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Enantioselective Hydroaminomethylation of Olefins Enabled by Rh/Brønsted Acid Relay Catalysis

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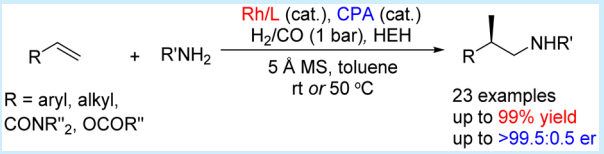
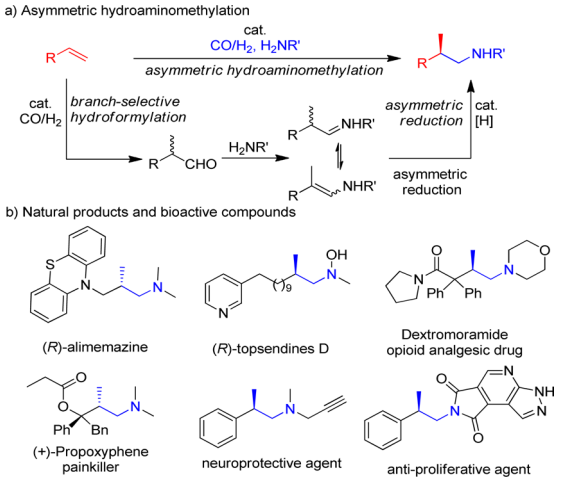
Supporting Information

ABSTRACT: Herein, by employing a rhodium catalyst with a commercial ligand and a phosphoric acid catalyst, highly chemo-, regio-, and enantioselective hydroaminomethylation of olefins is realized through a relay catalytic hydroformylation/dynamic kinetic reductive amination process. The method features mild conditions (1 bar of syngas, room temperature in most cases), high yields (up to 99%), and high enantioselectivities (up to >99.5:0.5 er). Besides styrenes, acrylamides also provided the products with high yields and enantioselectivities. Aliphatic alkenes and vinyl esters are also applicable for the current method, albeit lower yields and enantioselectivities were obtained.



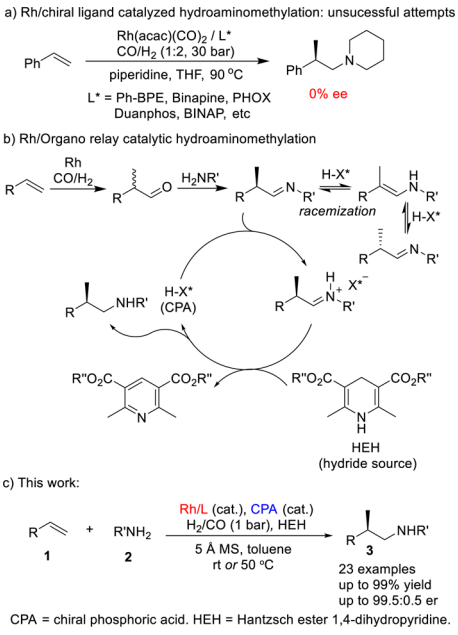
Hydroaminomethylation (HAM), a triple sequential reaction consisting of hydroformylation of an alkene, condensation of the generated aldehyde with an amine, and the reduction of the resulting imine or enamine, provides a highly efficient and atom-economical method to synthesize amines from alkenes, carbon monoxide, and hydrogen gas.[1] Since the discovery of HAM in the 1940s by Reppe,[2] tremendous efforts have been devoted to improve the chemo- and regio-selectivity, as well as the overall efficiency of the reaction.[3] However, the development of asymmetric HAM of olefins remained uncharted territory for a long time, despite the significant impact such reactions would have on academic research and the fine chemicals industry (Scheme 1a).[4] Asymmetric HAM of alkenes may also provide unique and straightforward approaches to access a large number of bioactive compounds, drugs, and natural products, as exemplified in Scheme 1b.[5]

Scheme 1. Asymmetric Hydroaminomethylation and Potential Synthetic Applications



Rhodium complexes are able to catalyze both hydroformylation and hydrogenation reactions and are thus often used for HAM.[6] In a recent publication from Urrutigoïty, Maron, and Kalck, a series of chiral diphosphine ligands were tested in the rhodium-catalyzed HAM of styrene and found to be completely unable to introduce any enantioselectivity, though excellent chemo- and regio-selectivities were often obtained (Scheme 2a).[4a] Zhang and co-workers very recently developed a rhodium-catalyzed asymmetric intramolecular interrupted hydroamino-

