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Asymmetric Catalysis

Polishing a Diamond in the Rough: "Cu–H" Catalysis with Silanes

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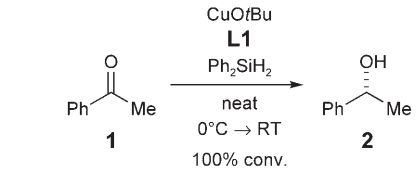
Dedicated to Professor Gerhard Erker on the occasion of his 60th birthday

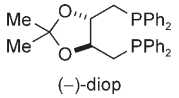
The value of a novel chemical transformation is often underappreciated at the time of its discovery. The reasons are doubtlessly manifold, but the "chemical zeitgeist" subtly determines how the new reaction will be received by the chemical community. The enantioselective reduction of carbonyls by copper-catalyzed hydrosilylation was certainly outshone by other asymmetric hydrogenation techniques. A seminal report at an early stage indicated the considerable potential of this catalytic process, yet it was disregarded for more than a decade. A refined mechanistic picture in connection with a plethora of new chiral ligands then led to copper-catalyzed 1,2- as well as 1,4-reductions of carbonyl compounds with excellent levels of enantioselection at high substrate-to-catalyst ratios and even more remarkable substrate-to-ligand ratios. The tide is turning for inexpensive copper catalysts in asymmetric hydride transfer reactions!

The past decade witnessed significant progress towards catalytic asymmetric 1,4-addition of carbon nucleophiles to α,β-unsaturated acceptors thereby expediently complementing the myriad asymmetric 1,2-addition reactions.[1] Copper(I)-based catalysts emerged as particularly useful for conjugate C–C bond formation.[1a] It is therefore interesting to note that despite the "similarity" of a carbanion and a hydride, copper(I)-catalyzed hydride transfer, in other words, the 1,4- and 1,2-reductions of (α,β-unsaturated) carbonyl compounds, had remained underdeveloped.[2] Initial setbacks in the catalytic generation of copper(I) hydrides might account for this omission. Nevertheless, the inherent attractiveness of such a methodology—catalytic in copper and, ideally, based on dihydrogen (H–H) or mildly hydridic silanes (X_3Si–H) as stoichiometric reducing agents—stimulated a lively field of research resulting in truly catalytic and enantioselective C–H bond-forming reactions.[2–4]

In a landmark publication dating back almost a quarter of a century, Brunner and Miehling reported on the first copper(I)-catalyzed reduction of acetophenone (**1**) using diphenylsilane as the reducing reagent (**1**→**2**, Scheme 1).[5] This catalyst–reagent combination comes surprisingly close to subsequently devised procedures, which produce high levels of enantioinduction. Owing to the limited availability and diversity of chiral ligands at that time, enantiomeric excesses are low compared to the present values. CuO*t*Bu as a precatalyst combined with a bidentate phosphine ligand is still considered a "perfect match". The substrate-to-catalyst (S/C) and substrate-to-



CuO*t*Bu	L1	S/C	S/L	*ee*
0.30 mol%	0.35 mol%	330:1	285:1	20%
0.040 mol%	0.084 mol%	2500:1	1200:1	17%



(–)-diop

L1

Scheme 1. A diamond in the rough: The first example of a "Cu–H"-catalyzed asymmetric hydrosilylation of a ketone by Brunner (1984).

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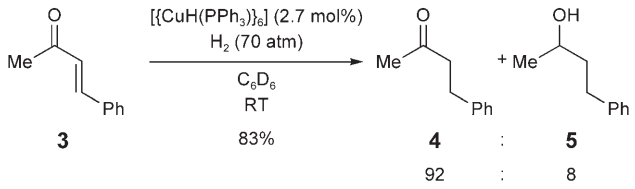
ligand (S/L) ratios of 2500:1 and 1200:1, respectively, foreshadow the efficient catalyst system discovered later. The catalyst-to-ligand ratios (C/L) surveyed (1.0:1.0 to 1.0:2.1),[5] however, indicate the vague picture of the active catalyst.

