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Regio- and Enantioselective Formal Hydroamination of Enamines for the Synthesis of 1,2-Diamines

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Abstract: *The asymmetric formal hydroamination of enamines using a CuH catalyst is reported. The method provides a straightforward and efficient approach to the synthesis of chiral 1,2-dialkyl amines in good yields with high levels of enantioselectivities for a broad range of substrates, and should have significant value for the preparation of molecules bearing a 1,2-diamine motif.*

Hydroamination is the direct formation of a C–N bond by the formal addition of an N–H bond across either an alkene or an alkyne. This effective strategy has attracted considerable attention from the scientific community over the past decade as it allows the rapid formation of either alkyl amines or enamines from readily available starting materials. To date, significant progress has been made in the field of catalytic hydroamination,[1] and the reaction has been applied to a variety of substrates.[2–6] As a result, the hydroamination reaction has been established as a powerful tool for the rapid synthesis of several types of amines, which themselves are valuable intermediates in organic and pharmaceutical chemistry.[7] Somewhat surprisingly, enamines have not been employed as substrates in the catalytic hydroamination reaction, perhaps because of the hydrolytic sensitivity of these compounds or their propensity to participate in enamine–imine tautomerization.[8] If successful, however, such transformation would result in the formation of 1,2-diamines, which has been recognized as a privileged scaffold.[9] It is also noted that 1,2-diamines are excellent Lewis bases with the possibility to chelate transition metals, thus adding an extra layer of complexity when attempting to develop a catalytic metal-mediated hydroamination.

Chiral 1,2-diamines have been identified as an essential structural motif since it is widely represented in natural products, biologically active compounds, synthetic building blocks, organocatalysts, and ligands (Figure 1).[9a,d,10] It is thus not surprising that the development of efficient routes to chiral 1,2-diamines have received considerable interest from the synthetic community. Although several elegant approaches for the preparation of this scaffold have been reported, the direct formation of 1,2-dialkylamines has remained elusive.[11] The hydroamination of a suitable precursor appeared to be an attractive solution to these problems. To the best of our knowledge, only two examples of the application of hydroamination for the synthesis of chiral 1,2-diamines have been documented: in the first a chiral aldehyde is used to tether a hydroxylamine and an allylic amine which is then followed by an intramolecular retro-Cope elimination to install the 1,2-diamine moiety (Scheme 1a),[12] while the other relies on an asymmetric Rh^{I}-MeO-BIPHEP-catalyzed asymmetic hydroamination of secondary allyl amines (Scheme 1b).[13]

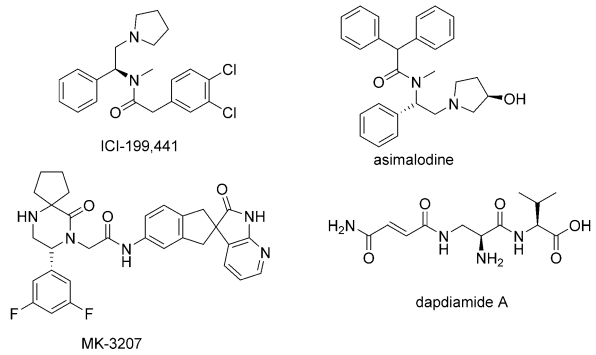
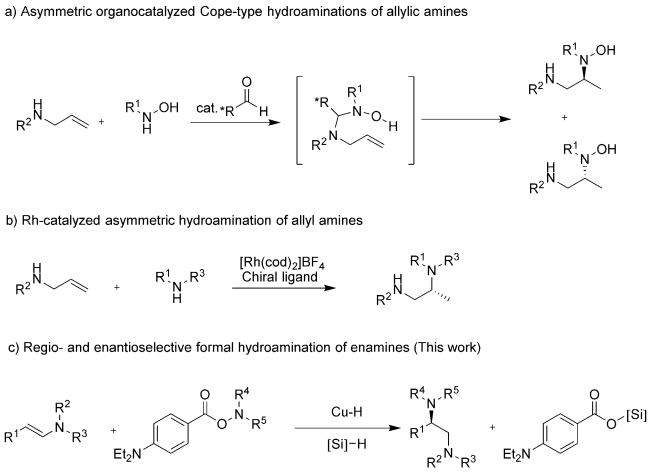


Figure 1. Biologically active compounds incorporating the 1,2-diamine unit.

