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Review

Organosilanes in Metal-Catalyzed, Enantioselective Reductions

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ABSTRACT: The growth and development of an extensive range of metals complexed with chiral ligands for the purpose of catalyzing a variety of reactions in an enantioselective manner has been impressive for its scope, chemical yields and high ee values. Chief among the classes of synthetic transformations has been that of the asymmetric reduction of prochiral substrates. These include the asymmetric reduction of prochiral ketones, imines, unsaturated aldehydes, ketones, esters, nitriles and olefins, as well as a number of asymmetric coupling reactions. In concert with these efficient catalyst systems, organosilanes have the ability to carry out any number of organic reductions under a variety of conditions. In these reactions, which in reality are hydrosilylations (hydrosilylation and reduction are considered interchangeable herein) in which the initially resulting silylated product is hydrolyzed to the ultimate desired functionality, the ability to sterically and electronically alter the organosilane reductant can contribute to the overall success of the transformation. In this review, we present a thorough compilation of the literature covering the use of organosilanes in metal-catalyzed asymmetric reductions (hydrosilylations) and coupling reactions.

KEYWORDS: *reduction, enantioselective, asymmetric, organosilane, metal-catalyzed, copper-catalyzed, CuH-catalyzed*

1. INTRODUCTION

The general application of organosilanes as an alternative to direct hydrogenation for a variety of reductions has been established for a number of years, and was extensively reviewed in an Organic Reactions chapter.[1] In addition to the large number of standard nonstereoselective reductive transformations, an extensive and growing number of asymmetric reductions have been reported, which are the subject of this review. In the interest of practicality, we have chosen for the most part to limit the entries to those that have shown enantioselectivities greater than 80% for a majority of substrates investigated. In addition, although in most cases the published works reviewed herein investigated a range of metal catalysts and nonracemic ligands, we have limited our entries to the particular system or systems used in the exploration of the reaction scope. We have decided to present the ligands and relevant metal complexes in the beginning of this review and encourage readers to refer to the tables while reading the document (Figures 1−4).

Several reviews of enantioselective silane reductions have appeared over the years, with the early reports highlighting the pioneering work of Ojima, Brunner and Itoh.[2,3] Other reviews have since been published that cover the general aspects of organosilane reductions and enantioselective hydrosilylations. These reviews have emphasized either the class of asymmetric reduction or the types of catalyst system employed, and have been directed primarily at the reduction of a specific functional group or the use of a specific class of chiral ligand to induce asymmetry. For reviews of relevant topics, one can consult the following: enantioselective additions to ketones and imines,[4−8] Ni-catalyzed reductive couplings and cyclizations,[9−11] asymmetric Cu−H chemistry,[12−17] *N*-heterocyclic carbenes (NHC) ligands[18] and organocatalysis.[19]

Of course the asymmetric reduction of prochiral substrates is not limited to the use of organosilanes; asymmetric hydrogenation and transfer hydrogenation providing viable alternatives.

It should be noted that the organosilane plays a critical role in providing stoichiometric hydrogen to reactions although in many cases it is not involved in determining the ultimate stereoselectivity. In many examples notably those in which Cu catalysis is invoked, the silane provides the hydrogen to form the active, nonracemic-ligated CuH complex through a metathesis transfer. This represents a significant advantage in that it prepares the active copper catalyst in situ and thereby removes the need for its separate preparation and isolation. In such cases, the choice of silane can more readily be based on economic and ease of product purification considerations. However, it is important to consider that in metathesis reactions the organosilane not only provides the necessary hydride but also serves to capture the leaving group (O-*t*-Bu, O_2CR, F) from the Cu source rendering it less reactive.

It is pleasing to note that many of the protocols available render themselves nicely to scale-up, several examples of which are noted herein. This is true not only of the chemistry but also importantly in economic and reaction condition terms. For example, the use of CuH-catalyzed enantioselective reductions the copper source is a simple Cu salt, usually $Cu(OAc)_2$, and the silane, which, as noted, provides the hydride to make the CuH,

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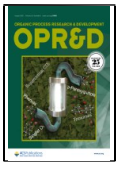

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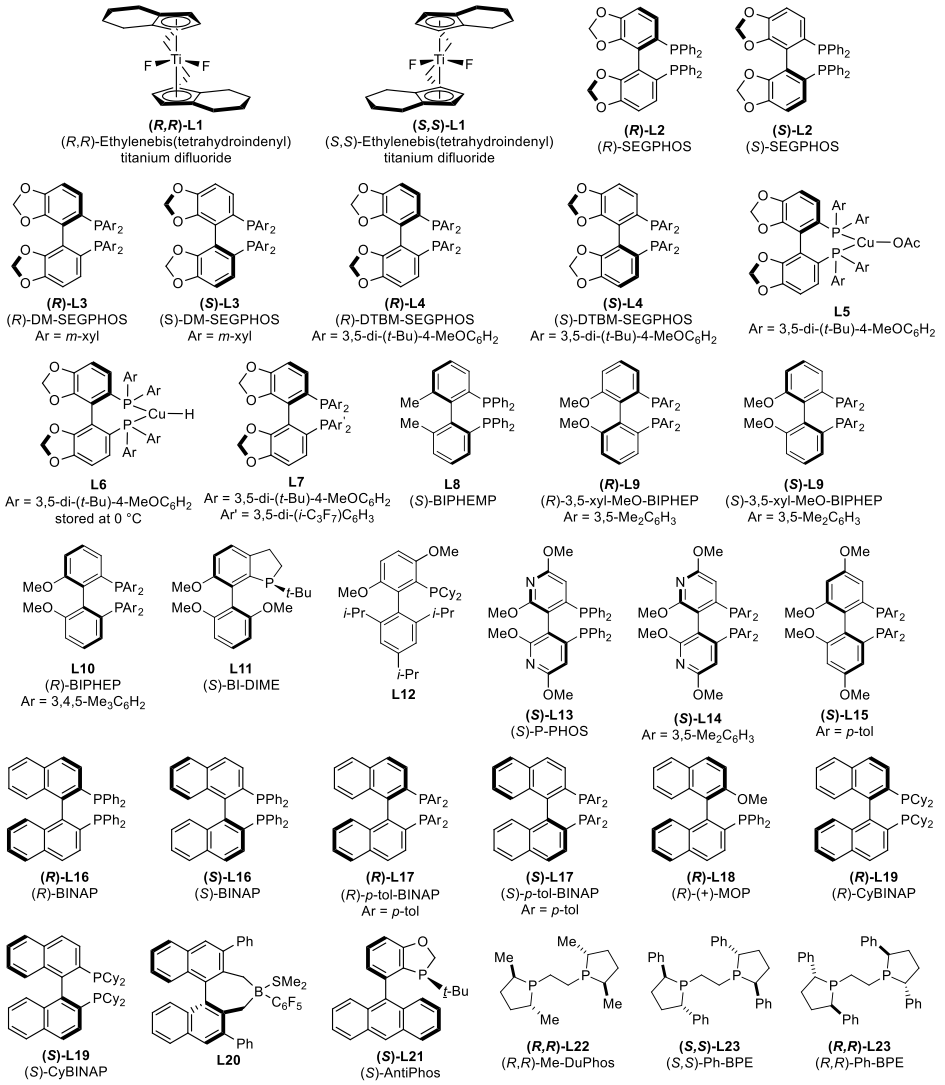

Figure 1. Ligands and catalysts 1 of 4.

can be chosen from a long list of candidates and is typically the inexpensive polymethylhydrosiloxane, PMHS. This reduces the overall economic challenge in many cases to that of the nonracemic ligand. A caveat regarding the use of PMHS is that the silicon byproduct is a polymeric siloxane, which can make product isolation difficult. Normally, one can extract the desired product from the polymeric reaction residue leaving the byproduct polysiloxane behind. However, if this is not possible, the use of PMHS can be offset via the use of one of a number of monomeric organosilanes.

Finally, the use of organosilanes as the source of the hydride in reductions warrants a comparison to the use of dihydrogen and hydrogen transfer for similar transformations. An extensive comparison of all the methods was deemed to be outside the scope of this review with its emphasis on the use of organosilanes as the stoichiometric reductants in the asymmetric reduction of the full range of prochiral substrates. Asymmetric hydrogenation and transfer hydrogenation processes have been reviewed with emphasis on specific functional groups rather than a complete coverage of a range of substrates.[20−32]

2. LIGANDS AND CATALYSTS

The ligands and catalysts discussed are presented in Figures 1−4.

3. SILANES AS REDUCING AGENTS

Organosilane reducing agents possess a number of advantages over both molecular hydrogen and traditional metal hydrides such as $LiAlH_4$, including safer handling and improved chemoselectivity. The relative electronegativities of Si (1.9) and H (2.2) result in a Si−H bond with a slightly hydridic H suitable for ionic nucleophilic reductions. The weakly hydridic Si−H bond allows for enhanced chemoselectivity, although it often requires activation of the substrate to be reduced.[1] Organosilanes are composed of an extensive range of readily prepared derivatives that offer steric, electronic, and economical distinctions. For example, triphenylsilane, diphenylsilane and phenylsilane possess distinct steric and electronic properties, while triethylsilane, *tert*-butyldimethylsilane and triisopropylsilane represent a range of steric encumbrance that one often finds employed in the classic silicon-based protection of functional groups, particularly alcohols. In many examples, the steric and electronic properties of the silane are tuned to maximize yield and enantioselectivity, but mostly can be chosen based on their

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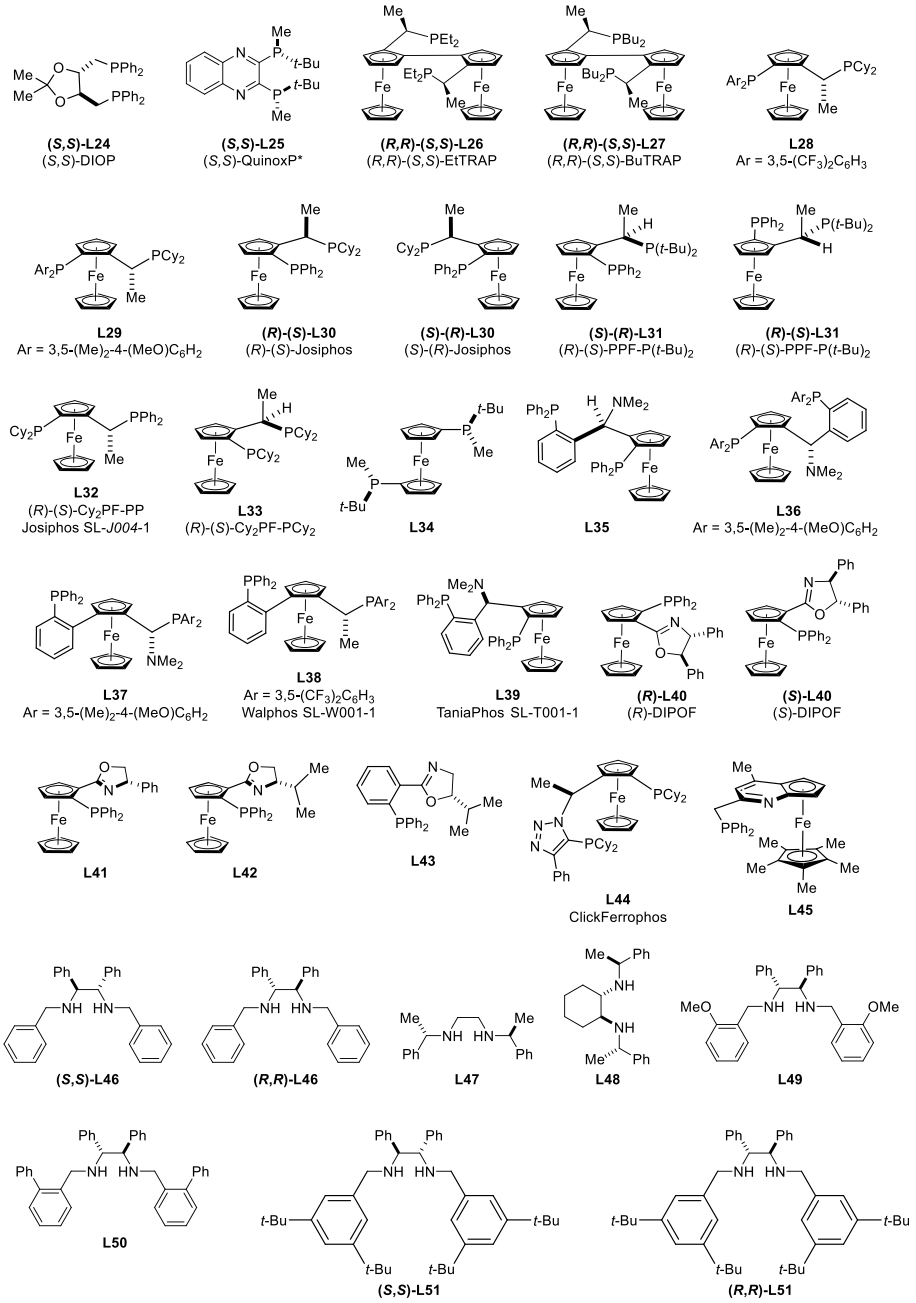

Figure 2. Ligands and catalysts 2 of 4.

byproducts and the ease of workup of a reaction mixture. For example, triethylsilane will provide triethylsilanol or hexaethyldisiloxane as the silicon-containing byproduct, whereas phenylsilane or diphenylsilane can give byproducts that still contain a Si−H bond in addition to being an arylsilane, which can protiodearylate giving a Si−H bond. These are safety concerns to be noted particularly when scale-up applications are considered. Where cost is a consideration, polymethylhydrosiloxane (PMHS) or tetramethyldisiloxane (TMDS) are economical reductant candidates. In addition, a number of other related and readily synthesized aryl, alkyl or polymeric organosilanes can be considered available reductants, which can be tailored not only to synthetic considerations but also for their potential in the isolation and purification of the desired final product. Even though PMHS, TMDS, and $PhSiH_3$ predominate in many of the applications, numerous examples of other organosilane reductants will be found herein.

4. ASYMMETRIC REDUCTION OF ARYL KETONES

The asymmetric reduction of prochiral aryl alkyl ketones to their corresponding alcohols is a popular endeavor in synthetic chemistry. Applications in this area include the use of dihydrogen and hydrogen transfer protocols, both of which, like the organosilane approaches, require the use of a metal catalyst. Versus dihydrogen the use of organosilanes as the hydride source provides enhanced chemoselectivity, handling, and safety. Acetophenone has routinely served as a benchmark substrate to assess the potential for a set of reagents and reaction conditions. As noted in several of the examples below, the success of acetophenone as a substrate does not necessarily translate to other aryl alkyl substrates; both electron-rich and

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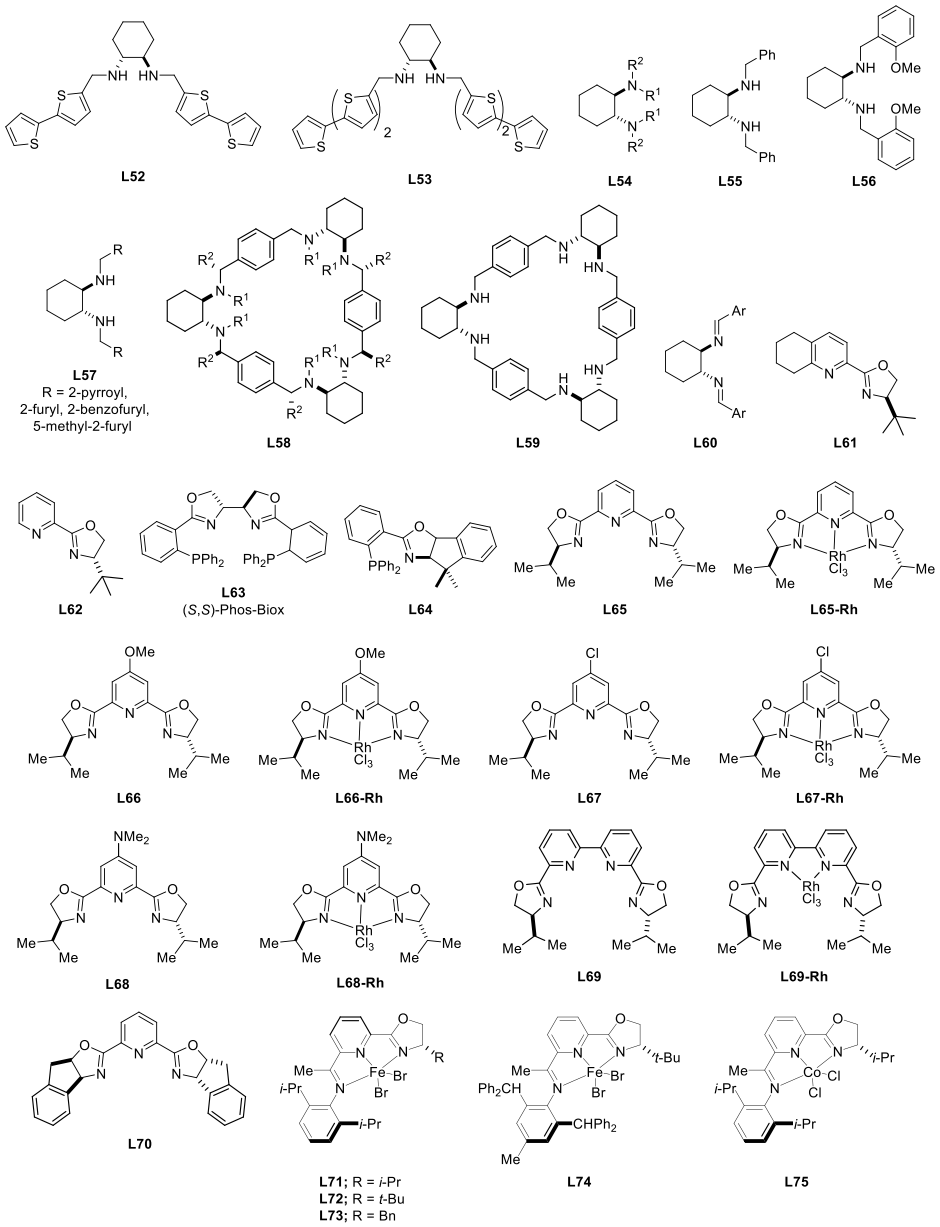

Figure 3. Ligands and catalysts 3 of 4.

electron-poor, as well as, unsurprisingly, *ortho*-substituted aryl ketones, can display distinct reactivities and enantioselectivities.

Although the degree of asymmetric induction was modest in range, the early pioneering work of Brunner and co-workers on metal-catalyzed asymmetric hydrosilylation of ketones and imines cannot be overlooked. This work has been nicely reviewed.[3]

Buchwald et al. developed a series of titanocene complexes, which upon conversion to titanium hydrides by the organosilane, can facilitate hydrosilylation of ketones (Scheme 1). To accomplish the hydrosilylation, the titanium precatalyst (*R,R*)-ethylenebis(tetrahydroindenyl) titanium difluoride (***R,R*)-L1** was converted to the active catalyst upon sequential treatment with *n*-BuLi and PMHS.[33] The subsequent addition of an aryl alkyl ketone and protiodesilylation of the resulting silyl ether produced benzyl alcohols from aryl alkyl ketones in good yields and with high ee's. Unfortunately, prochiral dialkyl ketones were reduced with lower enantioselectivity, albeit in good chemical yield.

They were able to improve the reduction protocol by several means.[34] First, the group discovered that titanocene precatalyst **(*S,S*)-L1**, (*S,S*)-ethylenebis(tetrahydroindenyl) titanium difluoride could be activated by phenylsilane in place of *n*-BuLi/PMHS. Second, they found that adding MeOH during the reaction resulted in an increase in reaction rate and enhanced enantioselectivity, concomitantly allowing for a significant decrease in catalyst loading compared to the typical 1 mol % or greater. Under these improved conditions, the reduction of aryl ketones as well as some α,β-unsaturated ketones could be achieved in excellent yield and with high enantioselectivity (Scheme 2). Interestingly, both (2-hydroxyethyl) phenyl ketone and (2-methoxyethyl) phenyl ketone were reduced in high enantiomeric excess, but at only about 50% conversion. Prochiral dialkyl ketones were reduced in good yields but with poor ee's, whereas alkenyl alkyl ketones were successful.

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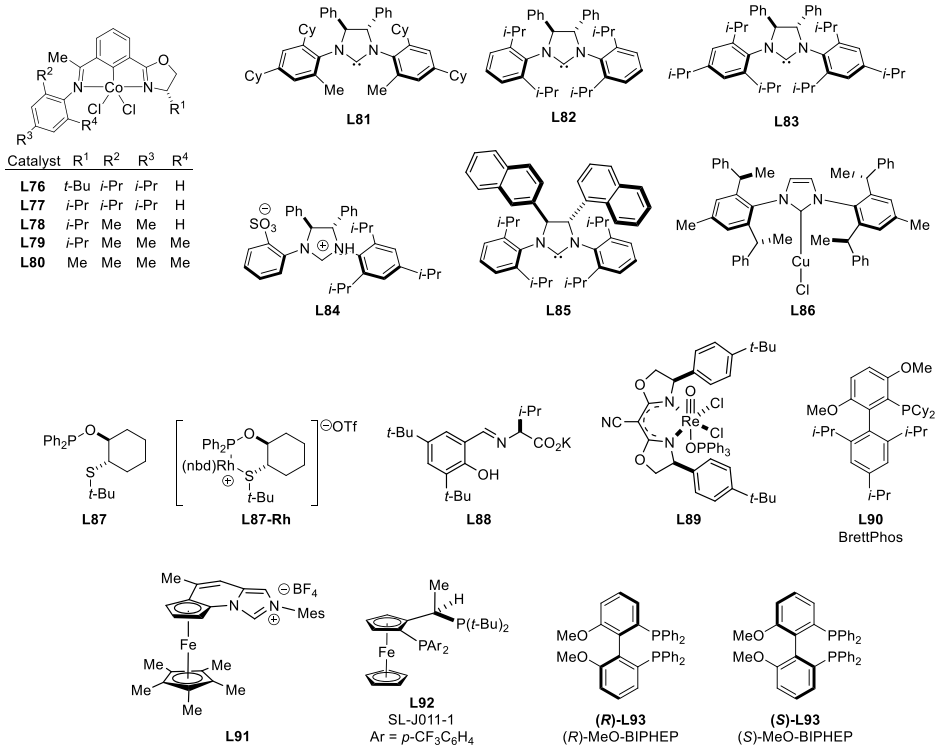
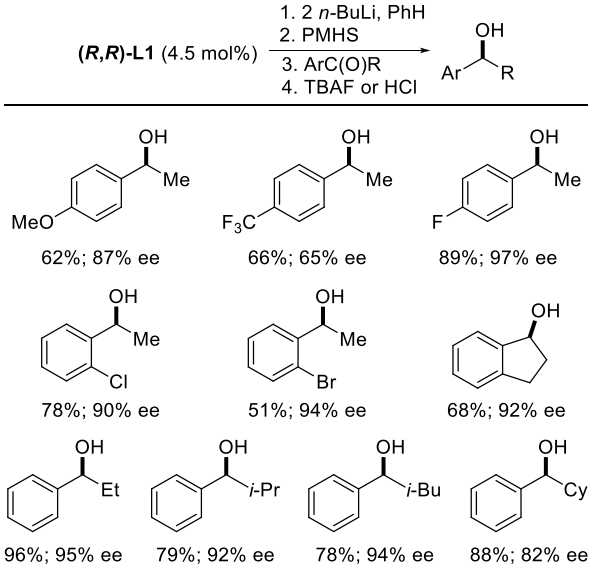
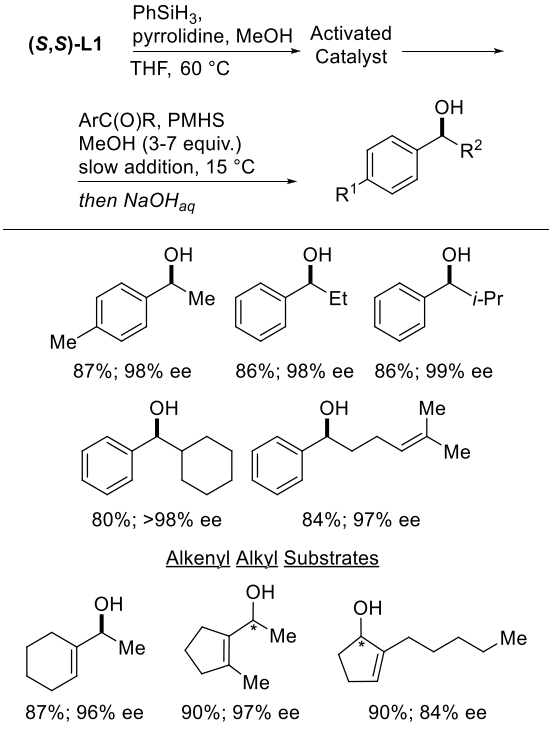


Figure 4. Ligands and catalysts 4 of 4.

Scheme 1. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with (*R,R*)-L1



Scheme 2. Asymmetric Phenylsilane Hydrosilylation of Acetophenone Derivatives with (*S,S*)-L1



During the introduction and development of asymmetric catalysis, chiral bisphosphine ligands were found to be mediocre for the hydrosilylation of prochiral ketones.[35] However, via an extensive number of examples, Brunner et al. demonstrated that chiral pyridine thiazolidine ligands complexed with rhodium could effectively hydrosilylate ketones with modest to good enantioselectivity using diphenylsilane as the reductant.[36] Building on Brunner results, Nishiyama et al. then developed a series of pyridine and oxazoline-based ligands which performed well in Rh-catalyzed hydrosilylations.[37] In the initial study, acetophenone, α-tetralone and (2-phenylethyl) methyl ketone were subjected to asymmetric reduction with diphenylsilane and various electronically modified rhodium catalysts **L65-Rh**−**L69-Rh**, which were prepared from the PyBOX ligands **L65**−**L68**, respectively (Scheme 3). The study investigated the effect of ligand substituents with different electronics on the reaction. For acetophenone, all four catalysts produced good yields (78−

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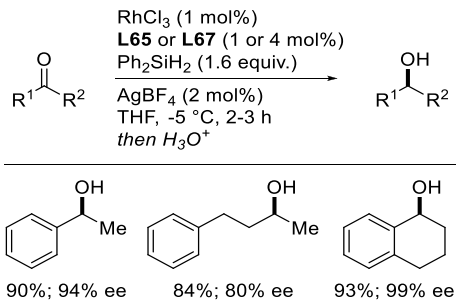
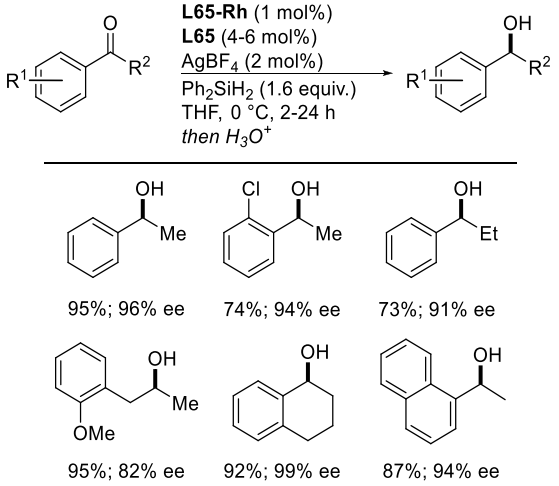
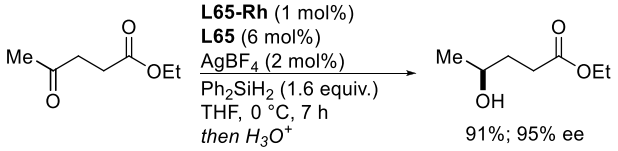
Scheme 3. Rhodium-Catalyzed Diphenylsilane Asymmetric Hydrosilylation of Acetophenone Derivatives with L65 or L67



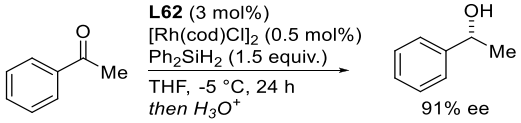
Scheme 4. Asymmetric Diphenylsilane Hydrosilylation of Ketones with L65-Rh



Scheme 5. Enantioselective Diphenylsilane Hydrosilylation of Ethyl Levulinate with Rh-L65

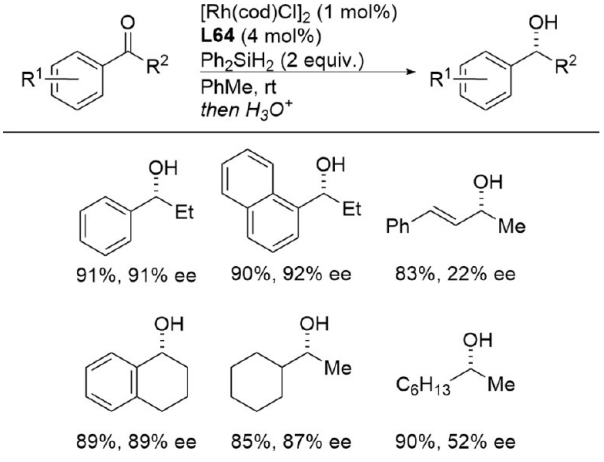


Scheme 6. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone with Rh-L62

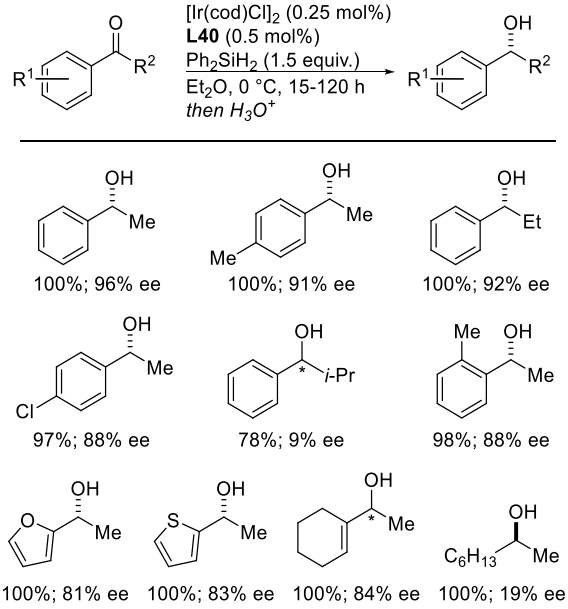


94%) and ee's (83−92%) at a 1 mol % loading. However, when the catalyst loading was lowered to 0.5 mol %, the yields (22−77%) and ee's (2−59%) dropped off considerably. α-Tetralone produced excellent results (92−95% yield; 97−99% ee's) at a 1 mol % catalyst loading, while the dialkyl ketone 2-phenylethyl methyl ketone produced good chemical yields (84−96%) with only modest enantioselectivities (49−80% ee's) with several of the catalyst systems. In general, the Rh-complexes **L67-Rh** and **L69-Rh** produced reactions that could be carried out at a lower

Scheme 7. Asymmetric Diphenylsilane Hydrosilylation of Prochiral Ketones with Rh-L64



Scheme 8. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone with Ir-L40



temperature and in a shorter time than with the less electron-rich **L66** and **L68**.

The Nishiyama group next expanded their studies to employ Rh complexes derived from the chiral PyBOX **L65** and bis(oxazolinyl)bipyridine) (bipymox) ligand **L69**.[38−40] The PyBOX **L65**-derived rhodium complex **L65-Rh** resulted in high yields and ee's for aryl ketones studied employing Ph_2SiH_2 (Scheme 4). Superior results were obtained via the use of additional ligand **L65** and the presence of $AgBF_4$ as a promoter. On the other hand, application to eight dialkyl prochiral ketones produced less favorable results (yields 60−95%; 27−95% ee's), with the exception of ethyl levulinate (91% yield; 95% ee) (Scheme 5). Employing the Rh catalyst **L69-Rh**, derived from bipymox **L69**, demonstrated similar results, reducing acetophenone in 98% yield and with 90% ee (Scheme 6). Interestingly, the pyridine-oxazoline **L62** (pymox) ligand scaffold also accomplished the hydrosilylation of acetophenone with 91% ee, but with an opposite configuration of the resulting alcohol to that obtained from **L69-Rh**.

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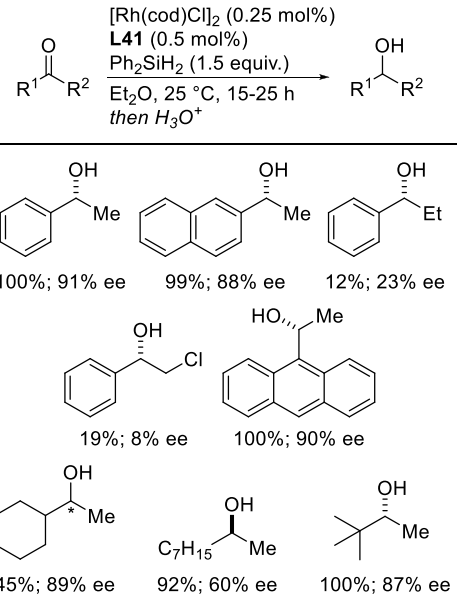
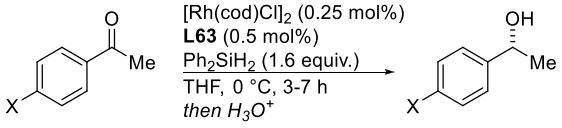
Scheme 9. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone Derivatives with Rh-L41

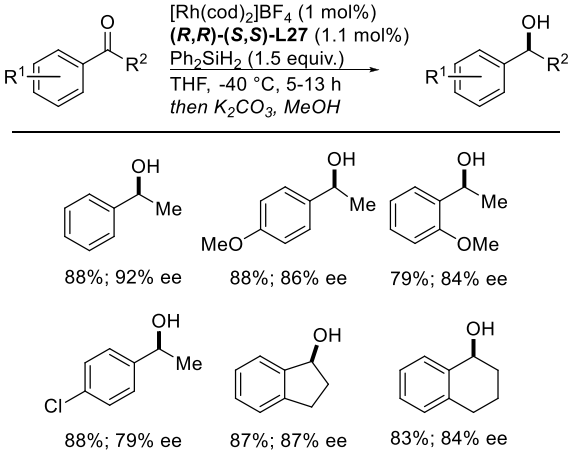


Scheme 10. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone Derivatives with Rh-L63



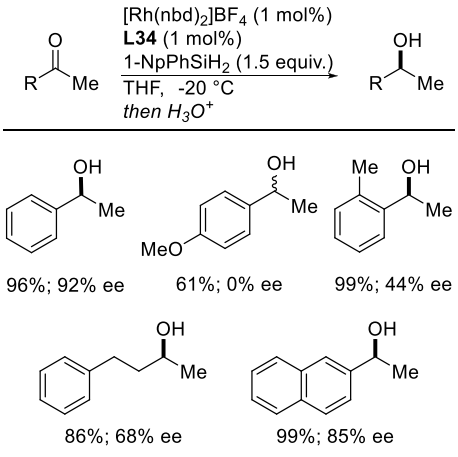
X	conv (%)	ee (%)
H	98	97
Me	98	93
Cl	97	91
OMe	99	21

Scheme 11. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone Derivatives with Rh-(*R*,*R*)-(*S*,*S*)-L27

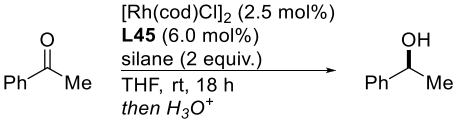


Under catalysis with *P*,*N*-type ligand **L64**, developed by Saigo and co-workers, and in the presence of [Rh(cod)Cl]$_2$, prochiral ketones were asymmetrically reduced with diphenylsilane in high yield (83−97%) and with moderate to high ee's (22−94%) (Scheme 7).[41] Yields were generally excellent, but high ee's were only obtained for substrates with considerable steric differ-

Scheme 12. Asymmetric 1-Naphthylphenylsilane Hydrosilylation of Acetophenone Derivatives with Rh-L34

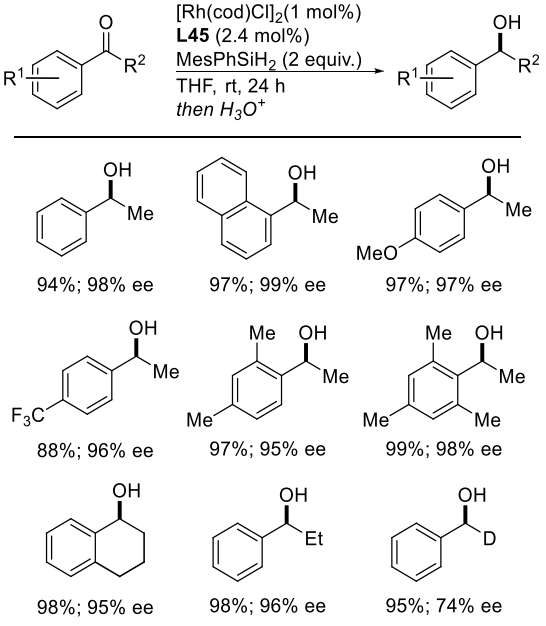


Scheme 13. Effect of Organosilane on the Asymmetric Hydrosilylation of Acetophenone Derivatives with Rh-(−)-L45



Silane	ee (%)
n-octylSiH$_3$	3
PhSiH$_3$	8
Et$_2$SiH$_2$	1
PhMeSiH$_2$	66
Ph$_2$SiH$_2$	80
o-TolPhSiH$_2$	95
o-Tol$_2$SiH$_2$	92
MesPhSiH$_2$	98
Mes$_2$SiH$_2$	NR

Scheme 14. Asymmetric Mesitylphenylsilane Hydrosilylation of Acetophenone Derivatives with Rh-L45



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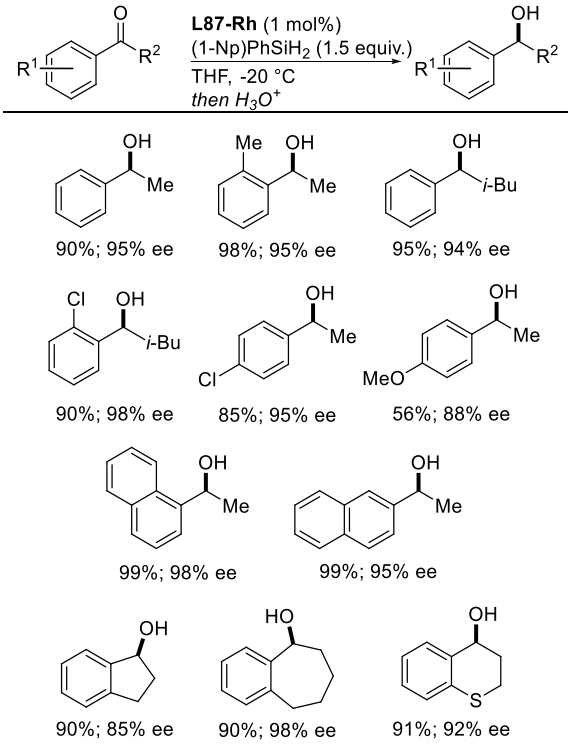
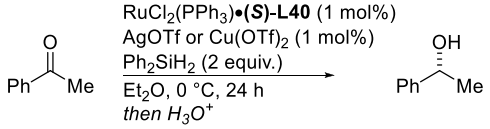
Scheme 15. Asymmetric (1-Naphthyl)phenylsilane Hydrosilylation of Acetophenone Derivatives with L87-Rh

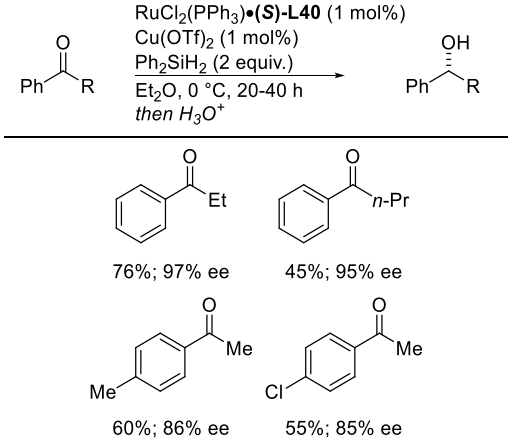


Scheme 16. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone with Ru-(*S*)-L40



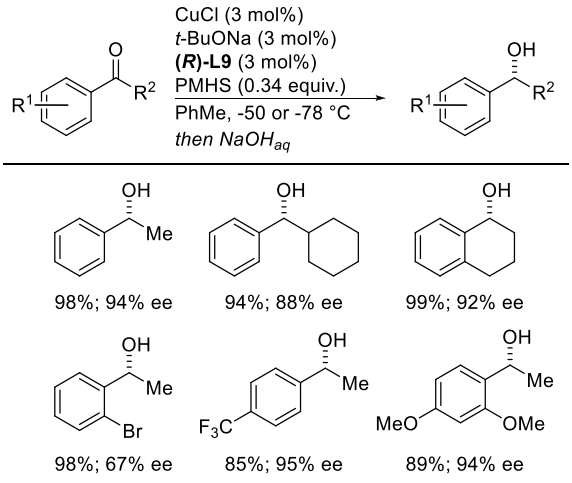
Additive	Yield (%)	ee (%)
AgOTf	56	93
$Cu(OTf)_2$	59	95

Scheme 17. Asymmetric Diphenylsilane Hydrosilylation of Aryl Ketones with Ru-(*S*)-L40

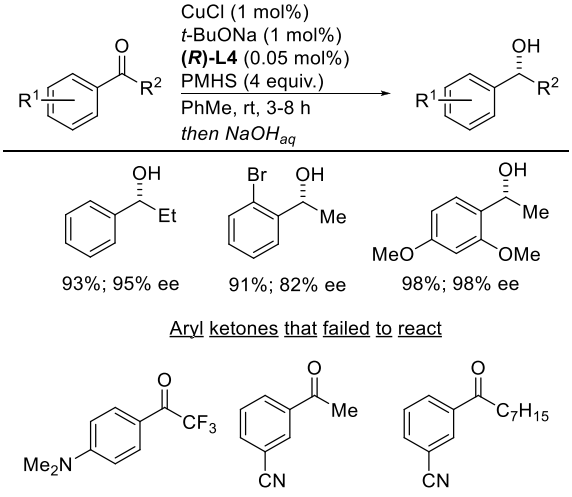


entiation between ketone substituents. Poor results were obtained in THF or ether, whereas toluene provided optimal results.

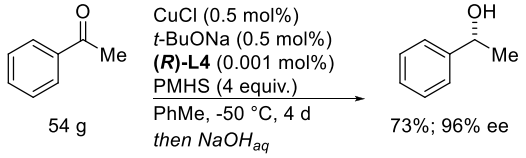
Scheme 18. Asymmetric PMHS Hydrosilylation of Acyl Ketones with Cu-(*R*)-L9



Scheme 19. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with Cu-(*R*)-L4



Scheme 20. Large-Scale, Enantioselective Hydrosilylation of Acetophenone with Low (*R*)-L4 Concentration



Uemara et al. developed chiral oxazolylferrocene-phosphine ligands (*R*)-DIPOF **L40** and (*S*)-DIPOF **L41**, which were complexed in situ to Rh or Ir to produce an active chiral catalyst. In practice, the Ir catalyst proved superior for the asymmetric hydrosilylation of prochiral ketones with diphenylsilane (Scheme 8).[42,43] While the results were excellent for aryl methyl ketones, more challenging substrates such as phenyl isopropyl ketone produced poor results (78% yield; 9% ee) after a 120-h reaction, as did 2-octanone (100% yield; 19% ee). However, the aliphatic 1-acetylcyclohexene produced good results (100% yield; 84% ee). Under Rh-catalysis, ligands **L40** and **L41** produced results comparable to those found with the Ir-

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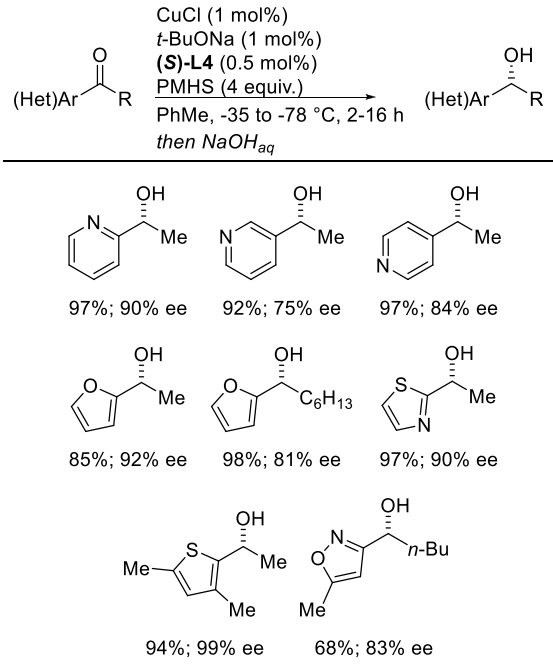
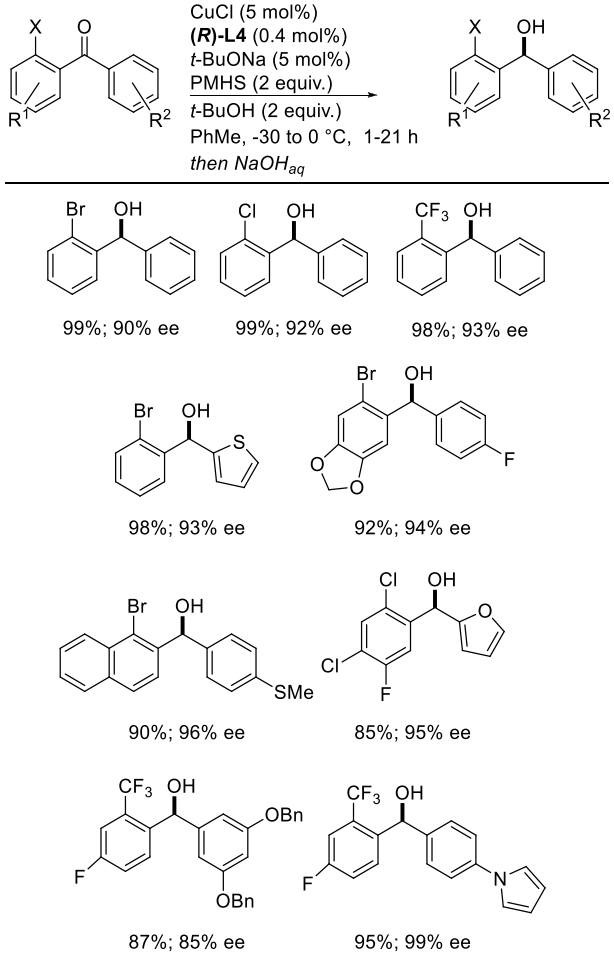
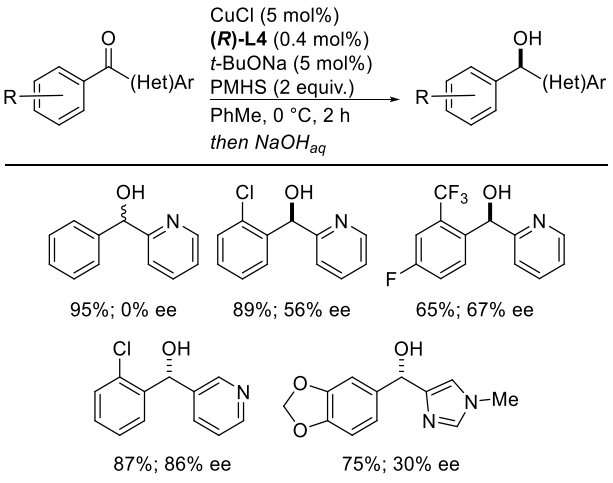
Scheme 21. Enantioselective PMHS Hydrosilylation of Acetophenone Derivatives with (*S*)-L4 and PMHS



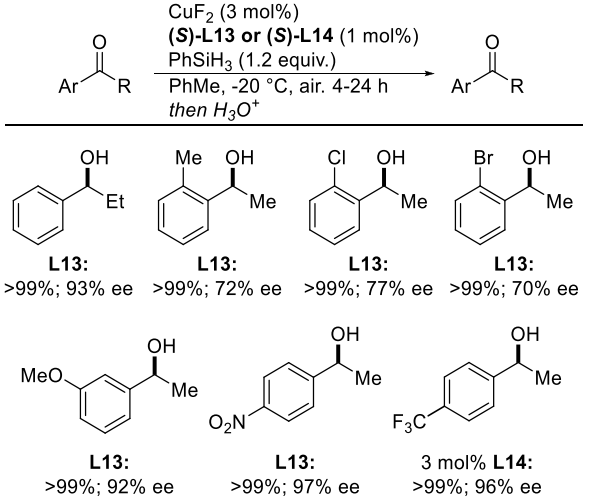
Scheme 22. Asymmetric PMHS Hydrosilylation of *ortho*-Substituted Di(aryl) Ketones with Cu-(*R*)-L4



Scheme 23. Effect of Aryl Nitrogen on the PMHS Enantioselective Reduction of Di(aryl) Ketones with (*R*)-L4



Scheme 24. Asymmetric Phenylsilane Hydrosilylation of Acetophenone Derivatives with Cu-(*S*)-L13 or Cu-(*S*)-L14



catalyzed examples (Scheme 9). Interestingly, the Rh-derived catalyst produced the opposite enantiomeric alcohols to those produced by the Ir catalyst with the same ligand.

Lee et al. developed (*S,S*)-Phos-Biox ligand **L63**, which was employed in a Rh(I)-catalyzed asymmetric diphenylsilane reduction of acetophenones.[44] Most substrates were reduced with high ee's and conversions, with only electron-rich 4-methoxyacetophenone showing poor results (Scheme 10). The system was demonstrated to be viable with both low catalyst and ligand loadings.

