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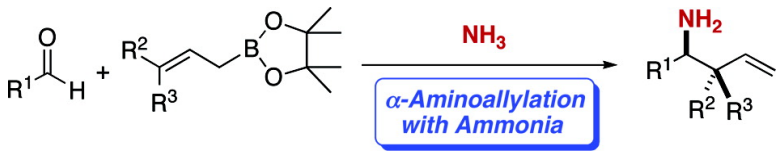

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α-Aminoallylation of Aldehydes with Ammonia: Stereoselective Synthesis of Homoallylic Primary Amines

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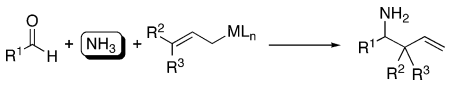
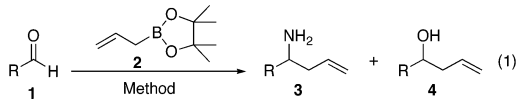
Ammonia occupies a pivotal position in chemical processes as one of the most versatile and inexpensive nitrogen sources.[1] The nucleophilic addition of ammonia to carbon−X single or multiple bonds (*X* = halides, heteroatoms, or carbon) enables incorporation of nitrogen atoms into organic molecules. Particularly useful are three-component reactions of carbonyl compounds, ammonia (or other *nitrogen* nucleophiles such as amines), and *carbon* nucleophiles that assemble both nitrogen−carbon and carbon−carbon bonds about the carbonyl carbon. These reactions are referred to as α-aminoalkylations of carbonyl compounds,[2] and several variations have been reported depending on the nucleophiles employed.[3,4] However, use of ammonia (or ammonium salts) in α-aminoalkylation has not been investigated systematically and often suffers from low yields.[2,3] Additionally, the stereochemical features have been little considered. Nevertheless, ammonia has a high potential because it can, in principle, realize direct and atom economical synthetic routes to primary amines. Envisioning further utility of ammonia in carbon−nitrogen/carbon−carbon bond-forming reactions, we have investigated α-*aminoallylation* of carbonyl compounds utilizing allylating agents as the carbon nucleophiles (Scheme 1). Herein, we describe novel three-component reactions of aldehydes, ammonia, and allylboronates that provide homoallylic primary amines with high chemo- and stereoselectivities.[4c,d]

Scheme 1. α-Aminoallylation Using Ammonia



Several types of allylmetals were initially screened in the reaction of benzaldehyde (**1a**) with ammonia; allylboronic acid and allylboronates emerged as effective allylating agents. The effect of varying the solvent (ethanol, 2-propanol, *tert*-butyl alcohol, acetonitrile, and 1,4-dioxane) was almost negligible; hence, ethanol was selected considering its environmental friendliness and the high solubility of ammonia. Variation of allylboronates had little effect, and pinacol allylboronate (**2**)[5] was chosen to take advantage of its high stability (eq 1). A large excess of ammonia (saturated in the solvent) was found to be crucial to obtain high chemoselectivity (amine **3** vs alchohol **4**) (Table 1, entry 1, Method A). Aqueous ammonia (28−30 wt %, ca. 20 equiv) could also be used instead of liquid ammonia, though chemoselectivity was slightly inferior (entry 2, Method B). Method A was selected for screening the substrate generality. The reaction was tolerant to benzaldehyde derivatives with electron-withdrawing and -donating substituents (entries 3−6) and heteoaromatic aldehydes (entries 7 and 8) to afford the corresponding homoallylic amines **3** in high yields. Cinnamaldehyde (**1h**) exhibited exclusive 1,2-addition selectivity (entry 9). Aliphatic aldehydes also gave rise to homoallylic amines with high selectivity by a simple modification of the addition order of the reactants (Method C) (entries 10−12). It is of interest that enolizable aldehydes did not complicate the reaction due to enamine formation.

