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Intermolecular Hydroamination of 1,3-Dienes to Generate Homoallylic Amines

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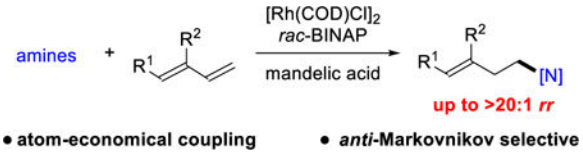
Abstract

We report a Rh-catalyzed hydroamination of 1,3-dienes to generate homoallylic amines. Our work showcases the first case of *anti*-Markovnikov selectivity in the intermolecular coupling of amines and 1,3-dienes. By tuning the ligand properties and Brensted acid additive, we find that a combination of *rac*-BINAP and mandelic acid is critical for achieving *anti*-Markovni- kov selectivity.

Graphical Abstract:



Coined in the 19th century, the concept of Markovnikov selectivity[1] remains relevant today in classifying and developing regiose-lective transformations of olefins, including hydroamination.[2] While hydroamination of alkenes typically furnishes the Markov-nikov product,[3] there have been breakthroughs in reversing the re-gioselectivity to obtain the *anti*-Markovnikov isomer.[4] However, the intermolecular hydroamination of 1,3-dienes[5] has been limited to producing allylic amines through 1,2-addition or 1,4-addition, presumably due to the intermediacy of a stabilized π-allyl-metal (Figure 1A, top).[6] Homoallylic amines are valuable synthetic building blocks that are typically generated by coupling imines to organometallic reagents (Figure 1B).[7] As a complement to using stoichiometric organometallics, we aimed to use simple dienes by developing a catalytic and regioselective hydroamination (Figure 1A, bottom). Herein, we disclose the first *intermolecular* hydroamination of 1,3-dienes to proceed with *anti*-Markovnikov selectivity.[8,9] Our Rh-catalyst transforms conjugated dienes into homoallylic amines with high regiocontrol and atom economy.[10]

Our laboratory recently rendered the hydroamination of 1,3-dienes enantio- and regioselective. In this previous study, we generated allylic amines by using a

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ASSOCIATED CONTENT
Supporting Information
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Experimental procedures and spectral data for all new compounds (PDF)

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[Rh(COD)OMe]2/JoSPOphos catalyst and triphenylacetic acid additive. [6m,11] In this communication, we focused on achieving a 1,2-*anti*-Markovnikov addition for the synthesis of homoallylic amines.

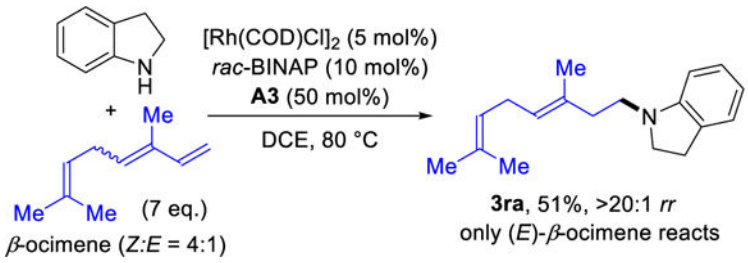
To begin this study, we chose indoline and isoprene as coupling partners. Isoprene, a common building block for polymers,[12] derives from thermal cracking of naphtha/oil and biosynthesis by many organisms.[13] We aimed to transform this feedstock into the corresponding homoallylic amine by studying the effects of biden-tate phosphine ligand and acid combinations. Table 1 summarizes our most relevant findings. Due to its use in alkyne hydroamination, phthalic acid was chosen as the initial acid for screening different bisphosphine ligands.[14] When using dppm, a small bite angle ligand,[15] we observe 1,2-Markovnikov addition product **A** as the major product (entry 1). Increasing the bite angle of the ligand decreases the reactivity and regioselectivity, leading to mixtures of **A**, **B**, **C**, and **D** (entries 2–4). Switching to a ferrocene-backbone ligand, dppf, we observed homoallylic amine **C** as the major product in 33% NMR yield (entry 5). When using *rac*-BINAP as ligand, the yield and regioselectivity of homoallylic amine **C** increases to 74% and 19:1 *rr* by ^{1}H NMR analysis (entry 6). $Rh(COD)_2SbF_6$ and $[Rh(COD)OMe]_2$ pre-catalyst give similar results with $[Rh(COD)Cl]_2$ (entry 7 and 8). In accordance with Hartwig's observations, the use of palladium as the catalyst yields 1,4-addition product D as the major isomer (entry 9).[6b] These results showcase an intermolecular hydroamination of isoprene where regioselectiv-ity is controlled by catalyst choice.[16]

