Copper Hydride-Catalyzed Enantioselective Olefin Hydromethylation

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ABSTRACT: The enantioselective installation of a methyl group onto a small molecule can result in the significant modification of its biological properties. While hydroalkylation of olefins represents an attractive approach to introduce alkyl substituents, asymmetric hydromethylation protocols are often hampered by the incompatibility of highly reactive methylating reagents and a lack of general applicability. Herein, we report an asymmetric olefin hydromethylation protocol enabled by CuH catalysis. This approach leverages methyl tosylate as a methyl source compatible with the reducing base-containing reaction environment, while a catalytic amount of iodide ion transforms the methyl tosylate *in situ* into the active reactant, methyl iodide, to promote the hydromethylation. This method tolerates a wide range of functional groups, heterocycles, and pharmaceutically-relevant frameworks. Density functional theory studies suggest that the methylation step is stereoretentive, taking place through an S_N2-type oxidative addition mechanism followed by a reductive elimination. The enantioselectivity is enforced by ligand–substrate steric repulsions during the hydrocupration step.

The introduction of a methyl group, despite its small size and simplicity, can induce profound changes in the properties of a molecule.[1-4] In biologically active compounds, the incorporation of a methyl group may result in conformational changes which increase the structural complementarity of a lead compound to its target receptor with minimal impact on its molecular weight and lipophilicity (Figure 1A).[5-7] While common approaches for the introduction of other single-carbon fragments rely on the asymmetric functionalization of olefins,[8-13] few strategies have been reported for the direct installation of methyl groups. Standard methods to directly install methyl groups rely on conjugate additions to polarized olefins using preformed organometallic reagents facilitated by chiral Lewis acid catalysts.[14-16]

Hydromethylation is an attractive approach for the introduction of a methyl group to an olefin. Even though not enantioselective, some notable methods to hydromethylate olefins include Kambe's Zr-catalyzed reductive coupling protocol[17] and Tilley's Sc-catalyzed methane C–H activation process.[18] Additionally, Baran has developed a formal olefin hydromethylation protocol, utilizing Fe-catalyzed H-atom transfer and a formaldehyde hydrazone as the methyl surrogate.[19] The reaction demonstrated a high degree of functional group tolerance and was used in the late-stage functionalization and isotopic labeling of complex molecules. More recently, Shenvi disclosed a hydromethylation protocol utilizing Ni/Mn dual catalysis,[20] and Nocera has reported on the use of photochemically generated Me-radical from acetic acid.[21] Finally, Frederich delineated the use of a superstoichiometric quantity of Tebbe's reagent.[22] Despite the emergence of several formal hydromethylation strategies, controlling the absolute stereochemistry at the newly formed C–Me bond remains a largely elusive goal (Figure 1B).[17-23] The most relevant asymmetric variant is limited to