Ito et al. developed a series of chiral bis(dialkylphosphino)-ferrocene ligands denoted as (*R,R*)-(*S,S*)-TRAP. The butyl-TRAP ligand (***R,R*)-(*S,S*)-L27** was reacted with $[Rh(cod)_2]BF_4$ to produce a catalyst that achieved the hydrosilylation of acetophenone with diphenylsilane in high yields and with ee's of 1-phenylethanols (Scheme 11).[45] The best results were obtained with *n*-propyl- and *n*-butylTRAP ligands, while branched isopropyl and isobutyl groups on phosphorus produced slow reactions and a mere 1% ee. Ten examples of aryl alkyl ketones were reduced with the *n*-butylTRAP ligand,

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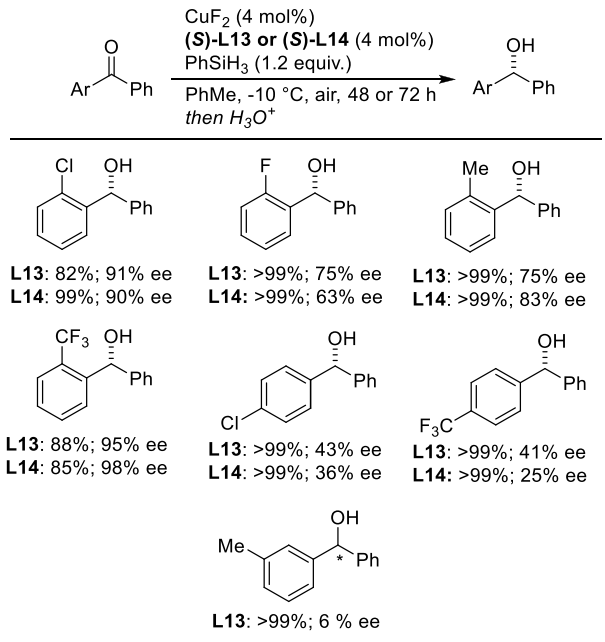
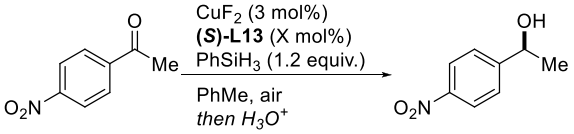
Scheme 25. Asymmetric Phenylsilane Hydrosilylation of Benzophenone Derivatives with Cu-(*S*)-L14 and Cu-(*S*)-L13

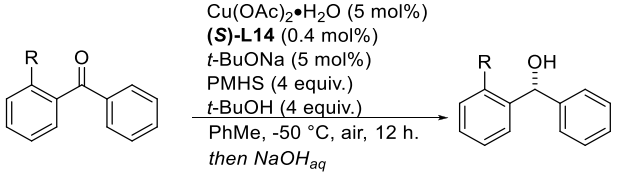


Scheme 26. Study of Catalyst Loading and Reaction Conditions on the Cu-(*S*)-L13-Catalyzed Enantioselective Phenylsilane Hydrosilylation of *p*-Nitroacetophenone



L16 (mol%)	Temp (°C)	Time (h)	ee (%)
1	rt	1	93
1	-20	4	97
0.005	rt	0.5	91
0.002	-10	48	94
0.001	rt	20	90

Scheme 27. Effect of ortho-Substitution on the Asymmetric PMHS Hydrosilylation of Di(aryl) Ketones with Cu-(*S*)-L14

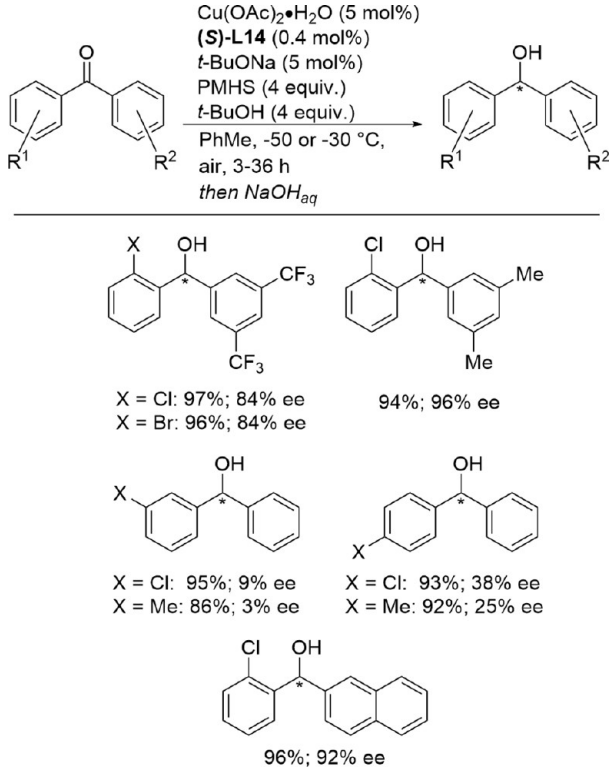


R	Yield (%)	ee (%)
Cl	94	90
F	95	70
Br	90	89
Me	95	81

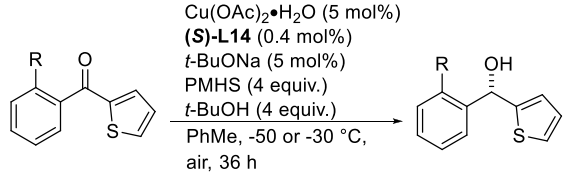
generating yields with good results (73−90% yields; 62−97% ee's).

Imamoto et al. introduced a series of chiral ferrocene-based bis(phosphino) ligands for asymmetric reactions. A rhodium catalyst prepared with ligand **L34** brought about the asymmetric reduction of acetophenones with modest-to-good ee values (Scheme 12).[46] Curiously, 4-methoxy phenylmethyl ketone produced a 61% chemical yield, but as the racemic alcohol. The dialkyl ketone 4-phenyl-2-butanone produced a good yield and a modest ee.

Scheme 28. Asymmetric PMHS Hydrosilylation of Various Substituted Di(aryl) Ketones with Cu-(*S*)-L14

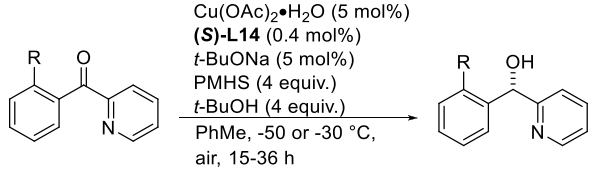


Scheme 29. Asymmetric PMHS Hydrosilylation of Aryl(2-Thiophenyl) Ketones with Cu-(*S*)-L14



X	Yield (%)	ee (%)
Br	86	74
Cl	92	83
H	88	19

Scheme 30. Asymmetric PMHS Hydrosilylation of Aryl (2-Pyridyl) Ketones with Cu-(*S*)-L14



R	Yield (%)	ee (%)
Cl	86	83
H	86	63

https://doi.org/10.1021/acs.oprd.1c00073
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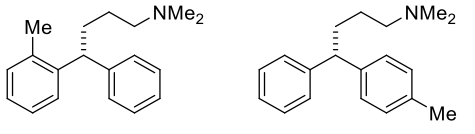
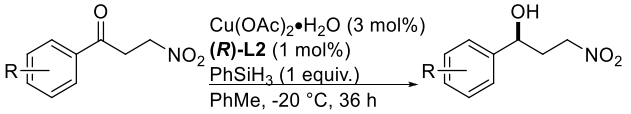
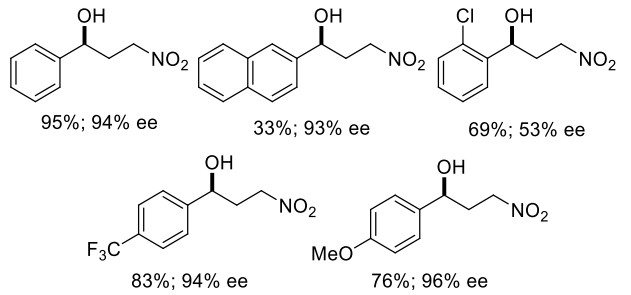
Scheme 31. Antihistaminic Targets Accessed by Asymmetric PMHS Hydrosilylation of Di(aryl) Ketones with Cu-(*S*)-L14



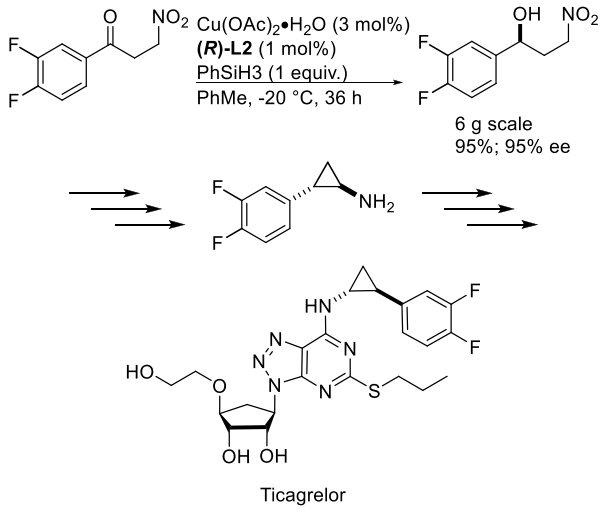
(R)-Orphenadrine; 81% ee *(S)*-Neobenodine; 91% ee

Scheme 32. Enantioselective Phenylsilane Hydrosilylation of *β*-Nitropropiophenones with Cu-(*R*)-L2



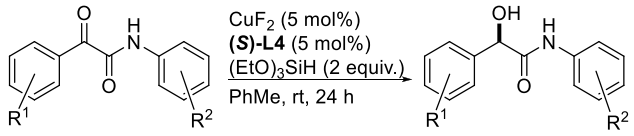


Scheme 33. Asymmetric Hydrosilylation in the Preparation of an Intermediate in a Synthesis of Ticagrelor



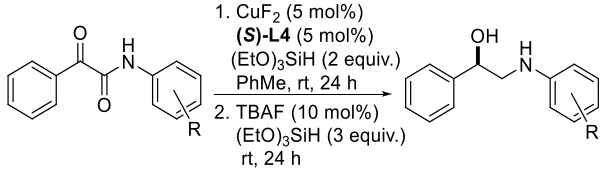
Tao and Fu demonstrated a new family of *P,N*-planar chiral ligands represented by **L45** which, complexed with Rh(I), successfully catalyzed the enantioselective reduction of aryl alkyl ketones (typically difficult prochiral dialkyl ketones) in high chemical yields and with exceptional ee's.[47] The authors explored the effect of the organosilane by using various silanes in the hydrosilylation of acetophenone (Scheme 13). Diarylsilanes resulted in useful enantioselectivities, with the sterically demanding mesitylphenylsilane and di-*o*-tolylsilane providing the best results. These findings coincide with previously discussed studies in which diarylsilanes were employed in Rh-catalyzed hydrosilylations; such studies illustrate the versatility and flexibility of the organosilane tool chest. The system of Rh-(−)-**L45** and $MesPhSiH_2$ was applied to the hydrosilylation of numerous acetophenone derivatives, providing (*S*)-enantiomeric alcohols with excellent yields and optical purities (Scheme 14). Substrates such as *α*-tetralone (95% yield; 98% ee), phenylethyl ketone (96% yield; 98% ee) and benzaldehyde-1d (74% yield; 95% ee) were also reduced with good results.

Scheme 34. Asymmetric Triethoxysilane Reduction of *α*-Keto Amides with Cu-(*S*)-L4



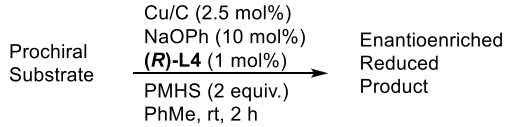
R^1	R^2	Yield (%)	ee (%)
H	H	97	99
H	*p*-Me	95	97
H	*o*-Me	96	97
H	*o*-Cl	94	86
H	*p*-OMe	97	97
H	*p*-CF_3	98	84
H	*m*-OMe	95	96
p-OMe	H	96	85

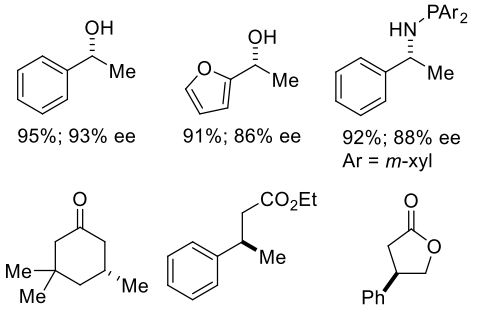
Scheme 35. Asymmetric Complete Triethoxysilane Reduction of *α*-Keto Amides with Cu-(*S*)-L4: Synthesis of Chiral *β*-Hydroxylamines



R	Yield (%)	ee (%)
H	94	97
p-Me	90	94
o-Me	93	99
o-Cl	91	82
p-OMe	91	94
p-CF_3	90	80
p-Cl	95	90
m-OMe	94	96

Scheme 36. Asymmetric PMHS Reduction of Prochiral Substrates with (*R*)-L4 and Cu/C





https://doi.org/10.1021/acs.oprd.1c00073
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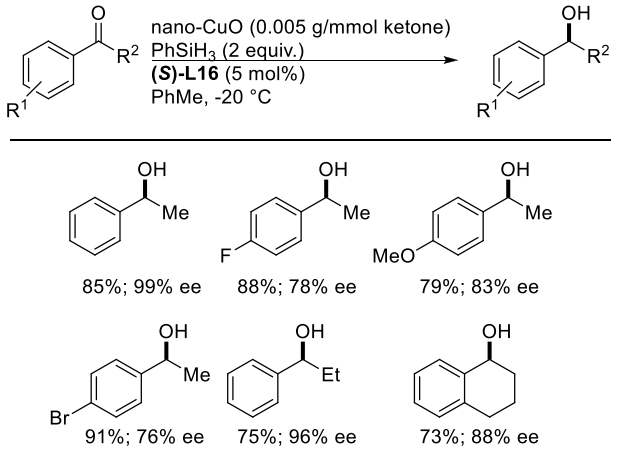
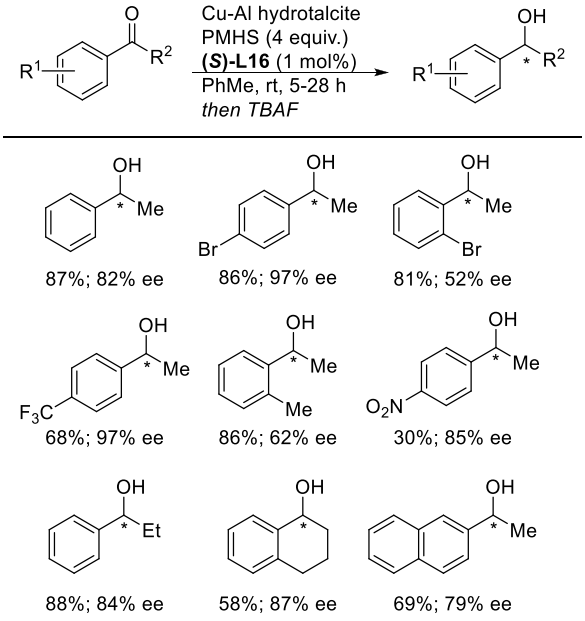
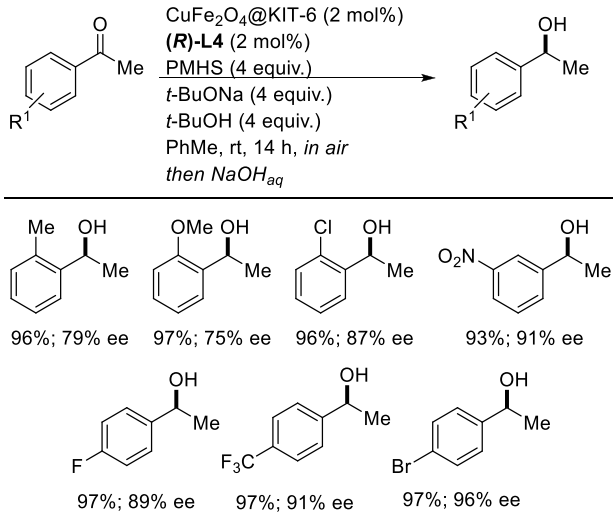
Scheme 37. Asymmetric Phenylsilane Hydrosilylation of Acetophenone Derivatives with Nano-Cu-(*S*)-L16



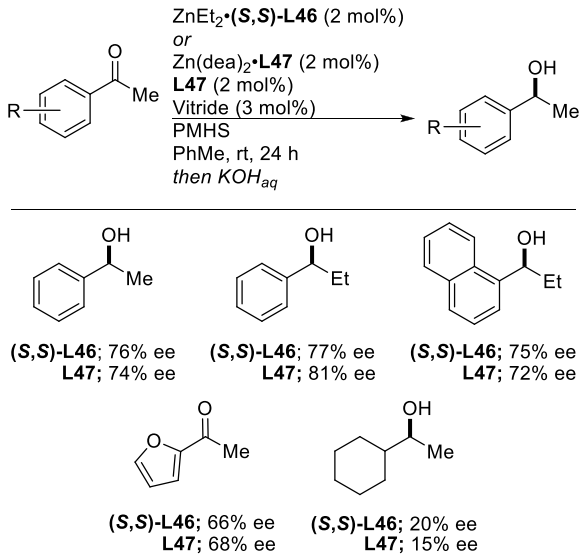
Scheme 38. Asymmetric Phenylsilane Hydrosilylation of Acetophenone Derivatives with Solid-Phase Cu-(*S*)-L16



Scheme 39. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with Solid-Phase Cu-(*R*)-L4



Scheme 40. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with Zn-(*S,S*)-L46 or Zn-L47



A novel *P,S*-ligand family developed by Evans et al. for Pd-catalyzed processes, and demonstrated to be effective for the asymmetric Rh-catalyzed hydrosilylation of ketones. Ligand **L87** was complexed with [Rh(nbd)]OTf to form active catalyst **L87-Rh**, which affected the asymmetric hydrosilylation of prochiral ketones in high yield and with high enantioselectivity. The screening of various silanes determined that diphenylsilane and (1-naphthyl)phenylsilane produced excellent results, whereas phenylsilane, methylphenylsilane, triethylsilane and PMHS generated poor outcomes.[48] These observations corroborated the trend reported in similar studies: that diarylsilanes are optimal partners for Rh- and Ir-catalyzed hydrosilylations. A variety of acyl aromatics were enantioselectively reduced with 1-naphthyl(phenyl)silane under Rh catalysis, and the resulting ee values were uniformly high (Scheme 15). Results were equally impressive when extended to longer chain phenyl alkyl ketones, which can often display remarkable differences in both yield and optical purity.

Uemura et al. applied a ruthenium catalyst system based on ligand (*S*)-**L40** to the asymmetric hydrosilylation of prochiral ketones, demonstrating the effectiveness of additional precious metals in hydrosilylation reactions.[49] The additive $Cu(OTf)_2$ proved superior to AgOTf in improving reactivity and enantioselectivity (Scheme 16). The results were excellent in terms of both yield and ee values when applied to aryl ketones (Scheme 17). The dialkyl ketones pinacolone and cyclohexyl methyl ketone produced only modest yields and ee's, however, indicating that the procedure is best applied to aryl alkyl ketones.

Lipshutz et al. explored a number of ligand scaffolds in CuH-mediated catalysis, with the goal of employing this inexpensive metal in asymmetric hydrosilylations and related processes. They found that the CuH-mediated reactions with bisphosphine ligands (e.g., BINAP) were readily scalable, could be successfully performed with very low ligand ratios, and could utilize PMHS as the stoichiometric hydride source.[50] They were also able to develop protocols for generating CuH from economical Cu(I)

https://doi.org/10.1021/acs.oprd.1c00073
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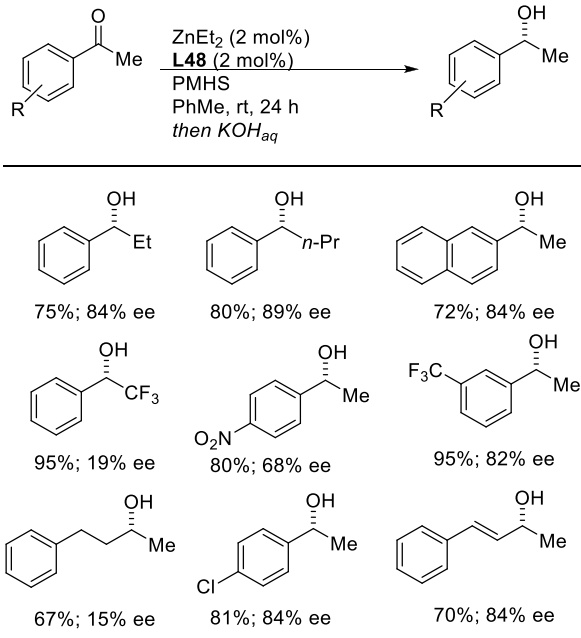
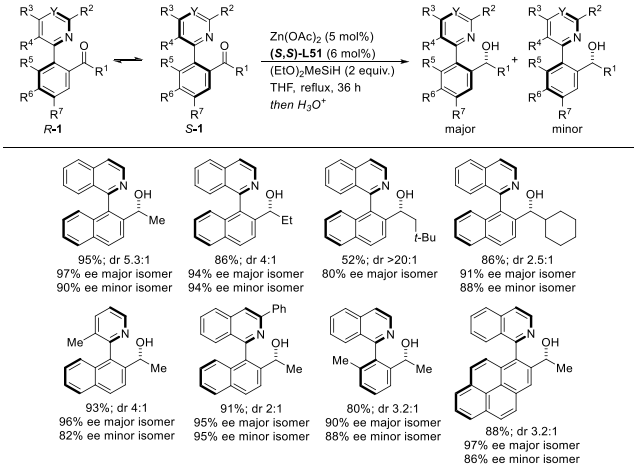
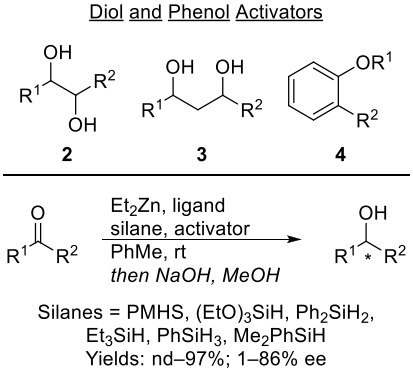
Scheme 41. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with Zn-L48



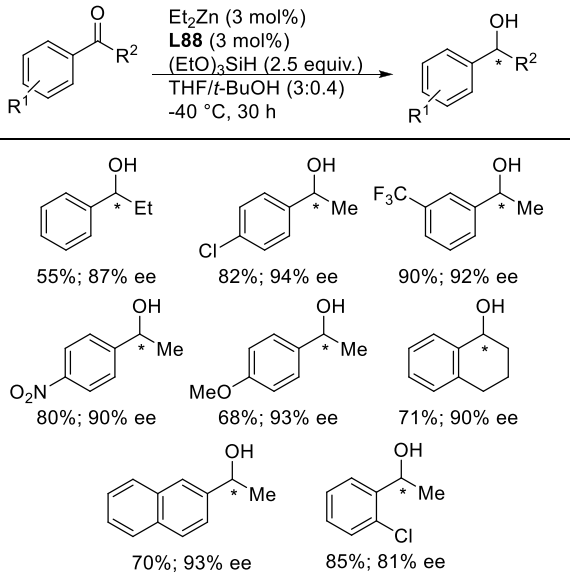
Scheme 42. Asymmetric Diethoxymethylsilane Reductive Kinetic Resolution of Acetophenone Derivatives with Zn-L51



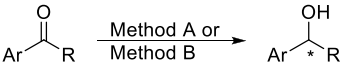
Scheme 43. Asymmetric Organosilane Hydrosilylation of Acetophenone Derivatives with Zn-Diamine Complexes



Scheme 44. Asymmetric Triethoxysilane Hydrosilylation of Acetophenone Derivatives with Zn-L88



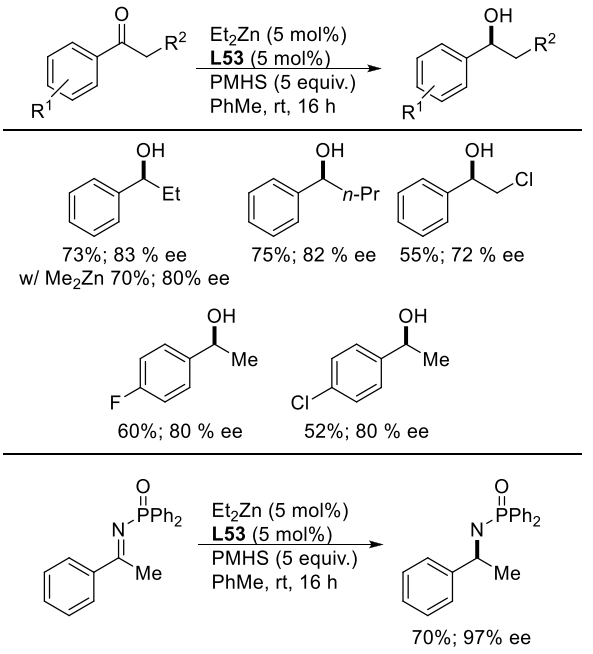
Scheme 45. Asymmetric Triethoxysilane Hydrosilylation of Acetophenone Derivatives with Zn-Diamine Complexes



Method A: $Zn(OAc)_2$ (2 mol%); **ligand** (8 mol%); $(EtO)_3SiH$ (2.5 equiv.); THF, rt, 48 h

Method B: $ZnCl_2$ (8 mol%); $KO_2CCH_2CH_2CH_3$ (3 mol%); **ligand** (8 mol%); $(EtO)_3SiH$ (2.5 equiv.) THF, rt, 48 h

Scheme 46. Asymmetric PMHS Hydrosilylation of Acetophenone Derivatives with Zn-L53



https://doi.org/10.1021/acs.oprd.1c00073
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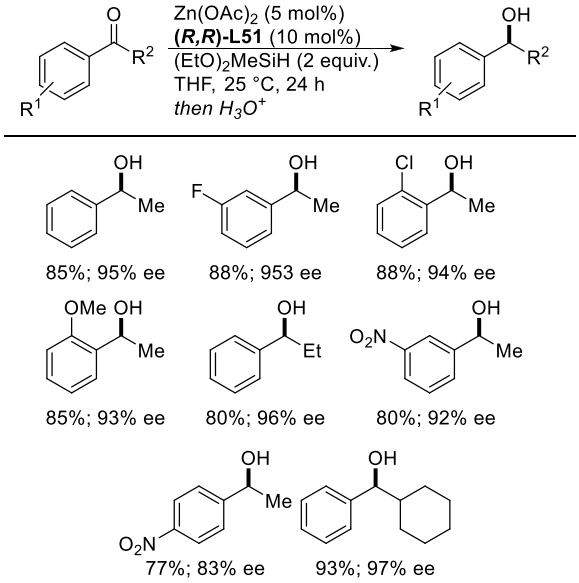
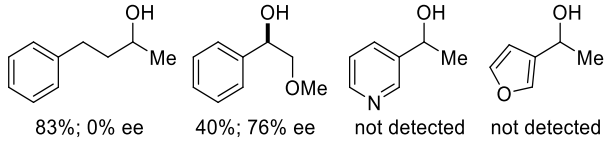
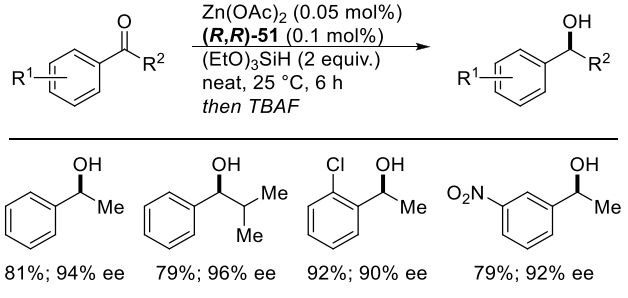
Scheme 47. Asymmetric Diethoxymethylsilane Hydrosilylation of Acetophenone Derivatives with Zn-(*R*,*R*)-L51



Scheme 48. Poor-Reacting Substrates under the Conditions of Scheme 47

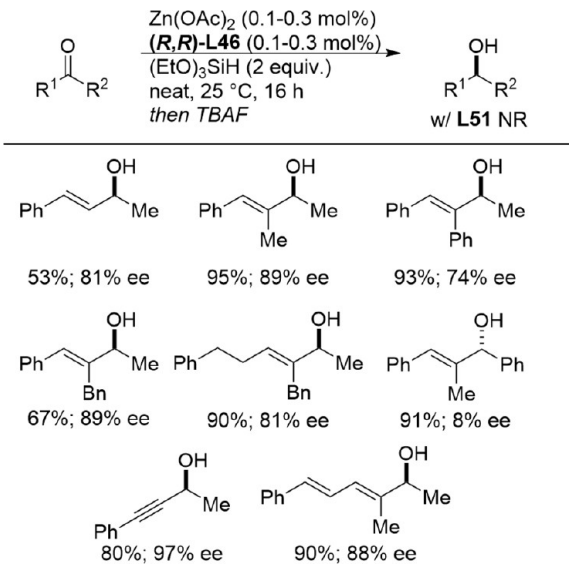


Scheme 49. Asymmetric Triethoxysilane Hydrosilylation of Acetophenone Derivatives with Zn-L51

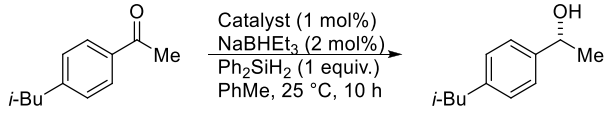


halides: in early studies, ligated CuH generated in situ from CuCl/PMHS/(*R*)-3,5-xyl-MeO-BIPHEP (***R*)-L9** provided an inexpensive, mild hydrosilylation of aryl ketones with excellent yields and enantioselectivities (Scheme 18).[51] The reactions were typically run at −50 °C, although −78 °C could also be employed under longer reaction times. Both electron-rich and electron-poor aryl substrates were reduced, with electron-poor substrates reacting faster. Significantly, it was found that a stoichiometric ratio of copper-to-ligand was not necessary. In fact, acetophenone was reduced with 92% ee using 3 mol % Cu and 0.005 mol % (***R*)-L9** displaying only a 2% reduction in enantiomeric purity compared to a stoichiometric metal-to-ligand ratio. The combination of a low-cost copper salt and a significantly reduced chiral ligand loading makes this protocol attractive.

Scheme 50. Asymmetric Triethoxysilane Hydrosilylation of Acyclic Enones with Zn-L46



Scheme 51. Asymmetric Diphenylsilane Hydrosilylation of Acetophenone Derivatives with Iminopyridine-oxazoline Fe and Co Catalysts



Catalyst	Yield (%)	ee (%)
L71	98	90
L72	95	92
L73	83	80
L74	97	93
L75	48	21

In a continuation of their initial work, Lipshutz et al. found that a number of chiral ligands were effective for the asymmetric hydrosilylation of ketones, with (*R*)-(−)-DTBM-SEGPHOS (***R*)-L4** proving optimal.[52] PMHS remained an ideal choice of silane, although diphenylmethylsilane and TMDS provided comparable results, while triethylsilane showed no reaction. Several aryl ketones were reduced with excellent results, although some acetophenone derivatives failed to react (Scheme 19). The feasibility of ppm-level ligand loading was clearly illustrated by the reduction of acetophenone on a 54-g scale (Scheme 20).

Applying the successful in situ generation of an asymmetric CuH catalyst from a copper salt, a silane and (***S*)-L4**, Lipshutz et al. achieved the enantioselective reduction of a number of heteroaromatic ketones.[53] The conditions were mild and continue to offer an attractive alternative to the more costly Rh and Ir protocols. In all, eight heteroaryl methyl ketones were reacted with (***S*)-L4** as the ligand, CuCl as the copper source and PMHS as the reductant (Scheme 21). By comparison, both yield and enantioselectivity were significantly diminished when (*R*)-BIPHEP (***R*)-L9** was employed to generate the asymmetric copper catalyst.

In a study of the asymmetric CuH-catalyzed reduction of diaryl ketones with the (*S*)-SEGPHOS ligands (***R*)-L4** and (***S*)-L4**, Lipshutz and Lee found that it was essential for one of the aryl groups to contain an *ortho* group in order to achieve

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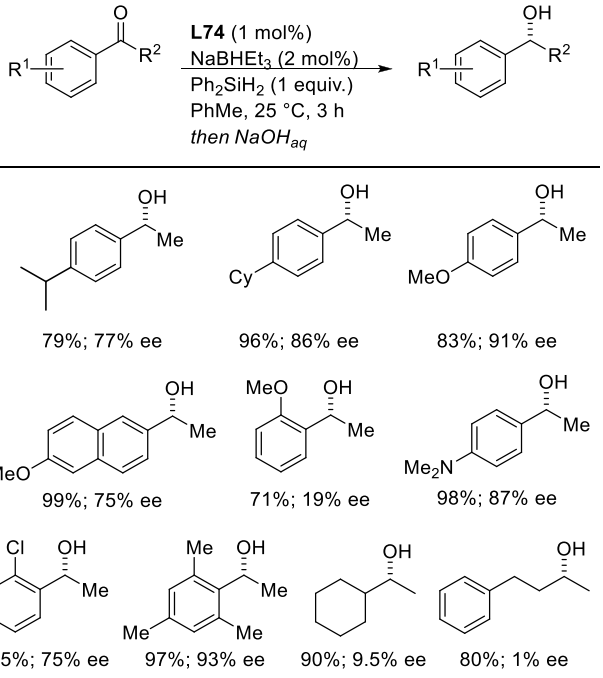
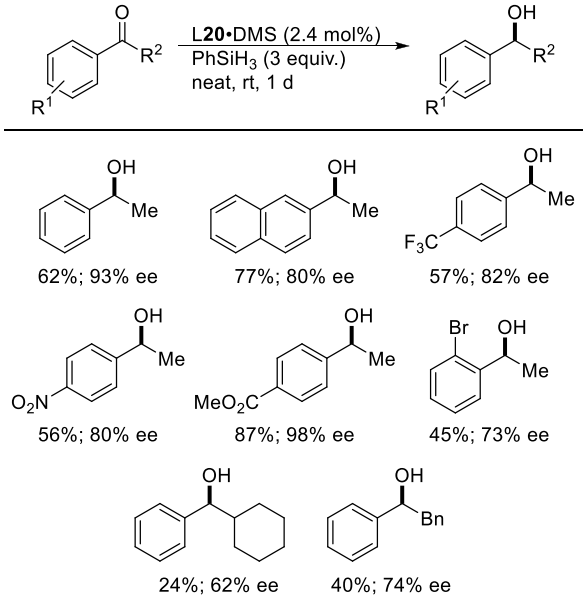
Scheme 52. Asymmetric Diphenylsilane Hydrosilylation of Acetophenones with L74



Scheme 53. Asymmetric Phenylsilane Hydrosilylation of Acetophenone Derivatives with Boron Catalyst L20



significant enantioselectivity (Scheme 22).[54] Substrates in which the aryl groups held a *meta* or *para* substituent exhibited no enantioselectivity. A comparison of phenyl 2-pyridyl ketones showed only modest ee values for *o*-substituted phenyl variants and no selectivity for (2-pyridyl)phenyl ketone (Scheme 23). To circumvent the shortcomings of the unsubstituted phenyl group, replacement of the *ortho*-H with a TMS group as a surrogate proton was investigated, resulting in a 74% ee and an 85% yield with ligand (*S*)-DM-SEGPHOS.

Asymmetric copper hydrosilylation reduction systems were improved with a CuH generation system in which the active catalyst is derived from CuF_2 and $PhSiH_3$. Chan et al. applied (*S*)-P-PHOS ligands **(*S*)-L13** and **(*S*)-L14** to the CuH-catalyzed hydrosilylation of a variety of prochiral aryl alkyl and diaryl ketones (Scheme 24 and Scheme 25).[55] The reactions were carried out at both −20 °C and room temperature without a significant decrease in either ee values or conversion. In a more detailed study of the reduction of 4-nitroacetophenone, the effects of temperature and catalyst load were investigated (Scheme 26). It was found that raising the temperature lowered the ee about 3%, while lowering the catalyst load by a factor of 500 and maintaining the temperature low (−10 °C) had a similar negative 3% effect. Finally, the ee was lowered by about 6% with a 0.001 mol % catalyst load at room temperature.

Expanding on the work of the Lee and Lipshutz teams, Chan et al. employed P-PHOS ligands **(*S*)-L13**, **(*R*)-L14**, and **(*S*)-L15** in the asymmetric reduction of diaryl ketones.[56] All three ligands showed promise, with **(*S*)-L14** used to fully investigate the reaction scope. $Cu(OAc)_2{\cdot}H_2O$ proved to be superior to CuF_2 as the Cu source and the presence of both *t*-BuOH and *t*-BuONa to promote the metathesis formation of the CuH was critical for complete conversion. The results showed that aryl groups containing an *ortho* substituent produced good-to-excellent ee's and high chemical yields (Scheme 27). Not surprisingly, the ee values dropped to single digits when a *meta* substituent was present in one of the aryl groups. On the other hand, a *para* substituent on one of the aryl groups led to a modest ee value, but still significantly higher than that produced with its *meta* counterpart. This intriguing finding led to an investigation of the asymmetric reduction of *o*-substituted/*m*- or *p*-substituted diaryl ketone combinations (Scheme 28). The yields and ee's in these cases were both very good. In those cases in which the absolute stereochemistry was not determined, it can be assumed based on the other results that the (*R*) configuration predominated under catalysis with ligand **(*S*)-L14**. In one case where differing *ortho* aryl groups were present, a lower ee value was obtained. The results were comparable when applied to aryl heteroaryl ketones (Scheme 29 and Scheme 30). Finally, the successful protocol was applied to short syntheses of the antihistaminic drugs (*R*)-orphenadrine and (*S*)-neobenodine (Scheme 31).

Zhang et al. developed a protocol for the asymmetric reduction of *β*-nitropropiophenones employing $PhSiH_3$ and (*R*)-SEGPHOS **(*R*)-L2** with $Cu(OAc)_2$. The procedure achieved excellent yields and ee's with multiple substrates (Scheme 32).[57] The transformation was used to prepare an intermediate that had been converted to Ticagrelor, a powerful anticlotting agent (Scheme 33). When applied to the dialkyl ketone 1-nitro-4-octanone, the alcohol was obtained in 91% yield, but with only 11% ee.

Sekar et al. applied (*S*)-DTBM-SEGPHOS **(*S*)-L4** to the asymmetric reduction of *α*-keto amides to either *α*-hydroxyamides or *β*-aminoalcohols under Cu(II) promotion with $(EtO)_3SiH$.[58] The *α*-hydroxyamide was obtained with 2 equiv of silane reducing agent (Scheme 34). These *α*-hydroxyamides could be further reduced without isolation via the addition of TBAF as well as an additional 3 equiv of Si−H (Scheme 35). Under either set of conditions, the chemical yields (>91%) and ee values (>80%; most >90%) were excellent. The reaction conditions employed were mild, although the use of triethoxysilane as the silane of choice requires added caution, as this reagent can cause vision loss. The reaction proved equally tolerant of electron-rich and electron-poor aryl amides.

Lipshutz et al. prepared a solid CuH precursor by embedding copper as either $Cu(OAc)_2$ or CuF_2 into a charcoal medium and

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then reacting with PMHS to provide the active CuH reagent.[59] The heterogeneous system, in combination with (*R*)-DTBM-SEGPHOS (*R*)-**L4**, was explored for the asymmetric reduction of prochiral ketones (3 examples: 89−95% yield; 86−94% ee), imines (2 examples: 90−92% yield; 98−99% ee), isophorone (70% yield; 92% ee), ethyl (*E*)-3-phenylbutenoate (99% yield; 98% ee) and 4-phenylfuran-2(5*H*)-one (83% yield; 99% ee) (Scheme 36). These results clearly demonstrate the utility of the solid phase catalyst in comparison with the more common homogeneous catalysts.

Chaudary et al. explored the potential of the commercially available nanocrystalline CuO (nano-CuO) in combination with (*S*)-BINAP (***S***)-**L16** and $PhSiH_3$ and found that it effectively reduced various aryl alkyl ketones in good yields and with good-to-excellent ee's (Scheme 37).[60] In comparison, PMHS provided slightly improved ee's coupled with a moderate loss in product yield. This heterogeneous catalyst system is distinct from the homogeneous systems commonly employed. Solvent and temperature proved to be crucial to the success of the reaction, with toluene and −20 °C being optimal. The catalyst was recycled 4 times for the reduction of acetophenone, with a small loss in both yield and ee of 2% for each reiteration.

Jagadeesh et al. investigated the inexpensive solid Cu catalyst copper−aluminum hydrotalcite combined with (*S*)-BINAP (***S***)-**16** and PMHS. The complex achieved the enantioselective reduction of aryl ketones in good yields and with modest-to-excellent ee's (Scheme 38).[61] This reaction has the advantages of mild conditions, inexpensive reagents, and high BINAP turnover number.

A range of acetophenone derivatives were enantiomerically reduced with solid-phase magnetic copper catalyst $CuFe_2O_4$@KIT-6, an intriguing nanoparticulate.[62] The asymmetry was brought about with (*R*)-DTBM-SEGPHOS (***R***)-**L4**, and it was possible to run the reactions in the presence of air and recycle the readily separated catalyst for further reactions, although the ee values showed a steady decline of 9% after 4 cycles. Both yields and ee values were very good, with only *ortho*-substituted substrates showing modest ee's (75−87%), albeit in very high chemical yield. Application to systems other than aryl methyl ketones, for example α-tetralone (60% ee), in general produced lower overall ee's (Scheme 39). However, the chemical yields were uniformly high. This combination of low-cost, an easily recycled Cu catalyst and the inexpensive reductant PMHS makes the process an attractive, scalable option.

As is the case for catalysts based on titanium or copper, those based on zinc can offer economic advantages when proven successful. Several investigations have explored diamine-complexed zinc catalysts.

Floriani et al. demonstrated two zinc systems for the enantioselective PMHS reduction of prochiral ketones (Scheme 40).[63] The chiral zinc catalyst was prepared from either chiral 1,2-diimines or 1,2-diamines. Among the many chiral ligands investigated, (*S*,*S*)-**L46** and **L47** produced the best enantioselectivities. The source of the zinc could be diethylzinc, dimethylzinc or zinc diethyl acetate ($Zn(O_2CCH(Et)_2)$ with vitride, which provided similar ee values to those observed with the PMHS protocol. The conversions were near quantitative. One substrate was converted on a 1-kg scale, illustrating excellent scalability. Though ee values are modest, the protocol represents a comparatively economical approach. Aliphatic substrates cyclohexyl methyl ketone and one α,β-unsaturated ketone produced very poor ee values.

Walsh et al. investigated the zinc-catalyzed asymmetric reduction of aryl alkyl ketones using a series of chiral diamine ligands, with **L48** proving to be the most advantageous, furnishing ee's up to 89% (Scheme 41).[64] Methyl phenethyl ketone produced poor results (67% yield; 15% ee), as did both the electron-poor phenyl trifluoromethyl ketone (95% yield; 19% ee) and the electron-rich 4-methoxyphenyl methyl ketone (87% yield; 11% ee).

Lassaletta et al. were able to accomplish the dynamic kinetic hydrosilylation of certain configurationally labile heterobiaryl ketones **1** under the catalysis of zinc complexed with (***S***,***S***)-**L51**.[65] A Lewis acid−base interaction of the pyridyl nitrogen and the carbonyl is argued to favor one rotational configuration for hydrosilylation. Thus, starting with the racemic mixture of the equilibrating heterobiaryl ketones **1**, (*R*)-**1** was found to react faster than (*S*)-**1** (dr values 2:1−20:1). In all cases, the ee values for both the major (80−97%) and minor alcohols (86−95%) were high (Scheme 42).

Gawronski et al. prepared a vast number of chiral diamine motifs (**L54**, **L57**, **L58**, and **L60**) for complexation with diethylzinc, and applied these systems to the asymmetric hydrosilylation of prochiral ketones.[66] This thorough study employed ligands **L56** and **L59** and involved a large number of ketones and organosilanes; chemical yield results were excellent, but ee values, unfortunately, did not exceed 86%. In addition, a series of diols and phenols **2**−**4** (R^1 and R^2 = H, OH and various alkyl groups) were prepared and utilized as activators in combination with chiral diamines for asymmetric hydrosilylation reactions. Again, these trials resulted in generally good chemical yields, but produced only poor-to-modest ee's (Scheme 43). The reactions carried out in the absence of a ligand but in the presence of the diol activator produced no reaction.

A series of 11 Schiff bases prepared from α-amino acids, e.g., **L88**, was investigated for asymmetric Zn-catalyzed hydrosilylations of aryl ketones.[67] The results were excellent, demonstrating that zinc complexes have the potential to provide an economical approach for the asymmetric hydrosilylation of aryl ketones (Scheme 44).

Peng et al. examined the Zn-catalyzed asymmetric hydrosilylation of prochiral ketones using *trans* 1,2-diaminocyclohexane ligands **L55** and **L57**.[68] The chemical yields were excellent (93−97%), but with disappointing chiral induction (ee's 19−94%, with only two >87%) (Scheme 45). The addition of potassium carboxylate as an activator did not improve the enantioselectivity of the alcohol produced. Triethoxysilane proved better than either triethylsilane or PMHS in the reduction, but the results were inferior to those obtained in their earlier work using the Schiff base ligated zinc catalysts.[67]

The well-endowed diamine ligands **L52** and **L53** were prepared, and **L53** was used to form chiral Zn complexes.[69] The Zn system was applied to the asymmetric reduction of acetophenone derivatives (Scheme 46). One example of the asymmetric reduction of an imine with the Zn system was also reported.

Mlynarski et al. investigated a number of nonracemic vicinal diaminoethane ligands complexed with $Zn(OAc)_2$ for the asymmetric hydrosilylation of ketones.[70] Diamine (***R***,***R***)-**L51** was shown to provide high yields as well as particularly excellent enantioselectivities (Scheme 47). Triethoxysilane and diethoxymethylsilane were both successful silane reductants. Significantly, *o*-substituted aryl substrates were reduced with high ee's

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and yields. Some systems, such as dialkyl, pyridyl and furyl ketones, reacted poorly or not at all (Scheme 48).

Mlynarski et al. expanded their findings on diaryldibenzylic ethylene diamine ligated zinc catalysts, showing that the reactions can be carried out in the absence of solvent and with the simple dibenzylic ligand (*R,R*)-**L46** as well as the previously introduced (*S,S*)-**L51**.[71] This work used triethoxysilane as the reducing agent. Various prochiral ketone substrates were investigated, including aryl ketones and acyclic enones (Scheme 49 and Scheme 50). Compared to their earlier work with ligand (*R,R*)-**L46**, its use under these revised conditions allowed for a considerable reduction in the amount of ligand needed to complete the reaction in a short time.[70]

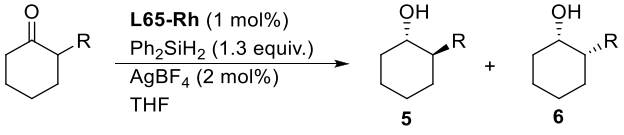
Huang et al. reacted chiral iminopyridine-oxazoline ligands with $FeBr_2$ and $CoCl_2$ to form the corresponding chiral complexes **L71**−**L74** and **L75**−**L80**, respectively. The resulting catalysts were investigated for the asymmetric hydrosilylation of aryl ketones.[72] An initial survey demonstrated that, other than for the Co complex **L75**, yields and ee's were very good (Scheme 51). Catalyst **L74** was chosen for a study on the scope of the reaction (Scheme 52). Interestingly, the 2,4,6-trimethyl-substituted ketone produced excellent results (97% yield; 93% ee), whereas the *o*-methoxyphenyl derivative produced only a modest yield (71%) and a very poor ee (19%). The investigation of two dialkyl ketones showed very poor enantioselectivities.

The Oestreich team presented a chiral version of the strong $B(C_6F_5)_3$ Lewis acid catalyst introduced by Piers et al.[73] to asymmetrically hydrosilylate acetophenone derivatives with modest-to-high ee's.[74] The catalyst prepared and employed was the very sterically encumbered **L20**, which contains a single pentafluorophenyl ligand and provided sufficient electron withdrawal to abstract hydride from an organosilane. For steric reasons, the best silane proved to be $PhSiH_3$, but reaction times at room temperature were on the order of 1−4 days. The reductions were also dependent on the aryl moieties, with electron-deficient aryl substituents providing excellent results while electron-rich substrates produced only modest yields and poor ee's (Scheme 53). Furthermore, acetophenones with *ortho* substituents generated sluggish reactions and resulted in mediocre ee values. Phenyl benzyl ketone (40% yield; 74% ee), phenyl cyclohexyl ketone (24% yield; 62% ee) and (4-bromophenyl) phenyl ketone (64% yield; 14% ee) all required 4 days to fully react, with only the latter reaching full conversion.

