Review

CuH-Catalyzed Reactions

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CuH-Catalyzed Reactions

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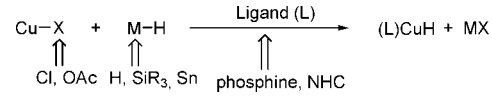
1. Introduction

Since the groundbreaking work by Gilman[1] in the 1950s, cuprates have become versatile tools in organic synthesis, more precisely, in 1,4-addition reactions to α,β-unsaturated acceptors,[2] as well as in S_N2'- and S_N2-substitutions[3] which can be performed with stoichiometric or catalytic amounts of copper in a stereo- and enantioselective fashion. Thus, it is surprising that the corresponding C−H bond formation using copper hydrides, which are enjoying a rich history dating back to the mid 1800s, stayed highly underdeveloped until the end of the last century. Modern usage of CuH in synthesis is well recognized to have begun with "Stryker's reagent" in 1988.[4] In a series of publications, Stryker et al. described the remarkable tendency of the phosphine-stabilized hexamer, $[(Ph_3P)CuH]_6$, to effect highly regioselective conjugate reductions of various carbonyl derivatives, including unsaturated ketones, esters and aldehydes. The mildness of the reaction conditions, functional group compatibility, and excellent overall efficiencies were deemed so impressive that this beautifully crystalline red solid was quickly propelled to the status of "Reagent of the Year" in 1991.

That this mild hydride source can also be used catalytically, in particular with inexpensive and environmentally benign silanes, has shifted the spotlight (insofar as development of new methodologies is concerned) toward asymmetric uses of these net hydrosilylation reactions. Following a previous review in 2002,[5] further advances of this fast growing field were recently highlighted by Oestreich and Rendler.[6] Herein the focus is on more details associated with developments beginning with the new millennium; for complete coverage of previous work, the reader is referred to the reviews mentioned above.

Scheme 1. Preparation of Ligated Copper Hydrides



2. Generating Stryker's Reagent and Alternatives

The most common and frequently used copper hydride species is the phosphine-stabilized hexamer, $[(Ph_3P)CuH]_6$, the so-called "Stryker's reagent".[7] The early recipe leading to this commercially available complex[8] that called for CuCl plus an equivalent of NaO*t*-Bu to generate CuO*t*-Bu is still used, especially since CuO*t*-Bu is no longer commercially available.[9] To avoid this extremely air-sensitive system, advances have been made of late such that the precursor Cu−O bond no longer needs to be formed *in situ* from these salts. That is, $Cu(OAc)_2 \cdot H_2O$ has been found to be an attractive replacement which streamlines the procedure to generate CuH.[10] *Yun* and co-workers pointed out that, if copper(II) acetate as copper source is used, in contrast to the CuCl/NaO*t*-Bu combination, repeated crystallization is not necessary to obtain Stryker's reagent in high purity and yields. Usually, the phosphine is present prior to addition of a silane to ensure stabilization of the *in situ* formed CuH through complexation.[11] (Scheme 1).

For generating copper hydride, silanes, which in general are inexpensive and environmentally friendly, are the most common source of stoichiometric hydride. A brief summary of several combinations that produce CuH is shown in Table 1. A more detailed description (with additional references) and reactivity studies for these "cocktails" are discussed herein.

Polymethylhydrosiloxane (PMHS)[22] is oftentimes listed as a 29-mer, and as a stoichiometric source of hydride it can vary widely in nature between vendors. Material from Lancaster (catalog #L14561) appears to give reproducible CuH chemistry, while PMHS from Acros can lead to different (vastly inferior) results. PMHS is used as received from the vendor, although it should be handled and stored under argon in a multiply septumed bottle to maximize lifetime. Tetramethyldisiloxane (TMDS; Alfa catalog #12934) is another inexpensive silane that, on occasion, is a superior source of hydride (*vide infra*). Also available are Fleming's

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Carl Deutsch, born 1978 in Dinslaken (Germany), studied chemistry in Dortmund, where he obtained his diploma, under the supervision of Prof. N. Krause, for work on the stereoselective synthesis of functionalized α-hydroxyallenes and their conversion into 2,5-dihydrofurans. His current research as Ph.D. student in the Krause group is focused on the copper-hydride catalyzed reduction of propargylic electrophiles to allenes and their application in target oriented synthesis. Parts of his research were carried out with Prof. B. H. Lipshutz (Santa Barbara, CA, U.S.A.) and, as JSPS fellow, with Prof. M. Murakami (Kyoto, Japan).

Norbert Krause obtained his Ph.D. degree in 1986 at the Technical University of Braunschweig and was Postdoctoral Fellow at the ETH Zürich (Switzerland) and Yale University (New Haven, CT, U.S.A.). He obtained his Habilitation for Organic Chemistry at the Technical University of Darmstadt in 1993, became Associate Professor at Bonn University in 1994 and Full Professor at Dortmund University in 1998. His research in organometallic and allene chemistry has been recognized through the award of the "Heinz-Maier-Leibnitz-Preis" (1991), a Heisenberg scholarship (1994), and a "Japan Society for the Promotion of Science (JSPS) Fellowship" (2003). He is member of the Editorial Board of the *European Journal of Organic Chemistry* (since 2006) and has been Guest Professor at the Université Catholique der Louvain (Louvain-la-Neuve, Belgium) in 2007.

silane ($PhMe_2SiH$) and phenylsilane ($PhSiH_3$) that are occasionally used.

Switching to nonracemic bis-phosphines from triphenylphosphine as ligand leads to a chiral copper hydride species that performs reactions in a diastereo- and enantioselective fashion. Virtually all success realized to date with asymmetrically ligated CuH has come from a relatively small subset of either biaryl or ferrocenyl bis-phosphines. Most notably, selected biaryls of the BIPHEP[23] and SEGPHOS[24] series deserve special merit not only for their remarkable discriminatory structural features but also for the turnover numbers (TONs) now possible as their CuH complexes. The same is true for certain chelators in the JOSIPHOS[25] series. The biaryl ligands and the ferrocenyl derivatives shown in Figure 1 are commercially available both in quantity and in

Bruce Lipshutz arrived at UC Santa Barbara as an Assistant Professor in 1979, following years of training by three exceptional mentors: Howard Alper (B.A.; SUNY Binghamton), Harry Wasserman (Ph.D.; Yale), and postdoctoral advisor E. J. Corey (Harvard). A considerable portion of his 29+ year career has been devoted to developing reagents of general use for the synthetic community (e.g., SEM-Cl, "Higher Order Cuprates", "Cuprate-in-a-Bottle", DCAD, "Copper Hydride-in-a-Bottle", Ni/C, Cu/C, etc.). The group's efforts have now turned to a mix of heterogeneous catalysis, including development of mixed metal-supported cross-coupling reagents, and homogeneous catalysis. The latter include considerable effort in micellar catalysis, where several "name" reactions can be carried out in pure water using the commercially available nonionic amphiphile "PTS". A number of projects in total or partial synthesis involving axially chiral biaryls (e.g., the A-B biaryl section of vancomycin, and the antimalarial korupensamines), and new technologies associated with, and/or derived from, coenzyme Q_{10} (e.g., total synthesis of piericidin A1) are also well underway.

enantiomerically pure form. They are stable solids best stored in a glovebox or equivalent fashion protected from air to avoid phosphine oxidation.

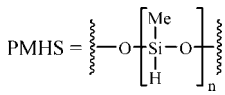
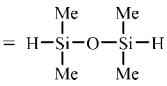
Nowadays, N-heterocyclic carbenes[26] (NHCs) are becoming very popular as an alternative to phosphine ligands. Use of isolated, air stable copper−carbene complexes,[27–29] in particular, has become an attractive alternative. NHCs are quite distinct from tertiary phosphines both electronically (as strong σ-donors and weak π-acceptors, effecting stronger interaction with the metal) and structurally (with a likely linear array between the carbene carbon, copper, and hydrogen atoms). Usually, the CuH catalyst is prepared from the starting imidazolium salt **4** by treatment with base and CuCl, followed by *in situ* conversion in the presence of a silane (Scheme 2). In contrast to the corresponding cuprates for C−C-bond formation, nonracemic carbene based copper hydride species have not been used in organic synthesis to date.

A drawback of the systems described so far is the fact that, except for Stryker's reagent itself, each of these reactive species must be generated *in situ*. This was recently addressed by Lipshutz and Frieman[30] who described a chiral copper hydride species bearing the SEGPHOS ligand **2b**, a complex which is exceptionally stable and can be easily stored in solution if kept under argon (Scheme 3). This so-called "CuH-in-a-Bottle" can be used directly without initial preparation of copper hydride, making it to a user-friendly, easy-to-handle alternative source of CuH.

The same group has also developed a heterogeneous catalyst by immobilizing copper oxides on charcoal together with DTBM-SEGPHOS **2b** as chiral ligand (Scheme 4).[31] This precursor, when treated with PMHS as stoichiometric hydride source in toluene leading to CuH, works in most cases as well as the corresponding homogeneous version of

Table 1. Frequently Used Reagent Combinations for Generating CuH

copper source	additive	hydride source	references
CuCl	NaO*t*-Bu	H_2	12
		Bu_3SnH	13
		$PhSiH_3$	14
		PMHS[a]	15
		TMDS[b]	16
$(Ph_3P)CuF\cdot 2EtOH$	–	$PhMe_2SiH$	17
$Cu(OAc)_2\cdot H_2O$	–	PMHS[a]	9, 10
$CuCl_2\cdot 2H_2O$	–	PMHS[a]	18
$[(3,5\text{-xylyl})_3P]_2CuNO_3$	–	H_2	19
CuO*t*-Bu	–	PMHS[a]	20
CuF_2	–	$PhSiH_3$/PMHS[a]	21

[a] PMHS =  [b] TMDS = 

this catalytic system, adding the advantage of simplicity of workup (just by filtration), recyclability of the catalyst, and minimization of waste. Therefore, this system is very attractive from both the ecological and economical points of view.

