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Asymmetric Skeletal Rearrangement of Symmetrically α,α-Disubstituted α-Amino Aldehydes: A New Entry to Optically Active α-Hydroxy Ketones

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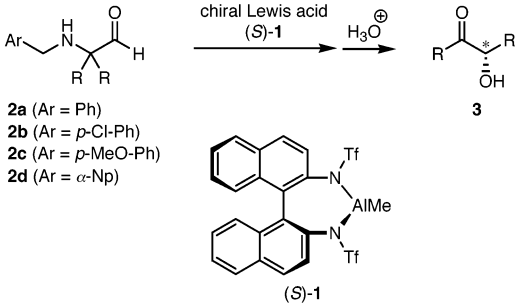
α-Amino aldehydes have been employed as useful building blocks in organic synthesis, taking advantage of the ready availability of both enantiomers from the corresponding α-amino acids,[1] particularly for the preparation of optically active 1,2-amino alcohols,[2] a pharmaceutically and biologically intriguing class of compounds.[3] As shown in extensive studies on this subject, most of the transformations of α-amino aldehydes reported to date have been categorized as the addition of external nucleophiles to aldehyde carbonyls,[1−4] and hence the transformations involving their skeletal rearrangement are extremely rare, contrary to the case with α-amino ketones.[5] Although α-amino aldehydes are known to undergo isomerization by treatment with strong acids to furnish several products depending on the reaction conditions,[6] there have been no reports on controlling the stereochemical outcome as well as the reaction pathways. Herein we wish to disclose the asymmetric skeletal rearrangement of symmetrically α,α-disubstituted α-amino aldehydes (Scheme 1). This unique reaction was found to be smoothly facilitated by a chiral organoaluminum Lewis acid of type **1**[7] and, upon acidic hydrolysis, afforded the corresponding α-hydroxy ketones with high enantiomeric purities.[8]

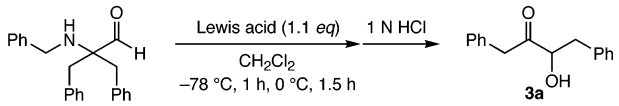
Scheme 1



Our initial examination was focused on the possibility of effecting selective rearrangement of α,α-dialkyl-α-amino aldehydes by using an appropriate Lewis acid under mild conditions. Several common Lewis acids were evaluated as promoters under identical conditions with *N*-benzyl α-amino aldehyde **2aa** as a representative substrate (Scheme 2).[9] Although both BF_3·OEt_2 and $TiCl_4$ mediated the rearrangement selectively, the reactions proceeded sluggishly to give the α-hydroxy ketone **3a** in 20 and 23% isolated yields, respectively, after hydrolysis with 1 N HCl. Trimethylsilyl triflate (Me_3SiOTf) exhibited comparable reactivity, and $SnCl_4$ provided only a trace amount of the product. In sharp contrast, however, the use of Me_2-AlCl as promoter led to clean formation of **3a** (94%), indicating the suitability of organoaluminum Lewis acids for this transformation.[10]

On the basis of these results, we next pursued the stereochemical control of this unique skeletal rearrangement in an absolute sense. For this purpose, we employed the optically active (*S*)-2,2′-bis-(trifluoromethanesulfonylamino)-1,1′-binaphthyl [(*S*)-**4**][11] as a chiral

Scheme 2



Lewis acid			
	BF_3·OEt_2	:	20%
	$TiCl_4$	:	23%
	Me_3SiOTf	:	14%
	$SnCl_4$	:	trace
	Me_2AlCl	:	94%

ligand, assuming a sufficient Lewis acidity of the corresponding chiral organoaluminum Lewis acid (*S*)-**1**. Treatment of (*S*)-**4** with Me_3Al (1.0 equiv) in toluene at room temperature for 15 min and at 110 °C for an additional 15 min produced (*S*)-**1**,[7] and, as expected, subsequent reaction with α-amino aldehyde **2aa** in CH_2Cl_2 at −78 °C for 4 h resulted in the smooth rearrangement to furnish, after acidic hydrolysis, the α-hydroxy ketone **3a** in 66% yield. The enantiomeric excess of **3a** was shown to be 91% ee by chiral HPLC analysis (entry 1 in Table 1). Use of toluene as solvent greatly improved the chemical yield (83%) and also enhanced the enantioselectivity to 94% ee (entry 2).[12] Furthermore, we examined the effect of the aromatic moiety (Ar) of the *N*-substituent of **2** on the reactivity and selectivity under similar reaction conditions. Although the reactions with **2ba** and **2ca** did not lead to the expected improvement (entries 3 and 4), an appreciable increase of chemical yield and enantioselectivity was observed in the rearrangement of **2da** possessing an α-naphthylmethyl group on nitrogen (entry 5),[13] and, consequently, the optically active α-hydroxy ketone **3a** was obtained in 93% yield with 95% ee by conducting the reaction at −40 °C (entry 6).

