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Direct Aldol Reactions Catalyzed by a Heterogeneous Guanidinium Salt/Proline System under Solvent-Free Conditions‡

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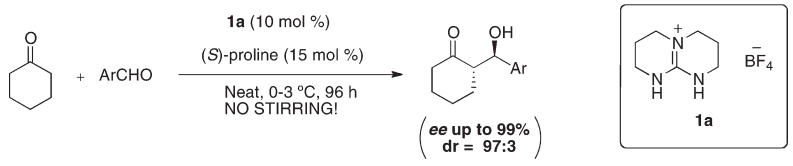
ABSTRACT



The combined activity of (*S*)-proline and an achiral cocatalyst (a TBD-derived guanidinium salt) allow direct aldol reactions to be carried out with high diastereoselectivity and enantioselectivity under solvent-free conditions with a rather simple reaction setup where stirring is not required.

The aldol reaction is certainly one of the most renowned transformations in organic synthesis.[1] However, since the breakthrough discovery of the first proline-catalyzed intermolecular aldol reaction by List, Lerner, and Barbas,[2] and the blossoming of general asymmetric organocatalyzed reactions[3] from the past decade, the aldol reaction is experiencing its second youth. Considering its ready availability and low price, it is evident that (*S*)-proline would be a first-choice catalyst for preparing aldol adducts with high diastereo- and enantioselectivity. However, proline itself presents some major drawbacks, namely: poor performance in direct aldol reactions with aromatic aldehydes, rather limited solubility and reactivity in nonpolar organic solvents, and potential parasitic side reactions that make using high catalyst loadings necessary to achieve acceptable conversions. To avoid these undesired issues different solutions were adopted: (A) in fully rational approaches, large efforts are devoted to the careful design (computer aided) and synthesis of novel tailor-made catalysts to be ultimately tested on aldol reactions. Evaluation of such catalysts in terms of reactivity, selectivity, and reaction scope allows judging of their efficiency and to propose a second generation of more active catalysts, normally based on the original design. Although impressive catalysts have been discovered by this approach, the time-consuming nature of this iterative method may reveal limitations (it has to be noted that before having found a good catalyst many analogs of a proposed design are normally prepared and evaluated); (B) an alternative consists of adding simple, readily available additives[4] to reactions containing known catalysts (ideally proline), whose behavior is thus re-evaluated under these new conditions. This late approach is clearly beneficial in evading tedious

‡ This work is dedicated to the memory of Professor José M. Concellón.

(1) For some recent monographs and reviews, see: (a) *Modern Aldol Reactions*, Vol. 1–2; Mahrwald, Ed.; Wiley-VCH: Weinheim, 2004. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506. (c) Guilena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249. (d) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131.

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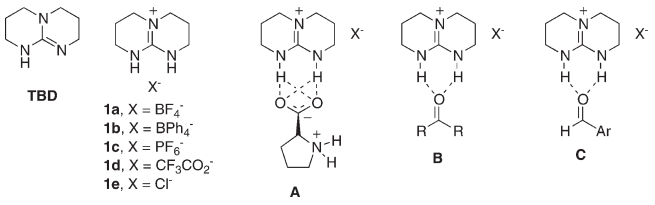


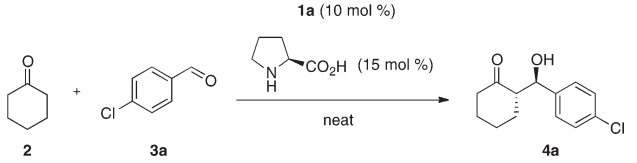
Figure 1. TBD-derived guanidinium salts **1a**−**e** used in this work. Possible doubly H-bonded motifs formed by interaction of the TBD-derived guanidinium salt with the carboxylate function of (*S*)-proline **A**, or the carbonyl moiety of a ketone **B**, or an aromatic aldehyde **C**.

