Asymmetric Catalysis

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Enantioselective Conjugate Borylation**

*Julia A. Schiffner, Kristine Müther, and Martin Oestreich**

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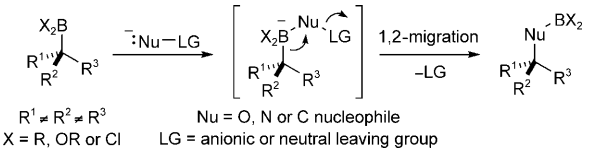
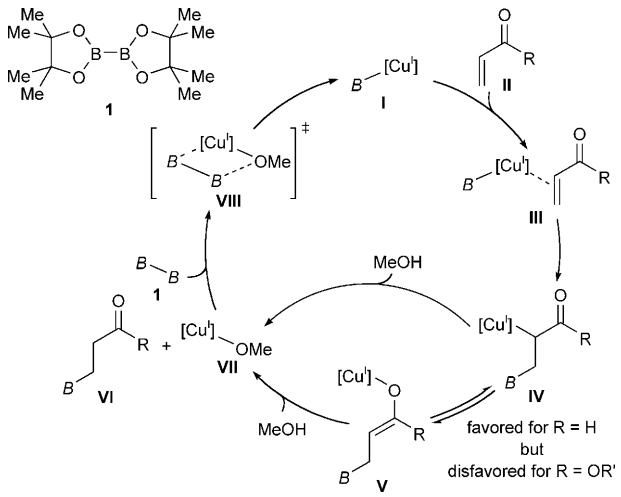
α-Chiral boron compounds are definitely stalwart linchpins in stereoselective synthesis, and the C–B linkage transforms into C–O, C–N, as well as C–C bonds through stereospecific 1,2-migration subsequent to ate complex formation with an adequate nucleophile (Scheme 1).[1] This portfolio was greatly



Scheme 1. α-Chiral boron compounds as synthetic building blocks.

extended through racemization-free Suzuki–Miyaura cross-coupling.[2] Novel protocols for the direct enantioselective construction of α-chiral boranes are therefore clearly welcomed, and recent stunning progress in (mainly) Cu^{I}-catalyzed 1,4-addition of nucleophilic boron is a fundamental addition to synthetic chemistry.[3]

A seminal report by Hosomi and co-workers set the stage for an enantioselective Cu^{I}-catalyzed conjugate borylation.[4] While still in the racemic series at that stage, it was shown that Cu^{I} sources (10 mol%) in combination with Bu_3P promotes activation of the B–B interelement bond in diboron reagent **1** and 1,4-addition to electron-deficient acceptors. Quantum-chemical calculations by Marder et al. now provide the necessary mechanistic understanding to guide the further development of this catalysis (Scheme 2).[5] Pertinent to experimental findings, this investigation rationalizes the reactivity difference between α,β-unsaturated carbonyl and carboxyl compounds and the related essential role of added MeOH. The catalytic cycle commences with the coordination of in situ generated Cu–B complex **I** to the C–C double bond of acceptor **II** (**I**→**III**) and its subsequent insertion into the Cu–B bond (**III**→**IV**). In this way, C-enolate **IV** and not O-



Scheme 2. Catalytic cycle of the Cu^{I}-catalyzed conjugate borylation. *B* = Bpin with pin = pinacolato.

enolate **V** is formed, a remarkable insight that is also supported by deuteration experiments.[6c] The calculated barriers of the σ-bond metatheses of **IV** and **V** with **1** verify that participation of a Cu–C bond in the σ-bond metathesis is energetically unlikely, whereas reaction of a Cu–O bond is almost barrierless. Therefore, the equilibrium between **IV** and **V** will profoundly dictate turnover, and its interconversion barrier becomes pivotal. Quantum-chemical data again assists understanding the subtle role of the electron-withdrawing group (EWG): For **IV**→**V**, both kinetic and thermodynamic stabilities are low for carbonyls ($\Delta G^{\ddagger} = 12.7$ kcal mol^{-1} and $\Delta G = 3.7$ kcal mol^{-1}) but high for carboxyl compounds ($\Delta G^{\ddagger} = 19.5$ kcal mol^{-1} and $\Delta G = 13.7$ kcal mol^{-1}),[5] clearly disfavoring **V** in the latter case. For these reasons, turnover is only secured for α,β-unsaturated carbonyls. This issue was solved by the addition of MeOH, which liberates the borylated acceptor **VI** through alcoholysis (**IV**/**V**→**VI**) along with reactive Cu–OMe complex **VII** (**IV**/**V**→**VII**). The final σ-bond metathesis of **VII** and **1** is of course facile and regenerates the active catalyst **I** (**VII**→**VIII**→**I**).

