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A Chiral Solvent Effect in Asymmetric Organocatalysis

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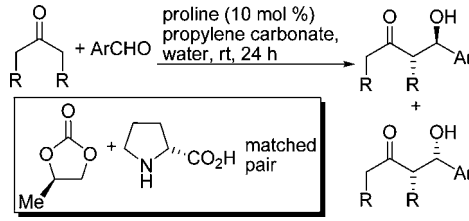
ABSTRACT



Proline-catalyzed aldol reactions between enolizable ketones and aromatic aldehydes can be carried out in propylene carbonate. When enantiomerically pure propylene carbonate is used, the combination of (*R*)-proline and (*R*)-propylene carbonate constitutes a matched pair, while (*S*)-proline and (*R*)-propylene carbonate constitutes a mismatched pair.

Over the last 10 years, asymmetric organocatalysis has developed from a minor curiosity into an extensively used tool in synthesis.[1] The first widely used catalyst was the amino acid proline,[2] building on its use in the Hajos−Parrish−Eder−Sauer−Wiechert reaction,[3] which had been reported over 30 years ago. While many other organocatalysts have since been designed and utilized, proline retains its place as the most sustainable of the organocatalysts as it is directly available from biological sources without any need for chemical transformations.

Organocatalyzed reactions are commonly carried out in traditional solvents such as DMSO, DMF, and chlorinated solvents.[1,2,4] Although both water[5] and ionic liquids[6] have also been used as solvents for organocatalyzed reactions, the green credentials of both of these solvents have been questioned.[7] In some cases, organocatalyzed reactions can also be carried out solvent-free.[8] Recently, we reported[9] the use of ethylene and propylene carbonate **1** and **2** (Figure 1) as sustainable[10,11] solvents for (*S*)-proline **3** catalyzed cross-aldol reactions between an enolizable ketone and an aromatic aldehyde. For reactions involving cyclohexanone, there was a significant difference in the chemical yield, diastereoselectivity, and enantioselectivity observed in the two solvents

(1) For recent reviews of asymmetric organocatalysis, see: (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (b) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.

(2) For reviews of proline-catalyzed reactions, see: (a) List, B. *Synlett* **2001**, 1675. (b) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (e) Kazmaier, U. *Angew. Chem., Int. Ed.* **2005**, *44*, 2186.

(3) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(4) (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (b) Kacprzak, K.; Gawroński, J. *Synthesis* **2001**, 961.

(5) (a) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (b) Hayashi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (c) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33.

(6) Toma, S.; Mečiarova, M.; Šebesta, R. *Eur. J. Org. Chem.* **2009**, 321.

(7) (a) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798. (b) Wu, B.; Liu, W.; Zhang, Y.; Wang, H. *Chem.—Eur. J.* **2009**, *15*, 1804.

(8) (a) Rodríguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *46*, 6924. (b) Rodríguez, B.; Bruckmann, A.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 4710.

(9) (a) North, M.; Pizzato, F.; Villuendas, P. *ChemSusChem* **2009**, *2*, 862. (b) Clegg, W.; Harrington, R. W.; North, M.; Pizzato, F.; Villuendas, P. *Tetrahedron: Asymmetry* in press.

(10) Cyclic carbonates are manufactured commercially by the reaction of epoxides with CO_2: Clements, J. H. *Ind. Eng. Chem. Res.* **2003**, *42*, 663.

10.1021/ol1007313
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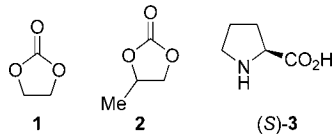
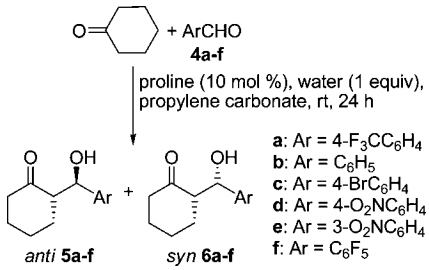


Figure 1. Structures of cyclic carbonates and proline.

with ethylene carbonate being the more effective solvent. In contrast, for reactions involving acetone as the enamine precursor, there was no consistent difference between the two solvents. This solvent effect was explained on the basis of the large difference in dielectric constant between the two solvents (90 and 65 for **1** and **2**, respectively).[12] In this letter, we show that propylene carbonate **2** also displays a pronounced chiral solvent effect in these reactions and that, by use of the appropriate combination of solvent enantiomer and proline enantiomer, the enantio- and diastereoselectivity of organocatalyzed aldol reactions can in some cases be significantly enhanced.