5. ASYMMETRIC REDUCTION OF DIALKYL KETONES

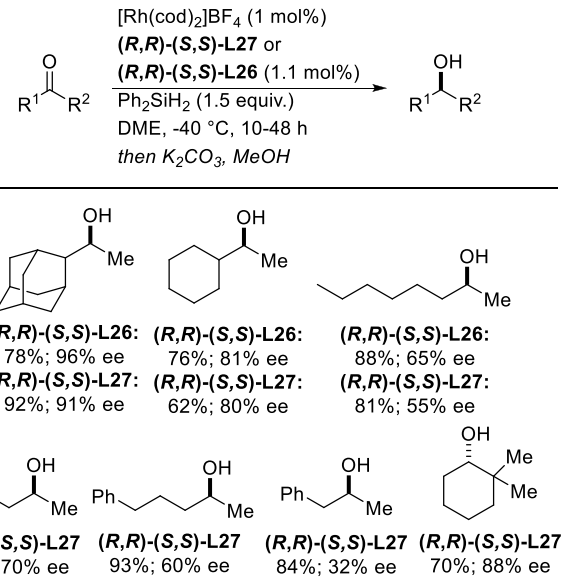
Unsurprisingly, the asymmetric reduction of prochiral dialkyl ketones is largely dependent upon the steric difference between the alkyl groups, as there is typically minimal electronic distinction between them. This trend is found to be the case

Scheme 54. Asymmetric Diphenylsilane Hydrosilylation of 2-Substituted Cyclohexenones with L65-Rh

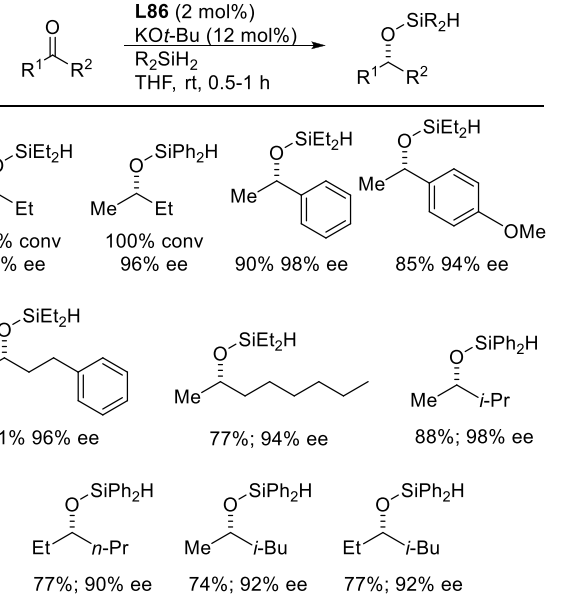


R	5:6	5 ee (%)	6 ee (%)
Me	41:59	91	89
Ph	51:49	99	96
CH_2CO_2Me	54:46	95	92

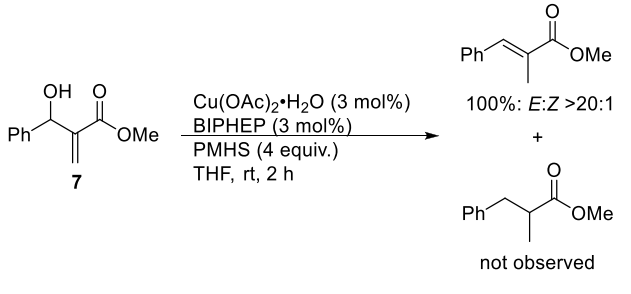
Scheme 55. Asymmetric Diphenylsilane Hydrosilylation of Prochiral Dialkyl Ketones with Trap Ligands (*R,R*)-(*S,S*)-27 or (*R,R*)-(*S,S*)-26



Scheme 56. Asymmetric Hydrosilylation of Prochiral Ketones with Diethylsilane or Diphenylsilane and L86



Scheme 57. PMHS Reductive Elimination of a *β*-Hydroxy-*α*-methylidene Ester 7



https://doi.org/10.1021/acs.oprd.1c00073
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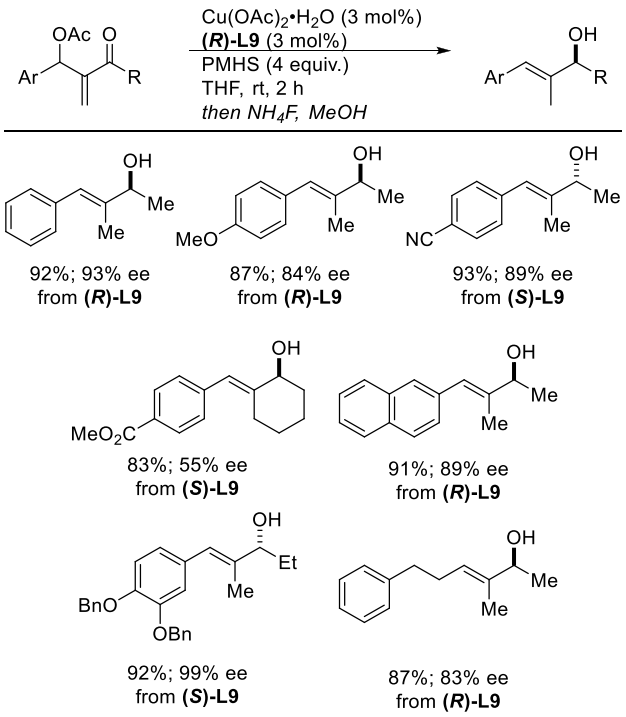
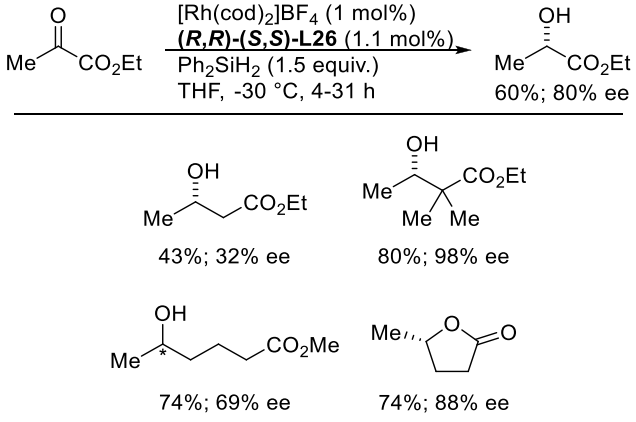
Scheme 58. Cu-Catalyzed Reductive Eliminations of β-Hydroxy-α-methylidene Esters with PMHS and Cu-(*R*)-L9



Scheme 59. Asymmetric Diphenylsilane Hydrosilylation of Keto Esters with Rh-L26

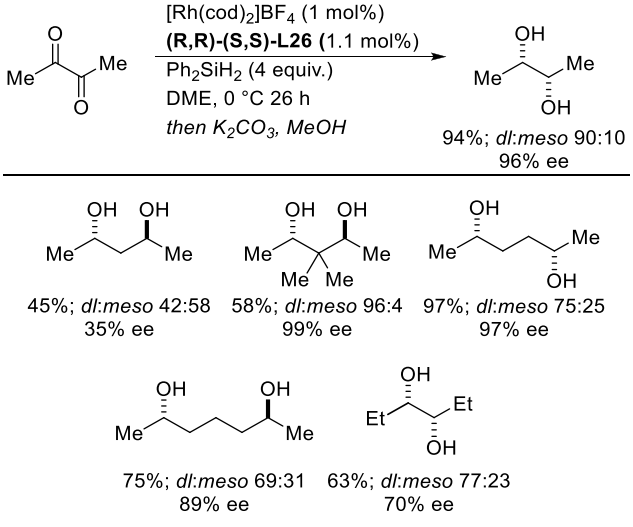


in most, but not all, instances. Here again the organosilane chemistry presents enhanced safety as opposed to direct asymmetric hydrogenation with dihydrogen.

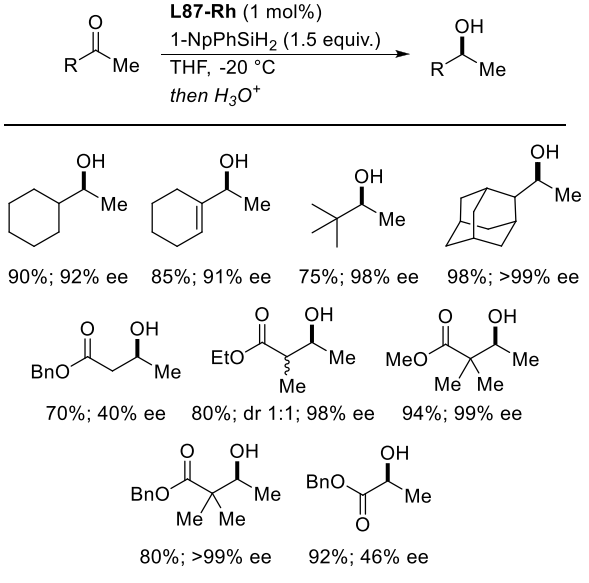
The chiral Rh-complex **L65-Rh** was applied to the asymmetric reduction of three 2-substituted cyclohexanones by the Nishiyama group, with interesting results.[75] The reductions produced clean (*S*)-configuration at C-1, but otherwise generated nearly equal amounts of *cis* and *trans* diastereomers, with each diastereomer possessing high enantiomeric purity (Scheme 54).

The TRAP ligands butylTRAP (*R*,*R*)-(*S*,*S*)-**27** and ethyl-TRAP (*R*,*R*)-(*S*,*S*)-**26** were further applied to the asymmetric reduction of simple prochiral ketones, with modest success.[46] When applied to enones, 1,2-addition predominated, with good yields and ee's (Scheme 55).

Scheme 60. Diastereo- and Enantioselective Diphenylsilane Hydrosilylation of Diketones with Rh-L26



Scheme 61. Asymmetric (1-Naphthyl)phenylsilane Hydrosilylation of Methyl Ketones with L87-Rh



Gawley and Albright used a chiral copper carbenoid complex in the successful asymmetric hydrosilylation of prochiral ketones, including dialkyl ketones.[76] Diethylsilane and diphenylsilane were employed as the stoichiometric reductants, with NHC-Cu **L86** as the catalyst. The products were isolated as silyl ethers (Scheme 56). Remarkably, even the very challenging 2-butanone was hydrosilylated in good yield and with high ee, with values comparable to those obtained for methyl isopropyl ketone and slightly better than those for methyl isobutyl ketone.

Lipshutz et al. demonstrated CuH-mediated (generated from $Cu(OAc)_2$ and PMHS) reduction of α,β-unsaturated ester **7**, with racemic BIPHEP producing allylic substitution as opposed to 1,4-reduction.[77] Over-reduction to the saturated ester was not observed with the simple BIPHEP ligand (Scheme 57). Other ligands produced lower yields, while diethoxymethylsilane produced a lower *Z*:*E* ratio. This discovery led to a study of the reduction of Morita−Baylis−Hillman-type ketones, in which

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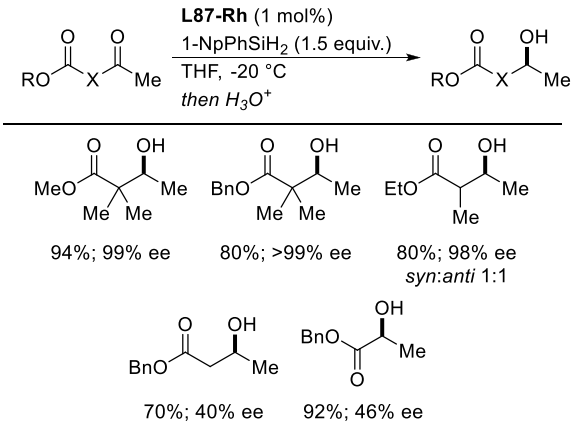
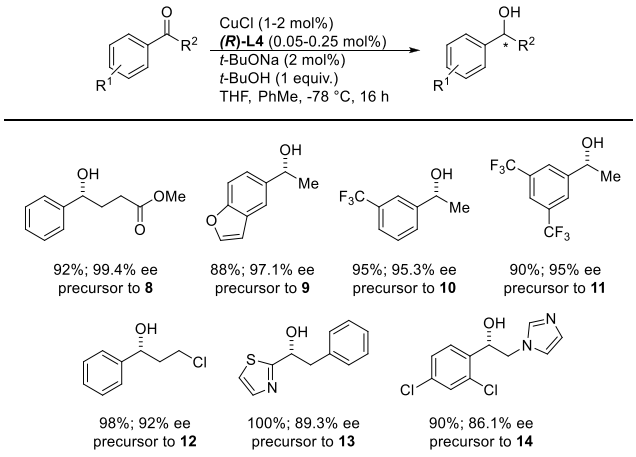
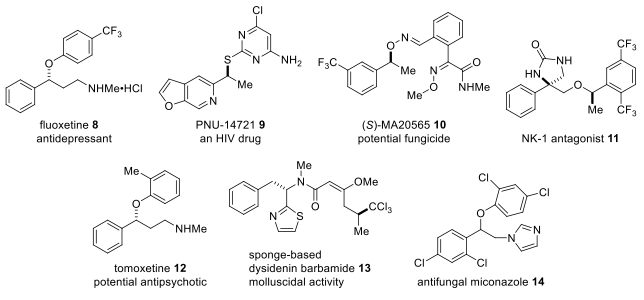
Scheme 62. Asymmetric (1-Naphthyl)phenylsilane Hydrosilylation of Keto Esters with L87-Rh



Scheme 63. Application of Asymmetric Hydrosilylation to the Syntheses of Physiologically Active Chiral Alcohols



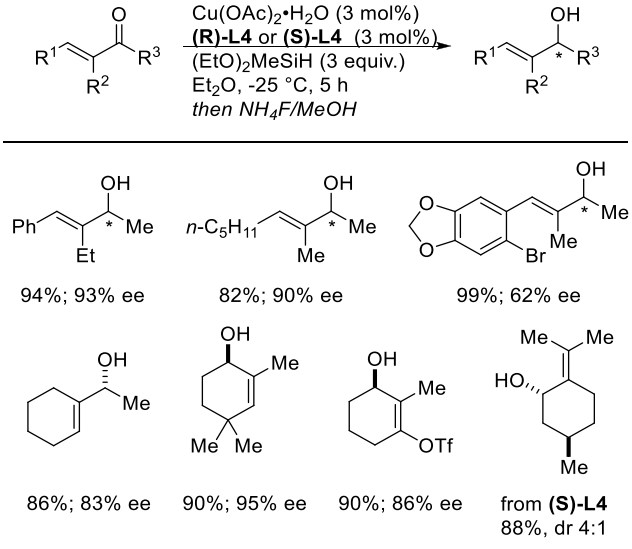
Scheme 64. Physiologically Active Drugs Prepared from Precursors in Scheme 63



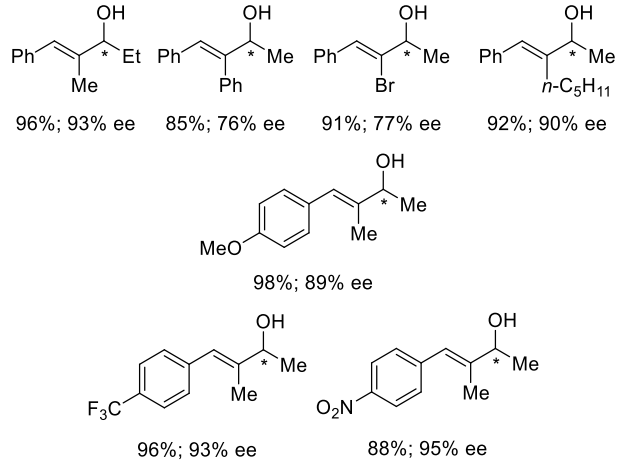
the allylic substitution was followed by the CuH reduction of the ketone to produce the allyl alcohol in high enantiomeric excess. In this work, the BIPHEP ligands (*R*)-**L9** and its enantiomer (*S*)-**L9** were used, providing the *α,β*-substituted allyl alcohols in good yield and with high ee (Scheme 58).

The TRAP ligands were further employed in the chemoselective asymmetric hydrosilylation of keto esters (Scheme 59).[46] The utilization of Ph_2SiH_2 as the hydride source proved critical as $PhSiH_3$ produced an incomplete reduction, while the bulkier (1-naphthyl)phenylsilane produced no reaction. The catalyst system could also produce a highly enantioselective

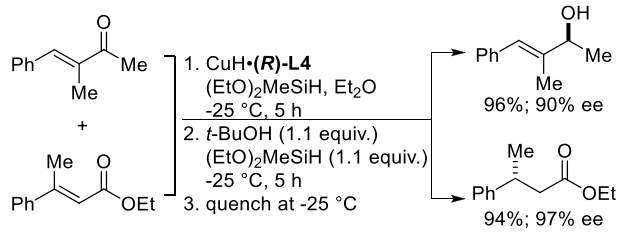
Scheme 65. Asymmetric Diethoxymethylsilane 1,2-Reduction of Enones with Cu-(*R*)-L4 or Cu-(*S*)-L9



Scheme 66. Asymmetric Diethoxymethylsilane 1,2-Reduction of Enones with (*S*)-L9



Scheme 67. Regioselectivity Difference in the Diethoxymethylsilane Hydrosilylation of an *α,β*-Unsaturated Ketone and an *α,β*-Unsaturated Ester with Cu-(*R*)-L4



reduction of symmetrical diketones, which in most cases were reduced with good diastereoselectivity and high enantioselectivity (Scheme 60).

The rhodium catalyst **L87-Rh** successfully applied to the asymmetric reduction of aryl ketones was also investigated for the reduction of prochiral alkyl ketones, with moderate-to-good success (Scheme 61).[49] A *β*-ketoester with no substituent on the

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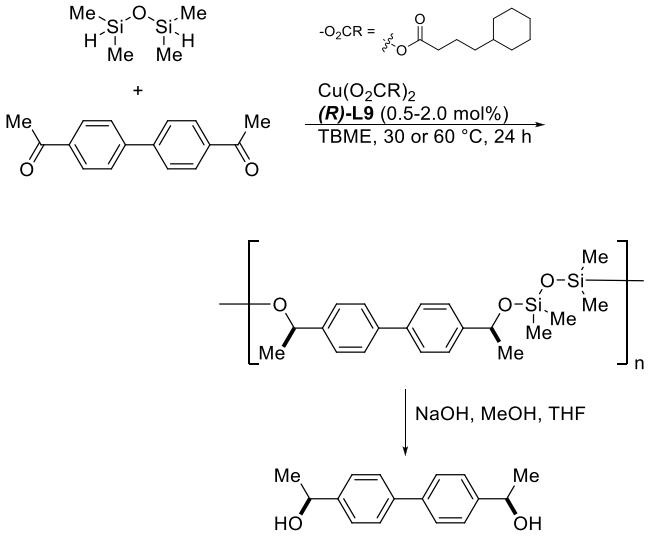
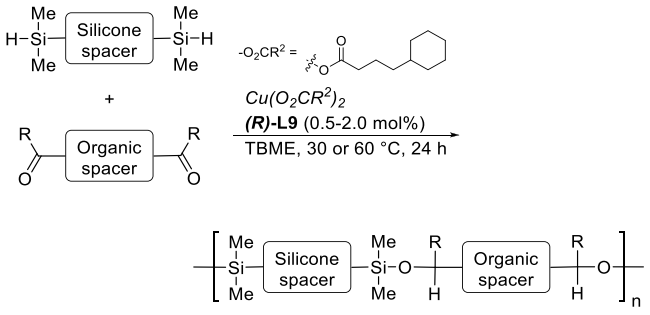
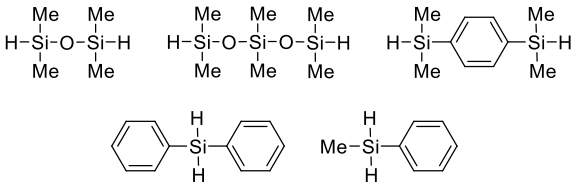
Scheme 68. Enantioselective Synthesis of Polysilyl Ethers from Tetramethylsiloxane and 4,4′-Bis(acyl)biphenyl



Scheme 69. General Outline of the Enantioselective Preparation of Various Polysilyl Ethers



Scheme 70. Silicon Reagents Employed in the Enantioselective Synthesis of Polysilyl Ethers

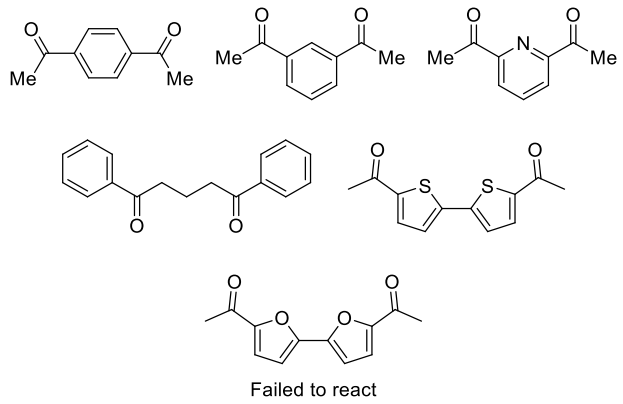


α-position produced an ee value similar to that obtained with an α-ketoester (Scheme 62).

Lipshutz et al. applied their asymmetric ketone hydrosilylation protocol to the preparation of a number of proven precursors to nonracemic physiologically active alcohols **8**−**14** (Scheme 63).[78] In general, the results improved upon the existing protocols for the syntheses of these alcohols and in cases where commercial applications are already in place (Scheme 64).

Lipshutz et al. were able to perform the selective 1,2 reduction of enones with high yields and ee's.[79] The reaction utilized CuH generated in situ and ligated with SEGPHOS (***R***)-**L4** or BIPHEP (***S***)-**L9**. Both chiral ligands provided excellent results and clean 1,2-reductions (Scheme 65 and Scheme 66). Another interesting experiment demonstrated that conditions favoring the 1,2-reduction of enones produced the conjugate 1,4-reduction of enoates. Thus, an equimolar mixture of 2-methyl-4-phenyl-2-butanone and (*E*)-ethyl butenoate subjected to the CuH reduction conditions produced 1,2-reduction of the ketone and 1,4-reduction of the ester, both with complete regioselectivity (Scheme 67).

Scheme 71. Organic Reagents Employed in the Enantioselective Synthesis of Polysilyl Ethers

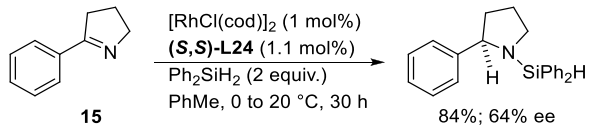


Polysilyl ethers have been developed for use as stationary materials for gas chromatographic applications. Their synthesis in enantioselective form would add to their value in their potential for chiral separations and analyses. Zhou et al. have accomplished the enantioselective synthesis of polysilyl ethers via the asymmetric coupling of various dihydridosilanes and diketoarenes (Scheme 68).[80] The initial study was undertaken with TMDS as the silane and 4,4′-bisacylbiphenyl as the diketone. This revealed optimal conditions of Cu-(***R***)-**L9** and *tert*-butylmethyl ether as solvent (Scheme 69). Employment of these conditions with a variety of disilanes and diketones gave a plethora of interesting polysilyl ethers in high yield and diastereoselectivity along with very high enantioselectivity, molecular weight distribution, and excellent polydispersity (Scheme 70 and Scheme 71).

6. ASYMMETRIC REDUCTION OF IMINES

Considering the numerous chiral secondary amines found in active pharmaceuticals and natural products, the asymmetric reduction of imines to amines constitutes an important synthetic transformation. An asymmetric hydrosilylation and hydrolysis approach to this endeavor has been shown to provide multiple advantages, in particular excellent chemical yields and high ee values as will be demonstrated in the examples to follow. The use of organosilanes as the hydride source in the asymmetric reduction of imines has been shown to provide excellent chemical yields along with very high enantioselectivities covering a range of imine substrates.

Scheme 72. Asymmetric Diphenylsilane Hydrosilylation of 15 with Rh-(*S*,*S*)-L24



Brunner and co-workers performed extensive pioneering work on the potential applications of asymmetric imine hydrosilylations. For example, they reported the enantioselec-

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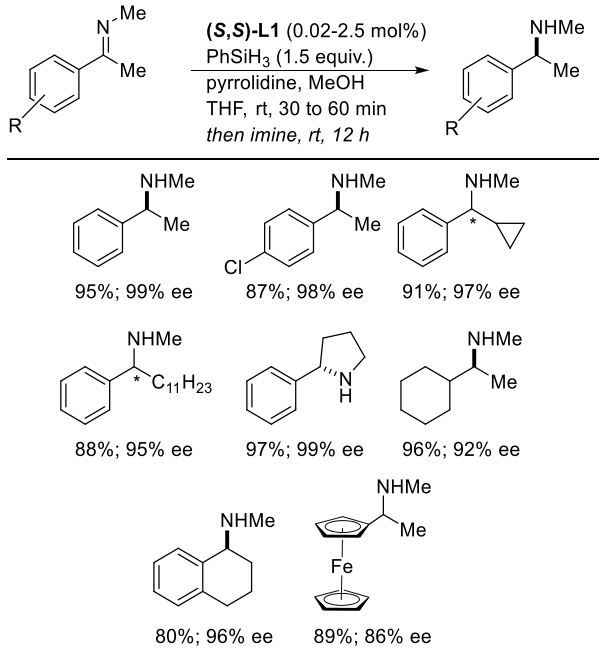
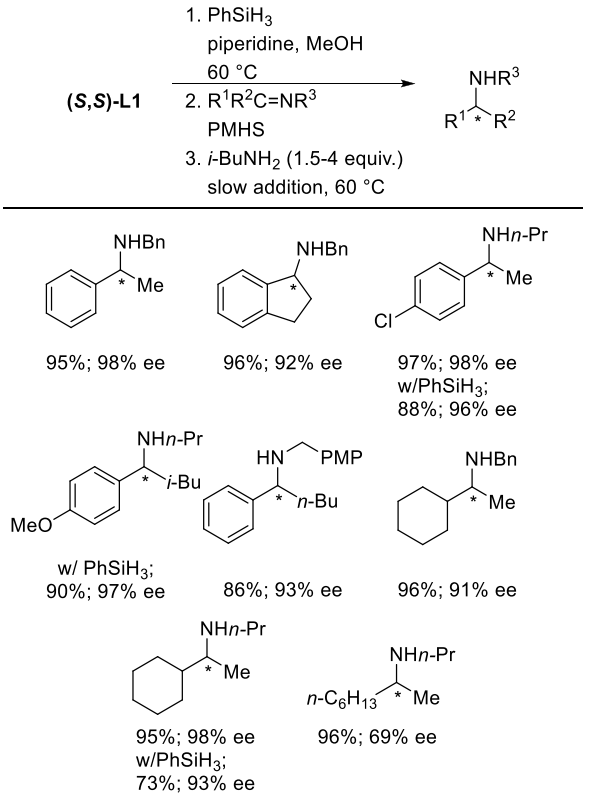
Scheme 73. Asymmetric Phenylsilane Hydrosilylation of Imines with Precatalyst (*S,S*)-L1

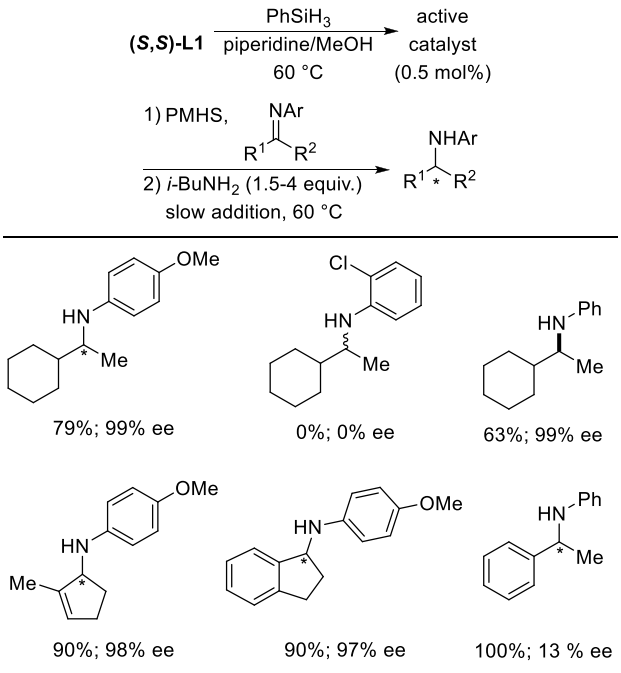


Scheme 74. Asymmetric Phenylsilane Hydrosilylation of Imines with Precatalyst (*S,S*)-L1

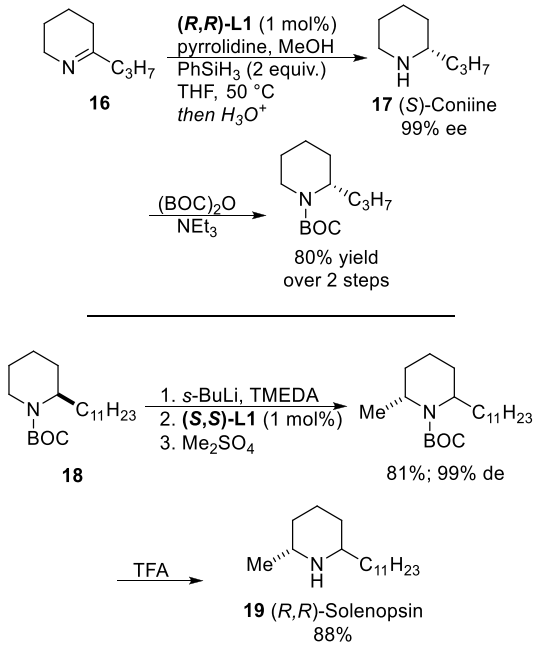


tive hydrosilylation of the endocyclic imine 5-phenyl-3,4-dihydro-2*H*-pyrrole **15** with a Rh(I)-diop catalyst, employing diphenylsilane as the reducing agent and (*S,S*)-DIOP (**S,S**)-**L24** as the chiral ligand with rhodium.[3,81] The chemical yields of the

Scheme 75. Asymmetric PMHS Hydrosilylation of Imines with Precatalyst (*S,S*)-L1



Scheme 76. Asymmetric Phenylsilane Hydrosilylation of Imines with Precatalysts (*R,R*)-L1 and (*S,S*)-L1: Synthesis of (*S*)-Conine 18 and (*R,R*)-Solenopsin 19



transformation were excellent, but the ee values obtained were only modest (Scheme 72).

As previously noted (sections 4 and 5) for prochiral ketone reductions, the Buchwald et al. determined that the titanium precatalyst (**S,S**)-**L1** can be activated by phenylsilane to an active catalyst in the presence of the imine to be reduced.[82] Phenylsilane thus serves as both the silane reductant and the catalyst activator. The combination of this catalyst and phenylsilane reduced a variety of imines with high yield and

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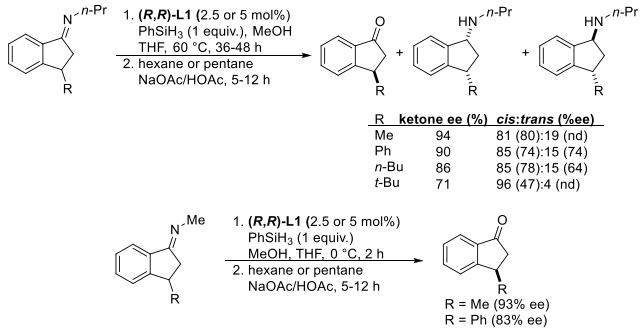
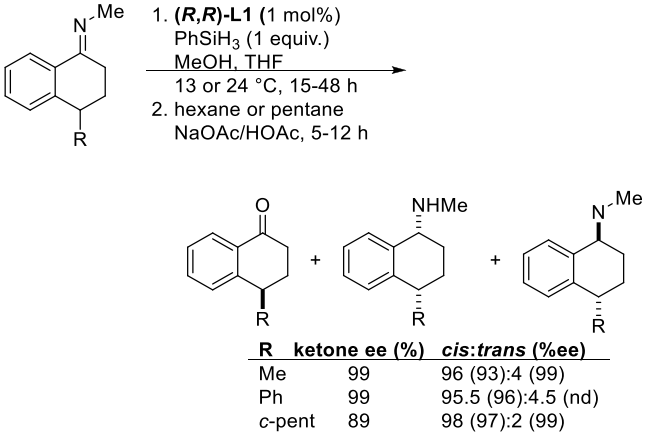
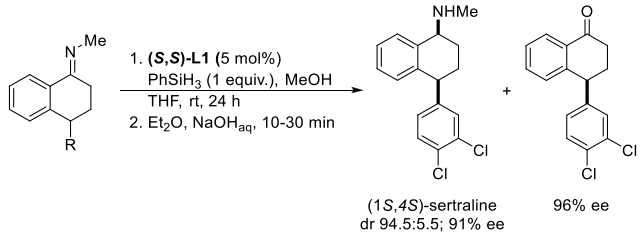
Scheme 77. Asymmetric Phenylsilane Hydrosilylation of Imino Indanones with Precatalyst (*S*,*S*)-L1



Scheme 78. Asymmetric Phenylsilane Hydrosilylation of Iminotetralones with Precatalyst (*R*,*R*)-L1



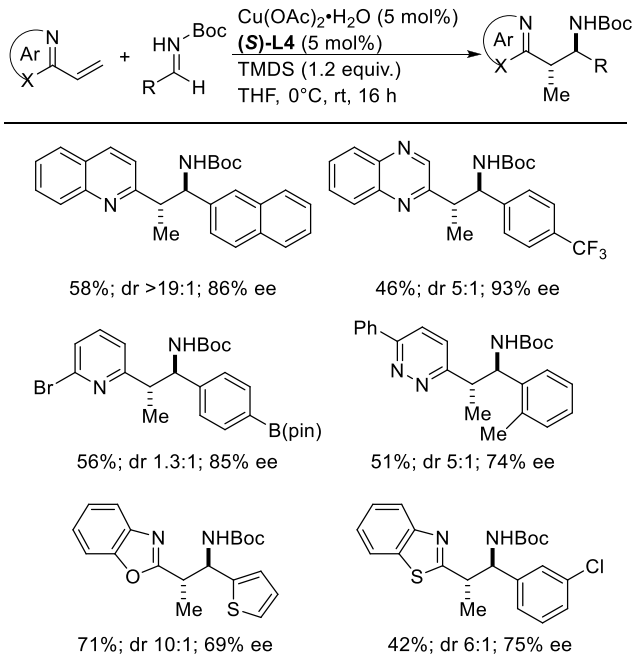
Scheme 79. Asymmetric Phenylsilane Hydrosilylation of Iminotetralones in the Synthesis of (1*S*,4*S*)-Sertraline



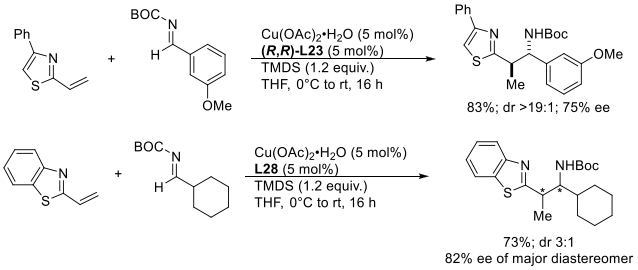
enantioselectivity after hydrolysis (Scheme 73). Under mild conditions, the reaction proceeded with equal efficiency whether the catalyst loading was as high as 1 mol % or as low as 0.02 mol %. The amines were isolated after a hydrolytic workup. The dialkyl imine *N*-methylcyclohexylmethyl imine was reduced in high yield and enantiomeric excess, as were the aryl alkyl imines.

Buchwald et al. found that titanium-mediated hydrosilylation was accelerated by the addition of a primary amine, isobutylamine being the optimal choice.[83] The additive allowed for the reduction of sterically hindered imines, which were inert toward hydrosilylation in their earlier efforts in the absence of isobutyl amine. Under these revised conditions, the primary amine is employed with $PhSiH_3$ to activate the catalyst (*S*,*S*)-**L1** and increase its activity. The modification permitted the use of PMHS as the reductant, although at a reduced reaction rate compared to $PhSiH_3$. Moreover, the enantiomeric excess of the amine product is independent of the *E* and *Z* isomeric ratio of

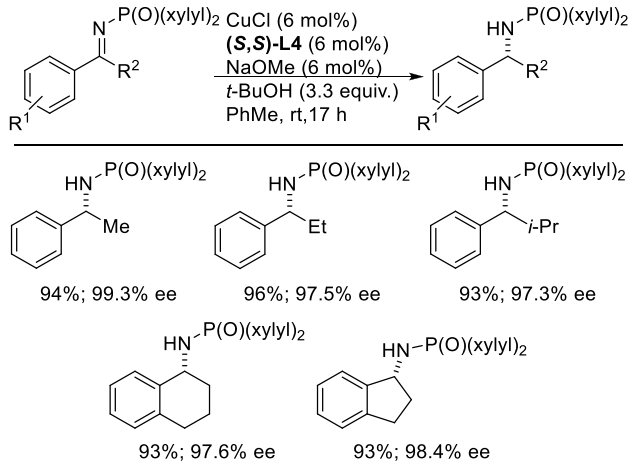
Scheme 80. Asymmetric TMDS Reductive Imine/Olefin Coupling of Imines with Cu-L4



Scheme 81. Asymmetric TMDS Reductive Imine/Olefin Coupling with Cu-(*R*,*R*)-L23 or Cu-L28



Scheme 82. Asymmetric TMDS Hydrosilylation of *N*-Phosphinyl Imines with Cu-(*S*,*S*)-L4



the imine. The linear *N*-benzylimine of 2-octanone, a linear dialkyl imine, produced only a modest 69% ee, whereas aryl alkyl imines were all reduced with greater than 92% ee (Scheme 74).

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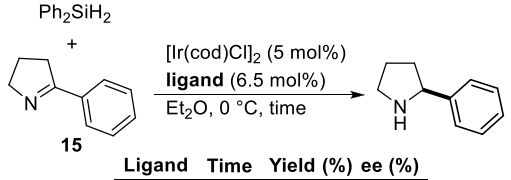
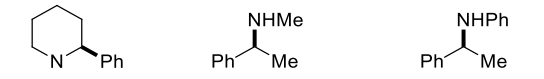
Scheme 83. Asymmetric Iridium-Catalyzed Diphenylsilane Reduction of Imines

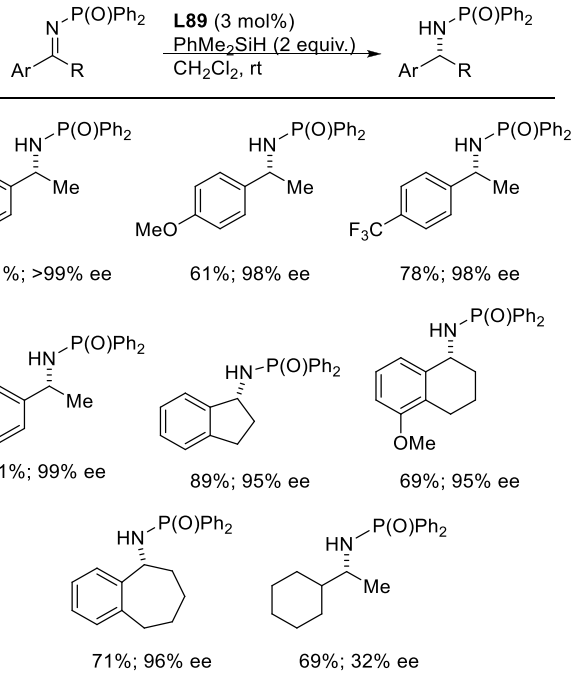


Ligand	Time	Yield (%)	ee (%)
(*S*)-L40	30 h	>95	71
L41	20 h	>95	85
L42	50 h	78	88
L43	40 h	>95	86

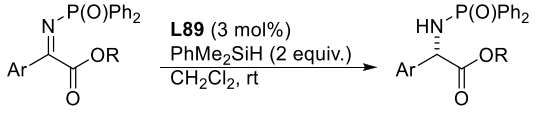
Scheme 84. Comparison of Results of Various Metals on the Asymmetric Diphenylsilane Hydrosilylation of Imines with L41



Scheme 85. Asymmetric TMDS Hydrosilylation of *N*-Phosphinyl Imines with L89

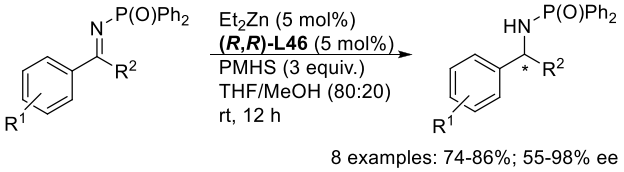


Scheme 86. Asymmetric Dimethylphenylsilane Hydrosilylation of α-Imino Esters with L89

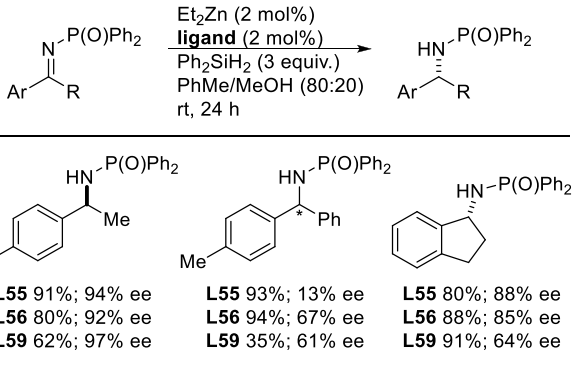


Ar	R	Yield (%)	ee (%)
Ph	Et	83	>99
4-MeOC$_6$H$_4$	Me	47	95
2-MeC$_6$H$_4$	Me	69	99

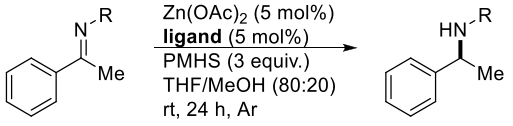
Scheme 87. TMDS Hydrosilylation of Imines with Zn-(*R*,*R*)-L46



Scheme 88. Asymmetric TMDS Hydrosilylation of *N*-Phosphinyl Imines with Zn-L55, Zn-L56, and Zn-L59

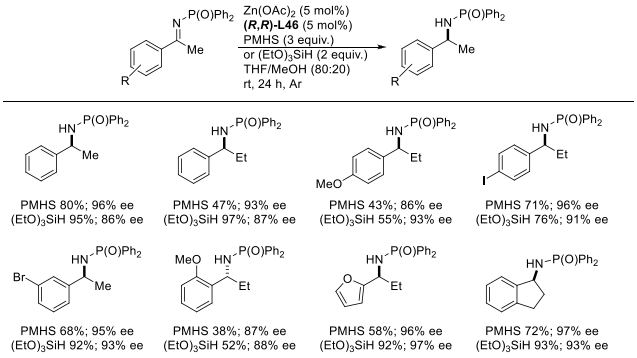


Scheme 89. PMHS Hydrosilylation of Imines with Zn Diamine Complexes



R	Ligand	Yield (%)	ee (%)
P(O)Ph$_2$	**(*R*,*R*)-L46**	80	96
P(O)Ph$_2$	**L51**	40	98
Ts	**(*R*,*R*)-L46**	90	75

Scheme 90. Asymmetric Hydrosilylation of *N*-Diphenylphosphinylamines with Zn-(*R*,*R*)-L46



Buchwald et al. extended the protocol to *N*-aryl imines, employing PMHS as the stoichiometric hydride source and $PhSiH_3$ to activate the titanium catalyst.[84] Both dialkyl and aryl alkyl imines were reduced in high chemical yields, but the dialkyl imines produced far superior ee values (Scheme 75).

The Buchwald titanium-mediated hydrosilylation protocol was employed in multiple natural product syntheses utilizing both catalysts (*R*,*R*)-**L1** and (*S*,*S*)-**L1**.[85] The phenylsilane reduction of the cyclic imine **16** provided an enantioselective

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synthesis of the piperidine alkaloid (*S*)-coniine **17**, and the phenylsilane reduction of imine **18** produced a concise route to (2*R*,6*R*)-*trans*-solenopsin A **19** (Scheme 76).

Buchwald et al. applied the titanium catalysts (***R,R***)-**L1** and (***S,S***)-**L1** to a kinetic resolution and asymmetric reduction of substituted imines of indanones and tetralones (Scheme 77 and Scheme 78).[86] After a hydrolytic workup, they isolated both the optically active ketone and a diastereomeric mixture of chiral amines resulting from the reduction of the reactive stereoisomer. In general, substituted tetralone imines were more reactive than indalone imines. The protocol was applied to a synthesis of (1*S*,4*S*)-sertraline (Scheme 79).

Tetramethyldisiloxane (TMDS) provided the hydride in the enantioselective reductive coupling of vinylazaarenes with *N*-Boc-protected aldimines by the Lam et al.[87] The coupling occurred at the benzylic position of the vinylazaarene and produced a range of diastereomers (1.3:1 → 19:1) and ee's (0−94% for the major diastereomer) (Scheme 80). Overall, the yields were modest-to-good (35−78%). The catalyst which performed best was (*S*)-DTBM-SEGPHOS (***S***)-**L4**. In addition, catalysts (***R,R***)-**L23** and **L28** were investigated in single examples, both with results comparable to other findings (Scheme 81).

Lipshutz et al. developed a CuH-catalyzed asymmetric reduction of *N*-phosphinyl aryl alkyl imines that provided highly enantiomerically enriched amines under ligation with DTBM-SEGPHOS (***S,S***)-**L4**, using TMDS as the stoichiometric hydride.[88] An investigation of the reaction parameters showed that the sterically hindered *N*-bis(3,5-xylyl)phosphinyl imine was the optimal class of imine, and that the addition of *t*-BuOH and NaOMe increased the rate of reaction without affecting enantioselectivity (Scheme 82). The chiral phosphinamide products could be converted to the primary amine by treatment with aqueous HCl.

Hidai et al. complexed ligand (***S***)-**L40** with Ru and applied the resulting catalyst to the hydrosilylation of **15**, producing a 60% yield of (*R*)-2-phenylpyrrole with 88% ee.[49] The (*S*)-DIPOF-type ligands were further investigated to form chiral hydrosilylation catalysts with Ru, Rh and Ir.[49,89] The resulting complexes were used in the asymmetric hydrosilylation of imines, with mixed results (Scheme 83). For example, when complexed with ligands (***S***)-**L41**, **L42** or **L43**, the Ir catalyst produced good results with cyclic imine **15**. The analogous Rh-catalyst and Ru-catalyst systems, however, generated inferior results (Scheme 84). Acyclic imines produced disappointing numbers in all cases.

In addition to the metals previously described, rhenium catalysts have also been utilized in the asymmetric hydrosilylations of imines. Toste et al. applied CNBox-Re(V) complexes to *N*-phosphinyl imines, which were enantioselectively reduced under catalysis with **L89** and phenyldimethylsilane.[90] Conversions were generally high, with most of the imines explored being reduced with greater than 90% ee (Scheme 85). Curiously, cyclohexyl methyl imine, although reduced in good yield, produced a poor ee of 32%. The reaction proved selective for imine reduction in the presence of an ester and an olefin (Scheme 86).

The zinc-catalyzed reduction of imines is particularly attractive due to the low cost and ready availability of zinc. Nishiyama et al. applied a modification of typical diamine ligand structures for the complexation of zinc, thereby greatly enhancing the enantioselectivity of Zn-catalyzed imine hydrosilylation. Thus, ligands (***R,R***)-**L46**, **L49** and **L50** were investigated for the PMHS, TMDS and diphenylsilane-mediated hydrosilylations of aryl alkyl *N*-phosphinylimines, with diamine (***R,R***)-**L46** proving to be optimal (Scheme 87).[91] This offers a practical, scalable and economical approach for the asymmetric reduction of imines.

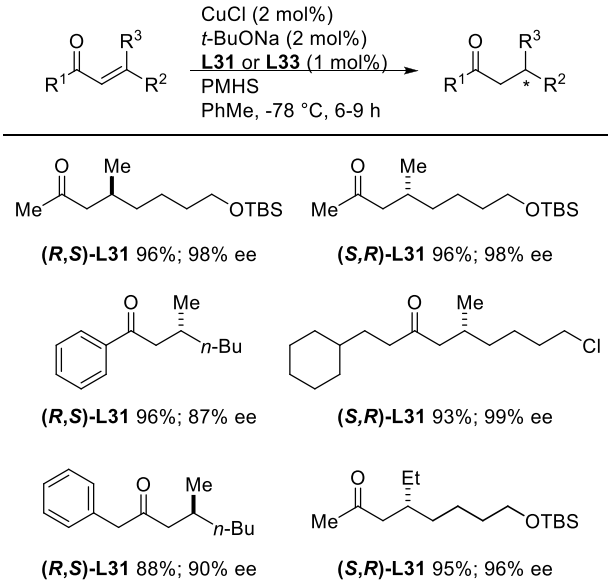
The ligands **L55**, **L56** and **L59** were applied to the Zn-catalyzed hydrosilylation of aryl alkyl phosphinylimines, employing a range of silanes as the stoichiometric reductant (Scheme 88).[92] In general, the reduction of the acetophenone diphenylphosphinylimine produced good results, with both diphenylsilane (up to 85% yield, >99% ee) and PMHS (up to 72% yield, 96% ee) both giving excellent ee values. Triethoxysilane produced only mediocre yields. Best results were obtained in a reaction medium composed of toluene/methanol.

Mlynarski et al. complexed a variety of diaminoethane ligands with $Zn(OAc)_2$ to form an active chiral catalyst which was then applied to the asymmetric hydrosilylation of aryl alkyl imines.[93] A survey of imine *N*-substituents revealed the diphenylphosphinyl group to be superior. A series of aryl methyl phosphinylimines were then subjected to asymmetric hydrosilylation, with PMHS and $(EtO)_3SiH$ serving as the optimal stoichiometric reductants and (***R,R***)-**L46** as the ligand of choice (Scheme 89 and Scheme 90).