A general enantioselective protocol of the Cu^{I}-catalyzed conjugate borylation of acyclic acceptors was accomplished by Yun and co-workers using CuCl/NaO*t*Bu/**L1** and MeOH (Scheme 3).[6] For all substrates, josiphos-type ligand **L1** emerged as optimal. It is noteworthy that Fernández et al. recently employed chiral N-heterocyclic carbene **L2** instead of a phosphine ligand in that transformation (Scheme 4).[7]

[*] J. A. Schiffner, K. Müther, Prof. Dr. M. Oestreich
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36501
E-mail: martin.oestreich@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/oestreich

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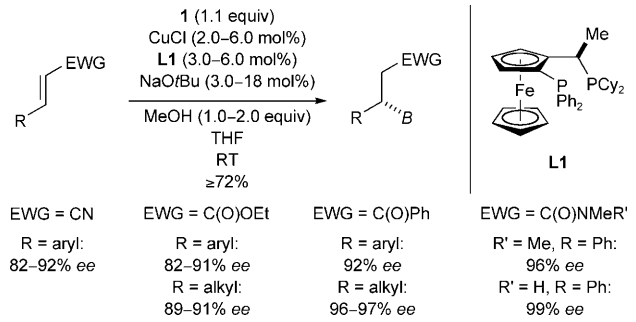
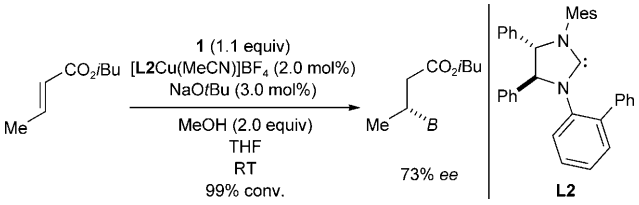
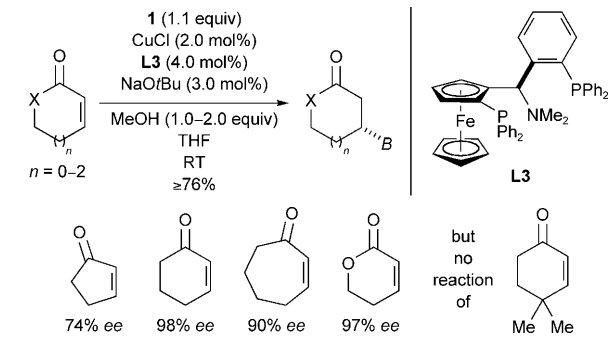


Scheme 3. A chiral Cu^{I}-phosphine complex for enantioselective borylation of acyclic α,β-unsaturated acceptors. Cy = cyclohexyl.



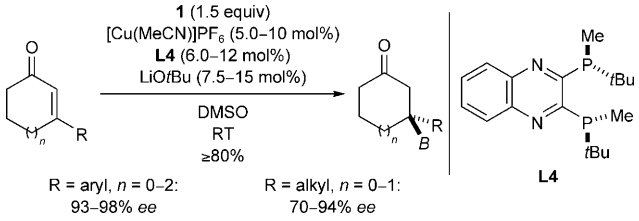
Scheme 4. A chiral Cu^{I} carbene complex for enantioselective borylation of an acyclic α,β-unsaturated carboxyl. Mes = 2,4,6-trimethylphenyl.

A minor modification of the well-established catalyst system introduced by Yun et al. further extended the scope. Replacement of **L1** with **L3** (taniaphos) allowed for the asymmetric conjugate boryl transfer onto thus far elusive cyclic substrates (Scheme 5).[8] While the protocol was



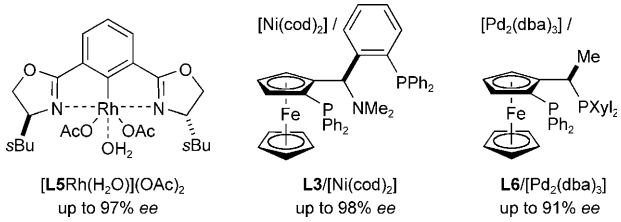
Scheme 5. Enantioselective conjugate borylation of cyclic α,β-unsaturated acceptors devoid of a substituent in the β-position.

certainly a step forward, γ,γ-disubstituted and β-substituted cyclic acceptors failed to react or performed poorly. Simultaneously, the latter limitation was overcome in work by Shibasaki and co-workers (Scheme 6),[9] who accessed tertiary alcohols with excellent levels of enantioselectivity (not shown). As a mechanistic twist, a protic additive is not required as in previous scenarios (Scheme 2). Instead, the catalysis is believed to involve formation of $LiPF_6$ (generated from $CuPF_6$ and LiO*t*Bu), a Lewis acid that might enhance the electrophilicity of **1** through oxygen-atom coordination in **1**.[9]



Scheme 6. Enantioselective conjugate boryl transfer onto cyclic β-substituted, α,β-unsaturated acceptors.

Although Cu^{I}-derived catalysts have dominated the field of asymmetric conjugate borylation, a handful of promising transition-metal/ligand combinations were also investigated, affording comparable enantioselectivities for acyclic acceptors (Scheme 7).[10]



Scheme 7. Rh^{III}-,[10a] Ni^{0}-,[10b] and Pd^{0}-based[10b] catalyst systems. cod = cycloocta-1,5-diene, dba = *trans*,*trans*-dibenzylideneacetone, Xyl = xylyl.

All these outstanding contributions provide a valuable access to enantioenriched α-chiral boron compounds, a class of particularly versatile synthetic building blocks (Scheme 1). Before closing, we would like to mention that Hoveyda and co-workers recently reported a carbene-catalyzed 1,4-addition of nucleophilic boron.[11] In this catalysis, the carbene alone activates the diboron reagent **1** by nucleophilic attack at one of the boron atoms. The next challenge will be the development of an asymmetric version of this metal-free process.

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