Table 1. α-Aminoallylation of Aldehydes



			yield (%)	
entry	RCHO (**1**)	method[a]	**3**[b]	**4**[c]
1	PhCHO (**1a**)	A	84 (**3a**)	3 (**4a**)
2	**1a**	B	80 (**3a**)	8 (**4a**)
3	*p*-$NO_2C_6H_4CHO$ (**1b**)	A	96 (**3b**)	<1 (**4b**)
4	*p*-BrC_6H_4CHO (**1c**)	A	92 (**3c**)	5 (**4c**)
5	*p*-$MeOC_6H_4CHO$ (**1d**)	A	91 (**3d**)	4 (**4d**)
6	*o*-HOC_6H_4CHO (**1e**)	A	76 (**3e**)	<1 (**4e**)
7	(pyridin-2-yl)CHO(**1f**)	A	85 (**3f**)	nd (**4f**)
8	(thiophen-2-yl)CHO (**1g**)	A	77 (**3g**)	12 (**4g**)
9	(*E*)-PhCH=CHCHO (**1h**)	A	75 (**3h**)	3 (**4h**)
10	$Ph(CH_2)_2CHO$ (**1i**)	C[d]	78 (**3i**)	3 (**4i**)
11	*c*-$C_6H_{11}CHO$ (**1j**)	C	80 (**3j**)	4 (**4j**)
12	(±)-PhCHMeCHO (**1k**)	C	69[e] (**3k**)	4 (**4k**)
13	$HO_2CCHO{\cdot}H_2O$ (**1l**)	B[f]	quant (**3l**)	nd (**4l**)

[a] Method A: Aldehyde **1** (0.5 mmol) in liquid ammonia and ethanol was stirred at −10 °C for 2 h. To the solution was added allylboronate **2** (1.2 equiv) dropwise. The mixture was stirred at −10 °C for 3 h and then at room temperature for 1 h before workup. Method B: Aldehyde **1** (0.5 mmol) in 28−30 wt % aqueous ammonia (ca. 20 equiv) and ethanol was stirred at room temperature for 30 min. To the solution was added allylboronate **2** (1.2 equiv). The mixture was stirred at room temperature for 2 h before workup. Method C: Allylboronate **2** (1.2 equiv) in liquid ammonia and ethanol was stirred at room temperature for 30 min. Aldehyde **1** (0.5 mmol) in ethanol was added to the solution, and the mixture was stirred at room temperature for 2 h before workup. For details, see Supporting Information. [b] Isolated yields. [c] Yields were determined by ^{1}H NMR analyses using 1,2,4,5-tetramethylbenzene as an internal standard; nd = not detected. [d] Aldehyde **1i** in ethanol was slowly added to the solution of **2a** in ammonia/ethanol over 2 h. [e] *Syn*/*anti* = 73/27. [f] Stirred for 3 h.

Although chemoselectivities were generally good, they were not perfect in some cases; it should be noted that the isolation procedure of **3** is very simple (acid−base extraction).[6] The reaction of glyoxylic acid (**1l**) proceeded smoothly with Method B to afford α-allylglycine (**3l**) in quantitative yield (entry 13).

It is noticeable that optically active α-oxyaldehydes **1m** and **1n** underwent α-aminoallylation without concomitant racemization or epimerization at the α-position even in the presence of excess ammonia (Scheme 2). Formation of hemiacetals (α-amino alcohols) might serve to prevent such racemization and epimerization. In these reactions, good to high *syn* diastereofacial selectivities were observed,[7] and stereoselective synthesis of an L-acosamine derivative,[8] an aminosugar, was achieved utilizing product Boc-**3n**.

Although the precise reaction mechanism is still unclear, there are two possible reaction pathways.[9] The first is preformation of *N*-unsubstituted imines from aldehydes and ammonia followed by allylation with allylboronates.[10,11] The second is in situ formation of a novel aminoallylating agent from the allylboronate and ammonia.[12] An excess of ammonia, present in this reaction (Methods A and B), may shift the equilibrium from aldehydes/

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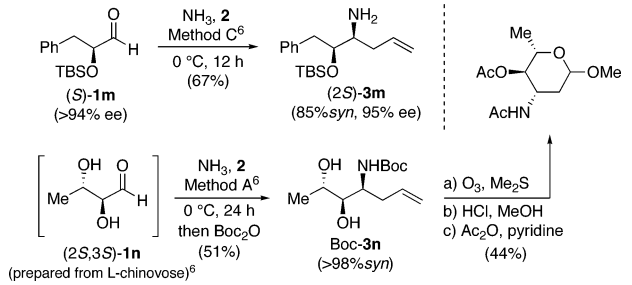
Scheme 2. Diastereoseleacitive Reaction of α-Oxyaldehydes

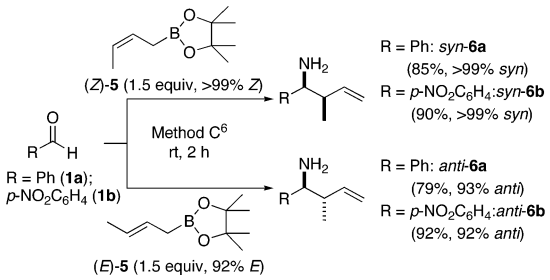


ammonia to imines and facilitate the former pathway. Meanwhile, that premixing of the allylboronate and ammonia led to higher chemoselectivity for reactions of aliphatic aldehydes (Method C) may support the latter pathway. When reaction of **1a**, isopropylamine, or benzylamine (5 equiv) instead of ammonia with **2** in ethanol was performed, no allylated products were formed, but the corresponding imine was observed,[13] indicating the importance of ammonia as a partner in the present reaction.

