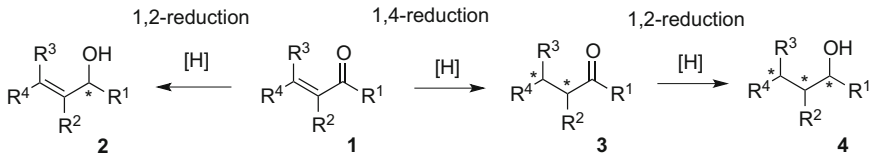
A.V. Malkov (✉) and K. Lawson
Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK
e-mail: a.malkov@lboro.ac.uk

1 Introduction

In organic chemistry, α,β-unsaturated carbonyls represent an important class of compounds with a multitude of ways for further synthetic modifications. These compounds are usually more reactive than their respective saturated analogues. Conjugation of the double bond with the carbonyl group makes them behave as a single unit, e.g. directing nucleophiles to the β-carbon, although with an appropriate choice of a reagent and/or reaction conditions, it is possible to exert nucleophilic attack selectively at either functional group.

Reduction of α,β-unsaturated ketones generally can lead to a variety of products, under certain circumstances resulting in a complete removal of the functional groups to give alkanes [1]. However, in the context of asymmetric reduction of ketones mediated by CuH species, three major scenarios generally attract practical interest (Scheme 1): 1,2-reduction to chiral allylic alcohols (**1**→**2**), 1,4-reduction to saturated ketones (**1**→**3**) and, to certain extent, consecutive 1,4- and 1,2-reduction leading to saturated alcohols (**1**→**4**) [2–4]. With the appropriate substitution pattern, the reactions shown in Scheme 1 will generate up to three new stereogenic centres, which naturally stimulated research interest in exercising high level of regio- and stereocontrol.

In the array of reductive asymmetric methods, hydrosilylation of carbon–carbon and carbon–heteroatom double bonds employing chiral CuH complexes occupies a privileged position due to the excellent record shown in application to a variety of substrate classes. Copper hydride coordinated to chiral ligand provided useful enantioselectivity in the conjugate reduction of various Michael acceptors, in the 1,2-reduction of prochiral ketones and ketimines [2–4]. Attractiveness of the catalytic systems based on Cu(I) owes it to their high catalytic activity, low cost and ability to employ hydrogen or ubiquitous hydrosilanes as stoichiometric reducing reagents. Therefore, over the years efforts have been directed at developing and refining practical methods to tackle the issues of regio- and enantioselectivity with a particular focus on selective 1,2- and 1,4-manifolds [3]. This overview will focus mostly on the achievements in this field in the last 5 years covering research published in 2010–2015 referring to earlier works for maintaining continuity.

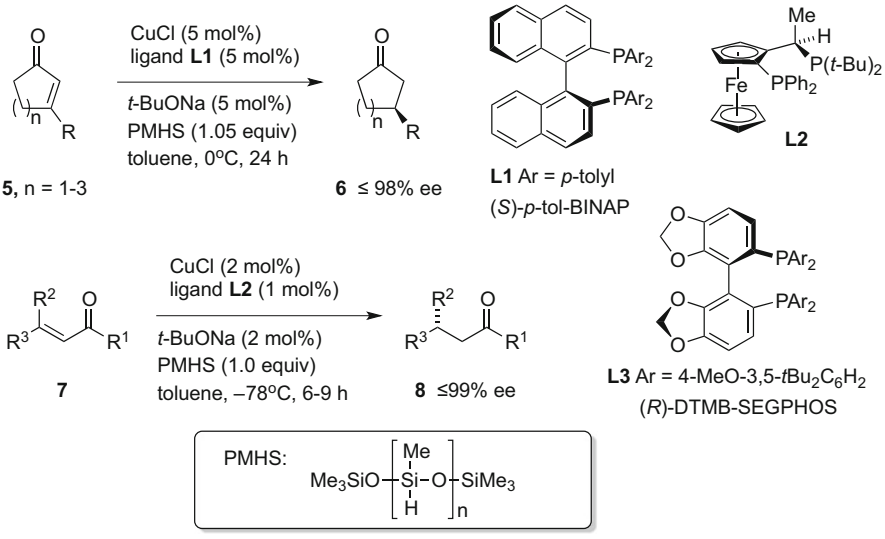


Scheme 1 Possible scenarios in the reduction of α,β-unsaturated ketones **1**

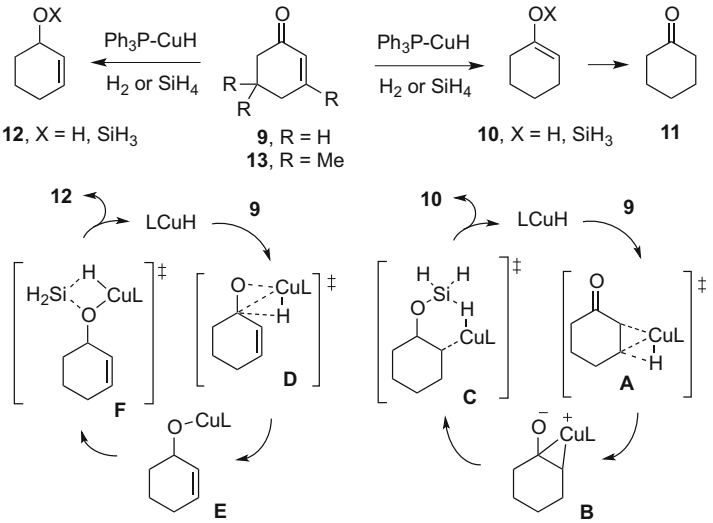
2 Asymmetric 1,2- Versus 1,4-Reduction of Ketones

In the case of unsaturated ketones, the inherent tendency of Cu to coordinate to C–C double bond renders 1,4-addition the thermodynamically preferred mode of action. This led to development of a number of highly efficient enantioselective protocols: Buchwald [5] reported reduction of cyclic enones (**5**→**6**, Scheme 2) using catalytic system based on (*S*)-*p*-tol-BINAP (**L1**), while Lipshutz [6] extended the method to the acyclic β,β-disubstituted substrates (**7**→**8**), employing ferrocene-derived ligand **L2**. It is noteworthy that reduction of enones is a ligand-accelerated process and with (*R*)-DTMB-SEGPHOS (**L3**), it produced high enantioselectivities with substrate-to-ligand ratio as high as 275,000:1 [7]. The conjugate reduction received further enhancement by coupling it in a one-pot procedure with the subsequent alkylation or arylation of the intermediate enolate [8–10].