chemical syntheses and would ultimately allow the construction of libraries of catalyst[5] systems by simply changing the additives of choice. In this sense, researchers have shown that the addition of catalytic or substoichiometric amounts of water,[6] chiral diols,[7] Schreiner's thiourea,[8] or other diarylthioureas[9] accelerates the reaction rate and increases the diastereo- and enantioselectivity of proline-catalyzed aldol reactions. Although a full-bodied picture of the role played by these additives in the reaction mechanism has not been disclosed, it seems clear that, in nonpolar solvents, a network of H-bonding interactions between the carboxylate function of proline, the corresponding additive, and the reaction substrates in the transition state is established.

Inspired by the aforementioned contributions, and considering the probed ability of guanidinium salts in binding carboxylic acids and carboxylates,[10] we contemplated the possibility of using guanidinium salts as new additives in the aldol reaction.[11] Herein, we report the results of the proline-catalyzed intermolecular direct aldol reaction between ketones and aromatic aldehydes using TBD (triazabicyclo[4.4.0]dec-5-ene)-derived guanidinium salts **1a**−**e** (Figure 1) as additives.

The reaction between cyclohexanone, **2**, and 4-chlorobenzaldehyde, **3a**, to afford aldol **4a**, was used as a model system to screen different reaction conditions (Table 1). Looking for an inexpensive and green process, we decided to avoid the use of any organic solvent, apart from **2** (10-fold excess), which acts as both reagent and reaction media.[12] Under these conditions, we postulate that the guanidinium core of salts **1** could form doubly H-bonded motifs with the carboxylate function of proline (model **A**, Figure 1), as well as with the carbonyl moieties of cyclohexanone (model **B**, Figure 1) and the aromatic aldehyde (model **C**, Figure 1), thus enhancing their electrophilicity. In ideal cases, these interactions could, in principle, modulate to our favor the reactivity and selectivity of proline in the aldol reaction. Nonetheless, we could also presume the participation of the anion counterpart X^- of salts **1** in the reaction scheme. An early blank experiment showed that aldol **4a** was rendered in 94% conversion (60:40 *anti*/*syn*, 56% *ee*) when a suspension of 4-chlorobenzaldehyde **3a** (1.0 equiv) and (*S*)-proline (15 mol %), in cyclohexanone **2** (10 equiv), was vigorously stirred for 48 h at 20 °C inside a

Table 1. Initial Screening of Conditions for the Formation of Aldol **4a**[a]



entry	temp (°C)	time (h)	conversion[b]	anti/syn[b]	ee %[c]
1[d]	20	48	94	60:40	56
2	20	48	99	76:24	82
3	0	96	98	93:7	96
4[e]	0−3	96	96	94:6	98
5[d,e]	0−3	96	81	69:31	54

[a] General conditions: **2** (4.0 mmol, 0.41 mL), **3a** (0.4 mmol) (*S*)-proline (15 mol %), **1a** (10 mol %), no solvent, reaction mixture was stirred. Results are determined as an average of two experiments. [b] Determined by ^{1}H NMR spectroscopy from crude reaction mixtures. *Anti* and *syn* diastereoisomers were identified by comparison with similar compounds previously described in the literature. [c] Enantiomeric excess of the major diastereoisomer, as determined by chiral HPLC on crude reaction mixtures. [d] No guanidinium salt **1a** was used. [e] The reaction mixture was left to stand inside a fridge (0−3 °C) with no stirring.

(4) For a high throughput screening of additives in organocatalyzed reactions, see: (a) Mase, N.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2003**, *5*, 4369. (b) Mase, N.; Tanaka, F.; Barbas, C. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (c) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F. *Tetrahedron Lett.* **2004**, *45*, 325.

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(6) (a) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891. (b) Amedjkouh, M. *Tetrahedron: Asymmetry* **2005**, *16*, 1411. (c) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347. (d) Pihko, P. M.; Laurikanien, P. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.