With the optimal ligand in hand, we investigated the effect of the acid additive. No product was observed in the absence of acid (entry 10). Diphenyl phosphate was successfully used to form C-C bonds in the hydrofunctionalization of alkynes.[17] Therefore acids with similar pK_a to diphenyl phosphate and phthalic acid were examined. As pK_a values are solvent dependent,[18] the pK_a of the acids in DCE were determined using UV-vis spectroscopy.[19,20a] In general, higher yields are obtained with stronger acids (entries 11–13); mandelic acid (**A3**) gives 81 % yield and the best regioselectivity.[20b]

With this protocol, we examined the coupling of various 1,3-dienes **1** with indoline **2a** (Table 2). In general, the hydroamination proceeds with 18:1 to >20:1 regioselectivities and 52–83% yields for various 2-aryl-1,3-butadienes (**3aa**-**3ia**). Substrates with an electron-donating group on the aryl ring show slightly higher reactivity than those with an electron-withdrawing group. When the aryl ring is *ortho*-substituted, the yield is lowered to 60% (**3ba**). In the case where the aryl ring contains an electron-withdrawing tri-fluoromethyl group (**3ha**), the regioselectivity is 18:1 *rr*. The transformation also proceeds with alkyl substituted dienes. 2-Cyclo- hexyl-1,3-butadiene undergoes hydroamination with 73% yield (**3ja**). Myrcene, a readily available monoterpene, furnishes the homoallylic amine (**3ka**) in 78% yield and >20:1 *rr.* The hydroamination proceeds efficiently for substrates bearing ether and amide groups and provides the corresponding products in 74% yield (**3la**) and 87% yield (**3ma**) with >20:1 regioselectivities.

Transformations of 1,2-disubstituted dienes also proceed well. Hydroamination of the fused ring substrates provide the homoallylic amines in 70% and 73% yields (**3na** and **3oa**) with >20:1 regioselectivities. In addition, we obtain the homoallylic amines **3pa** and **3qa** from

acyclic 1,2-disubstituted dienes in 53% and 73% yields with >20:1 regioselectivities by using $Rh(COD)_2SbF_6$ as precatalyst. When using the mixture of (*Z*)- and (*E*)-*β*-ocimene isomers, we observe that only the (*E*)-*β*-ocimene is transformed to give homoallylic amine (**3ra**) in 51% yield (7 equivalents diene used); (*Z*)-*β*-ocimene is unreacted (eq 1).



(1)

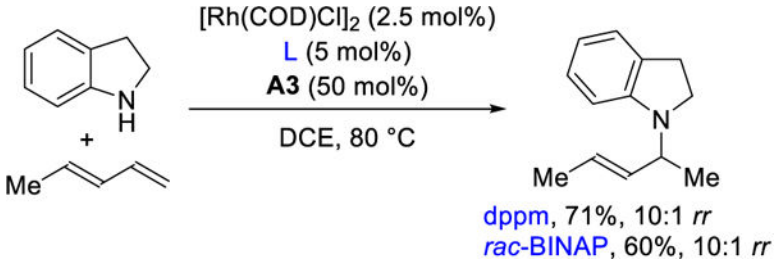
Next, we examined the hydroamination of 2-phenyl-1,3-butadi-ene **1a** with different amines **2** (Table 3). Indolines provide the hydroamination products (**3ab-3ai**) with 62–89% yield and 8:1 to >20:1 *anti*-Markovnikov selectivity. Indolines with electron-donating groups show higher regioselectivities than those with electron-withdrawing groups. The hydroamination of sterically hindered 2-methyl-indoline gives homoallylic amine (**3ab**) in 62% yield and 10:1 regioselectivity. Anilines bearing either electron-donating or electron-withdrawing groups both undergo hydroamination with 40–63% yields (**3aj-3al**). Hydroamination of the acyclic amine *N*-methylaniline yields the product **3am** in 47% yield with 3:1 regioselectivity. 1,2,3,4-tetrahydroquinoline can be used for hydroamination with 45% yield and 4:1 selectivity for the anfi-Mar-kovnikov product (**3an**). Under our hydroamination conditions, morpholine is an effective amine partner and provides the homoal-lylic amine **3ao** in 79% yield with >20:1 *rr*. Identifying a catalyst that can enable coupling with more challenging amines (such as primary alkyl amines and acyclic dialkyl amines) is still an ongoing challenge that needs to be solved.[20c]

We reason that the *anti*-Markovnikov selectivity results from a synergy between the substrate and catalyst structure. To probe the mechanism, we studied the kinetic profile for coupling 1,3-diene **1a** and indoline **2a**. When using $[Rh(COD)Cl]_2$ pre-catalyst, we observed a half order dependence on rhodium pre-catalyst, which suggests that breaking up the Rh-dimer is a slow step under our optimal conditions. Because this catalyst resting state is off-cycle, we switched to using monomeric $Rh(COD)_2SbF_6$ pre-catalyst to probe the mechanism further.