Theoretical investigation into the mechanistic details of the competing 1,4- and 1,2-manifolds in the reduction with H_2 or hydrosilanes was carried out by DFT method using cyclohexanone **9** as a model substrate that was converted either to saturated ketone **11**, via enol **10**, or to allylic alcohol **12**, which is illustrated by hydrosilylation (Scheme 3) [11]. For simplification, Ph_3P-CuH was employed as the catalysts while SiH_4 replaced the hydrosilanes. Both pathways can be divided into two stages: (1) addition of the ligated CuH to the C=C or C=O bonds (TS **A** and **D**, respectively) to give intermediates **B** and **E** followed by (2) regeneration of the catalytic CuH species (TS **C** and **F**, respectively). Computational analysis revealed that 1,4-manifold is favoured both thermodynamically and kinetically. This trend is not affected by the nature of the stoichiometric reducing reagent employed, whether it is hydrogen or hydrosilane. Additionally, according to the



Scheme 2 Asymmetric 1,4-reduction of unsaturated ketones

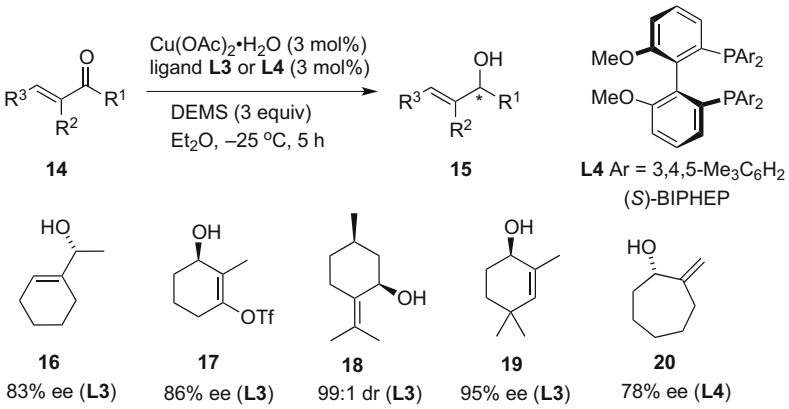


Scheme 3 Mechanistic dichotomy in the reduction of α,β-unsaturated ketones

computations, in the 1,4-reduction, coordination of CuH to the double bond is likely to be the rate-determining step (RDS), whereas in the 1,2-reduction, the RDS is the catalyst recovery step. In the same work, using the chiral (*R*)-SEGPHOS (**L3**, Ar=Ph) ligand for CuH, the calculations correctly predicted formation of the major enantiomer in the reduction of isophorone **13**. The origin of stereoselectivity was tracked down to the steric hindrance between the bulky fragment of the substrate and the P-phenyl group of the catalyst.

In spite of some earlier observations that the natural 1,4-regioselectivity of the CuH systems can be switched to the 1,2-mode by tuning the steric and electronic properties of the ligands [12], the asymmetric 1,2-version was not reported until 2010, when Lipshutz and co-workers succeeded in overcoming the intrinsic 1,4-manifold (Scheme 4) [13]. The main features of the developed method are as follows. In structure of the substrate ketones **14**, α-substitution is the prerequisite for 1,2-selectivity. High level of enantioselectivity was attained with chiral ligands DTMB-SEGPHOS (**L3**) and BIPHEP (**L4**), where ligand with *R* configuration of the chiral axis gives rise to *S*-allylic alcohols. Diethoxymethylsilane (DEMS) was found to be the best stoichiometric reducing reagent. Diethyl ether as the solvent and the temperature −25°C completed the set of optimal reaction conditions. As far as the substrate scope is concerned, α-methyl cinnamyl congeners (**14**, R^3 = aryl, R^2 = Me) produced the respective allylic alcohols in excellent yields (93–97%) and high enantioselectivities (89–95% ee). Homologues of the α-methyl group, such as ethyl and *n*-pentyl, behaved in the same way, although selectivity slightly dropped for α-phenyl and α-bromo substituents (76–77% ee).

Reduction of cyclic substrates followed the same pattern of regio- and enantiocontrol (**16**–**20**, Scheme 4), though several observations are worth noting. Allylic alcohol **20** was produced from the respective enone even in the absence of any steric



Scheme 4 1,2-Regioselectivity in the asymmetric reduction of α,β-unsaturated ketones using ligands **L3** and **L4**

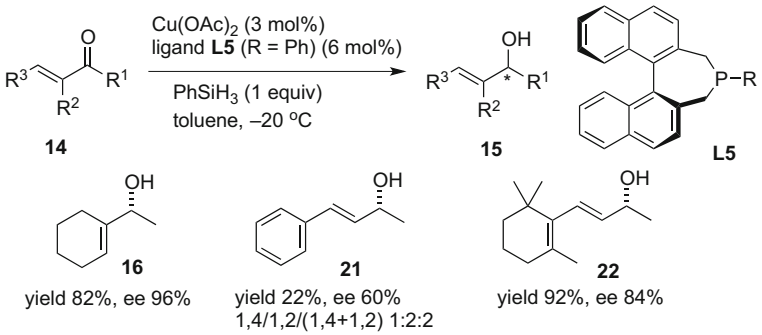
bias at the β-position but with α-substitution in place. Mild reaction conditions allowed for a clean 1,2-reduction of ketone **17** bearing an additional vinyl triflate functionality, which with harsher reducing reagents suffered extensive decomposition. In the reduction of (*R*)-pulegone, the sense of asymmetric induction proved to be controlled by the chiral ligand. Thus, the complex of CuH with (*R*)-**L3** produced pure *cis*-isomer **18** (dr 99:1), whereas in the mismatched case, the catalyst based on (*S*)-**L3** gave rise to the less common *trans*-product, albeit with lower diastereocontrol (dr 4:1).

The results of this investigation suggested that to promote 1,2-regioselectivity in the CuH-catalyzed asymmetric reduction of enones, α-substitution in the substrates appears to be a necessary condition; however, it is certainly not a sufficient one. Thus, with a chiral *o*-bis-(diphenylphosphino)benzene as a ligand, reduction of α-methyl cinnamyl derivative **14** (R^3=Ph; R^1, R^2=Me) proceeded predominantly along the 1,4-manifold [13]. Clearly, the ligands with their specific electronic and steric properties have an important role to play in the regioselectivity of the process.

