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Rapid Fluorescent Screening for Bifunctional Amine–Acid Catalysts: Efficient Syntheses of Quaternary Carbon-Containing Aldols under Organocatalysis

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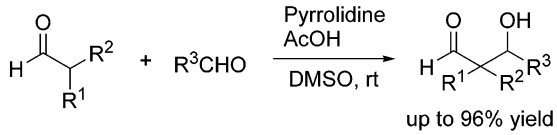
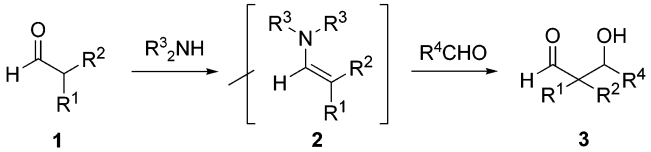
ABSTRACT



Direct catalytic aldol reactions of α,α-dialkylaldehyde donors and arylaldehyde acceptors have been performed using pyrrolidine–acetic acid bifunctional catalysts. This general and practical amine–acid combination was identified by screening catalysts using a new fluorescent detection system for carbon–carbon bond formation. Using 0.05 equiv of pyrrolidine and 0.25 equiv of acetic acid as catalyst, we obtained α,α-dialkylaldol product in 96% yield after 2 h at ambient temperature. Proline was a poor catalyst of this reaction.

The direct aldol reaction is one of the most powerful and efficient methods for carbon−carbon bond formation. Within the aldol reaction manifold, the development of standard syntheses of aldol products possessing a quaternary carbon has proven to be one of the more challenging topics.[1] Recently, Shibasaki et al. reported direct aldol reactions of α-hydroxyketones and aldehydes using an Et_2Zn/linked-BINOL complex for the asymmetric construction of a chiral quaternary carbon stereocenter.[2] Results using organocatalysts such as L-proline and small amines have been published;[3,4] however, there has been no report of a direct catalytic aldol reaction that generates a tetra-substituted carbon atom. Here, we report the intermolecular direct aldol reaction of α,α-dialkylaldehydes **1** to provide the aldol products **3** (Scheme 1).

Scheme 1. Direct Aldol Reaction To Form a Quaternary Carbon Atom via an Enamine Intermediate



First, we examined whether L-proline was a useful catalyst for this type of reaction. When the reaction was performed using isobutyraldehyde and *p*-nitrobenzaldehyde in the presence of L-proline according to our typical conditions,[3b] formation of the α,α-dimethylaldol product was slow and

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(1) Review: Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389−401. Aldol−Tishchenko reaction of naked aldehyde: Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601−603.

(2) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169−2178.

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the yield was unacceptably low (3 d, 34% yield). Therefore, we decided to search for efficient conditions for this challenging reaction. Since an amine-catalyzed aldol reaction proceeds via an enamine intermediate **2**, acceleration of the formation of **2** may be a key to enhancing the construction of the α,α-dialkylaldol product **3**. Recently, we have developed a fluorescent detection system to monitor the progress of C−C bond formation using the fluorogenic maleimide **4**.[5] The acetone enamine generated in situ reacts with **4** to give **6**, which exhibits a high fluorescence compared to that of **4**. Thus, this assay system should be useful in ranking catalysts of enamine formation. Catalysts that efficiently form an enamine with acetone should also be efficient in forming enamines with other carbonyl compound, in particular aldehydes. Since it is well-known that pyrrolidine can be used in enamine synthesis and that this process is catalyzed by acids,[6] we have screened pyrrolidine−acid combinations. The screening was initially performed by using various acid additives, such as Lewis, Brønsted, and organic acids on the reaction of **4** with **5** in the presence of pyrrolidine. Reactions were performed with pyrrolidine (3 mM), acid (3 mM), and **4** (6 μM) in 20% acetone/80% DMSO, and the initial reaction velocities were determined by monitoring the fluorescence (λ_{ex} 315 nm, λ_{em} 365 nm) over 20 min. Results are shown in Figure 1. Eight acids, including $Zn(OTf)_3$, $Y(OTf)_3$, and carboxylic acids, increased the fluorescence intensity compared to the reaction without acid. Acetic acid provided a 2.2-fold greater initial velocity compared to the same reaction without acid, while strong acids, such as H_2SO_4, CF_3SO_3H, *p*-TsOH, D-(+)-10-camphorsulfonic acid, and HNO_3, showed slower velocities.