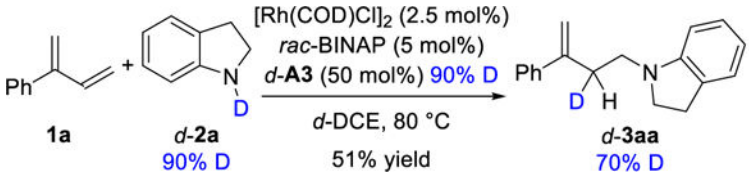
On the basis of both literature precedence and the following mechanistic studies, we propose the mechanism depicted in Figure 2. Rhodium pre-catalyst reacts with BINAP ligand to form the active catalyst **I**, which is the resting state as determined by ^1H and ^{31}P NMR. The amine and acid undergo proton transfer to form ammonium-ion **5** and carboxylate anion (X^-). Using HypNMR,[21] the equilibrium constant for this process was measured to be K_{eq}=10.5.[18] Ligand exchange of COD with carboxylate anion results in complex **II**. In the turnover-limiting step, the ammoniumion **5** oxidatively adds to the Rh(I)-complex **II** to generate Rh(III)-hydride **III**. In support of the proposed turnover-limiting step, we observe a

first order dependence on the Rh-catalyst and a first order dependence on the ammonium-ion **5**. Moreover, we see a zeroth order dependence on the diene, which means its involvement occurs after the turnover limiting step.[20d]

The 1,3-diene can exchange with the amine to form η^4-Rh-hy-dride intermediate **IV**, which is analogous to a Co-hydride intermediate implicated in the hydrovinylation of 1,3-dienes.[22] Because (*E*)-*β*-ocimene (and not the *Z* isomer) undergoes hydroamination (eq 1), we propose that *s-cis* conformation of the 1,3-diene is necessary for coordination to the catalyst. [23] Due to the steric clash between the R substituent and the catalyst, the hydride insertion is disfavored. In line with this idea, we observe only Markovnikov addition using substrates bearing hydrogen at the 2-position, regardless of the catalyst used (eq 2). When the hydroamination was performed with deuterated indoline *d*-**2a**, the deuterium is incorporated into the 3-position of product **3**, not the recovered diene (eq 3). This isotopic labeling result helps us rule out mechanisms that involve reversible diene insertion into the Rh-hydride.



(2)



(3)

In accordance with *anti*-Markovnikov hydroamination of al-kenes using directing groups,[24] we imagine that the amine attacks the activated 1,3-diene from the less substituted position to generate Rh-*π*-allyl intermediate **V**. Reductive elimination of **V** at the 3-position gives homoallylic amine **3**. This step is related to Rh-catalyzed alkyne or allene hydrofunctionalizations, which tend to favor the branched product after reductive elimination.[14,17,25] We reason that electron rich amines improve regioselectivity by promoting reductive elimination at the 3-position rather than 1-position.

Hydroamination of conjugated dienes represents an attractive way to transform dienes into amine building blocks, but achieving regioselective hydroamination is challenging given the extended π-system. To date, there are few reports of functionalizing the terminal carbon of 1,3-dienes through 1,2-hydrofunctionalization.[5b] Modification of the substrate structure has

been used to achieve challenging transformations, such as the regiodivergent arylboration of 1,3-dienes.[26] Through key interactions between the catalyst and the 2-substitution of the substrate, we were able to achieve a 1,2-*anti*-Markonvikov hydroamination of dienes to access homoal-lylic amines. Future studies are warranted to better understand the origin of this regiocontrol. Insights from this communication will guide the invention of new diene hydrofunctionalizations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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(20). See Supporting Information for: (a) details on determination of pK_a values.(b) a comprehensive list of acids evaluated (Table S1).(c) other amines that showed no reactivity (Figure S4).(d) details on mechanism studies.