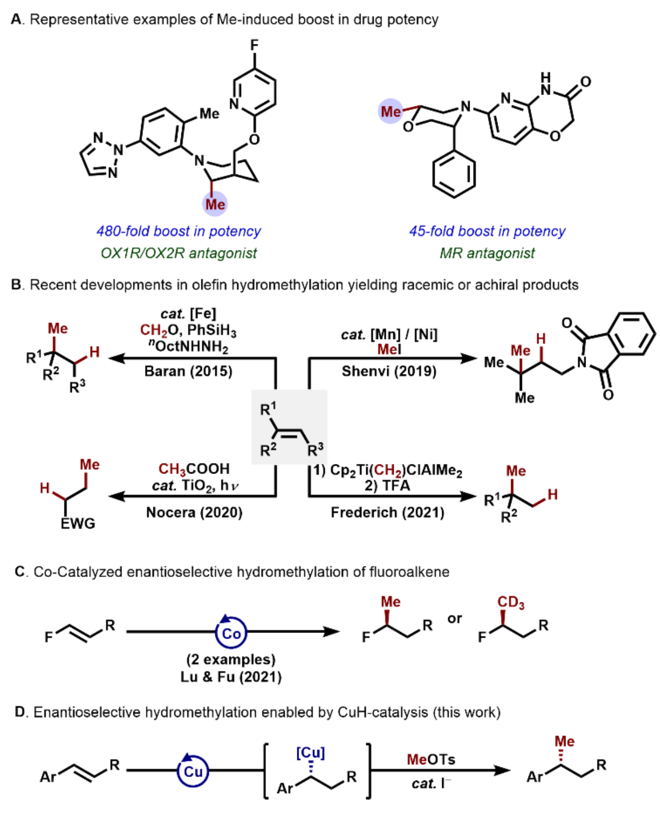


Figure 1. (A) Representative examples of drug potency increase resulting from the incorporation of a methyl group. (B) Recently reported synthetic protocols for olefin hydromethylation. (C) Co-catalyzed asymmetric hydromethylation of fluoroalkene precursors. (D) Asymmetric olefin hydromethylation using CuH-catalyst supported by chiral bisphosphine ligands.

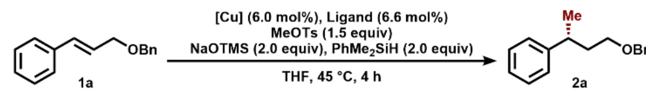
Lu and Fu's elegant Co-catalyzed hydromethylation of fluoroalkenes (Figure 1C).[24]

Our group and others have leveraged CuH-catalysis to forge C–C bonds in a variety of enantioselective transformations,[25] including intramolecular hydroalkylation,[26] intermolecular allylation,[27] and 1,2-carbonyl addition.[28-35] These reactions utilize an *in situ* generated enantioenriched Cu-alkyl species to engage various electrophiles. We sought to employ a CuH-catalyst system in combination with an appropriate electrophilic methyl source to effect the enantioselective hydromethylation of olefins (Figure 1D).[36, 37] Due to the highly reactive nature of common electrophilic methyl sources, such as methyl iodide,[38, 39] we anticipated the major challenge to be the incompatibility between the methylating reagents and reducing reaction conditions and/or the base necessary for CuH generation or regeneration. Therefore, we chose to employ a less reactive methyl source, methyl tolsylate (MeOTs).[40]

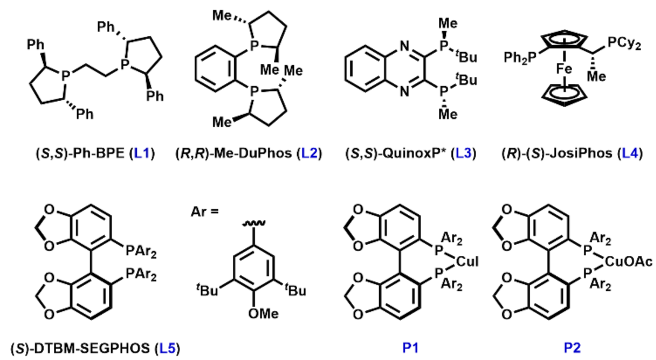
We commenced our investigation by examining the hydromethylation of a styrene allylic ether (**1a**), employing MeOTs as the methyl source. Utilizing several bidentate chiral bisphosphine ligands (**L1**–**L5**) in combination with CuOAc, the olefin hydromethylation product **2a** was formed in moderate yield and low er (entries 1-5, Table 1). We identified (*S*)-DTBM-SEGPHOS (**L5**) as the optimal ligand, among those we tested, for this transformation (entry 5). Examining various copper(I) halides (entries 6–8) revealed that the use of CuI provides the desired product in excellent yield and with a very high level of enantioselectivity. To simplify the reaction protocol, a precatalyst (**L5**)CuI (**P1**) was prepared and utilized in subsequent experiments. The use of **P1** afforded **2a** in similar yield and selectivity to that obtained using a mixture of CuI and **L5** (entry 9).

