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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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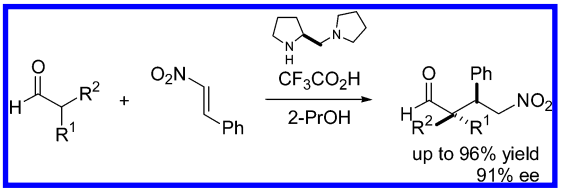
ABSTRACT



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.

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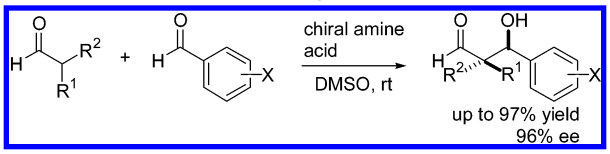
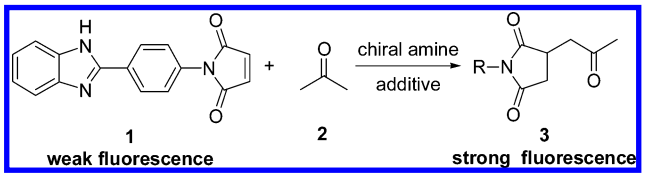
Scheme 1. Direct Cross-Aldol Reaction of α,α-Disubstituted Aldehyde



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 catalysts[5] 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**)

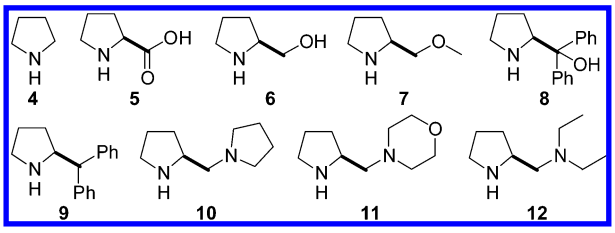
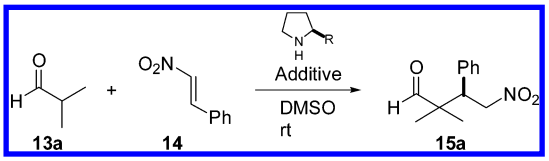


Figure 1. Various amine catalysts.

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 enantioselectivity was unacceptably low (23% ee) (entry 2). L-Prolinol (**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

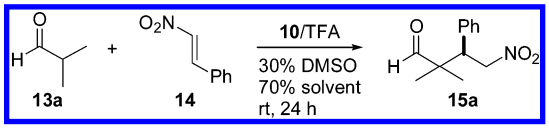
Table 1. Organocatalyzed Direct Michael Reactions for the Synthesis of Quaternary Carbon



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] Isobutylaldehyde (1.2 equiv) was used.

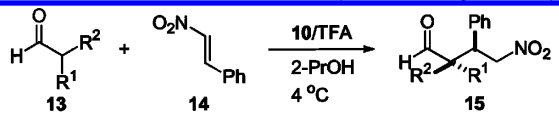
Table 2. Solvent Effect for Organocatalyzed Direct Michael Reactions



entry	solvent	yield (%)	ee (%)[a]
1	MeCN	10	56
2	MeOH	b	57
3	CH_2Cl_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_2O	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 ^{1}H 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).

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]PF_6 and [bmim]BF_4 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-

(3) Recent direct organocatalyic reactions using aldehyde and ketone donors: (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986. (b) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558−560. (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112−1115. (d) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790−4791. (e) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451. (f) Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109−1112. (g) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108−4109. (h) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III *J. Org. Chem.* **2003**, *68*, 9624−9634. (i) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233−4237. (j) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448−2449. (k) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Synlett* **2003**, 1910−1914. (l) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685−1688. (m) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, 1906−1909. (n) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842−1843. (o) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866−1867. (p) Watanabe, S.; Cordova, A., Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519−4522. (q) Chowdari, N. S.; Suri, J. T.; Barbas, C. F., III. *Org. Lett.* **2004**, in press.

(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.

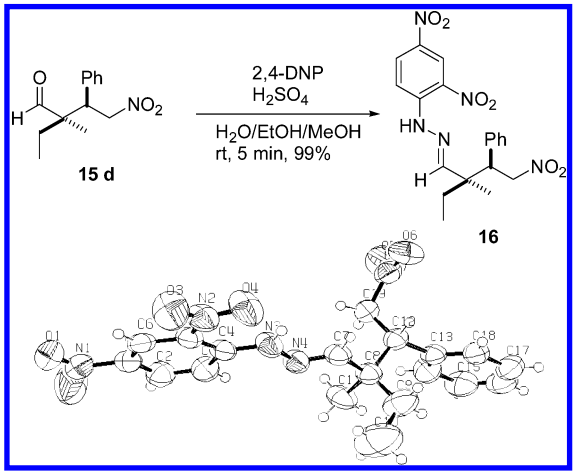
(6) Fluorogenic Michael acceptor: (a) Tanaka, F.; Thayumanavan, R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2003**, *125*, 8523−8528. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325−328. See also fluorogenic aldol acceptor: (c) Tanaka, F.; Mase,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

(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 cyclohexanecarboxaldehyde (**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]

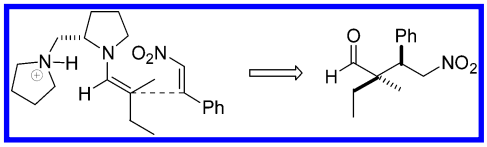


Figure 2. Proposed transition state.

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.

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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**: $C_{19}H_{21}N_5O_6$, triclinic, space group *P*-1 (No. 2), $a = 8.2921(17)$ Å, $b = 11.639(2)$ Å, $c = 12.066(2)$ Å; $\alpha = 64.65(3)°$, $\beta = 88.22(3)°$, $\gamma = 74.29(3)°$, $Z = 2$, $R_1(wR_2) = 0.0740(0.1795)$.

(11) Nie, Z.; Schweitzer, P.; Roberts, A. J.; Madamba, S. G.; Moore, S. D.; Siggins, G. R. *Science* **2004**, *303*, 1512−1514.

(12) Scarpi, D.; Lo Galbo, F.; Occhiato, E. G.; Guarna, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1319−1324.