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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Anti-Markovnikov Hydroamination of Homoallylic Amines

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Supporting Information

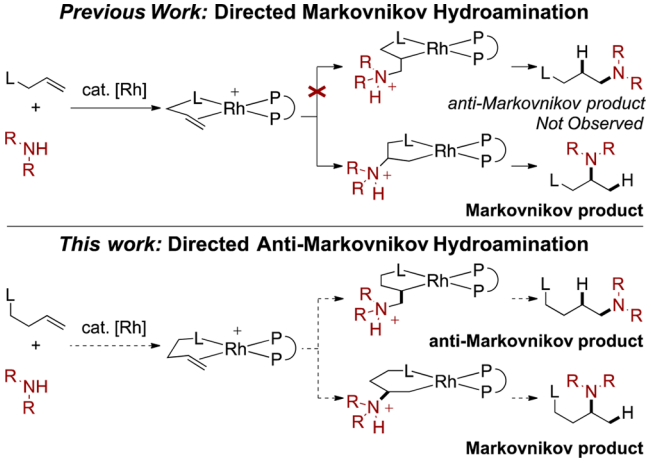
ABSTRACT: The development of an anti-Markovnikov-selective hydroamination of unactivated alkenes is a significant challenge in organometallic chemistry. Herein, we present the rhodium-catalyzed anti-Markovnikov-selective hydroamination of homoallylic amines. The proximal Lewis basic amine serves to promote reactivity and enforce regioselectivity through the formation of the favored metallacycle, thus over-riding the inherent reactivity of the alkene. The scope of both the amine nucleophiles and homoallylic amines that participate in the reaction is demonstrated.

Carbon−nitrogen bonds are prominent functionalities in organic molecules—for example, 84% of small-molecule pharmaceuticals contain at least one.[1] Hydroamination, the addition of an amine across an alkene or alkyne, couples two readily accessible functional groups to form new C−N and C−H bonds with 100% atom economy.[2] Hydroamination reactions are hindered by high activation energies and entropic costs; as such, a number of transition metal catalysts have been developed to promote this highly desirable transformation.[2]

The hydroamination of a terminal alkene can afford two possible regioisomeric products, the Markovnikov and the anti-Markovnikov, where the new C−N bond is formed at the internal or terminal carbon, respectively.[2−8] Anti-Markovnikov hydroamination of unactivated alkenes is considered to be particularly challenging, as it requires the nucleophilic amine to attack the less electrophilic primary carbon and generate the new [M]−C bond at the more sterically encumbered carbon.[2] Thus, unactivated alkenes typically undergo Markovnikov-selective functionalization.[3] Known metal-catalyzed approaches for anti-Markovnikov hydroamination require activated alkenes, such as 1,3-dienes,[4] styrenes,[5] allenes,[6] or methylenecyclopropanes,[7] which form stable π-allyl or π-benzyl intermediates upon aminometalation or where the nucleophile selectively attacks the sp^2 hybridized carbon. The direct addition of N−H bonds across unactivated alkenes in an anti-Markovnikov fashion is an unsolved challenge for organometallic chemists; therefore, several formal hydroamination reactions have been developed.[9]

Recently, we demonstrated that *N*-allylimines undergo a selective Rh-catalyzed hydroamination reaction to afford 1,2-diamines.[10] Coordination of the imine to the catalyst promotes the desired Markovnikov-selective hydroamination and slows undesired β-hydride elimination through the formation of a five-membered metallacyclic intermediate. Next, we sought to identify a rhodium-catalyzed Lewis base-directed anti-Markovnikov-selective hydroamination reaction of unconjugated alkenes. It is known that coordinating groups can promote anti-Markovnikov-selective olefin insertion reactions, where the C=C bond inserts into the metal−nucleophile bond.[11] However, cationic Rh(I)-catalyzed hydroamination with amine nucleophiles has been demonstrated to occur via coordination of the olefin followed by anti-aminometalation;[12] the ability of coordinating groups to promote an anti-Markovnikov-selective nucleophilic attack onto a coordinated alkene is unknown. Five-membered metallacycles are less strained than six-membered metallacycles; therefore, we hypothesized that substrates bearing a homoallylic Lewis basic group may over-ride the intrinsic alkene reactivity and form anti-Markovnikov hydroamination products (Scheme 1).[13] Additionally, coordination of the Lewis basic group may promote the functionalization of the alkene by increasing the relative concentration.[10,11] Moreover, it may slow the oxidative amination pathway, relative to the preferred hydroamination pathway, by occupying a *cis* coordination site and inhibiting β-hydride elimination.[10]