7. ASYMMETRIC REDUCTION OF α,β-UNSATURATED KETONES

As with the asymmetric reduction of unsaturated esters (cf. section 8), the hydrosilylation of α,β-unsaturated ketones has relied heavily on the enantioselective conjugate addition of CuH to create the desired optically active β-substituted ketone. This highly useful approach takes advantage of the unique chemistry of copper reagents to carry out the conjugate addition to α,β-unsaturated carbonyl substrates. The role of the organosilane in these reactions is not to directly provide the hydride to the substrate to be reduced, but rather to produce the CuH in a convenient in situ manner. These highly successful asymmetric reductions of pro-chirally substituted β,β-disubstituted carbonyl

Scheme 91. Asymmetric PMHS Reduction of Enones with Cu-L31



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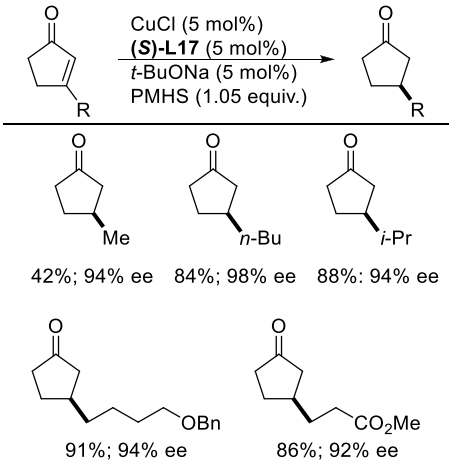
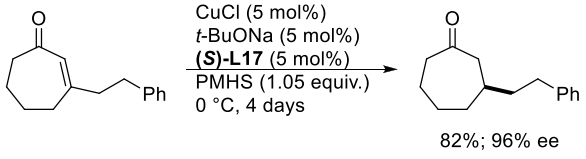
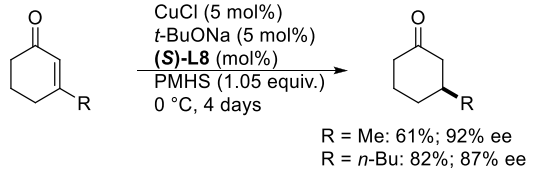
Scheme 92. Asymmetric PMHS Hydrosilylation of 3-Substituted Cyclopentenones with Cu-(*S*)-L17



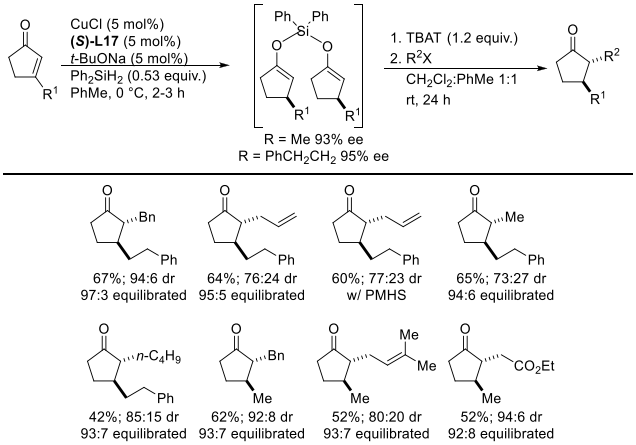
Scheme 93. Asymmetric PMHS Hydrosilylation of 3-Phenethylcycloheptenone with Cu-(*S*)-L17



Scheme 94. PMHS Hydrosilylation of Cyclohexenones with Cu-L8

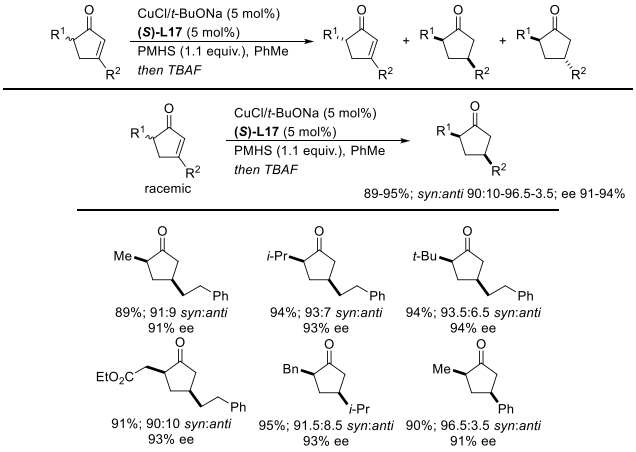


Scheme 95. Asymmetric Diphenylsilane Hydrosilylation of Cyclic Enones with Cu-(*S*)-L17

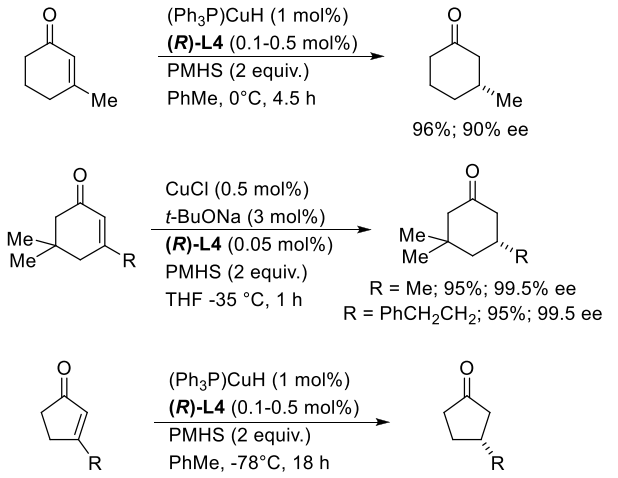


substrates nicely complement the asymmetric conjugate addition of organocopper reagents complexed with nonracemic ligands. The success of the CuH-catalyzed asymmetric reduction of pro-chiral α,β-unsaturated ketones has largely relied on the use of commercially available (*R*)-BINAP (**R**)-**L16**, (*S*)-BINAP

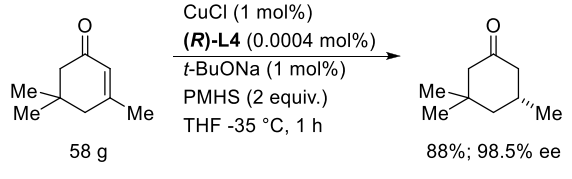
Scheme 96. Asymmetric PMHS Hydrosilylation of 3-Substituted Cyclopentenones with Cu-(*S*)-L17



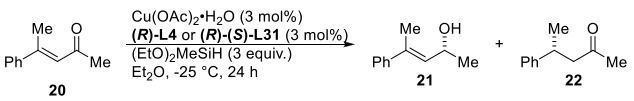
Scheme 97. Asymmetric PMHS Reduction of Cyclic Enones with Cu-(*R*)-L4



Scheme 98. Demonstration of Low Catalyst Loading in the Large-Scale Asymmetric HMDS Conjugate Hydrosilylation of 3,5,5-Trimethylcyclohexenone



Scheme 99. Diethoxymethylsilane Hydrosilylation of Enones with Cu-(*R*)-L4 and Cu-L31



Ligand	Yield (%)	21:22	ee 21(%)	ee 22(%)
(*R*)-L4	92	98:2	97	78
(*R*)-(*S*)-L31	90	5:95	38	99

https://doi.org/10.1021/acs.oprd.1c00073
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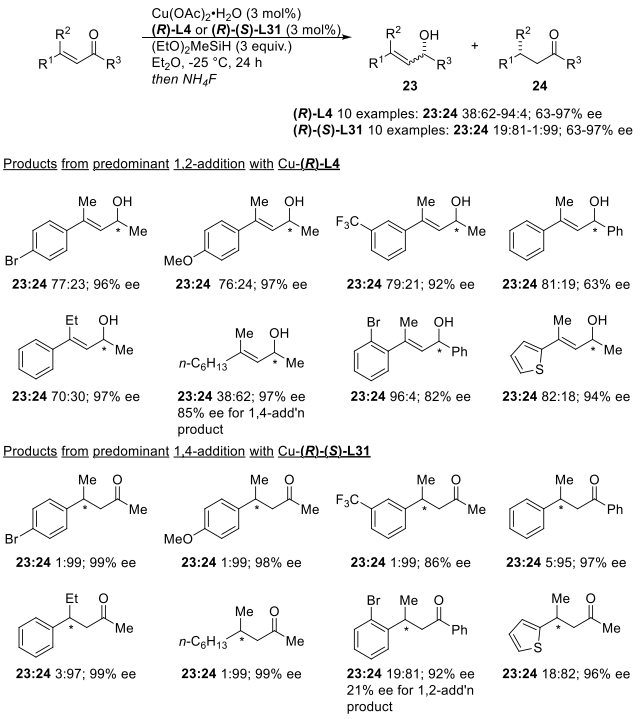
Scheme 100. Diethoxymethylsilane Hydrosilylation of Enones with Cu-(*R*)-L4 and Cu-L31



(*S*)-**L16**, (*R*)-*p*-tol-BINAP (*R*)-**L17**, (*S*)-*p*-tol-BINAP (*S*)-**L17** and SEGPHOS ligands, as well as phosphine derivatized ferrocene ligands. A computational investigation of the phosphine-ligated CuH-catalyzed reduction of enones showed that 1,4-reduction is favored, and that the first step is the addition of hydride to the β-carbon to form the copper enolate which generates the enantioselectivity.[94]

Lipshutz and Servesko performed the initial investigations into the CuH-catalyzed asymmetric reduction of acyclic enones, in which several ligands were found to perform well, while ligands (*R*)-(*S*)-**L31** and (*S*)-(*R*)-**L31** were found to excel (Scheme 91).[95] The ultimate stereochemistry of the final enantiomer could be controlled by the stereochemistry of either the starting enone or the ligand.

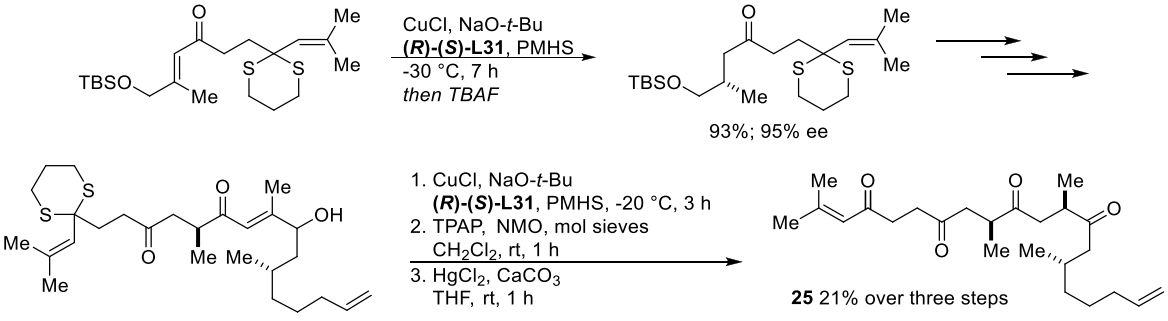
Buchwald et al. applied the CuH-catalyzed enantioselective 1,4-reduction to cyclic enones, producing excellent yields and ee's when utilizing the commercially available *p*-tol-BINAP (*S*)-**L17** (for cyclopentenones or cycloheptenones) chiral ligands to introduce the enantioselectivity and PMHS as the hydride source (Scheme 92 and Scheme 93).[96] Alternatively, BIPHEMP **L8** is optimal for use with cyclohexenones (Scheme 94). The reaction times were generally slow, with completion requiring 2−4 days and being accompanied by minor amounts of over-reduction to the alcohol, particularly in the presence of excess PMHS.

Buchwald et al. expanded the Cu(I)/Ph_2SiH_2 asymmetric 1,4-reduction of 3-substituted cyclopentenones to a one-pot, 1,4-reduction/2-alkylation sequence, forming enantiomerically enriched 2,3-disubstituted cyclopentanones in moderate yields but with excellent diastereomeric and enantiomeric control.[97] The ligand of choice was (*S*)-*p*-tol-BINAP (*S*)-**L17**. The alkylation step required the addition of a fluoride source, tetrabutylammonium triphenyldifluorosilicate (TBAT), to convert the intermediate silyl enol ether to the reactive enolate (Scheme 95). Equilibration (NaOMe/MeOH or NaOEt/EtOH) of the initially generated dialkylated cyclopentanone could be used to enhance the enantiomerically enriched *trans* diastereomer. One example with allylation showed very similar results when using either diphenylsilane or PMHS as the reductant. A small (<11%) amount of the 2,4-regioisomer was observed in two cases due to slow alkylation and isomerization of the enolate intermediate. The protocol provides an interesting approach to the basic scaffold of various prostaglandins.

Buchwald et al. were able to expand the Cu-catalyzed conjugate asymmetric hydrosilylation to reductive kinetic resolutions of 3,5-disubstituted cyclopentenones.[98] The process was made possible due to a strong selectivity differential between the two enantiomers at the 5-position, with the (*R*)-configuration reacting some 25 to 50 times faster than the (*S*)-enantiomer (Scheme 96). In addition, it proved possible to isolate the enantiomerically reduced product. The reaction proceeded with good conversions and high enantiomeric excess in establishing two nonadjacent stereocenters. The reaction was enhanced in the presence of *t*-BuONa, which served to epimerize the cyclopentenone and to increase the equilibration rate.

Lipshutz et al. carried out the asymmetric Cu-catalyzed reduction of 3-substituted cyclopentenones and 3-substituted cyclohexenones with PMHS as the silane reducing agent.[99] An economical ratio of up to 275,000:1 of substrate-to-chiral ligand (*R*)-(−)-DTBM-SEGPHOS) (*R*)-**L4** proved possible. Cyclohexenones were reduced in high yields (90−96%) and with high ee's (90−99.5%) over four examples (Scheme 97). Two cyclopentenones were reduced in yields over 92% with 97% ee. The small ligand loading and the use of PMHS make this process attractive for scale up. Similar results were obtained for two examples in which pinacolborane replaced PMHS as the stoichiometric reductant. The copper catalyst need not be

Scheme 101. Asymmetric PMHS Hydrosilylation of Enones with Cu-(*R*)-(*S*)-L31: Synthesis of Amphidinoketide 25



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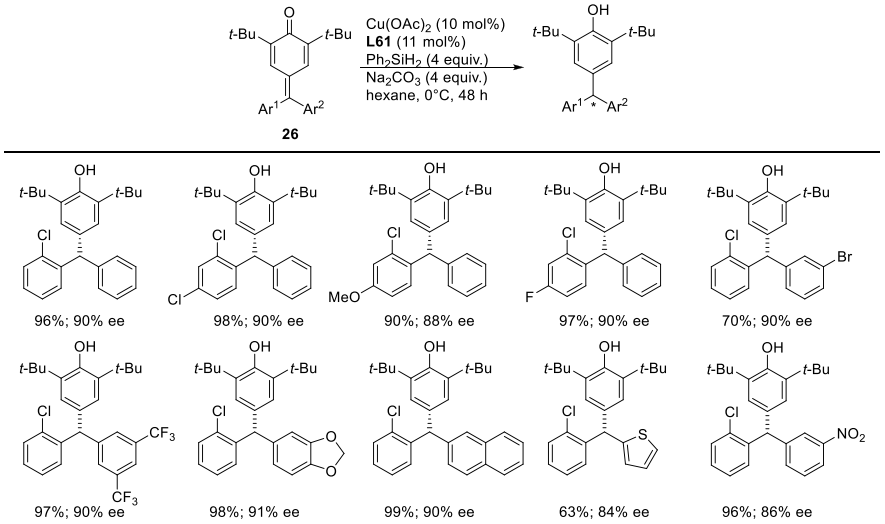
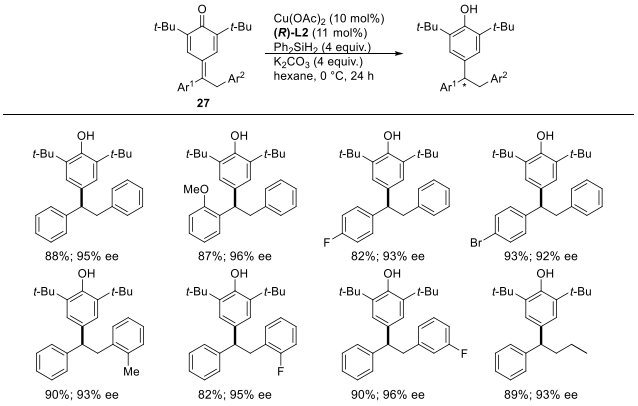
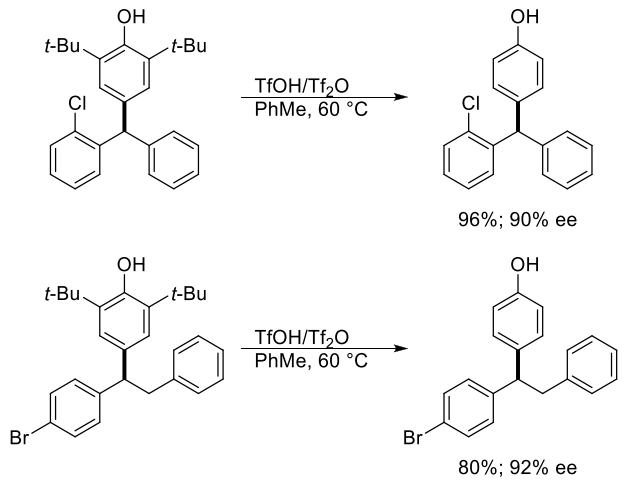
Scheme 102. Asymmetric Diphenylsilane Hydrosilylation of 26 with Cu-(*R*)-L61: Synthesis of Triarylmethanes



Scheme 103. Asymmetric Diphenylsilane Hydrosilylation of 27 with Cu-(*R*)-L2: Enantioselective Synthesis of Triarylethanes



Scheme 104. De-*tert*-butylation of *tert*-Butylarenes



preformed, as it can be generated in the reaction medium. Finally, the reaction was scaled up to a 58 g-level reduction of 3,5,5-trimethylcyclohexenenone, producing excellent results (Scheme 98).

Lipshutz et al. extended the Cu-catalyzed hydrosilylation of α,β-unsaturated ketones to include cinnamyl ketones. The regioselectivity, i.e. 1,2- versus 1,4-reduction, was found to be ligand dependent (Scheme 99). Ligand (***R*)-L4** employed in combination with in situ generated CuH led predominantly to 1,2-reduction of enone **20** to produce **21**.[100] On the other hand, ligand **L31** (*R*)-(*S*)-PPF-P(*t*-Bu)$_2$ favored 1,4-addition to produce β-chiral ketone **22**. The ee values of the lesser regioisomers isolated (i.e., **21** from (***R*)-L4** and **22** from **L31**) were low for both ligands. Overall, the regioselectivities and enantioselectivities were excellent, with only an *ortho*-bromophenyl and 3-phenylcyclohexenone showing inferior results (Scheme 100).

Lipshutz et al. deftly applied the asymmetric hydrosilylation of α,β-unsaturated ketones to the synthesis of the epimer of amphidinoketide **25**.[101] The protocol was applied in two different steps in the total synthesis (Scheme 101).

The 1,6-conjugate asymmetric diphenylsilane reduction of *p*-quinone methides was accomplished by Chu and Fan.[102] The asymmetric reduction of diaryl methides **26** made use of chiral ligand **L61**, while the asymmetric reduction of phenylbenzyl methides **27** used ligand (***R*)-L2** (Scheme 102 and Scheme 103). It was demonstrated that the two *tert*-butyl groups could be readily removed with TfOH/Tf$_2$O in warm toluene (Scheme 104).

8. ASYMMETRIC REDUCTION OF α,β-UNSATURATED ESTERS

The introduction of a stereocenter at the β-position of an ester has typically been achieved through the conjugate addition of an appropriately ligated organocopper reagent to an α,β-unsaturated ester. One alternative is to employ the reaction of a CuH reagent with an unsymmetrical β,β-disubstituted-α,β-unsaturated ester. The process results in the introduction of a hydrogen rather than an organic moiety, as well as in the creation of a chiral secondary center. The reaction has been carried out with a high degree of success using a CuH reagent or, more practically, an in situ generated CuH reagent in the presence of a variety of chiral ligands. The practical nature of the chemistry is further exemplified by the fact that the in situ generation of the CuH is accomplished with a stoichiometric silicon hydride reductant and common Cu(I) or Cu(II) salts.

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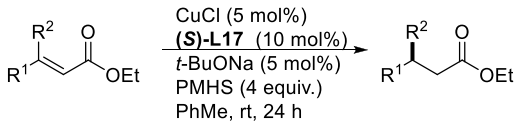
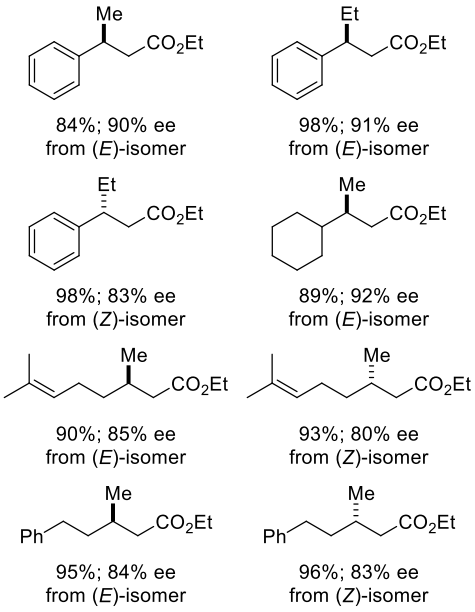
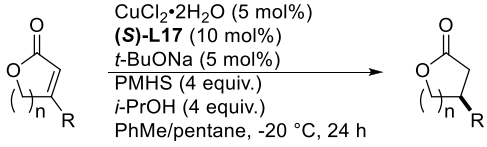
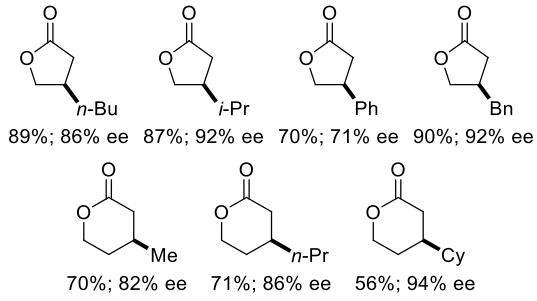
Scheme 105. Asymmetric PMHS Hydrosilylation of Unsaturated Esters with Cu-(*S*)-L17: Synthesis of Nonracemic *β*-Substituted Esters





Scheme 106. Asymmetric PMHS Hydrosilylation of Cyclic Unsaturated Lactones with Cu-(*S*)-L17: Synthesis of Nonracemic *β*-Substituted Lactones

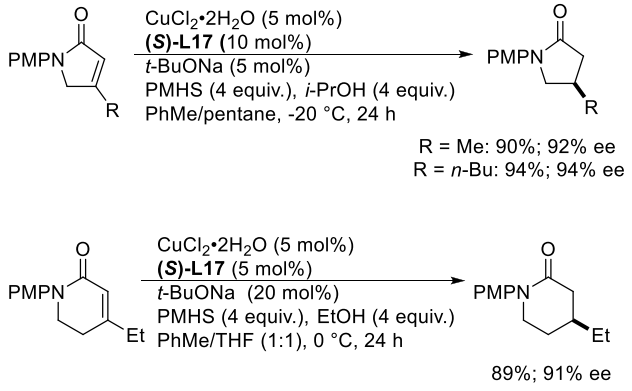




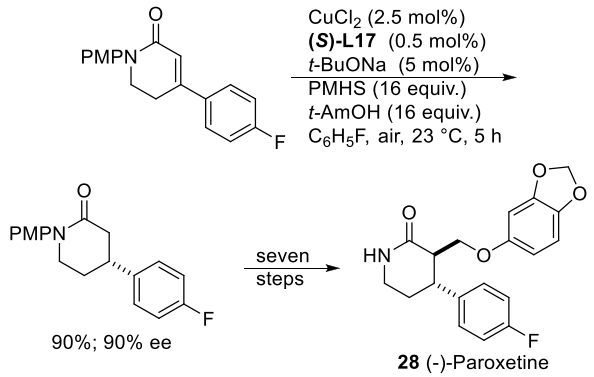
Buchwald et al. were the first to demonstrate that silane-promoted CuH conjugate reductions of suitable *α,β*-unsaturated esters provided *β*-chiral esters in good yields and with modest ee's. The silane PMHS provided the hydride, and (*S*)-*p*-tol-BINAP (***S*)-L17** generated the asymmetric induction in the process (Scheme 105).[103] The ultimate configuration of the final product was dependent on the regioisomers of the starting unsaturated ester.

Buchwald et al. extended the asymmetric conjugate reduction of *α,β*-unsaturated esters and amides to lactones and lactams (Scheme 106 and Scheme 107).[104] Their studies also revealed

Scheme 107. Asymmetric PMHS Hydrosilylation of Cyclic Unsaturated Lactams with Cu-(*S*)-L17: Synthesis of Chiral *β*-Substituted Lactams



Scheme 108. Asymmetric PMHS Hydrosilylation en Route to (−)-Paroxetine 28



that the addition of an alcohol to the reaction medium significantly enhanced both reaction rates and product yields. It was postulated that the alcohol protonates the copper enolate or silyl ketene acetal intermediate, thus preventing the conversion to byproducts. The methodology was successfully applied to a short synthesis of the antidepressant (−)-Paroxetine **28** (Scheme 108).

Lipshutz et al. demonstrated that, when suitably ligated, CuH can facilitate the asymmetric reduction of *α,β*-unsaturated esters with PMHS to produce *β*-chiral esters. Both SEGPHOS (***R*)-L4** and diphosphinoferrocene ligands such as **L31** produced excellent yields and ee's (Scheme 109).[105] The configuration of the *β,β*-disubstituted ester product depended on the stereochemistry of the starting unsaturated ester. The ligand (***R*)-L4** did not work as well for the (*Z*)-isomer (*Z*)-**29** as it did for the (*E*)-isomer (*E*)-**29**, indicating a limitation. On the other hand, ligand (***R*)-(*S*)-L31** worked very well for both (*E*)-**29** and (*Z*)-**29**, providing both enantiomers demonstrating the stereoselectivity of the transformation. In a successful scale-up reaction, 2.5 g of (*Z*)-ethyl 3-methylcinnamate produced ethyl 3-phenylbutyrate (2.3 g; 92% yield; 98% ee). Furthermore, the enantiomeric ligand (***S*)-(*R*)-L31** reacted with **30** to produce the opposite enantiomeric of the reduced ester, extending the utility of the protocol. Lactone **30** was converted to the corresponding saturated lactone **31** in high yield and with high ee.

A Cu catalyst generated in situ from either Josiphos-type ligand **L29** was successfully employed in the asymmetric conjugated reduction of 3-aryl-3-trifluoromethyl acrylates.[106]

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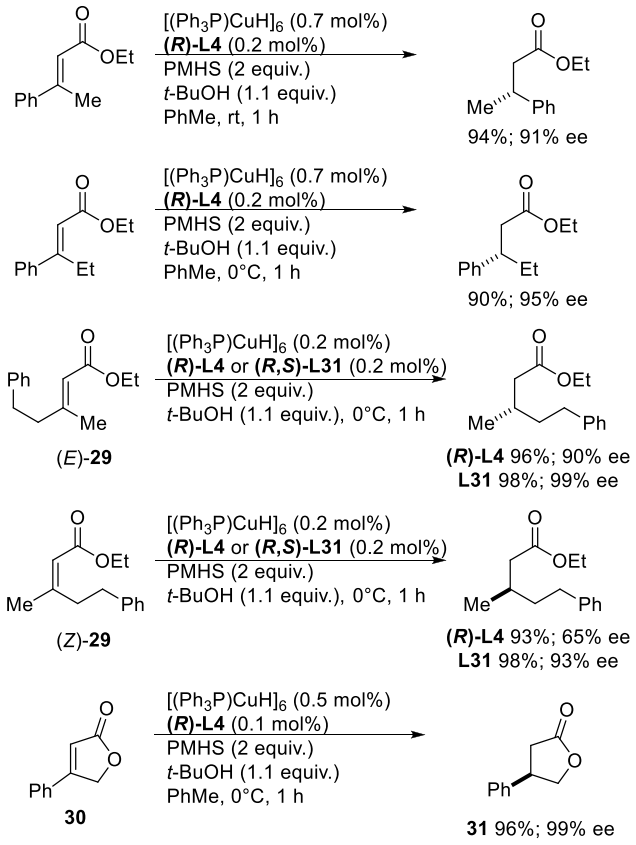
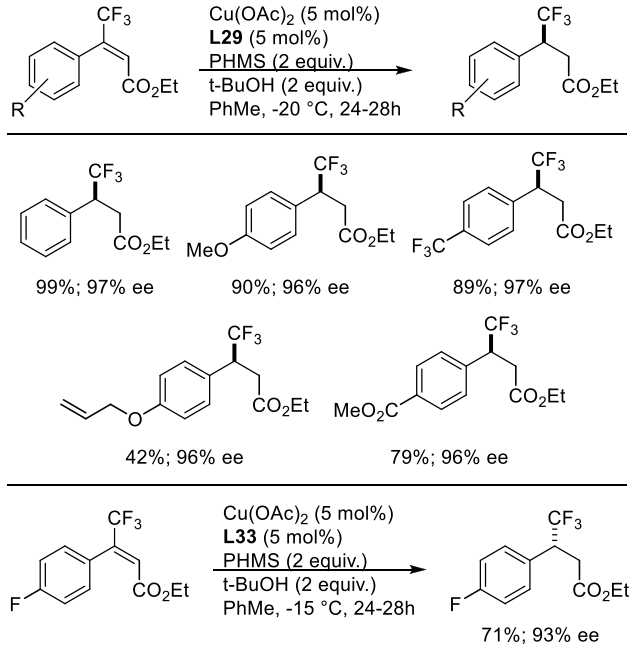
Scheme 109. Asymmetric PMHS Hydrosilylation of Unsaturated Esters with Cu-(*R*)-L4 and Cu-(*R*)-(*S*)-L31: Synthesis of Nonracemic *β*-Substituted Esters

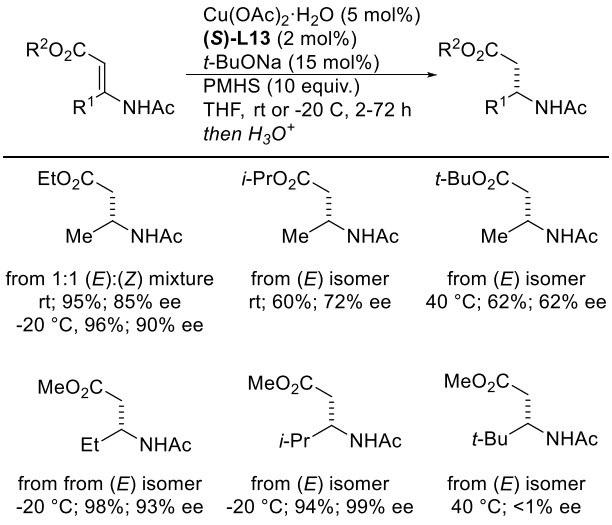


Scheme 110. Asymmetric PMHS Hydrosilylation of Unsaturated Esters with Cu-L29 or L38: Synthesis of Nonracemic *β*-Trifluoromethyl Esters

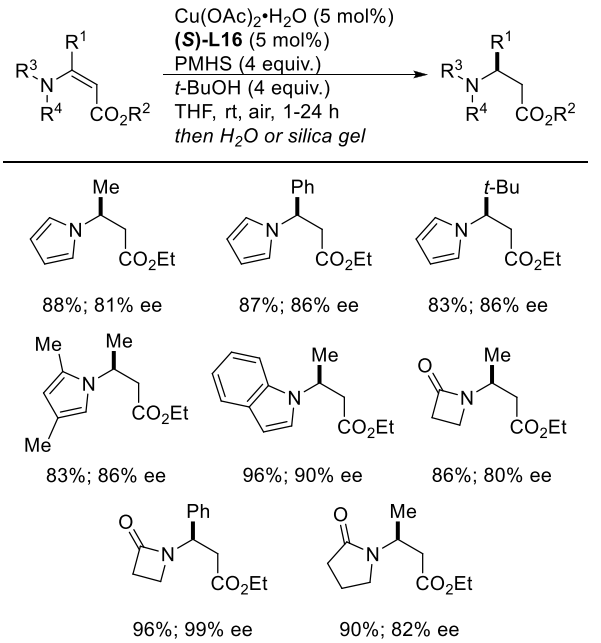


The chemical and enantioselective yields were excellent, with PMHS employed as the silane reducing agent (Scheme 110).

Scheme 111. Asymmetric PMHS Hydrosilylation of Unsaturated Esters with Cu-(*S*)-L13: Synthesis of Nonracemic *β*-Substituted *β*-Amino Esters: Synthesis of *β*-Amino Acids



Scheme 112. PMHS Hydrosilylation of *β*-Amino Unsaturated Esters with Cu-(*S*)-L16: Synthesis of Nonracemic *β*-Substituted-*β*-Amino Acid Esters



The degree of enantioselectivity depended strongly on the geometry and substitution pattern of the starting acrylate. Certain examples reacted poorly or failed to react, such as acrylates containing *ortho*-substituted aryl groups, *β*-benzyl acrylates, *α,β*-unsaturated phenylsulfones (no reaction) and nitrostyrenes (23% yield; 50% ee).

The Cu-catalyzed PMHS reduction of *β*-(acylamino)acrylates in high yield and enantiomeric excess has been accomplished, establishing an economical approach to the important transformation which produces *β*-amino acids with high enantiomeric purity (Scheme 111).[107] The stereochemistry and ee values were found to be independent of the starting stereo-

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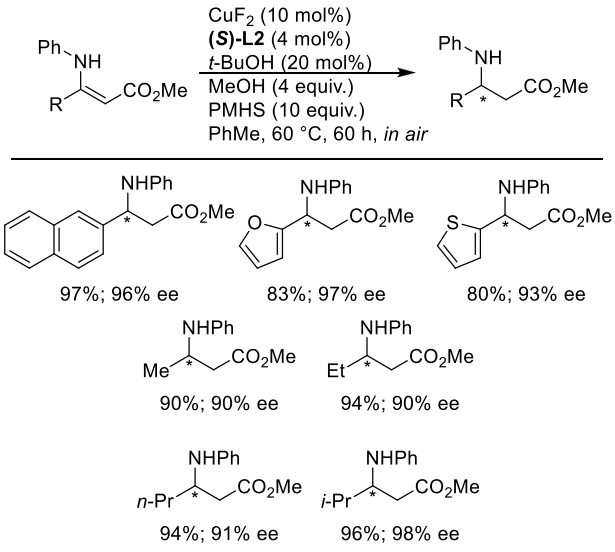
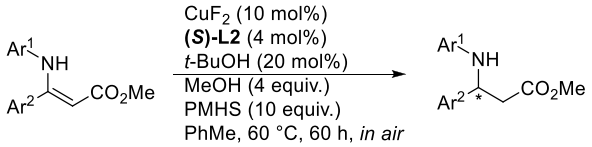
Scheme 113. AsymmetricPMHS Hydrosilylation of β-Amino Unsaturated Esters with Cu-(*S*)-L2: Synthesis of Nonracemic β-Substituted-β-Amino Acid Esters



Scheme 114. AsymmetricPMHS Hydrosilylation of β-Aryl-β-Amino Unsaturated Esters with Cu-(*S*)-L2: Synthesis of Nonracemic β-Aryl-β-Amino Acid Esters



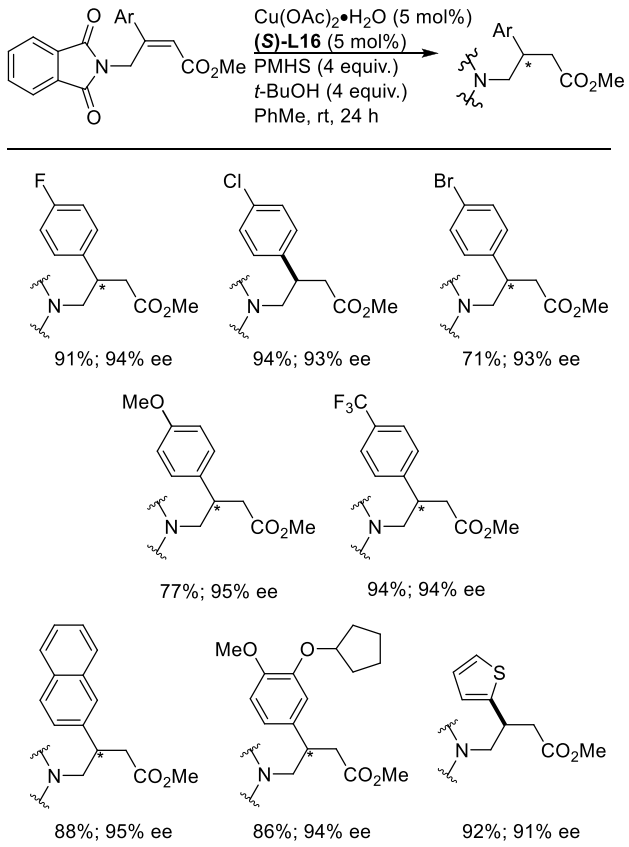
Ar^1	Ar^2	Yield (%)	ee (%)
Ph	*o*-OMePh	22	92
Ph	*m*-FPh	95	94
Ph	*m*-BrPh	93	98
Ph	*m*-CF_3Ph	95	96
Ph	*p*-OMePh	65	94
Ph	*p*-CF_3Ph	96	94
p-OMePh	Ph	30	94
p-OMePh	*p*-ClPh	30	95

chemistry of the acrylate, although (*Z*)-isomers reacted faster than (*E*)-isomers. In the absence of *t*-BuONa/*t*-BuOH, the yield and enantioselectivity suffered. Although PMHS was the preferred silane in this work, phenylsilane, triethoxysilane and diethoxymethylsilane performed comparably. The steric bulk of the ester influenced the reaction rate, and isopropyl and *tert*-butyl esters reacted considerably more slowly than methyl or ethyl esters. Several metal-catalyzed hydrogenation systems have since been applied to this transformation.[108−111]

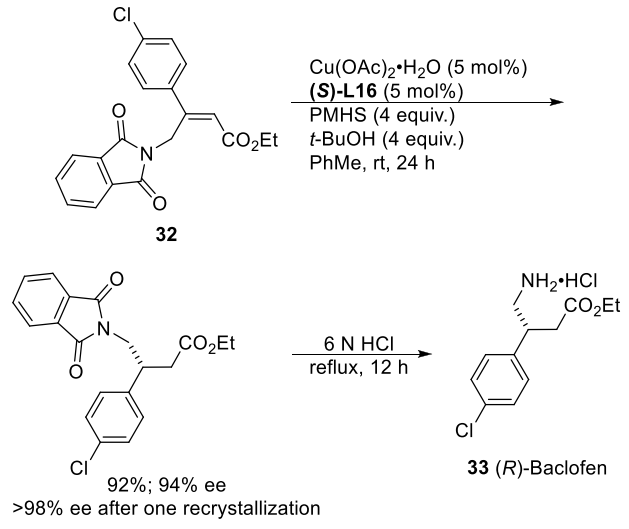
Wu et al. reported on the (*S*)-P-Phos (**S**)-**L13**/CuF_2 combination for the asymmetric reduction of β-amino-α,β-unsaturated esters, but this produced lower yields (33−65%) and overall lower ee's (23−91%) than those obtained using the $Cu(OAc)_2$ approach shown in Scheme 111.[112]

CuH-catalysis was also applied by Buchwald et al. to the conjugate reduction of β-substituted-β-azahetereocyclic-α,β-unsaturated esters to produce the corresponding β-azaesters in very good yield and with high enantioselectivity (Scheme 112).[113] A combination of (*S*)-BINAP (**S**)-**L16** and PMHS was used. Lactam-substituted systems had been shown to react more slowly than the pyrrole systems. Lactam-substituted systems had

Scheme 115. Asymmetric PMHS Hydrosilylation of γ-Amino Unsaturated Esters with Cu-(*S*)-L16: Synthesis of Nonracemic β-Substituted-γ-Amino Acid Esters



Scheme 116. Asymmetric PMHS Hydrosilylation of 32: Synthesis of (*R*)-Baclofen 33



previously been shown to react considerably more slowly than the pyrrole systems. The successful reduction protocol was applied to the unsaturated ester (*Z*)-3-phenylbutenoate (84% yield; 92% ee) and to 3-(2-phenylethyl)cyclopentenone (85% yield; 89% ee).

Wu et al. presented an interesting approach to exploiting prochiral precursors to produce β-amino acid esters by

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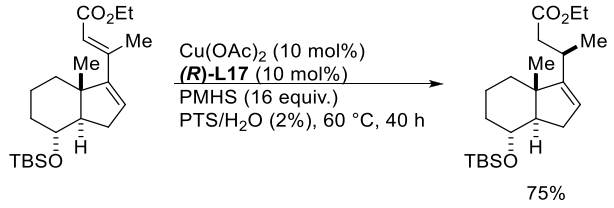
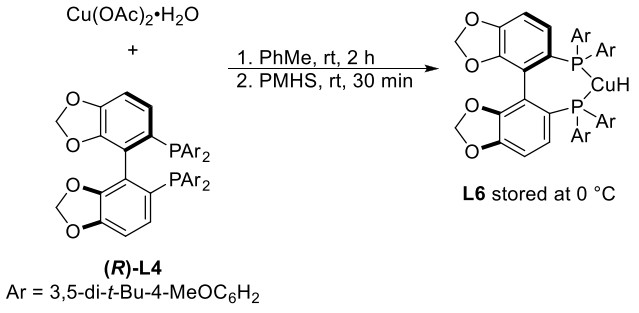
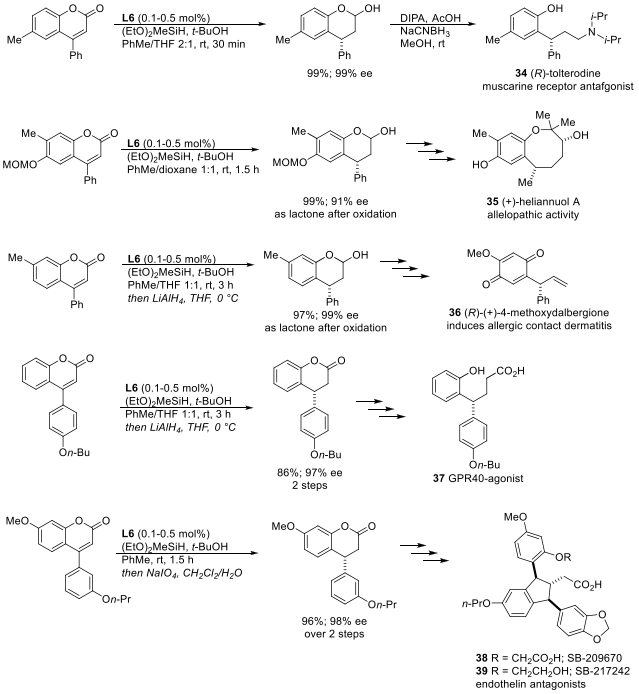
Scheme 117. Asymmetric PMHS Hydrosilylation of an Ethyl Dienoate with Cu-91: Applied to a Synthesis of Calcitriol and Vitamin D Analogs



Scheme 118. Preparation of a SEGPHOS-Cu Catalyst Employed in Various Asymmetric Cu-Catalyzed Hydrosilylations

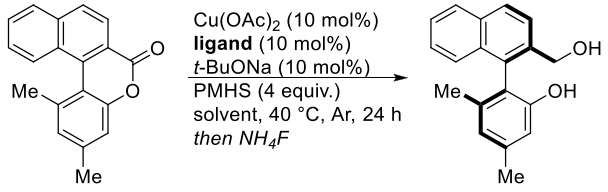


Scheme 119. Enantioselective Diethoxymethylsilane Reduction of Coumarins with L6



developing enantioselective conjugate reductions of (*β*-arylamino)-*β*-alkyl or *β*-arylacrylates.[114] The reaction was accomplished with a PMHS-derived CuH-catalysis system and (*S*)-SEGPHOS (**S**)-**L2**. Various alkyl and aryl-substituted substrates produced excellent results (Scheme 113 and Scheme 114). The reaction performed considerably better when using MeOH as the promoter rather than the usual *t*-BuOH. The

Scheme 120. AsymmetricPMHS Hydrosilylation of Bringmann's Lactones with Cu-(*S*)-L9, Cu-(*R*)-L4, Cu-(*R*)-(*S*)-L30, Cu-(*R*)-L16: Synthesis of Nonracemic Diaryl Diols

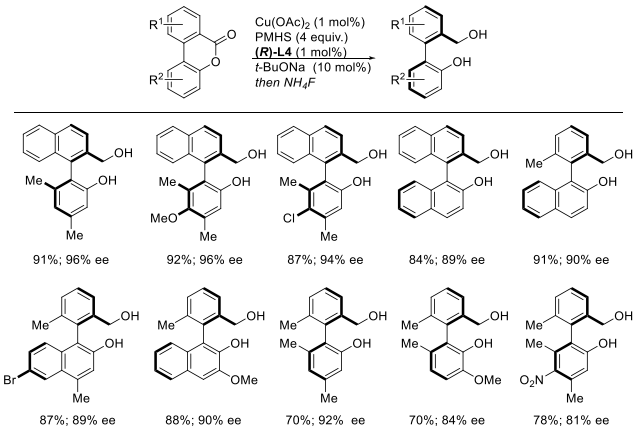


40

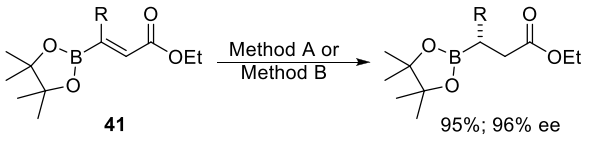
Ligand	Solvent	Yield (%)	ee (%)
(*R*)-L16	THF	89	46
(*R*)-L9	THF	90	61
(*S*)-L30	THF	92	6
(*R*)-L4	THF	92	91
(*R*)-L4	Me-THF	86	90
(*R*)-L4	PhMe	messy	--
(*R*)-L4	THF	91	96%*

* Reaction run at 1 mol% $Cu(OAc)_2$ and (*R*)-L4

Scheme 121. Atropoenantioselective PMHS Hydrosilylation of Dibenzo-*γ*-lactones



Scheme 122. Asymmetric PMHS Hydrosilylation of *β*-Boryl Unsaturated Esters with Cu-(*R*)-L17 and Cu-(*R*)-(*S*)-L31: Synthesis of Nonracemic *β*-Boryl Esters



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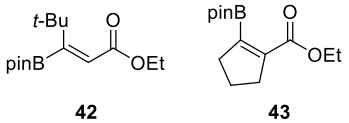
Method A: $Cu(OAc)_2$ (3 mol%), **L32** (3 mol%), *t*-BuOH 1.1 equiv) PMHS (4 equiv), PhMe, 0 °C, 24 to 14 h

Method B: CuCl (5 mol%), (*R*)-L17 (10 mol%), *t*-BuONa (5 mol%) PMHS (4 equiv); PhMe, 5-48 h

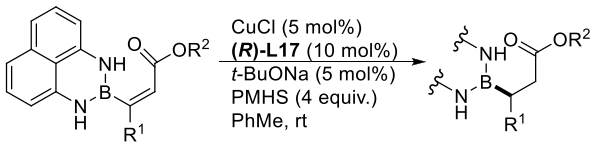
R	Yield (%) method A	ee (%) method A	Yield (%) method B	ee (%) method B
Me	93	70	92	97
Et	92	76	95	96
n-Pr	91	80	94	96
n-hex	82	68	90	94
Cy	80	48	79	81



42 43

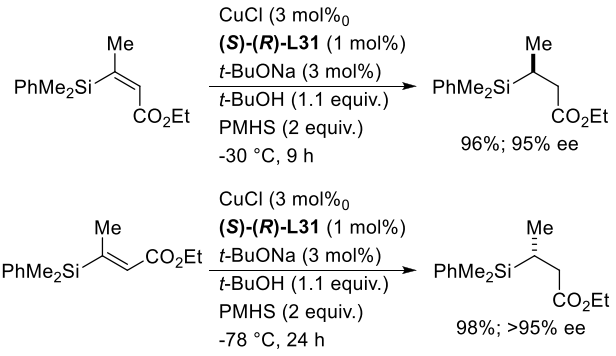
https://doi.org/10.1021/acs.oprd.1c00073
Org. Process Res. Dev. 2021, 25, 1719−1787

Scheme 123. PMHS Hydrosilylation of β-Boronyl Unsaturated Esters with Cu-(*R*)-R17: Enantioselective Synthesis of Nonracemic β-Boronyl Esters

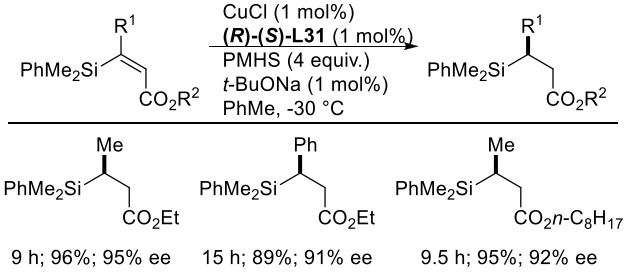


R^1	R^2	Yield (%)	ee (%)
Ph	Me	88	85
p-Tol	Me	72	51
p-OMePh	Me	77	65
p-FPh	Me	85	66
p-CO_2MePh	Me	87	97
c-C_6H_{11}	Et	87	97
n-C_6H_{13}	Et	80	94

Scheme 124. Asymmetric PMHS Hydrosilylation of β-Silyl Unsaturated Esters with Cu-(*S*)-(*R*)-L31: Enantioselective Synthesis of Nonracemic β-Silyl Esters



Scheme 125. Asymmetric PMHS Hydrosilylation of (*Z*)-β-Silyl Unsaturated Esters with Cu-(*R*)-(*S*)-L31: Enantioselective Synthesis of Nonracemic β-Silyl Esters

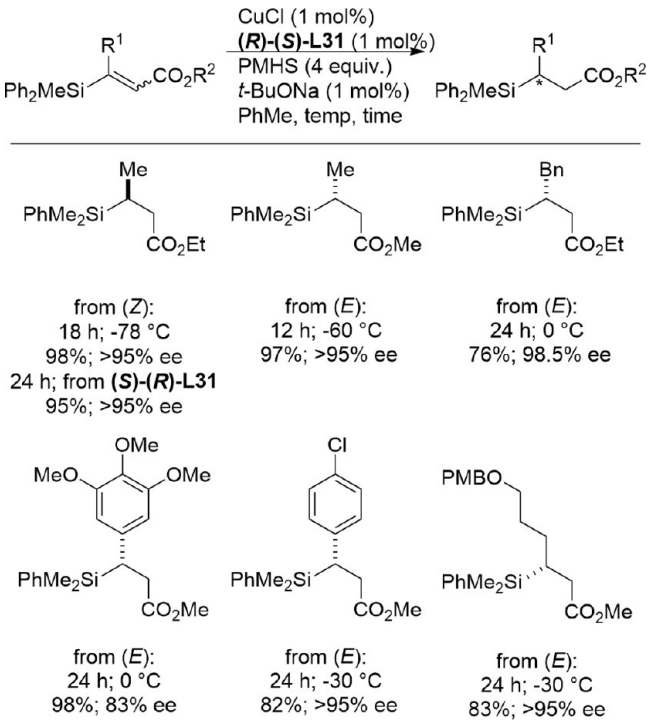


enantioenriched products could be converted to primary amines via the use of ceric ammonium nitrate (CAN).

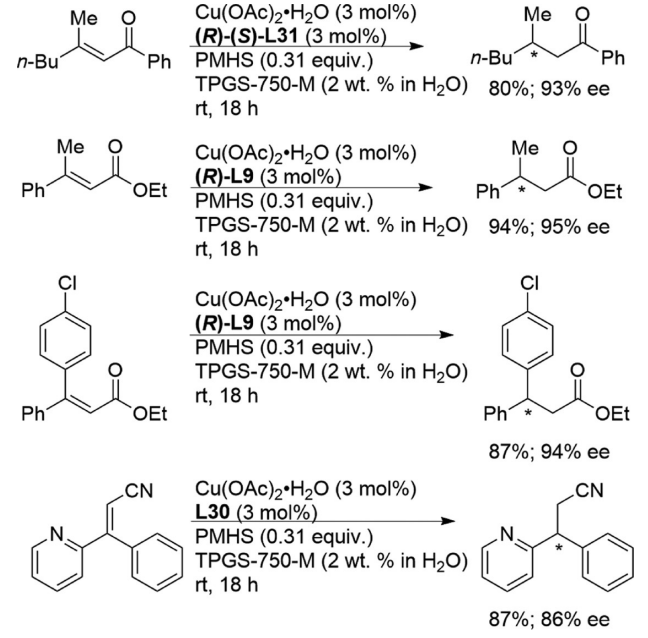
Zheng et al. reacted (*Z*)-3-phthalimido-3-arylbut-2-enoates with PMHS in the presence of $Cu(OAc)_2 \cdot H_2O$, *t*-BuOH and (*S*)-BINAP (*S*)-**L16** to produce the corresponding butanoate in good yield and with high ee (Scheme 115).[115] The protocol was applied to a synthesis of the muscle relaxant (*R*)-baclofen **33** from **32** (Scheme 116).

The Mouriño group employed the asymmetric reduction of an α,β-unsaturated ester in the synthesis of calcitriol as well as in the synthesis of 1α,25-dihydroxyvitamin D_3 analogs with modifications at the side chain as well as at the D-ring (Scheme 117).[116,117] (*R*)-*p*-tolBINAP (*R*)-**L17** was used as the chiral ligand.

