α-Aminoallylation of aldehydes in aqueous ammonia

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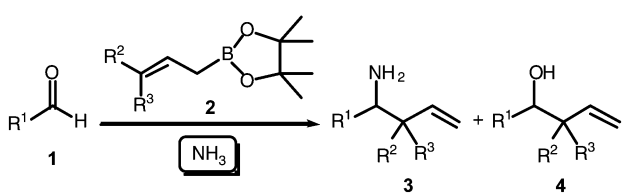
α-Aminoallylation of aldehydes in aqueous ammonia has been developed; commercial aqueous ammonia was successfully used, and this method does not require anhydrous conditions thus leading to easy and practical operations.

Although ammonia is a readily available nitrogen source, it has been barely utilized in C–N/C–C bond-forming reactions such as the Mannich reaction.[1] Especially, use of *aqueous ammonia* has often been avoided despite its advantages in terms of handling and safety.[2] This might be due to its incompatibility with water-sensitive, hydrophobic reagents and substrates.[3] We have recently found that aldehydes **1** react with ammonia and allylboronates **2** under mild conditions to afford homoallylic primary amines **3** with high chemoselectivity (amine **3** *vs.* alcohol **4**) (Scheme 1).[4] In this process, liquid ammonia was employed to saturate the solvent with ammonia, which was crucial to attain high chemoselectivity. Although aqueous ammonia could be used as an ammonia source in an organic solvent such as ethanol, the chemoselectivity was decreased. Meanwhile, organic reactions only in water have recently attracted a great deal of attention, not only because of environmental friendliness and easy handling, but also because of the unique reactivities and selectivities often observed.[5] In this context, we have been interested in the development of α-aminoallylation in aqueous ammonia, and herein report a solution of this issue.

At the outset, α-aminoallylation of 3-phenylpropanal (**1a**) as a probe was examined. Reactions were conducted with an aldehyde (0.5 mmol) and allylboronate **2a** (0.6 mmol) in 25% aqueous ammonia (1 mL) in the absence or presence of an additive at rt (Table 1). While the chemoselectivity was much lower without any additives (entry 1), it was found that acidic and anionic surfactant molecules (DBSA and lauric acid as well as SDS and SDBS) were effective as additives (entries 2–9).[6] Among these additives, DBSA was the best. It was suggested that both the acidic and hydrophobic parts of DBSA played an important role, since toluenesulfonic acid showed much lower activity (entry 10). With DBSA, further optimization of reaction conditions was performed (entries 11–16); the best result was obtained when reactions were carried out for 6–12 h in the presence of 10 mol% of DBSA (entries 15 and 16). It should be noted that the result was further improved compared to that under the reported conditions (NH_3/EtOH)[4] (entry 17).



Scheme 1 α-Aminoallylation of aldehydes using ammonia.

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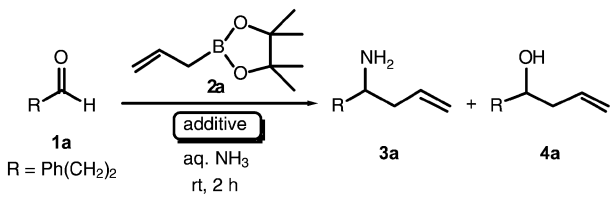
With the conditions using DBSA, α-aminoallylation of various aldehydes in aqueous ammonia was examined (Table 2).† It was found that reactions of benzaldehyde (**1b**) and its *para*-substituted derivatives **1c–d** showed moderate chemoselectivities (entries 1–3). It was unexpected to find that aromatic aldehydes, which exhibited high selectivity under the reported conditions,[4] provided lower chemoselectivity than 3-phenylpropanal (**1a**). On the other hand, salicylaldehyde (**1e**), heteroaromatic aldehydes **1f–1l**, and cinnamaldehyde (**1m**) provided the corresponding amines in high

