Synthetic Methods

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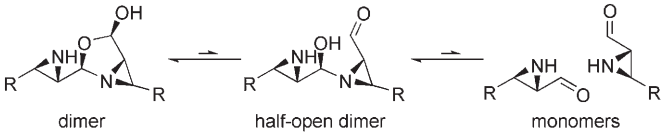
Amphoteric Amino Aldehydes Enable Rapid Assembly of Unprotected Amino Alcohols**

*Ryan Hili and Andrei K. Yudin**

A variety of molecules that contain functionally significant β-amino alcohol motifs[1] are assembled by the addition of carbon nucleophiles to *N*-protected α-amino aldehydes. This chemistry has been used in numerous industrial processes, including the production of marketed protease inhibitors containing hydroxyethylene isosteres.[2] Owing to the inherent incompatibility of the amine and aldehyde functionalities, the protection of the nitrogen atom has been unavoidable in all of these applications. Such protection disfavors undesired condensation reactions but increases the risk of racemization of chiral amino aldehydes.[3] The recourse to protecting groups has also produced complications in metal-mediated addition reactions to chiral α-amino aldehydes, as delicate tuning of the nitrogen substituent is required to selectively minimize the competing governance of stereocontrol by either chelation or nonchelation models.[4] Furthermore, the removal of the protecting groups from the amino alcohol product is often not trivial. This limitation is not restricted to the synthesis of amino alcohols from amino aldehydes. Both olefin aminohydroxylation[5] and more recent methods based on C–H activation require subsequent deprotection steps.[6]

The rapid assembly of stereochemically complex β-amino alcohol structures without recourse to the use of protecting groups has been a long-standing challenge. We sought a synthetic method that would not only deliver unprotected amino alcohols but would also enable downstream divergency. As direct progenitors of amino alcohols, unprotected amino aldehydes can be viewed as key strategic building blocks; however, there has been limited success with their synthesis. One hundred years ago, Fischer attempted to prepare glycinal, which was found to be unstable.[7] Many years later, Myers et al. described autoprotection of the amino functionality in α-amino aldehydes by treatment with trifluoroacetic acid in methanol. The resulting hemiacetal adducts are intriguing intermediates but are prone to self-condensation above pH 5.[8]

Our recent studies in the field of amphoteric molecules[9–11] provided an opportunity to address some of the long-standing problems associated with the rapid formation of complex nitrogen-containing molecules without protecting-group manipulations. Undesired intermolecular iminium ion formation from amphoteric aziridine aldehydes is disfavored thermodynamically owing to the increase in ring strain involved in such a process. Aziridine aldehydes can be prepared from simple starting materials, such as α-amino acids, and exist as stable dimers with the monomer/dimer equilibrium lying towards the dimer in a variety of solvents (Scheme 1). The addition of carbon nucleophiles to amphoteric aziridine aldehydes has been elusive until now. Herein we describe how the curious structural preferences in the course of aziridine aldehyde dimer dissociation enable the protecting-group-free, stereoselective synthesis of complex amino alcohols.



Scheme 1. Monomer/dimer dynamics in amphoteric amino aldehydes.

Initial investigations into the addition of carbon nucleophiles, such as Grignard and organolithium reagents, to aziridine aldehyde dimers resulted in quantitative recovery of the starting materials. We attribute this disappointing lack of reactivity to unfavorable dimer dissociation under basic conditions (Scheme 1). The deprotonated dimer is unreactive towards nucleophiles. To access aldehyde reactivity, a means for shifting the equilibrium to unveil the aldehyde functionality in the presence of a nucleophile was required (Scheme 1). Our attention was directed to the use of protic solvents and carbon–carbon bond-forming reactions mediated by the water-tolerant indium reagents.[12] Gratifyingly, the addition of allyl indium reagents to aziridine aldehyde dimers was successful (Table 1). The scope of amino alcohol formation was explored by using a variety of allyl bromides. In all cases the chemical yields were high, with exclusive production of the *syn* β-amino alcohols through γ addition. No undesired aziridine ring opening was observed in the reaction, in contrast to the well-known scission of epoxides by allyl indium reagents under similar conditions.[13] A 1:1 mixture of H_2O and THF[12] was optimal as the solvent in terms of both the yield and the rate of the reaction, with the *syn* diastereoisomers formed as the only detectable products. No conversion was observed with other solvents, such as trifluoroethanol, DMF, or anhydrous THF. The potential utility of the 1,2-amino alcohol template is immediately