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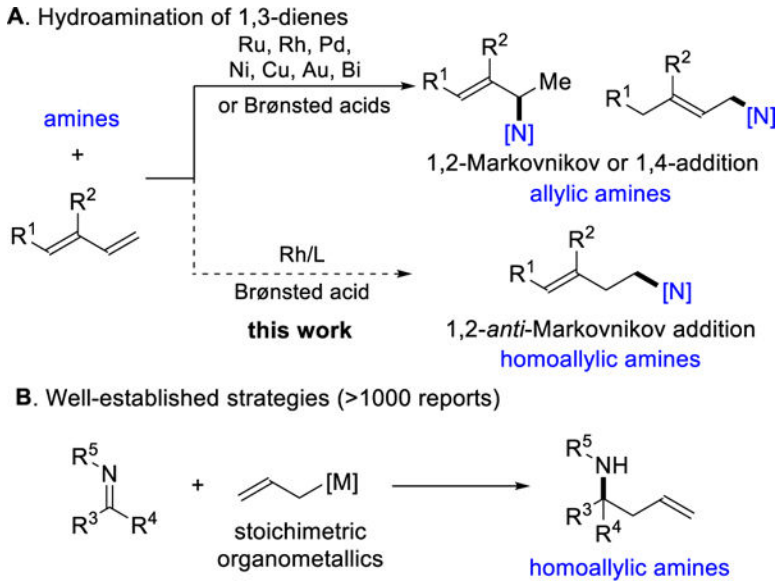


Figure 1.

Inspiration for *anti*-Markovnikov hydroamination of 1,3-dienes for synthesis of homoallylic amines

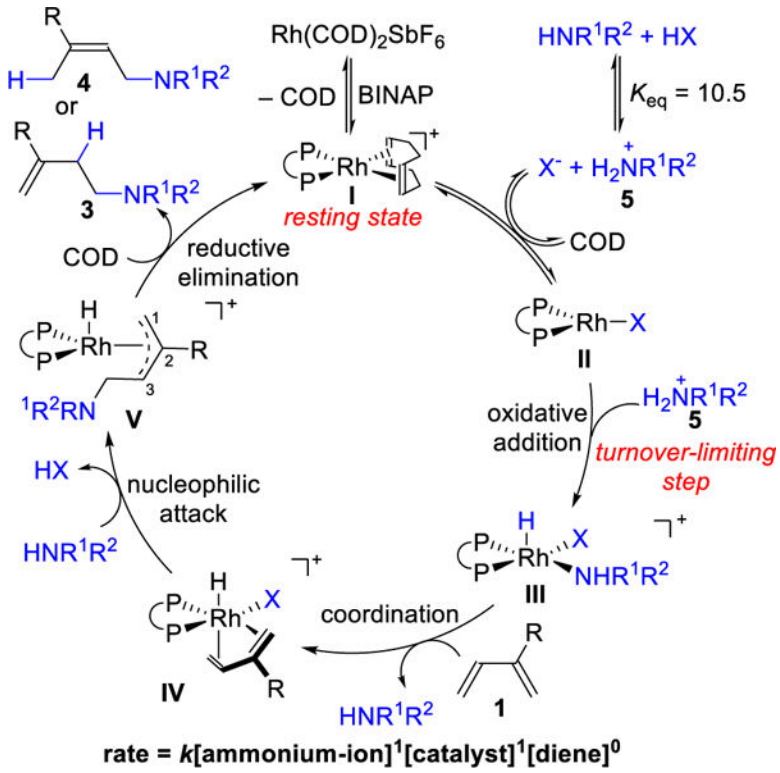
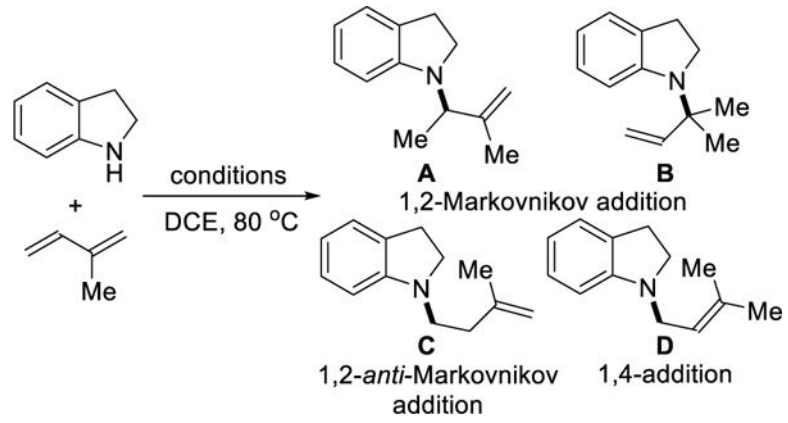


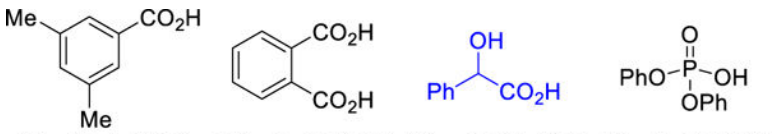
Figure 2.
Proposed mechanism for *anti*-Markovnikov selectivity

Table 1.

