Enantioselective hydromethylation of unfunctionalized olefins with copper-hydride catalysis

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Recently in the *Journal of the American Chemical Society*, Buchwald and co-workers achieved enantioselective installation of a methyl group through copper-catalyzed hydromethylation. They demonstrated the utility of this method through the methylation of several olefin substrates, including drug molecules.

Although the methyl group is relatively small in size, its incorporation into molecules has the potential to optimize initial leads in drug discovery. This "magic methyl" effect has been attributed to conformational changes that increase binding affinity to the receptor and, as a result, affords a more potent drug.[1] Methods that can easily install a methyl group enantioselectively, particularly those that allow for late-stage functionalization of drug candidates, are especially valuable to the pharmaceutical industry.[2]

Although there have been several recent advances in the racemic methylation of unfunctionalized olefins,[3–6] prior to this hydromethylation approach, methods of methylating olefins enantioselectively were limited to the conjugate addition to polarized π-systems[7,8]; only a single approach had been reported for the cobalt-catalyzed hydromethylation of fluoroalkenes.[9] Reporting in the *Journal of the American Chemical Society*, Buchwald and co-workers build on their previously reported Cu–H catalysis[10] to achieve the hydromethylation of aryl alkenes, a transformation with useful generality.[11]

The basic and reducing conditions required for Cu–H generation were initially proposed to be incompatible with highly electrophilic methyl sources, such as MeI. Therefore, the authors evaluated ligands by using the less reactive MeOTs with CuOAc as the copper source. Under this set of conditions, the optimal chiral bisphosphine ligand was determined to be (*S*)-DTBM-SEGPHOS and provided the methylated product **2a** in moderate yield (59%) and enantioselectivity (64:36 enantiomeric ratio [er]). Interestingly, when investigating other copper sources, the authors found that CuI gave both higher yield (76%) and higher enantioselectivity (99:1 er). They hypothesized that this result was due to the *in situ* formation of the MeI, a more reactive coupling partner. With the addition of further MeI to the reaction, higher enantioselectivity was observed (>99.5:0.5 er). However, they also observed a decrease in yield (47%). These observations led to the optimal reaction conditions (shown in Figure 1A), which use a preformed CuI complex with the chiral phosphine ligand and MeOTs as the methylating reagent. Using these optimized reaction conditions, the authors demonstrated the suitability of various substrates for obtaining methylated products in good yields (45%–83%) and enantioselectivities (78:22 to 99:1 er); a subset of products is shown in Figure 1B. Substrates containing both electron-donating and electron-withdrawing substitution, as well as several heterocycles, were well tolerated. Additionally, the derivatization of pharmaceuticals, such as oxaprozine and cinnarizine, proceeded well, thus demonstrating the capabilities of this methodology for late-stage functionalization and further illustrating the functional-group tolerance of the authors' method.

To probe the hypothesis that MeI generated *in situ* leads to higher levels of enantioselectivity, Buchwald and co-workers conducted a thorough investigation of different mechanistic possibilities with density functional theory studies. Through these studies, a significant difference in energy was calculated between the two activation barriers, leading to the opposite enantiomers of the product of copper-hydride insertion, **4** and *ent*-**4** (Figure 1C). After this step, the authors considered multiple mechanisms for the addition of the methyl group. The energy of the transition state for an S_N2-type oxidative addition was calculated with the different methyl sources, and it was found that the activation barrier was 12.8 kcal/mol lower with MeI (+5.7 kcal/mol) than with MeOTs (+16.5 kcal/mol). In addition, this was compared with the activation barrier for other mechanistic possibilities, including direct S_N2 substitution of MeI, the concerted oxidative addition of MeI, and the outersphere concerted dissociative electron-transfer mechanism. The activation barriers for these pathways were all calculated to be significantly higher in energy. With computational evidence supporting the facile oxidative addition of MeI, the authors proposed the mechanism shown in Figure 1C. Initial copper hydride insertion leads to intermediate **4**, where a higher energy activation barrier for the methyl addition with MeOTs would allow for epimerization to proceed, resulting in an erosion of enantioselectivity. Instead, MeOTs is converted to MeI, which undergoes an S_N2-type oxidative addition to furnish