Scheme 1. Directed Hydroamination Reactions[10]

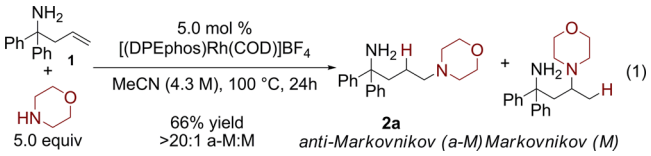


Our initial investigations employed 1,1-diphenyl homoallylamine derivatives, as they were hypothesized to promote coordination of the alkene through the Thorpe−Ingold effect.[14] When *N*-homoallylimines were subjected to the previously optimized conditions for the Markovnikov-selective Rh-catalyzed hydroamination of *N*-allylimines,[10] no hydroamin-

Received: August 19, 2015
Published: October 12, 2015

DOI: 10.1021/jacs.5b08500
J. Am. Chem. Soc. 2015, 137, 13748−13751

ation products were observed; rather, a Lewis acid-catalyzed aza-Cope rearrangement occurred (Table S1).[15] Alternative nitrogen-based coordinating groups were investigated, and while no reaction was observed with secondary amines or carbamates, primary amines were identified as effective directing groups. Excitingly, our hypothesis that coordination of a Lewis basic group would promote an anti-Markovnikov-selective reaction proved correct: high selectivity was observed for the anti-Markovnikov (1,4-diamine) over the Markovnikov (1,3-diamine), and no oxidative amination product was detected (eq 1). Further, the Lewis basic group significantly increases the reactivity of the alkene, as 1-octene was unreactive under the reaction conditions.

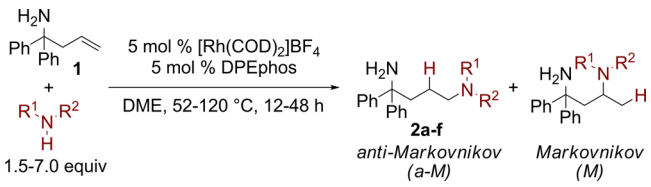


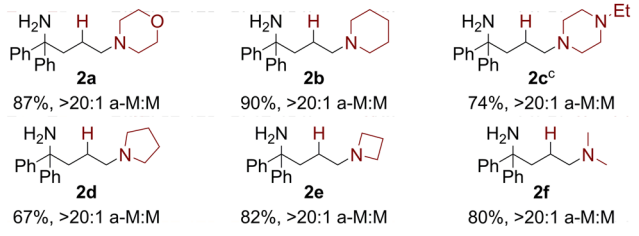
Next, we sought to optimize the reaction conditions (Tables S2–S4). Changing the solvent from acetonitrile (MeCN) to dimethoxyethane (DME) improved the *in situ* yield from 66% to 92% (Table S2). The reaction was very sensitive to the temperature: after 48 h at 40 °C, a 7% *in situ* yield was observed, while after 12 h at 100 °C, the reaction afforded 92% *in situ* yield of **2a** (Table S3). Variation of the bidentate phosphine ligand significantly affected the reaction: DPEphos afforded the product in nearly quantitative yield (100% *in situ* yield) and excellent selectivity for the anti-Markovnikov product, while other phosphine ligands afforded the desired product in significantly reduced yields (Table S4). The optimized reaction conditions are 1.0 equiv of **1**, 5.0 equiv of morpholine, 5 mol% $[Rh(COD)_2]BF_4$, 5 mol% DPEphos in DME (1.5 M) at 100 °C. All selectivities for **2a** were >20:1 during the course of optimization when DPEPhos was employed as a ligand.

The scope of amine nucleophiles in the Rh-catalyzed anti-Markovnikov-selective hydroamination reaction with **1** was examined (Table 1). In addition to morpholine, cyclic amine nucleophiles, including piperidine, *N*-ethylpiperazine, pyrrolidine, and azetidine, all afforded the anti-Markovnikov products **2a**–**2e** in good to excellent yields (67–90%) and excellent regioselectivities (>20:1). Further, an acyclic secondary amine nucleophile, *N*,*N*-dimethylamine, undergoes the hydroamination reaction to afford **2f** in 80% yield and >20:1 regioselectivity. Unfortunately, decreasing the nucleophilicity of the amine inhibits the hydroamination reaction; i.e., *N*,*N*-diethylamine does not afford significant quantities of the desired product (<5% yield).

