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Palladium-Catalyzed Allylic Amination Using Aqueous Ammonia for the Synthesis of Primary Amines

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Palladium-catalyzed allylic amination is a well-established method for the synthesis of allyl amines. During the past three decades, a variety of nitrogen nucleophiles have been applied for this useful transformation.[1] Surprisingly, however, there are no reports on the use of ammonia for metal-catalyzed allylic amination to give primary amines, even though ammonia is one of the most attractive nitrogen sources from a cost and atom-economy point of view.[2] Authoritative review articles dealing with allylic aminations have mentioned that "Ammonia does not react"[1b] and "Ammonia fails to act as an effective nucleophile for π-allylpalladium."[1a] In iridium-catalyzed allylic amination, Hartwig and co-workers[3] have recently reported the reaction of methyl cinnamyl carbonate with a dioxane solution of ammonia, although exclusive formation of the corresponding secondary amine instead of the primary amine was observed. Because of "the failure of ammonia,"[4] a variety of ammonia surrogates, such as *p*-toluenesulfonamide,[5] phthalimide,[6] di-*tert*-butyl iminodicarbonate,[7] and sodium azide,[8] for use in allylic amination to synthesize primary amines have been reported.[9] In general, difficulty in the use of ammonia for metal-catalyzed processes seems to originate from the fact that (i) many kinds of transition metals are deactivated by ammonia to give stable amine complexes and (ii) when a reaction forms a primary amine, this product is more reactive than ammonia and causes problematic overreactions. Although Overmann rearrangement instead of metal-catalyzed allylic amination is an alternative approach to various allylic amines from allylic acetimidates, direct access to unprotected primary allylic amines using ammonia seems to be desirable.[10] In the course of our continuing studies of the use of ammonia as a nitrogen source for organic synthesis,[11] we decided to revisit palladium-catalyzed allylic amination with ammonia and gratifyingly found that the reaction of 1,3-diphenylallyl acetate (**1**) with aqueous ammonia in the presence of a catalytic amount of $Pd(PPh_3)_4$ proceeded with full conversion at room temperature to give 14% of the primary amine **2a** along with 71% of the corresponding secondary amine **3**. It is noted that (1) these results are contrary to the common knowledge described in review articles and (2) we also found that ammonia gas did not give the product at all under these conditions (Scheme 1). These results prompted us to continue further investigation of this chemistry.

Scheme 1

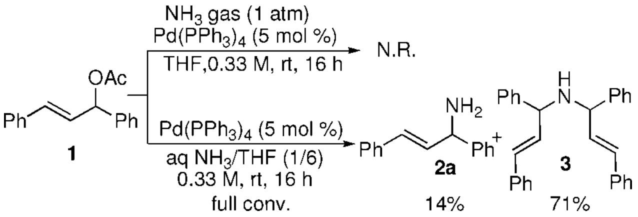

Table 1. Optimization of Reaction Conditions

$$\mathbf{1} \xrightarrow[\text{aq. NH}_3\text{/solvent, rt}]{\text{Pd(PPh}_3)_4\text{ cat.}} \mathbf{2a} + \mathbf{3}$$

entry	solvent	NH_3(aq)/ solvent	conc. (M)	cat. (mol%)	time (h)	selectivity (**2a/3**)[a]	yield (%)[b]	
							2a	**3**
1	THF	1:6	0.33	5	16	26:74	14	71
2	THF	1:2	0.33	5	6	28:72	20	66
3	THF	1:2	0.17	5	10	47:53	34	55
4[c]	THF	1:2	0.11	5	23	59:41	40	42
5	THF	1:2	0.11	10	12	62:36	44	39
6	toluene	1:2	0.11	10	12	–	trace	trace
7	DMF	1:2	0.11	10	12	68:32	48	37
8	acetonitrile	1:2	0.11	10	12	58:42	39	46
9	1,4-dioxane	1:2	0.11	10	12	77:23	61	29
10	1,4-dioxane	1:2	0.06	10	18	83:17	66	22
11	1,4-dioxane	1:2	0.04	10	18	89:11	71	16
12	1,4-dioxane	1:2	0.03	10	18	–	0	0
13[d]	1,4-dioxane	1:2	0.03	10	18	91:9	73	13

[a] The **2a/3** molar ratio was determined by ^1H NMR spectroscopic analysis of the crude material. [b] Isolated yield after chromatography (**2a** and **3** were separated). Yield of **3** was based on half the amount of **1**. [c] 12% of **1** was recovered. [d] 13 mol % of external PPh_3 was added.

Initially, we examined several reaction conditions using acetate **1** as a model substrate to improve primary/secondary amine selectivity. Changing the NH_3(aq)/THF ratio from 1:6 to 1:2 at 0.33 M in order to increase the quantity of ammonia resulted in a slight improvement of the selectivity (Table 1, entries 1 and 2). Fortunately, the dilution method was found to be effective for improvement of the selectivity (entries 2–4). Although combination of NH_3(aq) and nonpolar toluene resulted in no reaction, polar aprotic solvents such as DMF and acetonitrile showed similar efficiencies (entries 5–8). Among the solvents tested at 0.11 M, 1,4-dioxane gave the best result. We tried further dilution in the dioxane/NH_3(aq) system and found 0.04 M to be the critical concentration for this reaction (entries 9–11). At 0.03 M, the reaction did not proceed at all, probably because of deactivation of Pd(0) (entry 12). We assumed that under such high dilution conditions, liberated PPh_3 could not stabilize catalytically active Pd(0). Indeed, by addition of 13 mol % of external PPh_3, which made the total concentration of PPh_3 the same as that in the reaction at 0.04 M, the catalyst completely recovered its catalytic activity, giving the products in good yields (entry 13).