The improved reaction outcome with the use of CuI prompted further investigation into the role of iodide ion.[41, 42] A series of experiments were carried out by systematically varying the equivalents of iodide ion in the presence of a constant amount of copper (6 mol%;entry 10: 12 mol% I^-; entry 11: 3 mol% I^-; see Supporting Information, Table S2). We observed that increasing the iodide ion concentration concomitantly led to increased enantioselectivity of **2a** and decreased conversion of **1a** (entry 10). We hypothesized that the *in situ* formation of methyl iodide (MeI)[41, 42] facilitates the asymmetric hydromethylation through a proposed catalytic cycle shown in Scheme 1. Enantioselective hydrocupration of **1a** with ligated CuH species (**3**) generates the Cu-alkyl intermediate (**4**). Catalytic quantities of I^- converts MeOTs to the more reactive MeI,[43] which undergoes methylation with **4** to form product **2a**. The resulting ligated CuI intermediate regenerates **3** through sequential Cu-alkoxide generation and σ-bond metathesis with $PhMe_2SiH$. Two competing processes take place concurrently: (1) the epimerization of **4**,[44] and (2) the trapping of MeI by NaOTMS. With a higher iodide ion concentration, the more rapid methylation of **4** with MeI leads to the observed increase in enantioselectivity. At the same time, higher iodide ion concentrations increase the rate of MeOTMS formation, leading to the observed decrease in conversion. In a similar way, lowering the effective concentration of MeI increases the steady-state concentration of **4**, which facilitates the productive methylation while minimizing trapping of the

Table 1. Optimization of the Enantioselective Hydromethylation of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene (1a) Employing MeOTs as the Methyl Source[a]

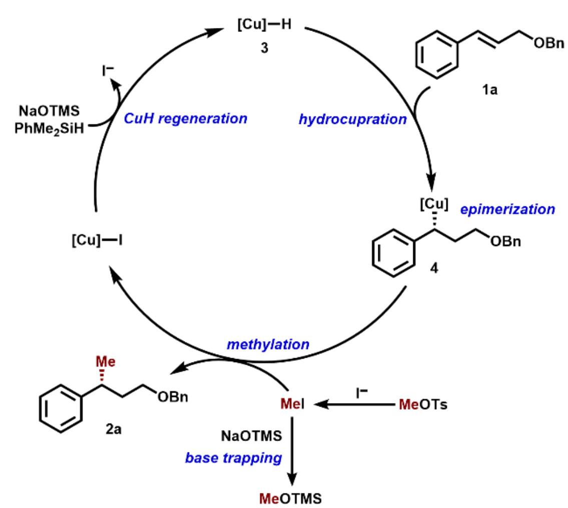


entry	catalyst mixture	yield 2a (%)	er (2a)
1	CuOAc + **L1**	46	37:63
2	CuOAc + **L2**	35	45:55
3	CuOAc + **L3**	<5	-
4	CuOAc + **L4**	55	42:58
5	CuOAc + **L5**	59	64:36
6	CuCl + **L5**	69	81:19
7	CuBr + **L5**	67	73:27
8	CuI + **L5**	76	99:1
9	**P1**	78	99:1
10[b]	**P1** + MeI	47	>99.5:0.5
11[c]	**P1** + **P2**	84	79:21



[a]Reaction conditions: 0.20 mmol of (*E*)-(3-(benzyloxy)prop-1-en-1-yl)benzene (**1a**, 1.0 equiv), 0.30 mmol of MeOTs (1.5 equiv), 0.40 mmol of sodium trimethylsilanolate (NaOTMS, 2.0 equiv), 0.40 mmol of $PhMe_2SiH$ (2.0 equiv), specified catalyst mixture, and THF (0.4 M); reaction yields were determined by ^1H NMR spectroscopy of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard (see SI for details). Enantiomeric ratio (er) of **2a** was determined by chiral supercritical fluid chromatography (SFC). [b]A catalyst mixture of **P1** (6.0 mol%) and MeI (6.0 mol%) was employed; significant amount of **1a** (43%) was observed in the product mixture. [c]A catalyst mixture of **P1** (3.0 mol%) and **P2** (3.0 mol%) was employed.