Catalyst and Acid Effects on Regioselective Hydroamination of Isoprene[a]



entry	pre-catalyst	ligand	acid[b]	yield (%)[c]	rr(A:B:C:D)[d]
1	$[Rh(COD)Cl]_2$	dppm	**A2**	71	15:<1:<1:1
2	$[Rh(COD)Cl]_2$	dppe	**A2**	20	2:2:1:4
3	$[Rh(COD)Cl]_2$	dppp	**A2**	14	2:1:1:3
4	$[Rh(COD)Cl]_2$	dppb	**A2**	<10	ND
5	$[Rh(COD)Cl]_2$	dppf	**A2**	33	<1:<1:5:1
6	$[Rh(COO)Cl]_2$	*rac*-BINAP	**A2**	74	<1:<1:19:1
7	$Rh(COD)_2SbF_6$	*rac*-BINAP	**A2**	71	1:1:>20:1
8	$[Rh(COD)OMe]_2$	*rac*-BINAP	**A2**	69	1:1:>20:1
9	$Pd(PPh_3)_4$	none	**A2**	84	1:1:1:>20
10	$[Rh(COD)Cl]_2$	*rac*-BINAP	none	NR	ND
11	$[Rh(COD)Cl]_2$	*rac*-BINAP	**A1**	17	1:1:>20:1
12	**$[Rh(COD)Cl]_2$**	***rac*-BINAP**	**A3**	**81**	**1:1:>20:1**
13	$[Rh(COD)Cl]_2$	*rac*-BINAP	**A4**	79	<1:<1:13:1



[a]Reaction conditions: indoline (0.1 mmol), isoprene (0.5 mmol), [M] (5 mol%), ligand (5 mol%), acid (50 mol%), DCE (0.2 mL), 24 h.

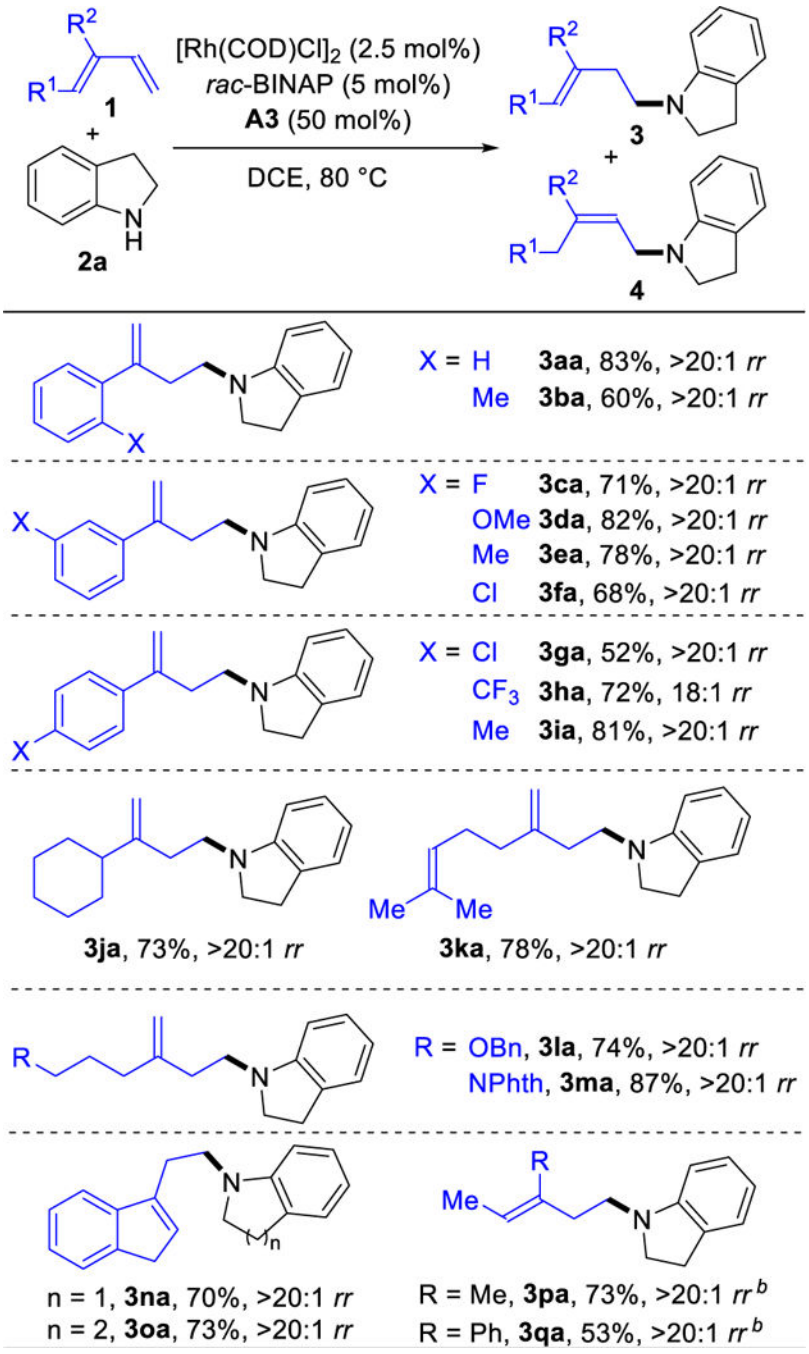
[b]pK_a in DCE and pK_a in water in parenthesis.