Scheme 1. Synthesis of Aldol Products from Cyclohexanone[a]



[a] Structures **5** and **6** show the relative configuration of the products. The absolute configuration of the major enantiomer depends on which enantiomer of proline is used as the catalyst.

As a test reaction, the aldol reaction between cyclohexanone and 4-trifluoromethylbenzaldehyde **4a** was selected (Scheme 1), with reactions being carried out under the optimized conditions we have previously reported[9] using 2 equiv of cyclohexanone, 10 mol % of proline, and 1 equiv of water (relative to the amount of aldehyde). The results of reactions carried out in both racemic and (*R*)-propylene carbonate are presented in Table 1.

Entry 1 of Table 1 shows the standard result obtained using racemic propylene carbonate **2** as solvent. Replacing racemic solvent **2** by enantiomerically pure (*R*)-**2** resulted in a dramatic decrease in the chemical yield, enantioselectivity of both diastereomers, and diastereoselectivity of the reaction (Table 1, entry 2). In contrast, when (*R*)-proline was used as the catalyst in (*R*)-**2**, the chemical yield, diastereoselectivity, and enantioselectivity of the major diastereomer of the product were all increased relative to those obtained in racemic solvent (Table 1, entry 3). A control experiment (Table 1, entry 4) in which racemic proline was used as catalyst in (*R*)-**2** showed that the aldol reaction did occur in moderate yield and with good diastereoselectivity, but with no asymmetric induction. These results clearly indicate that, while the chiral solvent by itself cannot induce asymmetry into the aldol reaction, it can appreciably alter the effectiveness of proline-catalyzed reactions. The combination of (*R*)-**2** and (*R*)-**3** constitutes a matched pair, while (*R*)-**2** and (*S*)-**3** forms a mismatched pair.

Table 1. Synthesis of Aldol Products **5a**−**f** and **6a**−**e** in Chiral and Achiral Propylene Carbonate

entry	aldehyde	solvent	proline	yield (%)[h]	de (**5**:**6**)[a]	ee **5** (%)[b]	ee **6** (%)[b]
1	**14a**	(*RS*)-**2**	(*S*)	49	4.7:1	93[c]	68[e]
2	**4a**	(*R*)-**2**	(*S*)	26	3.3:1	52[c]	44[e]
3	**4a**	(*R*)-**2**	(*R*)	63	6.3:1	96[d]	66[f]
4	**4a**	(*R*)-**2**	(*RS*)	43	6.1:1	1	0
5[g]	**4b**	(*RS*)-**2**	(*S*)	47	4.5:1	93[c]	77[e]
6[g]	**4b**	(*R*)-**2**	(*S*)	65	6:1	85[c]	55[e]
7[g]	**4b**	(*R*)-**2**	(*R*)	75	7:1	96[d]	75[f]
8	**4c**	(*RS*)-**2**	(*S*)	21	4.8:1	95[c]	73[e]
9	**4c**	(*R*)-**2**	(*S*)	22	3:1	60[c]	51[e]
10	**4c**	(*R*)-**2**	(*R*)	36	4.5:1	97[d]	82[f]
11	**4d**	(*RS*)-**2**	(*S*)	83	7.9:1	91[c]	86[e]
12	**4d**	(*R*)-**2**	(*S*)	89	3.6:1	85[c]	68[e]
13	**4d**	(*R*)-**2**	(*R*)	94	5.9:1	91[d]	79[f]
14	**4e**	(*RS*)-**2**	(*S*)	22	7.4:1	92[c]	91[e]
15	**4e**	(*R*)-**2**	(*S*)	67	7.6:1	95[c]	79[e]
16	**4e**	(*R*)-**2**	(*R*)	72	9.2:1	96[d]	86[f]
17	**4f**	(*RS*)-**2**	(*S*)	98	100:0	98[c]	
18	**4f**	(*R*)-**2**	(*S*)	89	100:0	98[c]	
19	**4f**	(*R*)-**2**	(*R*)	98	100:0	98[d]	

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis on a Chiralpak AD-H column and comparison of retention times with literature data[13] and racemic standards.[14] The low intensity of the HPLC peaks corresponding to compound **6** means that differences in ee of <10% are not significant. [c] Absolute configuration of major enantiomer: *S* adjacent to the carbonyl and *R* at the benzylic position. [d] Absolute configuration of major enantiomer: *R* adjacent to the carbonyl and *S* at the benzylic position. [e] Absolute configuration of major enantiomer: *SS*. [f] Absolute configuration of major enantiomer: *RR*. [g] Reaction time 6 days. [h] After chromatographic purification.