Other selected examples of this asymmetric skeletal rearrangement with **2d** are also listed in Table 1. The electronic property of the benzylic side chain of α-amino aldehyde slightly affected the reactivity and selectivity (entries 7 and 8). Excellent enantioselectivities were attained in the reactions involving the migration of allylic α-substituents (entries 9 and 10). These results clearly demonstrate the effectiveness of the present method for the hitherto difficult asymmetric synthesis of acyloins.[14] In addition, exposure of an α,α-diphenyl-α-amino aldehyde derivative to the optimized conditions afforded a facile access to an optically active benzoin (entry 11).

To gain insight into the reaction mechanism, we performed the ^1H NMR study of the mixture of **2da** and (*S*)-**1** in $CDCl_3$ at room temperature, which confirmed the formation of zwitterionic iminium intermediate **A**. This result indicates that the rearrangement is primarily facilitated by the activation of aldehyde carbonyl with the chiral Lewis acid, being responsible for the stereochemistry of the newly created stereogenic center in the 1,2-migration of the α-substituent as shown in Scheme 3.

This observation suggested that the treatment of the in situ generated iminium intermediate with certain nucleophiles would

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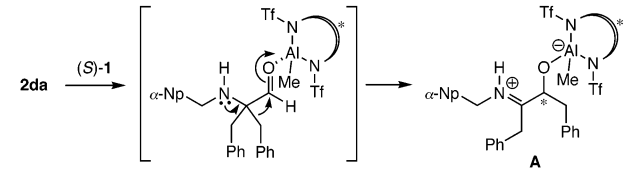
Table 1. Asymmetric Skeletal Rearrangement of Symmetrically α,α-Disubstituted α-Amino Aldehydes[a]

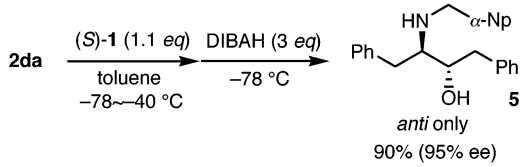
entry	R	Ar	condition (°C, h)	% yield[b]	% ee[c] (config)[d]
1	$PhCH_2$	Ph (**2aa**)	−78, 4	66	91 (*S*)[e]
2			−78, 4	83	94 (*S*)
3		*p*-Cl-Ph (**2ba**)	−78, 4	81	93 (*S*)
4		*p*-MeOPh (**2ca**)	−78, 4	77	94 (*S*)[f]
5		α-Np (**2da**)	−78, 4	87	95 (*S*)
6			−78, 4; −40, 12	93	95 (*S*)
7	*p*-Cl-$PhCH_2$		−78, 4; −40, 12	94	86
8	*p*-MeO-$PhCH_2$		−78, 5; −40, 13	80	94
9	$(CH_3)_2C{=}CHCH_2$		−78, 3; −40, 12	73	97
10	$PhCH{=}CHCH_2$		−78, 4; −40, 15	62	96
11	Ph		−78, 4; −40, 12	80	78 (*S*)

[a] Unless otherwise specified, the reaction was carried out with 1.1 equiv of (*S*)-**1** in toluene under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis of the hydroxy ketones using a chiral column with hexane-2-propanol or ethanol as solvent. [d] Determined by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA esters (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092). The absolute configuration of the product of entry 11 was also confirmed by comparison with the optical rotation of the commercially available (*S*)-benzoin. [e] Use of CH_2Cl_2 as solvent. [f] Use of CH_2Cl_2 as cosolvent (toluene/CH_2Cl_2 = 4:1) because of the insolubility of the starting aldehyde.

