

599.53, $a = 10.465(8)$, $b = 15.279(8)$, $c = 15.425(12)$ Å, $\beta = 104.60(5)^\circ$, $V = 2387(3)$ Å³, $Z = 4$, $\rho_{\text{calcd}} = 1.668$ 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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Diastereoselective Asymmetric Nitro-Aldol Reaction of α -Amino Aldehydes under High Pressure without Catalyst**

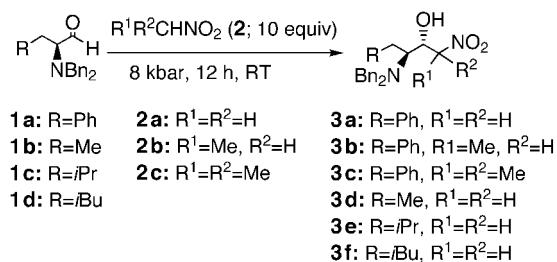
Yukihiro Misumi and Kiyoshi Matsumoto*

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

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- [15] A mixture of phen (0.117 g) or bpy (0.102 g), H₂tp (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, $\beta = 94.160(10)^\circ$, $V = 989.9(13)$ Å³, $Z = 2$.
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- [18] General crystallographic information: MoK α radiation ($\lambda = 0.71073$ Å). $T = 293$ K. Siemens R3m diffractometer, ω scan mode ($4 \leq 2\theta \leq 52^\circ$ for **1** and $4 \leq 2\theta \leq 52^\circ$ 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).
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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

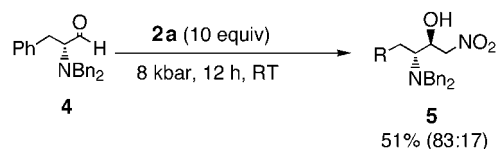


Scheme 1. Reaction of α -amino aldehydes **1** with nitroalkanes **2**.

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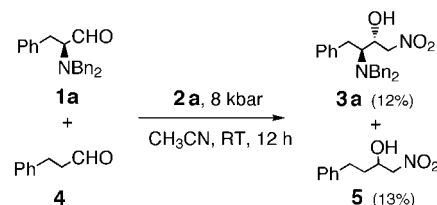
[**] This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors are also grateful to the Ministry of Education, Culture, Sports, Science, and Technology, Japan for the high-field NMR instruments (JEOL JNM-A500 and JNM-EX270) from the special fund to K.M. (1992).

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 (*2R,3S*)-**3a** and (*2S,3S*)-*epi*-**3a** (83:17, 81 %) (Scheme 1). The mixture was purified by means of chromatography on silica gel to give a pure sample of (*2R,3S*)-**3a** and (*2S,3S*)-*epi*-**3a**. The major product (*2R,3S*)-**3a** was identified by comparison with literature data (¹H and ¹³C 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, CH₃CN gave the best result; the yield of **3a** decreased in the order CH₃CN > CH₃NO₂ > MeOH > CHCl₃ > CH₂Cl₂ > toluene, whereas the diastereoselectivity of **3a** decreased in the order CH₃CN > MeOH > CH₃NO₂ > CHCl₃. The optical purity was > 99 % *ee* in CH₃CN 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).



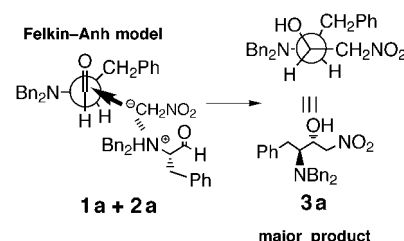
Scheme 2. Reaction of (*R*)-*N,N*-dibenzylphenylalaninal (**4**) with **2a**.

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 *2R,3S* 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]	<i>3/epi-3</i>	<i>ee</i> (3) [%]
1	1a	2a	CH ₃ CN	3a	81	83:17 ^[c]	> 99
2	1a	2a	CH ₃ NO ₂	3a	69	74:26	98
3	1a	2a	CH ₃ OH	3a	29	78:22	96
4	1a	2a	CHCl ₃	3a	27	71:29	89
5	1a	2a	CH ₂ Cl ₂	3a	3	— ^[d]	—
6	1a	2a	toluene	3a	trace	— ^[d]	—
7	1a	2b	CH ₃ CN	3b	78	59:25:9:7 ^[c]	—
8	1b	2a	CH ₃ CN	3d	67	71:29 ^[c]	99
9	1c	2a	CH ₃ CN	3e	66 (11)	89:11 ^[c]	96 ^[f]
				3e	79 ^[g]	86:14 ^[c]	96 ^[f]
10	1d	2a	CH ₃ CN	3f	70	73:27 ^[c]	90 ^[f]
				3f	83 (4) ^[h]	85:15 ^[c]	91 ^[f]
11	1a	2c	CH ₃ CN	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 ¹³C 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.

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 μ L, 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 (SiO₂, hexane/Et₂O 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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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.