With several sources of copper hydride now available, the focus of current CuH chemistry continues to be on catalytic asymmetric processes. Thus, both 1,2- and 1,4-additions of hydride to a variety of electrophilic centers have been

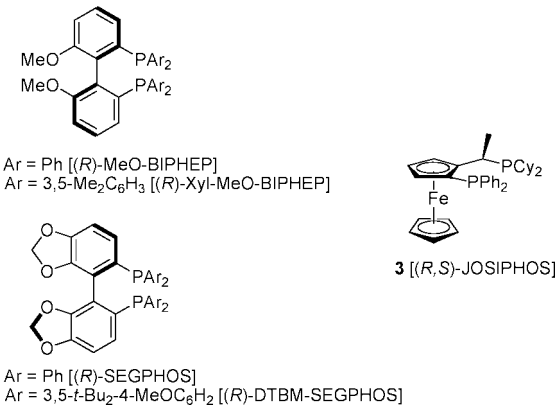
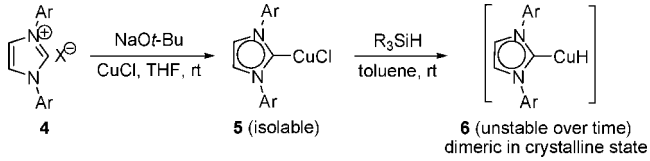
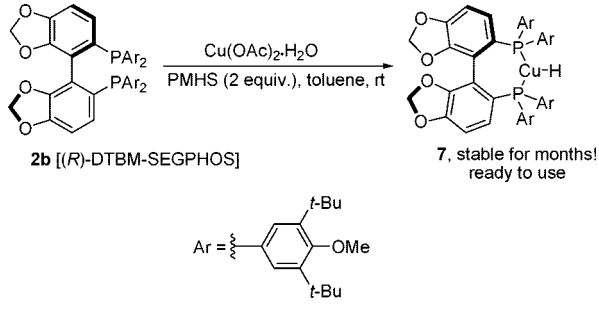


Figure 1. Bis-phosphines used for enantioselective copper hydride reactions.

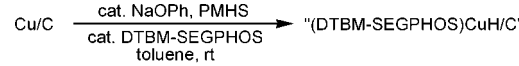
Scheme 2. Preparation of Copper Hydride–NHC Complexes



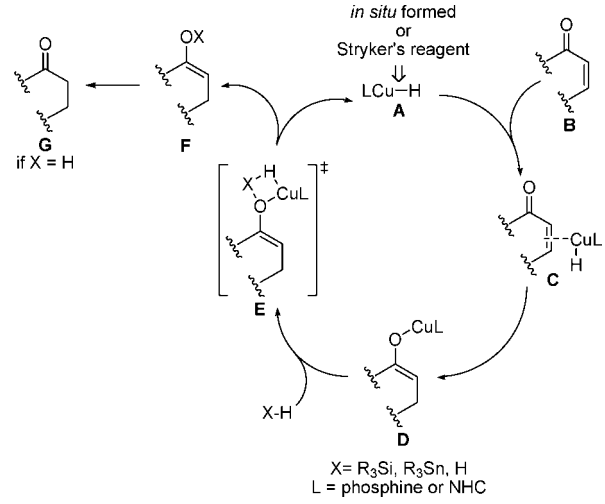
Scheme 3. Preparation of "CuH-in-a-Bottle"



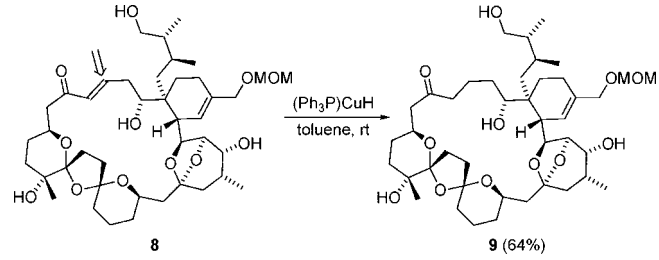
Scheme 4. Preparation of a Heterogeneous CuH Catalyst



Scheme 5. Proposed Catalytic Cycle for Conjugate Reductions



Scheme 6. 1,4-Reduction with Stoichiometric Amounts of $(Ph_3P)CuH$



developed, where the level of chiral induction derives from the innate bias of the ligand–metal complex. These results, as well as reactions with alkynes and applications of copper hydride to targets in total synthesis, will be discussed in the following sections.

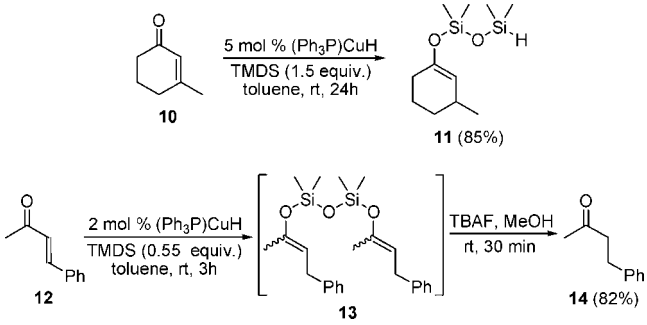
3. 1,4-Reductions and Related Reactions

3.1. 1,4-Reduction of Enones, Enoates and Related Michael Acceptors Mediated or Catalyzed by Copper Hydride

A very reliable method for the construction of tertiary centers of chirality is copper-mediated or -catalyzed C–C-bond formation using α,β-unsaturated Michael acceptors like unsaturated carbonyl compounds, sulfones etc.[32] These reactions take advantage of the carbophilic nature of copper, usually affording the 1,4-addition product exclusively. Nevertheless, an alternative and equally efficient means relies on introduction of hydrogen instead of carbon. This can be accomplished using phosphine-[4b] or NHC-stabilized copper hydrides (Schemes 5, 6).[27–29]

Not long after Stryker's initial report on stoichiometric uses of $[(Ph_3P)CuH]_6$, it was discovered that a catalytic cycle could be established in which molecular hydrogen serves as hydride source[33] (X = H, Scheme 5). Here, the carbophilic copper hydride species **A** reacts with the Michael acceptor **B** (in this particular case an enone) to form a π-complex **C**. Delivery of the hydride to the β-carbon atom affords the

Scheme 7. 1,4-Reduction with Catalytic Amounts of $(Ph_3P)CuH$



enolate **D**, which undergoes a σ-bond metathesis with the stoichiometric hydride source via transition state **E**, thus closing the cycle by regaining the catalytically active copper hydride species **A** and releasing species **F** which will tautomerize to product **G**. Although the yields are very good, a rather high hydrogen pressure (typically 70 bar) is required to obtain complete conversion, and therefore, over-reduction products are occasionally formed in varying amounts.

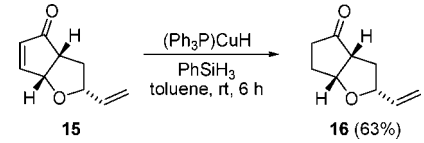
To avoid such undesirable secondary events, an appropriate method is the use of stoichiometric amounts of Stryker's reagent. Such a copper-mediated conjugate reduction was recently used by Hirama et al. in their total synthesis of the shellfish poison (+)-pinnatoxin A.[34] A key step in this synthesis was the chemoselective reduction of α,β-unsaturated ketone **8** with excess Stryker's reagent forming the macrocyclic intermediate **9**. Although only a moderate yield was obtained, this reaction showcases the benefits of copper hydride chemistry in an impressive way: high chemoselectivity, and considerable tolerance to a second double bond as well as a variety of functional groups (alcohols, acetals, ethers) and stereogenic centers.

These advantages, well documented by the Stryker group in their early contributions to the field,[4] were a driving force for further improvements. The basis for these new developments lies in an appreciation for the facility with which various silyl hydrides undergo transmetalation with copper enolates.[35] These hydride sources not only are easier to handle than hydrogen gas at elevated pressures but also essentially guarantee that no over-reduction will take place. Gratifyingly, the high tolerance toward functional groups, the mildness of the reaction conditions, and especially the chemoselectivity are not affected. As silanes, the earlier noted TMDS and PMHS are those most frequently used, allowing for reduction of α,β-unsaturated ketones with catalytic amounts of Stryker's reagent (Scheme 7).[16] It is remarkable that TMDS supplies both of its hydrides and, therefore, substoichiometric amounts of the silane can be used. It should be noted, however, that Stryker's reagent has a limited shelf life, and unless fresh material is first checked by ^1H NMR for hydride (δ 3.50 in C_6D_6), its use as catalyst can be unfruitful.

