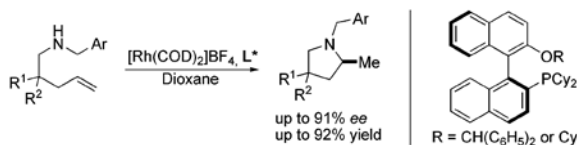# Rhodium-Catalyzed Asymmetric Intramolecular Hydroamination of Unactivated Alkenes[**]

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Abstract

Metal-catalyzed enantioselective intramolecular hydroamination of olefins[1] is one of the most conceptually simple and atom-economical approaches to the construction of enantioenriched nitrogen heterocycles,[2] which are valuable synthons in the preparation of natural products and biologically active molecules.[3] Despite significant advances,[4,5,6] no general solution for this challenging transformation has yet been realized. Some of the most reactive catalysts are based on lanthanides[5] and group 4 transition metals,[6] but only a small number of highly enantioselective (>90% ee) reactions have been described.[5a, 6b, 6c] Noteworthy is Schafer's[6c] elegant report of chiral zirconium amidate complexes which provide good enantioselectivity for a range of terminal alkenes, but require a geminal dialkyl group[7] to bias the substrates toward cyclization. Furthermore, the sensitivity of rare earth and group 4 metal catalysts toward air and moisture and their low functional group tolerance have limited their synthetic utility and motivated efforts to develop alternative systems. Some late transition metal complexes have been investigated for enantioselective hydroamination, with good results for alkynes,[8] allenes,[9] dienes,[10] and vinylarenes.[11] Very recently one example of an intermolecular hydroamination of unactivated 1-alkenes with an ee up to 78% was reported.[12,13] To the best of our knowledge, however, there are no examples of late transition metal-catalyzed enantioselective intramolecular hydroamination of unactivated olefins. Herein we disclose the first example of a rhodium-catalyzed[14] asymmetric intramolecular addition of amines to olefins for the synthesis of a variety of enantioenriched 2-methylpyrrolidines with good enantioselectivity (up to 91% ee).

Recent reports of the successful application of the dialkylbiaryl phosphines DavePhos[15a], t-BuDavePhos[15b] and JohnPhos[15c] in rhodium-, platinum- and gold-catalyzed intramolecular hydroamination by Hartwig[14a] and Widenhoefer[16,17] respectively, stimulated us to develop a late transition metal-catalyzed enantioselective version of this process using chiral ligands

of the type developed in our laboratory.[15] We began by examining the cyclization of N-benzyl-2,2-diphenyl-4-pentenamine **1a** to 1-benzyl-2-methyl-4,4-diphenylpyrrolidine **1b** as a test reaction (eq. 1). Following the seminal work of Hartwig,[14a] we exposed **1a** to 5 mol% [Rh(COD)$_2$]BF$_4$ and 6 mol% KenPhos **L1**,[18] providing pyrrolidine **1b** in 95% yield (GC) and 38% ee (entry 1). Varying the size of the substituent on nitrogen or phosphorus provided ligands[19,20] that gave the product in good yield but poor ee (entries 2 and 4). Control experiments in which the metal was omitted or replaced by a protic acid resulted in no product formation. No improvement in yield or enantioselectivity was seen if alternative Rh sources were employed (see supporting information).

We next turned our attention to MOP[21] derivatives, the use of Cy-MOP **L6**,[22] afforded **1b** in 96% yield with 53% ee (entry 6). Given this promising result, several Cy-MOP-type ligands were prepared using a slight modification of the literature procedure.[22] The selectivity of the hydroamination reaction improved with increasing size of the oxygen substituent (entries 6-8). We found that the dialkylphosphino group was essential for high activity; attempts to employ the diphenylphosphine **L10** furnished <10% yield of product (entry 10). Among the ligands evaluated, **L9** with a (diphenyl)methyl-substituted alkoxy group provided the best combination of reactivity and enantioselectivity, affording **1b** in 95% yield and 80% ee (entry 9).