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(8) Reis, Ö.; Eymur, S.; Reis, B.; Demir, A. S. *Chem. Commun.* **2009**, 1088.

(9) (a) El-Hamdouni, N.; Companyó, X.; Rios, R.; Moyano, A. *Chem.—Eur. J.* **2010**, *16*, 1142. (b) Companyó, X.; Valero, G.; Crovetto, L.; Moyano, A.; Rios, R. *Chem.—Eur. J.* **2009**, *15*, 6564.

(10) Reviews: (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609. (b) Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841. (c) Blondeau, P.; Segura, M.; Pérez-Fernández, R.; de Mendoza, J. *Chem. Soc. Rev.* **2007**, *36*, 198. (d) Coles, M. P. *Chem. Commun.* **2009**, 3659. (e) Kim, S. K.; Sessler, J. L. *Chem. Soc. Rev.* **2010**, *39*, 3784.

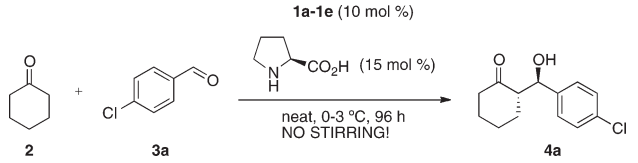
(11) The Liebscher group has reported improvements in (*S*)-proline catalyzed aldol reactions using guanidinium salts and ionic liquids as solvents: (a) Shah, J.; Blumenthal, B.; Yacob, Z.; Liebscher, J. *Adv. Synth. Catal.* **2008**, *350*, 1267. (b) Shah, J.; Liebscher, J. *Z. Naturforsch. B* **2011**, *66*, 88.

(12) For recent examples of aldol reactions carried out under solvent-free conditions, see: (a) Almasi, D.; Alonso, D. A.; Balaguer, A. N.; Najera, C. *Adv. Synth. Catal.* **2009**, *351*, 1123. (b) Worch, C.; Bolm, C. *Synlett* **2009**, 2425. (c) Almasi, D.; Alonso, D. A.; Najera, C. *Adv. Synth. Catal.* **2008**, *350*, 2467. (d) Rodríguez, B; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924. (e) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 4710.

screwed-capped test tube (Table 1, entry 1). To our delight, when a similar reaction mixture was treated with tetrafluoroborate guanidinium salt **1a** (10 mol %), *anti*-aldol **4a** was afforded with a comparable conversion although with a significantly higher diastereo- and enantioselectivity, revealing the advantageous effect of this additive (Table 1, entry 2). Aiming to improve further our catalytic system we next investigated the effect of temperature. Stirring the reaction mixture at 0 °C gives aldol *anti*-**4a** with high diastereoselectivity (93:7) and enantioselectivity (96%), although after a longer reaction time (Table 1, entry 3). Moreover, when a suspension of aldehyde **3a**, (*S*)-proline (15 mol %), and **1a** (10 mol %), in cyclohexanone, was left to stand for 96 h inside a standard laboratory fridge (temperature was set up and checked to be 0−3 °C), without needing any sort of stirring or mechanical agitation, aldol **4a** was produced in 96% conversion (*anti*/*syn* 94:6), peaking at 98% enantiomeric excess (Table 1, entry 4). When an analogous reaction was performed with 15 mol % of (*S*)-proline, with no additive **1a**, modest figures were observed for both the diastereo- and enantioselectivity of aldol **4a** (Table 1, entry 5). The efficiency of the aldol reaction is remarkable under these rather mild conditions taking into account that the reaction mixture is heterogeneous (neither proline nor aldehyde **3a** is fully soluble in the little excess of cyclohexanone used) and that it remains so all along the course of the reaction.