Scheme 126. Asymmetric PMHS Hydrosilylation of (*E*)-β-Silyl Unsaturated Esters with Cu-L31



Scheme 127. AsymmetricPMHS Hydrosilylation of Nonracemic β-Silyl Esters with Cu-(*R*)-L9 and Cu-L30 and Cu-L31: Enantioselective Synthesis of β-Substituted Esters in Water



Lipshutz and Frieman reported on the synthesis of the important chiral CuH complex **L6**.[118] The catalyst was shown to be stable for several weeks when stored with stringent exclusion of oxygen. The complex can be made and stored as a toluene solution or, more commonly, prepared in situ (Scheme 118). Tests of the efficiency of **L6** for reductions were conducted on substrates including isophorone (>99% ee), acetophenone (93% ee) and ethyl 3-methylcinnamate (98% ee). Additionally,

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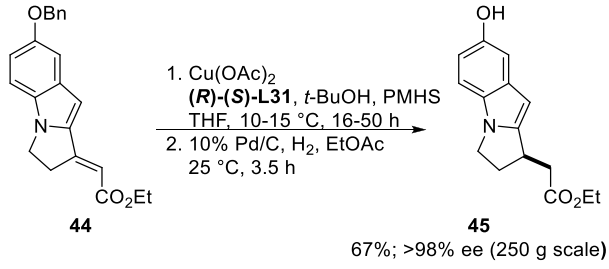
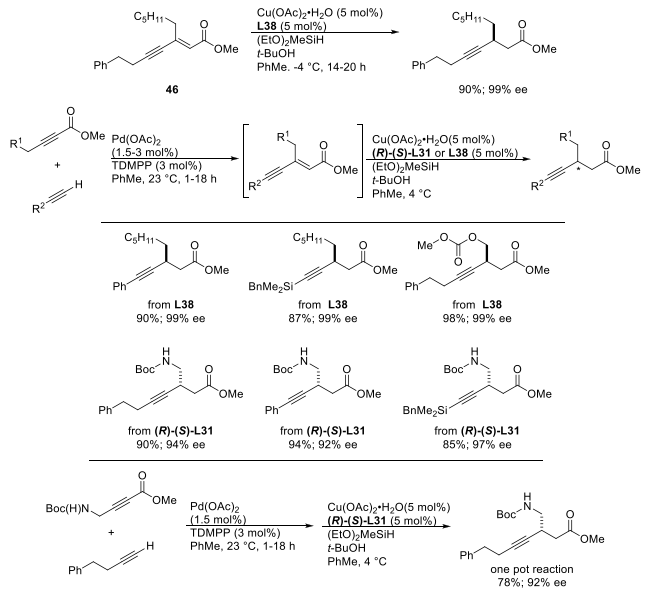
Scheme 128. Asymmetric PMHS Hydrosilylation in the Synthesis of (*R*)-2-(7-Hydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-yl)acetate 45



Scheme 129. Formation and Diethoxymethylsilane Hydrosilylation of ynenoates with Cu-(*R*)-(*S*)-L31 and Cu-L38



catalyst loadings as low as 1000:1 were demonstrated (isophorone, 95% yield; 99% ee). The methodology was applied to coumarin derivatives **34**–**39** of biological interest (Scheme 119).[119]

Zhang et al. applied BINAP and related ligands in the asymmetric hydrosilylations to unusual enantioselective hydrosilylation of Bringmann lactones to biaryl and arylnaphthyl systems (*S*)-**L9**, (*R*)-**L4**, (*R*)-(*S*)-**L30** and (*R*)-**L16**, with high ee values.[120] The reductions are catalyzed by in situ generated CuH in the presence of a suitable ligand. An initial study on the reduction of **40** revealed that PMHS was the best reductant and (*R*)-**L4** the best ligand, with $Cu(OAc)_2$ providing the metal (Scheme 120 and Scheme 121).

When Hall et al. applied boronated ethyl (*E*)-butenoate **41** (R = Et) to reduction conditions under the influence of $(PPh_3)_6$·CuH, Josiphos ligand (*R*)-(*S*)-**L31** and PMHS, the results were an excellent 95% yield with 96% ee (Scheme 122).[121] However, while yields remained high when the conditions were applied either to longer chains or to those with C3-sterically hindered systems such as ethyl 3-boronylpentenoate, enantioselectivity dropped into the 70–80% range. Increasing catalyst load and switching to the methyl ester did not remedy the situation. The authors thus developed two sets of conditions which generated CuH in situ: one method utilized ligand (*R*)-(*S*)-**L32** (method A), while the other employed (*R*)-*p*-tol-BINAP (*R*)-**L17** (method B). The replacement of Stryker's reagent had the effect of eliminating bulky PPh_3 and overcoming the steric bias introduced by larger alkyl groups at C3 and translated to excellent results for a range of substrates. Nevertheless, bulky substrates **42** and **43** failed to react.

Hall et al. extended the asymmetric Si–H-promoted CuH-catalyzed conjugate reduction of *β*-boronyl esters to *β*-boronyl-*β*-aryl derivatives (Scheme 123).[122] In order to make this system successful, the pinacolborane was replaced with planar 1,8-diaminonaphthalene (dan) ligated boron, which improved both yield and enantioselectivity.

Lipshutz et al. applied the CuH-catalyzed asymmetric reduction protocol to *β*-dimethylphenylsilyl-*β*-substituted esters in the presence of (*S*)-(*R*)-**L31** to produce chiral *β*-silyl esters in excellent yields (76–98%) and enantioselectivities (83–98%) (Scheme 124).[123] The reaction is stereospecific, and as such the predominant enantiomer is determined by the geometry of the olefin starting material.

Lipshutz et al. extended the asymmetric reduction of prochiral enoates with a more thorough investigation of a series of *β*-phenyldimethylsilyl unsaturated esters, with excellent results.[124] The chiral DTBM-SEGPHOS ligand provided good yields but low ee's, whereas Solvias ligand (*R*)-(*S*)-**L31** produced both high yields and high ee values for both geometric isomers of the starting olefin (Scheme 125 and Scheme 126). Conveniently, the stereochemistry of the reduced enoate could be directed by the stereoisomer of either the enoate or the ligand.

Lipshutz et al. expanded the asymmetric reduction of enoates, enones and acrylonitriles to be performable in water (Scheme 127).[125] The key experimental modification, which has been employed by Lipshutz in a number of applications, is the exploitation of a surfactant (TPGS-750-M) to encapsulate reagents away from the water. It is notable that a strong differentiation between a phenyl and a *p*-chlorophenyl group (enoates reduction) was observed, as was that of a phenyl and a 2-pyridyl group (acrylonitrile reduction); very high ee values were observed in both cases.

Schrader et al. employed an asymmetric reduction of *α,β*-unsaturated ester **44** in a key step in the preparation of the tricyclic indole **45**.[126] The reaction was successfully scaled up to 250 g. Compound **45** is an important synthon for the preparation of $S1P_1$ receptor agonists, which share the tricyclic backbone with **45** (Scheme 128).

Trost et al. subjected the ynenoate **46** to CuH-catalyzed conjugate reduction conditions and found that 1,4-conjugate reduction was the preferred route rather than the 1,6-pathway.[127] Based on these results, they devised a two-step sequence of a Pd-catalyzed hydroalkynylation of an enoate to form the ynenoate, which was then reduced with diethoxymethylsilane-generated CuH (Scheme 129). Both yields and ee values were excellent.

9. ASYMMETRIC REDUCTION OF *α,β*-UNSATURATED NITRILES

Chiral *β*-substituted nitriles are available via the asymmetric hydrosilylation of *β*-substituted acrylonitriles in procedures like those applied in the asymmetric reduction of *α,β*-unsaturated ketones and esters involving Cu-catalysis.

In conjunction with success in the hydrosilylation of *β*-CF_3-substituted *α,β*-unsaturated esters, Poutrel and co-workers performed the Josiphos ligated CuH-catalyzed reduction of *α,β*-unsaturated nitriles, obtaining similarly positive results

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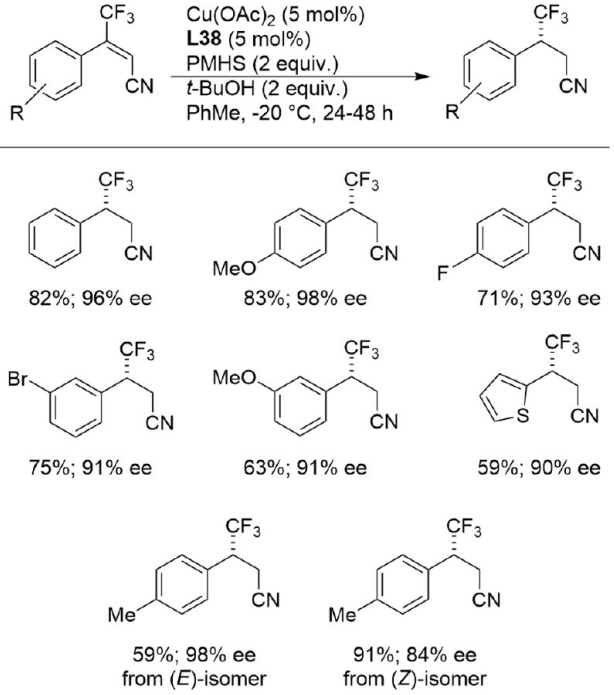
Scheme 130. Asymmetric PMHS Hydrosilylation of β-Trifluoromethyl Unsaturated Nitriles with Cu-L38: Synthesis of Nonracemic β-Trifluoromethyl Nitriles



when employing Walphos ligand **L38** (Scheme 130).[106] The starting olefin geometry has a strong influence on the stereochemical outcome.

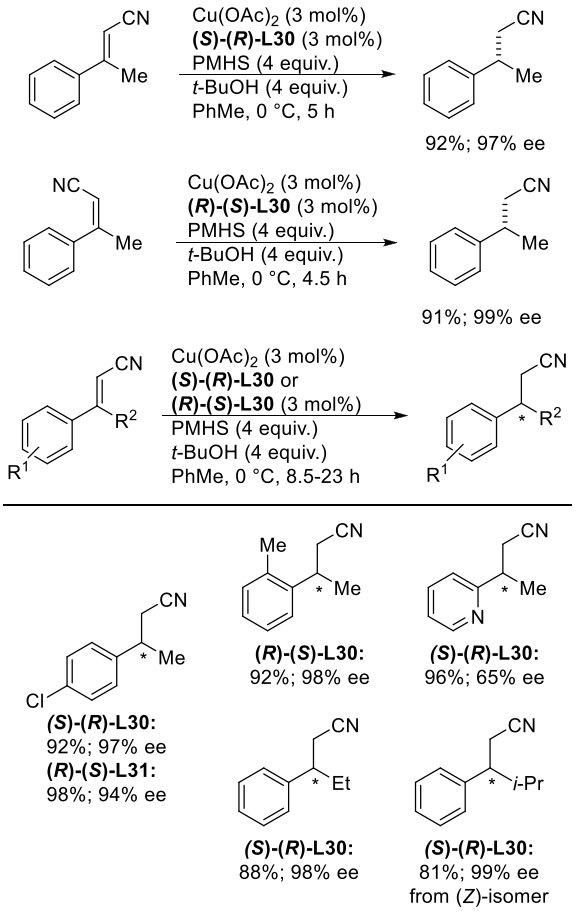
Yun et al. applied nonracemic diphosphinoferrocene **(*R*)-(*S*)-L30** to achieve the Cu-catalyzed enantioselective β-reduction of β,β-disubstituted acrylonitriles offering 3,3-disubstituted propionitriles, producing high yields and ee's (Scheme 131).[128] As noted in similar protocols, the stereochemistry of the product depended on both the geometry of the acrylonitrile derivative and the configuration of the ligand **(*R*)-(*S*)-L30**.

Through JOSIPHOS **(*R*)-(*S*)-L31** or **(*R*)-(*S*)-L30** ligated Cu-promoted reduction conditions, Yun et al. were able to enantioselectively reduce α,β-unsaturated nitriles in high yield and with impressive ee's (Scheme 132).[129] The results of the reaction were essentially the same at 0 °C or room temperature, and were not affected by the stereochemistry of the starting acrylonitrile derivative.

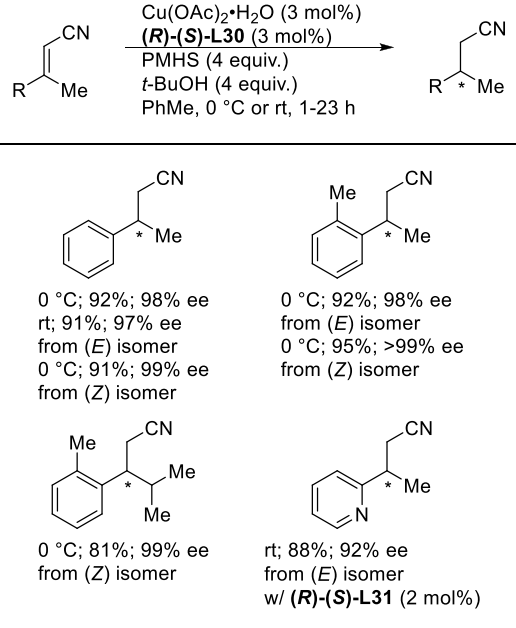
Yun et al. applied Josiphos **(*R*)-(*S*)-L30** to achieve the Cu-catalyzed enantioselective β-reduction of β,β-diaryl acrylonitriles offering 3,3-disubstituted propionitriles, producing high yields and ee's (Scheme 133).[130] As noted in similar protocols, the stereochemistry of the product depended on both the geometry of the acrylonitrile derivative and the configuration of the ligand **(*R*)-(*S*)-L30**.

Yun et al. expanded the asymmetric conjugate reduction of β,β-diarylacrylonitriles, showing that the starting geometry of the acrylonitrile is crucial for obtaining high enantioselectivity even when both aryl groups are very similar in size (Scheme 134 and Scheme 135).[131] Electronic factors on the aryl groups did not seem to play a significant role in the stereochemical outcome. Based on crystal structure analysis, it was observed that the aryl group *cis* to the cyano group was tilted about 82° from conjugation, with the plane of the C═C suggesting that this bias is responsible for the stereocontrol of the reduction.

Scheme 131. Asymmetric PMHS Hydrosilylation of β-Aryl Unsaturated Nitriles with Cu-(*R*)-(*S*)-L30: Synthesis of Nonracemic β-Aryl Butyronitriles



Scheme 132. Further Asymmetric PMHS Hydrosilylation of β-Aryl Unsaturated Nitriles with Cu-(*R*)-(*S*)-L30: Synthesis of Nonracemic β-Aryl Butyronitriles



https://doi.org/10.1021/acs.oprd.1c00073
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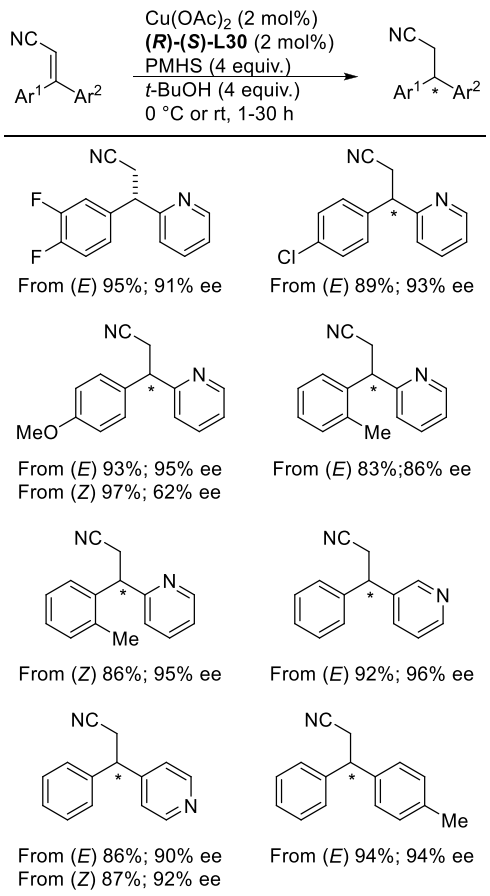
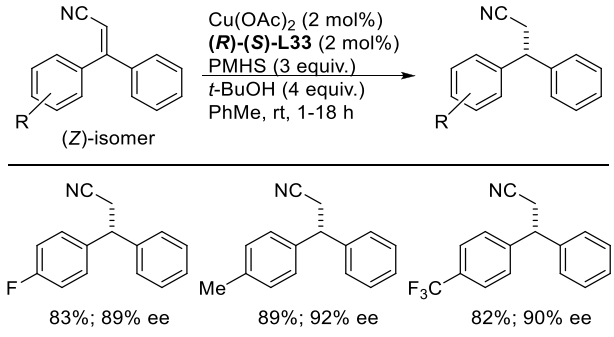
Scheme 133. AsymmetricPMHS Hydrosilylation of β,β-Diaryl Unsaturated Nitriles with Cu-(*R*)-(*S*)-L30: Synthesis of Nonracemic β,β-Diaryl Butyronitriles



Scheme 134. Additional Asymmetric PMHS Hydrosilylation of (*Z*)-β,β-Diaryl Unsaturated Nitriles with Cu-(*R*)-(*S*)-L33

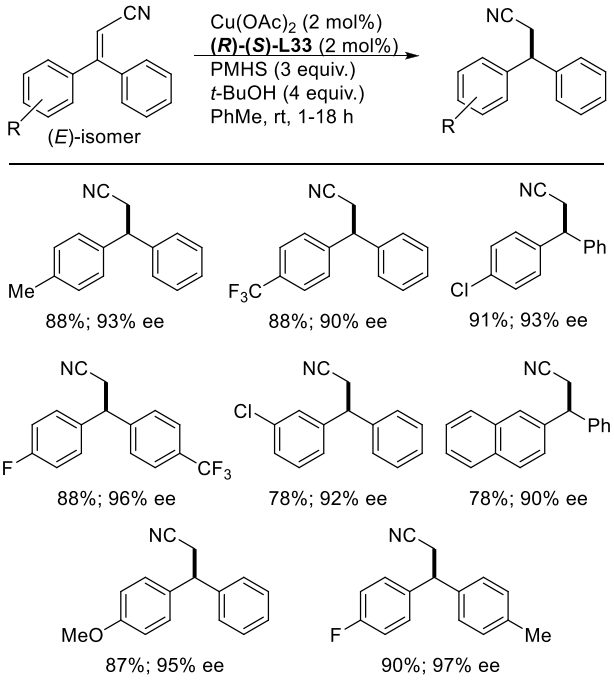


Yun et al. successfully applied their protocol for the asymmetric conjugate reduction of β,β-disubstituted acrylonitriles, and specifically that of **47**, to a synthesis of (*R*)-Tolterodine **34** (Scheme 136).[132]

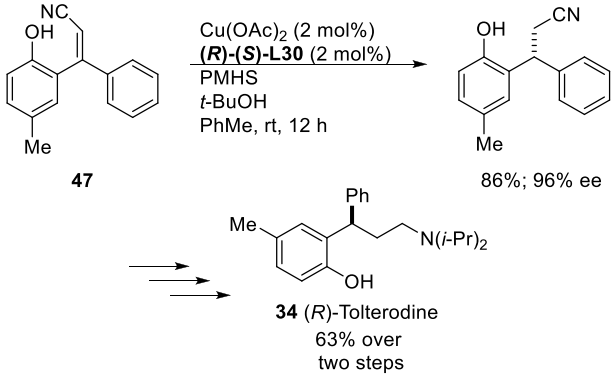
10. ASYMMETRIC REDUCTIVE COUPLING OF ALDEHYDES AND KETONES WITH OLEFINS, ACETYLENES, AND ALLENES

Silanes can serve as stoichiometric hydrogen donors via the formation of CuH in reductive couplings of aldehydes and ketones with olefins. In practice, styrene derivatives have provided the greatest degree of success; similarly, results are

Scheme 135. Additional Asymmetric PMHS Hydrosilylation of (*E*)-β,β-Diaryl Unsaturated Nitriles with Cu-(*R*)-(*S*)-L33



Scheme 136. Asymmetric PMHS Reduction Applied to a Synthesis of (*R*)-Tolterodine 34



better with arylalkynes as opposed to alkyl acetylenes, as the aryl groups increase the reactivity and the regioselectivity of the coupling. In addition, recent work has expanded the coupling of aldehydes and ketones to allenes to provide nonracemic homoallylic alcohol synthons. The reactions are proposed to proceed through the formation of an intermediate nonracemic Cu−H species into which the olefin inserts. The resulting intermediate organocuprate then adds to an aldehyde or ketone.

Buchwald et al. successfully performed the two-step hydroacylation−asymmetric reduction between aryl carboxylic acid anhydrides and vinyl arenes.[133] The reaction was shown to occur via an initial hydroacylation followed by the asymmetric reduction of the intermediate ketone to produce vicinal stereocenters (Scheme 137). The reaction did not occur with anhydrides of aliphatic acids, which produced a simple reduction of the acid anhydride. Vinyl arenes with electron-withdrawing groups performed poorly compared to those with electron-donating substituents. By lowering the temperature and eliminating the addition of triphenylphosphine, it proved

https://doi.org/10.1021/acs.oprd.1c00073
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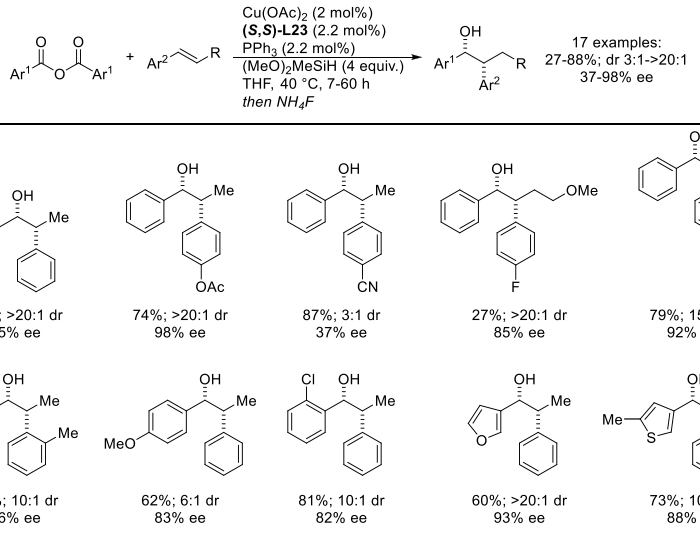
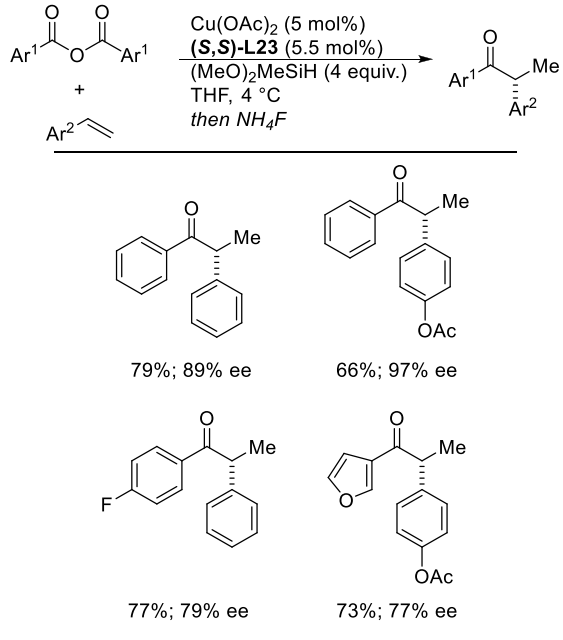
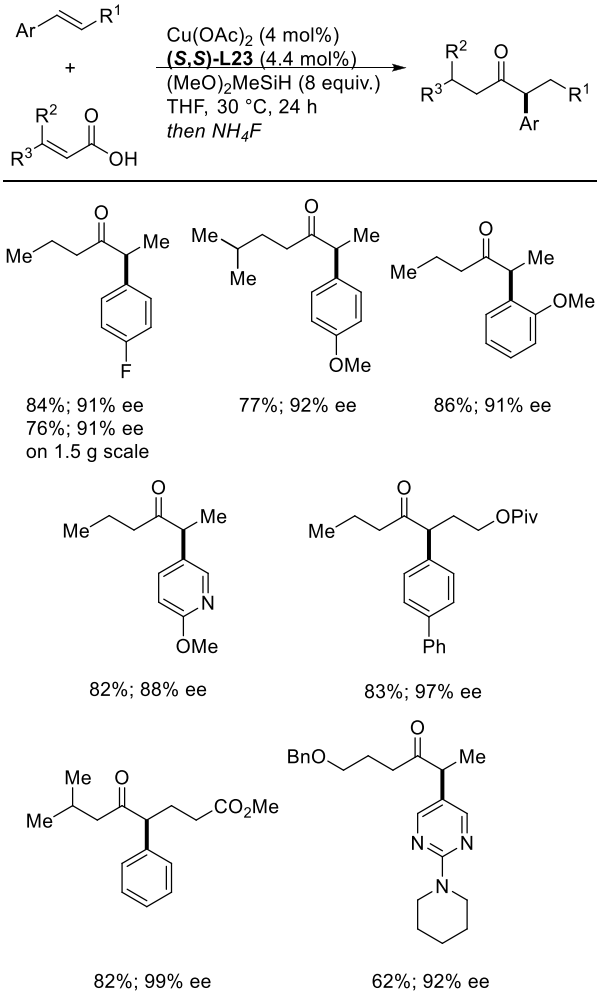
Scheme 137. Asymmetric Cu-Catalyzed Dimethoxymethylsilane Reductive Coupling of Styrenes with Acid Anhydrides: Diastereo- and Enantioselective Synthesis of β-Aryl Benzyl Alcohols



Scheme 138. Asymmetric Reductive Coupling of Benzoic Anhydrides with Vinylarenes: Enantioselective Synthesis of α-Aryl Ketones



Scheme 139. Asymmetric Dimethoxymethylsilane Reductive Coupling of Styrenes with α,β-Acids with Cu-(*S,S*)-L23



possible to isolate the intermediate ketone thereby providing chiral α-phenyl aryl ketones (Scheme 138). The asymmetric reduction of an α-chiral ketone resulted in the highly diastereo- and enantioselective formation of a β-chiral alcohol.

Buchwald et al. followed the aforementioned study with the direct asymmetric, three-component, CuH-catalyzed reductive coupling of α,β-unsaturated carboxylic acids with vinyl arenes (Scheme 139).[134] The reaction did not work with acrylic acid; however, employing (*E*)-β-ethoxyacrylic acid as a surrogate produced the ethyl ketones (Scheme 140).

Lam et al. explored reductive couplings of 2-alkenylazaarenes with cyclic and acyclic prochiral ketones, resulting in C−C bond formation at the benzylic position (Scheme 141).[135] The reactions proceeded in modest to good yield and with high ee's.

Two *bis*-phosphine ligands, **L39** and (*S,S*)-**L25**, provided stereochemistry to the Cu catalyst. In general, the greater the

https://doi.org/10.1021/acs.oprd.1c00073
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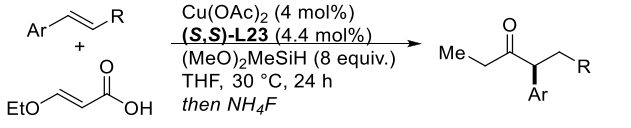
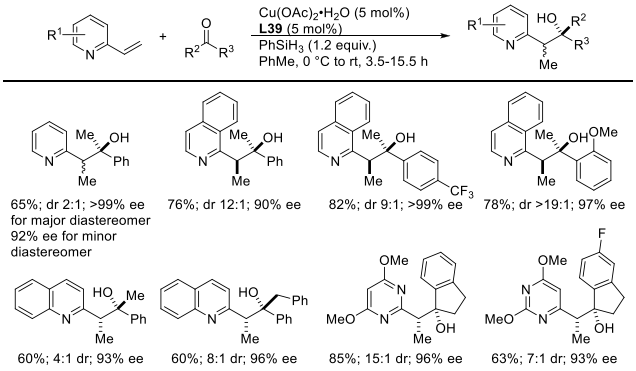
Scheme 140. Asymmetric Reductive Coupling of a Styrene and an α,β-Unsaturated Acid

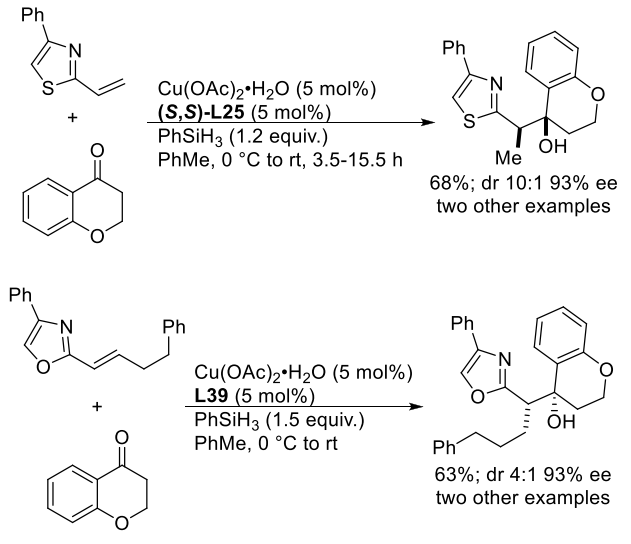


R = Me; Ar = 4-MeOC$_6$H$_4$:
66%; 95% ee
R = CH_2CH_2OPiv; Ar = 4-Ph-C$_6$H$_4$:
60%; 95% ee

Scheme 141. Cu-Catalyzed Asymmetric Phenylsilane Reductive Coupling of Vinylheteroarenes with Ketones: Diastereo- and Enantioselective Synthesis of β-(Het)aryl Alcohols



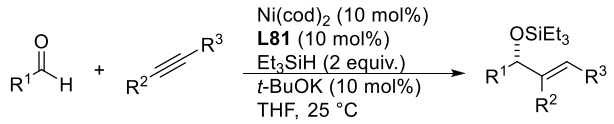
Scheme 142. Asymmetric Cu-Catalyzed Phenylsilane Reductive Coupling of Vinylheteroarenes

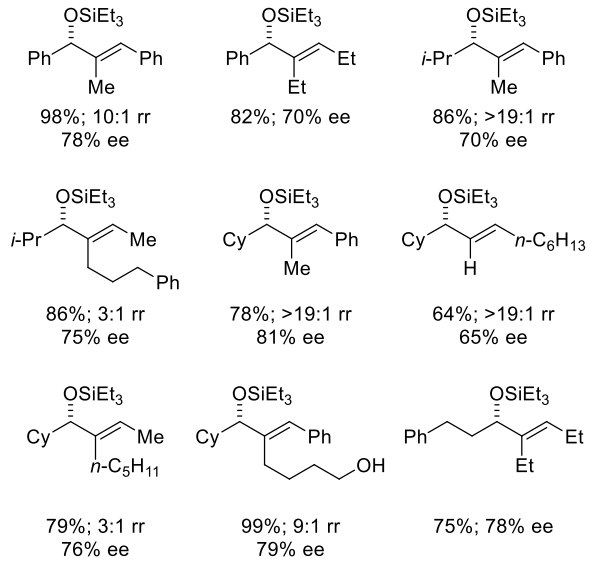


bulk of the azaarene, the better the diastereomeric ratio and other *N*-containing heterocycles are tolerated (Scheme 142).

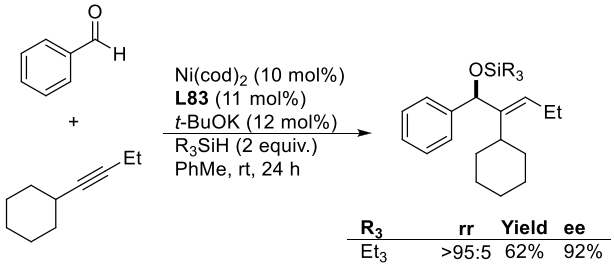
Montgomery et al. reported that a Ni-catalyzed triethylsilane asymmetric reductive coupling of an aldehyde and an alkyne produced the triethylsilylated allylic alcohol with good regioselectivity, yield and ee values (Scheme 143).[136] The aryl substituent of NHC ligand **L81** was critical for high enantioselectivity. Regioselectivity was influenced by the two alkyne substituents; an alkyne with an aryl and alkyl group was

Scheme 143. Asymmetric Triethylsilane Hydrosilylative Coupling of Alkynes with Aldehydes and Ni-L81





Scheme 144. Asymmetric Silane Reductive Coupling of Alkynes with Aldehydes and Ni-L83: Enantioselective Synthesis of Nonracemic Silylated Allyl Alcohols



R_3	rr	Yield	ee
Et_3	>95:5	62%	92%
t-BuMe_2	>95:5	80%	92%

optimal, while examples with two small alkyl groups exhibited poor regioselectivity.

Expanding on earlier studies, the Montgomery group carried out the three-component hydrosilylative enantioselective coupling between acetylenes and aldehydes to furnish silylated allyl alcohols. Multiple NHC substituent patterns were investigated, with **L83** being an excellent candidate for the source of the enantioselectivity.[146] This study demonstrated significantly improved ee values compared to previous work on the transformation.[137] *tert*-Butyldimethylsilane proved to be the optimal silane, although triethylsilane also worked well (Scheme 144). In contrast to previous reactions, unsymmetrical alkynes displayed reversed regioselectivity-favored coupling adjacent to the larger of the two groups, with regioselectivity ratios (rr) typically being >95:5 (Scheme 145). Further experimentation demonstrated the strong effect that ligand sterics have on regioselectivity, with some examples displaying a complete reversal of regioselectivity. Curiously, regioselectivity was >95:5 for 3-alkylated propynes, i.e., those containing one methyl group, but the enantioselectivity was less than 38%. The reaction

https://doi.org/10.1021/acs.oprd.1c00073
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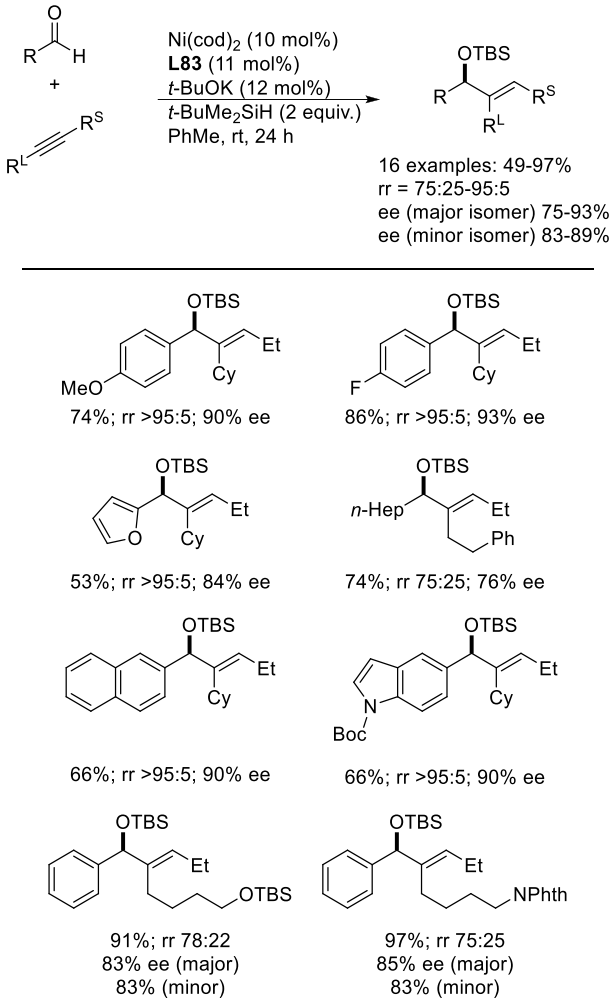
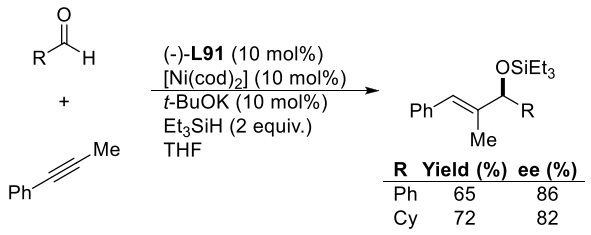
Scheme 145. Asymmetric Silane Reductive Coupling of Aldehydes and Internal Acetylenes with Ni-L83: Enantioselective Synthesis of Nonracemic TBS-Protected Allyl Alcohols



Scheme 146. Asymmetric Triethylsilane Reductive Coupling of Alkynes with Aldehydes and Ni-L91: Enantioselective Synthesis of TES-Protected Allyl Alcohols

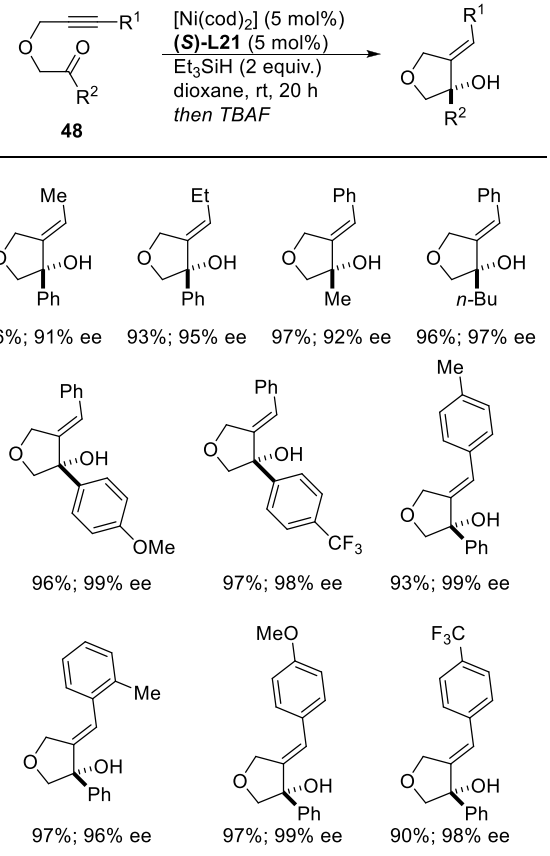


R	Yield (%)	ee (%)
Ph	65	86
Cy	72	82

of the simple monosubstituted acetylene ethynylcyclohexane produced a 72% yield and >95:5 rr, but with a very low 13% ee.

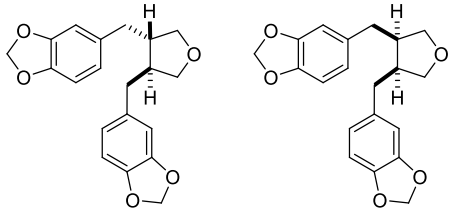
Scheidt et al. developed the planar azolium ferrocene salt catalyst **L91**, which brought about the Ni-catalyzed Et_3SiH reductive coupling of phenylpropyne with benzaldehyde or cyclohexanecarboxaldehyde (Scheme 146).[138] The regioselectivity of the coupling was excellent at >20:1 (benzaldehyde) and 10:1 (cyclohexanecarboxaldehyde) and was accompanied by good yields and ee's. The work represents a new chiral *N*-heterocyclic carbene ligand scaffold with potential for expanded utility in asymmetric catalysis.

Scheme 147. Triethylsilane Internal Reductive Coupling of Alkynones with Ni-(*S*)-L21 and Ni-L11: Synthesis of Cyclic Allyl Alcohols



Tang et al. applied a very efficient enantioselective reductive cyclization of alkynones **48**, which proved possible under Ni catalysis in the presence of either chiral phosphine ligand (*S*)-**L21** or **L11**.[139] The yields and ee's were impressively and consistently high (Scheme 147). The developed transformation was used in a short synthesis of a mixture of (*S*)-(+)-dehydroxycubebin **50** and *cis*-dehydroxycubebin **51** (Scheme 148).

Scheme 148. (+)-Dehydroxybubebin 49 and *cis*-Dehydroxycubebin 50



49, (+)-dehydroxycubebin **50**, *cis*-dehydroxycubebin

Buchwald et al. applied asymmetrically ligated CuH, generated in situ from an organosilane, $Cu(OAc)_2$ and *bis*-phosphine ligand **L92** to catalyze the coupling of prochiral ketones with monosubstituted allenes, producing optically active 3-substituted homoallylic alcohols with modest diastereoselectivity and high enantioselectivity (Scheme 149).[140]

https://doi.org/10.1021/acs.oprd.1c00073
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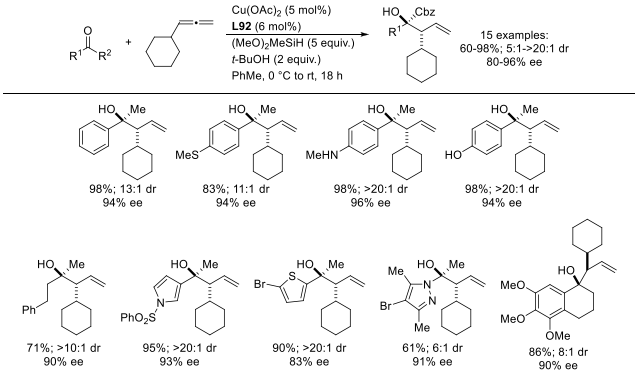
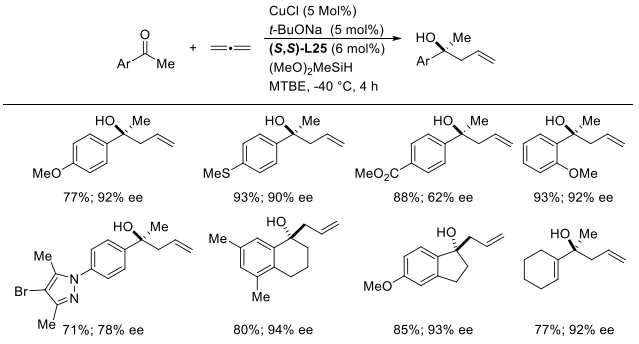
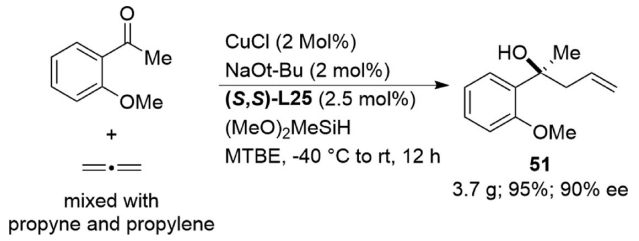
Scheme 149. Asymmetric Dimethoxymethylsilane Reductive Coupling of Allenes with Ketones and Cu-L92: Enantioselective Synthesis of Homoallylic Alcohols



Scheme 150. Dimethoxymethylsilane Reductive Coupling of Allenes with Ketones and Cu-(*S*,*S*)-L25: Synthesis of Homoallylic Alcohols



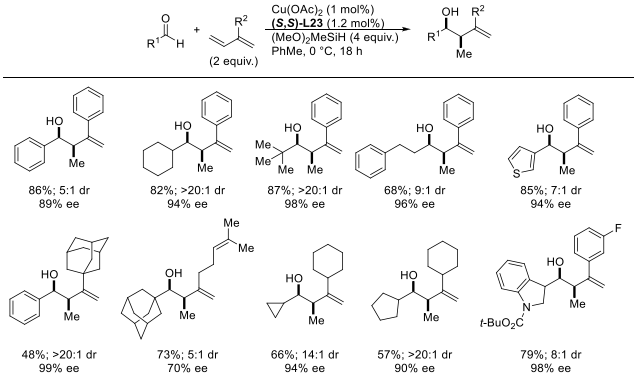
Scheme 151. Cu-Catalyzed Dimethoxymethylsilane Asymmetric Reductive Coupling of Aryl Ketones with Allene: Synthesis of Chiral Allyl Benzyl Alcohols



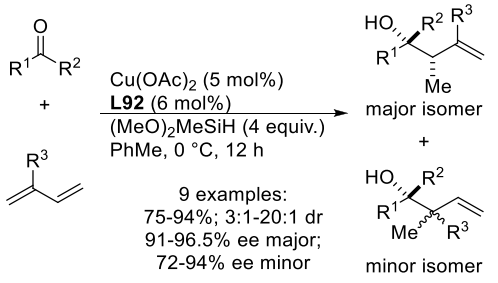
Regioselectivity favored the branched homoallylic alcohol almost exclusively. The reaction proved tolerant of hydroxyl, ester, Cl, Br, sulfone, tetrazole and amide functionalities. A minor correction to this work was submitted.[141]

Buchwald et al. extended the allene-derived allylation to allene itself (Scheme 150).[142] Allene is a gas that is produced in large amounts as a byproduct of the cracking process in petroleum refinement. Moreover, because allene is produced as a C3 component of the cracking process, it is mixed with propylene and propyne. It was thus of interest to investigate the use of the mixture as a source of allene, since the separation of the allene is difficult and not carried out industrially. Indeed, using the mixture provided comparable results, indicating a high preference for the CuH addition to allene over that to propyne or propylene (Scheme 151). This protocol was scaled to yield 3.7 g of **51**.

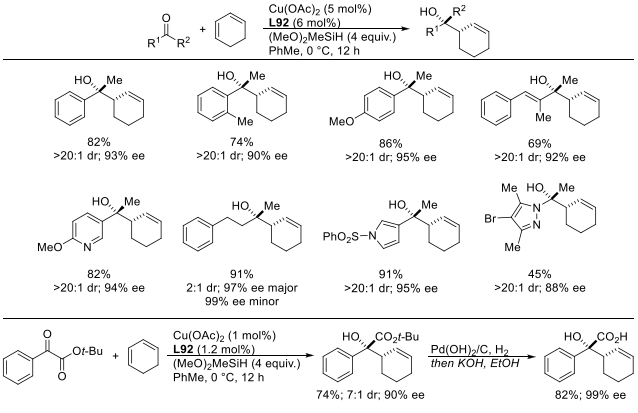
Scheme 152. Asymmetric Dimethoxymethylsilane Reductive Coupling of 2-Substituted 1,3-Dienes with Aldehydes and Cu-(*S*,*S*)-L23: Diastereo- and Enantioselective Synthesis 3-Methylhomoallylic Alcohols



Scheme 153. Dimethoxymethylsilane Reductive Coupling of Allenes with Ketones and Cu-L92: Applications to the Synthesis of Biologically Active Homoallylic Alcohols



Scheme 154. Asymmetric Dimethoxymethylsilane Reductive Coupling of Ketones with 1,3-Cyclohexadiene and Cu-L92



Buchwald et al. were able to minimize the direct reduction of the aldehyde in the CuH-catalyzed asymmetric reductive coupling of aldehydes and 2-substituted 1,3-dienes via the slow addition of a 2-fold excess of diene as well as by keeping the temperature at 0 °C (Scheme 152).[143] This resulted in moderate to good yields and diastereoselectivities, and with very good enantioselectivities. DFT analysis was used to explain the diastereoisomeric preference.

Buchwald et al. performed the asymmetric synthesis of homoallylic alcohols from ketones and 1,3-dienes under Cu-catalysis and employing the *bis*-phosphine ligand **L92**. The regioselectivity was excellent, with nearly all examples showing

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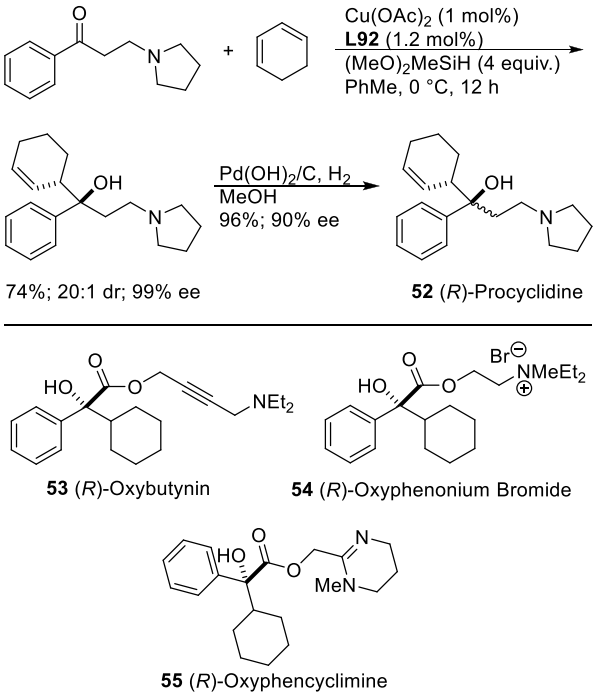
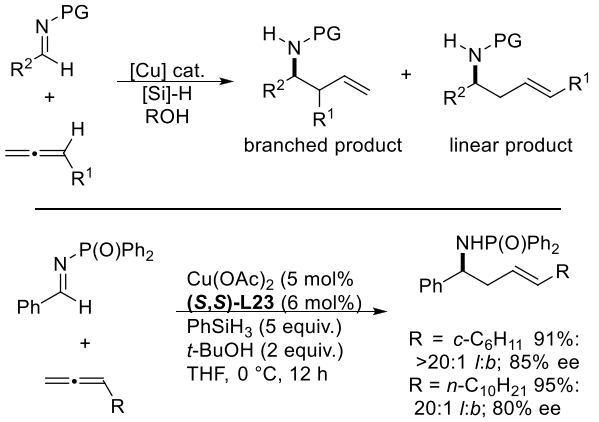
Scheme 155. Some Biologically Active Compounds Prepared via the Asymmetric Reductive Coupling of Ketones with 1,3-Cyclohexadiene as a Key Step



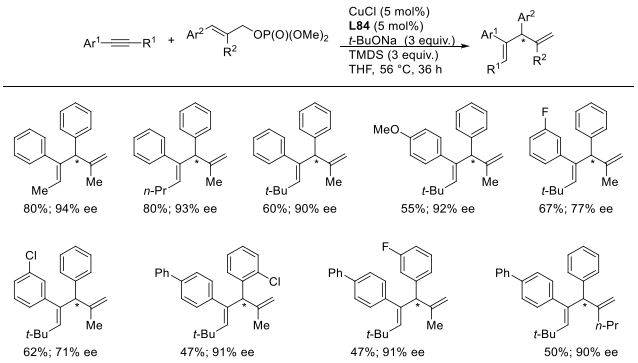
Scheme 156. Asymmetric Phenylsilane Reductive Coupling of Allenes with Imines and Cu-(*S*,*S*)-L23: Enantioselective Synthesis of Homoallylic Amines



>20:1; ee values were generally >90% (Scheme 153 and Scheme 154).[144] A number of interesting examples derived from 1,3-cyclohexadiene were prepared, including (*R*)-procyclidine **52**, which is used in the treatment of Parkinson's disease and to three anticholinergenic agents: (*R*)-oxybutynin **53**, (*R*)-oxyphenonium bromide **54** and (*R*)-oxyphencyclimine **55** (Scheme 155).

In using monosubstituted allenes as the allylating reagent for the Cu-catalyzed allylation of imines, one must address the question of linear versus branched allylation. Buchwald et al. demonstrated that the regioselectivity could be differentiated through use of the protecting group (PG) on the imine (Scheme 156).[145] Thus, imines protected with the benzyl and related groups produced high yields of the branched isomers (*syn*:*anti* 5:1−16:1), while those protected with the diphenylphosphinoyl group produced <2% of the branched isomers, instead strongly favoring the linear product as the (*E*)-isomer (*E*:*Z* > 20:1). Two asymmetric examples of the $PhSiH_3$-promoted branched reaction were presented.

Scheme 157. Asymmetric Phenylsilane Reductive Coupling of Allyl Phosphonates and Alkynes with Cu-L84: Enantioselective Synthesis of 3-Arylated 1,4-Dienes

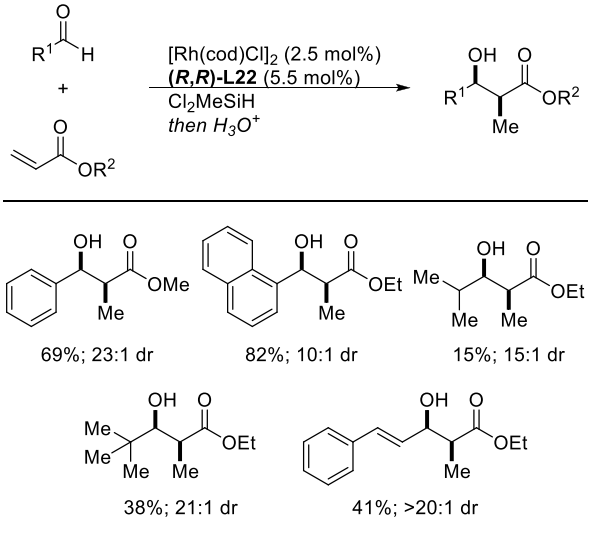


An asymmetric hydroallylation of aryl-alkyl alkynes to form highly substituted 3-chiral 1,4-dienes in modest-to-good yield and with good-to-excellent enantioselectivity has been presented (Scheme 157).[146] The reaction occurs under the catalysis of CuH with chiral NHC ligand **L84**, catalysis with an allyl phosphate providing the allyl moiety with the regioselectivity-favoring addition of the Cu to the aryl terminus of the alkyne.