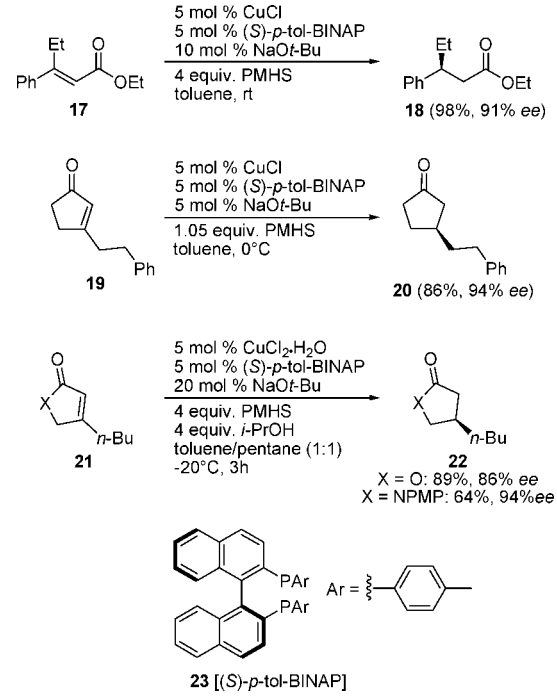
Chandler and Phillips used stoichiometric amounts of Stryker's reagent and phenylsilane for the synthesis of the ketone **16**, a precursor of the marine natural product (±)-*trans*-kumausyne (Scheme 8).[36]

Inspired by early work on CuH, Buchwald et al. developed the first enantioselective conjugate reduction[37] using *in situ* generation of a bis-phosphine-stabilized chiral CuH species from CuCl as copper source, NaO*t*-Bu as base, and (*S*)-*p*-tol-BINAP **23** as chiral ligand (Scheme 9). With this system,

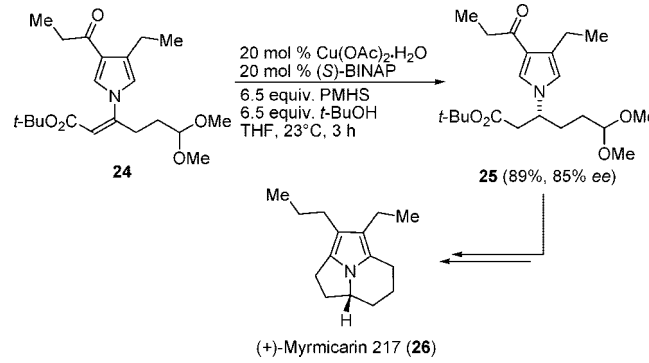
Scheme 8. 1,4-Reduction with Stoichiometric Amounts of $(Ph_3P)CuH$ and $PhSiH_3$



Scheme 9. Catalytic Enantioselective 1,4-Reduction of Enones and Enoates



Scheme 10. Synthesis of Myrmicarin 217 by Catalytic Enantioselective 1,4-Reduction

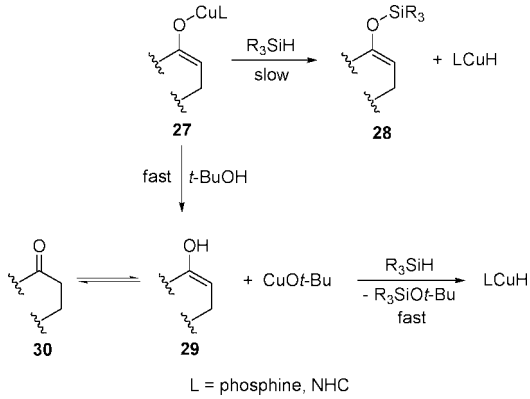


enones as well as unsaturated esters, lactones, and lactams undergo smooth 1,4-reduction furnishing the corresponding saturated systems in very good yields and high ee's.

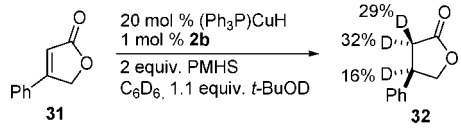
Advantage was taken of the method in its application to the synthesis of tricyclic myrmicarin alkaloids, e.g. myrmicarin 217 (Scheme 10).[38] Because of the high steric hindrance at the β-site in Michael acceptor **24**, somewhat higher catalyst loadings of the *in situ* formed chiral copper hydride complex were needed.

One of the key "tricks" to this chemistry is to take advantage of the tolerance of CuH complexes to alcohols and water. In fact, several methods rely on the presence of a bulky alcohol (e.g., *t*-BuOH) to enhance reaction rates; this can be the difference between considerable success and borderline total failure. Since the amount of added alcohol

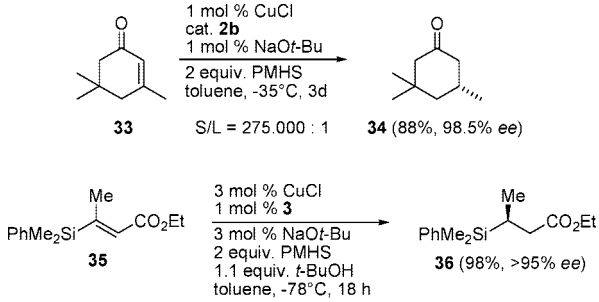
Scheme 11. CuH-Catalyzed Reduction in the Presence of Alcohols



Scheme 12. Deuteration Experiment: Effect of Alcohol in CuH-Catalyzed Reduction



Scheme 13. Catalytic Enantioselective 1,4-Reductions with SEGPHOS and JOSIPHOS Ligands

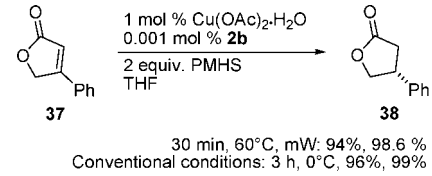


is usually on the order of only 1−3 equiv, it takes relatively little (volumewise) to accelerate these hydrosilylations. The role of this additive is usually ascribed to the more rapid quenching of an intermediate copper enolate, generating a copper alkoxide which is an ideal precursor to rapid re-formation of CuH in the presence of excess silane (Scheme 11). Thus, the rate increase is presumably due to bypassing a slow metathesis step between Cu−O and Si−H bonds that is otherwise essential for regenerating CuH in the catalytic cycle (cf. Scheme 5).

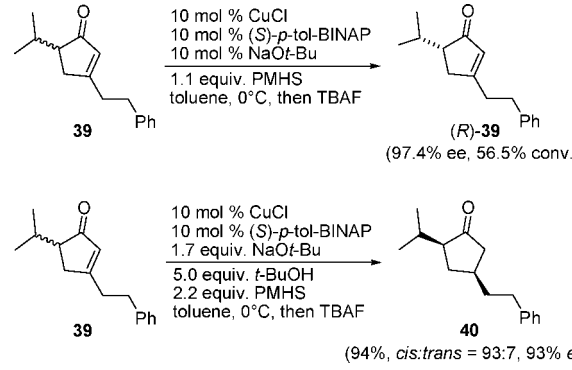
This proposed mechanism was supported in studies using *t*-BuOD (Scheme 12).[39] Asymmetric hydrosilylation of unsaturated lactone **31** revealed that most of the deuterium is incorporated at the α-position, while only small amounts were found at the *β*-position. Thus, since no exchange occurs between PMHS and *t*-BuOD, it would seem that the rate enhancement may well be due to more rapid quenching of a copper enolate by the alcohol than by the silane.[40]

Improvements in both enantioselectivity and reactivity toward sterically hindered systems followed these reports based on BINAP ligands. In a series of publications, Lipshutz and co-workers found that JOSIPHOS- and SEGPHOS-derived chiral CuH species lead to higher levels of chiral induction than those obtained with the corresponding BINAP-CuH derivatives (Scheme 13).[15,41] Whereas SEGPHOS (**2b**) ligands work best for cyclic enones, JOSIPHOS-type bis-phosphines (**3**) give excellent results for acyclic enones.

Scheme 14. Catalytic Enantioselective 1,4-Reduction under Microwave Conditions



Scheme 15. Kinetic and Dynamic Kinetic Resolution by CuH-Catalyzed 1,4-Reduction



Besides increased enantioselectivities, there are other benefits to using these chiral bis-phosphines in copper hydride chemistry. As nonligated CuH present in a reaction medium is not stable and thus likely to decompose, metal to ligand ratios larger than one can be used to ensure full complexation of the ligand (Scheme 14). To avoid elongated reaction times caused by low catalyst loadings, microwave irradiation can be used. Under these conditions (Scheme 14) almost no erosion of enantioselectivity was observed.[42]

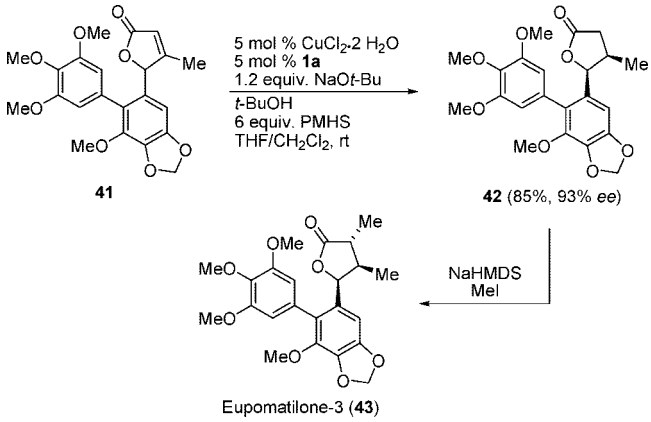
A remarkable extension for the generation of two stereogenic centers was reported by Buchwald and co-workers.[18,43] This group used their chiral CuH system for the kinetic resolution of α,*β*-unsaturated lactones,[37c] as well as the kinetic or dynamic kinetic resolution of 2,4-dialkylcyclopent-2-enones (Scheme 15).[43]

In the presence of catalytic amounts of NaO*t*-Bu as base, an efficient kinetic resolution of racemic enones takes place to afford the less reactive enantiomer with high ee. For dynamic kinetic resolution, however, an excess of NaO*t*-Bu and *t*-BuOH serves to accelerate racemization of the substrate to such an extent that the reduction product (e.g., **40**) can be isolated in high yield and enantiomeric excess. The usefulness of the method was demonstrated in a short synthesis of the lignan eupomatilone-3 (**43**; Scheme 16).[18]

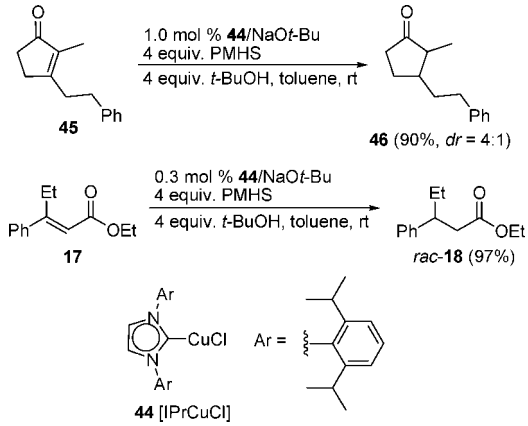
An interesting achiral alternative for Stryker's reagent can be generated by exchanging the phosphine against an N-heterocyclic carbene.[44] The isolable CuCl−carbene complex **44** was treated with a base to generate the corresponding NHC−CuO*t*-Bu complex *in situ*; this ultimately forms a reactive copper hydride complex in the presence of PMHS (Scheme 17).