In 2013, the groups of Hirano, Miura,[14] and Buchwald[15] independently developed an efficient copper(I) hydride protocol for the regio- and enantioselective formal hydroamination of olefins. Since then, this approach has been well



Scheme 1. Approaches to 1,2-diamines by applying hydroamination of alkenes.

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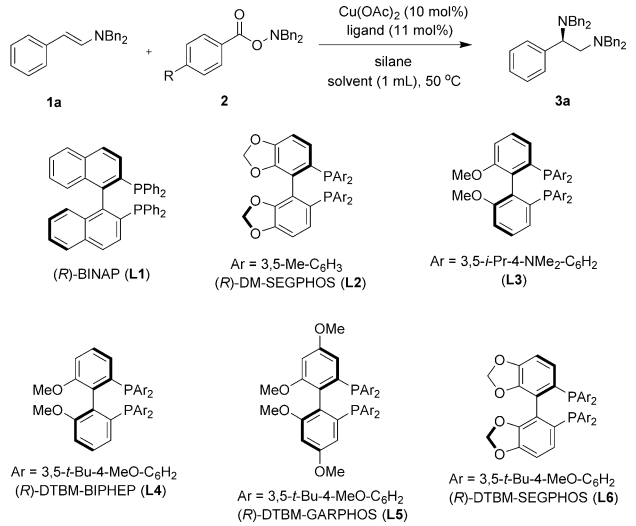
demonstrated for a variety of substrates, and has established its broad generality and applicability.[7d,e,g,16] We speculated that this approach could be extended to the regio- and enantioselective formal hydroamination of enamines, thus allowing ready access to 1,2-diamines, and herein report our results (Scheme 1c).

The investigation was initiated by examining the formal hydroamination of the enamine **1a** with the easily accessible hydroxylamine **2a** as an electrophilic aminating reagent,[16e] in the presence of $Cu(OAc)_2$/(*R*)-BINAP (**L1**) and $(EtO)_2MeSiH$ (DEMS) as the hydride source (Table 1). To our delight, the desired 1,2-diamine **3a** was detected in the crude reaction mixture (^{1}H NMR spectroscopy), albeit in trace quantities (entry 1). This result unequivocally demonstrated the potential of the approach and, equally clear, the need for a thorough optimization of the reaction conditions. It has previously been shown that the use of bulky bidentate phosphine ligands in the CuH catalyzed formal hydroamination of olefins has, somewhat counterintuitively, a beneficial effect on the reactivity.[15] Through computational studies this effect was traced to attractive dispersion interactions between the bulky ligands, for example, the *t*Bu moieties in DTBM-SEGPHOS (**L6**), and the substrate, lowering the energy of the transition state in the hydrocupration step.[17] Switching to the bulky bidentate phosphine ligands **L2**–**L4** resulted in increased yields and excellent enantioselectivities (entries 2–4). Encouraged by these results, two additional ligands were explored. Both the ligands **L5** and **L6** resulted in increased yields, compared to those obtained when using **L4**, while retaining excellent e.r. values, perhaps indicating a beneficial influence on the reactivity when increasing the electron-donating ability of the biphenyl backbone (entries 5 and 6). The optimization was then continued with (*R*)-DTBM-SEGPHOS (**L6**) and the influence of the O-acylhydroxylamine **2**, the aminating reagent, on the reaction outcome was investigated (entries 6–8). It was shown that having an electron-donating substituent on the benzoyl moiety in **2** was beneficial, as **2a** ($R = NMe_2$) and **2c** ($R = NEt_2$) both performed better than **2b** ($R = H$).[16d,e] Because of the slightly higher yield when using **2c**, compared to **2a**, it was selected for further optimization. Further screening of solvents and the amount of silane revealed that performing the reaction in THF with a slight excess (1.1 equiv) of silane was optimal (entries 9–12). Finally, it was shown that using $(MeO)_2MeSiH$ (DMMS) as the hydride source had a beneficial influence on the reaction outcome (entries 13 and 14), affording **3a** in 69% yield with an e.r. value of 97:3.

