

Ruthenium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes

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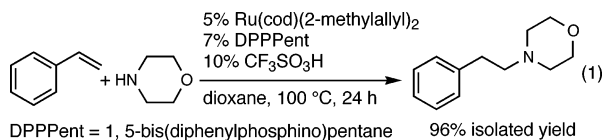
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Many ruthenium complexes catalyze additions of hydrogen^{1,2} and silanes^{3,4} to olefins. Ruthenium complexes also catalyze additions of amines⁵ and water⁶ to terminal alkynes. However, no complexes of this metal have been shown to catalyze additions of amines to olefins,^{7,8} despite increasing focus on the development of catalysts for the hydroamination of olefins.^{9–11}

Much effort has been spent seeking late-metal catalysts for anti-Markovnikov hydroamination because they are easily accessible, simple to handle, and could tolerate an array of functional groups.¹² Yet, such catalysts for selective anti-Markovnikov hydroamination are lacking. Palladium complexes catalyze the Markovnikov addition of amines^{13,14} to vinylarenes. Iridium complexes catalyze only the addition of aniline to norbornene.^{15,16} We recently reported a rhodium complex that catalyzes the anti-Markovnikov addition of secondary amines to vinyl arenes,¹⁷ but oxidative aminations to form enamines¹⁸ competed with hydroamination.

We disclose here selected ruthenium complexes that catalyze with exquisite chemo- and regioselectivity the anti-Markovnikov hydroamination of vinylarenes. Reactions of cyclic or acyclic, functionalized or unfunctionalized secondary amines with vinylarenes form terminal amines. In addition to demonstrating high selectivity for formation of terminal amines, these results demonstrate the tolerance of these late-metal catalysts toward Lewis basic and acid-labile functionality.



To uncover ruthenium catalysts for hydroamination, combinations of common ruthenium complexes and phosphine ligands were tested as catalyst for the addition of morpholine to styrene in the presence and absence of acid cocatalyst. Selected results are provided in Table 1. The reaction of styrene with morpholine occurred in the presence of Ru(cod)(2-methylallyl)₂ and a variety of phosphine ligands. The ratio of Markovnikov to anti-Markovnikov addition products depended on the ligand. Most striking, reactions of morpholine with 2 equiv of styrene in the presence of 5 mol % [Ru(cod)(2-methylallyl)₂], 7 mol % 1,5-bis-diphenylphosphinopentane (DPPPent), and 10 mol % TfOH (Table 1, entry 1) occurred in 96% yield with >99% selectivity for the terminal amine. The reaction with 1 equiv of styrene occurred with the same regioselectivity in 77% yield.

As shown in entries 2 and 3 of Table 1, reactions conducted without ligand or TfOH did not occur, and reactions with trifluoroacetic acid as cocatalyst occurred in lower yield (entry 4). The reaction conducted with 2% Ru(cod)(2-methylallyl)₂, 3% DPPPent, and 5% TfOH (entry 5) gave the product in slightly lower yield than that with 5% ruthenium. Use of [Ru(cod)(2-methylallyl)₂] as catalyst precursor was crucial to obtain the product in high yield. Catalysts generated from [Ru(*p*-cymene)Cl]₂ and [Ru(cod)Cl]_x gave only trace amounts of product, and that generated from Ru(2,3-

Table 1. Effects of Catalyst Components on the Hydroamination of Styrene and Morpholine in Dioxane at 100 °C^a

entry	Ru (%)	ligand	acid	yields: 1 ^b (%)	2 ^b (%)
1	5	7% DPPPent	10% TfOH	96	<1
2	5	—	10% TfOH	0	<1
3	5	7% DPPPent	—	0	0
4	5	7% DPPPent	10% TFA	8	0
5	2	3% DPPPent	5% TfOH	90	<1
6	5	14% PPh ₃	10% TfOH	36	9
7	5	14% PEtPh ₂	10% TfOH	61	3
8	5	7% DPPB ^c	10% TfOH	54	12
9	5	7% DPPHex ^d	10% TfOH	33	2
10	5	7% DPPF ^e	10% TfOH	55	44
11	5	7% DPEphos ^f	10% TfOH	19	2