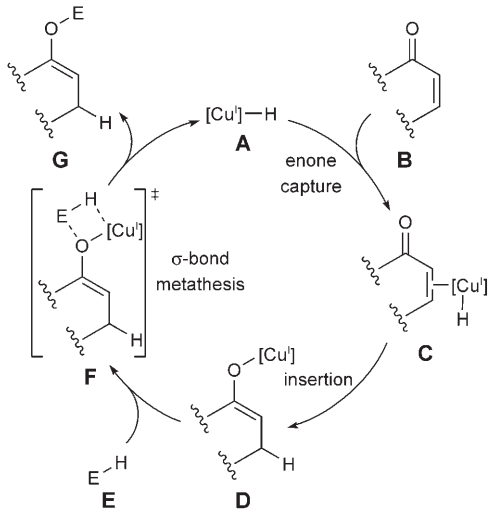
Whereas the nature of the catalytically active species was not discussed in the above-mentioned contribution,[5] the analogous application of the phosphine-stabilized hexameric copper hydride [{CuH(PPh_3)}$_6$] unveiled the apparent involvement of "Cu–H". This long-known[6a] well-defined complex is accessible by various protocols,[6] but it was Stryker and co-workers who disclosed the synthetic potential of this reagent,[7] which is why it is commonly referred to as "Stryker's reagent". Stoichiometric use led to chemoselective conjugate reductions of α,β-unsaturated carbonyl compounds including aldehydes.[7a,b,d,f] Chemoselectivity was less pronounced in the presence of catalytic amounts of [{CuH(PPh_3)}$_6$] under dihydrogen at elevated pressure (**3**→**4**/**5**, Scheme 2).[7c] The goal of achieving a general catalytic protocol for conjugate reduction was not realized, but these studies eventually resulted in chemoselective 1,2-reduction affording allylic alcohols as well as full reduction.[7a,e,g,h]



Scheme 2. Chemoselectivity in a "Cu–H"-catalyzed conjugate reduction by Stryker (1989).

The mechanism of these 1,4-reductions suggests several points for improving catalytic turnover (Scheme 3). Phosphine-stabilized copper hydride **A** coordinates to the C=C bond of substrate **B** (**A**→**C**) followed by hydride transfer onto the β carbon (**C**→**D**). The resulting copper enolate **D** then undergoes heterolytic σ-bond metathesis (**D**→**F**) with dihydrogen (**E**, E = H), thereby liberating the product **G** (**F**→**G**) and regenerating catalytically active **A** (**F**→**A**).

The catalytic system introduced by Stryker et al. has one crucial weak point: Dihydrogen activation in the σ-bond



Scheme 3. Proposed catalytic cycle for copper(I)-catalyzed conjugate reductions (E = H, SiX_3, SnX_3, BX_2).

metathesis step **F** (Scheme 3) is slow even at elevated pressures, and consequently the newly formed tautomer of **G** is overreduced. This is verified experimentally by the formation of **5** along with **4** (Scheme 2). Hence, replacement of dihydrogen (**E**, E = H) by a silane (**E**, E = SiX_3 with X = alkyl, aryl, alkoxy, or H) would completely prevent this overreaction by stabilizing the enol form **G** as its silyl ether. As indicated by the Brunner protocol (Scheme 1), heterolytic Si–H fission occurs substantially faster under nearly identical reaction conditions. This was realized almost simultaneously by the groups led by Mori[8a,c] and Hosomi[8b], both of which demonstrated the effectiveness of copper–silane combinations in conjugate reductions. The study conducted by Mori and co-workers also showed the possibility of catalytic turnover. Shortly after, Lipshutz and co-workers successfully applied Stryker's reagent in catalytic 1,4-reductions using $PhSiH_3$ as well as Bu_3SnH (**E**, E = SiX_3 or SnX_3);[9a] the latter had been identified as a suitable reducing reagent prior to silicon-based hydride sources.[9b]