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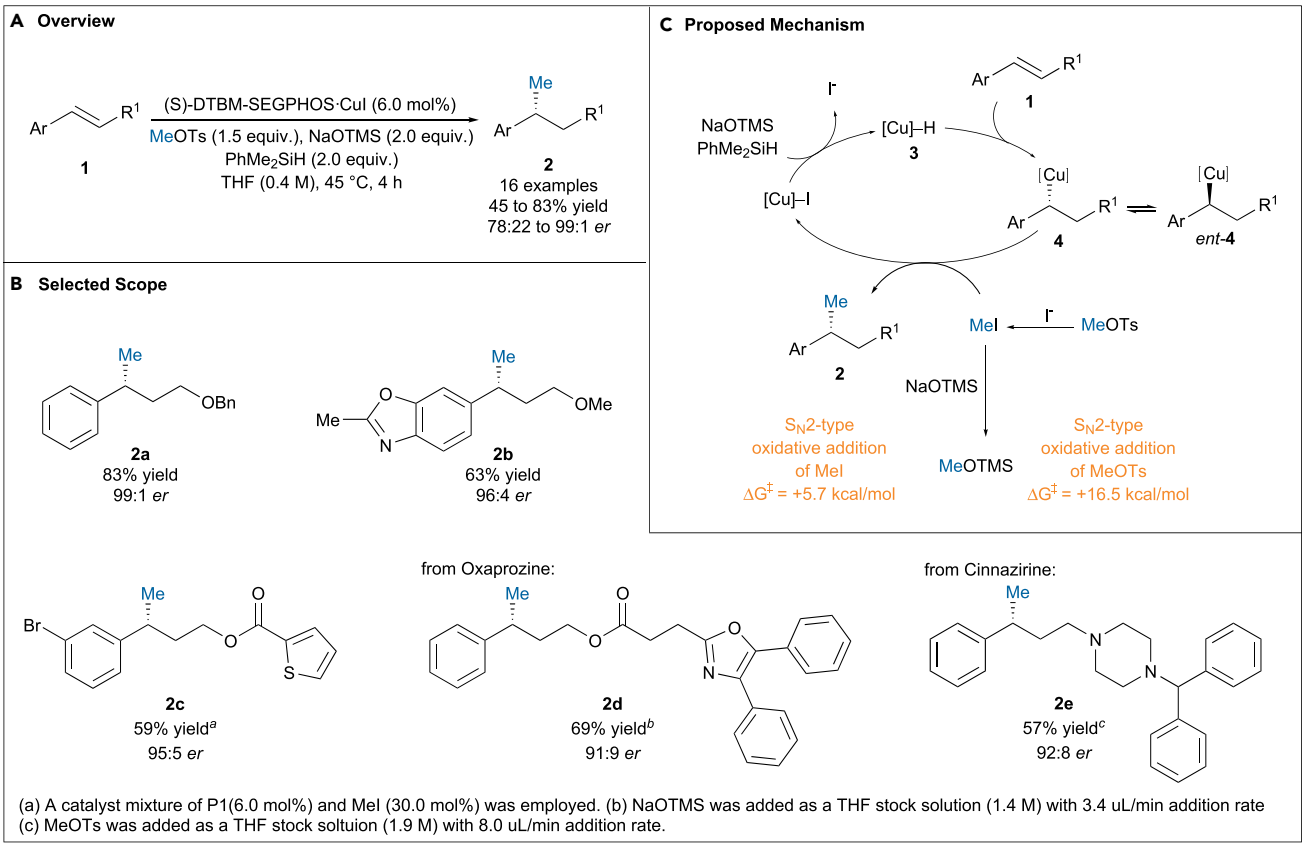

Figure 1. Copper-hydride catalyzed enantioselective hydromethylation

(A) Overview of the reaction conditions.

(B) Illustrative scope examples.

