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Ionic diamine rhodium complex catalyzed hydroaminomethylation of 2-allylanilines

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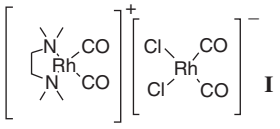
ABSTRACT

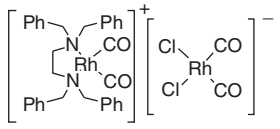
Ionic diamine rhodium complexes catalyze the hydroaminomethylation of 2-allylanilines. The reaction involves initial hydroformylation followed by reductive amination, which provides direct access to 1,2,3,4-tetrahydroquinolines and 2,3,4,5-1*H*-1-benzazepines.

Five- to seven-membered N-heterocycles, including fused ones, represent an important class of cyclic compounds since not only do many derivatives possess biological and pharmacological activities themselves but they also serve as versatile scaffolds for synthetic drug discovery.[1] For example, a series of 1,2,3,4-tetrahydroquinoline derivatives are useful synthetic intermediates for selective thrombin inhibitors.[2] Another example includes 2,3,4,5-tetrahydro-1*H*-1-benzazepine derivatives, several of which function as non-peptic vasopressin V2 receptor agonists.[3]

Hydroaminomethylation of olefin substrates having an amino group are considered to involve initial hydroformylation of the olefin unit, followed by intramolecular reductive amination. Such a reaction provides direct access to N-containing heterocycles, whose synthesis usually requires several steps to construct the heterocyclic ring when traditional methods are used.[4] We previously reported the synthesis and catalytic activity of a novel, air stable ionic diamine rhodium complex (**I**).[5] This unique rhodium complex can catalyze the hydroaminomethylation of 2-vinylanilines and (2-vinylaryl)methyl amines to form 1,2,3,4-tetrahydroquinolines and 2,3,4,5-tetrahydro-1*H*-2-benzazepines, respectively.[6,7] Pursuing our general interest in the hydroaminomethylation reaction due to the importance of the N-containing heterocyclic compounds, we launched a study of the hydroaminomethylation of allylaniline derivatives using the ionic diamine rhodium complex.



I



II

The hydroaminomethylation of 2-allylaniline (**1a**) was first examined to determine what conditions gave good results (Table 1). When **1a** was treated with 5 mol % of complex **I** in toluene at 100 °C for 24 h under CO/H_2 (700/100 psi), a mixture of six- and seven-membered ring hydroaminomethylation products **2a** and **3a**, and the six-membered ring cyclocarbonylation product **4a** was obtained in a ratio of 49:8:24 in yield (Table 1, entry 1). The corresponding seven-membered cyclocarbonylation product was not formed. Decreased partial pressure of CO reduced the extent of formation of **4a**; however, the selectivity for **2a** compared to **3a** also decreased (entries 2 and 3). In case of the reactions in THF, a higher partial pressure of H_2 was found preferable for the reaction (entries 4 vs 6), and no hydroaminomethylation took place under CO/H_2 of 700/100 (psi) though the starting material **1a** was completely consumed. It is conceivable that although initial hydroformylation followed by cyclic imine formation could occur at $CO/H_2 = 700/100$ (psi), the resulting imine may not undergo hydrogenation effectively at lower pressures of H_2. The reactions in CH_2Cl_2 or CH_3CN were inferior to those in toluene or THF in terms of both the yield and the selectivity. A control experiment with $[Rh(COD)Cl]_2$ clearly indicates that diamine rhodium complex **I** is

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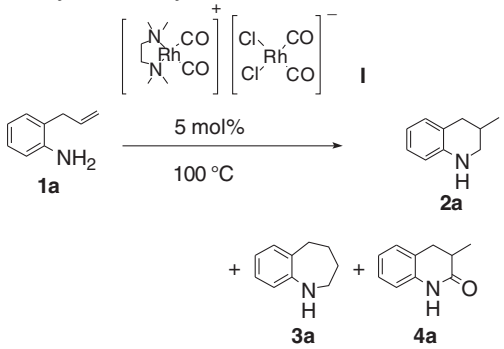
Table 1
Hydroaminomethylation of 2-allylaniline



Entry	Solvent	CO/H_2 (psi)	Yield[a] (%)		
			2a	**3a**	**4a**
1	Toluene	700/100	49	8	24
2	Toluene	400/400	22	13	18
3	Toluene	100/700	30	22	Trace
4	THF	700/100	0	0	3
5	THF	400/400	29	10	20
6	THF	100/700	31	36	2
7[b]	THF	100/700	20	8	5
8[c]	THF	100/700	28	17	11
9	CH_2Cl_2	700/100	Trace	Trace	0
10	CH_2Cl_2	100/700	22	18	0
11	CH_3CN	700/100	11	Trace	16
12	CH_3CN	100/700	21	11	16

[a] Isolated yield after column chromatography.
[b] Performed using 5 mol % of $[Rh(COD)Cl]_2$ instead of complex **I**.
[c] Performed at 80 °C.

