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Rhodium-Catalyzed Intramolecular, Anti-Markovnikov Hydroamination. Synthesis of 3-Arylpiperidines

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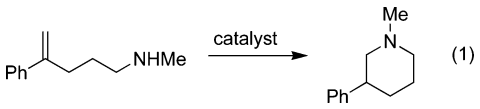
The intramolecular hydroamination of olefins[1] provides a route to nitrogen heterocycles[2] that involves common functional groups and generates no byproducts. As a result, this reaction has been used to prepare natural products and biologically active compounds.[3] However, a catalyst for intramolecular hydroamination with anti-Markovnikov selectivity is lacking, and few[4] of the published cyclizations can be conducted with catalysts conveniently assembled from air-stable components. Intramolecular hydroamination to form pyrrolidines and piperidines has been reported with catalysts based on lanthanide,[5−7] group IV transition metal,[8] platinum,[4] and even calcium complexes.[9] However, each of these catalysts forms products from cyclization with Markovnikov addition of the N−H bond across the olefin.

Thus far, products from anti-Markovnikov cyclization have been generated as part of a regiochemical mixture with stoichiometric amounts of platinum[10] or mercury,[11] from a photochemical reaction of a lithium amide,[12] or as the sole product by a stepwise process conducted with stoichiometric amounts of a rhodium−porphyrin complex.[13] Here, we report a catalytic, intramolecular, anti-Markovnikov hydroamination of vinylarenes. This cyclization forms 3-arylpiperidines, which comprise the core structure of known dopamine autoreceptor agonists, such as 3-PPP[14] and PNU96391.[15]

To develop intramolecular anti-Markovnikov hydroamination, we investigated reactions catalyzed by rhodium[16] and ruthenium[17] complexes that we had shown to catalyze intermolecular anti-Markovnikov hydroaminations of vinylarenes. Our data on the intermolecular reaction implied that an intramolecular reaction would be challenging because oxidative amination competed with rhodium-catalyzed intermolecular hydroamination, an excess of vinylarene was needed to obtain high yields of hydroamination products, and rhodium- and ruthenium-catalyzed olefin isomerization could compete with hydroaminations of substituted vinylarenes needed for most intramolecular processes.

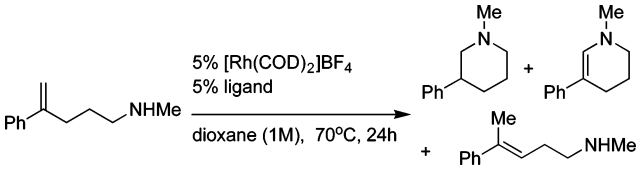


(1)

Our studies on intramolecular anti-Markovnikov hydroamination focused on the reaction in eq 1. We chose to study this cyclization for several reasons: the intermolecular hydroaminations occur with terminal vinylarenes, anti-Markovnikov cyclization would generate valuable piperidine products, and the substrate is easily accessible from the corresponding ketone.

Heating of this substrate in the presence of the ruthenium complex that is an active catalyst for the anti-Markovnikov hydroamination of vinylarenes simply led to isomerization of the α-alkyl styrene. Thus, further reactions with ruthenium catalysts were not investigated. However, studies of the cyclization in eq 1 with rhodium complexes revealed catalysts for the desired process.

Table 1. Ligand Effect on the Intramolecular Hydroamination



entry	ligand	yields: amine[a] (%)	enamine[b] (%)	isomerized olefin[b] (%)
1	DPEphos[c]	10	12	10
2	BINAP[d]	14	3	*i*
3	DPPF[e]	44	16	trace
4	Xantphos[g]	trace	5	41
5	DPPP[h]	*i*	*i*	*i*
6	DPPB[f]	84	7	trace
7	PPh_3	*i*	23	58
8	$PEtPh_2$	*i*	16	33

[a] Yield by GC with an internal standard. [b] NMR yield. [c] 2-(Diphenylphosphino)biphenyl ether. [d] 2,2′-Bis(diphenylphosphino)-1,1′-biphenyl. [e] 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl. [f] 1,4-Bis(diphenylphosphino)butane. [g] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene. [h] 1,3-Bis(diphenylphosphino)propane. [i] Not detected.

Results of the reactions conducted with catalytic amounts of rhodium complexes formed from a series of ligands are summarized in Table 1. The rhodium catalyst ligated by DPEphos (entry 1), which was active for the intermolecular hydroamination of vinylarenes, gave a mixture of amine, enamine, and isomerized substrate in a low combined yield, along with 30% of the starting material unreacted. Catalysts containing most other bidentate phosphines (entries 2−5), as well as catalysts containing triphenylphosphine (entry 7), gave low yields of the product. However, the catalyst containing DPPB (1,4-bis(diphenylphosphino)butane), which formed products from intermolecular hydroamination in less than 5% yield, formed the piperidine product from intramolecular hydroamination in a high 84% yield (entry 6).