Table 1: Optimization of the formal hydroamination of the enamine **1a** with O-benzoylhydroxylamines (**2**).[a]

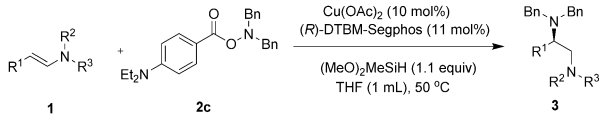


Entry	L	R	Solvent	Silane (equiv)	*t* [h]	Yield [%][b]	e.r.[c]
1	**L1**	NMe_2(**2a**)	THF	DEMS (2)	48	< 5	–
2	**L2**	NMe_2(**2a**)	THF	DEMS (2)	48	11	n.d.
3	**L3**	NMe_2(**2a**)	THF	DEMS (2)	48	26	96:4
4	**L4**	NMe_2(**2a**)	THF	DEMS (2)	48	37	99:1
5	**L5**	NMe_2(**2a**)	THF	DEMS (2)	48	44	98:2
6	**L6**	NMe_2(**2a**)	THF	DEMS (2)	48	53	97:3
7	**L6**	H(**2b**)	THF	DEMS (2)	24	38	94:6
8	**L6**	NEt_2(**2c**)	THF	DEMS (2)	48	57	96:4
9	**L6**	NEt_2(**2c**)	toluene	DEMS (2)	72	43	97:3
10	**L6**	NEt_2(**2c**)	1,4-dioxane	DEMS (2)	72	49	96:4
11	**L6**	NEt_2(**2c**)	THF	DEMS (1.1)	48	61	96:4
12	**L6**	NEt_2(**2c**)	THF	DEMS (3)	24	52	96:4
13	**L6**	NEt_2(**2c**)	THF	PMHS (1.1)	48	62	95:5
14	**L6**	NEt_2(**2c**)	THF	DMMS (1.1)	48	69	97:3

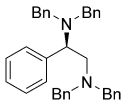
[a] Reactions performed with $Cu(OAc)_2$ (0.025 mmol), ligand (0.028 mmol), **1a** (0.75 mmol), **2a** (0.25 mmol), and silane in solvent (1 mL) at 50 °C. [b] Yield determined by using ^{1}H NMR spectroscopy and an internal standard [c] Determined by chiral-phase HPLC. DEMS = diethoxymethylsilane, DMMS = dimethoxymethylsilane, n.d. = not determined, PMHS = polymethylhydrosiloxane, THF = tetrahydrofuran.

Having identified the optimal reaction conditions, the scope and limitations of the formal CuH catalyzed hydroamination of a variety of enamines (**1**) was then investigated (Table 2). The influence of the N-substituents in **1** on the reaction outcome was relatively small as **3a**–**e** was formed with high e.r. values, although the yield of the N-methyl indole derivative **3d** was somewhat lower. Unfortunately, using either a N-Boc- (**1f**) or N-Ts-(**1g**) protected enamine failed to afford the desired product. In addition, enamines derived from morpholine (**3h**), 4-piperidinone (**3i**), and piperazine (**3j**, **3k**) can also be accommodated, providing the desired products in excellent yields but with slightly decreased enantioselectivities. Next the influence of the aryl moiety on the reaction outcome was investigated. Both electron-rich and electron-deficient enamines, as well as a heteroaryl enamine, reacted smoothly with **2c** to afford the desired products in moderate to good yields and high e.r. values (**3l**–**o**). The enamine **1p**, derived from ethyl 3-oxopropanoate, gave racemic diamine **3p** in good yield, while formal hydroamination of 9-vinylcarbazole gave the *anti*-Markovnikov product **3q** in low yield. When the alkyl enamine **1r** was subjected to the reaction conditions none of diamine **3r** was obtained. Instead the starting material was recovered unaffected and the O-acylhydroxylamine **2c** was reduced under the reaction conditions. Finally, attempts to formally hydroaminate the trisubstituted enamine derived from 1-phenyl-2-propane proved unsuccessful and produced none of the desired product.[18]

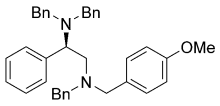
Table 2: Study of the scope with respect to the enamines **1** in the formal hydroamination reaction.[a,b,c]