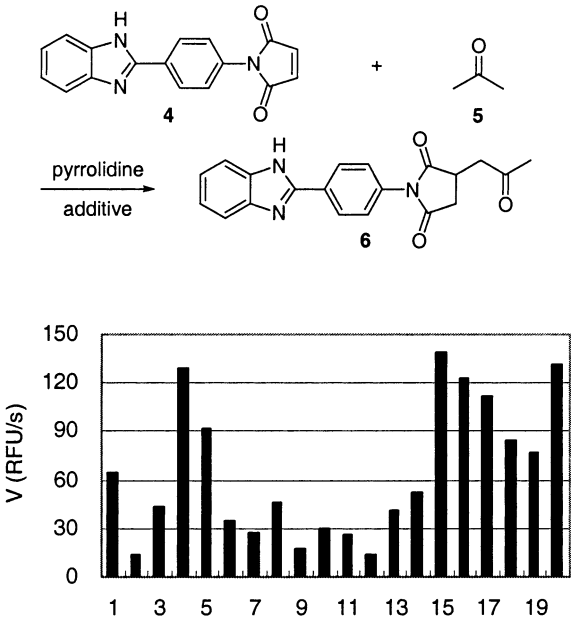


Figure 1. Initial velocities of reactions of pyrrolidine−acid combinations using fluorogenic substrate **4**. Conditions: see text. RFU = Relative fluorescence unit. Acid additives: **1**, none; **2**, $Sc(OTf)_3$; **3**, $Cu(OTf)_2$; **4**, $Zn(OTf)_2$; **5**, $Y(OTf)_3$; **6**, $La(OTf)_3$; **7**, $Eu(OTf)_3$; **8**, $Yb(OTf)_3$; **9**, H_2SO_4; **10**, CF_3SO_3H; **11**, *p*-TsOH; **12**, D-(+)-10-camphorsulfonic acid; **13**, HNO_3; **14**, CF_3CO_2H; **15**, CH_3CO_2H; **16**, $Ph(CH_2)_2CO_2H$; **17**, $CH_3(CH_2)_8CO_2H$; **18**, oleic acid; **19**, linoleic acid; **20**, 4-$CH_3C_6H_4CO_2H$.

These pyrrolidine−acid combinations were also screened in the same way but using a series of different solvents, such as DMSO, DMF, 1,4-dioxane, acetone, MeCN, THF, PhMe, *i*-PrOH, and MeOH. This study revealed DMSO to be the most effective solvent. We also evaluated different molar ratios of pyrrolidine to acetic acid and found that 1 or more equiv of acetic acid was more efficient than combinations involving less than 1 equiv of acetic acid.

To determine the utility of these reaction conditions to intermolecular aldol reactions involving α,α-dialkylaldehyde donors, the syntheses of a variety of quaternary carbon containing aldols were evaluated (Table 1).[7,8] Without acetic acid, the reaction of isobutyraldehyde (**7a**) and *p*-nitrobenzaldehyde (**8a**) provided aldol product **9a** in 74% yield after 2 days (entry 1). In contrast, addition of 1 equiv of acetic acid to pyrrolidine improved the yield to 89% after only 4 h (entry 2). With 5 equiv of acetic acid with respect to pyrrolidine, **9a** was obtained in 95% yield after only 15

(3) Selected aldol studies: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (c) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167−8177. (d) Cordova, A.; Notz, W.; Barbas, C. F., III. *J. Org. Chem.* **2002**, *67*, 301−303. (e) Kotrusz, P.; Kmentova, I.; Gotov, B.; Toma, S.; Solcaniova, E. *Chem. Commun.* **2002**, 2510−2511. (f) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591−9595. (g) Anders, B.; Nagaswamy, K.; Anker, J. K. *Chem. Commun.* **2002**, 620−621. (h) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798−6799. (i) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Qiao, A.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262−5263. (j) Darbre, T.; Machuqueiro, M. *Chem. Commun.* **2003**, 1090−1091.