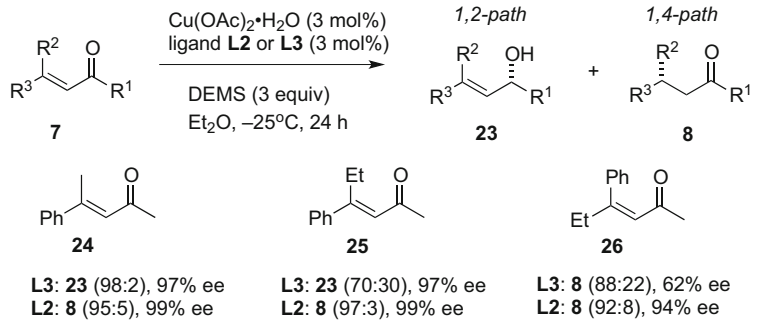
This thesis received further confirmation in the work of Beller and co-workers (Scheme 5) [14], who investigated CuH-catalyzed reduction of ketones employing monodentate phosphorus ligands **L5** and phenylsilane as a hydride source.

In the case of α,β-unsaturated ketones, chiral binaphthophosphepine ligands **L5** exhibited a clear preference towards 1,2-reduction. Thus, allylic alcohols **16** and **22** were formed in high yield and with high enantioselectivity using **L5** (R=Ph). The reaction with benzylidene acetone was less selective: 1,2-manifold was in competition with 1,4-manifold and a complete reduction pathways, which was also accompanied by a drop in enantiocontrol [14].

Further investigation by Lipshutz into the regioselectivity of Cu-catalyzed reduction of α,β-unsaturated ketones was aimed at β,β-disubstituted ketones with no substitution in α-position (**7**→**23**+**8**, Scheme 6) [15]. After screening several chiral ligands for the reduction of ketone **24** under the previously optimized



Scheme 5 1,2-Regioselectivity in the asymmetric reduction of α,β-unsaturated ketones using ligand **L5**



Scheme 6 Regioselectivity in the asymmetric reduction of β,β-disubstituted enones

conditions [13], the following pattern has emerged: SEGPHOS (**L3**) and BIPHEP (**L4**) favoured 1,2-pathway, whereas ligands of the JOSIPHOS series (e.g. **L2**) and some others favoured 1,4-manifold. For instance, reduction of **24** employing the catalytic system based on **L3** afforded the respective allylic alcohol in a 92% yield and an excellent 97% ee (1,2/1,4 ratio 98:2); remarkably, the catalyst made from **L2** under the same conditions furnished the respective 1,4-adduct (1,4/1,2 ratio 95:5) in a 90% yield and 99% ee. This trend appears to be general for acyclic ketones exhibiting good overall enantiomeric excesses (63–99%), as long as R^3 is aryl or hetaryl group while R^2 is alkyl. It is worth noting that hydride source can be changed from DEMS to $PhSiH_3$ with no adverse effect on the reaction.

Interesting results were attained with two isomeric enones **25** and **26**. While *E*-isomer **25** mirrored the behaviour pattern observed for **24**, in contrast, Z-**26** with both ligands **L2** and **L3** reacted only along 1,4-pathway; the reversal of regioselectivity with **L3** was also accompanied by a noticeable drop in ee.

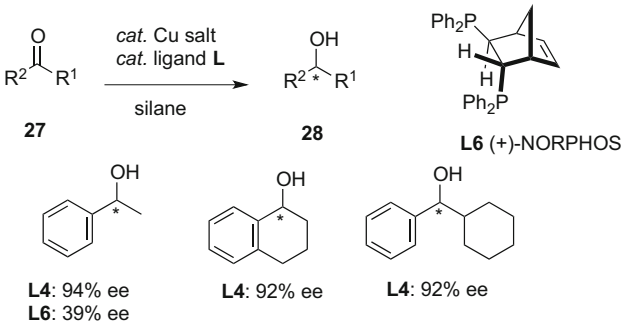
To shed more light on the factors governing the regiochemistry of the CuH-catalyzed reduction of β,β-disubstituted enones, DFT calculations were carried out [15]. The computed transition state energies confirmed that with a simple

ligand, 1,4-route had a lower energy barrier. However, as the steric bulk of the ligand increases, the 1,4-transition state becomes more crowded making the alternative 1,2-transition state more favourable. The computational results also suggested that switch in regioselectivity from 1,4- to 1,2-manifold will depend on the subtle interplay of a number of factors, including nature of solvent and steric bulk of the substrate and the ligand.

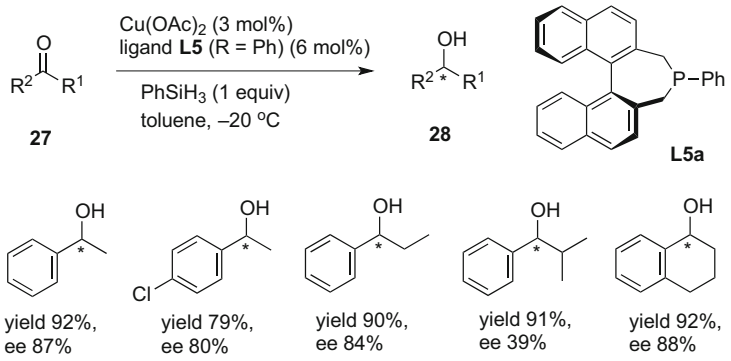
3 Asymmetric 1,2-Reduction of Ketones

In the absence of unsaturation, for example, in simple ketones or after 1,4-reduction has already occurred in α,β-unsaturated ketones, the 1,2-manifold is likely to be the main reaction pathway (**27**→**28**, Scheme 7). Since the pioneering report by Brunner [16] on a modestly enantioselective Cu-catalyzed hydrosilylation of acetophenone with diphenylsilane using (+)-NORPHOS (**L6**) (up to 39% ee) followed by the discovery by Lipshutz [17] of a highly enantioselective ligand-accelerated reduction of aryl ketones using BIPHEP (**L4**), various aspects of the Cu-catalyzed asymmetric 1,2-addition of a hydride to simple ketones have been under close scrutiny [2–4].

