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Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines

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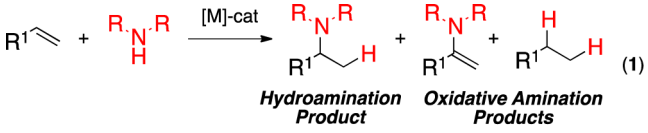
Supporting Information

ABSTRACT: The synthesis of 1,2-diamines via a Rh-catalyzed intermolecular hydroamination of *N*-allyl imines with cyclic amines is presented. Coordinating groups proximal to the olefin bind to the catalyst and promote the transformation. The reaction affords 1,2-diamines in very good yields and is functional-group-tolerant and highly diastereoselective.

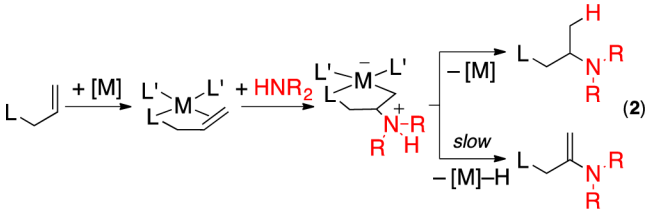
An effective method that allows the selective incorporation of amines into organic molecules would represent a significant advance for synthetic organic chemists.[1] Hydroamination, the addition of an amine N−H bond across an alkene or alkyne, is particularly appealing as it couples two easily accessible functional groups with 100% atom economy (eq 1).[2] The development of regio- and chemoselective



(1)

intermolecular hydroamination reactions is a critical unmet challenge for organometallic chemists. Recently, there have been several reports of hydroamination reactions catalyzed by late transition metals.[3−8] These transformations represent a significant step forward but are faced with several challenges: they are intramolecular[3] or need moderate to large excesses of olefin relative to amine,[4,7] and they are not chemoselective—hydroamination and oxidative amination occur competitively to afford mixtures of amine, enamine, and reduced products (eq 1).[3,4,7] Moreover, hydroamination reactions typically require activated alkenes (such as styrenes,[4] 1,3-dienes,[5] or strained cyclic olefins[6]); there are limited examples of intermolecular hydroamination reactions with 1-alkenes that are both electronically unactivated and unstrained.[7]

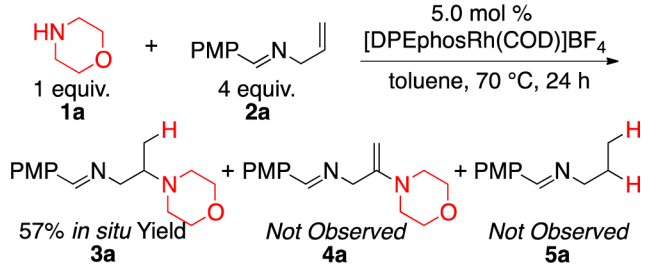
Our solution to these problems is to incorporate a Lewis basic functional group into the alkene substrate that can coordinate to the catalyst (eq 2), thereby increasing the propensity of the double bond to coordinate to the metal and induce reactivity, thus removing the requirement for conjugated or strained alkene substrates.[9−11] Moreover, upon aminometalation, a metallacyclic intermediate can be formed that should slow the rate of β-hydride elimination and thereby reduce or eliminate enamine generation (eq 2).[12]



(2)

The investigations began with *N*-allyl imines, as they are easy to synthesize[13] and are known ligands for transition metals;[14] moreover, they would generate differentially protected 1,2-diamine products upon hydroamination. Gratifyingly, it was observed that rhodium-catalyzed intermolecular hydroamination between morpholine (**1a**) and *N*-allyl imine **2a** occurs when they are subjected to known conditions for the hydroamination of styrene with **1a** (Scheme 1).[4c] The reaction

Scheme 1. Rh-Catalyzed Hydroamination between Morpholine (1a) and Allyl Imine 2a



affords **3a** in 57% in situ yield. Notably, neither **4a** nor **5a**, the products of oxidative amination, were observed. Styrene under identical conditions affords an 82% yield of a 3.1:1.0 amine/enamine mixture.[4c] The lack of oxidative amination with **2a** suggests that an imine proximal to the Rh−alkyl is superior to a π-benzyl at slowing β-hydride elimination and supports a metallacyclic intermediate (eq 2). Unfortunately, other Lewis basic groups, such as amines, amides, and imides, were unsuccessful in promoting the Rh-catalyzed hydroamination reaction (Table S6 in the Supporting Information).