^a Reaction conditions: morpholine 0.4 mmol, styrene 0.8 mmol, dioxane 0.2 mL, 100 °C, 24 h. ^b GC yields. ^c 1,4-Bis(diphenylphosphino)butane. ^d 1,6-Bis(diphenylphosphino)hexane. ^e 1,1'-Bis(diphenylphosphino)ferrocene. ^f Bis(2-diphenylphosphinophenyl)ether.

dimethyl-1,3-butadiene)(acac)₂ generated the product in lower yield, even under more forcing conditions.

The effects of ligand structure are revealed by entries 6–11. Monodentate ligands, such as PPh₃ and PEtPh₂, generated product in moderate yields (entries 6–7). The lower reactivity of catalysts generated from PEtPh₂ suggests that DPPPent acts as a chelating ligand. Reactions with catalysts generated from related biphosphines, such as DPPB and DPPHex, formed the hydroamination product in lower yield (entries 8–9). Reactions with catalysts generated from common biphosphines, such as BINAP, DPEphos (entry 11), and Xantphos, as well as triphos,¹⁹ gave the product in lower yields. All reactions formed only hydroamination products and polyvinylarenes. Reaction with the catalyst generated from DPPF gave full conversion to a mixture of Markovnikov and anti-Markovnikov products, but in a high combined yield (entry 10).

The scope of the reactions catalyzed by Ru(cod)(2-methylallyl)₂, DPPPent, and TfOH cocatalyst is summarized in Table 2. Reactions of vinylarenes with a series of cyclic and acyclic secondary amines formed β-phenethylamines with >99% regioselectivity. In most cases, the reaction yields were limited by conversion, not formation of side products. Polymerization of styrene competed with hydroamination, but no enamine from oxidative amination was formed.

Various cyclic amines reacted with styrene in good to excellent yields (entries 1–5). High yields for reaction of 4-piperidone ethylene ketal and Boc-piperazine underscore that the strength of the triflic acid is leveled by the presence of the alkylamine and that late-metal catalysts tolerate Lewis basic carbonyl groups and acid-labile functionality. In contrast to hydroamination or oxidative amination with rhodium catalysts, benzylic amines such as 1,2,3,4-tetrahydroisoquinoline reacted in good yield (entry 6) but with only 65% conversion.

The acyclic, secondary aliphatic, and benzylic amines *n*-hexyl methylamine (entry 7) and *N*-benzyl methylamine (entry 8) added across styrene. In contrast to the palladium-catalyzed Markovnikov

Table 2. Ruthenium-Catalyzed Hydroamination of Vinylarenes with Alkylamines^a

$$\text{HNRR}' + \text{R}'' \xrightarrow[\text{dioxane, 100 }^\circ\text{C, 24 h}]{\text{5 mol\% Ru(cod)(2-methylallyl)}_2, \text{7 mol\% DPPPPent / 10 mol\% CF}_3\text{SO}_3\text{H}}$$

$$\text{R}'' \text{---} \text{CH}_2\text{---} \text{CH}_2\text{---} \text{NRR}'$$

entry	product	yield ^b	entry	product	yield ^b
1		96%	8 ^{c, d, e}		50%
2		91%	9		81%
3 ^c		64%	10		72%
4		90%	11 ^{e, f, g}		91%
5		82%	12 ^{f, g, h}		71%
6 ^c		65%	13 ^h		51%
7 ^{c, d, e}		63%	14 ^{d, i, j}		40%

^a Amine/vinylarene/Ru/DPPPPent/TfOH = 1:2:0.05:0.07:0.10 (1 mmol of amine) in 0.50 mL of dioxane. ^b Isolated yield. ^c 4 mmol of vinylarene was used. ^d 80 °C. ^e 48 h. ^f 0.25 mL of dioxane. ^g 110 °C. ^h DiPPPF was used as ligand. ⁱ 1.5 mmol of vinylarene was used. ^j 72 h.

hydroamination,¹⁴ the exchange of benzyl groups between amines²⁰ was not observed. Thus, the lower yields of product from addition of these less reactive amines reflects 67 and 53% conversions. More hindered acyclic, aliphatic amines, such as dibutylamine, generated only trace product at 100 °C.