This system reacts smoothly with cyclic and acyclic enones furnishing the saturated products in excellent yields. With its application to the synthesis of the precursor **48** of kainic acid (Scheme 18), a natural non-proteinogenic amino acid, carbene complex **44** clearly offers a very useful alternative to Stryker's reagent.[45]

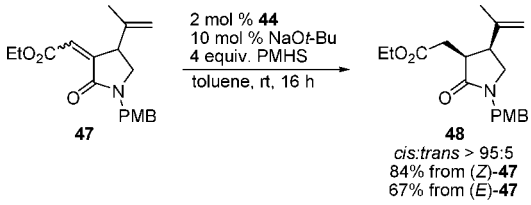
Scheme 16. Synthesis of Eupomatilone-3 by Dynamic Kinetic Resolution



Scheme 17. 1,4-Reduction with an NHC−Cu Complex



Scheme 18. Synthesis of a Precursor for Kainic Acid Using NHC−Cu Complex 44



3.2. Tandem Modifications

Conjugate reductions using *in situ* formed CuH can be exploited further when run in the presence of an electrophile, inducing an inter- or intramolecular trapping of the reduction product. In initial studies, Lipshutz et al. treated several enones with catalytic amounts of Stryker's reagent and a silane forming the silyl enol ether which, in the presence of a Lewis acid (e.g., $TiCl_4$), reacted with aldehydes to the corresponding aldol products (Scheme 19).[16] If a borane instead of a silane is used as hydride source, the transmetalation step can lead directly to a *Z*-boron enolate, thereby affording *syn*-aldol products.[46] Not long after this, Chiu and co-workers[47] reported an intramolecular reduction−aldol addition reaction as a key step in their total synthesis of lucinone (**55**), an antispasmodic drug (Scheme 19).[47b]

It is not surprising that enantioselective conjugate reductions with L*CuH (L* = chiral ligand) have also been used in tandem reactions. For example, Yun and Buchwald applied their (*S*)-*p*-tol-BINAP-stabilized CuH system toward a reduction−alkylation protocol,[48] as well as for Pd-catalyzed cross-coupling reactions (Scheme 20).[49] In the latter case, lower amounts of the CuH catalyst must be used, otherwise no cross-coupling is observed.

Chiral CuH catalysts have also been applied to the tandem 1,4-reduction−aldol reaction.[50] Thus, aromatic aldehydes and ketones (e.g., **62**) react with the copper enolate generated by 1,4-hydride addition to methyl acrylate **63** to afford the aldol adduct of type **65** with high *syn*-selectivity and good-to-excellent ee's (Scheme 21).[50] The chiral ligand of choice for this transformation is TANIAPHOS (**64**). Since the chirality transfer must derive from an asymmetrically ligated copper enolate, reactions are best carried out in toluene at low temperature; under these conditions, the aldol reaction occurs faster than metathesis with the silane ($PhSiH_3$) so that formation of the nonalkylated ester or silyl enol ether is avoided. The implication of a strong preference for formation of a *Z*-copper enolate has yet to be rationalized. Related trapping reactions with dialkyl ketones have also been reported with modest success.[50d]

Intramolecular versions leading to newly formed 5- and 6-membered ring lactones (e.g., **67**) are smoothly catalyzed by nonracemically ligated CuH formed *in situ* using $Cu(OAc)_2$/TMDS in THF or DME. Several biaryl bis-phosphines were surveyed; e.g., (*R*)-Xyl-MeO-BIPHEP **1b**, and (*S*)-SEGPHOS **2a** giving the best ee's (Scheme 22).[51] As hydride source, tetramethylsiloxane (TMDS) gave somewhat cleaner reactions relative to PMHS. Related reactions with unsaturated amides (e.g., **68**), in the achiral series using bis(diphenylphosphino)ferrocene (dppf), also show promise (Scheme 22).[51a]

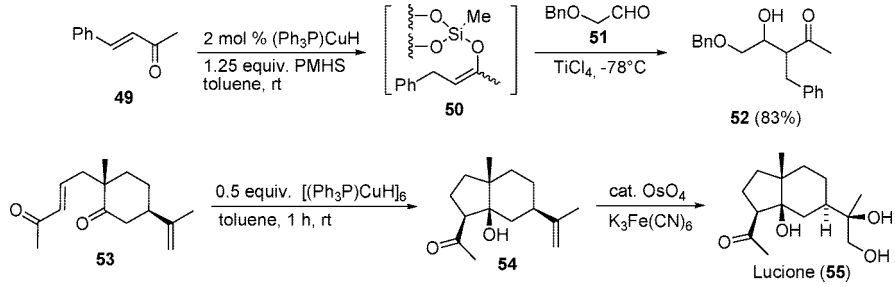
3.3. 1,4-Reduction of Other Michael Acceptors

The mild reaction conditions and improvements made in the (enantioselective) conjugate reductions of α,β-unsaturated ketones and esters have been a driving force for expanding this methodology to other Michael acceptors. Thus, Carreira and Czekelius showed that nitroolefins can be smoothly reduced to the corresponding saturated nitro compounds in the presence of functionality such as ethers, free alcohols, or even pyridine rings (Scheme 23).[20,21,52] Surprisingly, the nitro group itself is not affected by the CuH species. CuF_2 can preferably be used instead of very sensitive CuO*t*-Bu as precursor to copper hydride. In this case, nitromethane must be added as an activator, although it is unknown as to how it interacts with the catalytically active species.

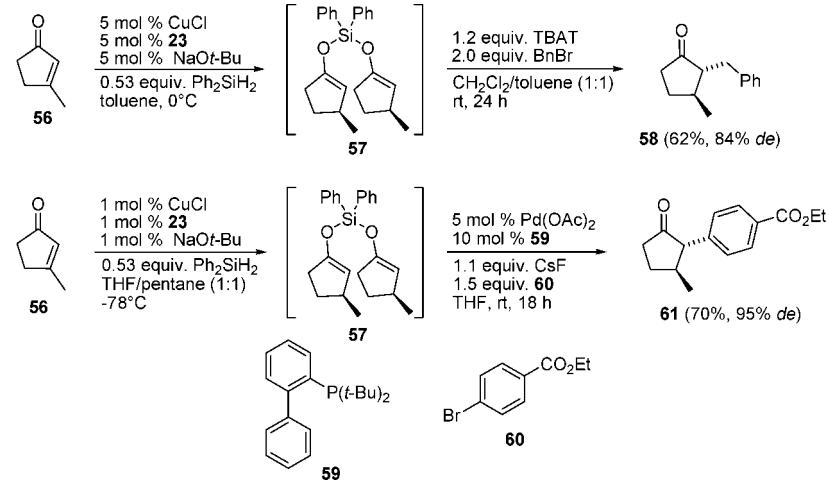
Shortly after the appearance of this study on nitroalkenes, new procedures for enantioselective reduction of unsaturated nitriles and dinitriles were published. Several chiral ligands, in particular BINAP (only working with dinitriles) and JOSIPHOS, afforded excellent levels of enantioselectivity (Scheme 24).[53]

Carretero et al. and Charette et al. reported that sulfones with a stereogenic center in the β-position are available by CuH-catalyzed asymmetric 1,4-reduction of unsaturated precursors (Scheme 25).[14,54] Carretero's group used pyridyl-substituted sulfones as starting material and SEGPHOS or BINAP ligands. Under these conditions the corresponding phenyl-substituted sulfones do not react at all.[14] This limitation was overcome by Charette and co-workers by employing the monooxygenated bis-phosphine DUPHOS ligand **77**. For nonstereoselective reductions, *n*-Bu_3P can be used as stabilizing ligand.[54] Chiral sulfones of type **75** are highly useful synthetic intermediates and can be transformed into a variety of different functionalities (e.g., olefins, ketones, esters).[14]

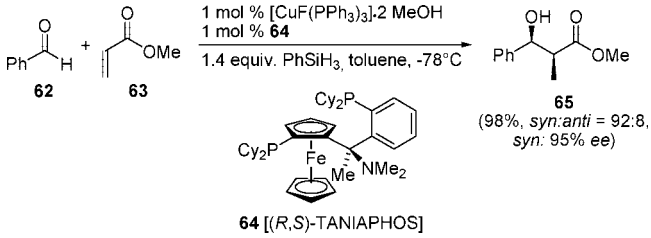
Scheme 19. Tandem 1,4-Reduction-Aldol Reactions Using Stryker's Reagent



