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Rhodium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes

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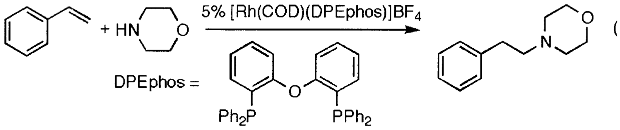
The transition metal-catalyzed anti-Markovnikov hydroamination of olefins was named[1] as one of 10 challenges for homogeneous catalysis because terminal amines are common commodity chemicals[2] and subunits of pharmaceuticals.[3] Nearly 10 years later, the reaction remains unknown, except for additions of amines to Michael acceptors such as acrylates and acrylonitriles.[4] Lanthanide complexes catalyze the intramolecular hydroamination of terminal alkenes.[5−7] Early metals catalyze additions to allenes,[8] and palladium complexes catalyze additions to vinylarenes,[9] but all these reactions give Markovnikov regioselectivity.[10−15] Anti-Markovnikov, rhodium-catalyzed oxidative aminations of olefins to form enamines have been reported recently by Beller,[16] but vinylpyridine[17] is the only olefin that gives amine as the major product. We report the transition metal-catalyzed anti-Markovnikov hydroamination of unactivated vinylarenes. The reaction occurs regiospecifically between a variety of vinylarenes and secondary amines in the presence of a rhodium complex of DPEphos.

During studies on the palladium-catalyzed Markovnikov addition of amines to vinylarenes,[9] we found that rhodium complexes of DPEphos generated high amine:enamine ratios and the same anti-Markovnikov regiochemistry as the oxidative aminations. Table 1 summarizes the selectivity of catalysts containing ligands related to DPEphos for the reaction of morpholine with styrene. Only DPEphos showed high conversion with amine as the major product. Even closely related analogues such as Xantphos and DBFphos generated little or no hydroamination product.

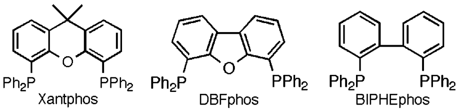


(1)

After optimization of the reaction conditions, the addition of morpholine to styrene occurred at 70 °C in toluene solution in the presence of 5 mol % $[Rh(COD)(DPEphos)]BF_4$ to produce the anti-Markovnikov hydroamination product in 71% yield (eq 1). The enamine from oxidative amination was formed as a minor product along with equimolar amounts of ethylarene. The reaction rate was faster with higher concentrations of styrene, but the selectivity for hydroamination vs oxidative amination product was lower (vide infra). Thus, we adopted for further studies reaction conditions for each substrate that provided an appropriate balance of rate and selectivity.

As summarized in Table 2, reactions of electron-poor and electron-rich vinylarenes with various cyclic secondary amines and the acyclic dimethylamine formed β-phenethylamines in the presence of 5 mol % $[Rh(COD)(DPEphos)]BF_4$. Isolated yields were above 70% for reactions of morpholine with these vinylarenes (entries 1−4), and the amine:enamine ratio was between 3:1 and 5.6:1. Reactions of piperidine and *N*-phenylpiperazine also gave mainly the products from hydroamination (entries 7−9), while reactions of *N*-Boc piperazine gave exclusively the amine product.

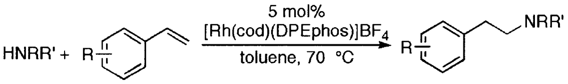
Table 1. Ligand Effects on the Reaction of Styrene with Morpholine in the Presence of Catalysts Containing DPEphos and Related Ligands[a]



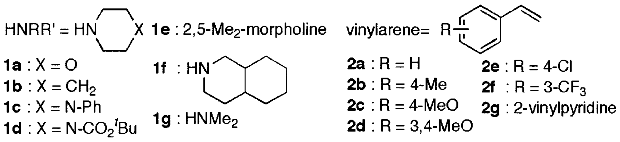
entry	ligand	amine yield[b] (%)	enamine yield[b] (%)
1	DPEphos (eq 1)	62	20
2	PPh_3	17	78
3	DPPE[c]	0	1
4	DPPB[d]	0	0
5	DPPPent[e]	1	1
6	Xantphos (**1**)	trace	9
7	DBFphos (**2**)	3	40
8	BIPHEphos (**3**)	0	0

[a] Reaction were run for 48 h at 70 °C. Morpholine:styrene:$[Rh(cod)_2]BF_4$:ligand = 1:4:0.05:0.05 (0.2 mmol of morpholine, PPh_3 = 0.1) in 0.2 mL of toluene. [b] GC yield. [c] 1,2-Bis(diphenylphosphino)ethane. [d] 1,4-Bis(diphenylphosphino)butane. [e] 1,5-Bis(diphenylphosphino)pentane.

Table 2. Anti-Markovnikov Hydroamination of Vinylarenes with Secondary Amines[a]



entry	amine	vinylarene	time (h)	yield[b] (%)	amine/enamine[c]
1	**1a**	**2a**	48	71	75:25
2	**1a**	**2b**	48	72	79:21
3	**1a**	**2c**	48	71	85:15
4	**1a**	**2d**	48	70	78:22
5[e]	**1a**	**2e**	72	48	60:40
6[e,f]	**1a**	**2f**	72	41	57:43
7[g]	**1b**	**2a**	72	57	63:37
8	**1b**	**2d**	48	66	77:23
9[g]	**1c**	**2a**	72	58	86:14
10	**1d**	**2a**	72	53	96:4
11[g,h]	**1e**	**2a**	72	51[k]	76:24
12	**1f**	**2c**	48	62[l]	72:28
13[i]	**1g**	**2b**	72	50[d]	54:46
14[i,j]	**1g**	**2d**	72	74	82:19
15[i]	**1g**	**2g**	48	79[d]	90:10



[a] Amine:vinylarene:Rh catalyst = 1:4:0.05 (1 mmol of amine) in 1 mL of toluene. [b] Isolated yield by silica gel column chromatography. [c] Selectivity was calculated from the GC area. [d] GC yield. [e] 10 mol % Rh catalyst was used. [f] 2.0 equiv of vinylarene was used. [g] 75 °C. [h] 0.5 mL of toluene was used. [i] Dimethylamine 2.0 M in THF solution (0.5 mL) and 0.5 mL toluene was used. [j] No toluene was added. [k] Diastereomer ratio of starting amine was 74:26, ratio of products was 82:18. The ratio was determined by GC area. [l] Diastereomer ratio of starting amine was 7:93, ratio of products was 17:83. The ratio was determined by GC area.