11. ASYMMETRIC REDUCTIVE COUPLING OF ALDEHYDES AND KETONES WITH α,β-UNSATURATED ESTERS

In asymmetric coupling reactions between aldehydes or ketones and unsaturated esters, the reaction proceeds through the initial addition of a Cu−H species to the olefin, thereby forming an ester cuprate. The organocuprate subsequently adds to the carbonyl of the aldehyde or ketone to produce a nonracemic β-

Scheme 158. Dichloromethylsilane Asymmetric Reductive Coupling of Aldehydes with Unsaturated Esters with Rh-(*R*,*R*)-L22: Diastereo- and Enantioselective Synthesis of 3-Methyl-4-hydroxy Esters



https://doi.org/10.1021/acs.oprd.1c00073
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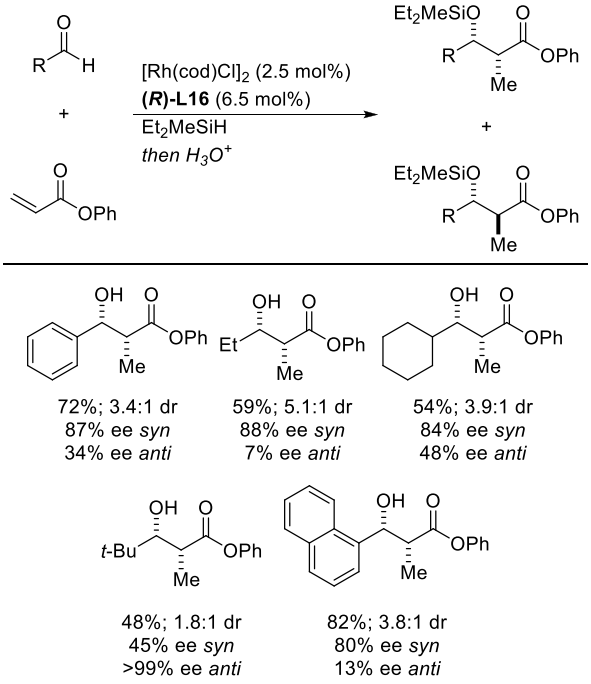
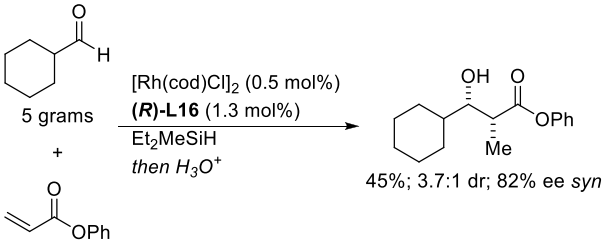
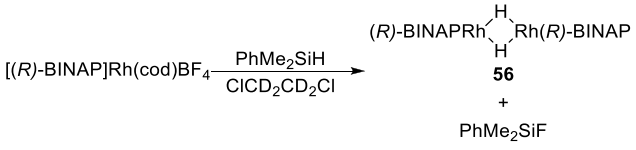
Scheme 159. Diethylmethylsilane Reductive Coupling of Aldehydes with Unsaturated Esters Using Rh-(*R*)-L16: Diastereoselective and Enantioselective Synthesis of 3-Methyl-4-(Diethylmethylsilyloxy)esters



Scheme 160. Large-Scale Asymmetric Rh-Catalyzed Diethylmethylsilane Reductive Coupling of Cyclohexylcarbaldehyde with Phenyl Acrylate with Rh-(*R*)-L16

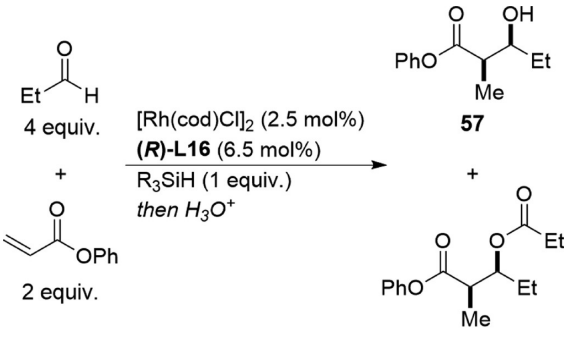


Scheme 161. Synthesis of (*R*)-BINAP-Rhodium Catalyst 56



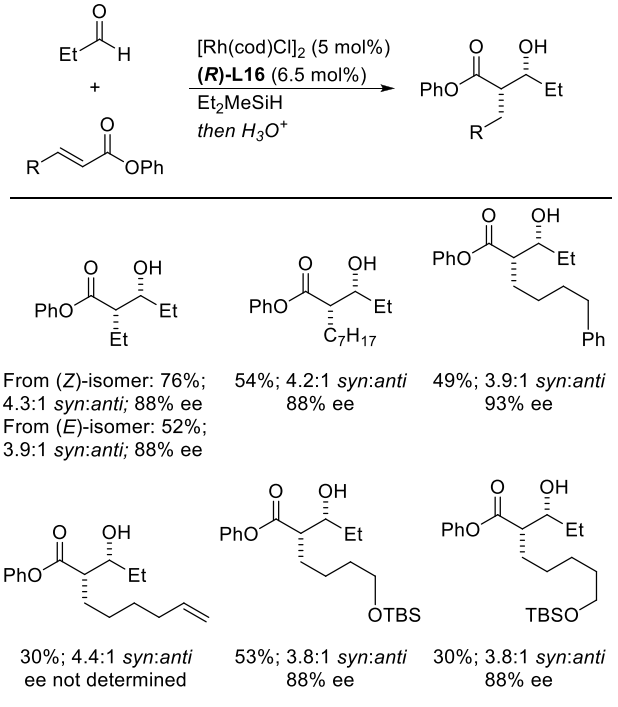
hydroxy (or silyloxy) ester. When rendered enantioselective, the reactions provide useful processes in which a new C−C bond is formed with vicinal stereocenters. Traditional methods for undertaking such coupling often require the quantitative formation of an enolate species (e.g., Mukaiyama aldol additions), chiral auxiliaries, and use of Lewis acid catalysts ($TiCl_4$) and typically lack strong diastereomeric control of products (often <4:1). As a consequence, accessing enolate species directly from α,β-unsaturated species under catalytic hydrometalation conditions presented an attractive synthetic target.

Scheme 162. Asymmetric Organosilane Reductive Coupling of Aldehydes and Phenylacrylate with Rh-(*R*)-L16: Diastereo- and Enantioselective Synthesis of 2-Methyl-3-hydroxy Esters

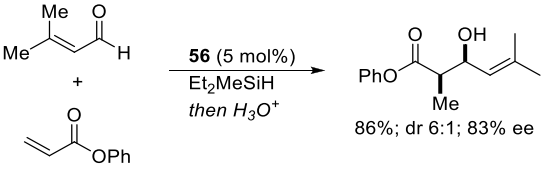


Silane	57 (%)	57 ee (%)	58 (%)	58 ee(%)
Et_2MeSiH	23	82	42	82
$PhMe_2SiH$	18	80	48	80
$(EtO)Me_2SiH$	0	--	29	78

Scheme 163. Asymmetric Organosilane Reductive Coupling of Aldehydes and α,β-Unsaturated Esters with Rh-(*R*)-L16: Diastereo- and Enantioselective Synthesis of 2-Alkyl-3-hydroxy Esters

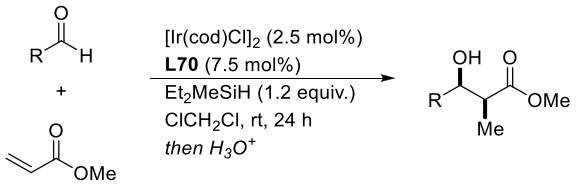


Scheme 164. Asymmetric Diethylmethylsilane Reductive Coupling of 3-Methylbutenal and Phenyl Acrylate with 56



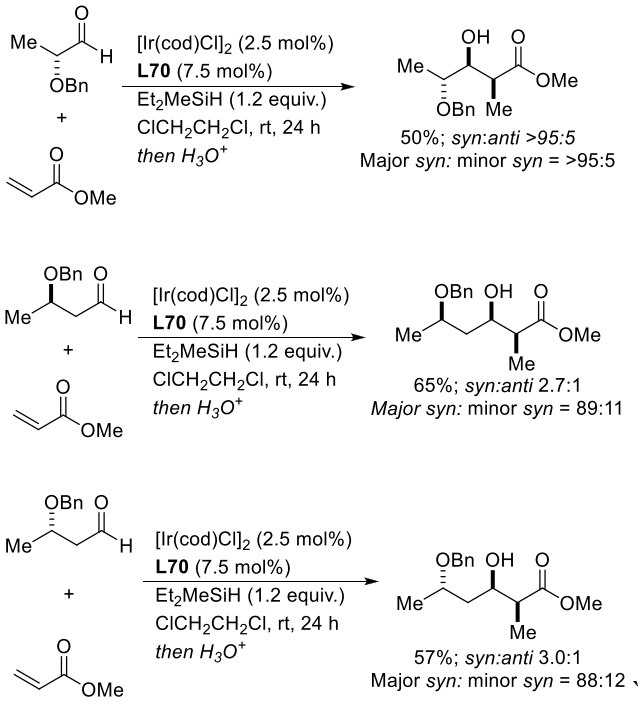
https://doi.org/10.1021/acs.oprd.1c00073
Org. Process Res. Dev. 2021, 25, 1719−1787

Scheme 165. Silane Reductive Coupling of Aldehydes and Unsaturated Esters with Ir-L70: Diastereo- and Enantioselective Synthesis of 3-Methyl-4-hydroxy Esters



R	Yield (%)	*syn*:*anti*	ee (%)
Ph	68	6.6:1	94
$BnOCH_2$	49	9.9:1	96
$TBSOCH_2$	47	8.2:1	96
Et	<5	nd	nd
$BnOCH_2CH_2$	65	2.7:1	82
(*E*)-PhCH=CH	nr	na	na

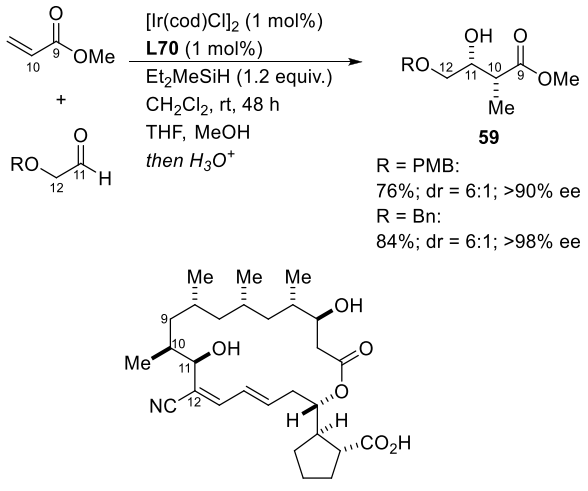
Scheme 166. Diethylmethylsilane-Mediated Diastereo- and Enantioselective Reductive Coupling of Nonracemic Aldehydes with Methyl Acrylate



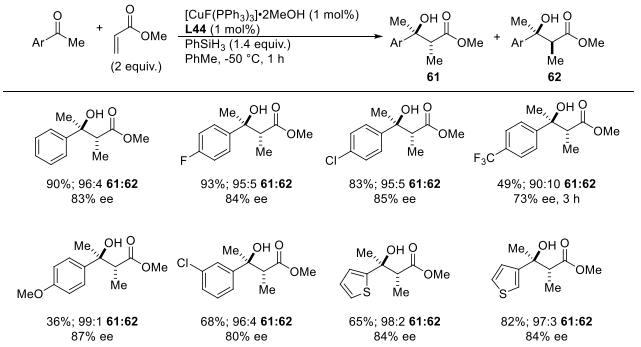
Based on initial studies of the metal-catalyzed, organosilane-mediated diastereoselective reductive aldol reaction between aldehydes and methyl methacrylate, Taylor and Morken proceeded to develop an enantioselective format for the three-component C−C bond forming transformation.[147] The work was enhanced by a thorough optimization study of a high-throughput evaluation of 192 combinations of silane, metal and ligand. The screening led to the choice of Rh, (*R,R*)-Me-DuPhos (***R,R*)-L22** and dichloromethylsilane as the optimal combination (Scheme 158). While the *syn*-diastereoselectivity was good, the enantioselectivity was disappointing, warranting future improvements.

Building on their initial comprehensive screening studies, the Morken team was able to achieve a practical enantioselective reductive coupling using a rhodium catalytic system derived from (*R*)-BINAP (***R*)-L16**, $Rh(cod)Cl]_2$ and Et_2MeSiH.

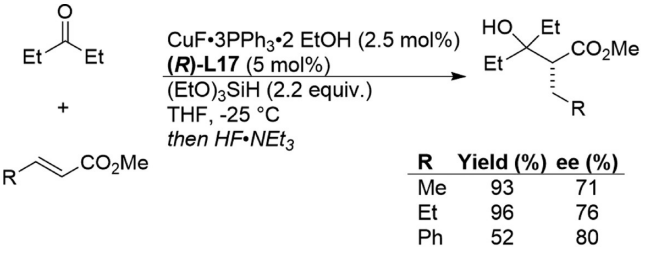
Scheme 167. Asymmetric Silane Reductive Coupling of Alkoxy Acetaldehyde and Methyl Acrylate with Ir-L70: Synthesis of Borrelidine 60



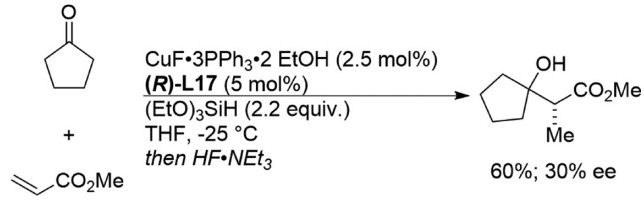
Scheme 168. Asymmetric Phenylsilane Reductive Coupling of Acetophenones and Methyl Acrylate with Cu-L44: Diastereo- and Enantioselective Synthesis of Methyl 3-Methyl-4-aryl-3-hydroxybutyrates 61 and 62



Scheme 169. Triethoxysilane Asymmetric Reductive Coupling of Ketones and Methyl Acrylates with Cu-(*R*)-L19: Diastereoselective and Enantioselective Synthesis of Methyl 3-Alkyl-4,4-dialkyl-3-hydroxybutyrates

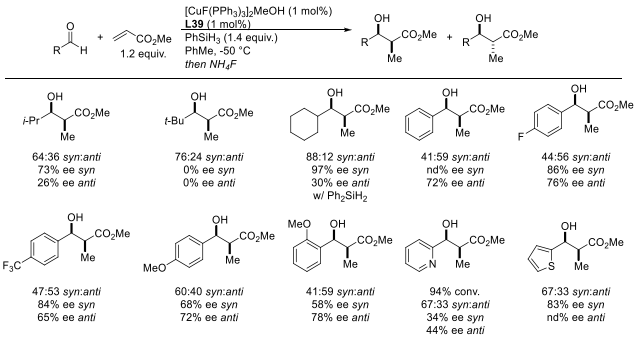


R	Yield (%)	ee (%)
Me	93	71
Et	96	76
Ph	52	80

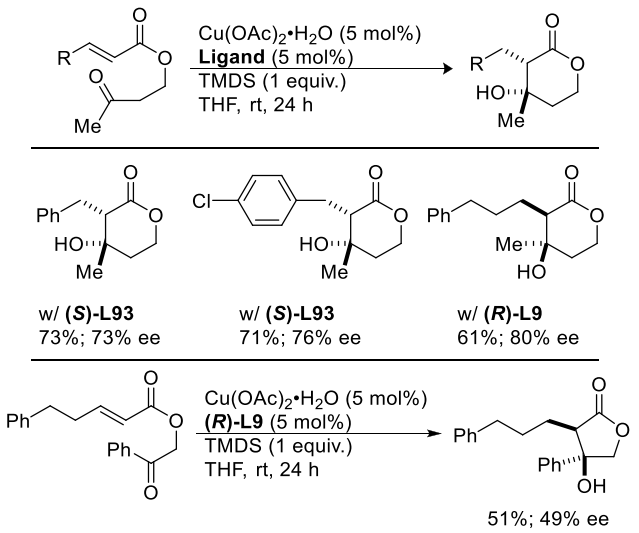


https://doi.org/10.1021/acs.oprd.1c00073
Org. Process Res. Dev. 2021, 25, 1719−1787

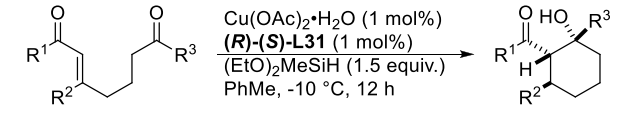
Scheme 170. Organosilane Reductive Coupling of Aldehydes and Methyl Acrylate with Cu-L39: Diastereoselective and Enantioselective Synthesis of 2-Methyl-3-alkyl-3-hydroxy Esters



Scheme 171. TMDS Asymmetric Reductive Cyclic Coupling of Keto Unsaturated Esters with Cu-(*R*)-L9 and (*S*)-L93: Diastereoselective and Enantioselective Synthesis of *α*-Alkyl-*β*-hydroxy-*γ*-lactones



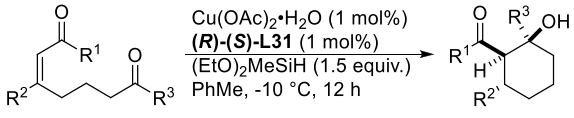
Scheme 172. Diethoxymethylsilane Asymmetric Reductive Cyclic Coupling of (*E*)-Configured Keto Unsaturated Esters with Cu-(*R,S*)-L31: Diastereo- and Enantioselective Synthesis of Highly-Substituted Cyclohexanols



R^1	R^2	R^3	Yield (%)	ee (%)
Me	Me	Me	91	96
Me	Me	Ph	77	97
Ph	Me	Me	98	85
n-Bu	Ph	Me	83	77

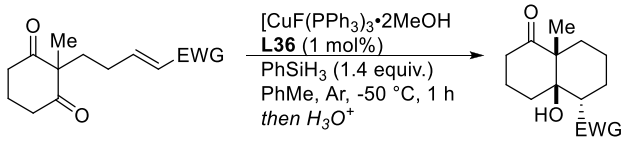
Applying the reaction conditions to the coupling of various aldehydes to phenyl acrylate produced reasonable yields of aldol products exhibiting modest diastereoselectivities favoring the *syn* adduct (Scheme 159). The enantioselectivity for the *syn* product was quite good in most cases, with the notable exception of pivaldehyde, which produced the *anti*-diastereomer in >99% ee.[148] Unexpectedly, cinnamaldehyde produced no reaction

Scheme 173. Asymmetric Diethoxymethylsilane Asymmetric Reductive Cyclic Coupling of (*Z*)-Configured Keto Unsaturated Esters with Cu-(*R,S*)-L31: Diastereo- and Enantioselective Synthesis of Highly-Substituted Cyclohexanols



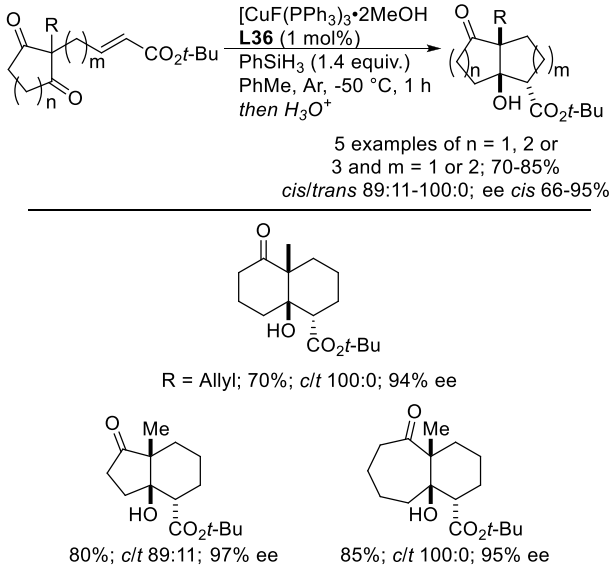
R^1	R^2	R^3	Yield (%)	ee (%)
Me	Me	Me	88	96
Me	Me	Ph	75	97
i-Pr	*i*-Pr	Me	66	84
Ph	Me	Me	98	75
n-Bu	Ph	Me	92	64

Scheme 174. Diethoxymethylsilane Reductive Cyclic Coupling of Keto Unsaturated Esters with Cu-L36: Diastereo- and Enantioselective Synthesis of *β*-Hydroxybicyclics



EWG	Yield (%)	*cis*/*trans*	*cis* (*trans* ee) (%)
CO_2Et	80	82:18	92 (33)
CO_2Me	75	72:28	84 (60)
CO_2t-Bu	80	100:0	95 (nd)
CN	85	100:0	0
C(O)Me	75	100:0	65 (nd)

Scheme 175. Asymmetric Cu-Catalyzed Reductive Cyclizations with Phenylsilane



under the standard protocol, despite the substrate reacting to previous iterations of the catalytic system. The reaction proved suitable for scale-up, as demonstrated by a 5-g scale reaction of cyclohexanecarboxaldehyde (Scheme 160).

Morken et al. undertook further expansion of the Rh-catalyzed asymmetric reductive aldol protocol by demonstrating

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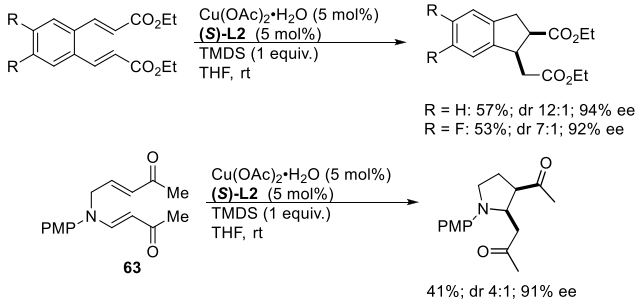
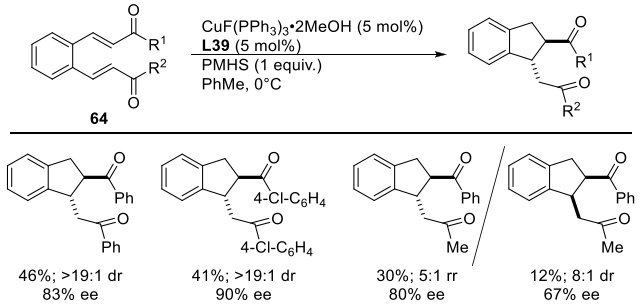
Scheme 176. TMDS Reductive Cyclic Coupling of Bis Unsaturated Esters with Cu-(*S*)-L2: Diastereoselective and Enantioselective Synthesis of Diesters



Scheme 177. Diastereo- and Enantioselective PMHS Reductive Cyclization of Benzodienones 64 with Cu-L39



that the key hydride contributing species was rhodium hydride **56**, produced in situ from the organosilane (Scheme 161).[149] This allowed the scope of the reaction to be expanded to include α,β-unsaturated aldehydes and β-substituted acrylates. Key to the reaction was the ability to find reaction conditions that allowed for the aldol sequence without direct reduction of the aldehyde or the methacrylate, reactions known to take place with organosilanes under certain conditions. Interestingly, initial studies showed that a small amount of the esterified β-hydroxy ester was formed when employing a 1:1 ratio of acrylate-to-aldehyde. The use of additional molar levels of aldehyde and $(EtO)Me_2SiH$ resulted in increased ester formation (Scheme 162). The ester was formed in the same diastereomeric and enantiomeric ratios as the free β-hydroxy ester, indicating that the esterification occurred after the aldol condensation step. Multiple examples were presented (Scheme 163), and 3-methyl-2-butenal reacted well (Scheme 164).

Morken et al. further demonstrated that Ir-PyBOX catalysis of the reductive aldol reaction of aldehydes with methyl acrylate produced aldol adducts with good enantio- and diastereoselectivities, complementing work with Rh systems (Scheme 165).[150] The diastereomer produced was dependent on starting geometry (Scheme 166). Best results were obtained with α- and β-alkoxy aldehydes, while propionaldehyde reacted in very low yield and cinnamaldehyde failed to react. The reaction proved to be strongly ligand-dependent, with simpler bis(oxazolines) and pyridine oxazoline either producing no reaction or only a simple, direct reduction of the carbonyl.

This successful protocol was then applied to the early steps in an asymmetric synthesis of the macrolide borrelidin **60**, a natural product with potential anticancer activity. The reductive aldol coupling of methyl acrylate and *p*-methoxybenzyl acetaldehyde produces the β-hydroxy ester **59** which constitutes the C9−C12 fragment of the natural product (Scheme 167).[151]

Cu(I) ligated with ferrocene ligand **L44** (termed ClickFerrophos) and $PhSiH_3$ as a hydride provider accomplished the asymmetric reductive aldol transformation of acetophenones with methyl acrylate (Scheme 168).[152] The reaction favored the *erythro* diastereomer, with high enantioselectivity.

Kanai and Shibasaki developed a three-component reductive aldol reaction between acetophenone and methyl acrylate. The reaction was catalyzed by copper complexed with (*R*)-*tol*-BINAP (***R*)-L19** in the presence of $(EtO)_3SiH$, which generated very modest diastereoselectivity (44:56−71:29) and low ee values (1−30%).[153] Significant improvement was achieved with the combination of a symmetrical ketone and a β-substituted acrylate in which only a single asymmetric center is produced (Scheme 169). When this modified protocol was applied to the condensation of acetophenones and allenic esters, the ee values were very high (5 examples: 87−99% ee) but the chemical yields were low (23−47%).

Riant et al. established a $CuH/PhSiH_3$ reductive aldol reaction of methyl acrylate to that with aldehydes.[154] The yields were very high, with modest diastereoselectivities but high ee's of the predominant diastereomer (Scheme 170). In addition, the TOF reached a very high value of 40,000 per hour. Some reduction of the aldehyde occurred, but this was minimal with TaniaPhos **L39**, which led to high conversions. The bulky substituent pivaldehyde produced good conversion and a 3:1 dr but generated racemic diastereomers.

Lam and Joensuu applied an intramolecular version of the Cu-catalyzed aldol condensation of α,β-unsaturated esters with TMDS as the hydride source to produce functionalized lactones in both modest chemical yields and enantiomeric excesses.[155] Of the five chiral ligands evaluated, (*S*)-MeO-BIPHEP (***S*)-L93**, (*R*)-3,5-xyl-MeO-BIPHEP (***R*)-L9** and (*S*)-SEGPHOS (***S*)-L2** were the best (Scheme 171).

Lipshutz et al. demonstrated that suitable keto enones could be nicely cyclized in a CuH-catalyzed reductive conjugate addition process generating three contiguous stereocenters in high diastereomeric ratios and with high ee's (Scheme 172 and Scheme 173).[156] The stereochemical outcome of the final product was directly dependent on the stereochemistry of the enone portion of the substrate. Diethoxymethylsilane was the reductant of choice.

Riant et al. applied a $Cu/PhSiH_3$/**L36** combination to produce highly functional bicyclic systems via an intramolecular conjugate reductive aldol cyclization route (Scheme 174 and Scheme 175).[157] A number of *bis*-phosphine catalysts were explored, with **L36** proving superior. In attempts to form larger rings, the *tert*-butyl esters of longer chains resulted in the simple reduction of the double bond without cyclization.

A reductive Michael cyclization of suitable bis-α,β-unsaturated esters under $Cu(OAc)_2$/(*S*)-SEGPHOS (***S*)-L2**/TMDS conditions was reported in earlier work from Lam et al.[158] This work was later extended to bis-α,β-unsaturated ketones (Scheme 176). The methyl diketone **63** produced a very modest yield but an excellent ee of the predominant diastereomer. On the other hand, aryl enones **64** produced both modest yields (30−42%) and ee values (52−90%) with **L39**-complexed CuF, and TMDS as the silane reductant (Scheme 177). In this case, the mixed diketone produced a mixture of regioisomers (rr = regioisomeric ratio).

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12. ASYMMETRIC HYDROAMINATION OF OLEFINS

The Cu-catalyzed hydroamination of alkenes and alkynes represents an excellent approach to the synthesis of nonracemic amines. There have been several review articles, which include examples of silane reductants employed in both racemic and asymmetric examples which address this trasnformation.[14,19]

In an interesting intramolecular hydroamination reaction, Buchwald et al. performed asymmetric organosilane reductive cyclization of *ortho* enaminostyrenes under CuH promotion. Ligand (*S*,*S*)-Ph-BPE (***S*,*S*)-L23** proved to be the optimal chiral ligand.[159] The cyclization was highly diastereoselective, with average ee values greater than 90% (Scheme 178).

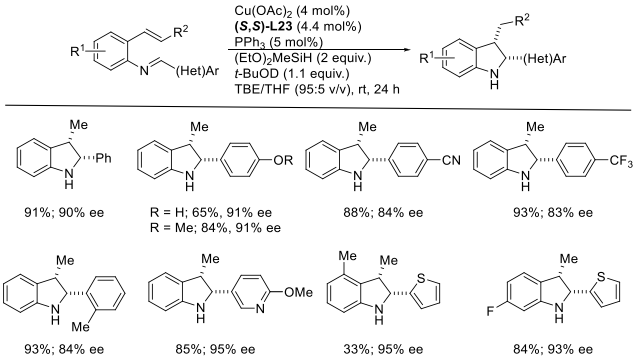
The asymmetric CuH-catalyzed hydroamination of olefins was nicely accomplished by the Buchwald et al. utilizing the benzoate ester of hydroxylamines such as **65**, $(EtO)_2MeSiH$ and (*R*)-DTBM-SEGPHOS (***R*)-L4**.[160] The reaction was used to provide Markovnikov addition of the amine to the double bond (Scheme 179 and Scheme 180). Conversely, application of the reaction conditions to nonactivated terminal alkenes resulted in *anti*-Markovnikov addition. The hydroamination of nonstyrenic terminal olefins with racemic DTBM-SEGPHOS thus produced the terminal aminated product. The asymmetric approach proved to possess high tolerance for structural variations on the aryl ring of vinyl arenes and was good for various hydroxylamine benzoates substituents.

Buchwald et al. extended the hydroamination of nonactivated olefins to the enantioselective synthesis of β-chiral amines. Utilizing prochiral 1,1-disubstituted ethylenes the protocol produced β-chiral ethylamines under catalysis of the CuH complex derived from $(EtO)_2MeSiH$ and chiral ligand (***R*)-L4** or (***S*)-L4** (Scheme 181).[161] The reaction was tolerant of multiple disubstituted amine benzoates as well as a wide variety of olefin substrates. The mechanistic cycle involves regiospecific hydrocupration of the olefin, which is followed by the organocuprate attacking the electrophilic nitrogen. Product release occurs with the formation of copper benzoate, which undergoes reaction with $(EtO)_2MeSiH$ to regenerate the active CuH species.

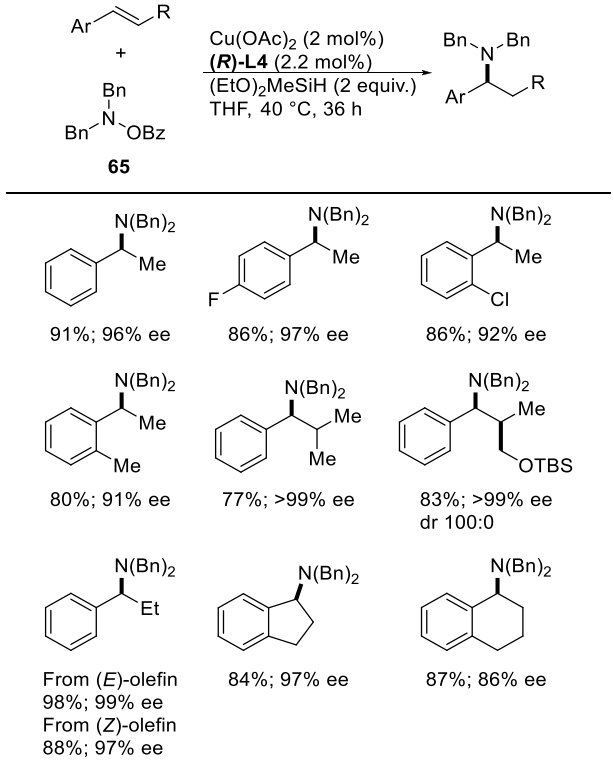
Buchwald et al. also accomplished the asymmetric hydroamination of allylic amines under CuH catalysis. The catalyst $Cu(OAc)_2$/(***R*)-L4**/PPh_3 (known as CuCatMix*) was applied to the hydroamination of allylic amines protected as pivaloyl carboxamides with electrophilic aminating agent **66** (Scheme 182).[162] The reaction produced modest-to-good regioselectivity and excellent ee values for vicinal diamines formation. The reaction's scalability was demonstrated with the preparation of 1.32 g of **67** in 64% yield. The mechanistic aspects of the CuH-catalyzed hydroamination reaction have been studied, with regeneration of the CuH by the silane found to be the rate limiting step.[163]

Based on a successful hydroamination of olefins, Buchwald et al. reported on the asymmetric copper-catalyzed construction of γ-aminoalcohols from enals (Scheme 183).[164] The reaction was catalyzed by CuH ligated with either (***R*)-L4** or (***S*)-L4**. The reaction sequence of hydrosilylation/hydroamination occurred first to reduce the enal in a 1,2-fashion, and second to add the amine function to the resulting silylated allyl alcohol. The reaction sequence resulted in high yields, >20:1 diastereomeric ratios and impressive ee values. In an addendum, the authors also reported the use of ammonium fluoride in the workup procedure prior to evaporation of the volatiles in order to avoid the toxicity (possible blindness) of the dimethoxymethylsilane

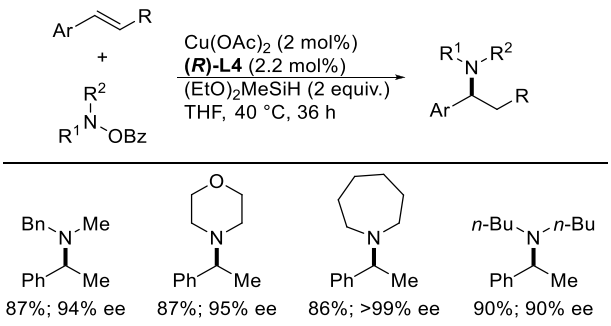
Scheme 178. Asymmetric Reductive Cyclization of *o*-Enaminostyrenes: Diastereo- and Enantioselective Synthesis of 2,3-Disubstituted Indoles



Scheme 179. Asymmetric Hydroamination of Styrenes with Diethoxymethylsilane and Cu-(*R*)-L4



Scheme 180. Asymmetric Hydroamination of Styrene with Diethoxymethylsilane and Cu-(*R*)-L4



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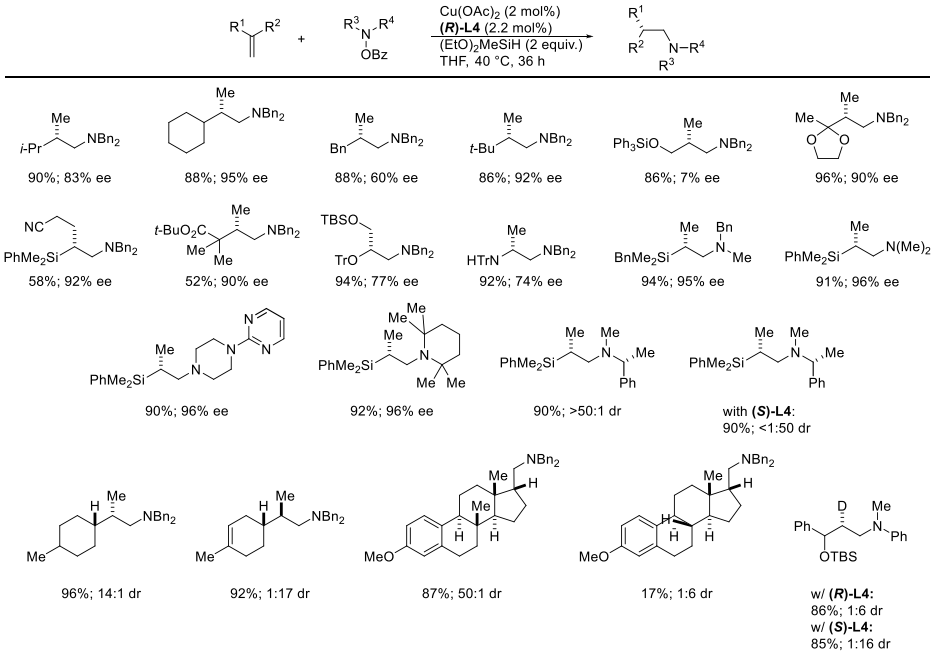
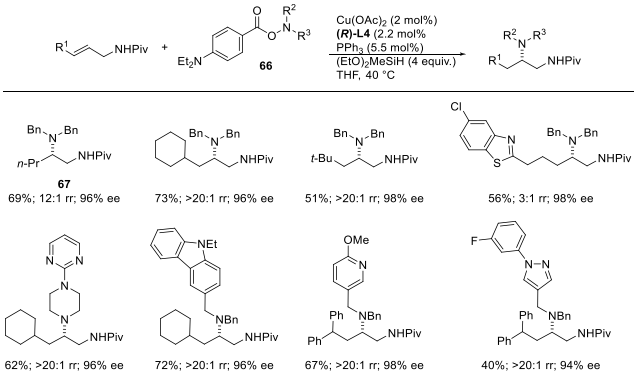
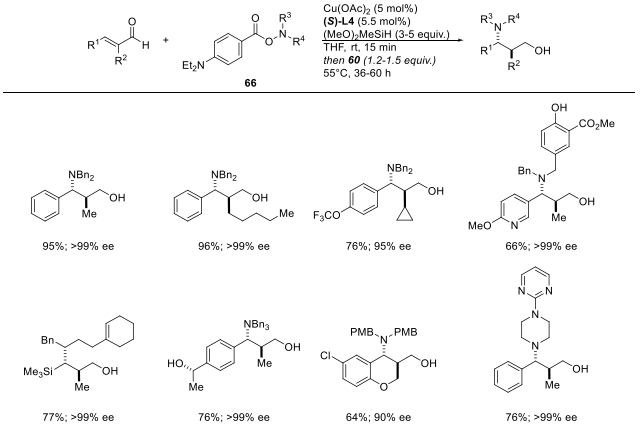
Scheme 181. Asymmetric Hydroamination of 1,1-Disubstituted Olefins with Diethoxymethylsilane and Cu-(*R*)-L4



Scheme 182. Asymmetric Hydroamination of Ally Amines with Diethoxymethylsilane and Cu-(*R*)-L4

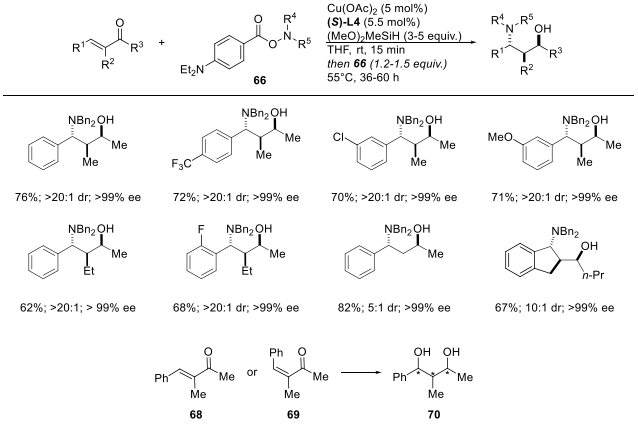


Scheme 183. Asymmetric Hydroamination of Enals with Dimethoxymethylsilane and Cu-(*S*)-L4

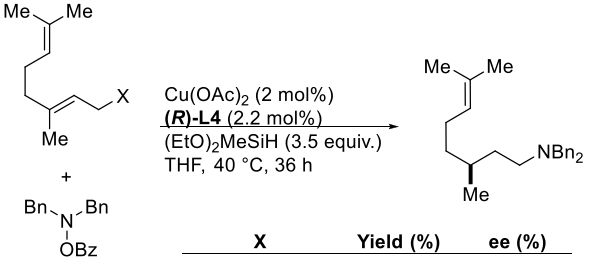


reductant. The reaction was also extended to suitable prochiral enones with excellent results (Scheme 184). Utilizing both

Scheme 184. Asymmetric Hydroamination of Enones with Dimethoxymethylsilane and Cu-(*R*)-L4



Scheme 185. Asymmetric Hydroamination of Allylic Ethers and Esters with Diethoxymethylsilane and Cu-(*R*)-L4



X	Yield (%)	ee (%)
OBn	77	97
O_2COMe	70	98
$OPO(OEt)_2$	80	97
OAc	70	96
OBz	88	98
$O_2C[(p\text{-}Me_2N)C_6H_4]$	92	99

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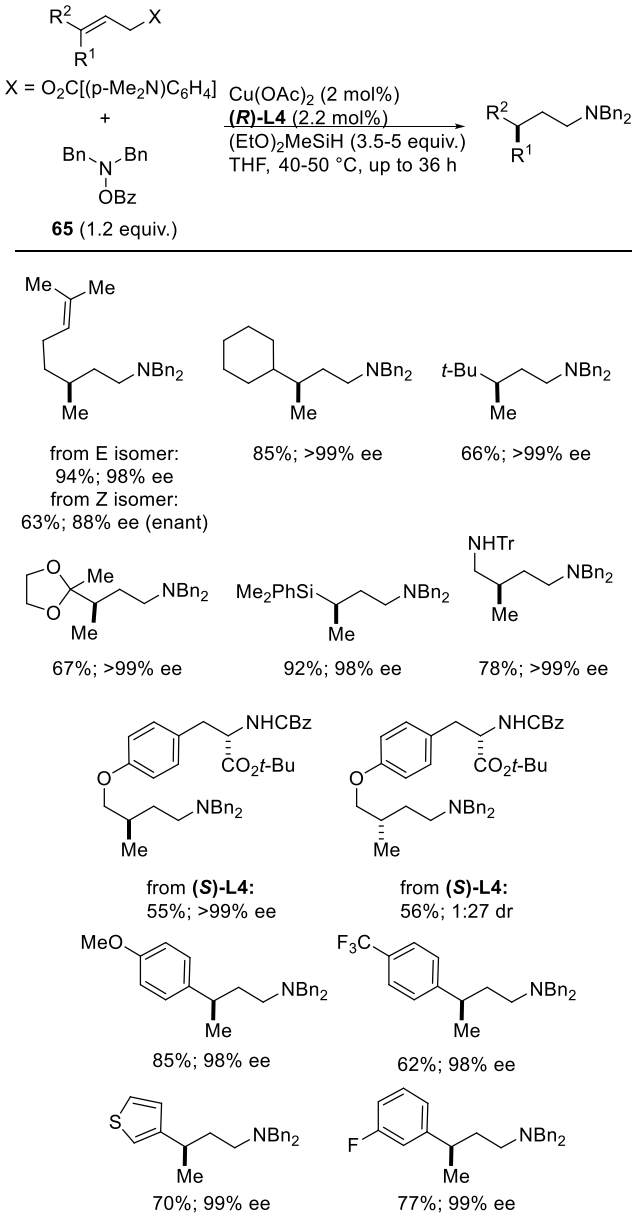
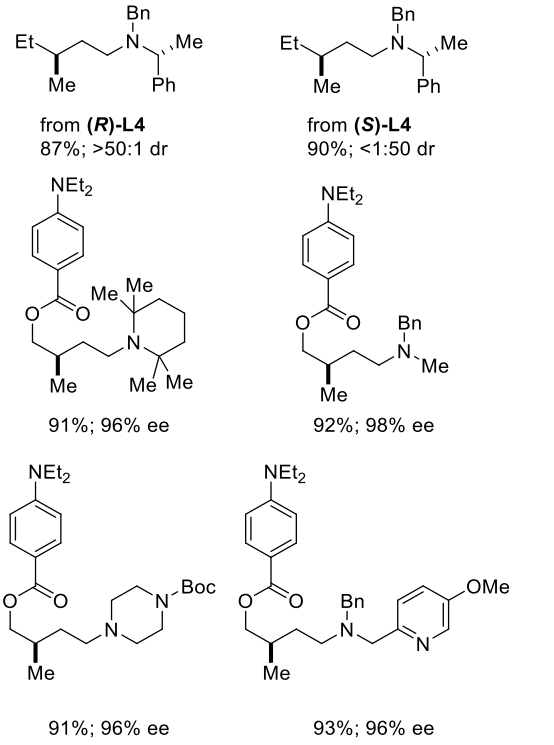
Scheme 186. Asymmetric Hydroamination of Allyl Esters with Diethoxymethylsilane and Cu-(*R*)-L4



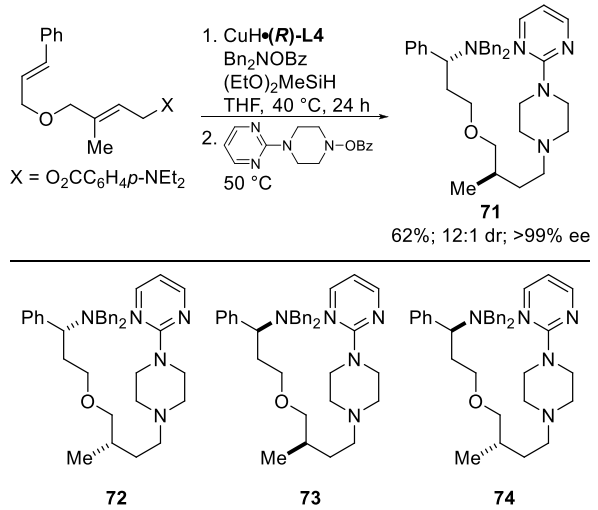
ligands (*R*)-**L4** and (*S*)-**L4**, alone or in combination, they were able to convert **68** and **69** to all eight stereoisomers of 3-methyl-4-dibenzylamino-4-phenyl-2-butanol **70**.

Buchwald et al. had observed that the hydroamination of allylic ethers and esters resulted in amination at the terminal position with loss of the ether or ester moiety. This discovery led to the application of an enantioselective reductive relay amination from allylic ethers with the potential to generate amines bearing a stereocenter at the γ-position.[165] The initial step in the development of the chemistry was a study of geraniol derivatives in which the terminal hydroxyl was converted to various potential leaving groups often encountered in metal-catalyzed allylic substitution chemistry (Scheme 185). The use of (*R*)-DTBM-SEGPHOS (***R***)-**L4** with *p*-dimethylaminobenzoates as the amine source offered the best conditions for the process (Scheme 186 and Scheme 187). The relative reactivity of the reagents was found to be cinnamyl ≫ allyl esters, and

Scheme 187. Examples of the Asymmetric Hydroamination of Terminal Olefins with (*R*)-1-Benzylaminophenylethane



Scheme 188. Asymmetric Reductive Amination of an Allylic Ether and Allylic Ester



monoalkyl aminating agent ≫ dialkyl aminating agent. These findings were applied to a synthesis of **71** and its three diastereomers, **72**−**74** (Scheme 188). Other leaving groups than esters, such as epoxy and ketal groups, proved useful, as were various electrophilic hydroxylamine derivatives; it also proved possible to carry out the conversion on the free alcohol (Scheme 189).

Buchwald et al. demonstrated the hydroamination of prochiral olefins, in particular styrene derivatives, with modified indoles **75** as nucleophiles. They were able to produce selectively *N*- or C3-alkylated indoles with high regioselectivity and modest-to-excellent enantioselectivities based on ligand

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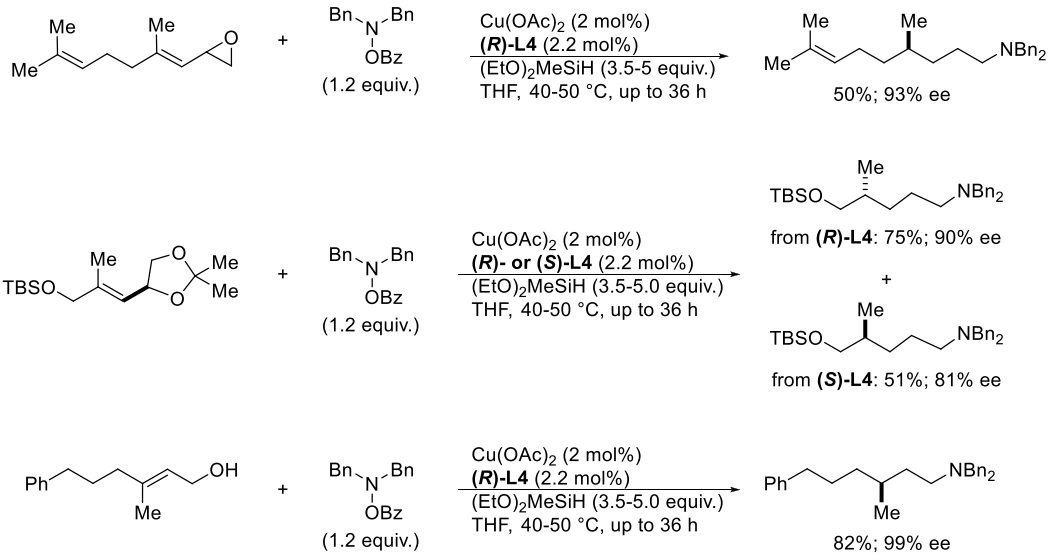
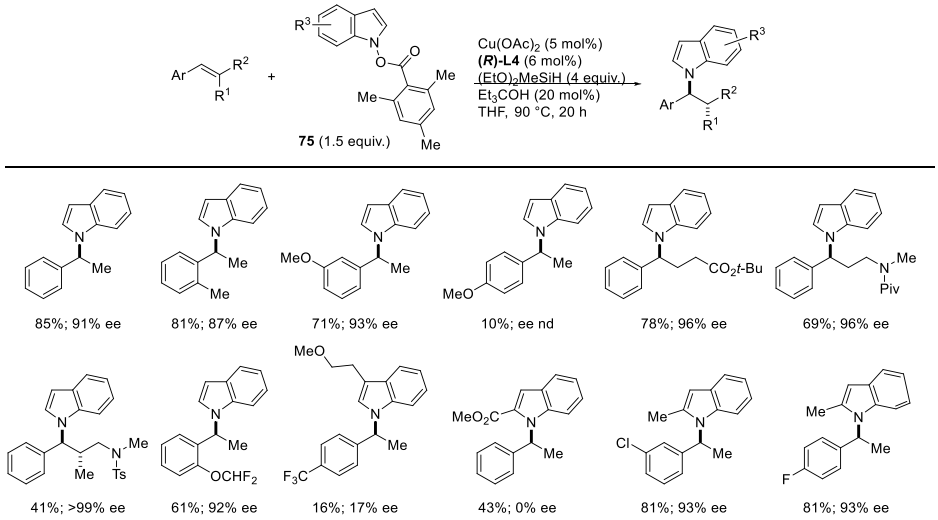
Scheme 189. Asymmetric Hydroamination of Vinyl Epoxide, Vinyl Ketal and an Allylic Alcohol with Diethoxymethylsilane and Cu-(*R*)-L4 or Cu-(*S*)-L4



Scheme 190. Asymmetric Hydroamination of Styrenes with Indoles Employing Diethoxymethylsilane and Cu-(*R*)-L4



choice (Scheme 190 and Scheme 191).[166] Ligand (*R*)-**L4** produced primarily *N*-alkylation, while (*S*,*S*)-**L23** provided alkylation at the C3 position. In either case, the regioisomeric ratios were >20:1.