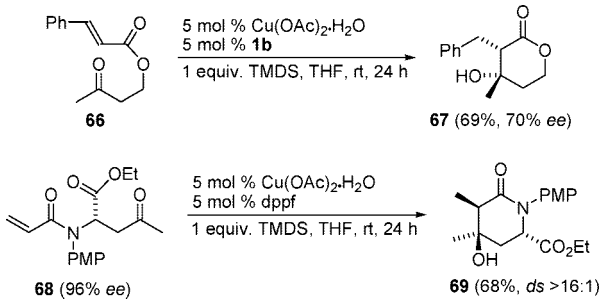
Scheme 20. Tandem Conjugate Reduction−Alkylation with Chiral Copper Hydride Catalysts



Scheme 21. Tandem 1,4-Reduction-Aldol Reaction with a Chiral Copper Hydride Catalyst



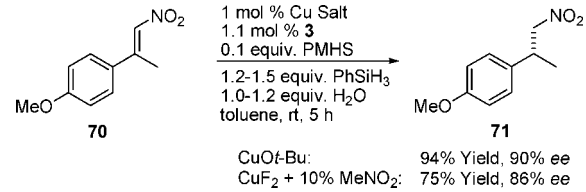
Scheme 22. Tandem Conjugate Reduction−Cyclization



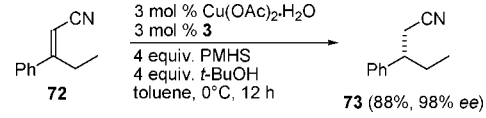
4. 1,2-Reductions Mediated or Catalyzed by Copper Hydride

The selective reduction of C═O or C═N bonds catalyzed by transition metals is of great interest in organic synthesis.[55] Hydrogenation and hydrosilylation[56] of carbonyl groups are usually catalyzed by transition metals such as Ti,[57] Rh[58] or Ru.[59] In 2000 Stryker and co-workers reported that a change of phosphine ligand, the primary purpose to which is to stabilize CuH, has a remarkable effect on the chemoselectivity of this reducing agent.[12,60] By adding dialkylarylphosphines to Stryker's reagent, 1,4-reduction is suppressed;

Scheme 23. Asymmetric Conjugate Reduction of a Nitroolefin



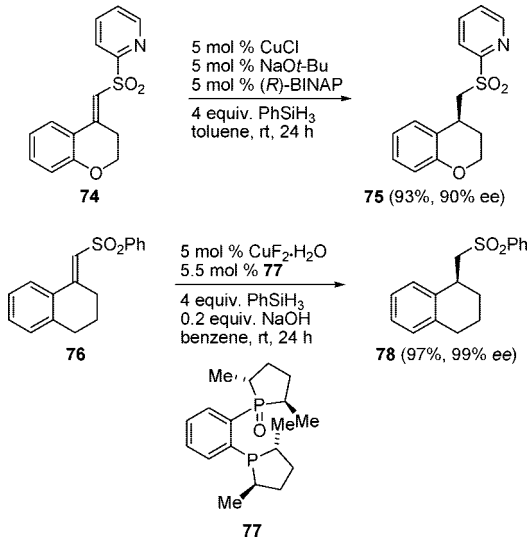
Scheme 24. Enantioselective Conjugate Reduction of an Unsaturated Nitrile



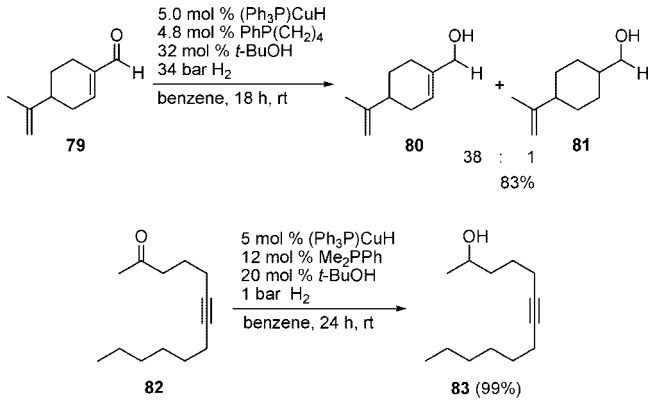
instead, an allylic alcohol is the predominant product. For example, treatment of enal **79** with catalytic amounts of $(Ph_3P)CuH$ and 1-phenylphospholane in the presence of hydrogen as stoichiometric reducing agents afforded mainly the allylic alcohol **80**, and only traces of the overreduction product **81** (Scheme 26). Under these conditions, a variety of functionalities, e.g., ethers, ester, isolated olefins, and triple bonds, are tolerated (Scheme 26), demonstrating considerable potential of this reduction system.[61]

Shortly after these studies, Lipshutz and co-workers improved the procedure by changing the hydride source from hydrogen to silanes.[62] By using Ph_2MeSiH as hydride source, it is possible to reduce aldehydes or ketones and to introduce the silane as protecting group at the same time (Scheme 27). If, on the other hand, PMHS was used for generating the reactive CuH species, the free alcohol could be isolated in good to excellent yields. When aldehyde **86** and ketone **87** were exposed to the reducing agent at the same time, only

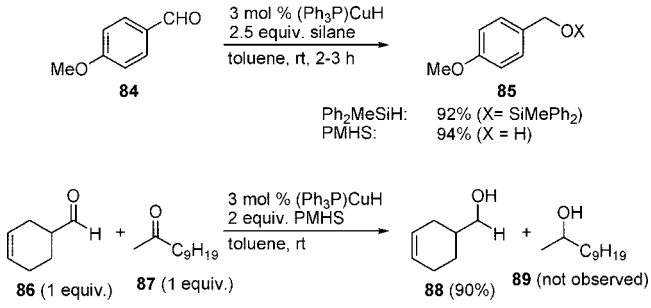
Scheme 25. Enantioselective 1,4-Reduction of Unsaturated Sulfones



Scheme 26. Chemo- and Regioselective 1,2-Reductions Catalyzed by Stryker's Reagent



Scheme 27. 1,2-Reductions with Stryker's Reagent and Silanes as Hydride Source

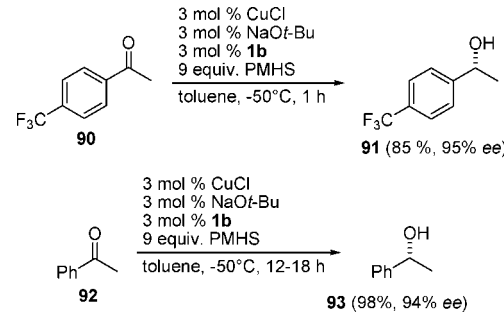


the aldehyde was reduced to the alcohol **88**, proving the high chemoselectivity of this reaction (Scheme 27).

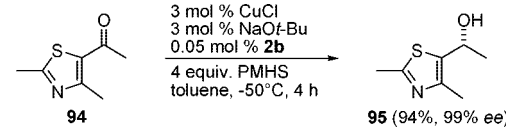
Encouraged by the observation that bidentate ligands (e.g., dppf and racemic BINAP) significantly enhance the rate of 1,2-reductions,[46] the same group explored chiral bis-phosphines for their potential in asymmetric hydrosilylations. Thus, copper hydride in the presence of Roche's (*R*)-Xyl-MeO-BIPHEP **1b** reduced ketones to the corresponding chiral alcohols cleanly with high yields and enantioselectivities (Scheme 28).[63]

As mentioned earlier, nonligated CuH is unstable and easily decomposes; therefore, copper to ligand ratios greater than one can be used without affecting stereoselectivity. In the case of acetophenone **92**, substrate to ligand ratios of

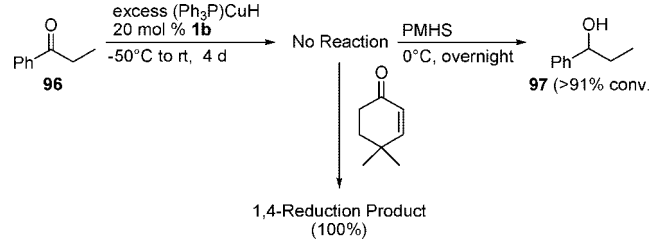
Scheme 28. Enantioselective 1,2-Reductions in the Presence of (*R*)-Xyl-MeO-BIPHEP (1b)



Scheme 29. Enantioselective 1,2-Reduction of Heteroaromatic Ketone 94



Scheme 30. Reactivity Study with Propiophenone and Stryker's Reagent

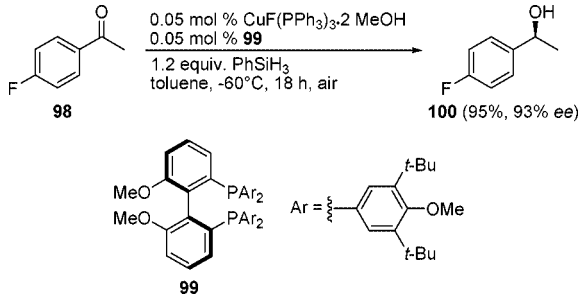


100,000:1 were used without loss of enantioselectivity. Combined with the possibility to reisolate and reuse the ligand without loss of activity, this finding makes this method highly attractive.