Scheme 2. Asymmetric Hydroaminomethylation of Alkenes



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methylation using allylamine substrates.[7] While transition metal-catalyzed direct asymmetric HAM encountered difficulties, a metal/organo relay catalytic strategy could provide an alternative way (Scheme 2b). This pathway consists of several consecutive processes: (1) rhodium-catalyzed selective hydroformylation of alkenes to generate α-branched aldehydes; (2) formation of imines; (3) chiral Brønsted acid-catalyzed dynamic kinetic reduction of imines to produce the chiral amines.[8−10] Very recently, during the course of our current research project, Xiao and co-workers applied this strategy for the asymmetric HAM of styrenes.[11] However, the transformation required harsh conditions (11 bar syngas) and showed unsatisfying enantioselectivities (most examples <95:5 er) and limited olefin scope (styrenes only).

Herein, as a continuation of our research in asymmetric metal/organo combined catalysis,[12,13] we report a highly enantioselective HAM of olefins employing a rhodium catalyst with a commercial ligand and a phosphoric acid catalyst. The transformation shows a broad substrate scope toward diversely substituted chiral amines with up to 99% yields and up to 99.5:0.5 er under mild conditions (Scheme 2c).

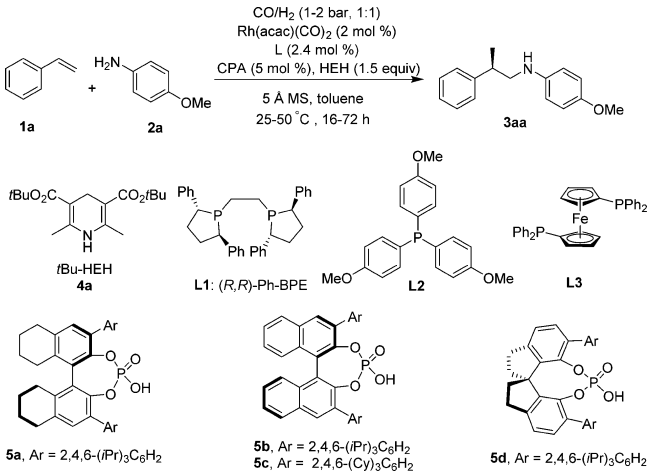
Our investigation initiated with styrene **1a** and *p*-anisidine **2a** as the model substrates, ^{t}Bu-HEH **4a** as the hydrogen source (Table 1). Rhodium complexes were chosen as the hydroformylation catalysts because of their excellent performance in alkene hydroformylations. The hydroformylation step should be highly branch-selective to avoid the formation of linear amines. Also, highly active hydroformylation catalyst is needed because the subsequent asymmetric hydrogen transfer process often requires much milder conditions. Among numerous ligands for rhodium catalyzed hydroformylation, commercially available (*R*,*R*)-Ph-BPE **L1** was selected due to its high activity, excellent branch-selectivity, and easy accessibility.[14] Racemic **L1** was not employed directly because it is not commercially available. In addition, (*S*,*S*)-**L1** almost provided identical results as shown later. In the beginning, a series of chiral phosphoric acids were examined in the presence of Rh/**L1** at 50 °C (entries 1−5). Compound **5a** was identified as the optimal chiral acid catalyst in regard to the enantioselectivity (entry 1). Notably, *ent*-**5b** provided *ent*-**3a** as the major enantiomer, indicating that the enantioselectivity of the reaction is controlled by chiral phosphoric acid. Other ligands, **L2** and **L3**, which have been previously used in the hydroformylation of alkenes, gave significantly inferior yields under identical conditions (entries 6−7). A prolonged reaction time facilitated the reaction to 65% NMR yield and 96:4 er (entries 7−8). Lowering the reaction temperature (entries 9−10) to room temperature could slightly increase the enantioselectivity without considerable loss of yield (entry 10). Performing the reaction at a higher concentration greatly increased the NMR yield to 89% with 81% isolated yield (entry 11). By lowering the pressure of syngas from 2 to 1 bar, a slightly higher isolated yield could be obtained (entry 12). As mentioned previously, (*S*,*S*)-Ph-BPE provided almost identical results, supporting the speculation that the *in situ* generated α-branched aldehyde could undergo a fast racemization in the presence of the amine and acid catalyst via an imine/enamine tautomerization (entry 13).