[c]^{1}H NMR yields of major isomer using 1,3,5-trimethoxybenzene as the internal standard.

[d]Regioselectivity determined by ^{1}H NMR analysis of reaction mixture.

Table 2.

Anti-Markovnikov Hydroamination of Various 1,3-Dienes[a]

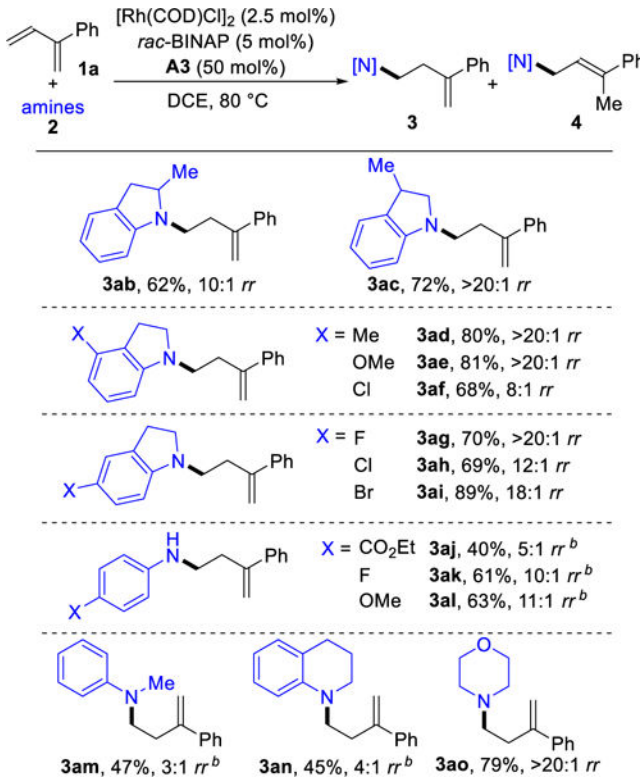


[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), [Rh(COD)Cl]2 (2.5 mol%), *rac*-BINAP (5 mol%), **A3** (50 mol%), DCE (0.4 mL), 80 °C, 15 h. Isolated yields. Regioselectivity ratio (*rr*) is the ratio of **3** to **4**, which is determined by ^{1}H NMR analysis of reaction mixture.

[b] Using $Rh(COD)_2SbF_6$ (5.0 mol%) instead of $[Rh(COD)Cl]_2$.

Table 3.

Anti-Markovnikov Hydroamination Using Various Amines[a]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), $[Rh(COD)Cl]_2$ (2.5 mol%), *rac*-BINAP (5 mol%), **A3** (50 mol%), DCE (0.4 mL), 80 °C, 15 h. Isolated yields. Regioselectivity ratio (*rr*) is the ratio of **3** to **4**, which is determined by ^{1}H NMR analysis of reaction mixture.

[b]Using $Rh(COD)_2SbF_6$ (5 mol%) instead of $[Rh(COD)Cl]_2$.