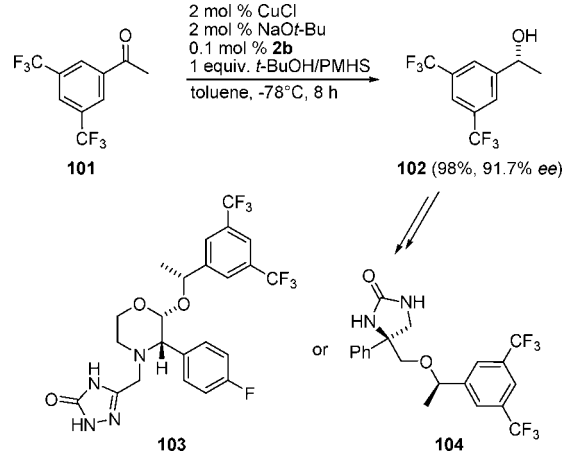
Although the CuH participating in these reductions must be ligated at some point by one or two phosphorus atoms, both sulfur and nitrogen (e.g., as part of a heteroaromatic array) can form strong bonds to copper(I) and could sequester the metal, thereby terminating the catalytic cycle. Thus, heteroaromatic ketones are challenging substrates and give either no reaction or low yields/enantiomeric excesses under standard conditions. This limitation was overcome by using SEGPHOS-type bis-phosphines **2** instead of the BIPHEP system **1**.[64] For example, thiazole **94** can be easily reduced with catalytic amounts of copper in the presence of ligand **2b**, yielding alcohol **95** in excellent enantioselectivity (Scheme 29). No degradation or inhibition of the catalyst by coordination to heteroatoms in either the substrate or the product was observed.

Surprisingly, not only the ligand but also the silane used has an effect on the reactivity of the catalytically active species and seems to be more than just a hydride donor (Scheme 30).[65] For the reaction of propiophenone **96** with an excess of Stryker's reagent and BIPHEP ligand **1b**, it was proposed that the bis-phosphine might form a more reactive CuH species which should undergo the desired reduction. Thus, it was surprising that even after four days no reaction occurred. The integrity of the catalyst was confirmed by addition of 4,4-dimethylcyclohex-2-enone at 0 °C, which led to complete conjugate reduction. Moreover, subsequent addition of PMHS to the reaction mixture at 0 °C induced the expected hydrosilylation, leading to nearly complete

Scheme 31. Enantioselective 1,2-Reduction Accelerated by Oxygen



Scheme 32. Application of an Enantioselective CuH-Catalyzed 1,2-Reduction



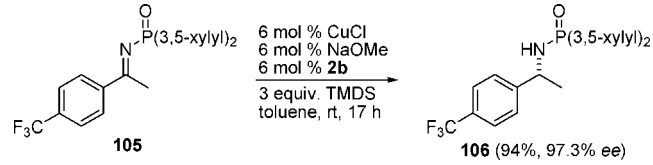
consumption of the ketone.[66] Therefore, further investigations as to the role of the silane are necessary.

To avoid the sensitive CuCl/NaO*t*-Bu system, Lipshutz[16] as well as Yun[67] showed that again $Cu(OAc)_2 \cdot H_2O$, often the copper source of choice in 1,4-reductions, can be used for generating copper hydride. At the same time, Riant et al. reported that the combination CuF_2/BINAP (or BIPHEP derivative **99**) can serve as precatalyst for the hydrosilylation of prochiral ketones.[68] In this case phenylsilane was used as hydride source and no additional base was necessary. It is noteworthy that, in contrast to other recipes involving CuH, not only is this system stable toward oxygen, but the reduction can even be accelerated by injecting air into the reaction mixture[69] (Scheme 31). This effect is not yet well understood, and further experimentation is needed. Nanocrystalline copper(II) oxide can also be used as copper source for this reduction, although it is not known whether the reaction is taking place in a heterogeneous or homogeneous fashion.[70]

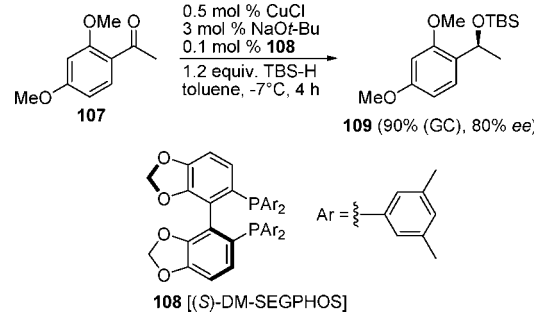
By reducing a variety of prochiral ketone precursors to targets of known biological activities, the potential of chirally ligated CuH has been shown.[71] An interesting example of potential preparative interest is alcohol **102**, an intermediate en route to Merck's NK-1 receptor antagonist **103**, as well as Schering-Plough's analogue **104**.[72] A large-scale production calls for an asymmetric transfer hydrogenation of **101** using 0.5 mol % of a *cis*-aminoindanol−ruthenium complex, affording the product in a reported 91% ee. A similar result can be obtained with CuH, employing a substrate/ligand ratio of 1000:1 (Scheme 32).

Very challenging substrates are imines due to the opportunity to form strong Cu−N bonds, thus terminating the

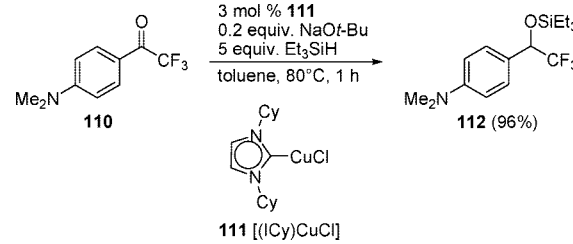
Scheme 33. Representative Enantioselective 1,2-Reduction of an Imine



Scheme 34. Enantioselective 1,2-Reduction−Protection of Ketone 107



Scheme 35. 1,2-Reduction Using a NHC−Cu Complex as Precatalyst

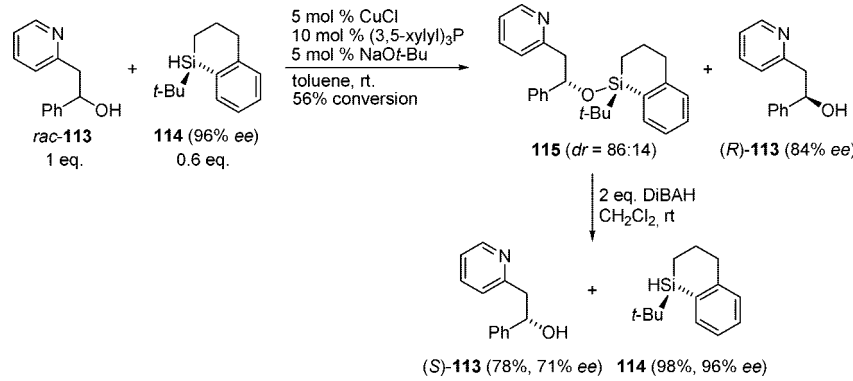


catalytic cycle. The choice of the substituent attached to nitrogen is crucial given the influence that *E*/*Z* isomerism can have in product formation. Both problems were solved using di-(3,5-xylyl)phosphinyl-substituted imines such as **105**, which can be reduced at room temperature to the corresponding amine in excellent yield and enantiomeric excess (Scheme 33).[73]

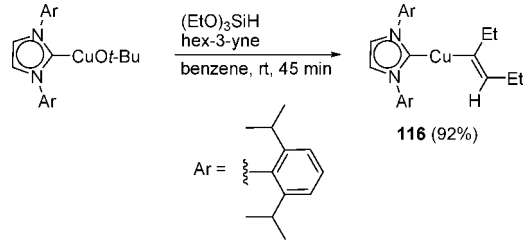
The CuH-catalyzed enantioselective 1,2-reductions described thus far only offer access to free alcohols after workup to remove polymeric silanes associated with the product (e.g., from 29-mer PMHS). Since several other silanes can act as hydride source, it would be desirable to employ monomeric alkylsilanes, e.g., *t*-butyldimethylsilane (TBS-H), thereby leading directly to isolation of the corresponding silyl ether (cf. Scheme 27). This method would be competitive with conventional two-pot approaches involving metal hydride reduction followed by silyl halide/triflate protection. Indeed, the reduction of ketone **107** leads to protected alcohol **109** in excellent yield and acceptable ee using a SEGPHOS-type ligand **108** (Scheme 34).[74]

In a series of publications, Nolan and co-workers[75] showed that NHC−copper complexes, *in situ* generated or isolated, can be used as precatalyst for the hydrosilylation of ketones (Scheme 35). Under their conditions even tertiary amino groups, e.g., as found in substrate **110**, are tolerated and the corresponding silyl ether **112** was isolated in excellent yield. These studies were carried out with achiral catalysts; it would be interesting to evaluate nonracemic versions of these carbene precursors as catalysts for enantioselective hydrosilylations of prochiral substrates.

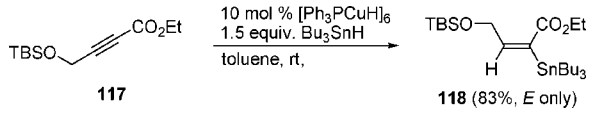
Scheme 36. Copper-Catalyzed Kinetic Resolution Using Chiral Silane 114



Scheme 37. Formation of a Vinylcuprate by Alkyne Hydrocupration



Scheme 38. Hydrostannylation of an Activated Alkyne Catalyzed by Stryker's Reagent



A completely different approach for generating enantiomerically enriched alcohols was developed by Oestreich and co-workers.[76] Using chiral silane **114** and an achiral copper−phosphine complex, they were able to perform a nonenzymatic kinetic resolution of secondary alcohols of type **113** (Scheme 36). The silyl ether **115** formed can be reductively cleaved to release the alcohol and the silane **114**.

