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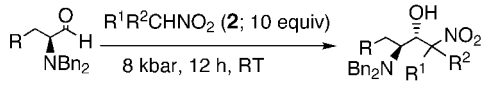
Diastereoselective Asymmetric Nitro-Aldol Reaction of α-Amino Aldehydes under High Pressure without Catalyst**

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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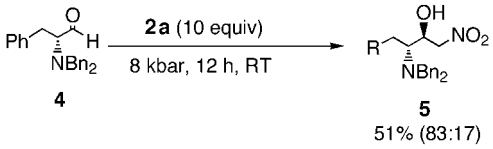
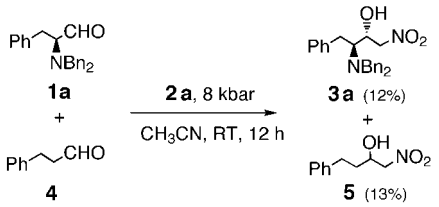
3-amino-2-hydroxy acids. First, we examined the nitro-aldol reaction of (*S*)-*N*,*N*-dibenzylphenylalaninal (**1a**) with nitromethane (**2a**) under high pressure without a catalyst. The starting optically active α-amino aldehyde (**1a**) was prepared from the corresponding (*S*)-phenylalanine in two 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).



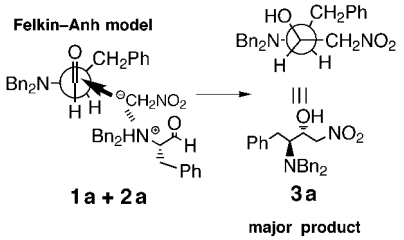
Scheme 2. Reaction of (*R*)-*N*,*N*-dibenzylphenylalaninal (**4**) with **2a**.

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

Tabelle 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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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.