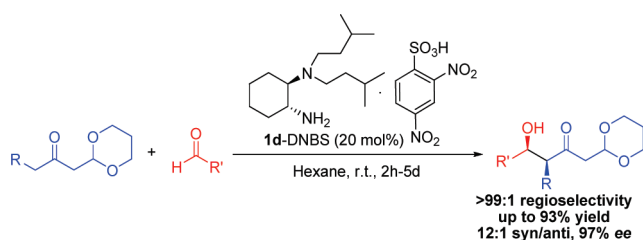


Asymmetric Direct Aldol Reactions of Acetoacetals Catalyzed by a Simple Chiral Primary AmineSanzhong Luo,^{*,†} Yupu Qiao,[†]
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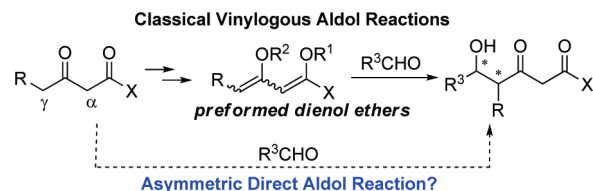
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An asymmetric direct aldol reaction of acetoacetals is described. Under the catalysis of a simple chiral primary amine, the direct aldol reactions of acetoacetals occur exclusively on the γ -position to give vinylogous-type aldol products with high diastereo- and enantioselectivity.

The asymmetric vinylogous aldol (AVA) reaction is a versatile C–C bond forming reaction that has been widely utilized in the synthesis of polyketides natural products.¹ In contrast to the well-developed asymmetric direct aldol reactions,² for which a number of asymmetric catalysts including both chiral transition metal catalysts³ and organocatalysts⁴ have been developed, the success of the AVA reaction has been largely limited to the use of preformed and activated dienol ether donors (i.e., Mukaiyama vinylogous aldol

reactions),^{1b} derived from either β -dicarbonyl or α,β -unsaturated carbonyl compounds.⁵ Asymmetric direct approaches for these reactions are highly valuable in terms of atom economy.⁶ However, such a reaction with high regio-, diastereo-, and enantioselectivity remains unknown to date. In addition, the range of vinylogous aldol donors has been primarily limited to the ester-derived dienol ethers. Examples with ketone or aldehyde counterparts are scarce and there is no report on the use of β -keto aldehyde in asymmetric vinylogous aldol reactions so far as we are aware.⁷

SCHEME 1

The development of asymmetric direct aldol reactions of β -keto aldehyde possesses a series of challenges. Besides difficulties in controlling both diastereo- and enantioselectivity, there are also issues such as chemoselectivity and regioselectivity that requires differentiation of the two carbonyl groups and selective reaction on the γ -position rather than the typical α -position as is usually observed in the classical Knoevenagel reaction with similar substrates (Scheme 1). Herein, we presented the first direct aldol reactions of acetoacetals with high regio-, diastereo-, and enantioselectivity. This process was made possible by utilizing the recently appearing chiral primary aminocatalysis,⁸ and our previous finding that simple chiral primary amines such as **1** (Table 1) were able to promote a range of direct aldol reactions of functionalized aliphatic ketones beyond the reach of typical secondary amines.⁹

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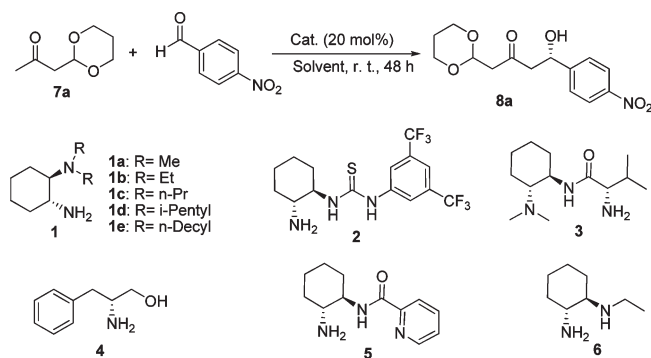
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TABLE 1. Selected Screening and Optimization Data^a