The aldol reaction between cyclohexanone and five other aromatic aldehydes **4b**−**f** was also carried out using both enantiomers of proline in (*R*)-**2**. The results along with those obtained in (*RS*)-**2** for comparison are shown in Table 1. Benzaldehyde **4b** (Table 1, entries 5−7) and 4-bromobenzaldehyde **4c** (Table 1, entries 8−10) were slow reacting substrates, and reactions involving benzaldehyde in propylene carbonate were left for 6 days to obtain moderate yields of aldol products **5** and **6b**. In these cases, the difference between the enantioselectivities obtained in racemic **2** and

(11) Recent catalyst developments allow the synthesis of cyclic carbonates to be carried out under very mild conditions using waste CO_2: (a) Meléndez, J.; North, M.; Pasquale, R. *Eur. J. Inorg. Chem.* **2007**, 3323. (b) Meléndez, J.; North, M.; Pasquale, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 2946. (c) Meléndez, J.; North, M.; Villuendas, P. *Chem. Commun.* **2009**, 2577. (d) North, M.; Villuendas, P.; Young, C. *Chem.—Eur. J.* **2009**, 11454. (e) Metcalfe, I. S.; North, M.; Pasquale, R.; Thursfield, A. *Energy Environ. Sci.* **2010**, *3*, 212.

(12) Silva, L. B.; Freitas, L. C. G. *J. Mol. Struct. (THEOCHEM)* **2007**, *806*, 23.

(13) (a) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417. (b) Gruttadauria, M.; Giacalone, F.; Marculescu, A. M.; Meo, P. L.; Riela, S.; Noto, R. *Eur. J. Org. Chem.* **2007**, 4688.

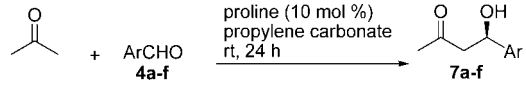
(14) Billimoria, J. D. *J. Chem. Soc.* **1955**, 1126.

in (*R*)-**2** was not particularly pronounced (Table 1, entries 5 and 7, and Table 1, entries 8 and 10), but there was still a significant difference between the results obtained in (*R*)-**2** using (*R*)- and (*S*)-proline (Table 1, entries 6 and 7, and Table 1, entries 9 and 10).

4-Nitrobenzaldehyde **4d** and 3-nitrobenzaldehyde **4e** were both excellent substrates for the proline-catalyzed aldol reaction. In the case of the 4-nitro isomer, the difference in results obtained using the matched and mismatched systems in chiral propylene carbonate (Table 1, entries 12 and 13) was again more pronounced than the difference between results carried out in racemic propylene carbonate and the matched chiral system (Table 1, entries 11 and 13), which both gave the major *anti*-aldol product **5d** in high yield and with 91% enantioselectivity. For the 3-nitro isomer, however, the chemical yield, diastereoselectivity, and enantioselectivity of **5e** were all better using the combination of (*R*)-proline and (*R*)-**2** than those obtained using racemic solvent or the mismatched pair of chiral solvent and chiral catalyst (Table 1, entries 14−16).

Pentafluorobenzaldehyde **4f** was an excellent substrate for proline-catalyzed aldol reactions in propylene carbonate (Table 1, entries 17−19). In all cases, only the *anti*-aldol product **5f** was formed, and the reactions exhibited high chemical yields and 98% enantioselectivities. Even in this case, however, the difference in yield between the matched and mismatched chiral solvent/catalyst pairs was notable (Table 1, entries 18 and 19).

Scheme 2. Synthesis of Aldol Products **7a**−**f** from Acetone[a]



a: Ar = 4-$F_3CC_6H_4$ **b**: Ar = C_6H_5
c: Ar = 4-BrC_6H_4 **d**: Ar = 4-$O_2NC_6H_4$
e: Ar = 3-$O_2NC_6H_4$ **f**: Ar = C_6F_5

[a] Structures **7a**−**f** show the absolute configuration of the major enantiomer obtained when (*S*)-proline is used as the catalyst.

To investigate if the chiral solvent effect was restricted to aldol reactions of cyclohexanone, the aldol reaction between aromatic aldehydes **4a**−**f** and acetone was investigated (Scheme 2). Acetone is a less reactive enamine precursor than cyclohexanone, and these reactions required 8 equiv of acetone relative to the aldehyde. Acetone is also significantly more polar than cyclohexanone, and we have previously shown that, for aldol reactions carried out in cyclic carbonates **1** or *rac*-**2**, no water need be added to the solvent, and comparable results are obtained in both solvents.[9] The results obtained using both enantiomers of proline in (*R*)-**2** along with results in *rac*-**2** are given in Table 2.