We then further investigated the reaction scope by subjecting a variety of substituted homoallylamines to the reaction conditions (Table 2). Substitution at the 2-position is well

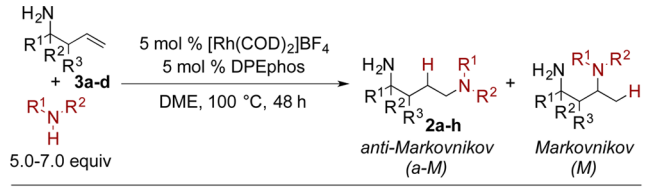
Table 1. Scope of Amines[a,b]

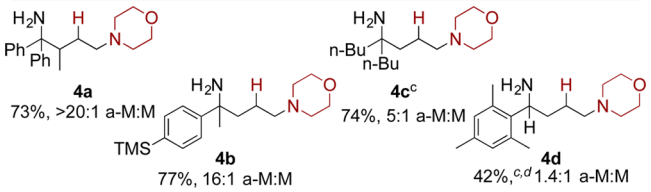




[a]Amine (3.0–10.0 equiv), **1** (1.0 equiv), $[Rh(COD)_2]BF_4$ (5.0 mol %), DPEphos (5.0 mol%), DME (1.5 M), 52–100 °C, 12–48 h. [b]Ratio of 1,4-diamine to 1,3-diamine after hydroamination was determined by gas chromatography, [c]The reaction was run for 72 h.

Table 2. Substituents Effect on Regioselectivity[a,b]





[a]Amine (5.0–7.0 equiv), **3a**–**3d** (1.0 equiv), $[Rh(COD)_2]BF_4$ (5.0 mol%), DPEphos (5.0 mol%), DME (1.0 M), 100 °C, 48 h. [b]Ratio of 1,4-diamine to 1,3-diamine after hydroamination was determined by gas chromatography. [c]The reaction was stirred at 120 °C for 72 h. [d]*In situ* yield determined by gas chromatography and comparison to an internal standard.

tolerated, as 1,1-diphenyl-2-methylbut-3-en-1-amine (**3a**) affords **4a** in excellent isolated yield (73%) and high regioselectivity (>20:1), demonstrating that the metallacyclic intermediate is tolerant of additional substitution. Reducing the size of the 1-substituents significantly reduces the regioselectivity: **3b**, where one of the aryl rings is replaced with a methyl, affords **4b** in 77% isolated yield as a 16:1 mixture of regioisomers. Further, hydroamination of 1,1-dibutyl-homoallylamine (**3c**) affords **4c** in 74% isolated yield as a 5:1 mixture of regioisomers. The loss in regioselectivity observed with sterically less encumbering substituents suggests that 1-substituted but-3-en-1-amines may be significantly less regioselective. Indeed, when 1-mesitylbut-3-en-1-amine (**3d**) is subjected to the hydroamination reaction conditions, **4d** is observed with 1.4:1 a-M:M selectivity and 42% yield.

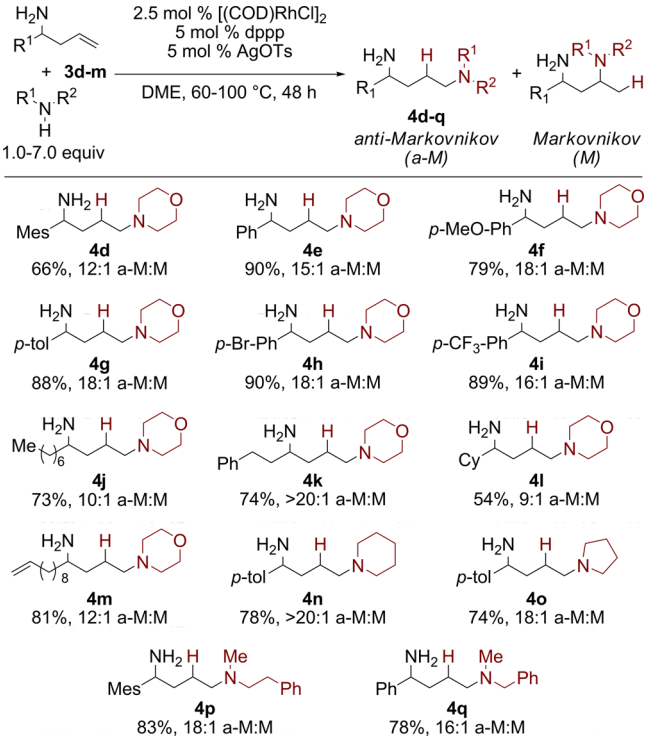
The observed trend of decreasing the steric bulk at the 1-position suggested that the difference in strain associated with the five- and six-membered metallacyclic intermediates was minimized. We hypothesized that variation of the ligands on the catalyst could restore the anti-Markovnikov selectivity. Indeed, changing the bidentate phosphine ligand (Table S5) and counteranion (Table S6) significantly improved both the reactivity and regioselectivity: employing 5 mol% [1,3-bis(diphenylphosphino)propane)Rh]OTs ([(dppp)Rh]OTs) as the catalyst afforded **4d** in 68% *in situ* yield and 14:1 a-M:M ratio, as determined by GC analysis. Interestingly, the relative ratio of products formed correlates with the bite angle and flexibility of the phosphine ligand (Table S4). The reoptimized reaction conditions are as follows: 2.5 mol%