These insights constituted the basis for the enantioselective copper(I)-catalyzed 1,4-reduction. In the first of a series of reports by Buchwald et al.,[10] a catalyst generated in situ from CuCl, NaO*t*Bu, and binap derivative **L2** was shown to

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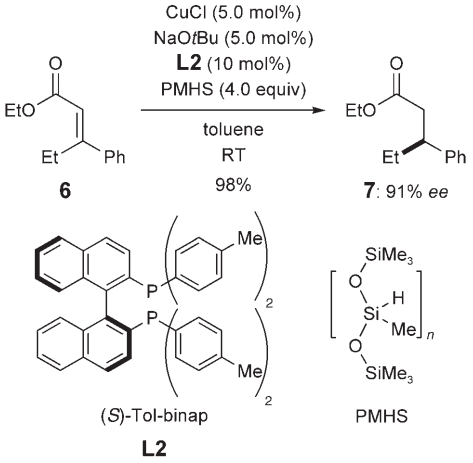
facilitate the asymmetric conjugate reduction of acyclic α,β-unsaturated esters (**6**→**7**, Scheme 4).[10a] This approach has several attractive features: no handling of extremely air- and moisture-sensitve CuO*t*Bu, simple screening of phosphine ligands, and polymethylhydrosiloxane (PMHS) as an easy-to-handle and inexpensive hydride source.



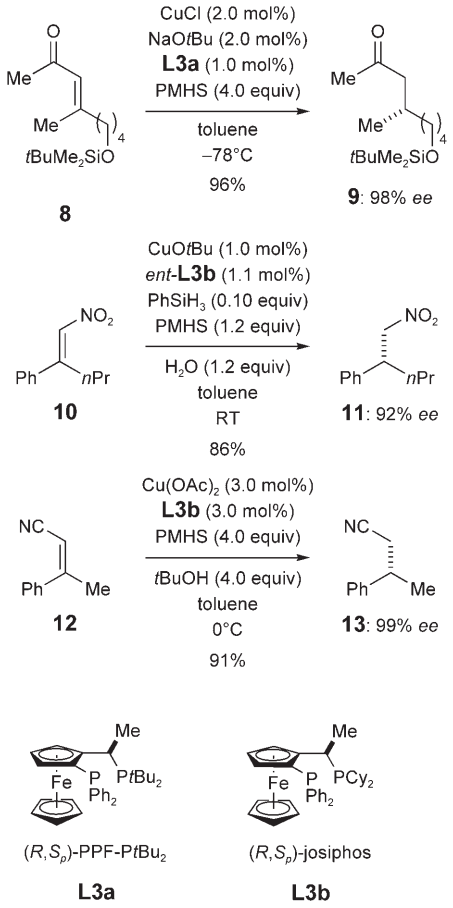
Scheme 4. Asymmetric conjugate reduction by Buchwald (1999).

Subsequent research by the Buchwald group led to the logical extension of the substrate scope to cycloalkenones,[10b] α,β-unsaturated lactones and lactams,[10c] and β-azaheterocyclic as well as α,β-unsaturated esters.[10d] Remarkably, replacing the copper(I) precatalyst with a copper(II) salt (such as $CuCl_2 \cdot 2H_2O$[10c] or $Cu(OAc)_2 \cdot H_2O$[10d]) made only little difference.

The observed enantiomeric excesses typically ranged between 80–90%, leaving room for improvement. By testing different novel chiral ligand scaffolds, the Lipshutz[11] and Carreira[12] groups independently discovered that josiphos-type ligands **L3** are particularly effective in conjugate reductions of acyclic systems (Scheme 5).[11a,12a] The success of these reactions was dependent on the copper source. CuCl and NaO*t*Bu allowed for the conversion of acyclic enone **8** to **9** with excellent enantioselectivity,[11a] whereas the importance of CuO*t*Bu was emphasized for the enantioselective reduction of nitroalkene **10** (**10**→**11**, Scheme 5). Besides these examples, previously mentioned[11b,c] and additional[11d] substrate classes were evaluated with josiphos and segphos ligands, resulting in even better optical purities.[11b–d] Yun and coworkers presented a related asymmetric variant for the reduction of α,β-unsaturated nitriles (**12**→**13**, Scheme 5).[13]