In order to accomplish the enantioselective formation of secondary amines via a CuH-catalyzed hydroamination, Buchwald et al. developed a series of novel *O*-benzoyl-*N*-alkylhydroxylamines to investigate the effect of the benzoyl leaving group.[167] The study revealed the potential of the *p*-dimethylaminobenzoyl motif: for example, compound **76**. When **76** was subjected to the standard Buchwald protocol in the hydroamination of a series of styrenes, the corresponding secondary benzylamines were formed in high chemical yield and ee's (>92%). The reaction was enhanced with the addition of triphenylphosphine. The scope of the amine in the hydroamination of styrenes was investigated with a variety of electrophilic amine derivatives under the influence of ligand (*S*)-**L4** (Scheme 192). Other olefins, such as a vinylsilane, were reacted to form amine **77** (Scheme 193). The reaction was amenable to two-step processes, such as in the case of 4-chloro-1-phenyl-1-butene, which underwent hydroamination and subsequent cyclization to form pyrrolidine **78** (Scheme 194). Finally, the successful transformation was applied to four biologically active compounds: **79** (a Tufnil glucose conjugate), **80** (a valine conjugate of Chlorpromazine), **81** an estrone derivative of Loratadine) and **82** (Sensipar, for hyperparathyroidism) (Scheme 195).

In an attempt to translate the successful CuH-catalyzed benzoylated hydroxylamine approach to the asymmetric hydroamidation of styrene-type substrates, Buchwald et al. attempted to utilize benzoyloxybenzamide as a nitrogenous electrophile.[168] The nucleophilic amide reagent did not work well, however, nor did pivaloyloxybenzamide. On the other hand, 3-phenyl-1-aza-2,4-dioxazol-3-one **83** did serve the desired function, producing excellent yields and ee's (Scheme 196). As with many of the chiral hydroaminations, the *bis*-phosphine (*S*,*S*)-**L23** produced the best results. Variations of motif **84** were similarly investigated, with comparable outcomes (Scheme 197).

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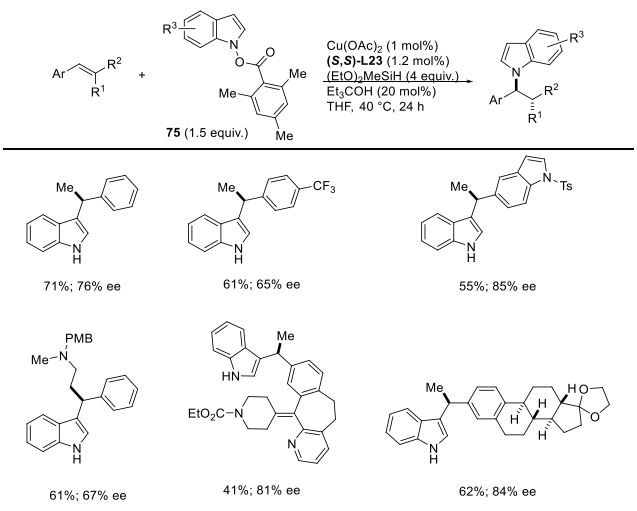
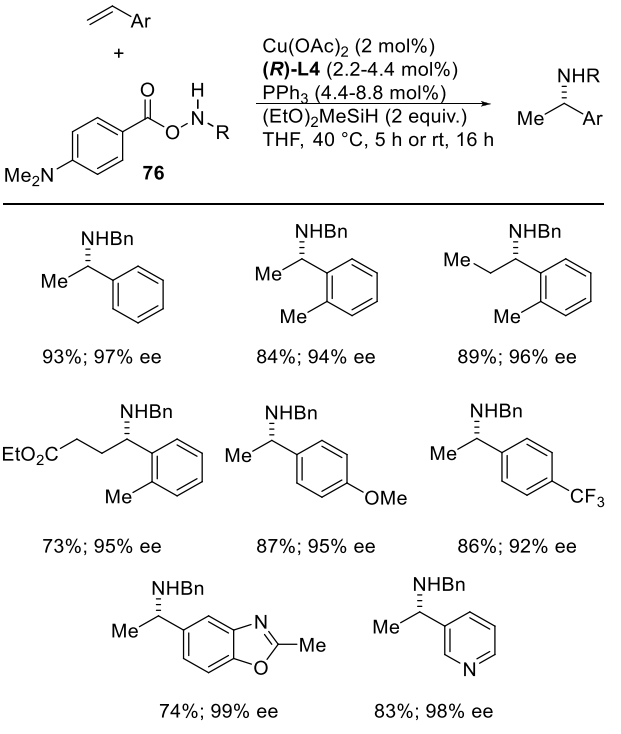
Scheme 191. Asymmetric Hydroamination of Styrenes with Indoles Employing Dimethoxymethylsilane and Cu-(*S,S*)-L23

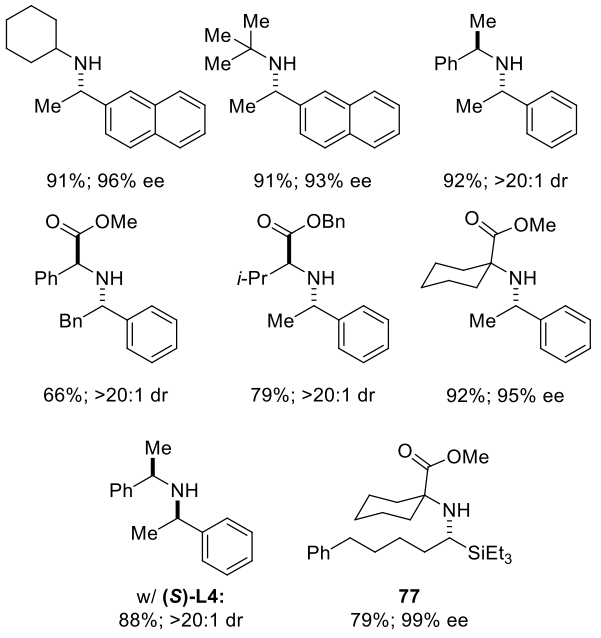


Scheme 192. Asymmetric Hydroamination of Styrenes with Benzylamine, Diethoxymethylsilane, and Cu-(*R*)-L4 in the Presence of Triphenylphosphine

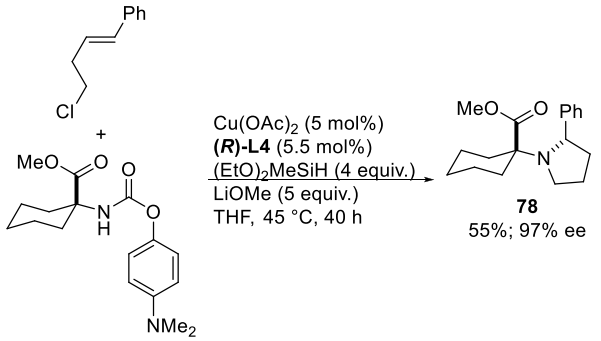


Application of the protocol for the asymmetric hydroamination of arenes failed to perform well for benzoyloxyaryl alkyl amines such as **85**[169] due to a competing reduction of the benzoyloxy amine to the aryl alkylamine. The addition of triphenylphosphine and a stoichiometric amount of *tert*-butanol to the standard reaction mixture solved this problem. The reaction worked well for arenes and 1,1-disubstituted olefins (Scheme 198 and Scheme 199). Terminal olefins performed well; however, anti-Markovnikov hydroamination generated a product with no stereoselective outcome. The transformation was expanded to various aryl alkylamines (Scheme 200).

Scheme 193. Amine Scope in the Asymmetric Hydroamination of Vinylarenes



Scheme 194. Asymmetric Hydroamination/Cyclization of *β*-(2-Chloroethyl)styrene



A further investigation into the asymmetric hydroamination of enamines conducted by Yu and Somfai employed Buchwald's electrophilic amine source **86** and (*R*)-DTBM-SEGPHOS (***R***)-**L4** as the chiral ligand (Scheme 201).[170] They found that aryl enamines reacted well with both electron-donating and electron-withdrawing groups; however, both Boc-protected enamines and nonaryl enamines failed to react. Unfortunately, the reactions required reaction times of 48 h or more.

You et al. employed the Buchwald protocol in the asymmetric hydroamination of benzofurans, which resulted in nonracemic *o*-hydroxybenzylamines.[171] The yields were low-to-modest, with a wide range of ee values (Scheme 202).

Buchwald et al. undertook a thorough investigation of the asymmetric hydroamination of internal olefins, which had been shown to be measurably less reactive than styrenes, terminal olefins, and 1,1-disubstituted olefins and thus presented a challenge.[172] In addition, in the case of unsymmetrical olefins the question of regioselectivity required attention. Due to the slow rate of the amination step the electron-rich electrophilic aminating reagents **87** were found to give optimal results. With *trans*-2-butene as a key olefinic substrate and (***S***)-**L4** employed as the nonracemic ligand, the reaction gave the tertiary amine in

https://doi.org/10.1021/acs.oprd.1c00073
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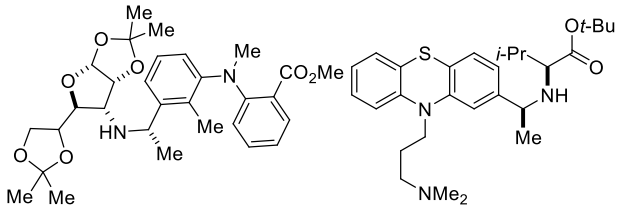
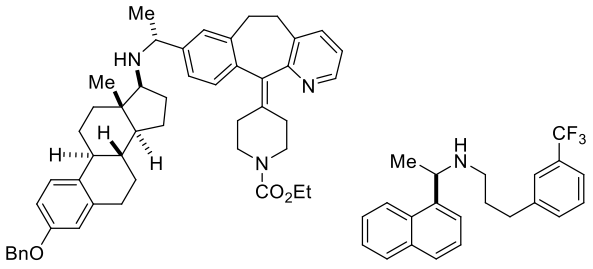
Scheme 195. Biologically Active Molecules Accessible via Asymmetric Hydroamination



79 Tufnil-Glucose Conjugate

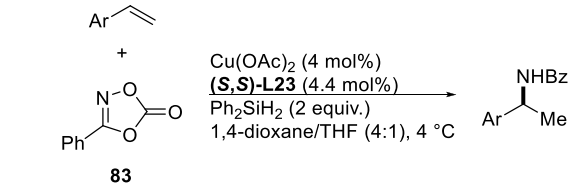
80 Chlorpromazine-Valine Conjugate
82%; >20:1 dr



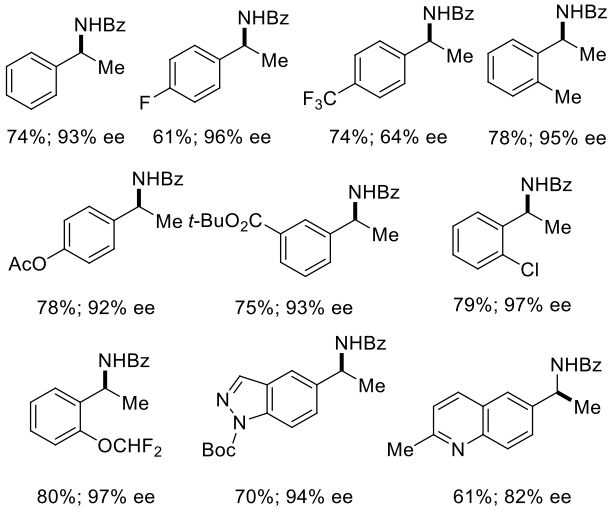
81 Lortadine-Estrone Conjugate

82 Sensipar
81%; 89% ee

Scheme 196. Asymmetric Diphenylsilane-Mediated Hydroamination of Styrenes with Benzoylamine Surrogate 83



83

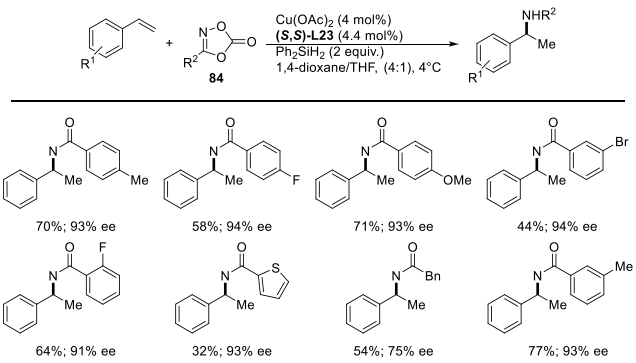


74%; 93% ee | 61%; 96% ee | 74%; 64% ee | 78%; 95% ee

78%; 92% ee | 75%; 93% ee | 79%; 97% ee

80%; 97% ee | 70%; 94% ee | 61%; 82% ee

Scheme 197. Asymmetric Diphenylsilane-Mediated Hydroamination of Styrenes with Benzoylamine Surrogates 84

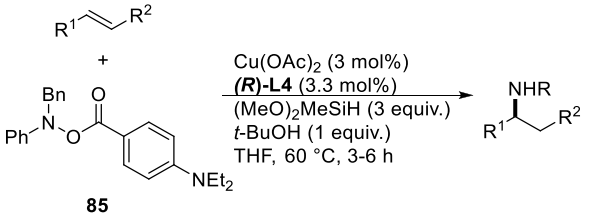


84

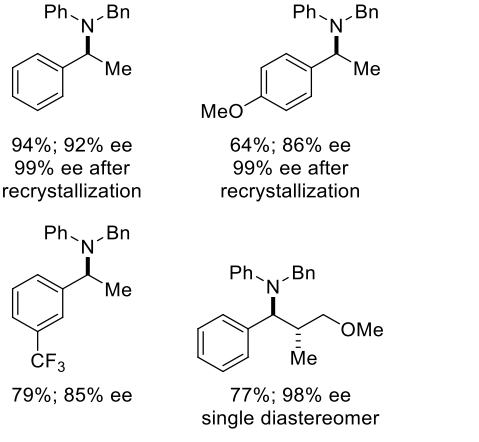
70%; 93% ee | 58%; 94% ee | 71%; 93% ee | 44%; 94% ee

64%; 91% ee | 32%; 93% ee | 54%; 75% ee | 77%; 93% ee

Scheme 198. Asymmetric Hydroamination of Olefins with Dimethoxymethylsilane and Cu-(*R*)-L4



85



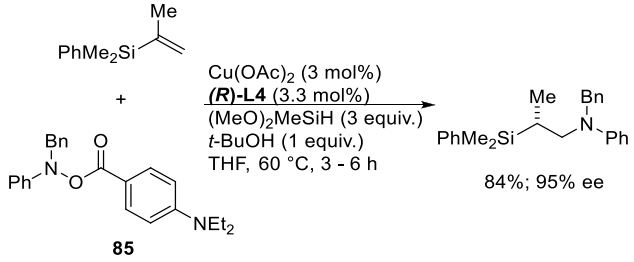
94%; 92% ee
99% ee after recrystallization

64%; 86% ee
99% ee after recrystallization

79%; 85% ee

77%; 98% ee
single diastereomer

Scheme 199. Asymmetric Hydroamination of a Vinylsilane with Dimethoxymethylsilane and Cu-(*R*)-L4



85

84%; 95% ee

modest to good yield (50−85%) and excellent ee values (>96%) (Scheme 203). Other symmetrical olefins gave similar results (Scheme 204). Unsymmetrical olefins **88** and **89** showed a >4:1 regioselectivity along with very high enantioselectivity of amine products **90**−**93** (Scheme 205). In one intriguing example *trans*-2-butene was reacted with **86** and Ph_2SiD_2 to give **94** on a 10 g scale with excellent diastereoselectivity (Scheme 206).

Utilizing the electrophilic aminating agents **95** and **96**, derived from the pharmaceutical drugs cinacalcet and paroxetine, respectively, the enantioselective amination of internal olefins

https://doi.org/10.1021/acs.oprd.1c00073
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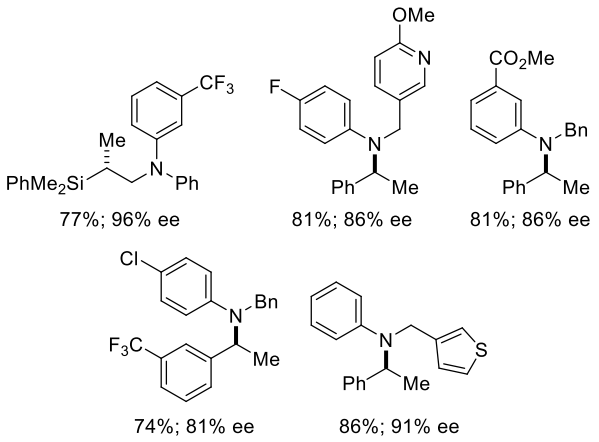
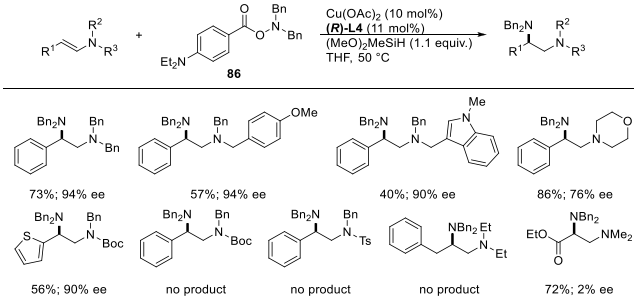
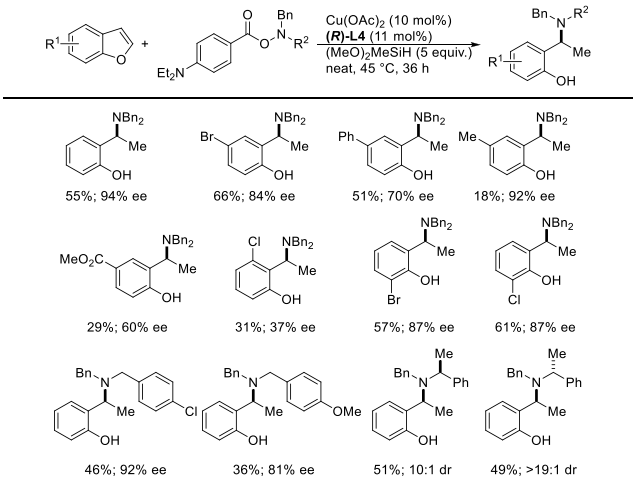
Scheme 200. Amine Scope in the Asymmetric Hydroamination of Olefins According to Scheme 199



Scheme 201. Asymmetric Dimethoxymethylsilane-Mediated Hydroamination of Enamines: Enantioselective Synthesis of 1,2-Diamines



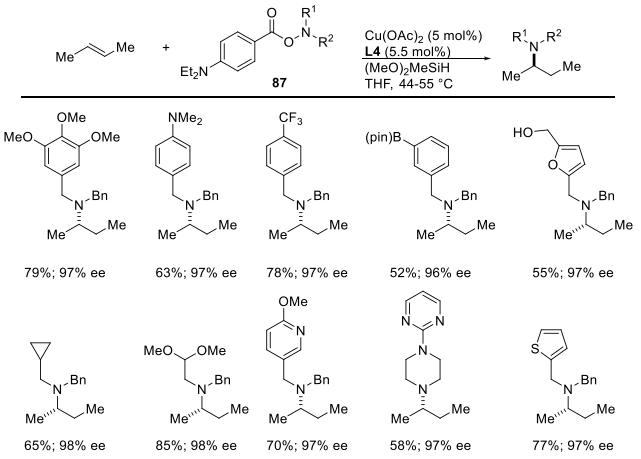
Scheme 202. Asymmetric Dimethoxymethylsilane-Mediated Hydroamination of Benzofurans: Synthesis of *ortho*-(Aminoethyl)phenols



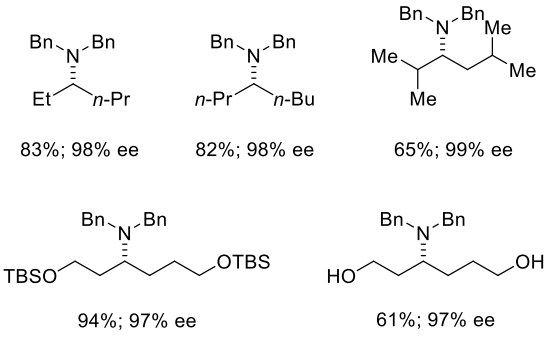
was conducted with good results in both cases to yield **96** and **98** (Scheme 207 and Scheme 208).

Hartwig et al. were able to regioselectively and asymmetrically hydroaminate internal homoallylic ethers and homoallylic amines, resulting in the formation of 3-aminoalcohols or 1,3-diamines, respectively.[173] Diethoxymethylsilane was employed as the reductant, with (*R*)- or (*S*)-DTBM-SEGPHOS (***R*)-L4** or

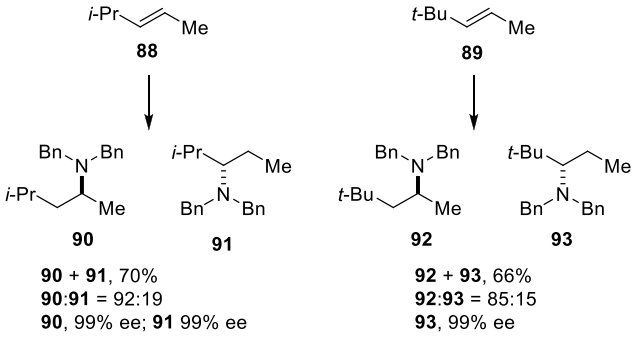
Scheme 203. Asymmetric Hydroamination of *trans*-2-Butene



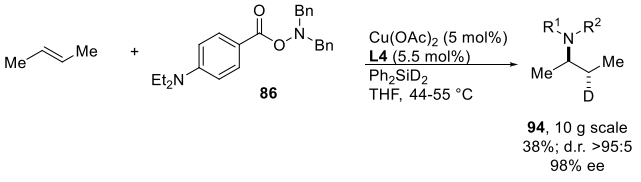
Scheme 204. Asymmetric Hydroamination of Symmetrical Olefins



Scheme 205. Enantioselective Hydroamination of Unsymmetrical Dialkyl Alkenes



Scheme 206. Evaluation of Diastereoselectivity with Deuterated Diphenylsilane



(*S*)-**L4** as the chiral ligand. Optimal regioselectivity was observed in substrates containing 2,4,6-trichlorobenzoate esters as the homoallylic directing group (Scheme 209). A *cis* internal

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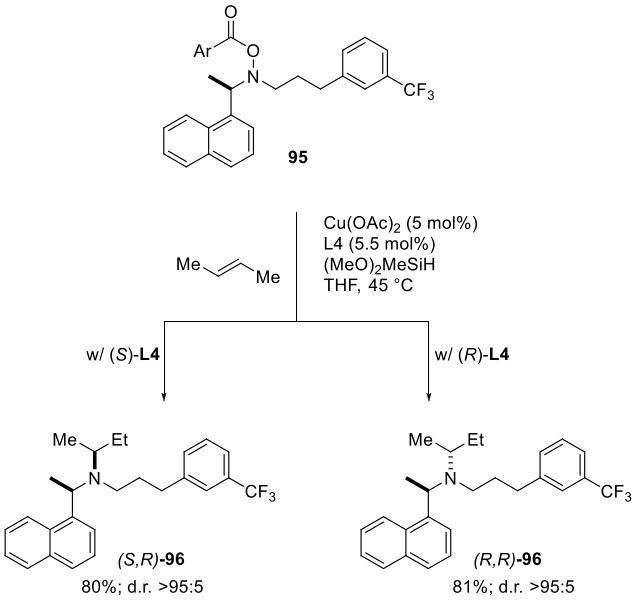
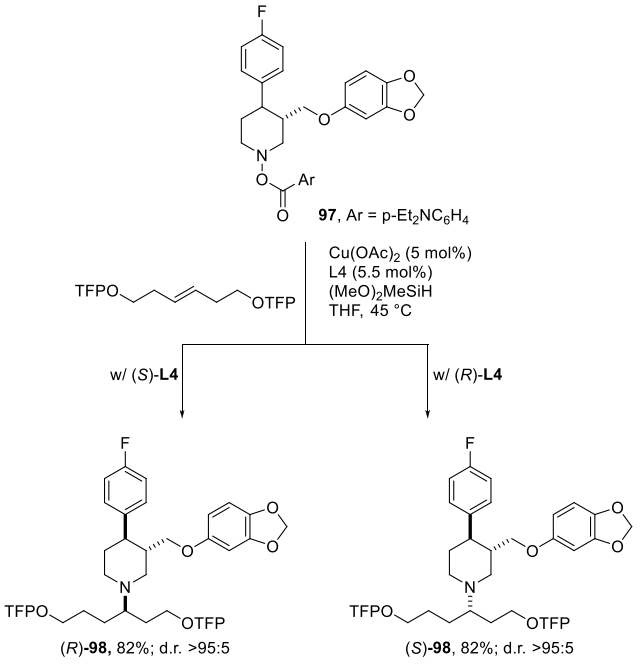
Scheme 207. Enantioselective Amination of *trans*-2-Butene with Electrophile Amination Agent 96 Derived from Cinacalcet



Scheme 208. Enantioselective Amination of *trans*-2-Butene with Electrophile Amination Agent 95 Derived from Paroxetine



olefin was shown to react slower than its *trans* counterpart and displayed much lower enantioselectivity (Scheme 210).

Buchwald et al. investigated the CuH-catalyzed hydroamination of alkynes with the primary objective of the possibility of a regioselective hydrocupration of the acetylene followed by protonation of the intermediate organocuprate to form an olefin, which would undergo an enantioselective addition of CuH and hydroamination to stereoselectively give the amine (Scheme 211).[174] When the reaction was carried out with aryl alkynes and $Cu(OAc)_2$ in the presence of *rac*-**L2** and diethoxymethylsilane in the absence of a proton source, enamines were formed in excellent yield (6 examples: 80−99%) (Scheme 212). By replacement of SEGPHOS with (***R***)-**L4** and adding ethanol or isopropanol as a proton source, chiral benzyl amines were prepared in good yield and with high ee's (Scheme 213). Control experiments demonstrated that the enantioselective reductive amination occurred via the hydrocupration of the olefin and not through the enantioselective reduction of the enamine. The developed protocol was cleanly applied to acetylene **99** in a synthesis of rivastigmine **100** (Scheme 214).

Using a mechanistic approach, Buchwald et al. designed and prepared a series of modifications to the prevalent DTBM-SEGPHOS scaffold and investigated the performance of the altered structures in the hydroamination of terminal olefins.[175] Although the study employed the racemic variants, it emphasized the value of mechanistic insight into the design of new ligands without having to prepare and investigate a large number of systems. The study resulted in the selection of **L7** as the ligand of choice (Scheme 215), which proved to be significantly better than DTBM-SEGPHOS in terms of chemical yield.

Li et al. applied anthranils to the enantioselective hydroamination of styrene derivatives, with excellent yields and ee's (Scheme 216 and Scheme 217).[176] The CuH-catalyzed reaction takes place under mild conditions with phenylsilane as the reductant. The synthetic utility of the prepared (hydroxymethyl)aryl amines was amply demonstrated by the conversion of (2-hydroxymethylphenyl)phenylmethyl amine to six different products. The reaction was scaled to 1.81 g employing (***S,S***)-**L23**, resulting in an (*R*)-configured amine (Scheme 218).

13. MISCELLANEOUS ASYMMETRIC ORGANOSILANE REDUCTIONS

Based on their work on the hydroacylation of cinammic acids,[134] Buchwald et al. presented the CuH-catalyzed asymmetric conjugate reduction of prochiral α,β-unsaturated acids to β-chiral aldehydes (Scheme 219).[177] Impressively, even β,β-diaryl-α,β-unsaturated carboxylic acids underwent the transformation with impressively high ee values (Scheme 220). The postulated mechanism proceeded through the initial formation of the silylated acid, followed by conjugate addition of CuH and, last, elimination of a silyloxycuprate species and formation of the ketene (Scheme 221). CuH then reacts with the ketene to produce the aldehyde as well as to reduce the silyloxycuprate to regenerate the catalyst species. Conveniently, the resulting aldehydes can undergo reductive amination in the same pot to furnish γ-chiral amines.

Similarly, Buchwald et al. also reported the direct conversion of prochiral α,β-unsaturated acids to β-chiral amides in a one-pot reaction.[178] (*S*)-CuCatMix (prepared from $Cu(OAc)_2$, (***S***)-**L4**, and PPh_3) was used as the catalyst, with dimethoxymethylsilane as the reductant (Scheme 222). TMDS also produced good results, though with fewer examples. Building on a previous mechanistic investigation of the reduction of cinnamic acids to aldehydes, Buchwald et al. demonstrated that the amidation reaction proceeds via the same silylated unsaturated acid, which undergoes CuH addition to the silylated copper enoate. The copper enoate eliminates Cu−O−Si, generating a ketene that is subsequently amidated. Direct amidation of the silylated unsaturated acid was not supported by experiments. Furthermore, a single example showed that the chiral amide could be further reduced to the amine without isolation of the amide via

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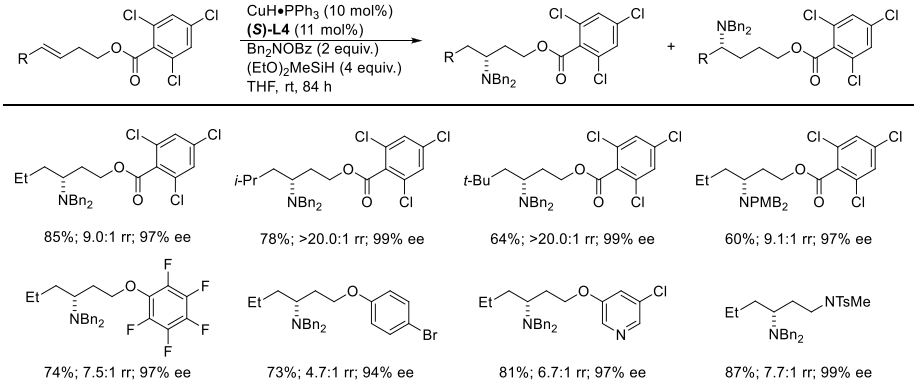
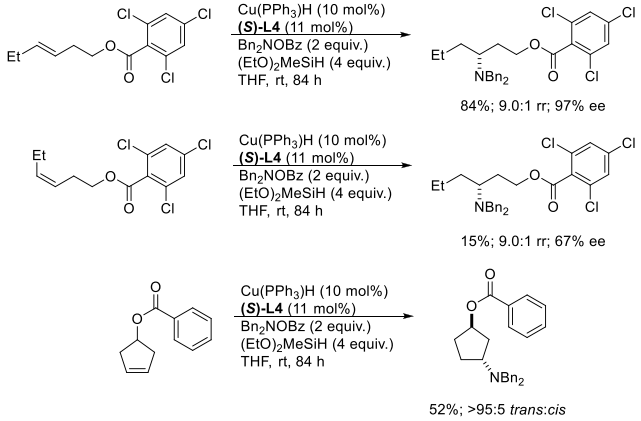
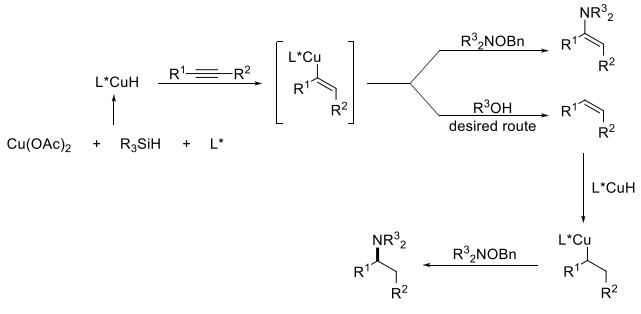
Scheme 209. Asymmetric Hydroamination of Homoallylic Esters with Diethoxymethylsilane and Cu-(*S*)-L4



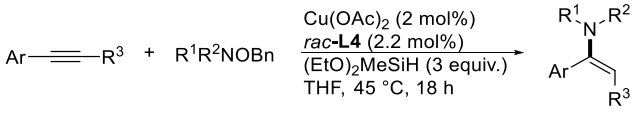
Scheme 210. Asymmetric Diethoxymethylsilane-Mediated Hydroamination of (*E*) and (*Z*) Isomeric Olefins



Scheme 211. Outline of CuH-Catalyzed Enantioselective Reduction/Hydroamination of Internal Acetylenes



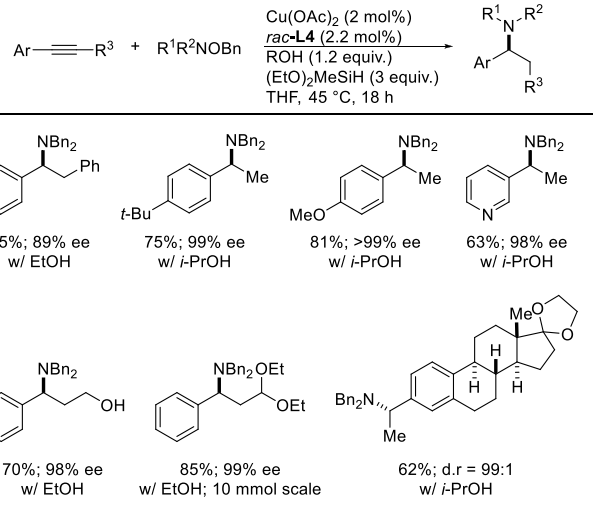
Scheme 212. CuH-Catalyzed Amination of Acetylenes: Regioselective Synthesis of Enamines



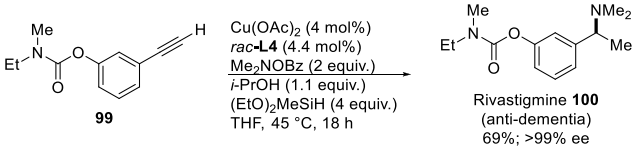
the addition of a second catalyst, $IrCl(CO)(PPh_3)_2$ (Scheme 223).

Yu et al. developed a process for the hydroxymethylation of styrenes to form homobenzylic alcohols using carbon dioxide as the source of the hydroxymethyl moiety. The reactions provided the 2-arylpropan-1-ols with good-to-excellent enantiomeric

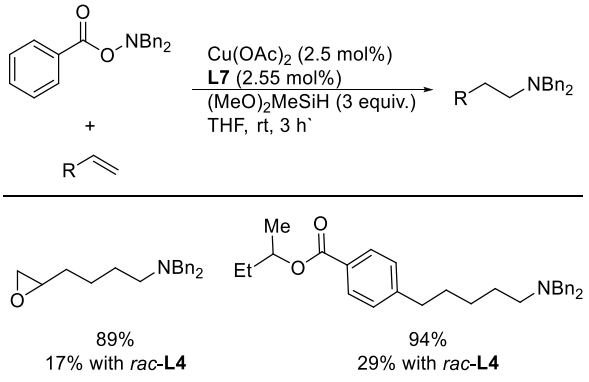
Scheme 213. Substrate Scope for CuH-Catalyzed Acetylene Hydroamination



Scheme 214. Synthesis of Rivastigimine 100 from Alkyne 99



Scheme 215. Ligand Studies on Dimethoxymethylsilane-Mediated Hydroamination of Terminal Olefins



https://doi.org/10.1021/acs.oprd.1c00073
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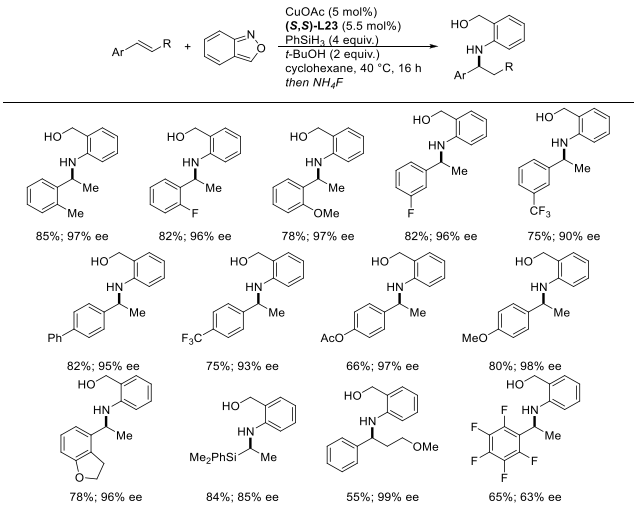
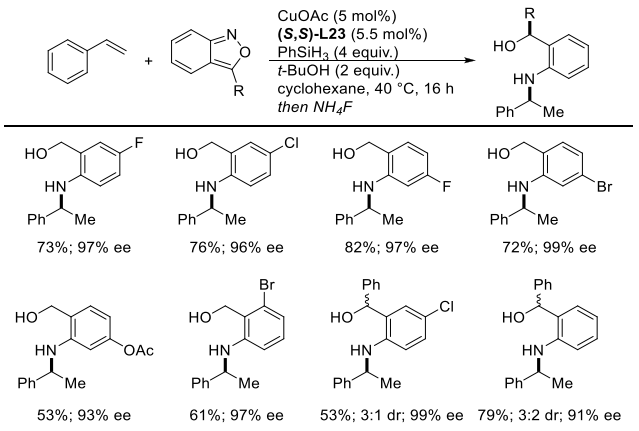
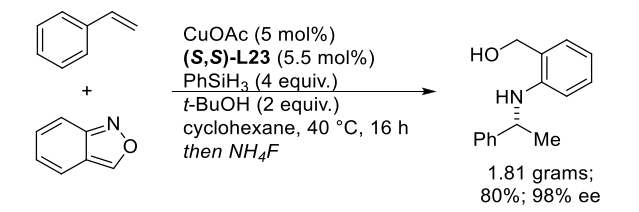
Scheme 216. Asymmetric Phenylsilane-Mediated Hydroamination of Styrenes with Anthranil



Scheme 217. Asymmetric Phenylsilane-Mediated Hydroamination of Styrene with 3-Substituted Anthranils: Synthesis of β-Aminobenzyl Alcohols



Scheme 218. Large-Scale Asymmetric Phenylsilane-Mediated Hydroamination of Styrene with Anthranils



purity.[179] The reaction performed well for *para*-, *meta*- and *ortho*-substituted, as well as electron-rich and electron-poor, styrenes (Scheme 224). The protocol was employed in short syntheses of (*S*)-ibuprofen and (*R*)-curcumene. The reaction was successfully extended to 1-aryl-1,3-butadienes, which produced excellent yields as well as regio-, stereo- and enantioselectivities (Scheme 225). $(MeO)_2MeSiH$ proved to be the silane of choice for dienes, while $(EtO)_3SiH$ was superior for styrenes.

The CO_2-driven hydroxymethylation of 1,3-dienes was the subject of a detailed examination of the substrate scope of the transformation, in which 1-aryl-1-alkyl-1,3-butadienes and 1-alkyl-1-methyl-1,3-butadienes were subjected to the reaction protocol (Scheme 226 and Scheme 227).[180] This resulted in the formation of a wide array of chiral homoallylic alcohols with high yields, *E*/*Z* ratios, and ee's. It is noteworthy that the (*E*)-alkene isomer is produced under the influence of **(*S*,*S*)-L23**, opposite to that produced by the protocol in Scheme 225.

Hu and Zheng employed the combination $Cu(OAc)_2 \cdot H_2O$/(*R*)-SEGPHOS **(*R*)-L2**)/PMHS/*t*-BuOH to successfully achieve β-aryl-α,β-vinyl phosphonates (Scheme 228). Two alkyl substituted examples produced promising, although lesser, results (68% yield and 89% ee; 68% yield and 86% ee).[181]

Buchwald et al. coupled styrenes with pyridines with high enantioselectivity and strong regioselectivity for C−C bond formation at the 4-position (rr average of 22:1 for 1,4:1,2 reduction) (Scheme 229).[182] The initial products formed from the dimethoxymethylsilane reductive dearomatization could be further oxidized to 4-alkylated pyridines or reduced to the corresponding piperidine (Scheme 230). The reaction protocol was further extended to pyridazines, with modest yields but excellent ee's (Scheme 231). 3-Fluorophenyl-2-methylstyrene produced a 7:1 mixture of regioisomers with pyridazine; however, both regioisomers were formed with high enantioselectivity.

The use of benzoyloxy derivatized amines was further applied to the selective C3 allylation of 1*H*-N indazoles under catalysis of CuH.[183] This generated a chiral quaternary center attached to the C3 position of the indazole, with high regioselectivity, enantioselectivity and yield. The allylating agent was a prochiral and 1,1-di- and monosubstituted allene (Scheme 232 and Scheme 233). The lone 1,1-dialkylallene examined produced only modest yields and ee's.

Buchwald et al. accomplished the asymmetric reductive cross-coupling of styrenes and aryl bromides via dual Cu and Pd catalysis.[184] The success of the reaction, which results in the formation of chiral 1,1-diaryl alkanes, is dependent on the stereoselective transmetalation between the benzylic copper intermediate and Pd, as well as on the choice of chiral ligand. A mechanism was proposed (Scheme 234). Initial studies with styrene and 4-bromoanisole revealed the advantages of employing Ph_2MeSiH, $[Pd(cinnamyl)Cl]_2$, ligand **(*R*)-L4** (for the CuH styrene reaction) and ligand **L90** (for the cross-coupling reaction) along with NaOTMS (Scheme 235).

Malcolmson et al. used the regioselective addition of CuH to 2-azadienes to form an α-cuprato imine, which would then add to a prochiral ketone.[185] Their initial work focused on the reaction of azadiene **101** with acetophenone and investigated the performance of five chiral ligands, with (*S*,*S*)-Ph-BPE **(*S*,*S*)-L23** proving superior. For most of the ligands tested, the reaction produced simple hydrosilylation of the acetophenone to give **103** and a smaller amount of imino pyrrolidine **104**. Treating the crude reaction mixture with $NaBH_4$ to reduce the imine, followed by acidic hydrolysis, produced the desired amino alcohol **106** in 73% yield, with a diastereomeric ratio of >20:1 and an ee value of 98%. The scope of the reaction demonstrated modest-to-good chemical yields, modest diastereomeric ratios of the intermediate silylated amino alcohols (e.g., **102**) and excellent ee's of the final amino alcohols (e.g., **105**) (Scheme 236). In a study of the reaction of 2-methoxyacetophenone with 4-substituted 2-azadienes, it was found that the yields were only modest, but that the diastereoselectivity was greatly enhanced (Scheme 237). In one example, the enantioselectivity of each diastereomer **106** and **107** was

https://doi.org/10.1021/acs.oprd.1c00073
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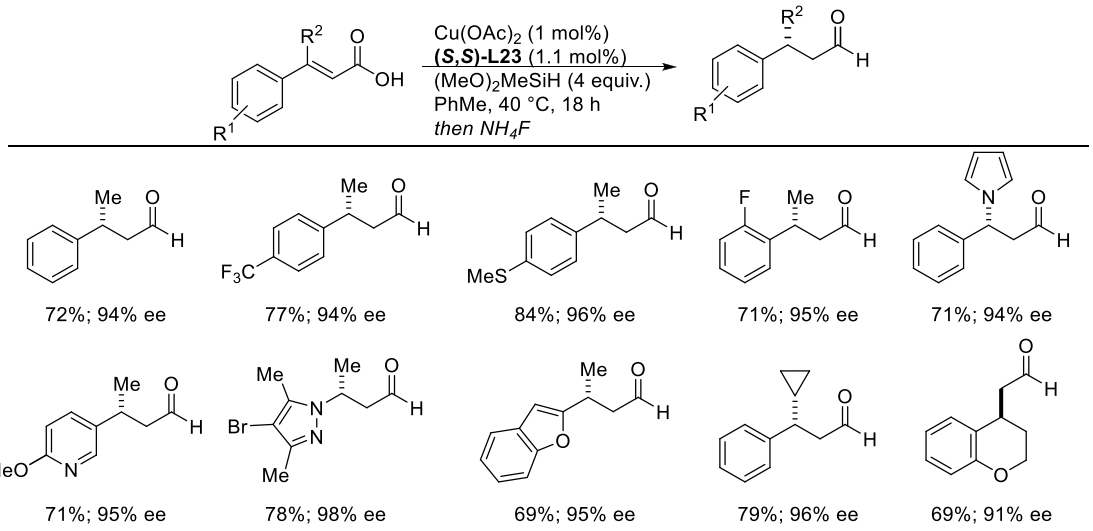
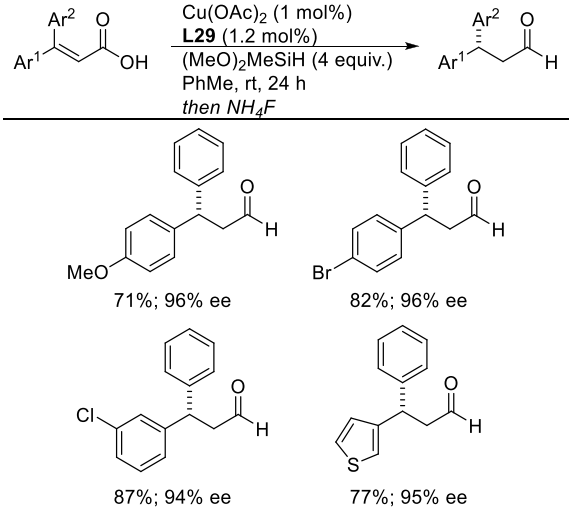
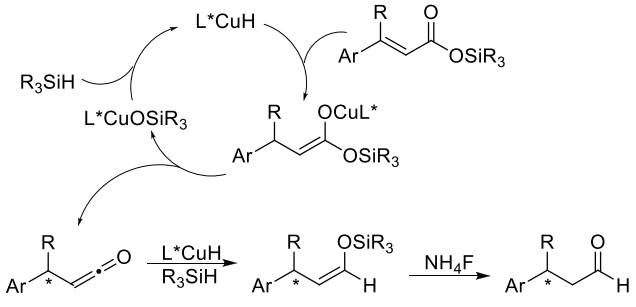
Scheme 219. CuH-Catalyzed Asymmetric Hydrosilylation of α,β-Unsaturated Acids with Dimethoxymethylsilane: Enantioselective Synthesis of β-Substituted Aldehydes



Scheme 220. Asymmetric Dimethoxymethylsilane Reduction of β,β-Diaryl-α,β-Unsaturated Acids with Cu-L29: Enantioselective Synthesis of β,β-Diaryl Aldehydes

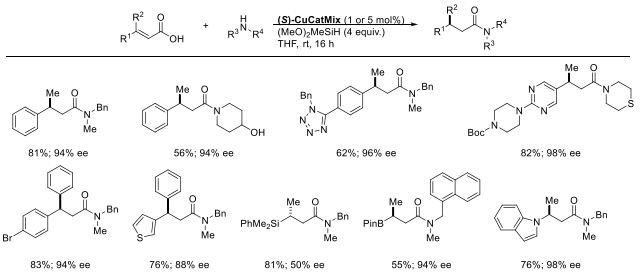


Scheme 221. Mechanism for the Cu-Catalyzed Dimethoxymethylsilane Reduction of α,β-Unsaturated Acids to β-Chiral Aldehydes

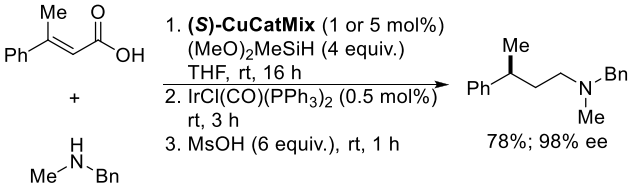


shown to be very high. In addition, in the reaction with the symmetrical ketones, benzophenone and acetone, the ee values of the imino alcohols **108** and **109** were >90%.

Scheme 222. Amine Scope in the Cu-Catalyzed Dimethoxymethylsilane Asymmetric Reduction of β,β-Diaryl-α,β-Unsaturated Acids: Enantioselective Synthesis of β,β-Diaryl Amides



Scheme 223. Asymmetric Dimethoxymethylsilane-Mediated Reductive Amination of α,β-Unsaturated Acids: Synthesis of γ-Chiral Amines



Murahashi et al. achieved enantiomerically enriched *N,N*-disubstituted hydroxylamines and hydroxylamines via asymmetric hydrosilylation of nitrones with diphenylsilane and ruthenium catalyst Ru_2Cl_4-(*S*)-*p*-tolBINAP (***R*)-L17**·(NEt_3) (Scheme 238).[186] 2-Phenyl-1-pyrroline *N*-oxide was converted to **110**, albeit in low yield and with modest ee. Hydroxylamine **111** was produced in high yield and with low ee (Scheme 239) and was converted (Zn/HCl) to the chiral amine **112**.