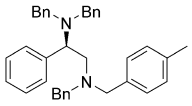
1 2c 3



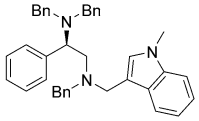
3a
yield 73% e.r. 97:3



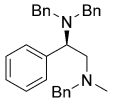
3b
yield 57% e.r. 97:3



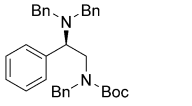
3c
yield 56% e.r. 97:3



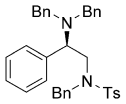
3d
yield 40% e.r. 95:5



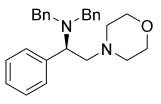
3e
yield 69% e.r. 88:12



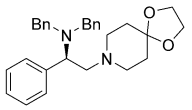
3f
no product



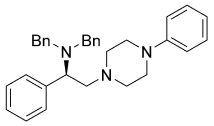
3g
no product



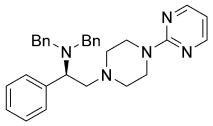
3h[d]
yield 86% e.r. 88:12



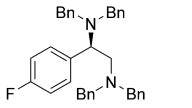
3i[d]
yield 51% e.r. 93:7



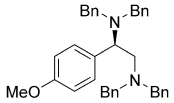
3j[d]
yield 85% e.r. 75:25



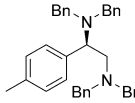
3k[d]
yield 96% e.r. 88:12



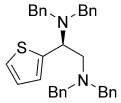
3l
yield 88% e.r. 96:4



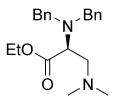
3m
yield 65% e.r. 98:2



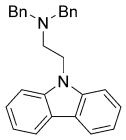
3n
yield 40% e.r. 97:3



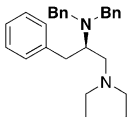
3o
yield 56% e.r. 95:5



3p[e]
yield 72% e.r. 51:49



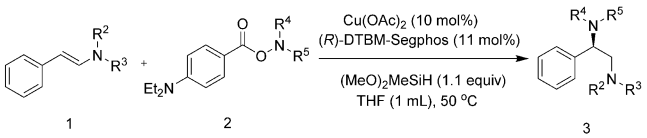
3q
yield 11%



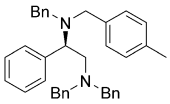
3r[e]
no product

[a] Reactions performed with $Cu(OAc)_2$ (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.028 mmol), **1** (0.75 mmol), **2a** (0.25 mmol), and DMMS (0.28 mmol) in THF (1 mL) at 50°C. [b] Yield of isolated product. [c] The e.r. value was determined by chiral-phase HPLC. [d] Reactions performed with $Cu(OAc)_2$ (0.013 mmol), (*R*)-DTBM-SEGPHOS (0.014 mmol), **1** (0.5 mmol), **2a** (0.25 mmol), and DEMS (0.5 mmol) in THF (1 mL) at 50°C. [e] Reactions performed with $Cu(OAc)_2$ (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.028 mmol), **1** (0.5 mmol), **2a** (0.25 mmol), and DEMS (0.5 mmol) in THF (1 mL) at 50°C.

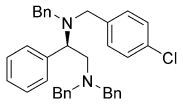
Table 3: Scope with respect to the O-aroylhydroxylamines **2** in the formal hydroamination of **1**.[a,b,c]



