Asymmetric Catalysis

International Edition: DOI: 10.1002/anie.201606701
German Edition: DOI: 10.1002/ange.201606701

Balancing C=C Functionalization and C=O Reduction in Cu–H Catalysis

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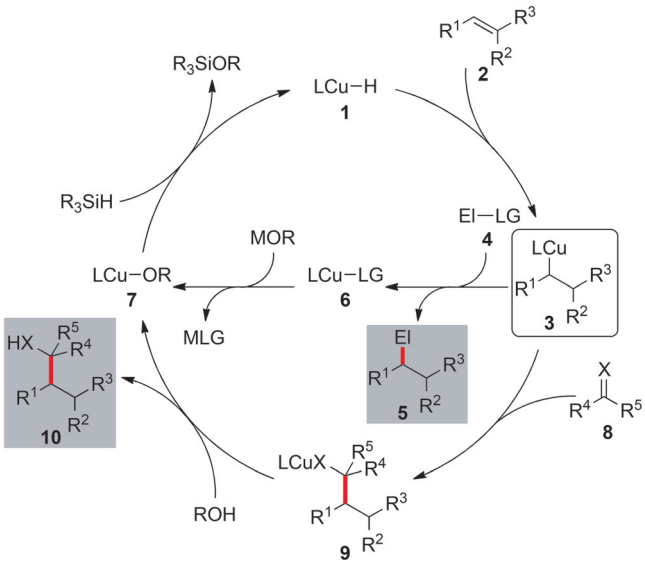
asymmetric catalysis · copper catalysis · copper hydride · hydrosilanes · reduction

Copper(I) hydrides have gained prominence as mild reagents for the reduction of polarized double bonds such as carbonyl groups. The combination of a copper salt with stoichiometric amounts of a hydride source, typically hydrosilanes or dihydrogen, has enabled the development of numerous processes that are catalytic in Cu–H.[1] Recently, these Cu–H-catalyzed reactions were extended beyond the aforementioned reduction when the groups of Hirano and Miura[2] as well as Buchwald[3] independently discovered that in situ generated copper(I) hydrides **1** are also able to add across unactivated alkenes **2** (Scheme 1). Interception of hydrocuprated intermediate **3** with an electrophile allows for the subsequent functionalization of unsaturated substrates **2**.[4] Electrophilic substitution with El-LG **4** creates either a C–Het or a C–C bond to form functionalized **5** along with copper salt **6**. When the leaving group is not oxygen-based, salt metathesis with a metal alkoxide will convert **6** into copper alkoxide **7** from which copper(I) hydride **1** is regenerated by σ-bond metathesis with a hydrosilane.[5] Alternatively, functionalization can occur through addition of copper intermediate **3** to a C=X electrophile **8**, resulting in the formation of adduct **9**. Protonation of **9** by an alcohol releases **10** with concomitant formation of copper alkoxide **7**.



Scheme 1. Cu–H-catalyzed functionalization of alkenes. El = electrophile, LG = leaving group, X = heteroatom (N or O).

Within the last few months, several methods for C=C functionalization have been presented where either the starting material or the target molecule contains the reactive C=O function. To outcompete the established (conjugate) C=O reduction in favor of the alkene reaction partner, the setup has to be well balanced. Careful optimization and a judicious choice of the ligand at copper indeed enabled joining of C=C functionalization (Scheme 1) with C=O reduction. Furthermore, a catalyst system was identified that would even completely silence the conventional C=O chemistry.

Buchwald and co-workers recently established a reduction/hydroamination sequence of enones and enals **11** to obtain γ-amino alcohols **12** (Scheme 2).[6] The generally more favorable Cu–H-catalyzed 1,4-reduction of the α,β-unsaturated acceptors **11** is outcompeted by 1,2-reduction,[7] leaving the C=C bond intact for the subsequent Cu–H-catalyzed hydroamination with electrophilic amination reagents **13**. The chemoselectivity of the initial reduction and the stereoselectivity of the amination are controlled by the same bisphosphine ligand, (*S*)-**L1**. The absolute configuration at the nitrogen-bearing carbon atom in γ-amino alcohol **12a** was dependent on the double-bond geometry in enal **11a** [(*E*)-**11a**→(*S*,*R*)-**12a** and (*Z*)-**11a**→(*S*,*S*)-**12a**]. The stereoselectivity was not affected by the use of a chiral amination reagent, which yielded (*S*,*R*,*R*)-**12b** with three stereogenic centers. When enones were employed as the substrates, the construction of an additional stereocenter in the 1,2-reduction step also proceeded highly stereoselectively to furnish amino alcohols such as (*S*,*S*,*R*)-**12c** with three consecutive stereogenic centers along the carbon chain.