DOI: 10.1021/jacs.5b08500
J. Am. Chem. Soc. 2015, 137, 13748–13751

[(COD)RhCl]$_2$, 5 mol% AgOTs, 5 mol% dppp in DME (1.5 M) for 2 days. Importantly, while a large excess of amine is often employed to maximize the yield of the hydroamination reaction, changing from 7.0 to 2.0 equiv of morpholine leads to moderately reduced yields of **4d**, 92 and 67%, respectively (Table S7).

Next, the scope of 1-substituted homoallylic amines was explored, as shown in Table 3. Reducing the size of the 1-aryl

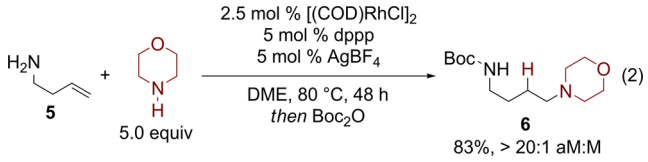
Table 3. Scope of Homoallylic Amines[a,b]



[a]Amine (1.0−7.0 equiv), **3d**−**3m** (1.0 equiv), [Rh(COD)$_2$]Cl (2.5 mol%), DPPP (5.0 mol%), AgOTs (5.0 mol%), DME (1.0−1.5 M), 52−100 °C, 12−48 h. [b]Ratio of 1,4-diamine to 1,3-diamine after hydroamination was determined by gas chromatography.

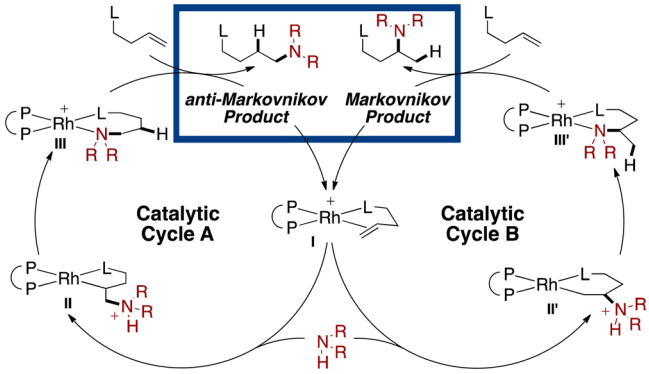
substituent from mesityl to phenyl slightly improved the yield and regioselectivity, affording **4e** in 90% isolated yield and 15:1 selectivity. Further, aryl rings bearing an electron-donating (OMe and Me), aryl bromide, or electron-withdrawing group (CF$_3$) were well tolerated, affording **4f**, **4g**, **4h**, and **4i** in 79, 88, 90, and 89% yield, respectively, all with ≥16:1 selectivity. Aliphatic substitution at the 1-position was varied: *n*-heptyl (**3j**), phenethyl (**3k**), and cyclohexyl (**3l**) groups had little effect on the regioselectivity of the reaction, affording the diamines in 73, 74, and 54% isolated yield with selectivities ≥9:1. Olefins distal from the amino group were unaffected under the reaction conditions, as **4m** is afforded in 81% isolated yield and 12:1 regioselectivity.[16] Finally, reactions with 1-substituted homoallylamines are not limited to morpholine as the nucleophile, as piperidine, pyrrolidine, *N*-methyl-*N*-(2-phenyl)ethylamine, and benzylmethylamine undergo the hydroamination reaction to afford **4n**−**4q** in very good yields (74−83%).

Excitingly, when homoallylamine **5**, which lacks any substitution, was subjected to slightly modified reaction conditions, **6** was obtained in 83% yield and a >20:1 regioselectivity favoring the desired anti-Markovnikov product (eq 2).