Extensive reaction optimization was performed by varying the ligand, counterion, concentrations, solvent, temperature, and **1a**/**2a** ratio, as summarized in Table S1 and further elaborated in Tables S2−S7. Interestingly, unlike previous

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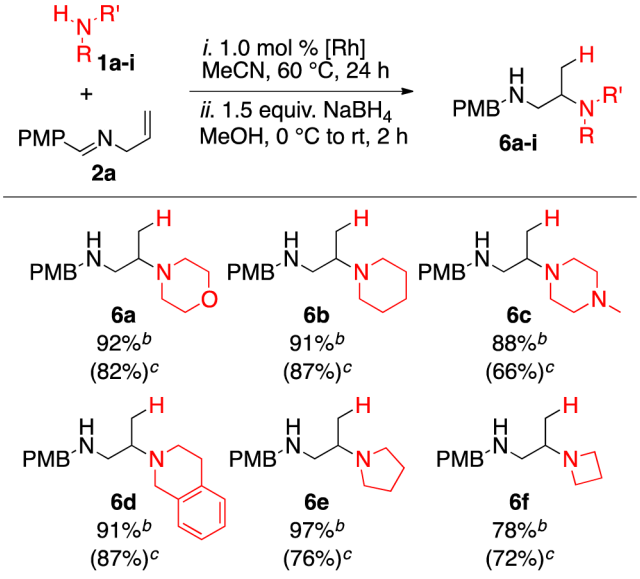
intermolecular hydroamination reactions,[4] an excess of olefin was not required; rather, the optimized conditions employed a 5:1 ratio of **1a** to **2a** and afforded **3a** in nearly quantitative yield (Table S1, entry 5). DPEphos proved to be the most effective ligand at promoting the desired reaction. The related, more rigid Xantphos ligand was not effective, essentially precluding the reaction (Table S1, entry 6). Other ligands, such as dppb, did facilitate the hydroamination reaction, albeit in lower yields (Table S1, entry 8; Table S2). Rhodium proved to be the superior catalyst compared with the analogous Ir complex, which did not promote the desired reaction (Table S1, entry 8). A cationic catalyst was most effective, as the noncoordinating anions BF_4^- and PF_6^- both afforded the product in >90% yield (Table S1, entries 5 and 13); coordinating ligands such as acetate and chloride were less efficient (Table S1, entries 12 and 14). Finally, the preformed [(DPEphos)Rh(COD)]BF_4 catalyst was shown to be equivalent to that generated in situ (Table S1, entry 15).

Upon scale-up, the hydroamination of **2a** occurred cleanly with a 1 mol % loading of the preformed [(DPEphos)Rh(COD)]BF_4 catalyst to afford aminoimine **3a** in 92% yield (as determined by ^{1}H NMR analysis of the crude reaction mixture).[15] As **3a** is not stable toward column chromatography, the product was isolated by initial reduction to the 1,2-diamine followed by purification via column chromatography. Following this protocol, **6a** was obtained in 82% yield. In addition to morpholine, a variety of cyclic amine nucleophiles participated in the desired hydroamination reaction to afford good to excellent yields of the 2-aminoimine products (Table 1). Unfortunately, acyclic secondary amines, anilines, amides, and imides did not afford significant quantities of the expected products, presumably because of their reduced nucleophilicities (Table S5).

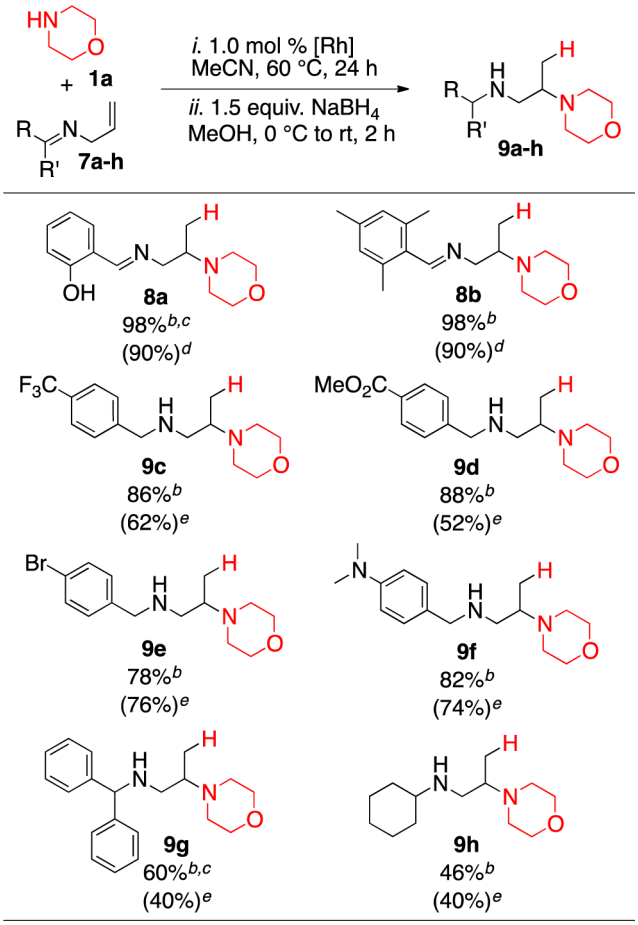
Table 1. Scope of Amines in the Reaction[a]



[a] *i.* Amine (1.5–5.0 equiv), olefin (1.0 equiv), [(DPEphos)Rh(COD)]BF_4 (1.0 mol %), MeCN (4.3 M), 60 °C, 24 h. *ii.* $NaBH_4$ (1.5 equiv), MeOH (0.1 M), 0 °C to rt, 2 h. [b]Yield of imine after hydroamination as determined by comparison to an internal standard in the ^{1}H NMR spectrum. [c]Isolated yield after reduction.