The scope of the reaction is summarized in Table 2. Cyclization of substrates with geminal substitution in the homoallylic position proved to be the most facile, the reactions proceeding in the highest yields and with good enantioselectivities. Typically these reactions could be carried out at 70 °C with 5 mol% Rh. However, for the easiest substrates the reaction still proceeded at an acceptable rate at 50 °C, affording a slight increase in enantioselectivity (entry 2 and 5). In the case of substrates lacking substitution that facilitate cyclization, the use of the less sterically demanding ligand **L8** was more efficient. Using a catalyst system based on **L8**, these substrates could be cyclized with comparable enantioselectivity, although in somewhat lower yield (entries 10-13). These results are some of the best reported for the enantioselective cyclization of unbiased substrates using a transition metal-based catalyst.[5a,5d] In the case of racemic N-2-methylbenzyl-2-phenyl-4-pentenamine **5a** no kinetic resolution was observed, the diastereomeric products were obtained in a 1.1:1 ratio with high enantiomeric excess (87% and 91% ee respectively, entry 8).

The nature of the protecting group on nitrogen had a pronounced influence on the outcome of the reaction. We found that N-(2-methyl)benzyl aminoolefins gave higher enantioselectivity than N-benzyl aminoolefins in some cases, without adversely effecting the yield (entries 3-8). Presumably the substituent at the 2-position results in a more ordered transition state. Increasing the size of this substituent or using a 2,6-dimethylbenzyl protecting group, however, elicited a profound decrease in reactivity, perhaps as a result of inhibition of metal binding. Varying the *para*-substituent on the aryl ring of the nitrogen protecting group had little effect on the enantioselectivity, but electron-donating substituents retarded the reaction and resulted in a lower yield. [23] Typically, unprotected aminoolefins exhibited poor reactivity, however, 2-allylaniline did undergo hydroamination to yield 2-methylindoline with moderate enantioselectivity (entry 14).

Functional groups including esters and aryl chlorides were tolerated under the reaction conditions rendering the products amenable to further synthetic manipulation (entry 11 and 13). The absolute configuration of the products was determined to be (*S*) by conversion of **1b** to the known (*S*)-MPTA amide,[6c] **6b-10b** to the known N-naphthyl amides[5e] and **11b** to the previously reported N-acetyl-2-methylindoline. [24]

The N-protecting groups on the products in Table 2 were easily removed to reveal the free amines via catalytic transfer hydrogenation[25] with ammonium formate as hydrogen source. For example, treatment of the cyclized product **2b** (Table 2, entry 5) with palladium on activated carbon and ammonium formate at 68 °C in methanol afforded the 2-methylpyrrolidine **2c** in 92% yield.
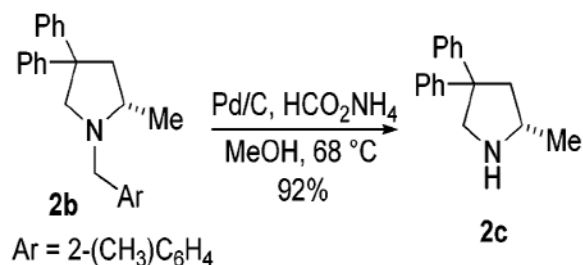
In summary, we have developed the first enantioselective rhodium-catalyzed intramolecular hydroamination of unactivated terminal alkenes. A variety of enantioenriched pyrrolidines have been synthesized in up to 91% ee using a binaphthyl-based electron-rich phosphine ligand. Further investigations to increase the generality of the process and to expand the scope to include intermolecular reactions are currently underway in our laboratories.

Experimental Section

Typical procedure: The aminoalkene (0.50 mmol) was added to a dry, screw-capped test tube at room temperature and the tube was then transferred into a glovebox. At this point, $[Rh(COD)_2]BF_4$ (0.025 mmol, 10.2 mg), phosphine ligand (0.030 mmol) and 0.5 mL of dioxane were added. The vial was sealed with a PTFE cap and removed from the glovebox. The reaction mixture was stirred at the temperature and for the time shown in Table 2. The reaction mixture was allowed to cool to ambient temperature, brine (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The crude product mixture was purified by flash chromatography on silica gel.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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23. Enantioenriched 2-methylpiperidine can be synthesized by this method in moderate yield and ee. For example, cyclization of N-benzyl-5-hexen-1-amine is promoted by 10 mol% [Rh(COD)$_2$]BF$_4$ and 12 mol% **L8** in 42% yield and 32% ee.