Table 2
Effect of the diamine ligand on the hydroaminomethylation of 2-allylaniline[a]

Entry	Catalyst	Solvent	CO/H_2 (psi)	Yield[b] (%)		
				2a	**3a**	**4a**
1	**II**	Tol	700/100	25	10	12
2		THF	100/700	46	12	Trace
3	$[Rh(COD)Cl]_2$ +tipeda	THF	100/700	31	4	8
4	$[Rh(COD)Cl]_2$ +tmbeda	THF	100/700	23	5	Trace

[a] Reaction conditions; **1a** (1.0 mmol), complex **II** (0.05 mmol), or $[Rh(COD)Cl]_2$ (0.05 mmol) + diamine (0.06 mmol), solvent (2 mL), 100 °C, 24 h.
[b] Isolated yield after column chromatography.

a more effective catalyst for the hydroaminomethylation reaction than $[Rh(COD)Cl]_2$ (entries 6 vs 7).

Since complex **I** showed reasonable selectivity for **2a** in toluene, and a good total yield of **2a** and **3a** with no selectivity in THF, we then tried a more sterically demanding diamine complex in order to try to improve the selectivity for **2a** or **3a** (Table 2). Complex **II**[5] could catalyze hydroaminomethylation, and **2a** was obtained in THF in 46% yield (Table 2, entry 2). Because the corresponding diamine rhodium complexes with *N,N,N′,N′*-tetra(isopropyl)ethylenediamine(tipeda)[8] or with *N,N,N′,N′*-tetra(*o*-methylbenzyl)ethylenediamine(tmbeda)[9] could not be isolated in pure form using similar conditions to those for preparing **I**,[5] a combined catalyst system of $[Rh(COD)Cl]_2$ with these diamines was employed. Although both catalyst systems induced hydroaminomethylation, the results were not comparable to those using complex **II** (Table 2, entries 3 and 4).

Table 3
Results of the Rh-catalyzed hydroaminomethylation of a variety of 2-allylaniline derivatives[a]

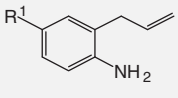
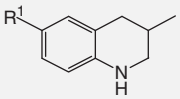
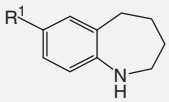
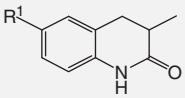
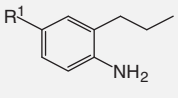
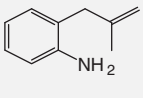
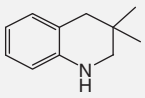
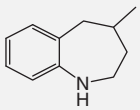
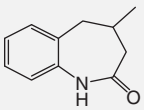
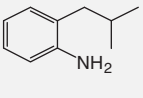
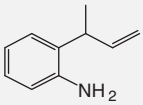
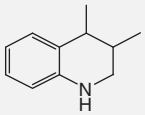
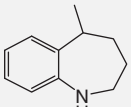
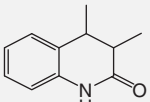
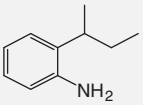
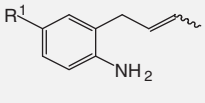
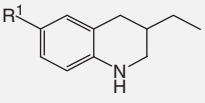
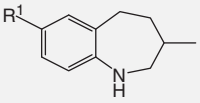
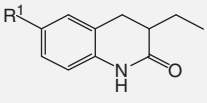
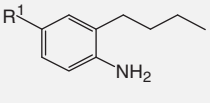
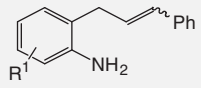
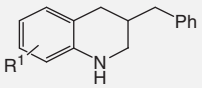
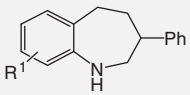
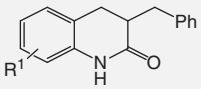
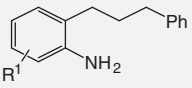
Entry	Starting material	R^1	Condition	Product and yield[b] (%)			
							
1	**1b**	Br	A	**2b** 21	**3b** 9	**4b** 18	**5b** 0
2			B	38	25	8	16
3			C	21	15	18	12
4	**1c**	OCH_3	A	**2c** 19	**3c** 13	**4c** 15	**5c** 0
5			B	27	11	11	5
6			C	37	15	7	17
							
7	**1d**		A	**2d** 0	**3d** 16	**4d** 0	**5d** 2
8			B	0	27	2	20
9			C	0	14	7	50
							
10	**1e**		A	**2e** 26	**3e** 17	**4e** 21	**5e** 0
11			B	26	9	8	0
							
12	**1f**	H	A	**2f** 26	**3f** 46	**4f** 10	**5f** 0
13			B	50	14	3	0
14			C	48	6	11	5

Table 3 (*continued*)

Entry	Starting material	R^1	Condition	Product and yield[b] (%)									
15	**1g**	CH_3	A	**2g**	27	**3g**	14	**4g**	7	**5g**	0		
16			B		27		21		2		12		
17			C		28		8		13		11		
													
