

Direct Asymmetric Organocatalytic Michael Reactions of α,α -Disubstituted Aldehydes with β -Nitrostyrenes for the Synthesis of Quaternary Carbon-Containing Products

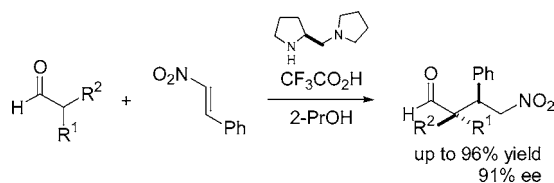
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ABSTRACT



Direct asymmetric catalytic Michael reactions have been performed using chiral-amine/acid bifunctional catalysts. Performed with 0.3 equiv of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine and 0.3 equiv of trifluoroacetic acid as the catalyst, the reaction of α,α -dialkylaldehydes with (*E*)- β -nitrostyrene provided the α,α -dialkyl Michael products in up to 96% yield with up to 91% ee. With respect to enantioselectivity, L-proline was a poor catalyst of this class of Michael reactions.

The organocatalytic direct asymmetric Michael reaction is one of the most powerful and efficient methods for carbon–carbon bond formation to provide enantiomerically enriched nitroalkanes.^{1,2} Use of α,α -disubstituted aldehydes should provide direct access to Michael products possessing an all-carbon quaternary stereocenter. Although reactions of unmodified α -monosubstituted aldehydes or ketones have been described,³ there are few reports of the use of α,α -disubstituted aldehydes.^{3j,q,4,5} The synthesis of all-carbon

quaternary stereogenic centers is considered a challenging topic in asymmetric synthesis. As detailed in this communication, we investigated the direct Michael reaction of α,α -disubstituted aldehyde donors with (*E*)- β -nitrostyrenes acceptors to generate all-carbon quaternary stereogenic centers.

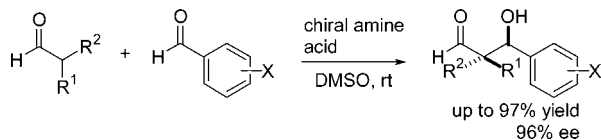
We have recently described organocatalytic direct asymmetric aldol reactions using α,α -disubstituted aldehydes as aldol donors to synthesize β -hydroxyaldehydes with stereo-

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(1) Enamine-based organocatalytic Michael reactions: (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441–4444. (b) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737–3740. (c) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611–3614. (d) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559–2561. (e) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151–4157. (f) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (g) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509–1521.

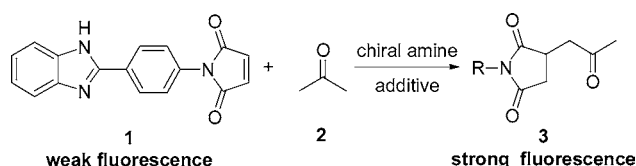
(2) Iminium-based organocatalytic Michael reactions: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370–4371. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173. (c) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331–8338. (d) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894–7895. (e) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192–1194. (f) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955–4957. (g) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661–665. (h) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272–1277.

Scheme 1. Direct Cross-Aldol Reaction of α,α -Disubstituted Aldehyde



genic quaternary carbon centers (Scheme 1).^{4,5} To rapidly screen catalysts and reaction conditions for the aldol reactions, we have developed a fluorescent detection system using fluorogenic maleimide **1** (Scheme 2).⁶

Scheme 2. Fluorescent Detection Systems for C–C Bond Formation



The results obtained using this fluorescent screening methodology were directly correlated with those obtained in the actual aldol reactions and allowed for the optimization of this reaction. Chiral-diamine/trifluoroacetic acid (TFA)⁴ and pyrrolidine/acetic acid combination catalysts⁵ were shown to be highly effective in the aldol reaction.⁷ Aldol products were obtained with high enantioselectivities when (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/TFA was used as the catalyst. Therefore, we have taken advantage of the results of the fluorescent screening^{4,6} and have focused on the use of amines and the selected amine/acid combination as catalysts for the actual Michael reaction.

First we examined amine catalysts **4–12** (Figure 1) with or without acid for the reaction of isobutyraldehyde (**13a**)

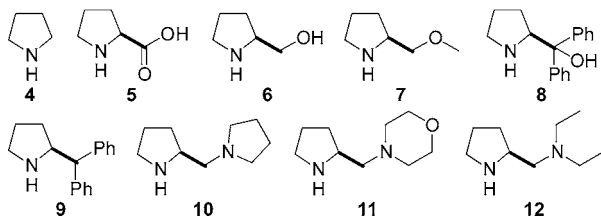
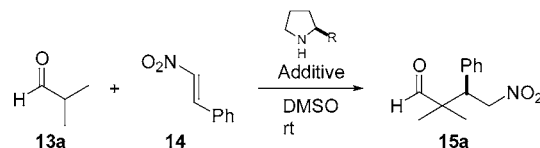


Figure 1. Various amine catalysts.

and β -nitrostyrene (**14**) to afford the Michael product **15a** possessing a quaternary carbon atom. The results are shown in Table 1. When pyrrolidine/acetic acid was used as the catalyst, **15a** was obtained in good yield (84%) after 12 h (entry 1). The reaction with L-proline proceeded smoothly and afforded **15a** in good yield (87%), but the enantiose-