Buchwald and co-workers also explored the Cu–H-catalyzed hydroacylation of aryl-substituted alkenes **14** (Scheme 3).[8] Anhydrides **15** emerged as useful acylation reagents, and downstream 1,2-reduction led to chiral alcohols **16**. A single chiral bisphosphine ligand, (*S*,*S*)-**L2**, is responsible for stereodiscrimination in both the functionalization and reduction steps, affording enantioenriched alcohols

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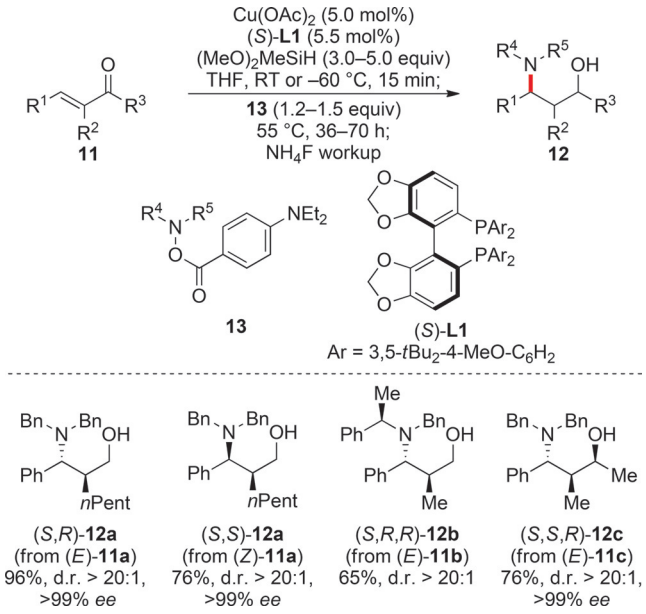
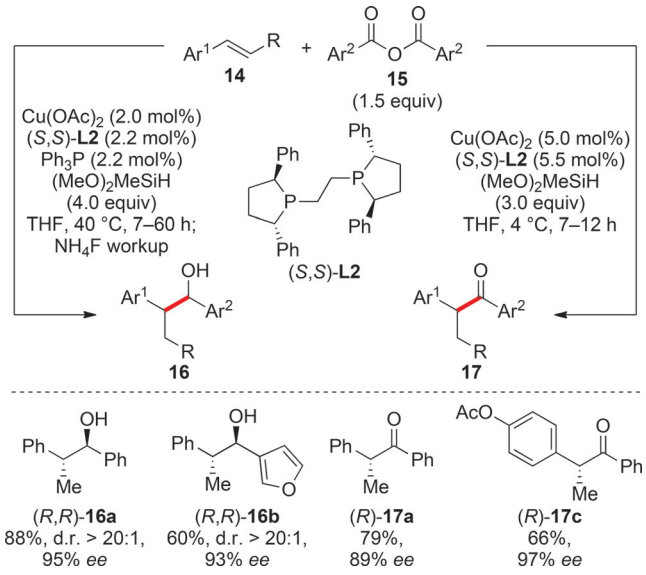
The ORCID identification number for an author of this article can be found under http://dx.doi.org/10.1002/anie.201606701.



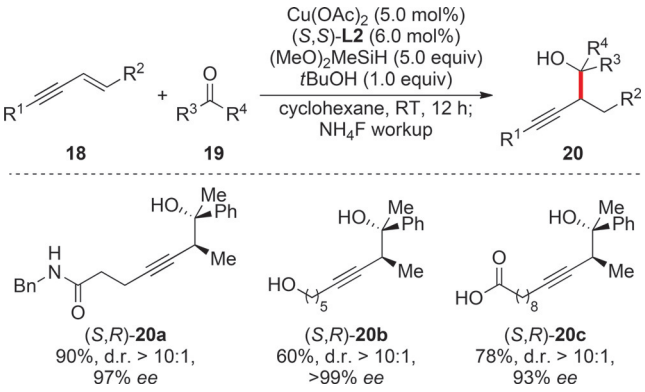
Scheme 2. Sequential 1,2-reduction and hydroamination of enals and enones.



Scheme 3. Hydroacylation of alkenes followed by optional reduction.

(*R*,*R*)-**16a** and (*R*,*R*)-**16b**. The authors found the 1,2-reduction to be slower than the hydroacylation; it did in fact not occur at lower temperature (4 °C instead of 40 °C). α-Chiral ketones such as (*R*)-**17a** and (*R*)-**17c** thus became accessible.

The groups of Liu and Buchwald even accomplished the addition of nucleophilic C=C/Cu–H adducts derived from enynes **18** to ketones **19** to furnish homopropargylic alcohols **20** with two adjacent stereocenters (Scheme 4).[9] DFT calculations had indicated that the ketone hydrocupration, that is, 1,2-reduction, would lose against the enyne hydrocupration with the right choice of bisphosphine ligand. In accordance with the computed data, the experimental results showed that reactions with ligand (*R*)-**L1** produced similar amounts of homopropargylic alcohol **20** and the alcohol resulting from ketone reduction. In contrast, hydrocupration of **18** was the major pathway with ligand (*S*,*S*)-**L2**, resulting in



Scheme 4. Addition of enyne-derived nucleophiles to ketones.

the high-yielding and stereoselective formation of the new C–C bond in **20**. This method exhibits excellent functional-group tolerance as showcased by the incorporation of an amide group as in (*S*,*R*)-**20a**, a free hydroxy group as in (*S*,*R*)-**20b**, and a carboxylic acid group as in (*S*,*R*)-**20c** in the enyne coupling partner.

The recent progress in Cu–H-catalyzed alkene functionalization demonstrates that conventional C=O reduction is not necessarily a competitive and thus detrimental pathway in this chemistry. The order of the bond-forming events can be influenced by careful optimization of the catalyst system and reaction setup. By combining Cu–H-catalyzed reduction and functionalization, chiral molecules with several stereocenters can be rapidly assembled, and, if required, the reduction of polarized double bonds can even be fully suppressed.

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 12148–12149
Angew. Chem. **2016**, *128*, 12330–12332

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Received: July 11, 2016
Published online: August 4, 2016