[*] R. Hili, Prof. Dr. A. K. Yudin
Davenport Research Laboratories
Department of Chemistry, University of Toronto
80 St. George Street, Toronto, ON, M5S3H6 (Canada)
Fax: (+1) 416-946-7676
E-mail: ayudin@chem.utoronto.ca

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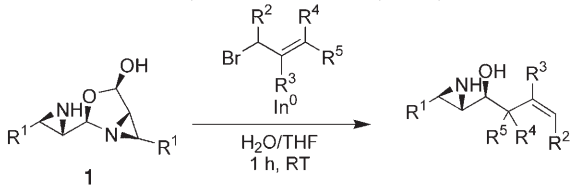
Table 1: Amino alcohol synthesis with a variety of allyl bromides.[a]



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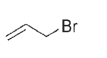
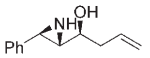
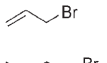
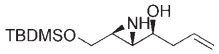
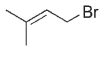
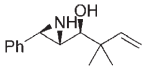
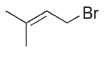
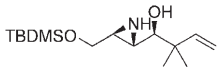
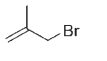
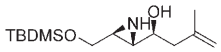
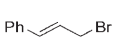
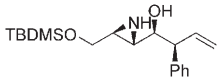
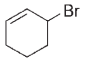
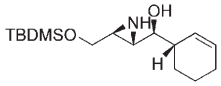
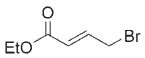
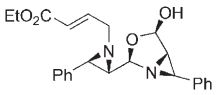
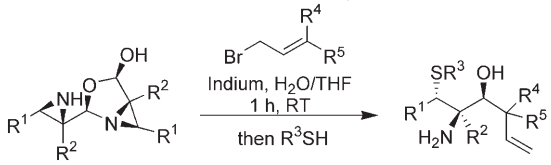
1			85[c]
2			95
3			96
4			96
5			81
6			90
7			87
8			86

[a] Reactions were performed on a 0.1 mmol scale (with respect to **1**) at 0.1 M in H_2O/THF (1:1 v/v) with a dimer/In/allyl bromide ratio of 1:2.2:2.2. [b] Yield of the isolated product. [c] The reaction was performed on a 1 mmol scale. TBDMS = *tert*-butyldimethylsilyl.

Table 2: Stereoselective formation of sulfanyl amino alcohols.[a]



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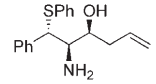
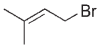
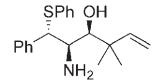
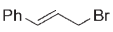
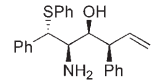
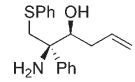
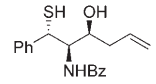
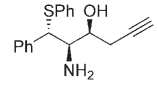
1			96
2			92
3			88
4			91
5			79
6			92

[a] Upon completion of the allyl indium addition (as determined by TLC analysis), the thiol (1 equiv) was added, and the reaction mixture was heated at 60 °C for 1 h. [b] Yield of the isolated product. Bz = benzoyl.

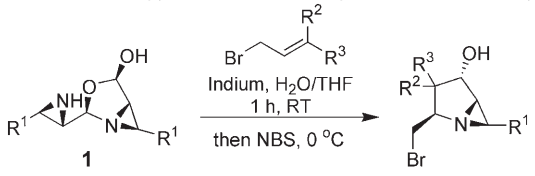
evident. Protease inhibitors containing 1,2-amino alcohol functionalities are not cleavable hydrolytically and are recognized at the atomic level by their targets through many different mechanisms.[14,15] Our versatile templates provide an enabling technology for the synthesis of a wide range of protease inhibitors.

To evaluate the possibility of one-pot operations that result in useful stereodefined triads, we pursued the assembly of sulfanyl amino alcohols. The sulfanyl amino alcohol motif is found in protease inhibitors, such as nelfinavir.[16] A one-pot allylation/nucleophilic ring-opening sequence was sought to enable access to an unprotected S, N, O structural motif. Upon completion of the allylation, benzenethiol was added to the reaction mixture, which was then heated at 60 °C for 1 h. The resulting products were obtained as single diastereoisomers (Table 2).

We also developed a one-pot strategy that takes advantage of the unprotected aziridine and olefin functionalities installed during the synthesis of the amino alcohol. An important feature of unprotected aziridines is their resistance to undesired oxidation to imines.[17] The addition of *N*-bromosuccinimide (NBS) to the allylation reaction mixture at 0 °C led to the clean production of [3,5]bicycles as single diastereoisomers (Table 3). This methodology enables the facile construction of substituted pyrrolidinols equipped with versatile aziridine substituents.