(4) Recent studies in organocatalysis: (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785−2788. (b) Juhl, K.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498−1501. (c) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677−3680. (d) Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661−665. (e) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16−17. (f) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475−2479. (g) Melchiorre, P.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151−4157. (h) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2003**, *5*, 1685−1688. (i) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249−1251. (j) Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923−1926. (k) Liu, H.; Peng, L.; Zhang, T.; Li, Y. *New J. Chem.* **2003**, *27*, 1159−1160. (l) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247−4250. (m) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233−4237. (n) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208−11209.

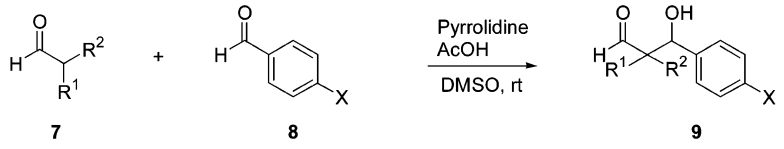
(5) Tanaka, F.; Thayumanavan, R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2003**, *125*, 8523−8528.

(6) (a) Kuehne, M. E. *J. Am. Chem. Soc.* **1959**, *81*, 5400−5404. (b) Spencer, T. A.; Neel, H. S.; Ward, D. C.; Williamson, K. L. *J. Org. Chem.* **1966**, *31*, 434−436. (c) Woodward, R. B. *Pure Appl. Chem.* **1968**, *17*, 519−547. (d) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1612−1615.

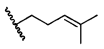
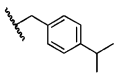
(7) Pyrrolidine−AcOH has been studied in intramolecular aldol reactions; see ref 6b−d. See also: (a) Desmaele, D.; d'Angelo, J. *Tetrahedron Lett.* **1989**, *30*, 345−348. (b) Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, *55*, 4392−4399. (c) Barros, M. T.; Santos, A. G.; Godinho, L. S.; Maycock, C. D. *Tetrahedron Lett.* **1994**, *35*, 3999−4002. (d) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, *33*, 5009−5012.

(8) The fluorescent screening results were roughly correlated to the aldol reaction results. For example, compared to pyrrolidine−acetic acid (V = 138.8 RFU/s in Figure 1), the pyrrolidine-D-(+)-10-camphorsulfonic acid combination (V = 13.5) did not catalyze the aldol reaction after 24 h. Pyrrolidine−$Yb(OTf)_3$ (V = 46.2) and pyrrolidine−*p*-toluic acid (V = 131.8) gave the aldol product in 82% (15 h) and 91% (5 h) yield, respectively.

Table 1. Pyrrolidine−Acetic Acid Catalyzed Direct Aldol Reactions for the Synthesis of Quaternary Carbon Bearing Aldols



7 + 8 → 9

entry	7	R^1	R^2	X	pyrrolidine (eq)	AcOH (eq)	time (h)	yield (%)[a]	product
1	**7a**	Me	Me	NO_2	0.3	none	48	74	**9a**
2	**7a**	Me	Me	NO_2	0.3	0.3	4	89	**9a**
3	**7a**	Me	Me	NO_2	0.3	1.5	15 min	95	**9a**
4	**7a**	Me	Me	NO_2	0.05	0.25	2	96	**9a**
5	**7b**	-$(CH_2)_5$-		NO_2	0.3	1.5	4	86	**9b**
6	**7c**	-$(CH_2)_2$-[b]		NO_2	0.3	1.5	48	75	**9c**
7	**7d**	Et	Me	NO_2	0.3	1.5	3	89	**9d**
8	**7e**		Me	NO_2	0.3	1.5	4	84	**9e**
9	**7f**		Me	NO_2	0.3	1.5	3	87	**9f**
10	**7a**	Me	Me	CN	0.3	1.5	24	92	**9g**