An application recently showcased the capability of copper(I)-catalyzed conjugate reduction processes in the context of the synthesis of eupomatilone-3 (**16**).[14] Enantioenriched **15** was accessed by dynamic kinetic resolution of lactone **14** using the MeO-biphep ligand **L4a** as the stereoinducor (**14**→**15**, Scheme 6). In this case, stoichiometric addition of NaO*t*Bu was necessary to racemize **14** at the O-substituted carbon atom.

Lipshutz et al. revisited the related hydrosilylation[5] of saturated carbonyl compounds. In their initial publication,

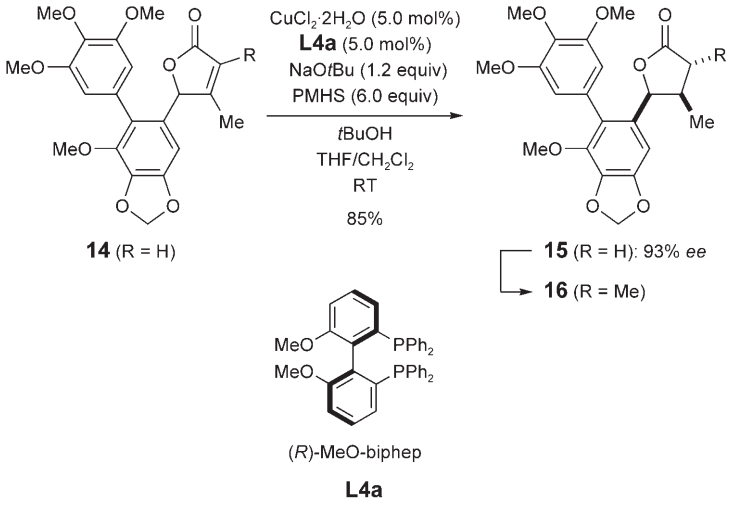


Scheme 5. Conjugate reductions by Lipshutz and Carreira (2003) and Yun (2006).

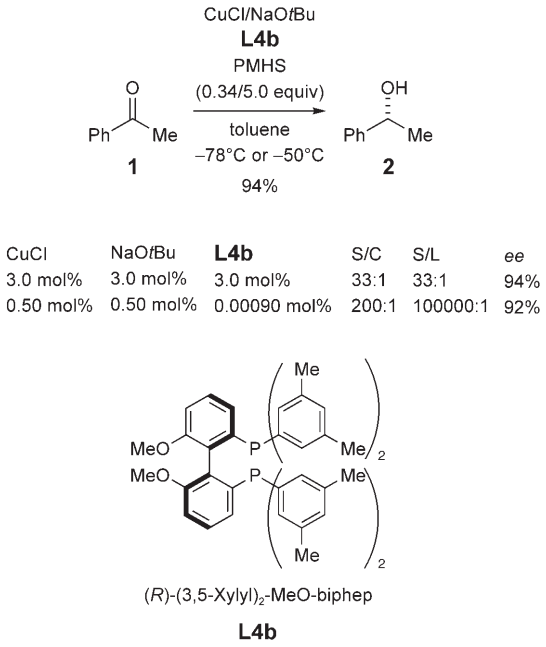
they reported a profound rate acceleration when a bidentate phosphine was added to catalytic quantities of Stryker's reagent.[15a] As ligand acceleration is a decisive feature of successful asymmetric catalysis, enantioselective copper(I)-catalyzed 1,2-reductions were presented by Lipshutz et al.[15b] and, independently, by Riant et al.[16] soon afterwards (**1**→**2**, Scheme 7). A highlight of the Lipshutz work are the remarkably high substrate-to-ligand ratios (S/L > 100000:1) accompanied by only marginal loss of enantioinduction.[15d] The reaction conditions for this transformation are similar to those elaborated by Buchwald et al. (Scheme 4).[10]