Scheme 1. Proposed Catalytic Cycle



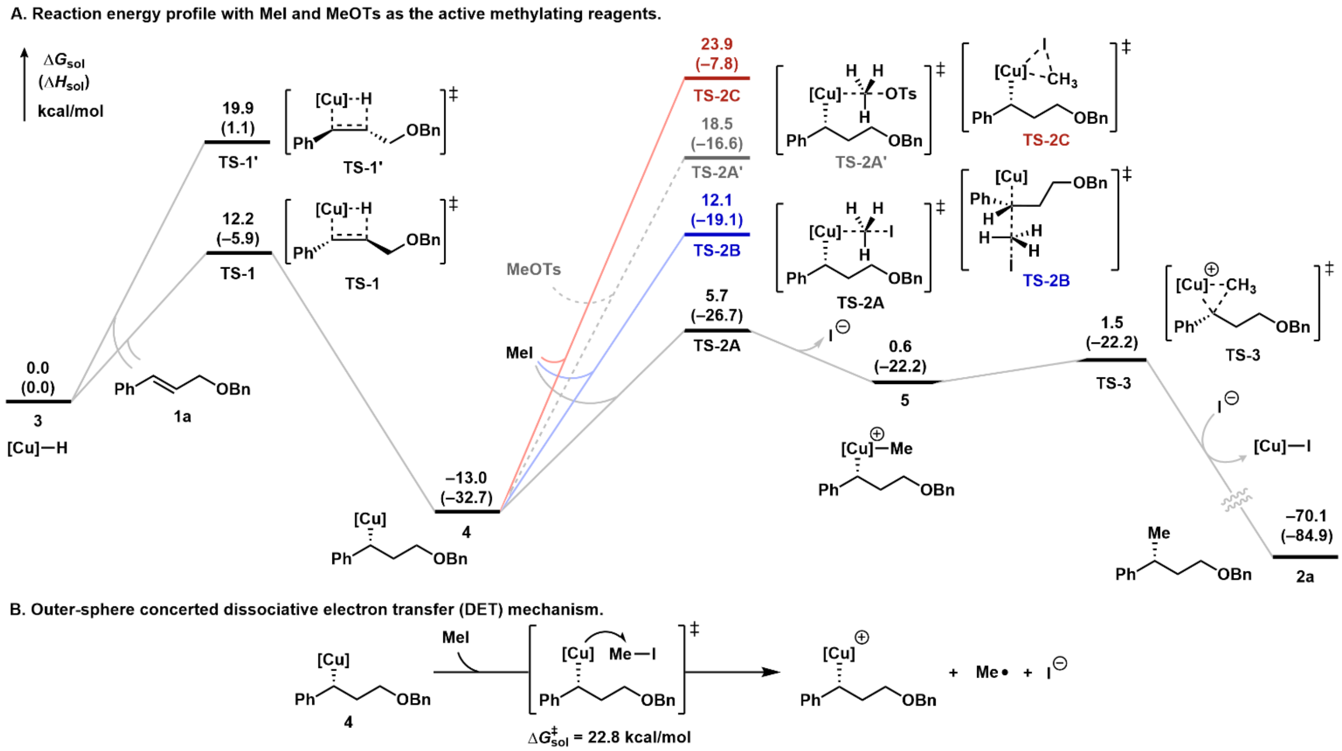


Figure 2. Computed reaction energy profile (kcal/mol) of the Cu-catalyzed asymmetric hydromethylation.

methylating reagent (see Supporting Information for detail, Scheme S1). Taken together, modulating the iodide ion concentration offers an operationally simple handle to tune the enantioselectivity or yield of this reaction.