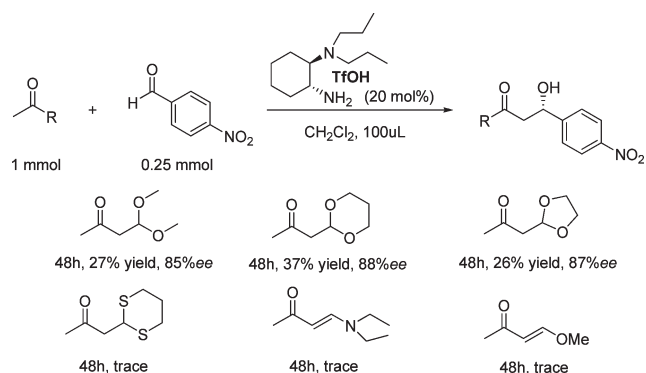
entry	cat.	solvent	yield (%) ^b	ee (%) ^c
1	1a /DNBS	CH ₂ Cl ₂	31	67
2	1b /DNBS	CH ₂ Cl ₂	26	74
3	1c /DNBS	CH ₂ Cl ₂	50	83
4	1d /DNBS	CH ₂ Cl ₂	49	86
5	1e /DNBS	CH ₂ Cl ₂	8	27
6	2	CH ₂ Cl ₂	5	42
7	3 /DNBS	CH ₂ Cl ₂	77	racemic
8	4	CH ₂ Cl ₂	15	10
9	5 /DNBS	CH ₂ Cl ₂	trace	
10	6 /DNBS	CH ₂ Cl ₂	63	19
11	1d /DNBS	H ₂ O	34	90
12	1d /DNBS	DMSO	35	87
13	1d /DNBS	DMF	24	88
14	1d /DNBS	Et ₂ O	73	86
15	1d /DNBS	hexane	79	89
16 ^d	1d /DNBS	hexane	85	90

^aThe reactions were carried out with 0.25 mmol of aldehyde, 1.0 mmol of **7a** in 100 μ L of solvent at rt. ^bisolated yield. ^cDetermined by chiral HPLC. ^d5 mol % of *m*-nitrobenzoic acid was added. DNBS: 2,4-dinitrobenzenesulfonic acid.

Acetoacetals, the common precursors for Danishefsky's dienes,¹⁰ were initially selected as the targeted direct aldol donors. It was envisioned that a properly protected acetal group would address the chemo- and regioselectivity issues via both electronic and steric tuning. To our delight, cyclic acetoacetals derived from propane-1,3-diol such as **7a** were identified, after trials, as the optimal donors affording a facile and clean reaction with exclusively γ -regioselectivity and good stereoselectivity. Other derivatives of **7a** such as the dimethyl acetal, dithiane analogue, and vinylogous amide or ester demonstrated lower or even no reactivity (Scheme 2).

The reaction of acetoacetal **7a** and *p*-nitrobenzaldehyde was selected as a model reaction and some selected screening and optimization data were collected in Table 1. Among a range of chiral primary amines examined, primary–tertiary vicinal diamines such as **1** were found to be the optimal catalysts for this type of aldol reaction (see the SI for full details on screening and optimization). Other types of primary amines such as primary amine-thiourea **2** or primary amine-amide **3**, L-phenylalaninol **4**, primary amine-pyridine **5**, or primary–secondary diamines **6** were either inactive or with low stereoselectivity (Table 1, entries 6–10), highlighting the critical nature of primary–tertiary vicinal diamines for direct aldol catalysis. Overall, the combination of a new chiral primary amine **1d** and 2,4-dinitrobenzenesulfonic acid was identified to be the optimal catalytic system producing

SCHEME 2. Screening of Vinylogous Donors



49% yield and 86% ee. Subsequent optimization indicated a dramatic solvent effect. While the reactions in polar solvents such as H₂O and DMSO were generally sluggish affording low yields (Table 1, entries 11–13), the use of nonpolar solvents such as Et₂O and hexane provided significant rate enhancement (Table 1, entries 14 and 15), of which hexane was found to be the optimal solvent. Moreover, the reaction in hexane could be further improved by the addition of a second weak acid additive, *m*-nitrobenzoic acid (Table 1, entry 16).^{9a,11} Under these optimal conditions, the reaction of **7a** provided 85% yield and 90% ee.

With the optimal conditions in hand, the scope of the direct aldol reaction was next explored with respect to both the acetoacetal donors and aldehyde acceptors in the presence of **1d**/DNBS. The reactions of **7a** with various aromatic aldehydes gave the desired vinylogous aldol products in moderate to excellent yields with high enantioselectivity (Table 2, entries 1–8). Notably, the reactions worked well with γ -substituted acetoacetal donors such as **7b–d**. In cases of **7b**, the reactions occurred regioselectively on the γ -position to give the desired vinylogous aldol products in good yields favoring the *syn*-diastereomers with excellent enantioselectivity (Table 2, entries 9–11). Remarkably faster reactions were achieved with γ -hydroxyl acetoacetals **7d**. In these reactions, the *syn*-diol vinylogous aldol products **11–13** were obtained in high yields with excellent diastereo- (*syn*/*anti* 5:1–12:1) and enantioselectivity (70–96% ee) (Table 2, entries 13–18). It is noted that the reactions also worked well with some activated carbonyl compounds such as 2,2-dimethoxyacetaldehyde and ethyl glyoxylate (Table 2, entries 17 and 18). In addition, the observation of improved reaction rate and stereoselectivity with **7d** over that with benzyl protected **7c** suggested a favorable participation of the free hydroxyl group in the reaction coordinate via intra/inter hydrogen-bonding interactions. A similar effect has also been observed in the direct aldol reactions of α -hydroxyketones.^{10b} Last, a large-scale reaction (2 mmol) has also been tried to give consistent results, demonstrating the practicality of this reaction (Table 2, entry 2).