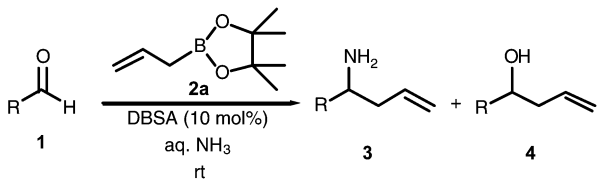
Table 1 α-Aminoallylation of 3-phenylpropanal (**1a**) with allylboronate **2a**[a]



Entry	Additive (mol%)	Yield (%)[b] 3a	4a
1	None	34	39
2	DBSA[c] (10)	72	6
3	Lauric acid (10)	67	19
4	SDS[d] (10)	56	9
5	SDBS[e] (10)	72	7
6	CTAB[f] (10)	44	21
7	3-(Dodecyldimethylammonio)propane-sufonate (10)	32	14
8	Triton X-100[g] (10)	33	12
9	PEG-400#[h] (10)	44	28
10	TsOH (10)	25	8
11	DBSA (5)	69	7
12	DBSA (20)	65	4
13	DBSA (50)	42	4
14	DBSA (10) (4 h)	72	6
15	DBSA (10) (6 h)	86 (79[i])	3
16	DBSA (10) (12 h)	84	4
17[j]	– (in NH_3/EtOH)	78	3

[a] Reactions were performed using aldehyde **1a** (0.5 mmol), allylboronate **2a** (0.6 mmol), and an additive (10 mol%) in 25% aqueous ammonia at rt for 2h. [b] Determined by ^{1}H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard. [c] Dodecylbenzenesulfonic acid. [d] Sodium dodecyl sulfate. [e] Sodium dodecylbenzenesulfonate. [f] Cetyltrimethylammonium bromide. [g] Polyethylene glycol *tert*-octylphenyl ether. [h] Polyethylene glycol (MW *ca.* 400). [i] Isolated yield. [j] Conducted in ammonia-saturated ethanol (ref 4).

Table 2 α-Aminoallylation of aldehydes **1** with **2a** in aqueous ammonia using DBSA[a]



Entry	R (**1**)	Time/h	Yield (%) **3**[b]	**4**[c]
1	Ph (**1b**)	6	61 (**3b**)	15 (**4b**)
2	*p*-$NO_2C_6H_4$ (**1c**)	6	60 (**3c**)	8 (**4c**)
3	*p*-$MeOC_6H_4$ (**1d**)	6	60 (**3d**)	17 (**4d**)
4	*o*-HOC_6H_4 (**1e**)	6	75 (**3e**)	0 (**4e**)
5	2-Pyridyl (**1f**)	6	88 (**3f**)	0 (**4f**)
6	3-Pyridyl (**1g**)	2	85 (**3g**)	0 (**4g**)
7	4-Pyridyl (**1h**)	2	83 (**3h**)	0 (**4h**)
8	2-Thienyl (**1i**)	6	60 (**3i**)	15 (**4i**)
9	3-Thienyl (**1j**)	2	95 (**3j**)	0 (**4j**)
10	2-Furyl (**1k**)	2	53 (**3k**)	2 (**4k**)
11	3-Furyl (**1l**)	2	93 (**3l**)	4 (**4l**)
12	(*E*)-PhCH=CH (**1m**)	2	78 (**3m**)	15 (**4m**)
13	*c*-C_6H_{11} (**1n**)	6	68 (**3n**)	trace (**4n**)
14	*n*-C_5H_{11} (**1o**)	2	49 (**3o**)	6 (**4o**)
15	*n*-C_9H_{19} (**1p**)	6	2 (**3p**)	52 (**4p**)

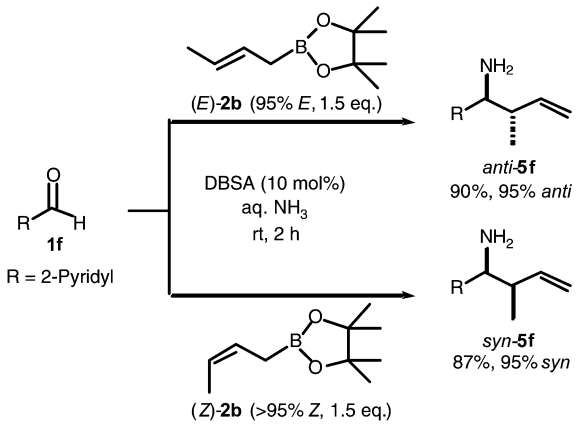
[a] Reactions were performed using aldehyde **1** (0.5 mmol), allylboronate **2a** (0.6 mmol), and DBSA (10 mol%) in 25% aqueous ammonia at rt for 2h. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard.