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Table 1

Effect of Ligand on the Enantioselectivity for Intramolecular Hydroamination[a]
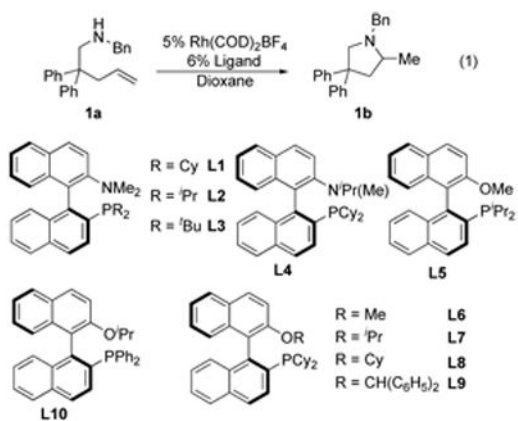
entry	ligand	yield [%][b]	ee [%][c]
1	**L1**	95	38 (*S*)
2	**L2**	83	20 (*S*)
3	**L3**	8	n. d.
4	**L4**	95	39 (*S*)
5	**L5**	94	42 (*S*)
6	**L6**	96	53 (*S*)
7	**L7**	98	70 (*S*)
8	**L8**	95	75 (*S*)
9	**L9**	94	80 (*S*)
10	**L10**	9	n. d.

[a]Reaction conditions: aminoolefin (0.15 mmol), 5 mol% Rh and 6 mol% ligand in 0.15 mL of dioxane at 70 °C for 7-15 h.

[b]GC yields.

[c]The *ee* values were determined by chiral HPLC analysis on a Chiralcel OJ column. The absolute configuration was determined by converting **1b** to the known (*S*)-MTPA amide. See supporting information for details.

Table 2

Rhodium-Catalyzed Enantioselective Intramolecular Hydroamination of Aminoalkenes[a]

entry	alkenyl amine	product	T(°C)	t(h)	yield [%][b]	ee [%][c]
1	1a	1b	70	15	91	80(S)
2			50	24	90	83(S)
3	2a	2b	70	15	92	84(S)
4[d]			70	20	88	84(S)
5			50	24	91	88(S)
6	3a	3b	70	20	75	62(S)
7	4a	4b	70	20	80	63(S)

1a: Ph₂C(NHBn)... ; 1b (product)
2a: Ar = 2-(CH₃)C₆H₄
3a: Ar = 2-(CH₃)C₆H₄
4a: Ar = 2-(CH₃)C₆H₄

entry	alkenyl amine	product	T(°C)	t(h)	yield [%][b]	ee [%][c]
8[e]	**5a**	**5a**	70	20	80 (1.1:1)	87(2S, 4S)
	Ar = 2-(CH$_3$)C$_6$H$_4$	**5b**				91(2S, 4S)
9[f]	Ar = C$_6$H$_5$ (**6a**)	**6b**	70	20	48	90(S)
10[g]	Ar = 2-(CH$_3$)C$_6$H$_4$ (**7a**)	**7b**	70	20	50	86(S)
11[g]	Ar = 4-(Cl)C$_6$H$_4$ (**8a**)	**8b**	70	20	63	85(S)
12[g]	Ar = 4-(MeO)C$_6$H$_4$ (**9a**)	**9b**	70	30	35	85(S)
13[g]	Ar = 4-(CO$_2$Me)C$_6$H$_4$ (**10a**)	**10b**	70	20	61	83(S)
14[h]	**11a**	**11b**	100	10	85	64(S)

[a]Reaction conditions: 0.5 mmol alkenyl amine, 5 mol% of [Rh(COD)$_2$]BF$_4$, 6 mol% of ligand **L9**, dioxane (0.5 mL).

[b]Isolated yields (average of two runs).

[c]The *ee* values were determined by chiral HPLC, GC or ^{1}H NMR analysis of its derivatives. The absolute configuration of **1b** was determined by converting it to the known (*S*)-MTPA amide. The configuration of **6b**, **7b**, **8b**, **9b** and **10b** were determined by converting them to the known N-α-naphthyl amide. The configuration of **11b** was determined by converting it to the known N-acetyl-2-methylindoline. See supporting information for details. The configurations of other amines were assigned by analogy.

[d]2.5 mol% Rh and 3 mol% ligand **L9**.

[e]Diastereomeric ratio given in parentheses.

[f] 10 mol% Rh and 12 mol% ligand **L9**.

[g] 5 mol% Rh and 6 mol% ligand **L8**.

[h] Yield of isolated product following derivatization with acetic anhydride.