Other TBD-derived guanidinium salts **1b**−**e**, featuring anions with different electronegativities and geometries, were also investigated as additives (Table 2). Again, suspensions of aldehyde **3a** (0.4 mmol), (*S*)-proline (15 mol %), and either of a guanidinium salt **1b**−**e** (10 mol %), in

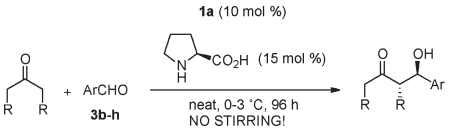
Table 2. Screening of Different Guanidinium Salts **1b**−**e** as Additives in the Proline-Catalyzed Aldol Reaction[a]

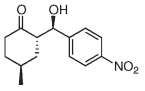
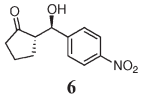
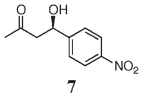


entry	guanidine salt	conversion[b]	anti/syn[b]	ee %[c]
1	**1b**	98	48:52	−75, −67[d]
2	**1c**	94	84:16	86
3	**1d**	92	75:25	77
4	**1e**	60	77:23	87

[a] General conditions: **2** (4.0 mmol, 0.41 mL), **3a** (0.4 mmol), (*S*)-proline (15 mol %), guanidinium salt **1a**−**e** (10 mol %), no solvent, reaction mixture was left to stand 96 h inside a fridge (0−3 °C) with no stirring. Results are determined as an average of two experiments. [b] Determined by ^{1}H NMR spectroscopy from crude reaction mixtures. *Anti* and *syn* diastereoisomers were identified by comparison with similar compounds previously described in the literature. [c] Enantiomeric excess of the major diastereoisomer, as determined by chiral HPLC on crude reaction mixtures. [d] Enantiomeric excess of *anti* and *syn* aldol, respectively. Both *anti* and *syn* diols are obtained with the opposite absolute configuration.

Table 3. (*S*)-Proline/Guanidinium Salt **1a** Cocatalyzed Synthesis of Aldols **4b**−**4h**, **5**−**7**[a]



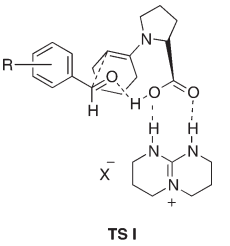
entry	ArCHO	product	yield %[b]	anti/syn[c]	ee %[d]
1[e]	**3b** 4-NO_2Ph	**4b**	92	92:8	99
2[e]	**3c** 4-CO_2MePh	**4c**	86	92:8	99
3[e]	**3d** 4-BrPh	**4d**	94	97:3	99
4[e]	**3e** 2-OMePh	**4e**	87	95:5	98
5[e]	**3f** 3-ClPh	**4f**	94	96:4	98
6[e]	**3g** 2-furyl	**4g**	73	86:14	91
7[e]	**3h** 2-thiophenyl	**4h**	70	93:7	90
8[f]	**3b** 4-NO_2Ph	 **5**	81	86:14:0:0[g]	97
9[h]	**3b** 4-NO_2Ph	 **6**	84	74:26	98
10[i]	**3b** 4-NO_2Ph	 **7**	88	-	74

[a] General conditions: ketone (4.0 mmol), ArCHO (0.4 mmol), (*S*)-proline (15 mol %), **1a** (10 mol %), no solvent, reaction mixture was left to stand 96 h inside a fridge (0−3 °C) with no stirring. [b] Isolated yield of analytically pure products. [c] Determined by ^{1}H NMR spectroscopy from crude reaction mixtures. *Anti* and *syn* diastereoisomers were identified by comparison with similar compounds previously described in the literature. [d] Enantiomeric excess of isolated pure products, as determined by chiral HPLC on crude reaction mixtures. [e] Cyclohexanone, **2**, was used as ketone. [f] 4-Methylcyclohexanone was used as ketone. [g] Only two diastereoisomers were detected by ^{1}H NMR spectroscopy. [h] Cyclopentanone was used as ketone. [i] Acetone was used as ketone.