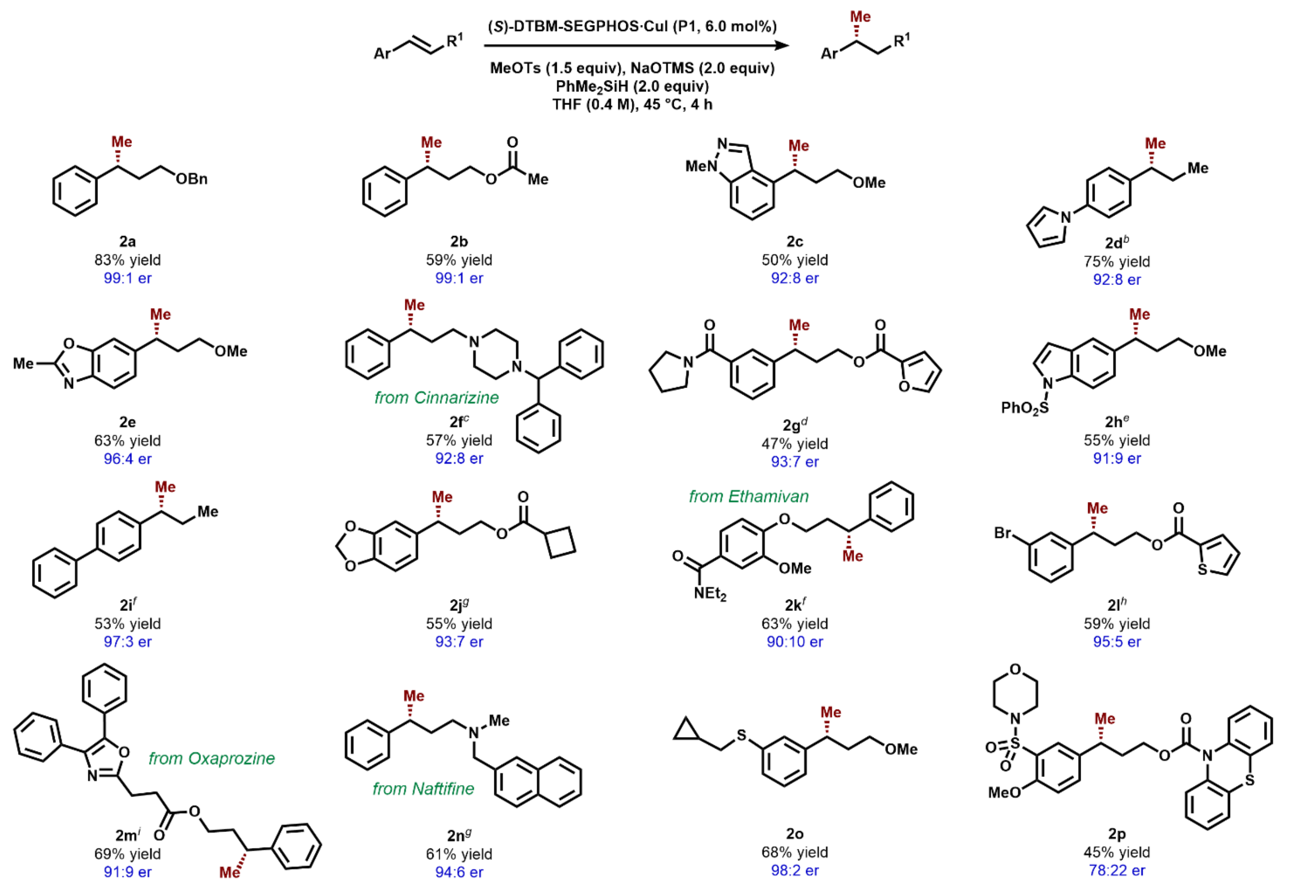
Density functional theory (DFT) calculations were carried out to corroborate our proposed hydromethylation catalytic cycle, namely the participation of *in situ* formed MeI and the apparent iodide effect. The calculations were performed at the M06/6-311+G(d,p)–SDD(Cu, I)/SMD(THF)//B3LYP-D3/6-31G(d)–SDD(Cu, I) level of theory using **1a** as the model substrate with **L5**-supported Cu catalyst (Figure 2. See Supporting Information for Computational Details). The hydrocupration of **1a** with CuH catalyst **3** through **TS-1** was found to be irreversible, preferentially giving (*R*)-Cu-alkyl intermediate **4**. The hydrocupration TS leading to (*S*)-Cu-alkyl intermediate (**TS-1'**) is 7.7 kcal/mol higher in energy than **TS-1**, due to the substituents of the alkene being placed in quadrants occupied by the C_2-symmetric ligand **L5**, leading to unfavorable steric repulsions (see Supporting Information, Figure S3).[45]