Studies on cyclizations of the parent α-(*N*-methylaminopropyl)-styrene in eq 1 and derivatives of this reagent with substituents on the aryl group catalyzed by preformed $[Rh(COD)(DPPB)]BF_4$ are summarized in Table 2. After conducting reactions of the parent substrate in varied solvents and at different temperatures, a 19:1 ratio of amine to enamine was obtained in THF solvent at 80 °C. Under these conditions, the desired piperidine was isolated in 76% yield (entry 1). Reactions of substrates containing electron-donating (entries 2, 3, and 5) or electron-withdrawing (entries 4 and 6) groups on the aryl ring also gave the desired amines in good yield and with excellent selectivity for formation of the amine over the enamine under these conditions. Reactions of the substrates containing the electron-donating substituents on the aryl ring were faster than those of analogous substrates containing electron-withdrawing substituents. For example, reaction of the difluoro-substituted reagent in entry 5 required longer times than the other

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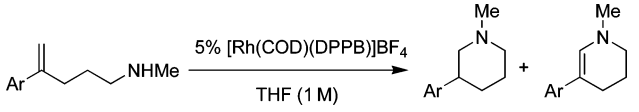
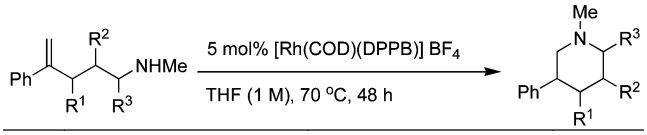
Table 2. Rhodium-Catalyzed Intramolecular Hydroamination

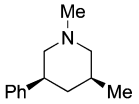
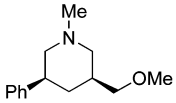
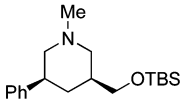


entry	Ar	temp (°C)/ time (h)	yields: amine[a] (%)	enamine[b] (%)
1	Ph	80/24	76	4
2	4-OMeC_6H_4	80/24	78	1
3	4-OMeC_6H_4	70/48	83	1
4	4-FC_6H_4	80/24	78	3
5	3,4-OMeC_6H_3	80/24	82	3
6	3,4-FC_6H_3	80/72	71	trace

[a] Isolated yield. [b] Yield by ^{1}H NMR spectroscopy.

Table 3. Stereoselective Rhodium-Catalyzed Intramolecular Hydroamination



entry	substrate	product	yield[a] (%)
1	R^1=Me, R^2=H, R^3=H	N.D.	-
2	R^1=H, R^2=Me, R^3=H		78 (94/6)
3	R^1= H, R^2=H, R^3= Me	N.D.	-
4	R^1=H, R^2=CH_2OMe, R^3=H		87 (95/5)
5	R^1=H, R^2= CH_2OTBS, R^3=H		74 *cis* only

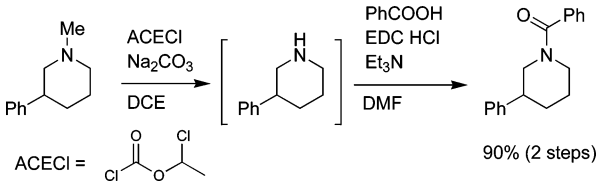
[a] Isolated yield. The ratio of *cis*/*trans* isomer is shown in parentheses. N.D. = Not Detected. TBS = *tert*-butyldimethylsilyl.

reactions, while reaction of the *p*-methoxy-substituted reagent in entry 2 occurred at a slightly lower temperature.

Reactions of aminoolefins with substituents α, *β*, and *γ* to the nitrogen on the alkyl chain are summarized in Table 3. Reactions of aminoolefins with substituents α or *γ* to the amino group gave mostly enamine and isomerized starting material (entries 1 and 3). However, reactions of aminoolefins containing an alkyl substituent, an alkoxyalkyl substituent, or a protected hydroxyalkyl substituent *β* to the amino group occurred in high yield (entries 2, 4, and 5). Further, these reactions occurred with high diastereoselectivity for formation of the cis product. This selectivity, presumably, results from a chair-like transition state in which the aryl and alkyl substituents are located in equatorial positions.

Consistent with our results on the rhodium-catalyzed intermolecular hydroamination of vinylarenes with acyclic secondary amines,[16] the cyclization process has, thus far, required an *N*-methyl substituent. Nevertheless, the *N*-methyl group of the products in Tables 2 and 3 are easily removed by the known reaction with ACECl[18] (1-chloroethyl chloroformate). For example, treatment of the cyclized product of entry 1 in Table 2 with ACECl at 70 °C in 1,2-dichloroethane afforded the free 3-phenyl piperidine, which was converted to the benzamide in 90% yield overall (Scheme 1).

Scheme 1



In closing, these rhodium-catalyzed reactions can be compared to those of the same type of substrate in the presence of other catalysts for hydroamination. Marks[6] and Molander[7] have reported intramolecular hydroaminations of the parent substrate, but these reactions formed pyrrolidines by Markovnikov addition of the NH bond to the olefin. This regiochemistry for cyclization is, perhaps, surprising because Marks[6] has reported that intermolecular additions of primary amines to vinylarenes occur to form the products from anti-Markovnikov addition in the presence of lanthanocene catalysts. Cyclizations of aminoolefins catalyzed by Pt(II) complexes also give products from Markovnikov addition.[4] Thus, the exclusive formation of anti-Markovnikov products from the intramolecular hydroamination catalyzed by [Rh(COD)(DPPB)]BF_4 in this work is particularly unusual. Studies to develop enantioselective versions of these reactions and to understand the mechanism of these processes are ongoing.

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Supporting Information Available: Reaction procedures and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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