Table 1. Organocatalyzed Direct Michael Reactions for the Synthesis of Quaternary Carbon

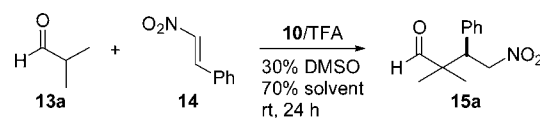


entry	catalyst ^a	additive (equiv)	time (h)	yield (%)	ee ^b (%)
1 ^c	4	AcOH (1.5)	12	84	
2	5		48	87	23
3	6		48	79	63
4	7		48	72	17
5	8	AcOH (0.3)	96	<1	65
6	9	AcOH (0.3)	96	82	21
7	10		0.5	90	50
8	10	TFA (0.3)	24	96	61
9	11	TFA (0.3)	96	19	73
10	12	TFA (0.3)	96	4	75

^a Catalyst structures are shown in Figure 1. ^b Determined by chiral HPLC using a CHIRALPAK AS-H column. ^c Isobutyraldehyde (1.2 equiv) was used.

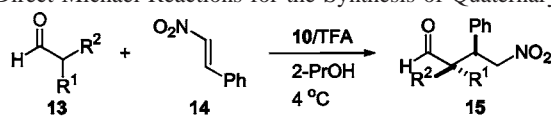
lectivity was unacceptably low (23% ee) (entry 2). L-Proline (**6**) was a good catalyst, providing the desired product in 79% yield and 63% ee (entry 3). Use of catalysts with bulky substituents (catalysts **8** and **9**) resulted in either poor yield or poor enantioselectivity (entries 5 and 6). (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (**10**)/TFA (0.3 equiv) afforded **15a** in an excellent yield with a 61% ee (entry 8). Addition of acid improved the enantioselectivity (entry 7 vs 8) as observed in aldol reactions, but the improvement was moderate.⁴ The combination of diamines **11**/TFA or **12**/TFA

Table 2. Solvent Effect for Organocatalyzed Direct Michael Reactions



entry	solvent	yield (%)	ee (%) ^a
1	MeCN	10	56
2	MeOH	b	57
3	CH ₂ Cl ₂	25	60
4	DMSO	96	61
5	DMF	18	61
6	2-PrOH	93	63
7	toluene	17	65
8	CHCl ₃	67	66
9	Et ₂ O	96	68
10	1,4-dioxane	11	70
11	THF	35	71
12	[bmim]PF ₆	23	73
13	[bmim]BF ₄	37	75
14 ^c	100% 2-PrOH, 4 °C	87	80

^a Determined by chiral HPLC using a CHIRALPAK AS-H column. ^b Mixtures of product and acetal. ^c No addition of DMSO. The reaction was carried out for 48 h.

Table 3. Diamine **10**/TFA-Catalyzed Direct Michael Reactions for the Synthesis of Quaternary Carbon

entry	donor 13	R ¹	R ²	time (h)	product 15	yield (%)	dr ^a (syn/anti)	ee (%) ^b (syn/anti)
1	13a	Me	Me	48	15a	87	-	80
2	13b	-(CH ₂) ₄ -		24	15b	93	-	91
3	13c	-(CH ₂) ₅ -		96	15c	90	-	59
4	13d	Me	Et	96	15d	94	74/26	81/75
5	13e	Me	Pr	96	15e	95	74/26	86/67
6	13f	Me	nonyl	96	15f	96	70/30	85/58
7	13g	Me		96	15g	93	84/16	75/45
8	13h	Me	Ph	96	15h	87 ^c	89/11	18/79
9	13i	Me		96	15i	75 ^c	55/45	65/65
10	13j	Me		96	15j	64 ^c	54/46	70/64
11	13k	Me		96	15k	75 ^c	67/33	74/43

^a Determined by ¹H NMR. ^b Determined by chiral HPLC analysis using CHIRALCEL OD-H, OJ-H, and/or CHIRALPAK AS-H columns. ^c Starting material was recovered in 9% (entry 8), 25% (entry 9), 30% (entry 10), and 16% (entry 11) yields.

gave a better enantioselectivity than **10**/TFA, but the reaction was slow and the yield was low after 4 days (entries 9 and 10).

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(4) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420–2423.

(5) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 4369–4372.

(6) Fluorogenic Michael acceptor: (a) Tanaka, F.; Thayumanavan, R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2003**, *125*, 8523–8528. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325–328. See also fluorogenic aldol acceptor: (c) Tanaka, F.; Mase, N.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2004**, *126*, 3692–3693.