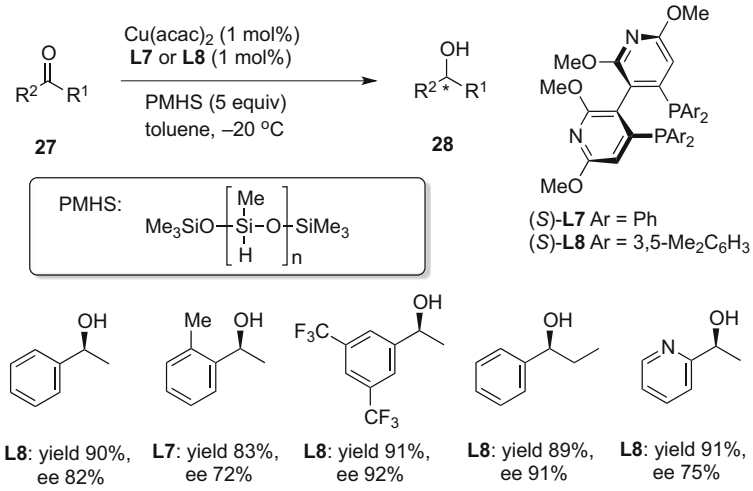
Investigation by Beller and co-workers [14] focused on the application of monodentate phosphine ligands **L5** (Scheme 8). Screening of copper precursor revealed that only copper acetate offered promising enantioselectivities, whereas the majority of other Cu(I) and Cu(II) salts produced inferior results. Interestingly, both hydrated and water-free copper(II) acetate performed equally well. Among the reducing agents, $PhSiH_3$ came on top in terms of yield and enantioselectivity. Several monodentate phosphorous ligands including phosphines, phosphates and phosphoramides were assessed in the model reduction of acetophenone (**27**, R^2=Ph, R^1=Me). The best in the series chiral binaphthophosphepine **L5a** afforded the respective alcohol **28** in a 92% yield and 87% ee. The optimized catalytic system performed reasonably well with a variety of aromatic ketones (selected



Scheme 7 Earlier examples of hydrosilylation of ketones with chiral CuH complexes



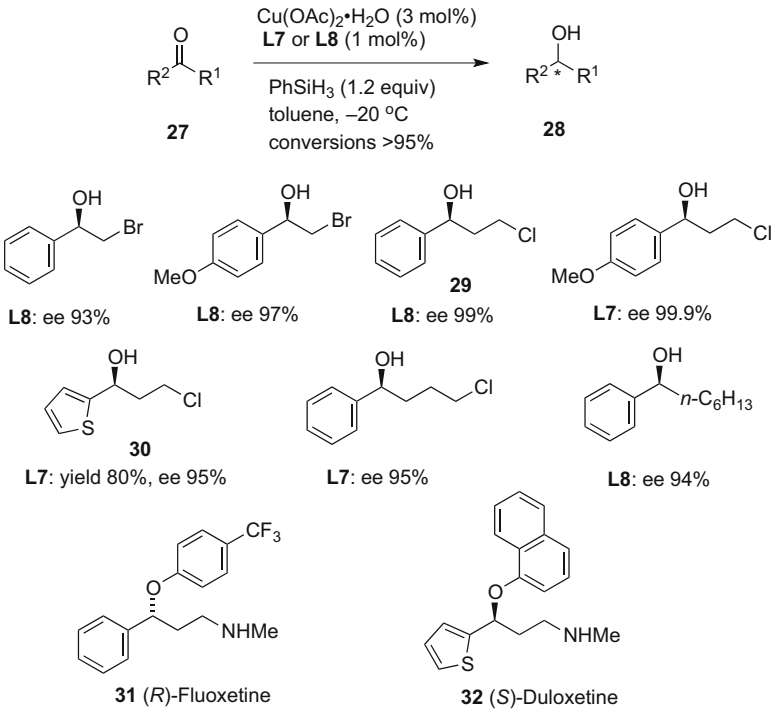
Scheme 8 Selected examples of asymmetric reduction of ketones using ligand **L5**



Scheme 9 Selected examples of asymmetric reduction of ketones using ligands **L7** and **L8**

examples are shown in Scheme 8); however, enantioselectivity drastically decreased with aliphatic ketones and with bulkier aromatic substrates. Furthermore, 2,6-disubstituted acetophenones failed to react due to the excessive steric bulk.

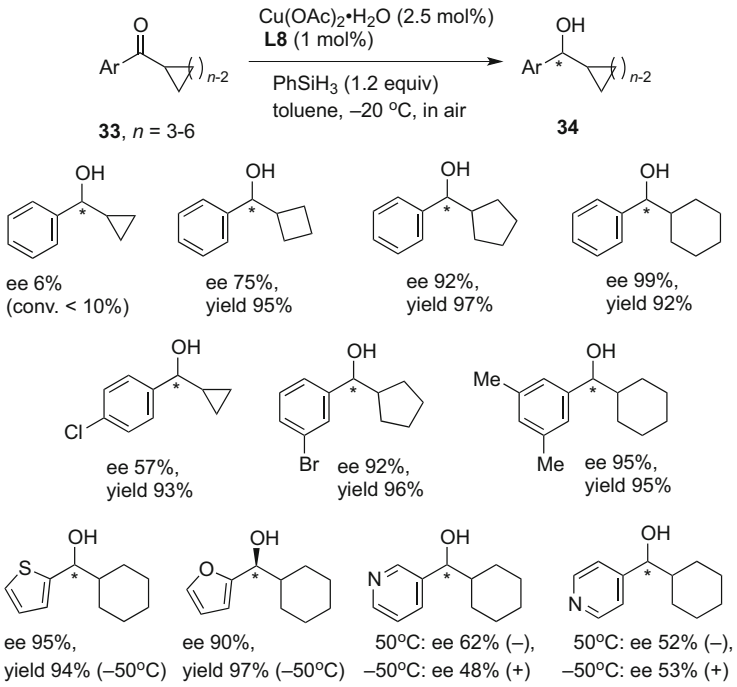
Wu and Chan [18] introduced a series of axially chiral dipyridylphosphine ligands **L7** and **L8** for transition metal-catalyzed asymmetric transformations that also included hydrosilylation of aromatic ketones employing $PhSiH_3$ as a hydride source and CuF_2 as the catalyst precursor [19]. In a more recent modification of the method, they opted for a less expensive, moisture and air-stable polymethylhydrosiloxane (PMHS) as a reducing reagent (Scheme 9) [20]. With PMHS, $Cu(acac)_2$ proved to be the optimal copper source. Using 1 mol% catalyst loading, high yield and moderate-to-high enantioselectivities were attained over a wide range of aromatic ketones including challenging heterocyclic substrates. Representative examples are shown in Scheme 9.



Scheme 10 Selected examples of reduction of functionalized ketones

Substrate scope for ligands **L7** and **L8** was extended to halo-substituted ketones (Scheme 10) [21, 22]. On this occasion, though, the best results were attained with the catalyst derived from hydrated $Cu(OAc)_2$ (3 mol%) and using $PhSiH_3$ as the reducing reagent. In most cases, high conversions (>95%) and high enantioselectivities (94–99.9% ee) were observed. This catalytic system also proved efficient over a broad range of alkyl aryl ketones. Ligand-accelerated nature of the catalytic process allowed to reduce the ligand quantity to 1 mol%. It is worth noting that in some instances substrate-to-ligand ratio as high as 50,000:1 could be used without affecting enantioselectivity or reaction rate; furthermore, the reactions can be performed in air [21]. Synthetic utility of the method was illustrated by enantioselective synthesis of antidepressant drugs (*R*)-fluoxetine (**31**) and (*S*)-duloxetine (**32**) from enantioenriched 1,3-haloalcohols. Thus, enantiomer of **29** was converted into **31** in four easy steps in 77% overall yield. A similar reaction sequence starting from alcohol **30** afforded **32** in 40% overall yield [22].