Reactions of substituted cyclic amines, such as 2,5-dimethylmorpholine and perhydroisoquinoline with vinylarenes occurred in

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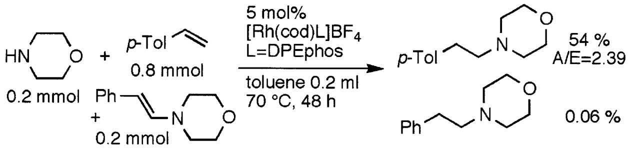
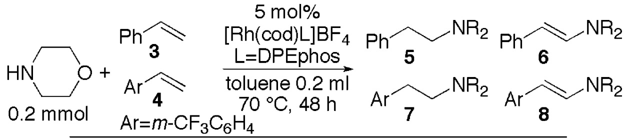
Scheme 1



Scheme 2



entry	**3** (mmol)	**4** (mmol)	**5** : **6**[a]	**7** : **8**[a]
1	0.4	0.4	50 : 50	47 : 53
2	0.8	0.0	72 : 28	–
3	0.0	0.8	–	38 : 62

[a] Ratios were determined from GC peak areas and are uncorrected.

moderate yields, but with high selectivity for amine over enamine (entries 11 and 12). Dimethylamine was the most reactive acyclic amine. Reactions of this substrate gave high yields of hydroamination products with electron-rich or -neutral styrenes and, in contrast to previous results with other catalysts, gave good yields of amine from reaction with 2-vinylpyridine.[17] Primary aliphatic and aromatic amines did not react, and pyrrolidine gave poor selectivity for the amine product.

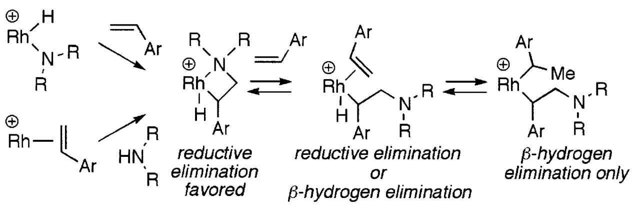
Electron-rich and electron-poor vinylarenes both gave amine as the dominant product under the appropriate reaction conditions. Reactions of electron-rich vinylarenes generally gave higher selectivities than the reactions of electron-poor vinylarenes under the same conditions. However, reactions at lower concentrations of vinylarene gave higher selectivities. Therefore, reactions of electron-poor vinylarenes, which were more reactive, were conducted at lower concentrations of olefin and gave acceptable selectivities for formation of amine versus enamine (entries 5 and 6).

Two results show that amine and enamine are formed in parallel, not sequential, steps. First, the two products were formed in a constant ratio over the course of the reaction.[18] Second, the reaction of *p*-methylstyrene with morpholine was conducted in the presence of an added enamine with a different aryl group, and only trace amounts of amine were formed from the added enamine (Scheme 1). This parallel formation of amine and enamine is consistent with Beller's results on the formation of the amine as side product during his studies of oxidative amination.[19]

The lower amine:enamine ratios at higher concentrations of vinylarene suggest that two vinylarenes are present in the transition state that controls selectivity. If the vinylarene is both a reactive and an ancillary ligand, then one vinylarene should affect the product ratio formed from another. To test this prediction, the reaction of morpholine with a mixture of styrene and *m*-trifluoromethyl styrene was conducted. Compared to ratios from reactions of the two vinylarenes alone, the ratio of amine to enamine formed from styrene was lower and the ratio of amine to enamine formed from *m*-trifluoromethyl styrene was higher (Scheme 2).[20] This result supports the presence of two vinylarenes in the complex that controls selectivity. A second amine does not participate in a similar way. The ratios of amine:enamine from reaction of morpholine and piperidine together were indistinguishable from the ratios produced from reactions of the two amines conducted separately.

Although further mechanistic studies are needed to define clearly the catalytic pathway, Scheme 3 provides one mechanism that rationalizes the effect of the second styrene. A metallacyclic β-amino, α-arylalkyl complex could form by either attack on coordinated olefin or insertion into a species formed by N−H activation. This metallacycle would favor formation of amine because the β-hydrogen would be inaccessible to the metal, but the alkyl and hydride could be mutually cis. Coordination of a second vinylarene[21] could then open the metallacycle to allow β-hydrogen elimination, or insertion of the vinylarene could generate a dialkyl complex that must undergo β-hydrogen elimination. Coordination of the electron-poor vinylarene is likely to be favored.[21] Reaction solutions containing electron-poor vinylarene would, therefore, create more enamine from β-hydrogen elimination than those with only electron-rich vinylarene. We cannot explain at this time the low selectivity from reactions of pyrrolidine, but further investigation of the reaction mechanism, studies toward synthesis of aminoalkyl intermediates, and an understanding of the role of DPEphos on selectivity are in progress.

Scheme 3



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Supporting Information Available: Procedures for synthetic and μ studies and characterization of reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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