Next, the scope of the imine coordinating groups and the functional group tolerance was examined. As shown in Table 2,

Table 2. Scope of Imines in the Rh-Catalyzed Hydroamination Reaction[a,b]



[a,b]See Table 1. [c]5 mol % [Rh] was used. [d]Isolated yield of the imine after filtration through alumina. [e]Isolated yield after reduction.

a variety of *N*-allyl aldimines underwent the hydroamination reaction to afford 1,2-diamines in very good to excellent yields. Sterically congested imines underwent the hydroamination reaction, as ortho substituents were compatible (**8a** and **8b**). Additionally, the reaction was tolerant of both electron-donating and electron-withdrawing groups on the aryl imine. Even potentially reactive functional groups such as aryl bromides, esters, and phenols were unaffected. Lastly, more hindered and less Lewis basic ketimines were also effective at promoting the hydroamination reaction to afford **9g** and **9h**, albeit in reduced yields.

The effect of substitution on the allyl groups on the Rh-catalyzed hydroamination reaction was also investigated (Scheme 2). Imine **10a** containing 1,1-disubstituted double bonds afforded **11a** containing a tertiary C–N bond in 78% NMR yield. Regrettably, substrates with 1,2-disubstituted double bonds (**10b–d**) did not afford the desired hydroamination products.[16]

Finally, the effect of substitution at the α-position on the allyl group was examined (Table 3). It was hypothesized that the metallacyclic intermediate formed prior to aminometalation would lead to a highly diastereoselective reaction (see Figure 1). Indeed, the Rh-catalyzed hydroamination reaction between

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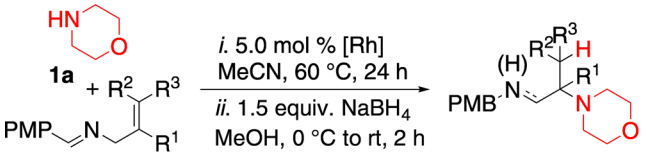
Scheme 2. Effect of Substituted Alkenes on the Hydroamination Reaction[a]

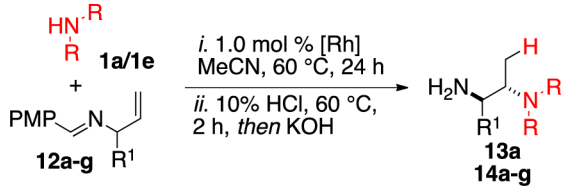


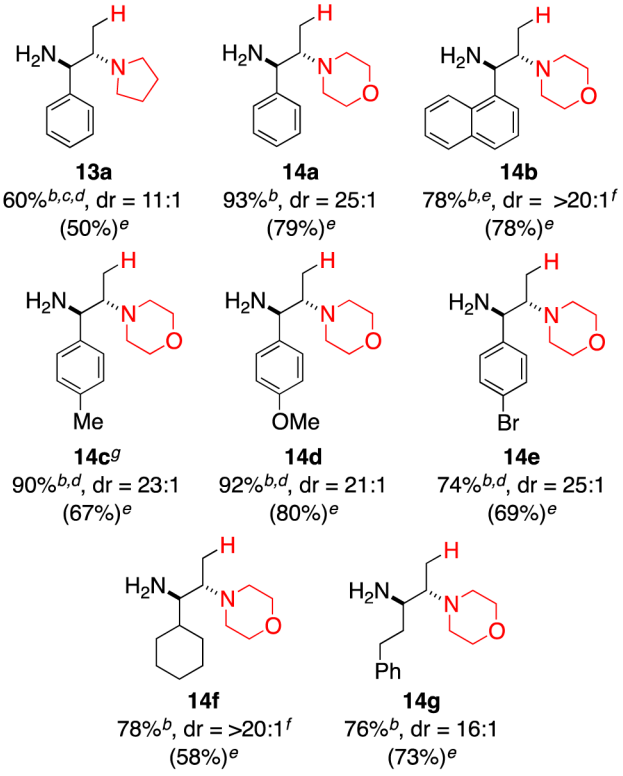
10a: R^1 = Me, R^2,R^3 = H
10b: R^1,R^2 = H, R^3 = Me
10c: R^1,R^2 = H, R^3 = Ph
10d: R^1,R^3 = H, R^2 = Ph

11a: 78%,[b] (58%)[c]
11b: <5%[d]
11c: <5%[d]
11d: <5%[d]

[a–c]See Table 1. [d]No hydroamination product was observed.