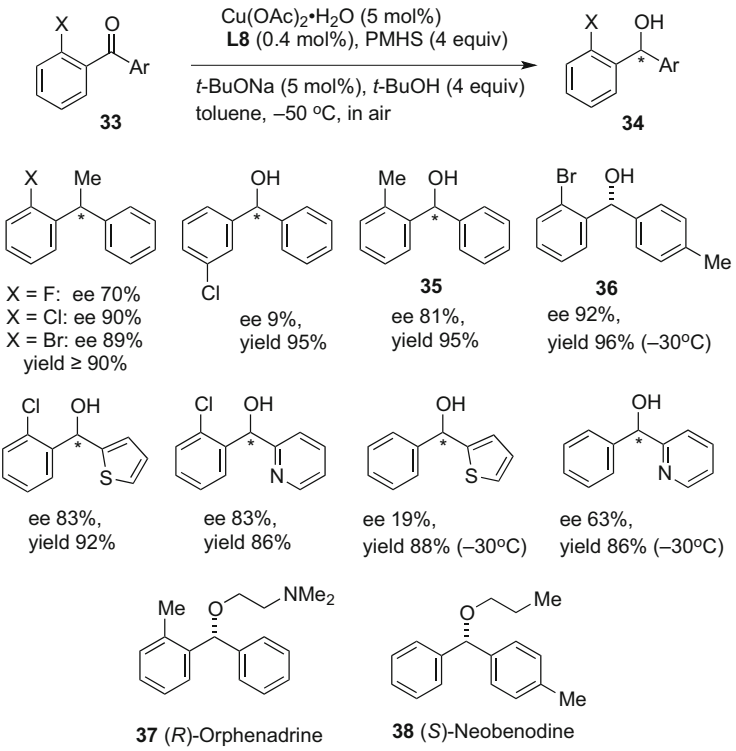
The catalytic system based on $Cu(OAc)_2 \cdot H_2O$ and ligand **L8** in combination with $PhSiH_3$ as a hydride source also proved efficient in the reduction of aryl- and heteroaryl cycloalkyl ketones (Scheme 11) [23]. The substrate scope was probed employing different size cycloalkyl groups along with variation of the aromatic or heteroaromatic fragment. Cyclopropyl derivatives proved particularly difficult;



Scheme 11 Selected examples of reduction of aryl- and heteroaryl cycloalkyl ketones

they reacted sluggishly and gave poor enantioselectivity. As the cycloalkyl ring size increased, the enantioselectivities dramatically improved, especially for cyclopentyl and cyclohexyl derivatives. Variation of substitution pattern in the aromatic ring did not reveal any clear trend, but the enantioselectivities generally remained high for larger cycloalkyl groups. In the heteroaromatic ketone series, thiophen and furan derivatives mirrored reactivity of their electron-rich aryl analogues. In contrast, enantioselectivity in the reduction of 3- and 4-pyridyl cyclohexyl ketones exhibited dramatic temperature dependence. Gradual inversion of the absolute configuration of the resulting alcohols was observed as the reaction temperature was changing from 50°C to −50°C. Thus, at 50°C both ketones produced laevorotatory enantiomers, whereas at −50°C the dextrorotatory products were formed in both cases (Scheme 11). Interestingly, the isomeric 2-pyridyl cyclohexyl ketone showed a normal pattern of temperature dependence (27% ee at 22°C increasing to 63% ee at −50°C in the same enantiomeric series).

Asymmetric reduction of prochiral diaryl ketones (**33** →**34**, Scheme 12) is an important chemical transformation due to the practical significance of the resulting diaryl methanol derivatives **34** for biochemical and pharmaceutical applications [24]. It is also a challenging problem due to the lack of sufficient stereochemical bias between the two aromatic groups and coupled with a lower reactivity of diaryl ketones compared to the related aryl alkyl analogues. Chan reported catalytic



Scheme 12 Selected examples of reduction of diaryl- and aryl heteroaryl ketones

system based on a complex of CuF_2 with ligand **L8** and $PhSiH_3$ as a hydride source that produced high enantioselectivities with substrates featuring *ortho*-substituent in one of the aromatic rings, whereas with *meta*- and *para*-substituted benzophenones, the enantioselectivity dropped to a moderate level [19]. To attain full conversions, this catalytic system required 48–72 h. An improvement in the catalytic activity was achieved by Lipshutz [25], who employed CuH coordinated to (*R*)-DTMB-SEGPHOS (**L3**). The requisite CuH was prepared in situ from CuCl, *t*-BuONa (both 5 mol%) and excess PMHS. With a 0.4 mol% ligand loading, this catalytic system in less than 24 h produced high yields and good to high enantioselectivities in the hydrosilylation of a range of *ortho*-substituted benzophenones. Again, *meta*- and *para*-substituted benzophenones proved to be poor substrates for this reaction giving nearly racemic products.

Further optimization of the catalytic system for the asymmetric reduction of diaryl- and aryl heteroaryl ketones was disclosed by Chan and Wu [26]. In modification of the blueprint of the successful catalyst introduced by Lipshutz [25] (vide supra), SEGPHOS **L3** was replaced with ligand **L8**, whereas CuH was prepared from hydrated $Cu(OAc)_2$ (5 mol%), *t*-BuONa (5 mol%), *t*-BuOH (4 equiv.) and PMHS (4 equiv.) (Scheme 12). With this catalytic system, the time required for

completion was generally less than 36 h; in many cases, the reaction was finished in 12–15 h. In the reduction of diaryl ketones, the same trend was observed: for high enantioselectivity, *ortho*-substitution was required (70–96% ee). Moving substituent to *meta*-position resulted in a dramatic drop in enantiomeric excess below practical level. Reactivity of the heterocyclic analogues exhibited similar pattern.

Among substituents, electron-withdrawing *o*-Cl and *o*-Br substituents appear to induce better enantioselectivities. Besides, they represent a convenient handle for further synthetic modification, e.g. through coupling reactions [25]. Chiral benzhydryl fragment can be found in a variety of pharmaceutically relevant molecules. Synthetic application of the reduction of prochiral diaryl ketones was illustrated by enantioselective synthesis of antihistamine agents (*R*)-orphenadrine (**37**) and (*S*)-neobenodine (**38**) [26]. The former was synthesized in two easy steps from alcohol **35**, whereas synthesis of **38** from **36** also included debromination step.

