599.53, $a = 10.465(8)$, $b = 15.279(8)$, $c = 15.425(12)$ Å, $\beta = 104.60(5)^\circ$, $V = 2387(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.668$ g cm^{-3}, $\mu = 1.827$ mm^{-1}, $F(000) = 1208$, $R = 0.0609$, $R_w = 0.1736$, GOF = 1.006 for 344 parameters, 2606 reflections with $|F_o| = 4\sigma(F_o)$.

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[1] C. Kaes, A. Katz, M. W. Hosseini, *Chem. Rev.* **2000**, *100*, 3553 – 3590.
[2] K. Warnmark, J. A. Thomas, O. Heyke, J.-M. Lehn, *Chem. Commun.* **1996**, 701 – 702.
[3] R. D. Gillard, *Coord. Chem. Rev.* **1975**, *16*, 67 – 94.
[4] M. S. Henry, M. Z. Hoffman, *J. Am. Chem. Soc.* **1977**, *99*, 5201 – 5203; M. S. Henry, M. Z. Hoffman, *J. Phys. Chem.* **1979**, *83*, 618 – 625.
[5] A. Gameiro, R. D. Gillard, M. M. R. Bakhsh, N. H. Rees, *Chem. Commun*. **1996**, 2245 – 2246.
[6] N. Serpone, G. Ponterini, M. A. Jamieson, *Coord. Chem. Rev.* **1983**, *50*, 209 – 302; O. Farver, O. Monsted, G. Nord, *J. Am. Chem. Soc.* **1979**, *101*, 6118 – 6120; W. A. Wickramasinghe, P. H. Bird, M. A. Jamieson, N. Serpone, *J. Chem. Soc. Chem. Commun.* **1979**, 798 – 800.
[7] D. Dandrini, M. T. Gandolfi, L. Moggi, V. Balzani, *J. Am. Chem. Soc.* **1978**, *100*, 1463 – 1468; E. C. Constable, *Polyhedron* **1983**, *2*, 551 – 572, and references therein.
[8] E. C. Constable, *Metals and Ligand Reactivity*, VCH, Weinheim, **1996**, pp. 245 – 262.
[9] S. M.-F. Lo, S. S.-Y. Chui, L.-Y. Shek, Z.-Y. Lin, X.-X. Zhang, G.-H. Wen, I. D. Williams, *J. Am. Chem. Soc*. **2000**, *122*, 6293 – 6294.
[10] C. Harding, V. Mckee, J. Nelson, *J. Am. Chem. Soc*. **1991**, *113*, 9684 – 9685.
[11] M. E. Barr, P. H. Smith, W. E. Antholine, B. Spencer, *Chem. Commun*. **1993**, 1649 – 1652.
[12] R. P. Houser, V. G. Young, W. B. Tolman, *J. Am. Chem. Soc.* **1996**, *118*, 2101 – 2102.
[13] F. Neese, W. G. Zumft, W. E. Antholine, P. M. H. Kroneck, *J. Am. Chem. Soc.* **1996**, *118*, 8692 – 8699.
[14] D. D. LeCloux, R. Davydov, S. J. Lippard, *J. Am. Chem. Soc*. **1998**, *120*, 6810 – 6811.
[15] A mixture of phen (0.117 g) or bpy (0.102 g), H_2tp (0.041 g), NaOH (0.02 g), and water (10 mL) in the molar ratio 1.3:0.25:0.5:1100 was sealed in 23-mL Teflon reactor, which was heated in an oven at 160 °C for 144 h. No solid hydroxylated organic product was observed.
[16] Crystal data for **3**: monoclinic, space group $P2_1/n$, $M_r = 517.47$, $a = 10.651(8)$, $b = 6.180(4)$, $c = 15.079(13)$ Å, $\beta = 94.160(10)^\circ$, $V = 989.9(13)$ Å^3, $Z = 2$.
[17] S. Ferguson-Miller, G. T. Babcock, *Chem. Rev.* **1996**, *96*, 2889 – 2907; G. A. Baranovic, J. Coyle, C. G. Coates, J. J. McGarvey, V. McKee, J. Nelson, *Inorg. Chem.* **1998**, *37*, 3567 – 3574; S. Iwata, C. Ostermeier, B. Ludwig, H. Michel, *Nature* **1995**, *376*, 660 – 669; T. Tsukihara, H. Aoyama, E. Yamashita, T. Tomizaki, H. Yamaguchi, K. Shinzawa-Itoh, R. Nakahima, R. Yaono, S. Yoshikawa, *Science* **1996**, *272*, 1136 – 1144.
[18] General crystallographic information: $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). $T = 293$ K. Siemens *R*3m diffractometer, ω scan mode ($4 \le 2\theta \le 52^\circ$ for **1** and $4 \le 2\theta \le 52^\circ$ for **2**), solved with direct methods (SHELXS-97)[19] and refined with full-matrix least-squares (SHELXL-97).[20] CCDC-170016 and CCDC-170017 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
[19] G. M. Sheldrick, SHELXS-97, Program for Crystal Structure Solution, Göttingen University, Germany, **1997**.
[20] G. M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, Göttingen University, Germany, **1997**.