yields with high chemoselectivities in most cases (entries 4–12). Interestingly, 3-furaldehyde (**1l**) or 3-thiophenecarboxaldehyde (**1j**) showed much better reactivity than their 2-substituted analogues. As for reactions of aliphatic aldehydes, cyclohexanecarboxaldehyde (**1n**) and *n*-hexanal (**1o**) gave amines **3n–o** in moderate yields with good chemoselectivity (entries 13 and 14), whereas *n*-decanal (**1p**), a highly hydrophobic linear aldehyde, reversed chemoselectivity to give alcohol **4p** as the major product. This suggested that hydrophobicity of aldehydes is one of the key factors determining chemoselectivity in this reaction. Although chemoselectivities were not perfect in several cases, it is noted that the simple acid–base extraction enables easy isolation of **3**.[7]

While DBSA was found to play an important role in the present reaction, the reaction of **1a** was found to work well in 25% aqueous ammonia and THF (1/1) without DBSA at rt for 2 h leading to almost the same result as the DBSA system (**3a**: 79%, **4a**: 12%). Two liquid phases were observed in this system, and a turbid mixture similar to that observed in the DBSA system was formed with vigorous stirring. However, these conditions exhibited low substrate generality, indicating a strong dependence on aldehyde structure.

Next, α-*aminocrotylation* in aqueous ammonia was investigated. Whereas 3-phenylpropanal (**1a**) and benzaldehyde (**1b**) afforded the corresponding amines in moderate yields,[8] 2-pyridinecarboxaldehyde (**1f**) exhibited high reactivity to give amine **5f** in high yield with high chemo- and diastereoselectivity (Scheme 2). In these cases, high stereospecificity (*Z* to *syn* and *E* to *anti*) was observed.

In conclusion, we have demonstrated that α-aminoallylation of aldehydes with allylboronates proceeded smoothly *in aqueous ammonia*. Several effective conditions such as use of DBSA as an additive were found. It should be noted that the use of commercial aqueous ammonia makes the reaction easy and practical.



Scheme 2 α-Aminocrotylation of aldehyde **1f** in aqueous ammonia.

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Notes and references

† **General procedure of α-aminoallylation of aldehydes using DBSA in aqueous ammonia**: A mixture of allylboronate **2** (0.6 mmol) and dodecylbenzenesulfonic acid (DBSA) (10 mol%) in 25 wt% aqueous ammonia (1 mL, *ca.* 30 equiv.) was stirred at rt for 30 min. To the suspension was added aldehyde **1** (0.5 mmol), and the mixture was stirred vigorously at rt for the indicated time. The mixture was acidified with 3 N hydrochloric acid and extracted with dichloromethane (3 × 20 mL); the combined organic phases afforded crude alcohol **4**. The aqueous layer was basified with 6 N sodium hydroxide and extracted with dichloromethane (3 × 20 mL). The combined organic phases were dried over Na_2CO_3, filtered, concentrated *in vacuo*, and purified by preparative TLC (hexane/isopropylamine) to give amine **3**.

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6 Examples from our group on the use of DBSA in water, see: (*a*) K. Manabe, Y. Mori and S. Kobayashi, *Synlett*, 1999, **9**, 1401; (*b*) K. Manabe, S. Iimura, X-M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 11971.
7 The lower yields compared with those in the previous protocol[4] could be ascribed to an adverse effect of excess water on the equilibrium between ammonia/aldehydes and water/imines.
8 Yields of α-aminocrotylated products: **1a** with (*E*)-**2a** (43%), **1a** with (*Z*)-**2a** (36%), **1b** with (*E*)-**2a** (30%), and **1b** with (*Z*)-**2a** (24%).