With the optimized conditions in hand, we then investigated the substrate generality of the present reaction system (Table 2). Not only a 1,3-diaryl- but also a 1,3-dialkyl allyl acetate could be applied to the present reaction, giving the primary amine **2b** in 79% yield (entry 2). The reaction of cyclic allyl carbonates possessing a variety of substituents at the vinylic position, such as aryl substituents with either electron-donating or electron-withdrawing groups as well as alkyl substituents, proceeded with excellent selectivities to afford

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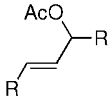
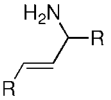
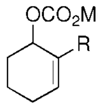
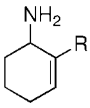
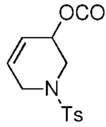
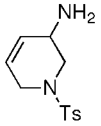
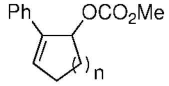
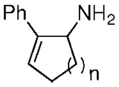
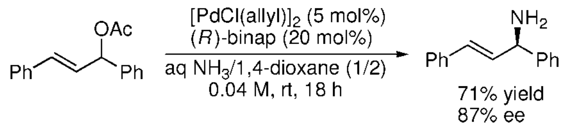
Table 2. Allylic Amination Using Aqueous Ammonia

Entry	Substrate	Product (**2**)		Cond-itions[a]	Select-ivity[b]	Yield (%)[c]
1			**a**: R = Ph	A	89/11	71
2			**b**: R = -$(CH_2)_2Ph$	A	93/7	79
3			**c**: R = Ph	B	96/4	81
4			**d**: R = *p*-$MeOC_6H_4$-	B	94/6	80
5			**e**: R = *m*-$NO_2C_6H_4$-	B	95/5	80
6			**f**: R = 3,5-$CF_3C_6H_3$-	A	97/3	82
7			**g**: R = -$(CH_2)_3Ph$	B	>99/<1	82
8			**h**	B	94/6[d]	85
9			**i**: n = 1	B	94/6	82
10			**j**: n = 3	B	93/7	76

[a] A: Table 1, entry 11. B: Table 1, entry 9. [b] The primary/secondary amine molar ratio was determined by ^1H NMR spectroscopic analysis of the crude material. [c] Isolated yield of **2** after chromatography. [d] Calculated on the basis of isolated products.

Scheme 2. Preliminary Investigation of Asymmetric Allylic Amination Using Aqueous Ammonia



the corresponding primary amines in yields of ~80% (entries 3−7).[12] It should be noted that the presence of a substituent at the vinylic position is not the reason for the high primary amine selectivity. Moreover, the reaction of the less sterically hindered, simple nitrogen-containing cyclic allyl carbonate gave the desired primary amine **2h** in high yield with high selectivity (entry 8). Five- and seven-membered cyclic allyl carbonates also reacted smoothly to afford the primary amines in high yields with high selectivities (entries 9−11).

We then performed a preliminary investigation on an asymmetric variant of this reaction. In the presence of catalytic amounts of $[PdCl(\eta^3\text{-allyl})]_2$ and (*R*)-BINAP, asymmetric allylic amination using aqueous ammonia proceeded to give the corresponding allyl amine in 71% yield with 87% ee (Scheme 2). The effective chiral induction observed here suggests that no replacement of the bisphosphine ligand by ammonia occurred under the present conditions. To the best of our knowledge, this is the first example of catalytic asymmetric synthesis using aqueous ammonia as a nitrogen source, although a rather large amount of chiral ligand is needed.[13] The absolute configuration of the product amine was assigned to be *R* by transformation of the product into the literature-known tosyl amine.[14] The sense of the stereochemistry in the chiral induction was the same as that in the allylic substitution reaction catalyzed by Pd/BINAP complexes.[15]

In summary, we have developed for the first time palladium-catalyzed allylic amination using aqueous ammonia for the preparation of primary amines. It is noteworthy that the use of aqueous ammonia is essential and that ammonia gas did not react at all. We have also demonstrated the first catalytic asymmetric synthesis using aqueous ammonia as a nitrogen source. Further investigations to clarify the role of water provided by the aqueous ammonia and of regioselective amination using unsymmetric allyl compounds and an asymmetric variant are now in progress in our laboratory.

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

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(12) The corresponding allyl acetate was found to be unreactive. Under the same conditions as in entry 3, the reaction of 2-phenylcyclohexenylallyl acetate proceeded with 38% conversion to give **2c** in 29% yield.

(13) At present, 20 mol % BINAP is required. With 12 mol % BINAP, the reaction did not proceed at all, probably for the same reason as discussed for Table 1, entry 12. Excess ligand may play a role in the stabilization of catalytically active Pd(0).

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