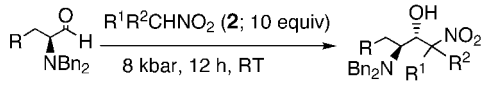
Diastereoselective Asymmetric Nitro-Aldol Reaction of α-Amino Aldehydes under High Pressure without Catalyst**

Yukihiro Misumi and Kiyoshi Matsumoto*

Dedicated to Professor Rolf Huisgen on the occasion of his 81st birthday

The Henry (nitro-aldol) reaction is one of the most valuable methods for carbon–carbon bond formation and its stereochemical control continues to be a challenge for organic chemists.[1–6] Specifically, an efficient synthesis of medicinally important intermediates such as phenylnorstatine through a diastereoselective catalytic (rare earth-Li-(*R*)-BINOL) asymmetric nitro-aldol reaction of optically active α-amino aldehydes with nitromethane has been reported.[4] Tetrabutylammonium fluoride has been also used, albeit with less success.[5] More recently, Corey and Zhang employed a rigid chiral quaternary ammonium salt for this reaction, which leads to a highly stereoselective synthesis of the HIV protease inhibitor amprenavir.[6] More generally, nitro-aldol adducts provide ready access to non-natural 3-amino-2-hydroxy acids and 1,3-diamino-2-hydroxy units, which are substructures of medicinally important compounds.[7, 8] One of us previously demonstrated that the Henry reaction is highly accelerated by pressure.[9] However, to our knowledge, no attempts have ever been made to perform a diastereoselective nitro-aldol reaction without a catalyst.[10] We envisaged that the amino group of optically active α-amino aldehydes might act as a base, and that such aldehydes would react with nitromethane under high pressure without a catalyst, thus offering a clean reaction system. Herein, we report the first example of the diastereoselective nitro-aldol reaction without any added catalyst.

N,*N*-Dibenzyl α-amino aldehydes **1** (Scheme 1) were chosen as a model substrate since they bear a free amino group and are relatively stable. The adducts may serve as versatile synthetic intermediates for the synthesis of non-natural



1a: R=Ph
1b: R=Me
1c: R=*i*Pr
1d: R=*i*Bu

2a: R^1=R^2=H
2b: R^1=Me, R^2=H
2c: R^1=R^2=Me

3a: R=Ph, R^1=R^2=H
3b: R=Ph, R1=Me, R^2=H
3c: R=Ph, R^1=R^2=Me
3d: R=Me, R^1=R^2=H
3e: R=*i*Pr, R^1=R^2=H
3f: R=*i*Bu, R^1=R^2=H

Scheme 1. Reaction of α-amino aldehydes **1** with nitroalkanes **2**.