With the established optimal reaction conditions (Table 1, entry 12), we continued to explore the substrate scope of the method (Scheme 3 and Table 2). Because the *p*-methoxyphenyl group could be removed conveniently by oxidation, *p*-anisidine **2a** was generally employed as the amine component. In general, high yields and with excellent enantioselectivities could be obtained with a broad series of styrene derivatives (**3aa**−**3na**). Noteworthy, ortho-substituted styrenes, which gave lower yields in a previous report,[11] were also well tolerated, providing the corresponding chiral amines in 73%−99% yields and excellent enantioselectivities (**3ba**−**3da**). Interestingly, styrenes bearing strong electron-withdrawing groups, 2,3,4,5,6-pentafluorostyrene and 3,5-bis(trifluoromethyl)styrene, are also suitable substrates for this method (**3ja** and **3ka**). Heteroaromatic systems (e.g., **3na**) could be employed as well. As for the amine component, while the enantiomeric ratios remain high, electron-rich anilines resulted in the best yields (**3md**, **3me**) but electron-deficient anilines only gave low yields (**3mb**, **3mc**). This is likely because of inefficient condensation between electron-deficient anilines and *in situ* generated aldehyde.

Besides styrenes, we also employed other alkenes using current method (Table 2). Alkyl alkenes, **1o** and **1p**, although with lower yields and enantiomeric ratios, can also be employed in the relay catalytic reaction. Interestingly, acrylamides, **1q** and **1r**, underwent the reactions smoothly, giving β-amino amides **3pa** and **3qa** in high yields with high enantiomeric ratio. Vinyl ester **1s** was also tolerated, providing chiral 2-amino alcohol **3sa** with moderate yield and enantiomeric ratio.

An example for the synthetic utility of chiral amine **3aa** was shown below (eq 1). Through a protection, oxidation, and

Table 1. Optimization of Catalysts and Reaction Conditions[a]



entry	L	CPA	temp (°C)	time (h)	yield (%)[b]	er[c]
1	**L1**	**5a**	50	16	50	95.5:4.5
2	**L1**	**5b**	50	16	34	95:5
3	**L1**	*ent*-**5b**	50	16	30	7:93
4	**L1**	**5c**	50	16	61	94.5:5.5
5	**L1**	**5d**	50	16	trace	
6	**L2**	**5a**	50	16	24	95:5
7	**L3**	**5a**	50	16	18	94.5:5.5
8	**L1**	**5a**	50	72	65	96:4
9	**L1**	**5a**	40	72	66	96.5:3.5
10	**L1**	**5a**	25	72	60	97:3
11[d]	**L1**	**5a**	25	72	89 (81[f])	96.5:3.5
12[d,e]	**L1**	**5a**	25	72	--(83[f])	96.5:3.5
13[d,e]	*ent*-**L1**	**5a**	25	72	--(82[f])	96.5:3.5

[a]Unless indicated otherwise, the reaction was carried out under CO/H_2 (1:1, 2 bar) atmosphere in the scale of **1a** (0.3 mmol), **2a** (0.2 mmol), **4a** (0.3 mmol), Rh(acac)$(CO)_2$ (0.004 mmol), ligand (0.0048 mmol), chiral phosphoric acid (0.01 mmol), and 5 Å molecular sieve (200 mg) in toluene (2.0 mL). [b]NMR yield with trimethylbenzene-1,3,5-tricarboxylate as the internal standard. [c]Determined by chiral HPLC. [d]Toluene (1.0 mL). [e]CO/H_2 (1 bar, 1:1). [f]Isolated yield.