In an effort to avoid the use of the oxygen and moisture-sensitive CuO*t*-Bu in the CuH-catalyzed reduction of β-aryl−β-alkyl disubstituted nitroalkenes, Czekelius and Carreira found that CuF_2 performed well in conjunction with $PhSiH_3$ and (*R*)-(*S*)-Josiphos (***R*)-(*S*)-L30** (Scheme 240).[187] It proved advantageous to add $PhSiH_3$ in portions in order to achieve high

https://doi.org/10.1021/acs.oprd.1c00073
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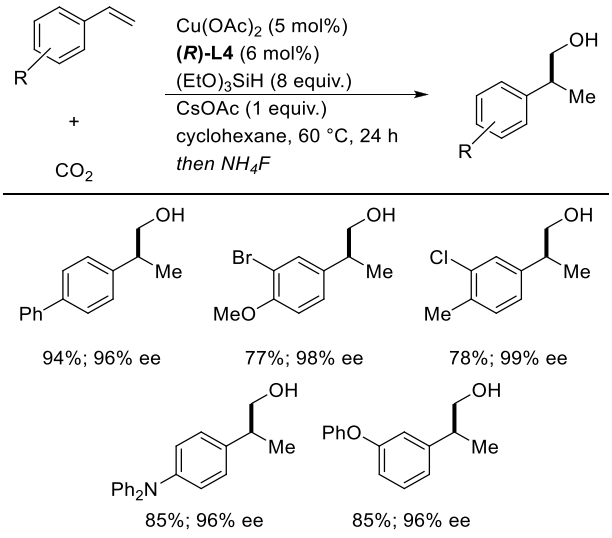
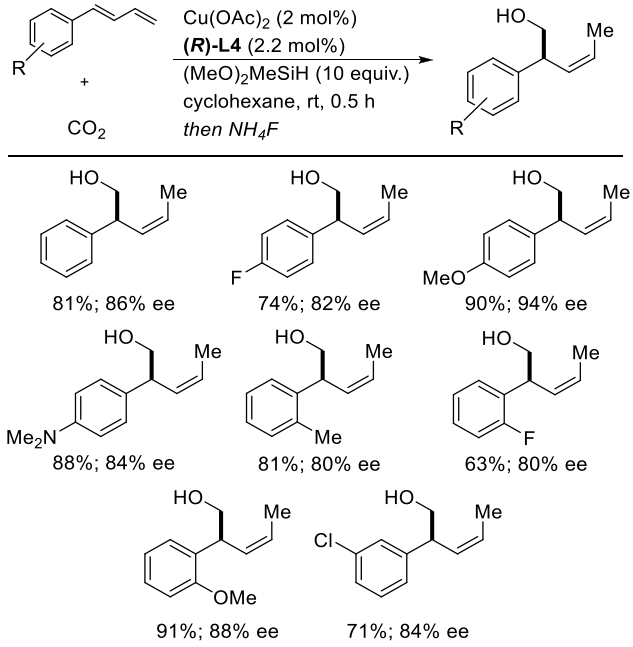
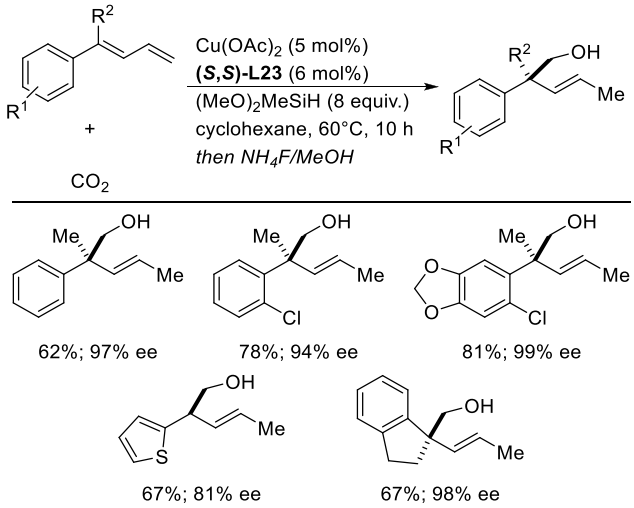
Scheme 224. Asymmetric Triethoxysilane-Mediated CuH-Catalyzed Hydroxymethylation of Styrenes with Carbon Dioxide: Enantioselective Synthesis of 2-Aryl-1-propanols



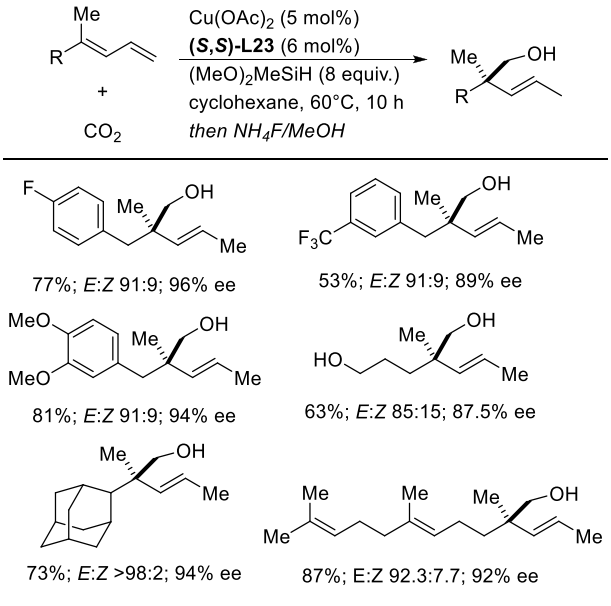
Scheme 225. Asymmetric CuH-Catalyzed Hydroxymethylation of 1-Aryl-1,3-butadienes with Carbon Dioxide: Synthesis of (*Z*)-2-Arylpent-3-ene-1-ols



Scheme 226. Asymmetric Hydroxymethylation of Aryl 1,3-Dienes: Enantioselective Synthesis of Quaternary Homoallylic Alcohols



Scheme 227. Asymmetric CuH-Catalyzed Hydroxymethylation of 1,1-Disubstituted-1,3-butadienes with Carbon Dioxide: Enantioselective Synthesis of (*E*)-2,2-Disubstituted Pent-3-ene-1-ols



conversions. Under the standard conditions, certain electron-rich substrates, which reacted nicely with the CuO*t*-Bu procedure, failed to react with the CuF_2 process. The problem was remedied by the addition of nitromethane, based on the hypothesis that a nitronate was responsible for generating the active Cu(I) species **113** (Scheme 241).

A unique application for the hydrocyanation of olefins employed 2-phenyl-4-methyl-5-bromooxazole **113** as a cyanide equivalent in the enantioselective hydrocyanation of olefins.[188] The initial hydroarylation was Pd-catalyzed, with the asymmetric addition to the olefin promoted by the CuH (Scheme 242). Two catalysts were involved: **L5** for the hydroarylation and BrettPhos **L90** for the chiral hydrocupration. The sequential [4 + 2] cycloaddition with an alkyne and the *retro*-[4 + 2] cycloaddition allowed the formation of the cyano group along with a furan. This highly useful transformation was applied to the synthesis of a precursor to the USP28 inhibitor **114**. The hydrocyanation of terminal olefins was also carried out, resulting in terminal nonchiral nitriles, and was applied to the synthesis of a precursor to the cardiovascular drug Cilostazol **115**.

Buchwald et al. was able to produce chiral 2,3-disubstituted cyclobutanes and cyclopentanes via the enantioselective reductive cyclization of 3- and 4-halo-substituted alkyl styrenes (Scheme 243 and Scheme 244).[189] In addition, three 3,4-disubstituted six-membered heterocycles were prepared, which were exploited in a short synthesis of (−)-paroxetine **28** (Scheme 245).

https://doi.org/10.1021/acs.oprd.1c00073
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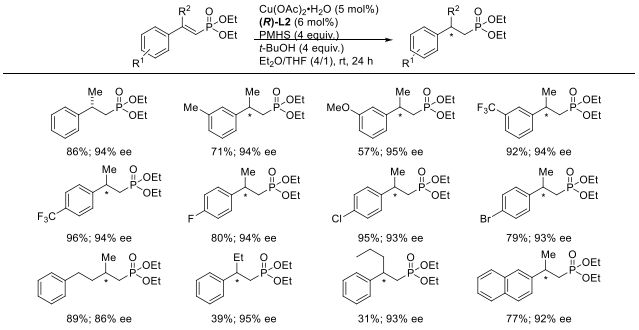
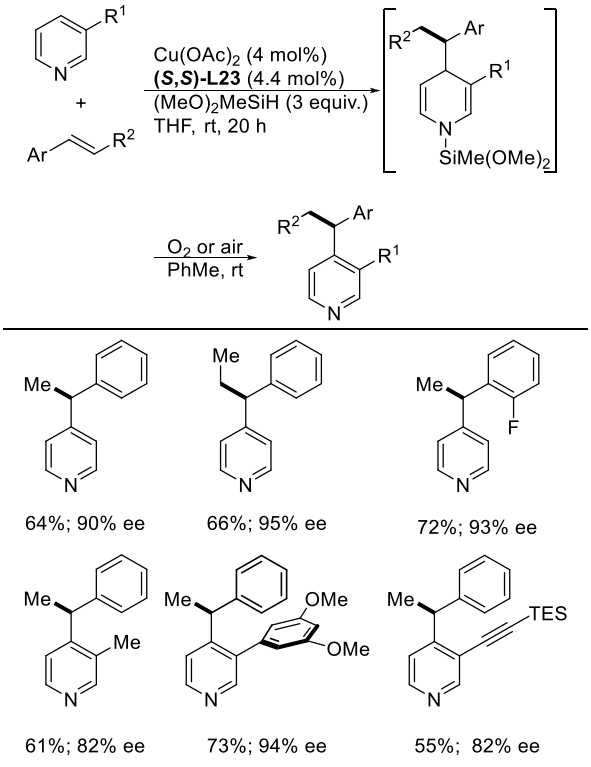
Scheme 228. Asymmetric Cu-Catalyzed PMHS Hydrosilylation of α,β-Unsaturated Phosphonates



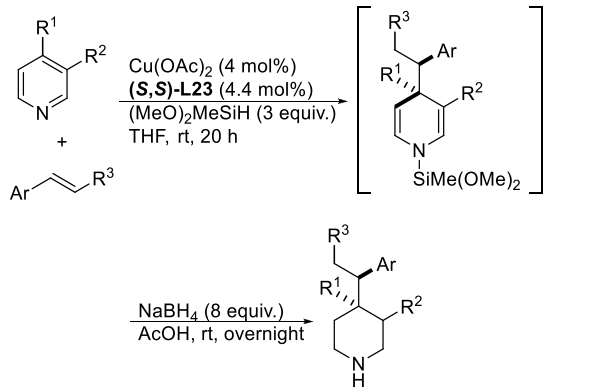
Scheme 229. Asymmetric Reductive Coupling of Pyridines with Styrenes: Enantioselective Synthesis of 4-Alkylated Pyridines



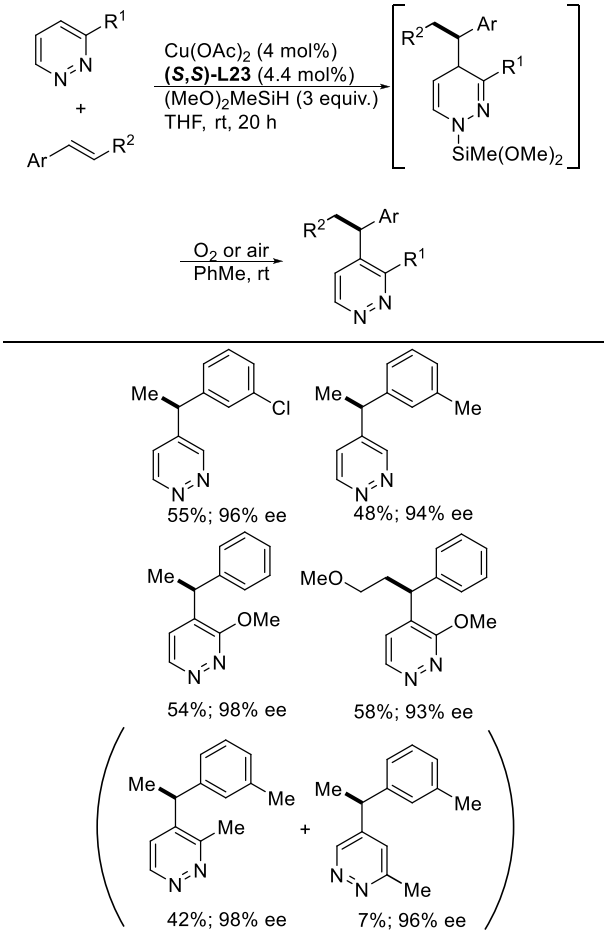
Although not formally an enantioselective reduction Oestreich et al. found that a kinetic resolution of a racemic mixture of secondary alcohols could be accomplished via a selective CuH-catalyzed dehydrogenative silylation in which the CuH is ligated with **(*R*,*R*)-L23** (Scheme 246).[190] This resulted in the preparation of enantiomerically enriched tri-*n*-butylsilylated secondary alcohols and free secondary alcohols. The less reactive enantiomer typically showed the higher ee value for the free alcohol compared to the more reactive alcohol that resulted in the silylated enantiomer.

The first reported nonracemic NHC ligands derived from enantiopure diamines with aryl groups other than phenyl were investigated by the Cramer et al. in the Ni-catalyzed asymmetric three-component coupling of norbornene, an aldehyde and an organosilane to form tricyclic system **118** (Scheme 247).[191] Although triisopropylsilane was the preferred reductant in this

Scheme 230. Asymmetric Dimethoxymethylsilane Reductive Coupling of Pyridazines with Styrenes: Synthesis of Nonracemically Alkylated Pyridazines



Scheme 231. Asymmetric Dimethoxymethylsilane Hydrosilylative Alkylative Dearomatization of Pyridazines with Styrenes: Enantioselective Synthesis of 4-Nonracemically Alkylated Pyridazines



work, triethylsilane, *tert*-butyldimethylsilane and *tert*-butyldiphenylsilane worked equally well.

Hayashi carried out the asymmetric hydrosilylation of isomeric dihydrofurans **119** and **120** with (*R*)-MOP **(*R*)-L18** and trichlorosilane (Scheme 248).[192] The use of trichlorosilane allowed for facile oxidation to the corresponding alcohol. The reaction thus resulted in the reduction/oxidation of the C═C,

https://doi.org/10.1021/acs.oprd.1c00073
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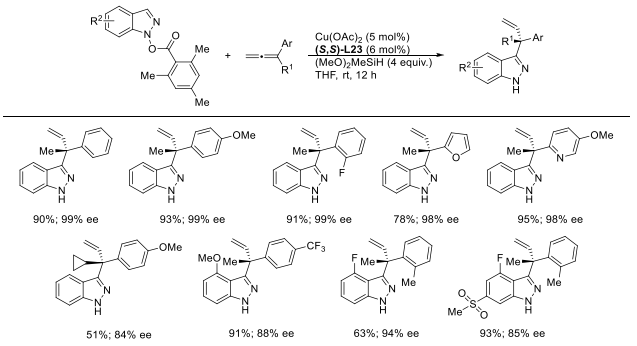
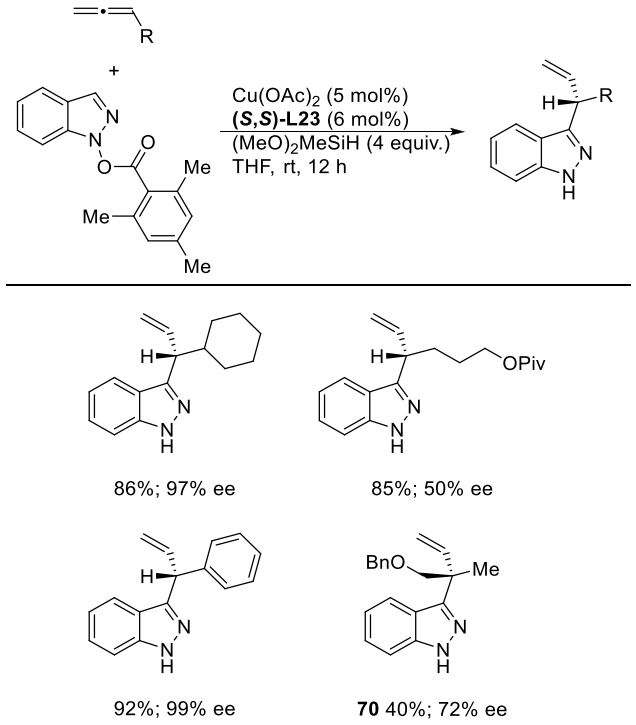
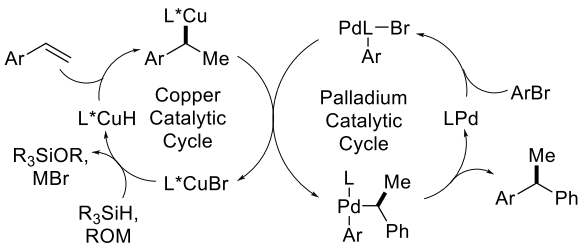
Scheme 232. Asymmetric Allylation of Indazoles with Prochiral 1,1-Disubstituted Allenes: Preparation of Chiral 3-Alkylated Indazoles



Scheme 233. Asymmetric Allylation of Indazoles with Prochiral Allenes: Enantioselective Preparation of 3-Alkyl Indazoles

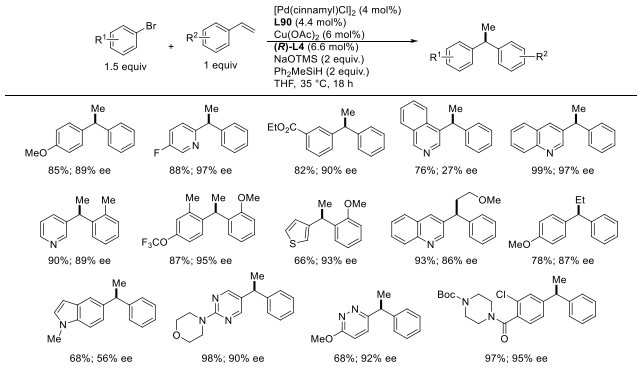


Scheme 234. Proposed Mechanism for the Asymmetric Reductive Coupling of Aryl Bromides with Styrenes



resulting in the overall hydration of the C═C in an asymmetric fashion. The protocol was extended to bicyclic trichlorosilylfurans **121** and **122**.

Scheme 235. Asymmetric Diphenylmethylsilane Reductive Coupling of Aryl Bromides with Styrenes: Enantioselective Synthesis of 1,1-Diarylethanes



In an interesting turnabout, the prochiral silane (1-naphthyl)-phenylsilane reduced three symmetrical ketones to produce the silylated alcohol 1-NpPhSiH(OR) in high enantiomeric excess at silicon (Scheme 249).[193] A number of chiral BINAPs ligated onto Rh successfully produced the silane, with (*R*)-Cybinap (***R*)-L19** or (*S*)-Cybinap (***S*)-L19** proving best.

Buchwald et al. presented a Cu-catalyzed hydrosilylation of styrene derivatives that proceeded not only in a Markovnikov fashion, in contrast to most other known hydrosilylations of styrenes, but also in a highly enantioselective manner (Scheme 250).[194] The reaction was also successfully applied to vinyl heterocycles (Scheme 251). This adds chirality to a list of known organosilane transformations. Diphenylsilane and phenylsilane were both used with good results. In some cases, the diphenylsilyl group was oxidized to the alcohol under Fleming−Tamao conditions, with configuration retention.

Buchwald et al. asymmetrically reduced monosubstituted enyne **123** with CuH generated from 2,4,6,8-tetramethylcyclotetrasiloxane **124** and chiral ligand (***S*,*S*)-L23** to produce 1,3-disubstituted allenes (Scheme 252).[195] This process produced the axially chiral allene in excellent yield and extremely high enantiomeric excess. A number of functional groups proved tolerant of the reaction conditions. The protocol was applied to a synthesis of labailenic acid **126** from enyne **125** (Scheme 253).

Lu et al. reported the sequential asymmetric diphenylsilylation−hydrogenation of aryl acetylenes with a series of cobalt complexes, **L76**−**L80**, of which **L79** proved optimal.[196] The asymmetric step is the hydrogenation of the initially regioselectively formed vinylsilane. Various arylacetylenes were reacted, though none with an *ortho*-substituted aryl group (Scheme 254). Both *tert*-butylacetylene and cyclopropylacetylene produced only the hydrosilylation product, with the subsequent hydrogenation step then taking place. Phenylacetylene was scaled up to a 1.34-g yield, with good results. The reaction between phenylacetylene and bis(3,5-dimethylphenyl)-silane and di-2-naphthylsilane to form **127** and **128**, respectively, was also successful.

14. EXAMPLES OF SCALE-UP APPLICATIONS

A handful of examples were published where a procedure was scaled up to generate significant amounts of the desired product and to further demonstrate the potential for consideration by the process chemist. Those examples are duplicated in this isolated section to fully illustrate some of the scale-up advantages.

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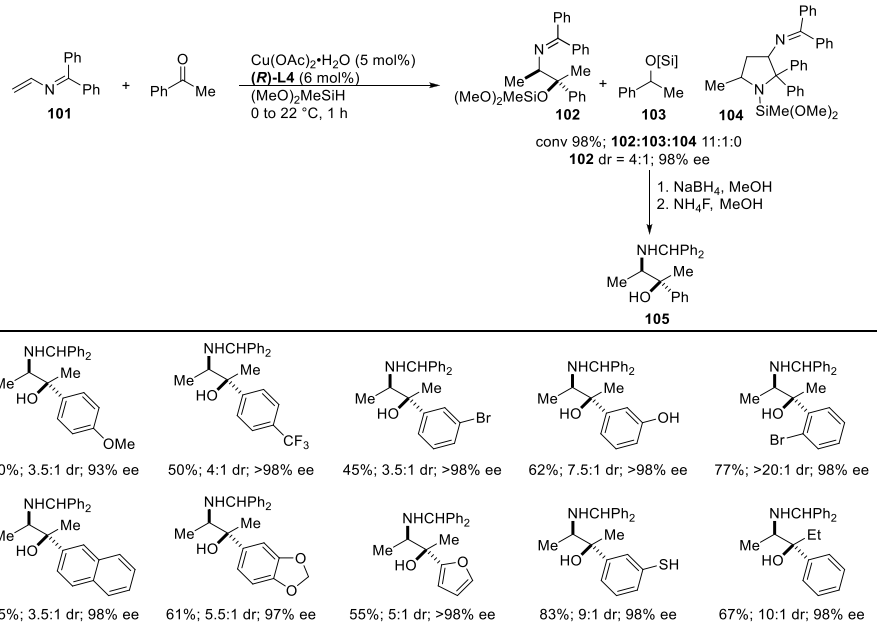
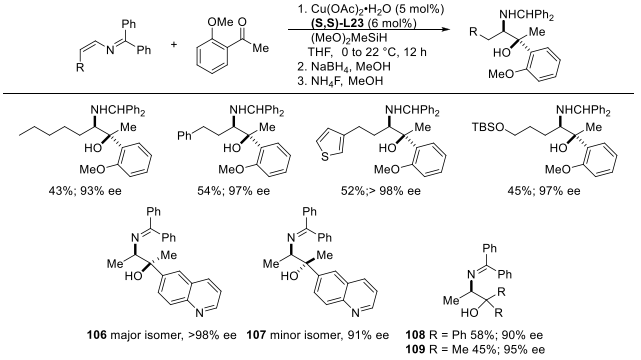
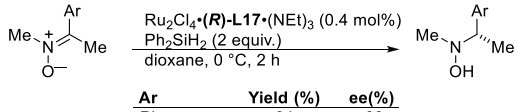
Scheme 236. Asymmetric Dimethoxymethylsilane Reductive Coupling of an *N*-Vinyl Imine with an Aryl Ketone: Diastereo- and Enantioselective Synthesis of *β*-Aminoethanols



Scheme 237. Scope of *N*-Vinyl Imines in the Asymmetric Coupling with 2-Anisyl Methyl Ketone



Scheme 238. Asymmetric Ru-Catalyzed Diphenylsilane Hydrosilylation of Nitrones

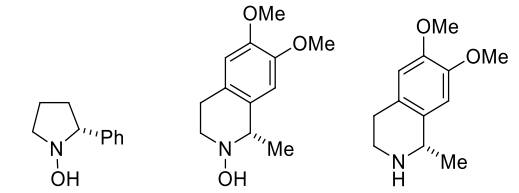


Ar	Yield (%)	ee(%)
Ph	84	83
4-ClC$_6$H$_4$	90	73
4-F-C$_6$H$_4$	59	86
4-MeOC$_6$H y$_4$	63	60
3-ClC$_6$H$_4$	37	86

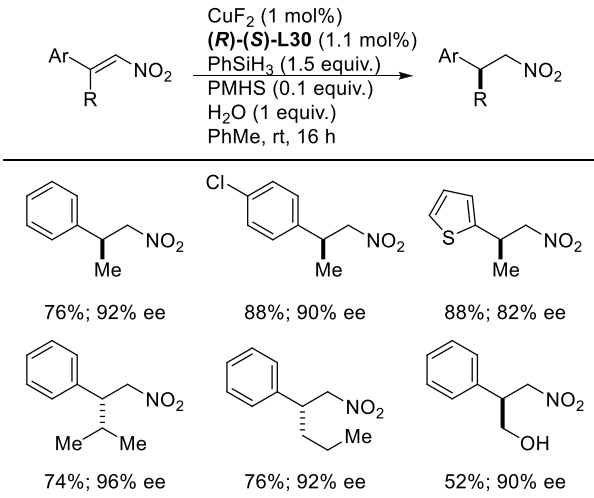
Floriani et al. applied their Zn-catalyzed-diamine ligated protocol to the 200 g scale of the enantioselective reduction of acetophenone (Scheme 255).[63] Although the enantiomeric excess is not ideal, the use of the inexpensive metal and a diamine ligand makes the method worthy of consideration.

Lipshutz et al. carried out the asymmetric conjugate reduction of ethyl (*Z*)-3-phenylbutyrate (Scheme 256).[105] The scale-up resulted in very comparable results from those of the small-scale developmental reaction (see Scheme 40).

Scheme 239. Products from the Asymmetric Reduction of Nitrones According to Conditions of (Scheme 238)



Scheme 240. Asymmetric Cu-Catalyzed Phenylsilane Hydrosilylation of Nitroalkenes



The use of CuCl as the metal and the commercially available (*R*)-**L4** ligand coupled with excellent results makes this an attractive method for application to the asymmetric reduction of aryl ketones (see Scheme 20).[52] This nicely demonstrates the

https://doi.org/10.1021/acs.oprd.1c00073
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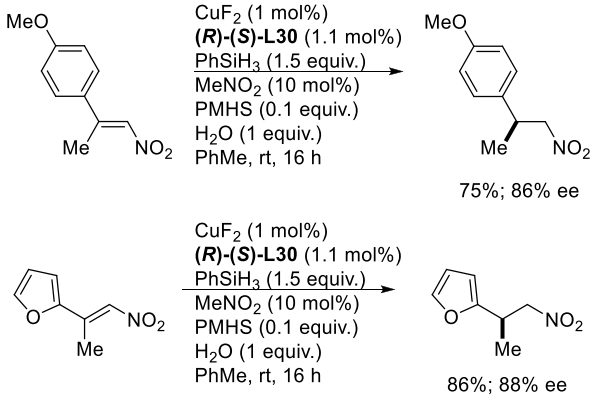
Scheme 241. Asymmetric Cu-Catalyzed Phenylsilane Reduction of Nitroalkenes with Cu-(*R*)-(*S*)-L30 in the Presence of Nitromethane



scalability with practical reagents and an impressisvely low catalyst loading (Scheme 257).

The reductive allylation with allene as the allylating agent was scaled up in high yield and ee with Cu-(*S,S*)-**L25** (see Scheme 151).[142] The allene used was that obtained as a mixture with propyne and propylene, as it comes from the petrochemical industry (Scheme 258).

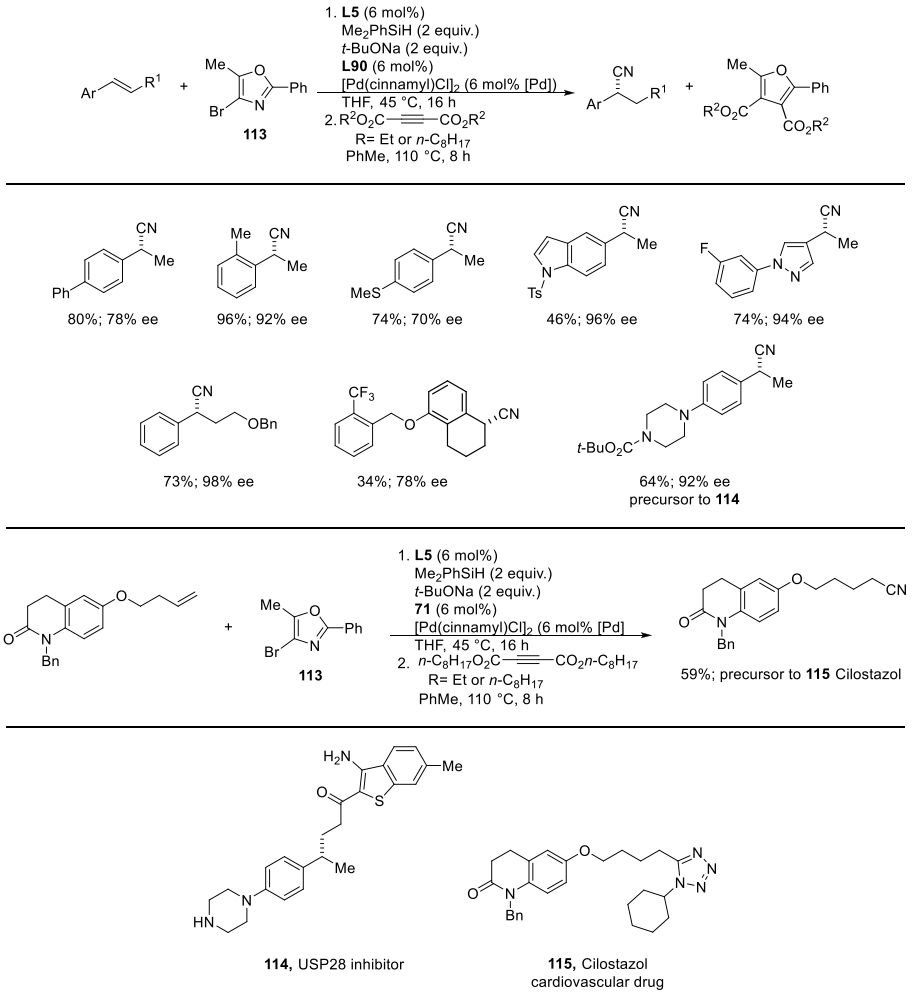
The large-scale CuH-catalyzed asymmetric conjugate reduction of 3,3,5-trimethylcyclohexenone was accomplished with a high yield and ee and with a very low ligand to substrate ratio (Scheme 259).[99] The yield and ee value were similar to those of a number of examples carried out at small scale (Scheme 98). Here again, the use of Cu and the low load of a commercially available ligand bodes well for scale-up.

The reductive coupling of cyclohexanecarboxaldehyde with phenyl acrylate was accomplished in modest yield and ee (Scheme 260).[148] These results were consistent with those of the investigative examples (see Scheme 160). The use of the costly Rh catalyst and the moderate yield and ee values however do not make it a good candidate for commercial applications.

trans-2-Butene was asymmetrically deuterioaminated at a 10 g scale with diphenyldideuteriosilane (Scheme 261).[172] This represents a convenient method for the practical and scalable introduction of deuterium in the β-position of an amine (see Scheme 206).

The asymmetric hydroamination of styrene with anthranil was scaled up to a gram level without loss of yield and ee versus the small-scale examples (Scheme 262).[176] However, the use of

Scheme 242. Asymmetric Dimethylphenylsilane Hydrocyanation of Vinylarenes and Terminal Olefins with Cyanide Equivalent 113: Enantioselective Synthesis of Benzylnitriles



https://doi.org/10.1021/acs.oprd.1c00073
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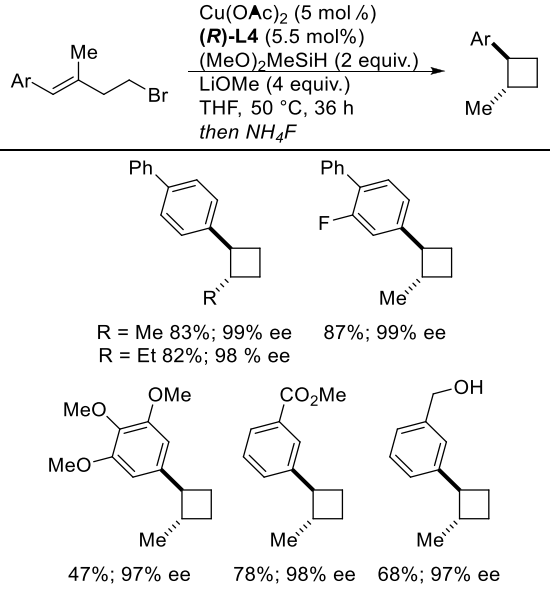
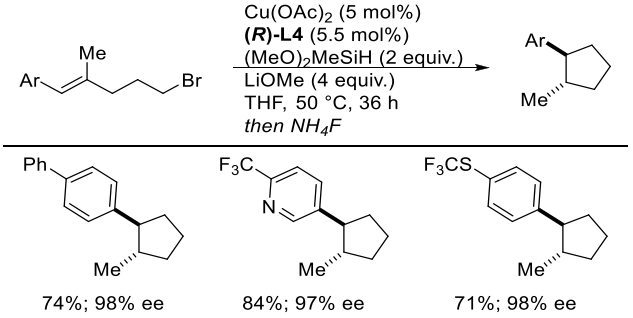
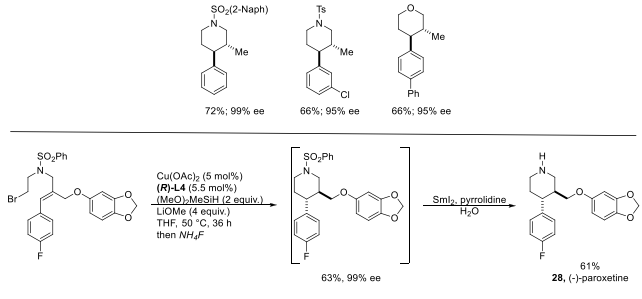
Scheme 243. Asymmetric Reductive Cyclization of a β-Bromoethylstyrene with Dimethoxymethylsilane and (*R*)-L4: Diastereo- and Enantioselective Synthesis of Trans 1,2-Disubstituted Cyclobutanes



Scheme 244. Asymmetric Reductive Cyclization of a γ-Bromopropylstyrene with Dimethoxymethylsilane and (*R*)-L4: Diastereo- and Enantioselective Synthesis of Trans 1,2-Disubstituted Cyclopentanes



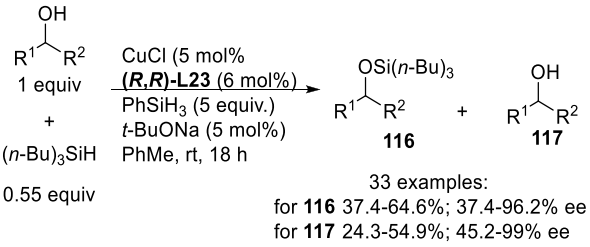
Scheme 245. Examples of Cyclizations of Bromoalkylstyrenes Under Conditions of Scheme 235; Application to a Synthesis of (−)-Paroxetine 28



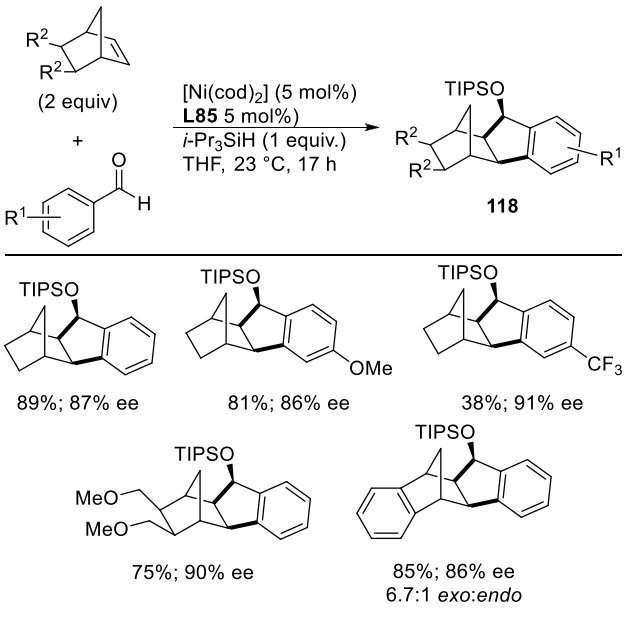
phenylsilane speaks against its potential for commercial applications (see Scheme 218).

As pointed out in Scheme 128, unsaturated ester **44** was asymmetrically reduced in high enantioselectivity and modest yield (Scheme 263).

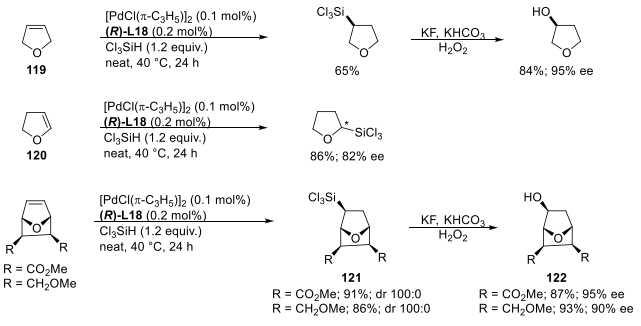
Scheme 246. Kinetic Hydrosilylation of Racemic Secondary Alcohols with Phenylsilane



Scheme 247. Asymmetric NiH-Catalyzed Triisopropylsilane-Mediated Reductive Coupling of Norbornene with Aryl Aldehydes



Scheme 248. Enantioselective Hydrosilylation of 2,5-Dihydrofurans with Trichlorosilane



The asymmetric hydrosilylation of phenylacetylene (see Scheme 254) was scaled up to a 5 mmol level with comparable results to those found in similar reactions at small scale (Scheme 264).[193]

15. OUTLOOK

It is not surprising that based on the considerable utility of organosilanes in numerous racemic reductions that their application to asymmetric reductions would follow. It is abundantly clear from the broad scope of highly successful

https://doi.org/10.1021/acs.oprd.1c00073
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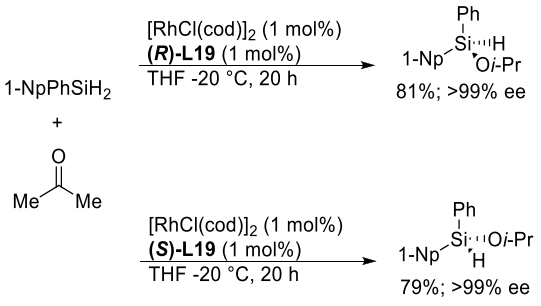
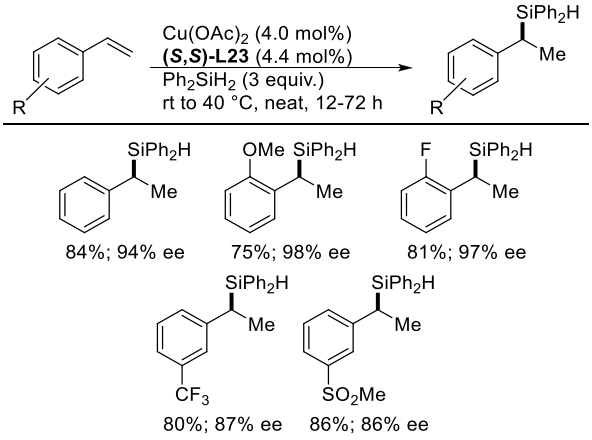
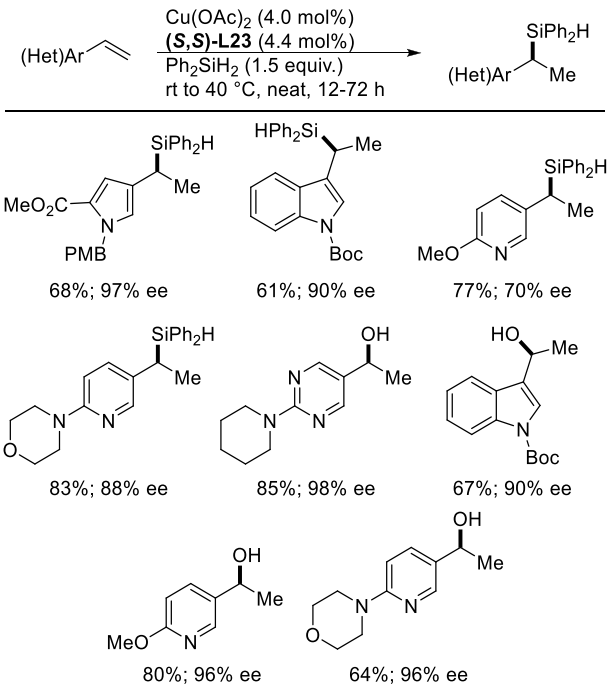
Scheme 249. Asymmetric Hydrosilylation of Acetone with (1-Naphthyl)phenylsilane: Enantioselective Synthesis of (1-Naphthyl)(phenyl)isopropoxysilane



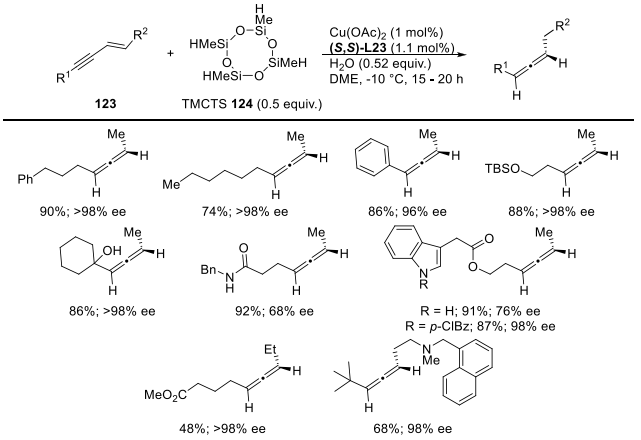
Scheme 250. CuH-Catalyzed Asymmetric Hydrosilylation of Styrenes with Diphenylsilane: Enantioselective Synthesis of 1-(Arylethyl)diphenylsilanes



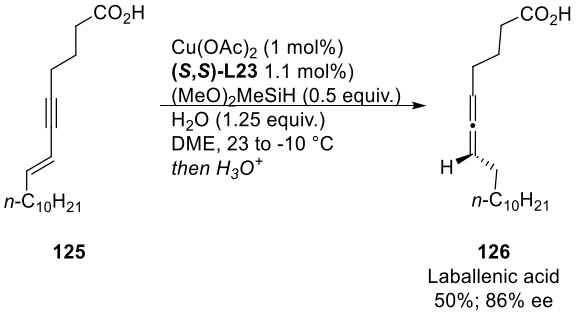
Scheme 251. Asymmetric Hydrosilylation of Vinylheteroaromatics with Diphenylsilane



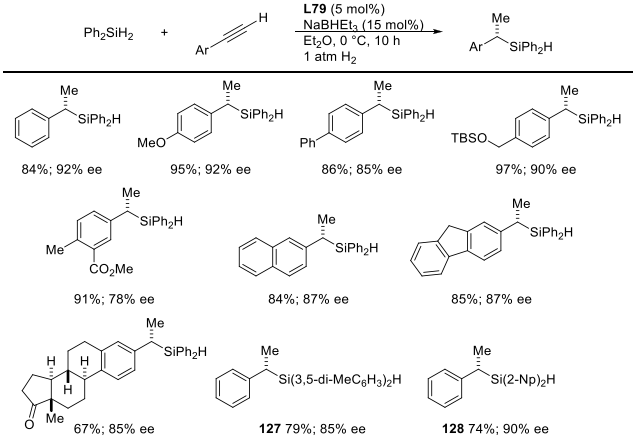
Scheme 252. Asymmetric Dimethoxymethylsilane Reduction of Enynes to Allenes: Enantioselective Synthesis of 1,3-Disubstituted Allenes



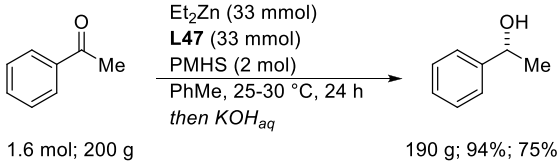
Scheme 253. Asymmetric Reduction of Enyne 125 to Laballenic Acid 126



Scheme 254. Asymmetric Hydrosilylation of Ethynyl Arenes with Diphenylsilane



Scheme 255. Large-Scale Asymmetric PMHS Reduction of Acetophenone with L47



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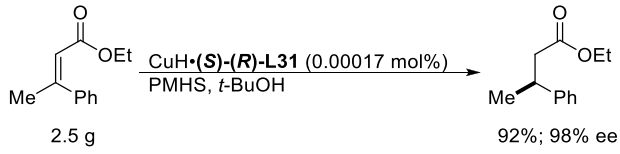
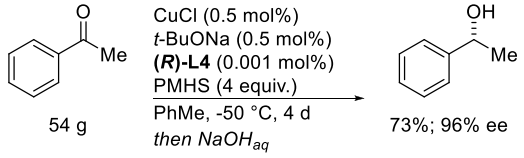
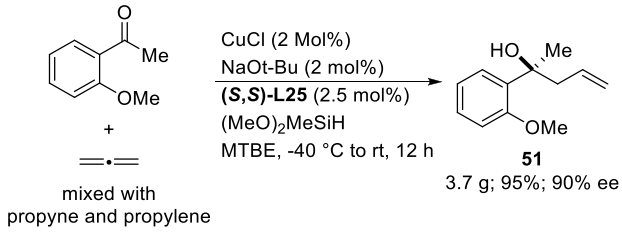
Scheme 256. Large-Scale Asymmetric Reduction of Ethyl (*Z*)-3-Phenylbutyrate with CuH·(*S*)-(*R*)-L31



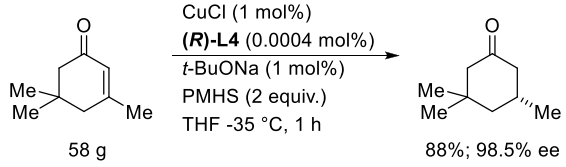
Scheme 257. Large-Scale Asymmetric Reduction of Acetophenone with Cu-(*R*)-L4



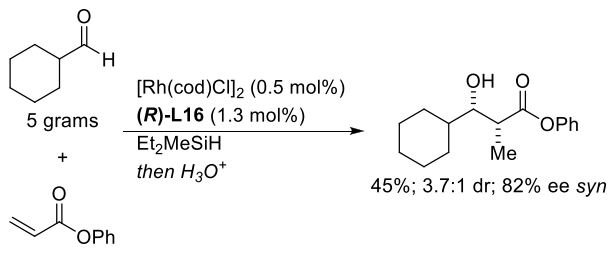
Scheme 258. Large-Scale Asymmetric Allylation of 2-Methoxyacetophenone with Cu-(*S,S*)-L26 and Allene



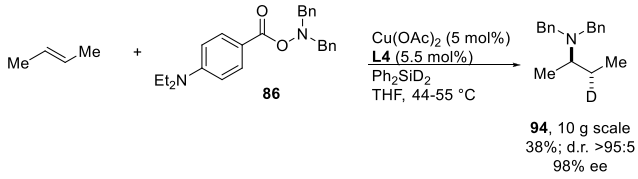
Scheme 259. Large Scale Asymmetric Reduction of an Enone with Cu-(*R*)-L4



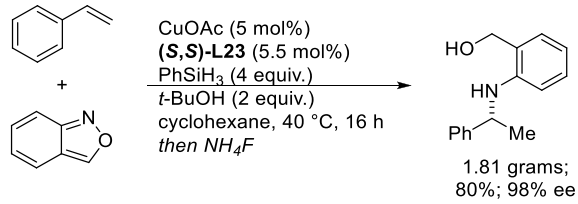
Scheme 260. Large-Scale Asymmetric Coupling of an Cyclohexylcarbaldehyde and Phenyl Acrylate with Rh-(*R*)-L16



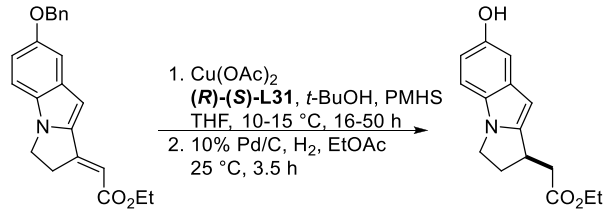
Scheme 261. Deuterioamination of *trans*-2-Butene with Ph_2SiD_2 and Cu-L4



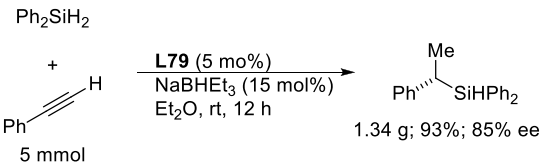
Scheme 262. Large-Scale Asymmetric Phenylsilane-Mediated Hydroamination of Styrene with Anthranil



Scheme 263. Large-Scale Asymmetric Reduction of α,β-Unsaturated Ester 44 with Cu-(*R*)-(*S*)-L31



Scheme 264. Scale-up of Asymmetric Hydrosilylation of Phenylacetylene



protocols and range of applications presented herein that the application of the use of nonracemic organometallic reagents in conjunction with organosilanes as the stoichiometric hydride source will continue. Like many of the now commonly used transition metal catalyzed reactions, work will proceed, not only in seeking catalysts based on new nonracemic ligands but also with an emphasis on applying the existing chemistry to more readily scalable and economical protocols. The use of organosilane reductants in the many examples shown herein has the advantages of being safe and plentiful with the strength of the Si−O bond being a strong driving force in the reactions. In addition future work in the area has the opportunity for the reactions to be carried out under aqueous conditions thereby excluding the wasteful use of organic solvents. Work along these lines continues to appear (consult *Org. Lett.* **2021**, *23*, 3282).

For example, numerous examples with excellent chemical yields and enantioselectivities rely on high catalyst loads and costly ligands along with expensive metals such as rhodium or iridium. Thus, the authors anticipate efforts to continue the use of less expensive metals such as copper, zinc, and nickel, among others. In the area of the organosilane, the range is wide with many examples requiring the more expensive phenylsilane or diphenylsilane, whereas a good many make use of the more economical and more easily handled polymethylhydrogensiloxane (PMHS) and tetramethyldisiloxane (TMDS). Of particular note along these lines is the application of CuH-catalyzed enantioselective reduction of α,β-unsaturated ketones, esters, and nitriles and the asymmetric hydroamination. In these reactions the CuH is very conveniently generated in situ via the

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reaction of an inexpensive copper salt and the silane of choice, and typically PMHS. These asymmetric reductions are essentially without competition from other protocols.

In addition to the continued improvements on the work presented, the authors envision further applications toward the syntheses of biologically important products. In short, we foresee a widespread continuation of applications along with improvements based on the results reviewed herein.

16. CONCLUSIONS

The modest polar nature of the Si−H bond provides a hydridic hydrogen which gives organosilanes an advantage over that of dihydrogen, particularly in terms of chemoselectivity. The polarization is in addition to organosilanes offering a range of steric, electronic and ease of handling characteristics. This review highlights the numerous efforts in advancing the well-established area of organosilane reductions to organosilane-promoted stereoselective reductions (hydrosilylations). These studies have been successfully applied to an extensive variety of prochiral substrates, notably ketones, imines, unsaturated carbonyls, three-component reductive coupling protocols and hydroaminations among others. Moreover, in many cases they have been scaled up and applied to short syntheses of biologically important products. The applications represent a number of metal catalysts for reactivity, nonracemic ligands for stereoselectivity and organosilanes as a stoichiometric hydrogen source, thus providing the synthetic chemist with numerous options. The various metal catalysts incorporate not only reactivity differences but also economic and handling differences. Importantly, the vast majority of the silanes, metal catalysts and ligands are commercially available. Most notably, the large number of protocols cited and their numerous applications fully demonstrate the range of possibilities that include, in addition to the obvious yield and enantioselectivity results, the ability to design systems for more convenient product purification, ease of reaction, scale up and economic issues. The large number of impressive applications presented will clearly generate further useful applications and variations and will aid the chemist in many future synthetic endeavors.

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Notes

The authors declare no competing financial interest.

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