From Cu-alkyl intermediate **4**, we first assessed the relative reactivity of MeI toward methylation through an S_N2-type oxidative addition[46-48] via **TS-2A** ($\Delta G^{\ddagger}$ = 18.7 kcal/mol with respect to **4**; see Supporting Information, Figure S4 for 3D TS structures). The resulting cationic species **5** undergoes rapid stereoretentive reductive elimination (via **TS-3**) to furnish **2a**,[46] which is consistent with the absolute configuration of the hydromethylation products (*vide infra*). The activation barrier for the methylation using MeOTs as the methylating reagent via **TS-2A'** is 12.8 kcal/mol higher in energy than **TS-2A**, suggesting that MeI is indeed the active form of the methylating reagent, thereby validating our hypothesis regarding the observed iodide effect.

Several alternative methylation mechanisms involving MeI were also considered. Methylation through the direct S_N2 nucleophilic substitution via **TS-2B**,[47, 48] involving simultaneous formation of the C–C bond and the dissociation of the C–I and Cu–C bonds, requires a 6.4 kcal/mol higher barrier than **TS-2A**. This indicates that this stereoinvertive pathway is less favorable than the stereoretentive pathway via **TS-2A** and **TS-3**. The concerted oxidative addition via a three-centered transition state **TS-2C** is 18.2 kcal/mol less favorable. Finally, the outer-sphere concerted dissociative electron transfer (DET) mechanism[49, 50] was also ruled out due to the high activation barrier ($\Delta G^{\ddagger}_{sol}$ = 22.8 kcal/mol with respect to **4**) calculated using the modified Marcus theory (see SI for details).[51] Collectively, these computational results corroborated our proposed catalytic cycle and provided insight into the mechanism by which the critical C-CH_3 bond is formed.

With our mechanistic understanding of the olefin hydromethylation protocol, we set out to probe substrates amenable to this transformation (Table 2). Given our understanding of the role of iodide ions in this reaction, we first optimized reaction conditions by modulating the loading of **P1** and/or adding sub-stoichiometric quantities of MeI. For instance, in the case of olefins that delivered good yields in the presence of **P1** alone, sub-stoichiometric MeI was added to increase the enantioselectivity of the transformation (**2g** and **2l**). For substrates that exhibited low conversions under the standard reaction conditions, decreasing the amount of **P1**, thereby reducing the effective iodide ion concentration, led to an increased product yield at the

Table 2. Substrate Scope of the Enantioselective Hydromethylation Reaction[a]



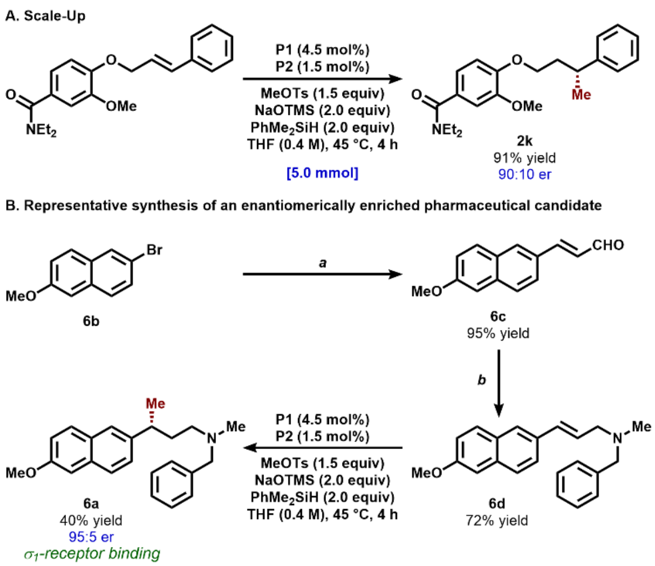
[a]All yields represent the average of two isolated yields using 0.50 mmol of olefin substrate. Enantiomeric ratio (er) was determined by chiral SFC. Precatalyst **P1** (6.0 mol%) was employed unless otherwise noted. [b]MeOTs was added as a THF stock solution (1.9 M) with 2.0 µL/min addition rate. [c]MeOTs was added as a THF stock solution (1.9 M) with 8.0 µL/min addition rate. [d]A catalyst mixture of **P1** (6.0 mol%) and MeI (6.0 mol%) was employed. [e]A catalyst mixture of **P1** (1.5 mol%) and **P2** (4.5 mol%) was employed. [f]A catalyst mixture of **P1** (4.5 mol%) and **P2** (1.5 mol%) was employed. [g]A catalyst mixture of **P1** (3.0 mol%) and **P2** (3.0 mol%) was employed. [h]A catalyst mixture of **P1** (6.0 mol%) and MeI (30.0 mol%) was employed. [i]NaOTMS was added as a THF stock solution (1.4 M) with 3.4 µL/min addition rate.