When 4-trifluoromethylbenzaldehyde **4a** was used as the substrate (Table 2, entries 1−3), there was little difference in yield or enantioselectivity between reactions carried out in racemic or enantiomerically pure propylene carbonate, though the highest yield and enantiomeric excess were

Table 2. Synthesis of Aldol Products **7a**−**f** in Chiral and Achiral Propylene Carbonate

entry	aldehyde	solvent	proline	yield (%)[b]	ee (%)[a]
1	**4a**	(*RS*)-**2**	(*S*)	94	62 (*R*)
2	**4a**	(*R*)-**2**	(*S*)	99	61 (*R*)
3	**4a**	(*R*)-**2**	(*R*)	99	64 (*S*)
4	**4b**	(*RS*)-**2**	(*S*)	58	63 (*R*)
5	**4b**	(*R*)-**2**	(*S*)	29	64 (*R*)
6	**4b**	(*R*)-**2**	(*R*)	69	66 (*S*)
7	**4b**	(*R*)-**2**	(*RS*)	50	0
8	**4c**	(*RS*)-**2**	(*S*)	71	67 (*R*)
9	**4c**	(*R*)-**2**	(*S*)	69	60 (*R*)
10	**4c**	(*R*)-**2**	(*R*)	81	77 (*S*)
11	**4d**	(*RS*)-**2**	(*S*)	96	64 (*R*)
12	**4d**	(*R*)-**2**	(*S*)	85	56 (*R*)
13	**4d**	(*R*)-**2**	(*R*)	99	66 (*S*)
14	**4e**	(*RS*)-**2**	(*S*)	99	51 (*R*)
15	**4e**	(*R*)-**2**	(*S*)	98	47 (*R*)
16	**4e**	(*R*)-**2**	(*R*)	99	57 (*S*)
17	**4f**	(*RS*)-**2**	(*S*)	85	83 (*R*)
18	**4f**	(*R*)-**2**	(*S*)	99	76 (*R*)
19	**4f**	(*R*)-**2**	(*R*)	99	83 (*S*)

[a] Determined by chiral HPLC analysis on a Chiralpak AD-H (**7b**,**e**,**f**) or AS-H (**7a**,**c**,**d**) column and comparison of retention times with literature data[8,15] and racemic standards.[16] [b] After chromatographic purification.

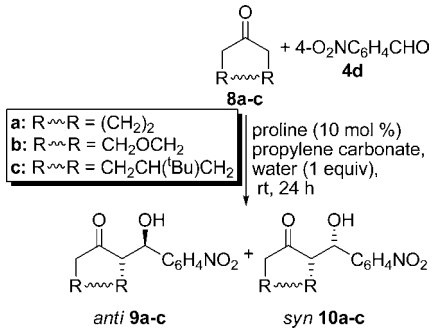
obtained using the matched pair of (*R*)-**2** and (*R*)-proline (Table 2, entry 3). Reactions involving benzaldehyde **4b** as substrate also showed little difference in enantioselectivity when carried out in racemic or nonracemic **2** (Table 2, entries 4−6). However, in this case, there was a significant difference between the chemical yields obtained using the matched and mismatched pairs of chiral catalyst/solvent, and these bracketed the chemical yield obtained in racemic **2**. A control experiment was also carried out using aldehyde **4b** in which racemic proline was used as the catalyst in (*R*)-**2** (Table 2, entry 7). While this reaction gave a reasonable yield of aldol product **7b**, the product was found to be racemic, showing that the chiral solvent alone cannot induce asymmetry into aldol reactions involving acetone.

When 4-bromobenzaldehyde **4c**, 4-nitrobenzaldehyde **4d**, or 3-nitrobenzaldehyde **4e** were used as substrates, the enantioselectivity obtained in racemic **2** was intermediate between the results obtained for the matched and mismatched pairs of solvent and catalyst (Table 2, entries 8−16). In the case of substrates **4c** and **4d**, the same trend was apparent in the chemical yields (Table 2, entries 8−13), though for substrate **4e**, the chemical yield was always 98−99% (Table 2, entries 14−16). For pentafluorobenzaldehyde **4f** (Table 2, entries 17−19), the mismatched solvent/catalyst system gave a product with lower enantiomeric excess than either the matched system or the use of racemic solvent.