Early investigations were performed with the MeO-biphep ligand **L4b**.[17] Although this was a good starting point, subsequent extensive screening of a plethora of chiral ligands identified segphos-type ligands—particularly **L5**—as the best choice (Scheme 8 and Scheme 9).[15c–f] Using this ligand, heteroaryl[15c] and aryl ketones[15d] and even more functionalized substrates (**17**→**18**, Scheme 8) were reduced with excellent chemoselectivity.[15f] As an important extension of this methodology, Lipshutz and Shimizu later reported the analogous reduction of ketimines (**19**→**20**, Scheme 9).[15e]

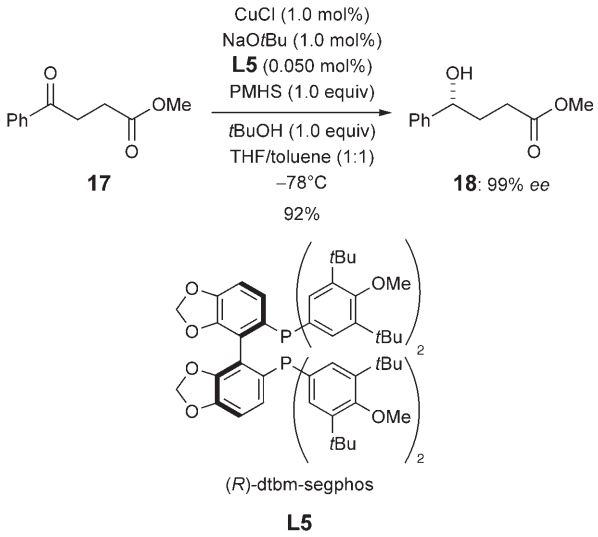
In the transformations described so far a single new stereogenic center is created upon C–H bond formation. A closer look at the catalytic cycle of the conjugate reduction (Scheme 3) reveals that it might be suitable for tandem



Scheme 6. Dynamic kinetic resolution of an unsaturated lactone (2005).



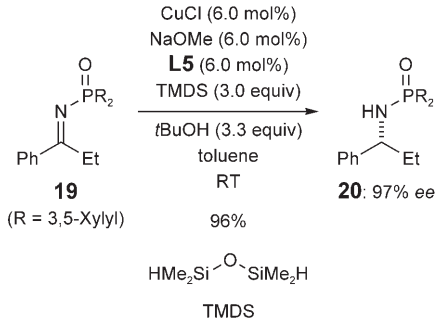
Scheme 7. Catalytic asymmetric ketone reduction by Lipshutz (2001).



Scheme 8. Segphos as a highly efficient ligand.

processes. It is therefore not surprising that several research groups devised tandem protocols based on the intermediacy of enolate derivative **G**. This type of one-pot process might be considered umpolung catalysis as the catalytic cycle starts with an a^3 synthon (**B**, electrophilic), which is then transformed into a d^2 synthon (**G**, nucleophilic). Enantioselective conjugate reduction followed by diastereoselective enolate chemistry establishes at least two adjacent stereocenters. Indeed, Stryker et al. had already observed such a tandem sequence as an undesired side reaction with substrates containing a tethered C–Y bond (Y = Br, I, and OTs).[7f]

The deliberate design of tandem processes was initiated by Chiu and co-workers in conjunction with a total synthesis.[18a] Further methodological development by this group led to appealing tandem conjugate reduction/intramolecular aldol or conjugate reduction/Henry reactions[18e] mediated[18a–c] or catalyzed[18d] by Stryker's reagent.[18,19] Lipshutz et al. had previously demonstrated the feasibility of a variant catalytic in copper for reduction and subsequent intermolecular aldol reaction.[20a] Moreover, these workers used boranes



Scheme 9. Asymmetric reduction of substituted ketimines (2004).

and boronic esters (**E**, X = Et or pinacol) as the hydride source; the intermediate boron enolates (**G**, E = BX_2) smoothly reacted with aldehydes in high diastereoselectivities.[20b] However, no asymmetric tandem reaction had been reported to that date although pinacolborane had been used in catalytic enantioselective 1,4-reductions![20b]