Table 3. Effect of Substitution on the Rh-Catalyzed Hydroamination Reaction[a]



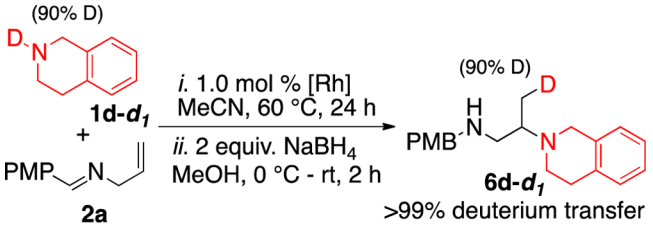


[a]*i.* **12a–g** (1.0 equiv), **1a** (5.0 equiv), [(DPEphos)Rh(COD)]BF_4 (1.0 mol %), MeCN (4.3 M), 60 °C, 24 h. *ii.* 10% HCl, 60 °C, 2 h, then KOH. [b]NMR yield of imine after hydroamination. [c]Pyrrolidine (**1e**) (1.0 equiv) was used. [d]2.0 mol % [Rh] was used. [e]Combined isolated yield of diastereomers after hydrolysis and isolation. [f]The minor diastereomer was not observed by either ^{1}H NMR or GC. [g]The *p*-tolyl imine was used.

12a (R^1 = Ph) and pyrrolidine (**1e**) afforded **13a** with 11:1 diastereoselectivity favoring the *anti*-1,2-diamine.[17,18] Increasing the size of the nucleophile to morpholine increased the diastereoselectivity to afford **14a** with a 25:1 dr. Aromatic substituents led to excellent diastereoselectivities, affording **14b–e** in very good yields with >20:1 dr. Likewise, aliphatic groups, including cyclohexyl and phenethyl, lead to high diastereoselectivities and very good yields of **14f** and **14g**.

To obtain preliminary mechanistic insight, *N*-deuterotetrahydroisoquinoline (90%-d_1) (**1d-d_1**) was subjected to the hydroamination reaction (Scheme 3). The deuterium was

Scheme 3. Deuterium Incorporation Study



incorporated exclusively at the terminal position (90%-d_1), indicating that the C–D bond formation is faster than β-hydride elimination–reinsertion from the metallacycle **16** (Figure 1).[15]

As shown in Figure 1, the proposed catalytic cycle is based on mechanistic evidence for related hydroamination reactions[19]

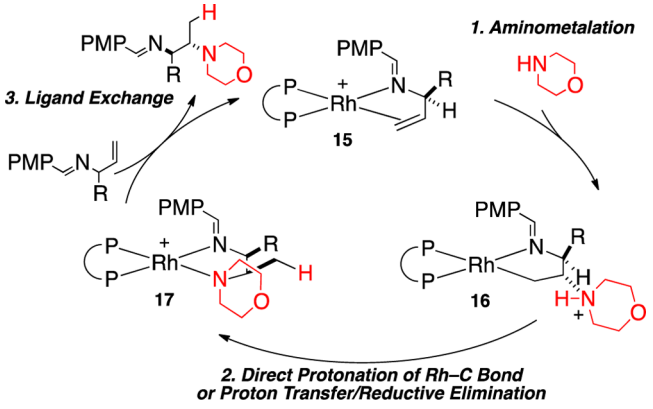


Figure 1. Proposed catalytic cycle.

and involves three key steps: (1) coordination of both the imine and the olefin to the cationic [Rh], (2) nucleophilic attack by the amine, and (3) direct protonation of the [Rh]–C bond or proton transfer to generate a [Rh]–H complex followed by reductive elimination. When R ≠ H, the aminometalation occurs in such a way that the nucleophile attacks the less-hindered face of the activated olefin, generating the *anti*-1,2-diamine (Table 3).

In summary, the ability of olefinic substrates with Lewis basic groups to undergo intermolecular rhodium-catalyzed hydroamination reactions with cyclic amine nucleophiles has been demonstrated. *N*-Allyl imines are functionalized in a highly regio-, chemo-, and diastereoselective fashion to afford the 1,2-diamine products in good to excellent yields. Ongoing studies are focusing on expanding the scope, identifying conditions for an asymmetric reaction, and developing a better understanding of the mechanism.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information.

(16) Substitution at the γ-position on the allyl group led to either no reaction or products resulting from olefin isomerization and enamine−amine exchange.

(17) Diastereoselectivities were determined by analysis of the crude ^{1}H NMR spectra.

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