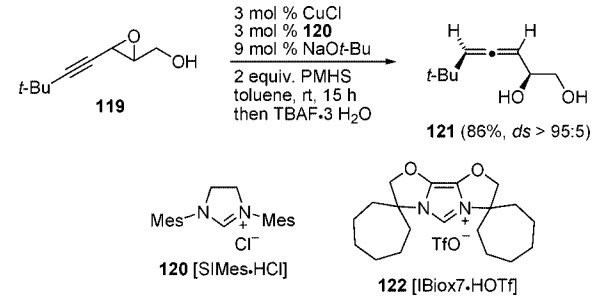
5. Hydrocupration and S_N2'-Reduction of Alkynes

Because of the carbophilic nature of the coinage metal copper, prospects for reactivity of copper hydride toward triple bonds have also been investigated. Stryker and co-workers had already found in 1990 that CuH can be used for reduction of selected alkynes, furnishing alkenes with high *Z*-selectivity.[77] That these olefins are the result of a hydrocupration was proven by Sadighi et al., who were able to isolate vinylcopper compound **116** as a result of the addition of a NHC-stabilized copper hydride species to hex-3-yne (Scheme 37).[78] A crystal structure of **116** was also obtained, showing that vinylcopper species may be more stable than expected, potentially expanding their scope in organic synthesis.

In a series of publications, Chiu's group showed that activated alkynes undergo hydrostannation reactions catalyzed by Stryker's reagent (Scheme 38).[13,79] The high regioselectivity is explained by a hydrocupration of the unsaturated ester **117** as initial step followed by a transmetalation with tin hydride.[80] Vinyltin compounds of type **118** are highly useful for Stille cross-coupling reactions.

During studies on the reduction of alkynes, Stryker et al. found that a terminal propargyl acetate undergoes an S_N2'-reduction to the corresponding allene rather than hydrocupration,[77] a procedure that was used by Brummond and Lu for the synthesis of a precursor to (±)-hydroxymethylacylfulvene.[81] Stryker also pointed out that this method is restricted to terminal alkynes. This limitation was recently overcome by Deutsch, Lipshutz and Krause, who investigated several copper−carbene complexes as precatalysts for the *anti*-stereoselective S_N2'-reduction of propargyl oxiranes (Scheme 39).[82]

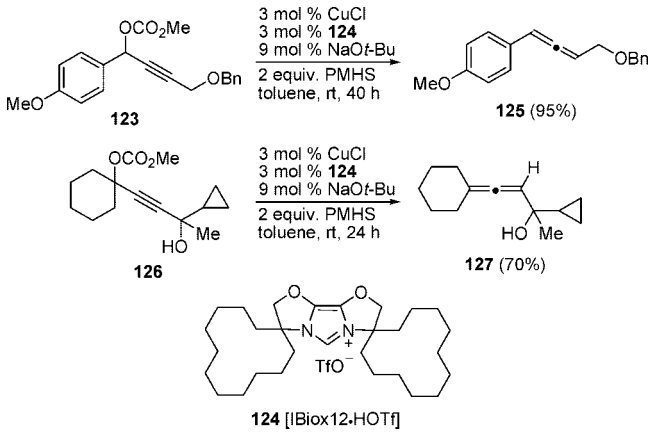
Scheme 39. CuH-Catalyzed S_N2'-Reduction of a Propargyl Oxirane



Here, an *in situ* prepared NHC-CuH species affords the desired α-hydroxyallenes **121**, which are versatile building blocks in synthesis,[83] in high yields with excellent center-to-axis chirality transfer. Not only the stereoselectivity but also the chemoselectivity of this reducing agent is remarkable; it tolerates a variety of functionalities including double and triple bonds, alcohols, esters, cyclopropanes, CF_3 groups, as well as electron-rich and electron-deficient aromatic rings. In most cases, the SIMes (**120**)[84] and IBiox7 (**122**)[85] carbene precursors imparted the highest reactivity and selectivity. Recently, the same researchers expanded the method to another substrate class by choosing carbonates as leaving group (Scheme 40).[86] For example, propargyl carbonates **123** and **126** can be smoothly converted into allenes **125/127**, respectively, in good yields. In these transformations, the IBiox12 ligand **124**[85] affords the best results. Gratifyingly, a high tolerance toward functional groups is again observed.

It is worthy of mention that the key step in these transformations is not the substitution itself, but regeneration of the CuH catalyst by reaction of the silane with the initial copper salt formed in the reduction. Here, the crucial point relates to the basicitiy of the Cu salt, because only sufficiently basic copper salts (e.g., alkoxides) undergo a smooth transmetalation with the hydride source. Hence, other leaving groups such as acetate or nitrobenzoate (which produce less basic copper salts) lead to lower levels of conversion and reduced yields.

Scheme 40. CuH-Catalyzed S_N2'-Reduction of Propargyl Carbonates



6. Conclusion

During the past decade, copper hydride chemistry has evolved dramatically and can nowadays be considered as an integral part of modern organic synthesis. Procedures that rely on mild silanes of general structure R_3SiH for maintaining catalytic cycles involved have opened doors to tandem processes, allowing the construction of several bonds and stereogenic centers in a single pot procedure. By expanding the diversity of ligands that stabilize copper hydride, from phosphines and their oxides to N-heterocyclic carbenes, new copper hydride systems with unprecedented reactivities have become available. Because of the nucleophilicity of hydride on Cu(I), akin to carbon-based systems, many copper-catalyzed reactions developed in the recent past involving C−C-bond formation may well be reinvestigated using an alternative C−H-bond construction. The high chemo-, regio- and stereoselectivity of catalytic copper hydride chemistry makes it also a highly attractive reagent for applications to target-oriented synthesis. With the advent of new biaryl- and ferrocenyl-based ligands with remarkable innate levels of stereocontrol, hydrosilylations catalyzed by chiral CuH complexes have begun to compete with asymmetric hydrogenation on several levels. Thus, while economics have always been on the side of basic metals like copper, TONs and ee's have begun to compete. Undoubtedly, the last words on this chapter of organocopper chemistry are far from being written.

7. References

(1) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630–1634.

(2) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 224−258.

(3) (a) Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 188−223. (b) Karlström, A. S. E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 259−288.

(4) (a) Brestensky, D. M.; Huseland, D. E.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1988**, *29*, 3749–3752. (b) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (c) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677–5680. (d) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237–3240. (e) For the first application of CuH in synthesis, see: Brunner, H.; Miehling, W. *J. Organomet. Chem.* **1984**, *275*, C17–C21.

(5) Lipshutz, B. H. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002, pp 167−187, and references cited therein.

(6) Rendler, S.; Oestreich, M. *Angew. Chem.* **2007**, *119*, 504–510; *Angew. Chem., Int. Ed.* **2007**, *46*, 498−504.

(7) Fátima, A. *Synlett* **2005**, 1805–1806.

(8) Listed as "(Triphenylphosphine)Copper hydride hexamer"; Aldrich Catalog 36497-5, CAS: 33636-93-0.

(9) Chiu, P.; Li, Z.; Fung, K. C. M. *Tetrahedron Lett.* **2003**, *44*, 455–457.

(10) Lee, D.-w.; Yun, J. *Tetrahedron Lett.* **2005**, *46*, 2037–2039.

(11) Nonligated CuH decomposes very easily and can be regarded as unstable.

(12) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789–2798.

(13) Leung, L. T.; Leung, S. K.; Chiu, P. *Org. Lett.* **2005**, *7*, 5249–5252.

(14) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem.* **2007**, *119*, 3393–3396; *Angew. Chem., Int. Ed.* **2007**, *46*, 3329−3332.

(15) Lipshutz, B. H.; Servesko, J. M.; Petersen, T. B.; Papa, P. P.; Lover, A. A. *Org. Lett.* **2004**, *6*, 1273–1275.

(16) Lipshutz, B. H.; Chrisman, W.; Noson, K.; Papa, P.; Scalfani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779–2788.

(17) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573–4582.

(18) Rainka, M. P.; Milne, J. E.; Buchwald, S. L. *Angew. Chem.* **2005**, *117*, 6333–6336; *Angew. Chem., Int. Ed.* **2005**, *44*, 6177−6180.

(19) Shimizu, H.; Igarashi, D.; Kuriyama, W.; Yusa, Y.; Sayo, N.; Saito, T. *Org. Lett.* **2007**, *9*, 1655–1657.

(20) Czekelius, C.; Carreira, E. M. *Org. Process Res. Dev.* **2007**, *11*, 633–636.

(21) Czekelius, C.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4575–4577.

(22) Lawrence, N. J.; Drew, M. D.; Bushell, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3381–3391.

(23) BIPHEP: Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131–138.

(24) SEGPHOS: Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumbayashi, T. *Adv. Synth. Catal.* **2001**, *343*, 264–267.

(25) JOSIPHOS: Blaser, H.-U.; Brieden, W.; Pugin, B.; Spindler, F.; Studer, M.; Togni, A. *Top. Catal.* **2002**, *19*, 3–19.

(26) (a) Review: Herrmann, W. A. *Angew. Chem.* **2002**, *114*, 1342–1362; *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309. (b) *Topics in Organometallic Chemistry*; Glorius, F., Ed.; Springer: Berlin, Heidelberg, NY, 2007; Vol. 21. (c) Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH: Weinheim, 2006.

(27) Díez-González, S.; Nolan, S. P. *Synlett* **2007**, 2158–2167.

(28) Díez-González, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355–2358.

(29) Yun, J.; Kim, D.; Yun, H. *Chem. Commun.* **2005**, 5181–5183.

(30) Lipshutz, B. H.; Frieman, B. A. *Angew. Chem.* **2005**, *117*, 6503–6506; *Angew. Chem., Int. Ed.* **2005**, *44*, 6345−6348.

(31) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E. *Angew. Chem.* **2006**, *118*, 1281–1286; *Angew. Chem., Int. Ed.* **2006**, *45*, 1259−1264.

(32) (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279–1300.

(33) Mahoney, W. S.; Stryker, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 8818–8823.