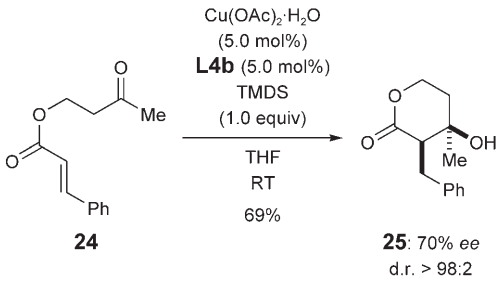
This gap was filled by Buchwald and Yun with a one-pot sequence, which included a fluoride-promoted α-alkylation of the intermediate silyl enol ether **22**. The resulting *trans*-α,β-disubstitued cyclopentanones were isolated in good yields, diastereomeric ratios, and enantioselectivities.[21a] A tandem process, in which the conjugate reduction (**21**→**22**) is followed by a diastereoselective palladium(0)-catalyzed α-arylation (**22**→**23**), is depicted in Scheme 10.[21b]

Recently, Lam and Joensuu reported the first asymmetric tandem sequence consisting of reduction and an intramolecular aldol reaction, which proceeded with promising enantioselectivity (Scheme 11).[22] Reduction of the α,β-unsaturated ester **24** was performed using an air-stable copper(II) salt and various axially chiral biaryl phosphines such as the MeO-biphep ligand **L4b**; no further activation of the intermediate silyl ether was needed for the aldol cyclization, and **25** was obtained as a single diastereomer.[22a]

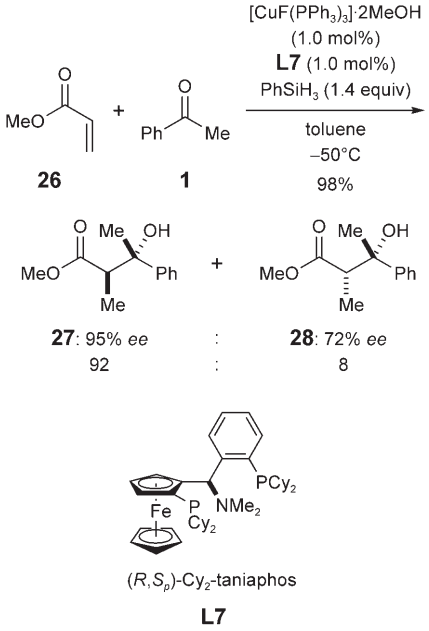
Noteworthy examples of tandem reduction/intermolecular aldol sequences were reported by the groups of Riant[23] and Shibasaki and Kanai.[24] Both groups investigated the conjugate reduction of methyl acrylate (**26**)—without installation of a stereogenic center in the reduction step—and the subsequent reaction with aromatic ketones. Riant et al. found that complexes originating from the taniaphos ligand **L7** and copper fluoride performed best in terms of yield and diastereo- and enantioselectivity (**26**→**27**, Scheme 12). The involvement of a copper enolate rather than a silyl enol ether in the aldol reaction is clearly suggested by the remarkable optical purity as well as diastereomeric ratio.[23]

Parallel to these synthetic studies, efforts towards the development of general catalyst/ligand/hydride source "cocktails" were undertaken. Parts of these achievements have already been mentioned above:

- replacement of dihydrogen by silanes or polymethylhydrosiloxane (PMHS),[5,6d,8–18,20–26]
- use of air-stable copper(II) salts,[6e,10c,d,12b,13,14,16,17,22,25a,26]
- variation of the base,[25b]