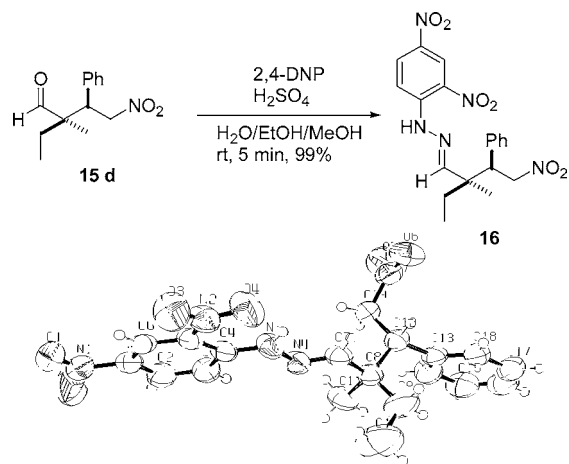
Using diamine **10**/TFA as a catalyst, a series of different solvent systems was evaluated as shown in Table 2.⁸ DMSO, 2-propanol, and diethyl ether were superior solvents in terms of product yield (entries 4, 6, and 9). Diethyl ether gave the highest ee of the solvents tested; however, the solubility of diamine **10**/TFA catalyst was poor in diethyl ether. Ionic liquids such as [bmim]PF₆ and [bmim]BF₄ showed over 70% ee, but yields were low (entries 12 and 13). Therefore, we chose 2-PrOH as a solvent for further study. The Michael reaction was carried out in 2-PrOH at 4 °C, rather than room temperature, to give the Michael product in 87% yield with 80% ee (entry 14).⁹

Encouraged by these results, we further examined the scope of this class of Michael reactions with a series of α,α -disubstituted aldehyde donors **13a–k** using **10**/TFA catalyst under the same reaction conditions (Table 3). Cyclopentane-

(7) For additional studies of amine–acid combination catalysts in organocatalytic reactions, see ref 1f and: Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167–8177.

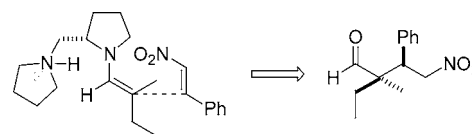
(8) We used DMSO to dissolve the diamine **10**/TFA catalyst. Ratio of DMSO/solvent was 30/70.

(9) **Typical Procedure for Table 2 entry 14 and Table 3.** A catalyst stock solution (1.0 M in 2-PrOH) was prepared as a mixture of (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (0.5 mmol) and trifluoroacetic acid (0.5 mmol) in 2-PrOH (0.5 mL, HPLC grade) before use. β -Nitrostyrene **14** (0.5 mmol) was dissolved in 2-PrOH (0.85 mL), and isobutyraldehyde **13a** (1.0 mmol) was added. To the mixture was added the catalyst stock solution (1.0 M in 2-PrOH, 0.15 mL, 0.15 mmol) at 4 °C. The reaction mixture was stirred at 4 °C for the indicated time and then purified by flash silica gel column chromatography without further workup to provide Michael product **15a**.

Scheme 3. Determination of Stereochemistry

carboxaldehyde (**13b**) was an excellent donor: the reaction provided the Michael product **15b** in excellent yield in 24 h with 91% ee (entry 2), while the reaction of cyclohexane-carboxaldehyde (**13c**) afforded 59% ee (entry 3). When α -methyl- α -alkylaldehydes **13a–g** were used as the donors, the expected Michael products were obtained with at least 87% yield with good enantioselectivities (entries 1–7). The reaction of aldehyde donors **13h–k** possessing an aromatic group afforded Michael products in moderate yield with moderate enantiomeric excesses (entries 8–11).

The major Michael product **15d** was determined to have a syn configuration by X-ray crystallographic analysis of the 2,4-dinitrophenylhydrazone derivative (Scheme 3).¹⁰ Therefore, diamine **10**/TFA catalyzed a *si*-facial attack on the β -nitrostyrene via an enamine intermediate (Figure 2). This result is in accord with previously proposed diamine-based Michael transition states.^{1b}

**Figure 2.** Proposed transition state.

In summary, the diamine **10**/TFA bifunctional catalyst demonstrated good reactivity and enantioselectivity in this class of Michael reactions. This method provides direct access to chiral γ -nitroaldehydes, which are versatile precursors for γ -aminobutyric acid neurotransmitters,¹¹ 1,4-amino alcohols for use as chiral ligands,¹² and unusual γ -amino acids.

Acknowledgment. This study was supported in part by the NIH (CA27489) and by the Skaggs Institute for Chemical Biology. We thank Dr. Raj K. Chadha for X-ray structural analysis.

Supporting Information Available: Complete analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) A diastereomixture of the Michael product **15d** (syn/anti = 74 (81% ee)/26 (75% ee), which is reported in Table 3, entry 4, was used for derivatization. A single crystal of the syn isomer was collected after recrystallization of the 2,4-dinitrophenylhydrazone; however, it was unfortunately a racemate crystal. The absolute configuration was deduced from previous investigations of α -monoalkyl Michael products.^{1b} Crystal structure data for 2,4-dinitrophenylhydrazone derivative **16**: C₁₉H₂₁N₅O₆, triclinic, space group *P*-1 (No. 2), *a* = 8.2921(17) Å, *b* = 11.639(2) Å, *c* = 12.066(2) Å; α = 64.65(3)°, β = 88.22(3)°, γ = 74.29(3)°, *Z* = 2, *R*₁(*wR*₂) = 0.0740(0.1795).

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