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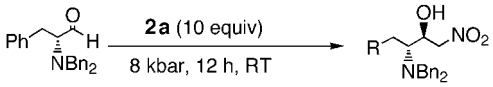
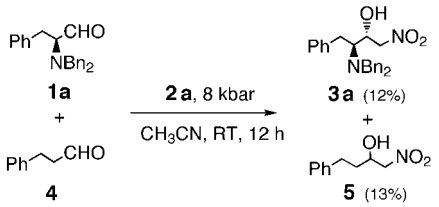
3-amino-2-hydroxy acids. First, we examined the nitro-aldol reaction of (*S*)-*N*,*N*-dibenzylphenylalaninal (**1a**) with nitromethane (**2a**) under high pressure without a catalyst. The starting optically active α-amino aldehyde (**1a**) was prepared from the corresponding (*S*)-phenylalanine in two steps according to the procedure of Corey and Zhang.[6] Under atmospheric pressure, **1a** did not react with **2a** (10 equiv) in acetonitrile. However, to our delight, the reaction did occur at 8 kbar (room temperature, 12 h) to give a mixture of diastereomers (2*R*,3*S*)-**3a** and (2*S*,3*S*)-*epi*-**3a** (83:17, 81%) (Scheme 1). The mixture was purified by means of chromatography on silica gel to give a pure sample of (2*R*,3*S*)-**3a** and (2*S*,3*S*)-*epi*-**3a**. The major product (2*R*,3*S*)-**3a** was identified by comparison with literature data (^{1}H and ^{13}C NMR spectroscopy).[6] The correct choice of solvent is crucial for an efficient diastereoselective nitro-aldol reaction (Table 1, entries 1–6). Among the solvents examined thus far, CH_3CN gave the best result; the yield of **3a** decreased in the order $CH_3CN > CH_3NO_2 > MeOH > CHCl_3 > CH_2Cl_2 >$ toluene, whereas the diastereoselectivity of **3a** decreased in the order $CH_3CN > MeOH > CH_3NO_2 > CHCl_3$. The optical purity was >99% *ee* in CH_3CN which indicates that no racemization occurred during the reaction.[11] (*S*)-*N*-(*tert*-Butoxycarbonyl)-phenylalaninal did not react with **2a** at 8 kbar, presumably because of the lower basicity of the amino group. The reaction is quite general (e.g. Table 1, entries 7–11). The pressure and the amount of **2a** did not significantly affect the diastereoselectivity, although the yields did increase under pressure. Notably, very high diastereoselectivity was observed in the reaction of **1a** with 2-nitropropane (**2c**) (Table 1, entry 11). The diastereoselective reaction of (*R*)-*N*,*N*-dibenzylphenylalaninal (**4**) with **2a** produced the corresponding *anti* nitroalcohol **5** as a single enantiomer. Thus there was also no racemization in this case (Scheme 2).



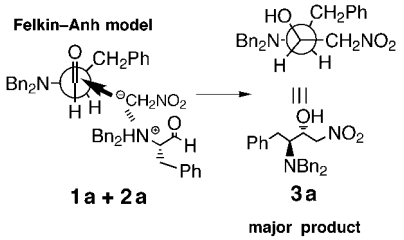
Scheme 2. Reaction of (*R*)-*N*,*N*-dibenzylphenylalaninal (**4**) with **2a**.

To elucidate a plausible mechanism (e.g. inter- or intramolecular), a control experiment was performed: the cross nitro-aldol reaction of **1a** (1.0 equiv) and 3-phenylpropanal (**4**) (1.0 equiv) with **2a** (1.0 equiv) was carried out under pressure (8 kbar) at room temperature, and provided a mixture of **3a** and **5** in yields of 12 and 13%, respectively (Scheme 3).



Scheme 3. Cross nitro-aldol reaction of (*S*)-*N*,*N*-dibenzylphenylalaninal (**1a**) and 3-phenylpropanal (**4**) with **2a**.

A plausible mechanism for this reaction involves the initial reaction of the base **1a** with **2a** to give a carbanion. Nucleophilic attack of the carbanion at the formyl carbon atom from the *Re* face gave predominantly the 2*R*,3*S* nitroalcohol, in agreement with the Felkin–Anh model (Scheme 4). This was further supported by the fact that the reaction of sterically hindered 2-nitropropane (**2c**) with **1a** was highly diastereoselective (Table 1, entry 11).



Scheme 4. Plausible mechanism for nitro-aldol reaction without catalyst.

In conclusion, we have presented the first diastereoselective nitro-aldol reaction without a catalyst. Although the diastereoselectivities do not rival those of reactions that require

Table 1. Diastereoselective nitro-aldol reaction of α-amino aldehydes **1** with nitroalkanes **2** without catalyst under high pressure.[a]

Entry	Aldehyde	Nitroalkane	Solvent	Product	Yield [%][b]	**3**/*epi*-**3**	*ee* (**3**) [%]
1	**1a**	**2a**	CH_3CN	**3a**	81	83:17[c]	>99
2	**1a**	**2a**	CH_3NO_2	**3a**	69	74:26	98
3	**1a**	**2a**	CH_3OH	**3a**	29	78:22	96
4	**1a**	**2a**	$CHCl_3$	**3a**	27	71:29	89
5	**1a**	**2a**	CH_2Cl_2	**3a**	3	–[d]	
6	**1a**	**2a**	toluene	**3a**	trace	–[d]	
7	**1a**	**2b**	CH_3CN	**3b**	78	59:25:9:7[c]	
8	**1b**	**2a**	CH_3CN	**3d**	67	71:29[c]	99
9	**1c**	**2a**	CH_3CN	**3e**	66 (11)	89:11[e]	96[f]
				3e	79[g]	86:14[e]	96[f]
10	**1d**	**2a**	CH_3CN	**3f**	70	73:27[e]	90[f]
				3f	83 (4)[h]	85:15[e]	91[f]
11	**1a**	**2c**	CH_3CN	**3c**	68 (17)	99:<1	92