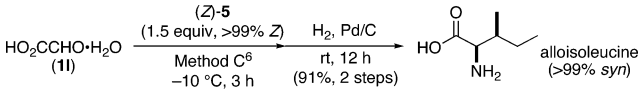
The reaction of aldehydes with (*Z*)- or (*E*)-crotylboronates **5**[14] (α-*aminocrotylation*) was also investigated (Scheme 3). High γ-addition selectivity and high stereospecificity were observed. (*Z*)-Crotylboronate **5** afforded *syn*-adduct **6**, whereas *anti*-**6** was obtained from (*E*)-**5**. It should be noted that the stereochemical outcome is not the same as that of crotylation of most *N*-substituted imines, but similar to that of aldehydes via cyclic transition states.[15]

Diastereoselective α-aminocrotylation was applied to a concise, one-pot synthesis of alloisoleucine which is an uncommon α-amino acid found in certain peptide antibiotics (Scheme 3).[16] Treatment of glyoxylic acid with (*Z*)-crotylboronate **5** in aqueous ethanol/ammonia (Method C)[6] provided the *syn*-crotylated product. After removal of ammonia by aspiration, the product was subsequently hydrogenated over Pd/C to afford alloisoleucine in high yield with high diastereoselectivity.

Scheme 3. Stereospecific α-Aminocrotylation

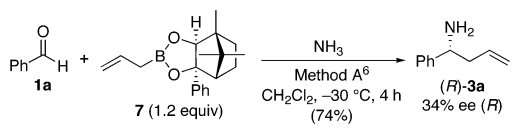


Scheme 4. Concise Stereoselective Synthesis of Alloisoleucine



Furthermore, a preliminary study using chiral boronate **7**[17] has revealed the potential for an enantioselective α-aminoallylation methodology to be developed (Scheme 5).

Scheme 5. Enantioselective α-Aminoallylation



In summary, three-component reactions of aldehydes, allylboronates, and ammonia were found to afford homoallylic primary amines in high yields with high chemo- and stereoselectivities, the synthetic utility was demonstrated by syntheses of an aminosugar and an uncommon α-amino acid, alloisoleucine. Further investigations concerning the reaction mechanism and asymmetric catalysis are now in progress.

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Note Added after ASAP Posting: After this paper was posted ASAP on 05/22/2004, the first sentence of the second paragraph was rephrased. The corrected version was posted 05/25/2004.

Supporting Information Available: Experimental details and physical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Roush, W. R.; Walts, A. E. *Tetrahedron Lett.* **1985**, *26*, 3427.
(6) See Supporting Information and/or Table 1.
(7) It should be noted that the sense of diastereofacial selectivity is different from that of reactions with vinyl or arylboronic acids; see ref 4b.
(8) A recent synthesis of L-acosamine: Ginesta, X.; Pastó, M.; Pericas, M. A.; Riera, A. *Org. Lett.* **2003**, *5*, 3001.
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(11) Formation of the imine derived from benzaldehyde and ammonia was confirmed by ^{1}H NMR analysis. See Supporting Information.
(12) It was recently reported that bis(dialkylamino)cyanoboranes or diaminoboron enolates react with carbonyl compounds to give α-amino nitriles or β-amino ketones; see: (a) Suginome, M.; Yamamoto, A.; Ito, Y. *Chem. Commun.* **2002**, 1392. (b) Suginome, M.; Uehlin, L.; Yamamoto, A.; Murakami, M. *Org. Lett.* **2004**, *6*, 1167.
(13) Formation of a *N*-homoallylimine derived from **1a** and **3a** was observed in the reaction of **1a** with **2** when the amount of ammonia was reduced, while the reaction of *N*-alkylimines with allyl(dimethoxy)borane was reported to be sluggish; see: Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem.* **1983**, 2000.
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