cyclohexanone **2** (4.0 mmol, 0.41 mL), were left to stand for 96 h inside a laboratory fridge (0−3 °C) without stirring, before they were worked up and analyzed by ^{1}H NMR spectroscopy and chiral HPLC. From the collection of experiences outlined in Table 2 we can conclude that all the salts **1b**−**e** improve the efficiency of proline in the aldol reaction in terms of diastereo- and enantioselectivity. Salts **1b**−**e** are less efficient additives for the aldol reaction than the tetrafluoroborate salt **1a** previously examined. Satisfyingly, as we anticipated, participation of the tetraphenylborate derivative **1b** suffices for reverting the absolute configuration of both the *anti* and *syn* aldols **4a** without changing the source of chiral information ((*S*)-proline). Although the justification for this result is not clear for us, we believe the bulkiness of the anion forcing an alternative reaction mechanism.

To establish the scope of our aldol protocol a selection of aldehydes **3b**−**h** bearing diverse functional groups and substitution patterns were reacted with cyclohexanone (or other ketones) under our finest reaction conditions (Table 3). A 10-fold excess of the ketones investigated proved to be sufficient as reagent and reaction media (solvent). All reactions shown in Table 3 proceeded smoothly. Aldols **4b**−**f**, derived from cyclohexanone (Table 3, entries 1−5), were isolated in good or very good yield, and with very high diastereo- and enantioselectivity. Particularly relevant are aldols **4g** and **4h**, prepared from 2-furfural, **3g**, and 2-thiophenecarboxaldehyde, **3h**, respectively, which are challenging substrates for the direct aldol reaction (Table 3, entries 6−7). 4-Methylcyclohexanone was successfully desymmetrized by means of this methodology, affording aldol **5** with high diastereo- and enantioselectivity, in a process where the absolute configuration of three stereogenic centers is fixed (Table 3, entry 8). Reactions carried out with cyclopentanone or acetone were also successful. Aldol reactions performed without additive **1a** showed lower conversion, as well as poorer diastereoisomeric ratios and enantiomeric excesses, thus demonstrating the positive effect of this salt on the reaction course (see Supporting Information for details).

Different papers have appeared in the literature that give remarkable insights into the behavior of proline and other amino acids under heterogeneous conditions.[13] It has been accepted that, in the case of proline, a saturated solution lives in equilibrium with a crystalline phase. Taking this consideration as a working basis, we believe that, in our system, there is some (*S*)-proline dissolved in cyclohexanone (or alternatively the ketone used), and it controls the reaction course. Then, as proposed by other authors,[2,8b,14] the stereochemical outcome of the reaction could be explained considering that it operates through a Zimmerman−Traxler transition state. Therefore, the formation of a 1:1 complex between the guanidinium cation of additive **1a** and the solubilized (*S*)-proline would stabilize the chairlike transition state **TS I** (Figure 2) that leads to the observed aldols. Notwithstanding this mechanistic hypothesis, issues such as the role played by the anion counterpart of salts **1** in the reaction mechanism are still unclear and are the subject of further investigations currently underway in our laboratory.



TS I

Figure 2. Zimmerman−Traxler-type transition state proposed to explain the observed stereochemistry of aldols **4**.

In summary, we have developed and implemented a simple, green, efficient, and highly selective methodology for the direct aldol reaction of ketones with aromatic aldehydes using (*S*)-proline as a chiral catalyst. Catalytic amounts of TBD-derived guanidinium salts have been used for the first time as an additive for this reaction. This aldol protocol works under solvent-free conditions, in closed-cap test tubes placed inside a standard laboratory fridge, without agitation or mechanical stirring. The development of other enantioselective reactions promoted by guanidinium salts is ongoing in our laboratory and will be reported in due course.

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Supporting Information Available. General procedures, spectroscopic data, copies of ^{1}H and ^{13}C NMR spectra, and chromatographic data for compounds **4a**−**h**, **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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