[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 mmol), solvent (3 mL), 8 kbar, 12 h, room temperature. [b] Yield of isolated product, based on **1**. Values in parentheses are the amounts of **1** recovered (%). [c] Separable by chromatography. [d] Not determined. [e] The ratio was determined by means of ^{13}C NMR spectroscopy. [f] The *ee* value was not accurate because of partial overlap of peaks in chiral HPLC analysis. [g] Reaction time: 24 h. [h] Reaction conditions: **1d** (0.4 mmol), **2a** (4.0 mmol), acetonitrile (2.7 mL), 8 kbar, 12 h, room temperature.

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highly sophisticated catalysts,[4, 6] the experimental procedure is extremely simple, because there is no need to quench the catalyst (see Experimental Section). Partial racemization that would result from using a catalyst is avoided. Furthermore, the use of toxic and expensive catalysts that are difficult to prepare is not necessary. This strategy, that is, pressure-mediated substrate-catalyzed reactions might also be amenable to other reactions (Michael, Mannich, Baylis–Hillman), which are accelerated by pressure.[12] Further work along these lines is in progress.

Experimental Section

3a: A solution **1a** (66 mg, 0.2 mmol) and **2a** (108 μL, 2.0 mmol) in acetonitrile (3 mL) was placed in a sealed Teflon vessel. The reaction mixture was stirred at room temperature under atmospheric pressure until most of **1a** had dissolved (5 min). The tube was placed in a high-pressure reactor, and pressurized to 8 kbar at 25 °C. After 12 h, the pressure was released, and the reaction mixture was transferred from the Teflon vessel into a flask. The solvent was removed under reduced pressure. The crude products were purified by means of column chromatography (SiO_2, hexane/Et_2O 10:1) to give the *anti* isomer **3a** (52 mg, 67 %) and the *syn* isomer (11 mg, 14 %) (total yield 81 %, *anti*/*syn* 83:17). The enantiomeric excess was determined by means of HPLC analysis on DAICEL CHIRALCEL OJ.

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[1] For the most recent reviews on the Henry condensation, see: a) G. Rosini in *Comprehensive Organic Synthesis, Vol. 2* (Eds.: B. M. Trost, I. Fleming, C. H. Heathcock), Pergamon, Oxford, **1991**, pp. 321–340; b) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915, and references therein.

[2] For recent examples of non-asymmetric nitro-aldol reactions based on achiral catalysts and promoters, see: D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607; S. W. Youn, Y. H. Kim, *Synlett* **2000**, 880; R. Ballini, G. Bosica, M. Parrini, *Chem. Lett.* **1999**, 1105; T. Saiki, Y. Aoyama, *Chem. Lett.* **1999**, 797; V. J. Bulbule, V. H. Deshpande, S. Velu, A. Sudalai, S. Sivasankar, V. T. Sathe, *Tetrahedron* **1999**, *55*, 9325; G. Jenner, *New J. Chem.* **1999**, *23*, 525; H. M. S. Kumar, B. V. Subba Reddy, J. S. Yadav, *Chem. Lett.* **1998**, 637; I. Morao, F. Cossio, *Tetrahedron Lett.* **1997**, *38*, 6461; R. S. Varma, R. Dahiya, S. Kumar, *Tetrahedron Lett.* **1997**, *38*, 5131; D. Simoni, F. P. Invidiata, S. Manfredini, R. Ferroni, I. Lampronti, G. P. Pollini, *Tetrahedron Lett.* **1997**, *38*, 2749; R. Ballini, G. Bosica, *J. Org. Chem.* **1997**, *62*, 425; R. Ballini, G. Bosica, P. Forconi, *Tetrahedron* **1996**, *52*, 1677; S. Kiyooka, T. Tsutsui, H. Maeda, Y. Kaneko, K. Isobe, *Tetrahedron Lett.* **1995**, *36*, 6531; F. A. Luzzio, R. W. Ficth, *Tetrahedron Lett.* **1994**, *35*, 6013; U. Costatino, M. Curini, F. Marmottini, O. Rosati, E. Pisani, *Chem. Lett.* **1994**, 2218; H. Sasai, S. Arai, M. Shibasaki, *J. Org. Chem.* **1994**, *59*, 2661; R. Ballini, G. Bosica, *J. Org. Chem.* **1994**, *59*, 5466.