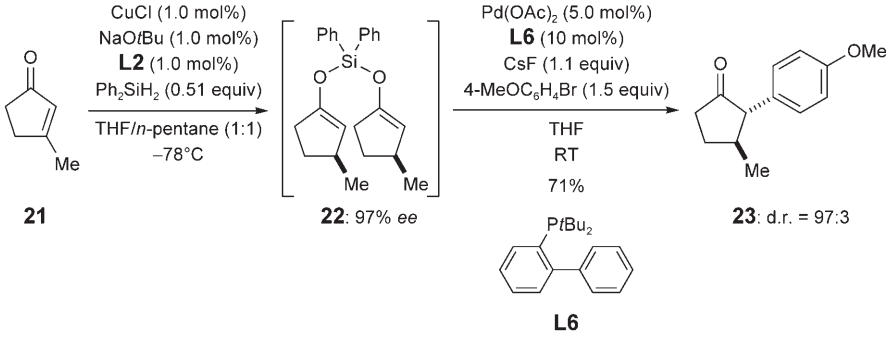
Scheme 11. Intramolecular tandem sequence consisting of reduction and aldol reaction (2005).



Scheme 12. Enantioselective tandem process consisting of reduction and aldol reaction by Riant (2006).

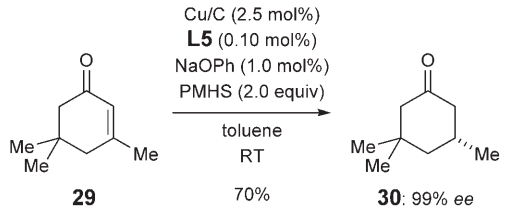
- use of copper complexes with the N-heterocyclic carbene ligands[13b,25d–f] originally introduced by Buchwald and Sadighi,[25c]
- microwave heating.[25g]

Intuitively one would assume that copper hydrides must be relatively labile, but Lipshutz and Frieman demonstrated the exact opposite. Copper(I) hydrides decorated with



Scheme 10. Tandem sequence consisting of conjugate reduction and arylation (2004).

segphos **L5** are unexpectedly stable, and they can be stored in solution if kept under inert atmosphere.[26a] Complementary to this homogeneous "Cu–H in a bottle", Lipshutz et al. recently presented a heterogeneous catalyst for a variety of asymmetric reductions.[26b] Copper(II) immobilized on charcoal, that is, copper-in-charcoal, was employed as a precatalyst in combination with a small amount of **L5** (**29**→**30**, Scheme 13).



Scheme 13. Heterogeneous asymmetric reduction using recyclable "copper-in-charcoal" by Lipshutz (2006).

Due to the latent instability of non-ligated copper hydride species, the optical purity of **30** is not adversely affected by catalyst-to-ligand ratios of greater than 1.[15b,d] Consequently, substrate-to-ligand ratios can exceed substrate-to-catalyst ratios by several orders of magnitude—this is a pivotal characteristic of these catalyses! Detailed investigations indicate that the catalysis occurs in a hetero- and not a homogeneous fashion and is therefore not attributable to "Cu–H" leaching into solution.

The extension of copper catalysis from C–C to C–H bond formation was realized in a variety of impressive examples. Fundamental advances in the field of "Cu–H" catalysis in connection with silanes as the stoichiometric hydride source were achieved.[27] The seminal ketone hydrosilylation by Brunner was not only perfected in terms of enantioselectivity and catalytst turnover but also extended to synthetically useful asymmetric conjugate reduction protocols and related tandem reactions. Moreover, the advances in catalyst preparation and handling have certainly turned these methods into attractive alternatives for the targeted synthesis of complex molecules and for the preparation of fine chemicals. The latter will benefit from the substrate-to-catalyst as well as remarkable substrate-to-ligand ratios of 100000:1 and higher achieved with a relatively inexpensive late-transition-metal catalyst.

Ultimately, the question arises where "Cu–H" catalysis is now positioned in hydrosilylation chemistry. If one considers other transition-metal-catalyzed hydrosilylations of carbonyl and imino groups,[3] in particular rhodium(I)-catalyzed reactions, the high substrate-to-ligand ratios possible with "Cu–H" catalysis stand out. Clearly underestimated for years, enantioselective copper(I)-catalyzed reductions rank among the valuable and broadly applicable C–H bond-forming reactions. With further improvements underway, this method might even become as useful as asymmetric hydrogenation.[28]

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