expense of enantioselectivity (*vide supra*, **2h–k**, **2n**). Additionally, slow addition of MeOTs demonstrated to be a viable method to increase the product yield (**2d** and **2f**). The reaction proceeded effectively with substrates bearing both electron-donating and -withdrawing functional groups. A range of heterocycles were also well-tolerated, such as indazole (**2c**), pyrrole (**2d**), benzoxazole (**2e**), piperazine (**2f**), pyrrolidine (**2g**), furan (**2g**), indole (**2h**), thiophene (**2l**), oxazole (**2m**), morpholine (**2p**), and phenothiazine (**2p**). Several pharmaceuticals were derivatized to further demonstrate the functional group compatibility of this protocol, including from antihistamine Cinnarizine (**2f**), respiratory stimulant Ethamivan (**2k**), nonsteroidal anti-inflammatory Oxaprozin (**2m**), and anti-infective Naftifine (**2n**). To access **2m** in high yield, NaOTMS was slowly introduced to the reaction mixture to prevent deprotonation at the α-carbon of the ester. The absolute configuration of the products was determined by comparing the optical rotation of **2b**, **2d** and **2i** to literature values.[52-54]

To further highlight the synthetic utility of the asymmetric olefin hydromethylation protocol, the synthesis of **2k** was carried out on a 5.0 mmol scale, resulting in improved yield and comparable enantioselectivity to the 0.5 mmol scale reaction (Scheme 2A). To showcase the utility of our method, we devised a three-step asymmetric synthetic sequence to **6a**, a substrate which binds the σ_1-receptor (Scheme 2B).[55] Starting from commodity chemical 2-bromo-6-methoxynaphthalene (**6b**), a Pd-catalyzed Heck reaction between **6b** and 1,1-diethoxyethene furnished the α,β-unsaturated aldehyde **6c** in high yield. Subsequent reductive amination (**6d**) followed by CuH-catalyzed hydromethylation furnished **6a** in high enantiomeric purity (95:5 er) and 27% yield over three steps. The general substructure of **6a** is widely present in a range of pharmaceutical lead compounds.[56-63]

In summary, we have developed a CuH-catalyzed enantioselective olefin hydromethylation protocol. This method is tolerant of a wide range of functional groups and heterocycles. This method was also used for the derivatization of several pharmaceuticals, and in a concise three-step asymmetric synthesis of a σ_1-receptor binding molecule. Mechanistic evidence suggests a crucial role of catalytic iodide ion in effecting both the yield and enantioselectivity of the asymmetric methylation. Density functional theory calculations revealed that the methylation occurs through an S_N2-type oxidative addition giving a formally Cu(III) intermediate, which undergoes reductive elimination to furnish the methylated product.

Scheme 2. Application of the CuH-Catalyzed Asymmetric Hydromethylation Reaction



[a]Reaction conditions: 1,1-diethoxyethene (3.0 equiv), $Pd(OAC)_2$ (10.0 mol%), KCl (1.0 equiv), K_2CO_3 (1.5 equiv), $(^nBu_4N)(OAc)$ (2.0 equiv), DMF, 90 °C, 16 h. [b]Reaction conditions: (1) *N*-methylbenzylamine (4.0 equiv), H_2SO_4 (5 mol%), DCM, 25 °C, 2 h; (2) $NaBH_4$ (2.0 equiv), DCM, 25 °C, 6 h.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and characterization data for all new compounds, including NMR spectra, SFC traces, computational details, and Cartesian coordinates of all computed structures (PDF)

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Notes

The authors declare no competing financial interest

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