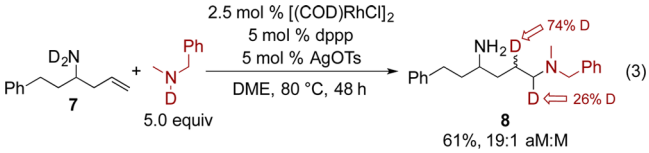
The proposed mechanism for the transformation is shown in Scheme 2: Catalytic Cycle A forms the anti-Markovnikov (1,4-diamine) product, while Catalytic Cycle B affords the Markovnikov (1,3-diamine) product.[12] First, coordination of

Scheme 2. Proposed Catalytic Cycle



both the amine and alkene to the catalyst generates intermediate I. Next, the regioselectivity-determining step occurs: nucleophilic attack by the secondary amine onto the alkene affords metallacyclic intermediate II or II′. Under the optimized conditions, selectivity is determined by the formation of the favored metallacyclic intermediate II. Direct protolytic cleavage of the Rh−C bond or proton transfer/reductive elimination generates the C−H bond, and coordination of the amine to the catalyst generates III or III′. Finally, ligand exchange of the product for the olefinic substrate continues the catalytic cycle.

Deuterium incorporation experiments were conducted as a mechanistic probe. Subjection of **7** to the hydroamination reaction with *N*-deuterio-*N*-methylbenzylamine gives insight into the selectivity of the C−H bond formation. As with the hydroamination of *N*-allylimines,[10] no H/D exchange is observed into the nucleophile nor the C−H bond adjacent to the amine directing group. Interestingly, as seen in eq 3, both



1,2- and 1,1-addition of the N−D bond to the alkene is observed, in a 74:26 ratio. This indicates that once the metallacyclic intermediate II is formed, *β*-hydride elimination/reinsertion occurs to exchange the exocyclic C−H bond.[17]

To further support our proposed catalytic cycle, attempts were made to isolate an amino−olefin bound complex. [DPEphosRh(**1**)]BF$_4$ (**9**) was synthesized by heating **1**, [(COD)RhCl]$_2$, AgBF$_4$, and DPEphos in THF. X-ray-quality crystals were grown by crystallization from hot THF (Figure 1).

DOI: 10.1021/jacs.5b08500
J. Am. Chem. Soc. 2015, 137, 13748−13751

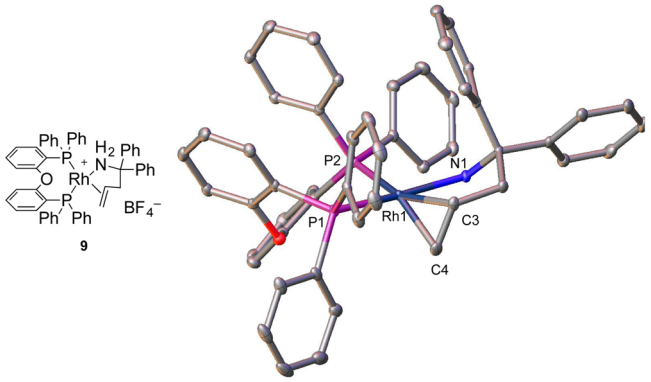


Figure 1. X-ray crystal structure of **9**·THF. Hydrogens atoms, BF_4^-, and THF are omitted for clarity. Ellipsoids are drawn at the 50% probability level.

The rhodium is in a distorted square planar geometry, with the two phosphorus atoms and the amine ligands coplanar. The two Rh−C bonds are of similar lengths, Rh−C4 = 2.2369(14) Å and Rh−C3 = 2.2662(14) Å. The C3−C4 bond is 1.375(2) Å, consistent with a Rh−olefin complex rather than a metallacyclopropane. Importantly, **9** is a competent catalyst for the hydroamination reaction.[17]

In conclusion, we have demonstrated the ability of homoallylic primary amines to reverse the inherent regioselectivity of the Rh-catalyzed hydroamination reaction and afford selectively the anti-Markovnikov product. The product distribution is primarily dependent upon the substitution pattern on the homoallylic amine and the ligand employed. Current efforts toward the development of directed hydroamination reactions are focusing on determination of the mechanism and expansion of the scope of both the amine nucleophile and coordinating groups which promote the anti-Markovnikov hydroamination reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08500.

X-ray crystallographic data for **9**·THF (CIF)
Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Illinois, Urbana−Champaign, for their generous support.

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(17) See Supporting Information for more details.

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DOI: 10.1021/jacs.5b08500
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