Scheme 3



Scheme 4



afford the corresponding optically active 1,2-amino alcohols, expanding the synthetic utility of our approach. Indeed, the reaction of **2da** with (*S*)-**1** in toluene followed by the addition of DIBAH at −78 °C gave rise to anti amino alcohol **5** exclusively in 90% yield with 95% ee,[15] allowing an asymmetric synthesis of pharmaceutically useful 2-hydroxy-3-amino-1,4-diphenylbutane (Scheme 4).[16]

In conclusion, we have developed a highly enantioselective skeletal rearrangement of symmetrically α,α-disubstituted α-amino aldehydes using a chiral organoaluminum Lewis acid **1**. This method casts light on the previously unexplored yet potential utility of α-amino aldehydes as synthetic building blocks and also provides a new entry to optically active α-hydroxy ketones and 1,2-amino alcohols.

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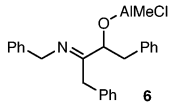
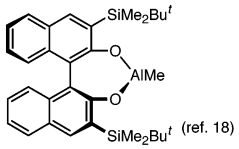
Supporting Information Available: Representative experimental procedures as well as spectroscopic characterization of all new compounds and the reaction intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

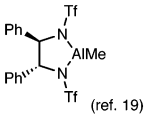
References

(1) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.
(2) Tramontini, M. *Synthesis* **1982**, 605.
(3) Reviews: (a) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (c) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935.
(4) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
(5) For an excellent review on the thermal rearrangement of α-amino ketones, see: Stevens, C. L.; Pillai, P. M.; Munk, M. E.; Taylor, K. G. *Mech. Mol. Migr.* **1971**, *3*, 271 and references therein.
(6) (a) Duhamel, L.; Duhamel, P.; Jarry, A. *Tetrahedron Lett.* **1970**, 1053. (b) Kirrmann, A.; Nouri-Bimorghi, R.; Elkik, E. *Bull. Soc. Chim. Fr.* **1969**, 2385.
(7) Noyori, R.; Kitamura, M.; Takemoto, K. *Jpn. Kokai Tokkyo Koho* **1992**, JP0491093.
(8) For asymmetric synthesis of α-hydroxy ketones, see: (a) (asymmetric dihydroxylation of enol ethers) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067. (b) (asymmetric oxidation of ketone enolates with chiral oxaziridines) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. (c) (asymmetric oxidation of ketones by chiral phase-transfer catalysis) Masui, M.; Ando, A.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 2835.
(9) The starting symmetrically α,α-disubstituted α-amino aldehydes can be prepared by simple reduction of the corresponding amino acid esters, which were readily synthesized either by the Strecker reaction of symmetric ketones[17] or by the double alkylation of glycine Schiff base.
(10) The ^{1}H and ^{13}C NMR analyses of an equimolar mixture of **2aa** and Me_2-AlCl in CD_2Cl_2 revealed the formation of the neutral imine **6**; thus, the reaction might be driven by coordination of the aluminum on aldehyde carbonyl and the N−H proton abstraction in this case.



(11) (a) Shi, M.; Sui, W.-S. *Chirality* **2000**, 574. (b) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H. *Synlett* **1995**, 975.
(12) The results of the attempted rearrangements of **2aa** with other representative chiral organoaluminum Lewis acids in toluene at −78 °C for 4 h are as follows.[18,19]





(13) α,α-Disubstituted α-amino aldehydes are stable and easy to handle as compared to α-monosubstituted aldehydes, and, particularly, **2d** is generally obtained as a solid with enhanced stability.
(14) (a) Guo, Z.; Goswami, A.; Nanduri, V. B.; Patel, R. N. *Tetrahedron: Asymmetry* **2001**, *12*, 571. (b) Gill, M.; Kiefel, M. J.; Lally, D. A. *Tetrahedron Lett.* **1986**, *27*, 1933.
(15) The stereochemistry of **5** was assigned by ^{1}H NMR analysis after conversion to the oxazolidin-2-one derivative. See the Supporting Information.
(16) For example, see: Howarth, J.; Lloyd, D. G. *J. Antimicrob. Chemother.* **2000**, *46*, 625.
(17) (a) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1700. (b) Wysong, C. L.; Yokum, T. S.; Morales, G. A.; Gundry, R. L.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem.* **1996**, *61*, 7650.
(18) Maruoka, K.; Banno, H.; Yamamoto, H. *Tetrahedron: Asymmetry* **1990**, *112*, 7791.
(19) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 30.

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