The complete diastereoselectivity observed during the synthesis of unprotected amino alcohols called for a mechanistic explanation. At the outset, our efforts were aimed at shifting the equilibrium towards the aldehyde, which was projected to act as the electrophile (Scheme 1). However, is the monomeric aldehyde the reactive species involved? Evidence against the involvement of the monomeric aldehyde is afforded by the reaction described in entry 8 of Table 1. Only the *N*-allylated dimer was produced from the starting allyl bromide; the *N*-allylated monomer was not observed. That the monomeric species is not formed under these reaction conditions is supported further by the lack of crossover between two different aziridine aldehyde dimers. A plausible mechanism that would operate in the absence of complete dimer dissociation involves addition of the allyl indium reagent to the latent aldehyde of type **2** (Scheme 2). The latter is expected to chelate the allyl indium species to facilitate the stereoselective delivery of the allyl group to the aldehyde carbon atom. Quantum chemical calculations[18] were performed to locate the transition-state structure for the allylation reaction. It was found that the allyl indium(I)[19] species chelates preferentially between the carbonyl oxygen atom and the aziridine nitrogen atom to form the concave transition state **3**, which exhibits hydrogen bonding between the incipient alkoxide and the hydroxy group of the carbinolamine. This interaction both directs the facial selectivity of the allylation and stabilizes negative-charge buildup.[20] The resulting product **4** is expected to undergo proton transfer between the alkoxide and the hydroxy group of the carbinolamine to release the amino alcohol product **6** and the

Table 3: Formation of pyrrolidinols from amphoteric amino aldehydes.[a]



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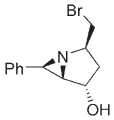
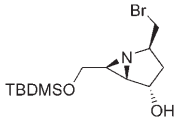
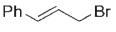
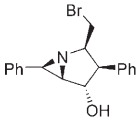
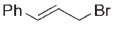
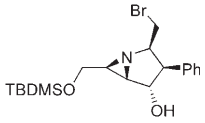
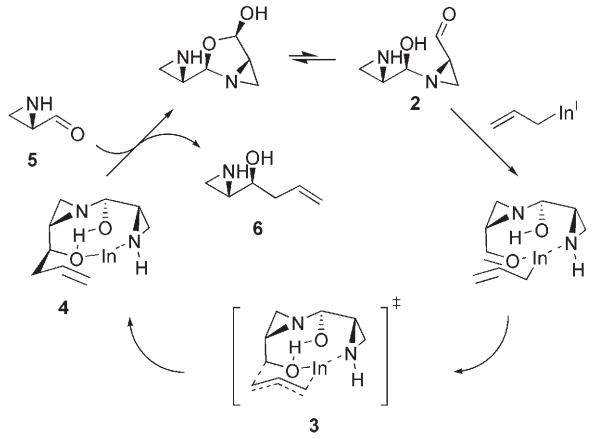
1			79
2			74
3			78
4			72

[a] Upon completion of the allyl indium addition (as determined by TLC analysis), NBS (1.1 equiv) was added to the reaction mixture at 0 °C, and the mixture was stirred at 0 °C for 2 h. [b] Yield of the isolated product.



Scheme 2. Proposed mechanism of β-amino alcohol formation.

monomeric aziridine aldehyde **5**. Upon release, **5** undergoes rapid dimerization to reform the homochiral dimer adduct with previously noted fidelity.[10]

In summary, a direct approach to unprotected *syn* amino alcohols is possible through the indium-mediated addition of carbon nucleophiles to readily available amphoteric amino aldehydes. Efforts to shift the dimer/monomer equilibrium revealed an important feature of the transformation: The half-open species appears to be optimal with regard to both reactivity and selectivity during amino alcohol formation. The downstream utility of the resulting products has been demonstrated in several one-pot operations, which led to stereochemically complex scaffolds. This late-stage incorporation of unprotected aziridines will facilitate the synthesis of diverse *syn* amino alcohols, ubiquitous components of therapeutically relevant protease inhibitors and other bioactive compounds.