(C) Proposed mechanism.

the methylated product **2**. The authors postulate that the lower yields from the addition of further MeI result from trapping of the NaOTMS base with a higher concentration of this reactive species to give MeOTMS. To close the catalytic cycle, the Cu–H is regenerated through ligand exchange of the resulting CuI with NaOTMS followed by σ-bond metathesis with $PhMe_2SiH$.

This methodology developed by the Buchwald group provides a way to enantioselectively install methyl groups on unpolarized double bonds, solving a difficult endeavor with the potential to provide a wide range of applications. A detailed mechanistic investigation has led to a thorough understanding of the reactivity and specific roles of CuI and MeOTs, leading to the capability of modulating the reactivity to optimize the enantioselectivity and yield for a variety of different substrates. Finally, the potential of the methodology for late-stage functionalization is demonstrated through the derivatization of several pharmaceuticals.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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Organosulfide catalysis for chiral iodinated molecules

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In a recent issue of the *Journal of the American Chemical Society*, Zhao et al. reported an organocatalytic strategy for asymmetric intermolecular iodofunctionalization of alkenes by chiral sulfide. The method showed a broad substrate scope, good enantio-control, and wide synthetic utility.

Enantioselective halofunctionalization of alkenes is a fundamental yet still fast-evolving transformation that provides direct access to chiral halogenated synthons and bioactive compounds. For electro-rich alkenes, halofunctionalization proceeds through a fleeting three-membered haliranium ion intermediate that poses notorious difficulties to achieve stereocontrol. In particular, the haliranium ion may undergo facile olefin-to-olefin transfer that causes racemization.[1,2] Hence, to achieve intermolecular halofunctionalization of alkenes with high level of stereocontrol is of great challenge, and progress along this line is rather limited. With respect to intermolecular iodofunctionalization, there are only two recent examples on catalytic asymmetric version, which both involved metal Lewis acid catalysis (Figure 1A). Feng reported Chiral *N*,*N*′-dioxide/[$Sc(OTf)_3$] complex (Figure 1A, **1a**) for iodoamination of chalcones and the reaction proceeds via nucleophilic addition process instead of iodiranium formation.[3] Recently, a dinuclear zinc complex (Figure 1A, **1b**) was developed for asymmetric iodoesterification of simple alkenes.[4] An organocatalytic version remains to be developed for enantioselective intermolecular iodofunctionalization.

In a recent paper in the *Journal of the American Chemical Society*, Zhao et al. described a delicately designed indane-derived chiral organosulfide catalyst for asymmetric intermolecular iodinative difunctionalization of allylic sulfonamides (Figure 1B).[5] Key structural features of this catalyst include an asymmetrically substituted phenylthiol unit at the two *ortho*-positions and a free N–H sulfamide H-bonding motif (Figure 1B, **2e**). Both groups are critical for both catalytic activity and stereoselectivity. In addition, a stoichiometric amount of MsOH was essential to facilitate complete conversion, and no reaction was observed in its absence. The developed catalytic protocol overrides the already fast non-selective background reactions and ensures a perfect stereocontrol for this challenging transformation. The catalysis can be applied to both γ,γ-disubstitued and β-substituted (γ-unsubstituted) allylic sulfonamides with high yields and enantioselectivity. Nucleophiles including phenols, fluoride, azide, and alcohols can be equally applied with good reactivity and high enantioselectivity (Figure 1D). Moreover, if R_2 changed from methyl to other larger groups like ethyl, the enantioselectivity would suffer dramatic decrease (Figure 1B, **2a**). This indicates that differentiation between R_1 and R_2 is very crucial in facial selectivity of alkenes.

To demonstrate the practicability of this strategy, several synthetic transformations of products were conducted. Compounds **4a** and **4f** were prepared in gram scale, maintaining good yield and enantioselectivity. The β-iodioamide moiety could undergo amino-migration to a variety of nitrogen-containing compounds with high stereoselectivity by exposure to different types of nucleophiles.

Mechanistically, the authors proposed a catalytic cycle (Figure 1C) based on

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