(34) (a) Sakamoto, S.; Sazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M. *Angew. Chem.* **2004**, *116*, 6667–6672; *Angew. Chem., Int. Ed.* **2004**, *43*, 6505−6510. Other applications to total synthesis: (b) Gaul, C.; Njardarson, J. T.; Shan, D.; Dorn, D. C.; Wu, K.-D.; Tong, W. P.; Huang, X.-Y.; Moore, M. A. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 11326–11337. (c) Coogan, M. P.; Ooi, L.-l.; Wilkins, D. S. *J. Organomet. Chem.* **2005**, *690*, 1861–1865. (d) Moon, B.; Han, S.; Yoon, Y.; Kwon, H. *Org. Lett.* **2005**, *7*, 1031–1034. (e) Wakefield, B.; Halter, R. J.; Wipf, P. *Org. Lett.* **2007**, *9*, 3121–3124.

(35) Chiu, P. *Synthesis* **2004**, 2210–2215.

(36) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493–3495.

(37) (a) Apella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474. (b) Moritani, Y.; Apella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797–6798. (c) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11253–11258. (d) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821–5823.

(38) Movassaghi, M.; Ondrus, A. E. *Org. Lett.* **2005**, *7*, 4423–4426.

(39) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353.

(40) It is likely that CuH (20 mol % present) and *t*-BuOD (1.1. equiv) undergo a facile H/D-exchange at room temperature, which accounts for the 16% deuterium incorporation at the β-site. For details see ref 39.

(41) (a) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem.* **2003**, *115*, 4937–4940; *Angew. Chem., Int. Ed.* **2003**, *42*, 4789−4792. (b) Lipshutz, B. H.; Tanaka, N.; Taft, B. R.; Lee, C.-T. *Org. Lett.* **2006**, *8*, 1963–1966. (c) Lipshutz, B. H.; Lee, C.-T.; Taft, B. R. *Synlett* **2007**, *20*, 3257–3260.
(42) Lipshutz, B. H.; Frieman, B. A.; Unger, J. B.; Nihan, D. M. *Can. J. Chem.* **2005**, *83*, 606–614.
(43) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892–2893.
(44) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417–2420.
(45) Thuong, M. B. T.; Sottocornola, S.; Prestat, G.; Broggini, G.; Madec, D.; Poli, G. *Synlett* **2007**, 1521–1524, and references cited therein.
(46) Lipshutz, B. H.; Papa, P. *Angew. Chem.* **2002**, *114*, 4762–4764; *Angew. Chem., Int. Ed.* **2002**, *41*, 4580−4582.
(47) (a) Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901–1903. (b) Chiu, P.; Szeto, C. P.; Geng, Z.; Cheng, K. F. *Tetrahedron Lett.* **2001**, *42*, 4091–4093. (c) Chiu, P.; Leung, S. K. *Chem. Comm.* **2004**, 2308–2309. (d) Chung, W. K.; Chiu, P. *Synlett* **2005**, 55–58.
(48) Yun, J.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1129–1131.
(49) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809–4812.
(50) (a) Deschamp, J.; Chuzel, O.; Hannedopuche, J.; Riant, O. *Angew. Chem.* **2006**, *118*, 1314–1319; *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1297. (b) Chuzel, O.; Deschamp, J.; Chausteur, C.; Riant, O. *Org. Lett.* **2006**, *8*, 5943–5946. (c) With NHC-Cu as precursor: Welle, A.; Díez-González, S.; Tinant, B.; Nolan, S. P.; Riant, O. *Org. Lett.* **2006**, *8*, 6059–6062. (d) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 1403–1407. (e) For a recent review, see: Nishiyama, H.; Shiomi, T. In *Topics in Current Chemistry*; Krische, M. J., Ed.; Springer: New York, 2007; Vol. 279.
(51) (a) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743–5746. (b) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228.
(52) Czekelius, C.; Carreira, E. M. *Angew. Chem.* **2003**, *115*, 4941–4943; *Angew. Chem., Int. Ed.* **2003**, *42*, 4793−4795.
(53) Enantioselective procedures: (a) With BINAP: Ren, Y.; Xu, X.; Sun, K.; Xu, J. *Tetrahedron: Asymmetry* **2005**, *16*, 4010–4014. (b) Lee, D.; Kim, D.; Yun, J. *Angew. Chem.* **2006**, *118*, 2851–2853; *Angew. Chem., Int. Ed.* **2006**, *45*, 2785−2787. (c) Lee, D.; Yang, Y.; Yun, J. *Org. Lett.* **2007**, *9*, 2749–2751. (d) Lee, D.; Yang, Y.; Yun, J. *Synthesis* **2007**, 2233–2235. (e) For a non-enantioselective procedure, see: Kim, D.; Park, B.-M.; Yun, J. *Chem. Commun.* **2005**, 1755–1757.
(54) Desrosiers, J.-N.; Charette, A. B. *Angew. Chem.* **2007**, *119*, 6059–6061; *Angew. Chem., Int. Ed.* **2007**, *46*, 5955−5957.
(55) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: 1991, Vol. 8.
(56) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943–2958.
(57) Selected examples: (a) Carter, M. B.; Schiott, B.; Gutiérrez, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11667–11670. (b) Haltermann, R. L.; Ramsey, T. M.; Chen, Z. *J. Org. Chem.* **1999**, *59*, 2642–2644. (c) Harrod, J. F.; Xin, S. *Can. J. Chem.* **1995**, *73*, 999–1002. (d) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640–5644. (e) Beagley, P.; Davies, P. J.; Blacker, A. J.; White, C. *Organometallics* **2002**, *21*, 5852–5858.
(58) Selected examples: (a) Evans, D. A.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534–3543. (b) Tao, B.; Fu, G. C. *Angew. Chem.* **2002**, *114*, 4048–4050; *Angew. Chem., Int. Ed.* **2002**, *41*, 3892−3894.
(59) Selected examples: (a) Zhu, G.; Terry, M.; Zhang, X. *J. Organomet. Chem.* **1997**, *547*, 97–101. (b) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420–3422.
(60) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153–2166.
(61) Recently, an asymmetric reduction with hydrogen gas as stoichiometric reducing agent was reported: see ref 19.
(62) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367–371.
(63) Lipshutz, B. H.; Noson, K.; Chrisman, W. *J. Am. Chem. Soc.* **2001**, *123*, 12917–12918.
(64) Lipshutz, B. H.; Lower, A.; Noson, K. *Org. Lett.* **2002**, *4*, 4045–4048.
(65) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779–8789.
(66) For significant insight see: Schubert, U.; Mayer, B.; Ruzz, C. *Chem. Ber.* **1994**, *127*, 2189–2190.
(67) Lee, D.-w.; Yun, J. *Tetrahedron Lett.* **2004**, *45*, 5415–5417.
(68) (a) Sirol, S.; Courmarcel, J.; Mostefai, N.; Riant, O. *Org. Lett.* **2001**, *3*, 4111–4113. (b) Courmarcel, J.; Mostefai, N.; Sirol, S.; Chopin, S.; Riant, O. *Isr. J. Chem* **2002**, *41*, 231–240.
(69) Mostefai, N.; Sirol, S.; Courmarcel, J.; Riant, O. *Synthesis* **2007**, 1265–1271.
(70) Kantam, M. L.; Laha, S.; Yadav, J.; Likhar, P. R.; Sreedhar, B.; Choudary, B. M. *Adv. Synth. Catal.* **2007**, *349*, 1797–1802.
(71) Lipshutz, B. H.; Lower, A.; Kucejko, R. J.; Noson, K. *Org. Lett.* **2006**, *8*, 2969–2972.
(72) Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M. M.; Li, J.; Craig, B.; Song, Z. J.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P. G.; Reamer, R. A.; Welch, C. J.; Mathre, D. J.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129–2135.
(73) Lipshutz, B. H.; Shimizu, H. *Angew. Chem.* **2004**, *116*, 2278–2280; *Angew. Chem., Int. Ed.* **2004**, *43*, 2228−2230.
(74) Lipshutz, B. H.; Caires, C. C.; Kuipers, P.; Chrisman, W. *Org. Lett.* **2003**, *5*, 3085–3088.
(75) (a) Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2004**, *23*, 1157–1160. (b) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784–4796. (c) Díez-González, S.; Scott, N. M.; Nolan, S. P. *Organometallics* **2006**, *25*, 2355–2358.
(76) (a) Rendler, S.; Auer, G.; Oestreich, M. *Angew. Chem.* **2005**, *117*, 7793–7797; *Angew. Chem., Int. Ed.* **2005**, *44*, 7620−7624. (b) Rendler, S.; Auer, G.; Keller, M.; Oestreich, M. *Adv. Synth. Catal.* **2006**, *348*, 1171–1182. See also: (c) Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267–1269. (d) Schmidt, D. R.; O'Malley, J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190–1191.
(77) Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 2397–2400.
(78) Mankad, N. P.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 3369–3371.
(79) (a) Leung, L. T.; Chiu, P. *Pure Appl. Chem.* **2006**, *78*, 281–285. (b) Miao, R.; Li, S.; Chiu, P. *Tetrahedron* **2007**, *63*, 6737–6740.
(80) For a detailed discussion of the possible reaction mechanism see ref 65.
(81) Brummond, K. M.; Lu, J. *J. Am. Chem. Soc.* **1999**, *121*, 5087–5088.
(82) Deutsch, C.; Lipshutz, B. H.; Krause, N. *Angew. Chem.* **2007**, *119*, 1677–1681; *Angew. Chem., Int. Ed.* **2007**, *46*, 1650−1653.
(83) (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538. (b) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759–1774. (c) Deutsch, C.; Gockel, B.; Hoffmann-Röder, A.; Krause, N. *Synlett* **2007**, 1790–1794.
(84) (a) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron* **1999**, *55*, 14523–14534. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54.
(85) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.
(86) Deutsch, C.; Lipshutz, B. H.; Krause, N.; in preparation.

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