18	**1h**	H	A	**2h**	27	**3h**	0	**4h**	8	**5h**	0		
19			B		60		0		Trace		28		
20			C		54		0		11		37		
21			D		69		0		0		0		
22	**1i**	5-CH_3	D	**2i**	60	**3i**	0	**4i**	0	**5i**	0		
23	**1j**	6-OCH_3	D	**2j**	63	**3j**	0	**4j**	0	**5j**	0		

[a] Reaction conditions; A: anilines (1.0 mmol), **I** (0.05 mmol), toluene, CO/H_2 = 700/100 (psi); B: anilines (1.0 mmol), **I** (0.05 mmol), THF, CO/H_2 = 100/700 (psi); C: anilines (1.0 mmol), **II** (0.05 mmol), THF, CO/H_2 = 100/700 (psi); D: anilines (1.0 mmol), **I** (0.05 mmol), THF, CO/H_2 = 300/700 (psi).
[b] Isolated yield after column chromatography.

The reactions of a variety of 2-allylaniline derivatives were then examined under typical conditions utilized for **1a**, and the results are summarized in Table 3. The reactions of **1b**[10] and **1c**[10] gave lower yields compared to the reaction of **1a**, implying that the reaction is sensitive to the electronic nature of the substituents at the *para*-position of the amino group. The reactions of 2-(methallyl)aniline (**1d**)[11] gave a different product distribution from those of 2-allylanilines (**1a**–**c**). A rhodium hydride intermediate formed in the initial catalytic step (i.e., hydroformylation), could add to the double bond in such a way that the Rh atom binds selectively to the less hindered terminal carbon atom, resulting in the exclusive formation of seven-membered compounds regardless of hydroaminomethylation or cyclocarbonylation. The reaction of **1f**[11] in toluene showed interesting selectivity in that the seven-membered hydroaminomethylation product **3f** was the major product. In contrast, the substrate **1g** having a methyl group *para* to the amine, was hydroaminomethylated less selectively. It should be noted that 2-(3-phenyl-2-butenyl)aniline (**1h**)[11] underwent hydroaminomethylation upon treatment with complex **I** in THF to furnish 3-benzyl-1,2,3,4-tetrahydroquinoline **2h** in upto 60% yields with no seven membered product being formed (entry 19). The reaction of **1h** using complex **II** also gave **2h** in moderate selectivity (entry 20). Substrate **1h** also provided a significant amount of hydrogenation product **5h** as a side product. The hydrogenation might compete with hydroaminomethylation under high partial pressure of H_2 due to steric hinderance of the double bond. When the reaction was repeated with complex **I** under increased relative CO pressure to H_2, the yield of **2h** improved substantially up to 69% and **5h** was no longer detected (entry 21). Other substrates (**1i**, **1j**) having the same substitution pattern on the allyl group with **1h**, also afforded the corresponding 3-benzyl-1,2,3,4-tetrahydroquinoline derivatives (**2i**, **2j**) as a single product in 60–63% yields (entries 22 and 23).

In conclusion, we have demonstrated that the hydroaminomethylation of allylanilines, catalyzed by ionic diamine rhodium complexes, can afford 6-membered ring heterocycles sometimes in reasonable yields. This methodology can also be applied to the synthesis of fused N-containing heterocyclic compounds.

Acknowledgment

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9. A mixture of ethylenediamine (10 mmol, 600 mg), *o*-methylbenzyl bromide (60 mmol, 11.1 g), K_2CO_3 (60 mmol, 8.28 g) in NMP (70 mL) was heated at 100 °C for 20 h. After being cooled to room temperature, water was added (140 mL) and the precipitated *N*,*N*,*N*′,*N*′-tetra(*o*-methylbenzyl)ethylenediamine was filtered off.
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11. To a THF solution of 2-iodo(phenylmethylidene)aminobenzene, which was prepared from 2-iodoaniline (56 mmol, 12.0 g) and benzaldehyde (56 mmol, 5.9 g) with a catalytic amount of concd H_2SO_4 (a few drops) in toluene, was added *i*-PrMgCl (2.0 M THF, 64 mmol, 32 mL) at −20 °C. On completion of the addition, the reaction mixture was stirred for 30 min at −10 °C. The reaction mixture was cooled to −50 °C, after which CuI (8 mmol, 1.52 g) and then 3-chloro-1-butene (80 mmol, 7.24 g) was slowly added while keeping the temperature below −40 °C. Thereafter, the reaction mixture was further stirred for 5 h at −40 °C, and then warmed to room temperature. The reaction was quenched using saturated NH_4Cl (aq). After the usual work-up, crude 2-(2-buten-1-yl)phenylmethylideneaminobenzene was obtained with a small amount of 2-(3-buten-2-yl)phenylmethylidenaminobenzene, and the ratio was 94:6 as determined by an ^1H NMR. The crude product was treated with 1 N HCl (30 mL) at room temperature for 5 h to give 2-(2-buten-1-yl)aniline (**1f**), which was carefully purified by column chromatography on silica gel (5.70 g, 74%). In a similar manner, **1d**, **1g**, **1h**–**j** were prepared with 1-chloro-2-methylpropene, 3-chloro-1-butene, cinnamyl bromide, respectively, as an electrophile.