4 Conclusions

Of the two most common 1,2- and 1,4-manifolds in the asymmetric reduction of α,β-unsaturated ketones, the former is less thermodynamically favourable; therefore, in the absence of any steric or electronic bias, conjugate reduction prevails. However, the regioselectivity appears to be highly sensitive to the nature of solvent, substitution pattern and steric bulk of substituents in the substrate and steric bulk of the ligand. Subtle combination of any of these factors can trigger switch in regioselectivity. Empirical screening of ligands and conditions may be avoided by engaging DFT analysis of the reaction coordinate for the given set of reactants for predicting the likely reaction outcome. This area of research still has not reached its full potential.

When the 1,4-reduction is taken out of equation, the 1,2-reduction occurs readily to give chiral products. With several potent ligands introduced and the conditions rigorously optimized, the asymmetric reduction with chiral CuH complexes reached the level of maturity and is ready for challenging synthetic application.

References

1. Hudlicky M (1984) Reductions in organic chemistry. Ellis Horwood, Chichester
2. Rendler S, Oestreich M (2007) Polishing a diamond in the rough: “Cu–H” catalysis with silanes. Angew Chem Int Ed 46:498–504. doi:10.1002/anie.200602668
3. Deutsch C, Krause N, Lipshutz BH (2008) CuH-catalyzed reactions. Chem Rev 108: 2916–2927. doi:10.1021/cr0684321
4. Lipshutz B (2009) Rediscovering organocopper chemistry through copper hydride. It’s all about the ligand. Synlett 2009:509–524. doi:10.1055/s-0028-1087923

5. Moritani Y, Appella DH, Jurkauskas V, Buchwald SL (2000) Synthesis of β-alkyl cyclopentanones in high enantiomeric excess via copper-catalyzed asymmetric conjugate reduction. J Am Chem Soc 122:6797–6798. doi:10.1021/ja0009525
6. Lipshutz BH, Servesko JM (2003) CuH-catalyzed asymmetric conjugate reductions of acyclic enones. Angew Chem Int Ed 42:4789–4792. doi:10.1002/anie.200352313
7. Lipshutz BH, Servesko JM, Petersen TB, Papa PP, Lover AA (2004) Asymmetric 1,4-reductions of hindered β-substituted cycloalkenones using catalytic SEGPHOS–ligated CuH. Org Lett 6:1273–1275. doi:10.1021/ol0400185
8. Lipshutz BH, Amorelli B, Unger JB (2008) CuH-catalyzed enantioselective intramolecular reductive aldol reactions generating three new contiguous asymmetric stereocenters. J Am Chem Soc 130:14378–14379. doi:10.1021/ja8045475
9. Yun J, Buchwald SL (2001) One-pot synthesis of enantiomerically enriched 2,3-disubstituted cyclopentanones via copper-catalyzed 1,4-reduction and alkylation. Org Lett 3:1129–1131. doi:10.1021/ol015577f
10. Chae J, Yun J, Buchwald SL (2004) One-pot sequential Cu-catalyzed reduction and Pd-catalyzed arylation of silyl enol ethers. Org Lett 6:4809–4812. doi:10.1021/ol048313c
11. Liu H, Zhang W, He L, Luo M, Qin S (2014) Computational investigations on the phosphine-ligated CuH-catalyzed conjugate reduction of α-β unsaturated ketones: regioselectivity and stereoselectivity. RSC Adv 4:5726. doi:10.1039/c3ra44015j
12. Chen JX, Daeuble JF, Brestensky DM, Stryker JM (2000) Highly chemoselective catalytic hydrogenation of unsaturated ketones and aldehydes to unsaturated alcohols using phosphine-stabilized copper (I) hydride …. Tetrahedron 56:2153–2166. doi:10.1016/s0040-4020(99)01098-4
13. Moser R, Bošković ZV, Crowe CS, Lipshutz BH (2010) CuH-catalyzed enantioselective 1,2-reductions of α, β-unsaturated ketones. J Am Chem Soc 132:7852–7853. doi:10.1021/ja102689e
14. Junge K, Wendt B, Addis D, Zhou S, Das S, Beller M (2010) Copper-catalyzed enantioselective hydrosilylation of ketones by using monodentate binaphthophosphepine ligands. Chem Eur J 16:68–73. doi:10.1002/chem.200902442
15. Voigtritter KR, Isley NA, Moser R, Aue DH, Lipshutz BH (2012) Regioselective reductions of β, β-disubstituted enones catalyzed by nonracemically ligated copper hydride. Tetrahedron 68:3410–3416. doi:10.1016/j.tet.2011.10.056
16. Brunner H, Miehling W (1984) Asymmetrische katalysen: XXII. Enantioselektive hydrosilylierung von ketonen mit CuI-katalysatoren. J Organomet Chem 275:c17–c21. doi:10.1016/0022-328X(84)85066-4
17. Lipshutz BH, Noson K, Chrisman W (2001) Ligand-accelerated, copper-catalyzed asymmetric hydrosilylations of aryl ketones. J Am Chem Soc 123:12917–12918. doi:10.1021/ja011529e
18. Wu J, Chan ASC (2006) P-Phos: a family of versatile and effective atropisomeric dipyridylphosphine ligands in asymmetric catalysis. Acc Chem Res 39:711–720. doi:10.1021/ar0680015
19. Wu J, Ji J-X, Chan ASC (2005) A remarkably effective copper(II)-dipyridylphosphine catalyst system for the asymmetric hydrosilylation of ketones in air. Proc Natl Acad Sci 102:3570–3575. doi:10.1073/pnas.0409043102
20. Zhang X-C, Wu F-F, Li S, Zhou J-N, Wu J, Li N, Fang W, Lam KH, Chan ASC (2011) Copper-dipyridylphosphine-polymethylhydrosiloxane: a practical and effective system for the asymmetric catalytic hydrosilylation of ketones. Adv Synth Catal 353:1457–1462. doi:10.1002/adsc.201100105
21. Yu F, Zhou J-N, Zhang X-C, Sui Y-Z, Wu F-F, Xie L-J, Chan ASC, Wu J (2011) Copper(II)-catalyzed hydrosilylation of ketones using chiral dipyridylphosphane ligands: highly enantioselective synthesis of valuable alcohols. Chem Eur J 17:14234–14240. doi:10.1002/chem.201102157
22. Zhou J-N, Fang Q, Hu Y-H, Yang L-Y, Wu F-F, Xie L-J, Wu J, Li S (2014) Copper(II)-catalyzed enantioselective hydrosilylation of halo-substituted alkyl aryl and heteroaryl ketones:

asymmetric synthesis of (R)-fluoxetine and (S)-duloxetine. Org Biomol Chem 12: 1009–1017. doi:10.1039/c3ob42214c
23. Qi S-B, Li M, Li S, Zhou J-N, Wu J-W, Yu F, Zhang X-C, Chan ASC, Wu J (2013) Copper-dipyridylphosphine-catalyzed hydrosilylation: enantioselective synthesis of aryl- and heteroarylcycloalkyl alcohols. Org Biomol Chem 11:929–937. doi:10.1039/C2OB27040D
24. Schmidt F, Stemmler RT, Rudolph J, Bolm C (2006) Catalytic asymmetric approaches towards enantiomerically enriched diarylmethanols and diarylmethylamines. Chem Soc Rev 35:1–17. doi:10.1039/b600091f
25. Lee C-T, Lipshutz BH (2008) Nonracemic diarylmethanols from CuH-catalyzed hydrosilylation of diaryl ketones. Org Lett 10:4187–4190. doi:10.1021/ol801590j
26. Sui Y-Z, Zhang X-C, Wu J-W, Li S, Zhou J-N, Li M, Fang W, Chan ASC, Wu J (2012) Cu II-catalyzed asymmetric hydrosilylation of diaryl- and aryl heteroaryl ketones: application in the enantioselective synthesis of orphenadrine and neobenodine. Chem Eur J 18:7486–7492. doi:10.1002/chem.201200379

Index

A
Acetophenone, 116, 127, 174, 213, 214
Acids, hard/soft, 170
2-Acylcycloheptatrienes, 198
Acyloxazolidinones, borylated, 141
Acylsilanes, 117
Addition–cyclization, cascade, 183, 201
1,2-Addition, 99
  copper(I)-catalyzed125
1,4-Addition, 99, 137
  copper(I)-catalyzed, 119
Alcohols, chiral, 109
Aldehydes, 10, 105, 111, 127, 139, 147, 160, 173, 196
  allylation, 154, 163
  cycloaddition, 192
  β-substituted, 9, 94
Aldimines, 147
Aldimino esters, cyclic, 194
Aldoses, 177
Alkenes, 6, 34, 51, 85, 140, 151, 163, 188, 192
  cyclic, 138
  electron-deficient, 184
  oxabicyclic, 24
Alkenyl aluminium, 48
Alkenyl cyclopropane malonates, cyclic, 30
Alkenyl(pseudo)halides, 15
Alkenylboronates, 172
Alkenylsilicones, 172
(*E*)-(γ-Alkoxyallyl)boronates, α-chiral, 154
3-Alkylidene-4-chromanones, 193
3-Alkylidene oxindoles, 193
1-Alkyl-1-nitroolefins, 72
Alkynes, 26, 29, 49, 60, 177, 195, 202
Alkynylaluminium, 27
Alkynylation–lactamization, cascade, 203
Allyl cyanide 174
Allyl–allyl cross-coupling, 7
Allylation, 1, 20, 34, 154, 163
Allylboronates, 172
Allylic acceptors, racemic, 157
Allylic substitution, 151
Allylmgbr, 7
Allylsilicones, 172
Aluminium enolates, 47
2-Amido pyrrolidines, 188
Amino acids, 82
Aminoalkynylation, anomeric, copper(I)-catalyzed, 177
Ansalactam A, 8
Aphanorphine, 43
Arduengo's carbene, 74
(*S*)-Arundic acid, 23
Aryl dialkylzinc, 83
Aryl heteroaryl ketones, 217
Aryl heteroaryl methanols, tertiary, 118
Aryl pyrroloindoline, 201
Arylation–cyclization, cascade, 201
Arylboronates, 172
Arylsilicones, 172
Asymmetric allylic alkylation (AAA), 1
Asymmetric allylic substitutions, 1
Axane family, 43
5-Aza-spiro[2,4]heptanes, 192
Azide–alkyne cycloadditions, asymmetric, 200
Azoalkenes, 199, 200
Azomethine ylides, [3+2] cycloadditions, 184

B
2-Benzoylthiophene, 119
Benzyl 4-bromocrotonate, 11
α-Benzylidene-β-ketoesters, 199
Bifluoride anion, 148
Binaphthophosphepine, 213
Biphenyl phosphoramidites, 4
BIPHEP, 111, 210, 213
Bis(pinacolato)diboron, 86
Boron nucleophiles,1,2-addition, 147
1,6-addition, 145
Borrelidin, 105
Borylation, 135, 163, 202
Butenolides, 144
Butyrolactams, 143
Butyrolactones, 12, 82, 174, 194

C
Camptothecin, 109
Carbocupration, 120
Carbonyls, 147, 207
Cascade addition–cyclization, 183
Cascarillic acid, 201
Catalysis, asymmetric, 99, 135, 169
enantioselective 41
4-Chromanone-3,3′-pyrrolidine, 193
Chromones, 106
Cinnamyl bromide, 4
Cinnamyl chlorides, copper-catalysed allylic alkylation, 3
Clemastine, 109
Cognac lactone, 12
Conjugate addition, 41, 100, 137
Copper aldolate, 175
Copper alkoxide, 173
Copper alkynides, 178
Copper catalysis, 1, 41, 99, 135, 169, 183, 207
Copper–phosphinamine, 50
Coumarins, 105
Crinipellin, 43
Cu-acetylide, 195
Cu/ferrocenyl diphosphine, 104
CuOt-Bu, 173
Cu(I)/bisoxazoline, 201
Cu(I)/tBu-Phosferrox, 196
Cu(I)/TFBiphamPhos, 194, 198
Cu(I)/Tol-BINAP, 104
Cuparene, 43
Cyanocarboxylic acids, 172
Cycloadditions, asymmetric, 183
[2+2], 199
[3+3], [3+6], 196
[4+1], [4+2], 199
Cycloheptanones, 69
Cycloheptatrienes, 198
Cyclohexa-1,3-diene, 158
Cyclohexanones, 69, 75, 77, 209
Cyclohexenes, 33, 34
Cyclohexenones, 44, 45, 70, 77, 138, 171
Cyclopropanes, 151
trans-1-alkyl-2-substituted, 201
Cyclopropylboronates, 151