In all cases examined, the reaction occurred dominantly on the γ -position and no α -regioisomers were observed. Furthermore, the reactions were generally clean even in cases with deactivated aldehydes though long reaction times were normally employed. No acetal ring-opening products were

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(11) In the presence of 25 mol % of DNBS, the reaction gave 76% yield and 89% ee.

TABLE 2. Asymmetric Direct Aldol Reactions of Acetoacetals^a

7a: R = H; 7c: R = BnO⁻;
7b: R = Me; 7d: R = OH

entry	donor	R'	time	yield (%) ^b	dr ^c	ee (%) ^d
1	7a	4-NO ₂ Ph	48 h	8a/85		90
2 ^e	7a	4-NO ₂ Ph	48 h	8a/81		90
3	7a	2-NO ₂ Ph	72 h	8b/91		86
4	7a	3-NO ₂ Ph	72 h	8c/73		84
5	7a	4-CNPh	72 h	8d/64		87
6	7a	2-ClPh	4 d	8e/77		84/95 ^f
7	7a	2-Napt	5 d	8f/27		86
8	7a	2-BrPh	4 d	8g/66		85
9	7b	4-NO ₂ Ph	4 d	9a/74	3:1	97
10	7b	3-NO ₂ Ph	4 d	9b/69	3:1	97
11	7b	4-CNPh	5 d	9c/60	4:1	93
12	7c	4-NO ₂ Ph	48 h	10a/84	2:1	90
13	7d	4-NO ₂ Ph	6 h	11a/92	9:1	96
14	7d	2-NO ₂ Ph	8 h	11b/90	9:1	95
15	7d	4-CNPh	6 h	11c/93	9:1	94
16	7d	4-CF ₃ Ph	2 h	11d/92	12:1	96
17 ^g	7d	CH(OMe) ₂	24 h	12/72	10:1	86
18	7d	CO ₂ Et	72 h	13/54	5:1	70

^aThe reactions were carried out with 0.25 mmol of aldehyde, 1.0 mmol of 7a, and *m*-nitrobenzoic acid (5 mol %) in 100 μ L of hexane at rt.

^bIsolated yield. ^cDetermined by ¹H NMR. ^dDetermined by chiral HPLC.

^e2 mmol of *p*-nitrobenzaldehyde, 8 mmol of 7a, and *m*-nitrobenzoic acid (5 mol %) in 800 μ L of hexane at rt. ^fee after one recrystallization.

^g1 equiv of anhydrous Na₂SO₄ was added. DNBS: 2,4-dinitrobenzenesulfonic acid.

observed under the present conditions. Unfunctionalized aliphatic aldehydes are currently not workable substrates in the present reaction due to their low activity and the accompanying by-pathways. The reactions of α,β -unsaturated aldehyde also showed low activity in the present reaction. The absolute and relative configurations of the vinylogous aldol products, as determined unambiguously by X-ray crystallography of adduct 8e (see Supporting Information for details)¹² and NMR analysis of compound 14b, respectively, suggested the reaction would occur through *Z*-enamine-type transition state with *Re*-Si attack to the aldehyde, being consistent with the model proposed previously (Figure 1).⁹

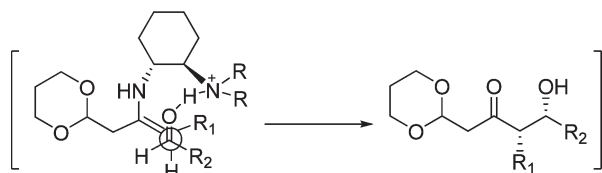
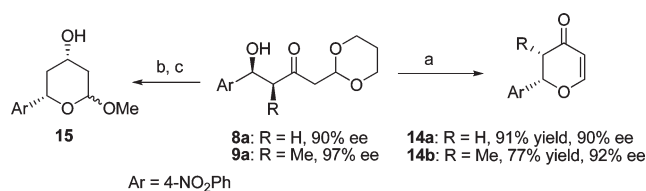


FIGURE 1. The proposed transition state.