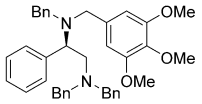
1 2 3



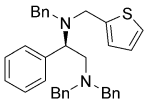
3s
yield 60% e.r. 95:5



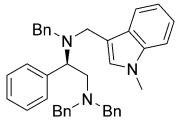
3t
yield 71% e.r. 97:3



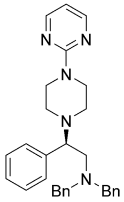
3u
yield 44% e.r. 88:12



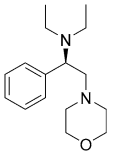
3v
yield 59% e.r. 93:7



3w
yield 50% e.r. 96:4



3x
yield 60% e.r. 99:1

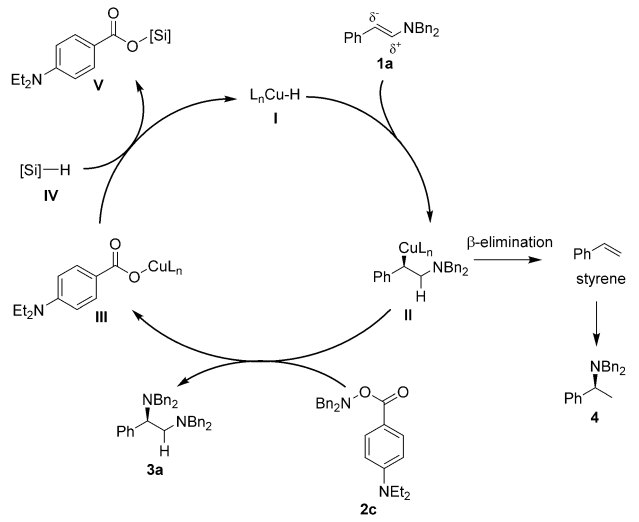


3y[d]
yield 79% e.r. 95:5

[a] Reactions performed with $Cu(OAc)_2$ (0.025 mmol), (*R*)-DTBM-SEGPHOS (0.028 mmol), **1** (0.75 mmol), **2a** (0.25 mmol), and DMMS (0.28 mmol) in THF (1 mL) at 50°C. [b] Yield of isolated product. [c] The e.r. values were determined by chiral-phase HPLC. [d] Reactions performed with $Cu(OAc)_2$ (0.013 mmol), (*R*)-DTBM-SEGPHOS (0.014 mmol), **1** (0.5 mmol), **2a** (0.25 mmol), and DEMS (0.5 mmol) in THF (1 mL) at 50°C.

The influence of the **2** on the reaction outcome was next explored (Table 3). Hydroxylamines having either electron-rich (**2s** and **2u**) or electron-deficient (**2t**) benzyl groups were tolerated, as were the heterocyclic derivatives **2v** and **2w**, affording the corresponding 1,2-diamines **3v** and **3w** in good yields with high e.r. values. Interestingly, the hydroxylamine **2x**, having a Lewis-basic 1-pyrimidylpiperazine substituent, was also successfully utilized as an electrophilic aminating reagent, providing **3x** with high yield and e.r. value. The dialkyl hydroxylamine **2y** also gave desired dialkylamine product **3y** in good yield with high e.r. value. The absolute configuration of **3y** was determined to be *R* by comparing its optical rotation ($[\alpha]_D^{25} = -1.3$ ($c = 2.00$, $CHCl_3$)) with literature data ($[\alpha]_D^{25} = +1.3$ ($c = 3.00$, $CHCl_3$)),[19] and the configuration of the other compounds described in this work are assigned in analogy to **3y**.

Based on the previously proposed mechanism for the CuH-catalyzed hydrofunctionalization reaction of alkenes, a plausible catalytic cycle for the formal hydroamination of enamines is proposed (Scheme 2).[20] Regio- and enantioselective hydrocupration of **1a** with the in situ generated copper(I) hydride generates the alkyl copper intermediate **II**. In the hydroamination of alkenes it has been shown that this step is irreversible and enantiodetermining, and it is reasonable to assume that this is also the case for the present reaction. Oxidation of **II** with **2c** then furnishes the enantioenriched **3a** and releases the copper benzoate **III**, which is reconverted into **I** upon transmetalation with the silane **IV**. In this reaction trace amounts of the amine **4** were detected in



Scheme 2. Proposed catalytic cycle.

the crude reaction mixture, and it is believed to be formed by a β-elimination of **II** to form styrene, followed by a formal hydroamination.[16m,21]

In summary, a regio- and enantioselective formal hydroamination of enamines has been developed, allowing a direct access to the 1,2-dialkylamines motifs. The reaction proceeds with high efficiency and excellent enantioselectivity for a broad range of substrates and should provide a valuable entry to substrates containing a 1,2-diamine motif. Efforts towards the application of this formal hydroamination of enamines are ongoing in our group.

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Conflict of interest

The authors declare no conflict of interest.

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