[3] For recent examples of (diastereoselective) asymmetric nitro-aldol reactions, see: A. V. Davis, M. Driffield, D. K. Smith, *Org. Lett.* **2001**, *3*, 3075; K. R. Knudsen, T. Risgaard, N. Nishiwaki, K. V. Gothelf, A. K. Jorgensen, *J. Am. Chem. Soc.* **2001**, *123*, 5843; A. Menzel, R. Ohrlein, H. Griesser, V. Wehner, V. Jager, *Synthesis* **1999**, 1691; E. Takaoka, N. Yoshikawa, Y. M. A. Yamada, H. Sasai, M. Shibasaki, *Heterocycles* **1997**, *46*, 157; J. Oshida, M. Okamoto, S. Azuma, T. Tanaka, *Tetrahedron: Asymmetry* **1997**, *8*, 2579; S. Hanessian, P. V. Devasthale, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2201; K. Iseki, S. Oishi, H. Sasai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 9081; P. Magnus, P. Pye, *J. Chem. Soc. Chem. Commun.* **1995**, 1933; H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 6656; H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 7388; A. P. Davis, K. J. Dempsey, *Tetrahedron: Asymmetry* **1995**, *6*, 2829; T. Nataka, T. Komatsu, K. Nagasawa, H. Yamada, T. Takahashi, *Tetrahedron Lett.* **1994**, *35*, 8225; R. Chinchilla, C. Najera, P. Sanchez-Agullo, *Tetrahedron: Asymmetry* **1994**, *5*, 1393; H. Sasai, Y. M. A. Yamada, T. Suzuki, M. Shibasaki, *Tetrahedron* **1994**, *50*, 12313; H. Sasai, N. Itoh, T. Suzuki, M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 855; H. Sasai, T. Suzuki, N. Itoh,; M. Shibasaki, *Tetrahedron Lett.* **1993**, *34*, 851; H. Sasai, T. Suzuki, S. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4.

[4] H. Sasai, W.-S. Kim, T. Suzuki, M. Shibasaki, M. Mitsuda, J. Hasegawa, T. Ohashi, *Tetrahedron Lett.* **1994**, *35*, 6123, see also references in [3] from this group.

[5] S. Hanessian, P. V. Devasthale, *Tetrahedron Lett.* **1996**, *37*, 987.

[6] E. J. Corey, F.-Y. Zhang, *Angew. Chem.* **1999**, *111*, 2057; *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.

[7] M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 15.

[8] M. T. Reetz, M. W. Drews, A. Schmitz, *Angew. Chem.* **1987**, *99*, 1186; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1141.

[9] K. Matsumoto, *Angew. Chem.* **1984**, *96*, 599; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 617.

[10] For a review on stereoselective reactions under high pressure, see: G. Jenner, *Tetrahedron* **1997**, *53*, 2669.

[11] The effect of pressure and solvent on the diastereoselectivity of reactions under high pressure have been discussed extensively by Tietze and co-workers; see: M. Buback, K. Gerke, C. Ott, L. F. Tietze, *Chem. Ber.* **1994**, *127*, 2241; L. F. Tietze, M. Henrich, I. Rothert, G. Kuchta, M. Buback, *Pol. J. Chem.* **1997**, *71*, 1749; M. Buback, G. Kuchta, A. Niklaus, M. Henrich, I. Rothert, L. F. Tietze, *Liebigs Ann.* **1996**, 1151; L. F. Tietze, M. Henrich, A. Niklaus, M. Buback, *Chem. Eur. J.* **1999**, *5*, 297.

[12] For reviews of organic reactions under high pressure from our laboratory, see: *Organic Reactions at High Pressures* (Eds.: K. Matsumoto, R. M. Acheson), Wiley, New York, **1991**; M. Ciobanu, K. Matsumoto, *Liebigs Ann.* **1997**, 623; K. Matsumoto, M. Kaneko, H. Katsura, N. Hayashi, T. Uchida, R. M. Acheson, *Heterocycles* **1998**, *47*, 1135.

Sigmatropic Shiftamers: Fluxionality in Broken Ladderane Polymers**

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Construction principles: Consider the hypothetical ladder polymer **1**-"[∞]-ladderane."[1, 2] A formal [2+2] cycloreversion would lead to **2** in which a local "defect," consisting of two parallel π bonds, is formed. Cope rearrangement via a boatlike transition structure would give **2′**, which is, of course, equivalent to **2** (Scheme 1). Continued indefinitely, this process would lead to a pair of double bonds running down the polymer chain.

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Supporting information for this article (Coordinates and energies for computed structures from Scheme 2, as well as structures involved in the Cope rearrangements of **6** and **7**.) is available on the WWW under http://www.angewandte.com or from the authors.