Experimental Section

Representative procedure (Table 1, entry 1): The dimer **1** (R^1 = Ph; 294 mg, 1 mmol) was dissolved in a mixture of H_2O and THF (1:1 (v/v); 10 mL) in a vial equipped with a magnetic stirring bar and a screw-cap lid. Indium (255 mg, 2.2 mmol) was added, followed by allyl bromide (186 μl, 2.2 mmol), and the reaction mixture was stirred at room temperature for 1 h. Water and EtOAc were then added, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. The crude product (321.5 mg, 85%) was isolated by flash column chromatography on silica gel (EtOAc; R_f = 0.15). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.18 (m, 5H), 5.95–5.81 (m, 1H), 5.20–5.10 (m, 2H), 3.61 (dd, J = 6.4, 12 Hz, 1H), 2.91 (d, J = 3.2 Hz, 1H), 2.43–2.38 (m, 2H), 2.30 (br s, 1H), 2.20–1.40 ppm (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 134.2, 128.8, 127.5, 125.9, 118.3, 71.1, 45.0, 40.7, 37.4 ppm; HRMS (ESI): m/z calcd for $C_{12}H_{16}NO$: 190.1232 $[M+H]^+$; found: 190.1234.

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[1] For a review on the synthesis of amino alcohols, see: S. C. Bergmeier, *Tetrahedron* **2000**, *56*, 2561–2576.
[2] K. Izawa, T. Onishi, *Chem. Rev.* **2006**, *106*, 2811–2827.
[3] a) R. W. Hoffmann, *Synthesis* **2006**, 3531–3541; b) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404–408.
[4] M. Reetz, *Angew. Chem.* **1991**, *103*, 1559–1573; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546.
[5] G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449–452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451–454.
[6] a) E. J. Alexanian, C. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691; b) K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276.
[7] a) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 956; b) E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1019.
[8] A. G. Myers, D. W. Kung, B. Zhong, *J. Am. Chem. Soc.* **2000**, *122*, 3236.
[9] A. K. Yudin, R. Hili, *Chem. Eur. J.* **2007**, *13*, 6538–6542.
[10] R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772–14773.
[11] X. Li, A. K. Yudin, *J. Am. Chem. Soc.* **2007**, *129*, 14152–14153.
[12] a) C. J. Li, T.-H. Chan, *Tetrahedron* **1999**, *55*, 11149–11176; b) V. Nair, S. Ros, C. N. Jayan, B. S. Pillai, *Tetrahedron* **2004**, *60*, 1959–1982.
[13] J. S. Yadav, S. Anjaneyulu, Md. M. Ahmed, B. V. S. Reddy, *Tetrahedron Lett.* **2001**, *42*, 2557–2559.
[14] a) A. Krohn, S. Redshaw, J. C. Ritchie, B. J. Graves, M. H. Hatada, *J. Med. Chem.* **1989**, *32*, 1532–1538; b) J. Dohnálek, J. Hašek, J. Dušková, H. Petroková, M. Hradilek, M. Souček, J. Konvalinka, J. Brynda, J. Sedláček, M. Fábry, *Acta Crystallogr. Sect. D* **2001**, *57*, 472–476; c) E. Specker, J. Böttcher, H. Lilie, A. Heine, A. Schoop, G. Müller, N. Gribenow, G. Kleber, *Angew. Chem.* **2005**, *117*, 3200–3204; *Angew. Chem. Int. Ed.* **2005**, *44*, 3140–3144.
[15] C. E. Lee, E. K. Kick, J. A. Ellman, *J. Am. Chem. Soc.* **1998**, *120*, 9735–9747.

[16] K. Luzuriaga, M. McManus, L. Mofenson, P. Britto, B. Graham, L. J. Sullivan, *N. Engl. J. Med.* **2004**, *350*, 2471 – 2480.
[17] a) M. Sasaki, A. K. Yudin, *J. Am. Chem. Soc.* **2003**, *125*, 14242 – 14243; b) G. Chen, M. Sasaki, X. Li, A. K. Yudin, *J. Org. Chem.* **2006**, *71*, 6067 – 6073.
[18] The optimized geometries of structures were calculated at the B3LYP/STO-3G* level by using Gaussian 03. The transition state was located by employing the QST2 routine with optimization and frequency analysis (NoRaman) performed at the B3LYP/STO-3G* level. See the Supporting Information for output files. Gaussian 03, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**.
[19] T. H. Chan, Y. Yang, *J. Am. Chem. Soc.* **1999**, *121*, 3228 – 3229.
[20] Hydrogen bonding between a developing alkoxide and an appropriate donor group is known to act as a control element that leads to lower activation energies; see: C. Allemann, R. Gordillo, F. R. Clemente, P. H. Y. Cheong, K. N. Houk, *Acc. Chem. Res.* **2004**, *37*, 558 – 569.