D
Dialkynes, 200, 201
Diazo 2,6-diisopropylphenyl ester, 199
Diboron compounds, 163
Diborylalkanes, 163
Diels–Alder reaction, 13, 42, 197, 200
Dienes, 10, 190
1,3-Dienes, 158, 190
1,4-Dienes, 9, 25
1,5-Dienes, 6
Diethoxymethylsilane (DEMS), 210
Diethyl ethylidenemalonate, 100
Diethyl sodiomalonate, 100
Dihydrofurans, chiral, 116
Dihydropyranones, 174
Dimethyl itaconate, 187
Dimethyl 1-methyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate, 48
Diphenylethylenediamine, 149
Diphosphine copper(I) bifluoride, 148
Diphosphoramidite, 4
Dipyridylphosphine, 214
Doliculide, 105
Domino reactions, 159
DTMB-SEGHPHOS, 111
Duloxetine, 215

E
Efavirenz, 109
Enantioselective conjugate addition (ECA), 42
Enantioselectivity, 1, 3, 41, 207
Enokipodin, 43
Enolates, 43, 47, 55, 72–80, 86, 89, 105, 121, 170, 173, 209
Enynes, 8, 116, 158–162, 202
Enynones, 74–76, 108
Escitalopram, 109
3-Ethylcyclohex-2-enone, 69
Ethyl 2-cyclopropylideneacetate, 193

F
3-(Fluoromethyl)-4-nitroproline, 187
Fluoxetine, 215

o-Formyl methyl benzoates, 202
Fulvenes, 197
Furanoside phosphite–phosphoramidite, 4

G
Gilman reagents, 120
Glycylsultam, 192
Grenadamide, 201
Grignard reagents, 99
  nucleophiles, 67
  α,β-unsaturated carbonyls, 101
Guanacastepen, 43

H
Hard and soft acid and base (HSAB) theory, 170
Hard anion-conjugated soft metal catalysis (HASM), 172
Heck coupling, 12, 20, 42
Hemiaminals, 176
Hennoxazole A, 8
Heptadiynes, 200
Heteroaryl cycloalkyl ketones, 216
Heteroarylsilylimines, 189
N-Heterocyclic carbenes (NHC), 2, 29, 58, 107, 114, 139,
Hydrazides, 196
Hydroalumination, 26
2-(2-Hydroxyethyl)indole, 180

I
Imidazolidines, 195
Imidazolinium, 68
Imines, fluorinated, 195
α-Iminoamides, 188,
Indoles, 180, 200, 201
Isochromenes, 178

J
Josiphos, 74, 104, 112, 119, 137, 145, 212

K
Ketene silylacetals, 172
Ketimines, 130, 139, 150, 208
Ketones, asymmetric alkylation, 116
  copper(I)-catalyzed enantioselective condensation, 176
  α,β-unsaturated, 208

L
Lejimalide, 8
Lewis acids, 23, 44, 117, 126, 138, 169
Lewis bases, 170
Lithium cyanobis(methyl) (3-trimethylsiloxycyclohex-2-en-1-yl) cuprate(III), 121
Lithium dimethylcuprate, 120

M
Me-DuPhos, 158
Meldrum's acids, 43, 80–83
Mesitylcopper (MesCu), 179
Metathesis, σ-bond, 135
Methyl phenylpropiolate, 122
α-Methylene-γ-butyrolactone, 194
2-Methyleneglutarate, 187
3-Methylene-2-oxindoles, 192
Methyllithium, 17
Methylvinyl ketone (MVK), 78
Morita–Baylis–Hillman adduct, 187
Mycobacterium tuberculosis, 105

N
Neobenodine, 218
Nitrile aldol reaction, 173
Nitroalkenes, 43, 80, 174, 187–191
2-Nitrosopyridine, 199
NORPHOS, 213
Nyasol, 26

O
Organoaluminium, 2, 25, 43, 50, 101, 108, 110
Organoboron, 43, 86, 88, 91, 92, 111
Organocuprates, 76, 120–125, 171
Organolithium, 1, 15, 25, 34, 101
Organomagnesium, 2, 31, 109, 110
Organometallic reagents, 1, 43
Organosilanes, 43, 111
Organozinc, 2, 24, 29, 43, 80, 101, 109, 124
  nucleophiles, 80
Organozirconium reagents, 2
  nucleophiles, 84
Orphenadrine, 218
Oxabenzonorbornadiene, 24
Oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylates, 47
1,2-Oxazetidine-3-ones, 199

P
Paracyclophane, 141
Pauson–Khand reactions, 13
3-Phenyl-cyclohexenone, 47
Phenylsulfonylenones, 184
Phorbasins, 8
Phosphine oxide allylic bromides, 11
Phosphoramidites, 8
Picolinates, 16
Pinacolborane, 163
Piperidines, 12, 176, 197, 199
Prolines, 144
Propargylic ether, 160, 202
  β-borylation, 202
Protecting group-minimized, 169
Pulegone, 211
Pyrazolines, 195
Pyrazolo[1,2-*a*]pyrazolone, 195
Pyridyl cyclohexyl ketones, 216
2-Pyridyl pyrrolidines, 188
N-(2-Pyridylmethyl)imines, 188

Q
Quaternary centres, 41
QuinoxP, 87, 92, 138, 152, 164

R
Rasfonin, 105
Regioselectivity, 4, 20, 73, 100, 106, 207
Ring closing metathesis (RCM), 12

S
Silanes, 207
Silicon nucleophiles,
  1,2-addition, 148
  1,4-addition, 142
  1,6-addition, 145
  allylic substitution, 155
Silver-*N*-heterocyclic carbene (NHC), 58
Silylation, 135
α-Silylimines, 189
Soft carbon nucleophile, 169
Spiro[butyrolactone-pyrrolidine], 194
Spirooxindoles, 192
Spiropyrrolidines, 192
Succinic acids, 82
N-Sulfonylimines, enantioselective silylation, 150
Suzuki–Miyaura cross-coupling, 10

T
Tamao oxidation, 152
Taniaphos, 5, 14, 18, 103, 106, 137, 141
Tetrabutylammonium acetate (TBAA), 12
Tetrabutylammonium bromide (TBAB), 12
Tetrahydroisoquinoline, 202
Thioesters, 62, 89, 91, 95, 104, 128, 140, 145, 201
Thorpe–Ingold effect, 179
Titanium isopropoxide, 110
Titanium tetraisopropoxide, 110
Tocopherol, 113
Transmetalation, 135
Trialkylaluminium, 47
Triazinane, 197
Triazoles, 200
Trifluorocrotonate, 185
α-Trifluoromethylacetamide, 174
Triisobutylaluminium, 46
Tropone, 198

V
Vibsanin, 43
Vinylaluminium, 25

Y
Ynones, 174

Z
Zinc, 1, 25, 67, 80, 101, 123, 156
Zirconium, 1, 2, 25, 34, 43, 50, 62, 84