(15) (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285. (c) Zhou, Y.; Shan, Z. *Tetrahedron: Asymmetry* **2006**, *17*, 1671. (d) Chandrasekhar, S.; Reddy, N. R.; Sultana, S. S.; Narsihmulu, Ch.; Reddy, K. V. *Tetrahedron* **2006**, *62*, 338.

(16) Shokat, K.; Uno, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 2261.

Scheme 3. Synthesis of Aldol Products from Cyclic Ketones **8a**−**c**[a]



[a] Structures **9** and **10** show the relative configuration of the products. The absolute configuration of the major enantiomer depends on which enantiomer of proline is used as the catalyst.

Having shown that the combination of (*R*)-**2** and (*R*)-**3** was the matched pair for all aldol reactions involving cyclohexanone or acetone, the application of this system to aldol reactions of three other cyclic ketones **8a**−**c** with 4-nitrobenzaldehyde **4d** was investigated (Scheme 3) using the reaction conditions used for cyclohexanone, and the results are presented in Table 3. In racemic **2**, cyclopentanone **8a** gave products **9**/**10a** with essentially no diastereoselectivity, and with good enantioselectivity only for *anti*-isomer **9a** (Table 1, entry 1). Use of (*R*)-proline in (*R*)-**2** increased the diastereoselectivity to 2:1 in favor of the *anti*-isomer but did not change the enantioselectivities (Table 2, entry 2).

4-Pyranone **8b** was an excellent substrate for the aldol reaction, even in racemic **2** (Table 3, entry 3), but the diastereoselectivity and enantioselectivity of the major *anti*-isomer **9b** were enhanced still further when the aldol reaction was catalyzed by (*R*)-**3** in (*R*)-**2** (Table 3, entry 4). Finally, 4-*tert*-butyl cyclohexanone **8c** was only a moderate substrate for the aldol reaction in racemic **2** (Table 3, entry 5), though

(17) (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (b) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649. (c) Gandhi, S.; Singh, V. K. *J. Org. Chem.* **2008**, *73*, 9411. (d) Da, C.-S.; Che, L.-P.; Guo, Q.-P.; Wu, F.-C.; Ma, X.; Jia, Y.-N. *J. Org. Chem.* **2009**, *74*, 2541.

Table 3. Synthesis of Aldol Products **9a**−**c** and **10a**−**c** in Chiral and Achiral Propylene Carbonate

entry	ketone	solvent	proline	yield (%)[h]	de (**9**:**10**)[a]	ee **9** (%)[b]	ee **10** (%)[b]
1	**8a**	(*RS*)-**2**	(*S*)	99	1.2:1	83[c]	12[e]
2	**8a**	(*R*)-**2**	(*R*)	99	2.1:1	80[d]	11[f]
3	**8b**	(*RS*)-**2**	(*S*)	99	7:1	88[c]	30[e]
4	**8b**	(*R*)-**2**	(*R*)	99	13:1	94[d]	25[f]
5	**8c**	(*RS*)-**2**	(*S*)	58	1.7:1	99[c]	*g*
6	**8c**	(*R*)-**2**	(*R*)	72	3.9:1	99[d]	*g*

[a] Determined by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC analysis on a Chiralpak AD-H column and comparison of retention times with literature data[8,13,15a,17] and racemic standards made using racemic proline in racemic **2**. Due to the low intensity of the HPLC peaks corresponding to compound **10b**, the differences in ee of **10b** in entries 3 and 4 are not significant. [c] Absolute configuration of major enantiomer: *S* adjacent to the carbonyl and *R* at the benzylic position. [d] Absolute configuration of major enantiomer: *R* adjacent to the carbonyl and *S* at the benzylic position. [e] Absolute configuration of major enantiomer: *SS*. [f] Absolute configuration of major enantiomer: *RR*. [g] The sample had to be purified prior to HPLC analysis, resulting in removal of the *syn*-diastereomer. [h] After chromatographic purification.

the *anti*-product **9c** was obtained with excellent enantioselectivity. The chemical yield and diastereoselectivity were, however, significantly enhanced by use of (*R*)-**2** in (*R*)-**3** (Table 3, entry 6).

In conclusion, we have demonstrated the first chiral solvent effect in asymmetric organocatalysis. The methodology is generally applicable and can enhance the enantioselectivity, diastereoselectivity, and chemical yield obtained in proline-catalyzed reactions.

Acknowledgment. The authors thank Shasun Pharma Solutions Ltd. for a generous donation of (*R*)-propylene carbonate.

Supporting Information Available: Experimental procedures and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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