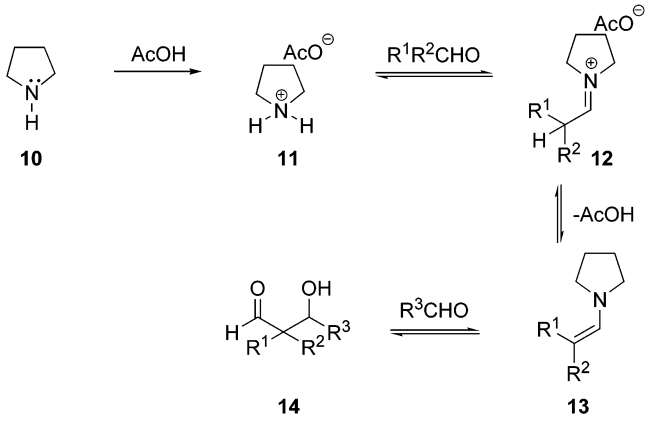
[a] Isolated yields of pure product after column chromatography. [b] 10 equivalent of cyclopropanecarboxaldehyde (**7c**) was used. Typical procedure: To a solution of arylaldehyde **8** (0.5 mmol) and α,α-dialkylaldehyde **7** (0.6 mmol) in DMSO (0.5 mL) were added acetic acid and pyrrolidine, in the molar ratios indicated. The reaction mixture was stirred at room temperature for the indicated time and then purified by flash silica gel column chromatography without workup to give the aldol product **9**.

min (entry 3). When both acetic acid and pyrrolidine were decreased (entry 4) the yield after 2 h was 96%. All of the α,α-dialkylaldehydes except **7a** required longer reaction times for their reactions to complete; therefore, we used 0.3 equiv of amine−acid catalyst in the reactions of α,α-dialkylaldehydes **7b**−**f** with **8a**. Except in the case of cyclopropanecarboxaldehyde (**7c**), reactions of cyclohexanecarboxaldehyde (**7b**) and/or the α-alkyl-α-methylaldehydes, such as 2-methylbutyraldehyde (**7d**), 2,6-dimethyl-5-heptenal (**7e**), and 3-(4-isopropylphenyl)isobutyraldehyde (**7f**), yielded at least 80% of the expected product within 4 h (entries 5−9). The reaction of 4-cyanobenzaldehyde (**8b**) with **7a** also afforded the aldol product **9g** in 92% yield (entry 10).

These reaction conditions were readily scaled. To study a multigram-scale synthesis, acetic acid (0.25 equiv) and pyrrolidine (0.05 equiv) were added to a solution of *p*-nitrobenzaldehyde (10.0 g) and isobutyraldehyde (1.2 equiv) in THF (66 mL) at room temperature. The reaction mixture was stirred for 2 h and then concentrated to give the crude product, which was purified by flash silica gel column chromatography to afford aldol product **9a** (14.0 g, 95%).

We confirmed the formation of the presumed enamine intermediate by ^{1}H NMR for the reaction in Scheme 2. To a solution of pyrrolidine (10 μmol) in DMSO-d_6 (500 μL) was added acetic acid (10 μmol). The chemical shift at 2-H of pyrrolidine was shifted from 2.65 to 2.83 ppm, indicating the formation of the salt **11**. To this solution was added isobutyraldehyde (10 μmol, −C*H*O 9.55 ppm), and the formation of enamine **13** (−N−C*H*═C(CH$_3$)$_2$ 5.56 ppm) was

Scheme 2. Proposed Mechanism of the Pyrrolidine−Acetic Acid Catalyzed Direct Aldol Reaction



observed within 5 min. In the absence of acetic acid, enamine formation was observed after 1 h when the same enamine chemical shift became predominant. These NMR studies suggest that acceleration of enamine formation is key to increasing the rate of this reaction and is therefore at least partially rate-determining.

In summary, we have used a rapid fluorescence assay to determine optimal reaction conditions for intermolecular direct aldol reactions of α,α-dialkylaldehydes **7** with arylaldehyde **8**. The reaction proceeds via an enamine intermediate as shown by ^{1}H NMR. The pyrrolidine−acetic acid bifunctional catalyst system utilizes inexpensive chemicals, does not require preactivation of the donor and/or acceptor, can be carried out under simple and mild reaction conditions, and can be applied to multigram reactions. Further studies focusing on the full scope of this catalyst system are currently under investigation and will be reported in due course.

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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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