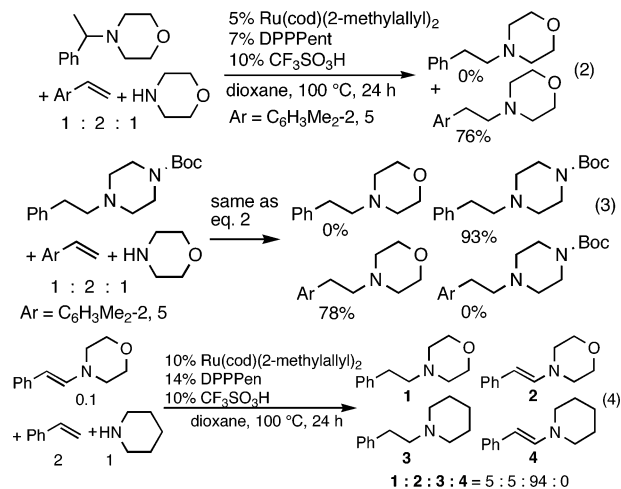
The hydroamination of vinylarenes with morpholine in the presence of Ru(cod)(2-methylallyl)₂ and DPPPPent encompassed electron-poor to electron-neutral styrenes (entries 9–11). Further, the first transition metal-catalyzed hydroamination of α -methyl styrene was observed (entry 14). Conversions of α -methyl styrene were modest, but a single-addition product was observed.

The combination of Ru(cod)(2-methylallyl)₂ and di-isopropylphosphinoferrrocene (DiPPPF) was more active for hydroaminations of vinylarenes containing electron-withdrawing groups. For example, the reactions of vinylarenes containing 3- and 4-CF₃ groups in the presence of 5% Ru(cod)(2-methylallyl)₂ and 7% DiPPPF gave the addition products in good to moderate yields (entries 12–13), while the same reactions in the presence of the catalyst with DPPPPent occurred in less than 20% yield.

One might propose that isomerization of the Markovnikov product to the terminal amine or hydrogenation of an enamine formed by oxidative amination accounts for the anti-Markovnikov hydroamination products. Three results show that the amines are formed by direct, irreversible, anti-Markovnikov hydroamination.

First, the reaction of 2,5-dimethylstyrene with morpholine was conducted in the presence of the isolated, branched amine. No isomerization of the branched to the terminal amine occurred (eq 2). Second, the reaction of morpholine with 2,5-dimethylstyrene was conducted in the presence of the amine containing an *N*-Boc piperazinyl group. The reaction generated neither free styrene nor the product from exchange of morpholine with the *N*-Boc piperazinyl group (eq 3). Third, the reaction of styrene with piperidine was conducted in the presence of 10% enamine containing the

morpholino group. With 10% catalyst and conversion of the styrene and piperidine to 94% of the hydroamination product, half the added enamine remained, and no enamine from piperidine accumulated (eq 4).



The precise mechanism of the ruthenium-catalyzed hydroamination has not yet been revealed, but it is likely to be distinct from that of the rhodium-catalyzed process. The rhodium catalysts for hydroamination and oxidative amination induced isomerization of *N*-deuteriomorpholine to form 2-deuteriomorpholine.^{21,22} This exchange did not occur in the presence of the ruthenium catalysts. Studies to increase catalyst activity by determining the detailed mechanism of this reaction are in progress.

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Supporting Information Available: Experimental procedures for catalytic reactions (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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