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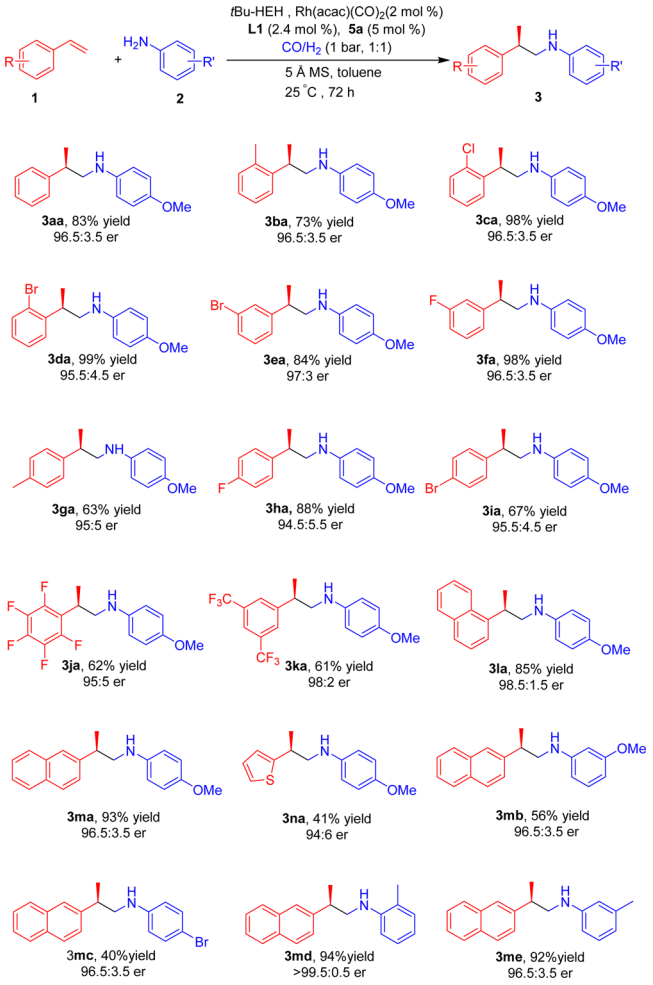
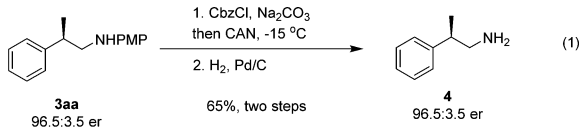
Scheme 3. Substrate Scope of Styrene Derivatives and Aromatic Amine[a]



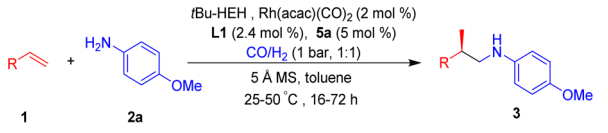
[a]Reaction conditions: reaction of **1** (0.3 mmol), **2** (0.2 mmol), **5a** (0.01 mmol), (*R*,*R*)-Ph-BPE (0.0048 mmol), ^{t}Bu-HEH (0.3 mmol), $Rh(acac)(CO)_2$ (0.004 mmol) 5 Å MS (200 mg), CO/H_2 (1 bar,1:1) were carried out in toluene (1 mL) at 25 °C for 72 h.



deprotection sequence, compound **4** could be obtained with no enantiomeric loss. Optically pure primary amine **4**, which was prepared by chiral resolution therein, has been employed as a key intermediate in the development of a large number of bioactive compounds and pharmaceuticals.[5a,15]

In summary, we have developed a highly enantioselective hydroaminomethylation of olefins by employing a rhodium catalyst with a commercial ligand and a phosphoric acid catalyst. The relay catalytic reaction consists of a rhodium-catalyzed hydroformylation step and Brønsted acid catalyzed subsequent dynamic kinetic reductive amination process. The salient features of this reaction include mild conditions (1 atm of syngas, room temperature in most cases), high yields (up to 99%), and high enantioselectivities (up to >99.5:0.5 er). Besides styrenes, other olefins, including aliphatic alkenes, acrylamides, and vinyl esters can also undergo this transformation. Further studies regarding the expansion of the substrate scope and development of related transformations are underway and will be reported in due course.

Table 2. Asymmetric HAM of Nonaromatic Alkenes[a]



alkene	product	conditions and results
1o	3oa	25 °C, 72 h 36% yield, 75:25 er
1p	3pa	50 °C, 16 h 71% yield, 73:27 er
1q	3qa	50 °C, 72 h 77% yield, 94.5:5.5 er
1r	3ra	50 °C, 72 h 84% yield, 94:6 er
1s	3sa	25 °C, 72 h 52% yield, 87:13 er

[a]Reaction conditions: reaction of **1** (0.3 mmol), **2** (0.2 mmol), **5a** (0.01 mmol), (*R*,*R*)-Ph-BPE (0.0048 mmol), ^{t}Bu-HEH (0.3 mmol), $Rh(acac)(CO)_2$ (0.004 mmol) 5 Å MS (200 mg), CO/H_2 (1 bar,1:1) were carried out in toluene (1 mL).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00100.

Complete description of methods and additional results; spectroscopic data for all new compounds **3** and **4** (PDF)

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Notes

The authors declare no competing financial interest.

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