Given the multifunctionalized nature of vinylogous aldol products, versatile synthetic applications are conceivable. As a demonstration, the products 8a and 9a could be readily transformed into pyran-4-one 14 and tetrahydropyranol 15 in excellent yields and high enantioselectivities (Scheme 3).

(12) CCDC 749280 contains the supplementary crystallographic data for compound 8e. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data-request/cif.

SCHEME 3. Synthetic Applications of the Aldol Products^a

^aReagents and conditions: (a) TFA, CH₂Cl₂, rt, 6 h; (b) 8a, NaBH₄, THF, rt, 82%, anti/syn = 3:1; (c) TFA, MeOH, 87%, β/α = 1:2.

In summary, we have developed unprecedented regio-, diastereo-, and enantioselective direct aldol reactions of acetoacetals catalyzed by a simple chiral primary amine. The current reaction represents a rare example of direct aldol reaction of β -ketoaldehyde affording vinylogous-type aldol adducts.

Experimental Section

General Experimental Procedure. To a given anhydrous ketone (1 mmol) in 0.1 mL of hexane was added the corresponding aldehyde (0.25 mmol), *m*-nitrobenzoic acid (0.0125 mmol), and catalyst 1d-DNBS (0.05 mmol) (prepared in CH₂Cl₂ with 1 equiv of 1d and 1 equiv of DNBS). The resulting mixture was stirred at room temperature for the indicated reaction time and then purified by flash chromatography on silica gel to afford the pure products.

8a: starting from *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) to give 8a as a colorless solid (63 mg, 85% yield). [α]_D²⁰ -13.6 (*c* 1.0, CH₃OH). IR (KBr, cm⁻¹) 3402, 3356, 3044, 2979, 2951, 2921, 2857, 1720, 1600.63, 1519, 1469, 1458, 1352, 860, 815. ¹H NMR (300 MHz, CDCl₃) δ 8.20 (2H, d, *J* = 8.7 Hz), 7.54 (2H, d, *J* = 8.7 Hz), 5.27 (1H, s), 4.95 (1H, t, *J* = 5.1 Hz), 4.09 (2H, dd, *J* = 10.8 Hz, 5.1 Hz), 3.78 (2H, m), 3.66 (1H, s), 2.91 (2H, t, *J* = 7.5 Hz), 2.76 (2H, d, *J* = 5.1 Hz), 2.14–1.97 (1H, m), 1.37 (1H, dt, *J* = 13.5 Hz, 1.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 207.1, 150.1, 147.3, 126.5, 123.7, 98.5, 68.9, 67.0, 52.2, 48.9, 25.4. HRMS calcd for C₁₄H₁₇NO₆⁺ 295.1056, found 295.1060. Enantiomeric excess was determined to be 90% ee (determined by HPLC on a Chiralpak AD-H column, 254 nm, 2-propanol/hexane 20:80, 25 $^{\circ}$ C, 0.5 mL/min, *t*_R = 37.13 min (major), *t*_R = 41.17 min (minor)).

9a: starting from *p*-nitrobenzaldehyde (38 mg, 0.25 mmol) to give 9a as a pale yellow solid (57.2 mg, 74% yield). [α]_D²⁰ +16.4 (*c* 1.0, CH₃OH). IR (KBr, cm⁻¹) 3455, 3081, 2964, 2925, 2857, 1712, 1604, 1519, 1347, 1133, 854. ¹H NMR (300 MHz, CDCl₃) δ 8.14 (2H, d, *J* = 8.7 Hz), 7.44 (2H, d, *J* = 8.7 Hz), 5.26 (1H, s), 4.92 (1H, t, *J* = 5.2 Hz), 4.06–4.01 (2H, m), 3.73–3.69 (2H, m), 3.35 (1H, br s), 2.88–2.67 (3H, m), 2.09–1.98 (1H, m), 1.31 (1H, dt, *J* = 13.5, 1.20 Hz), 0.90 (3H, d, *J* = 7.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 211.3, 149.0, 147.2, 126.7, 123.5, 99.0, 71.4, 67.1, 53.1, 47.0, 25.4, 8.5. HRMS calcd for C₁₅H₁₉NO₆Na⁺ 332.1110, found 332.1105. Enantiomeric excess was determined to be 97% ee (syn) (determined by HPLC on a Chiralpak AD-H column, 254 nm, 2-propanol/hexane 10:90, 25 $^{\circ}$ C, 0.8 mL/min, *t*_R = 40.44 min (minor), *t*_R = 45.30 min (major)).

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Supporting Information Available: Experimental details, characterizations of new compounds, and X-ray crystallography of 8e. This material is available free of charge via the Internet at <http://pubs.acs.org>.