

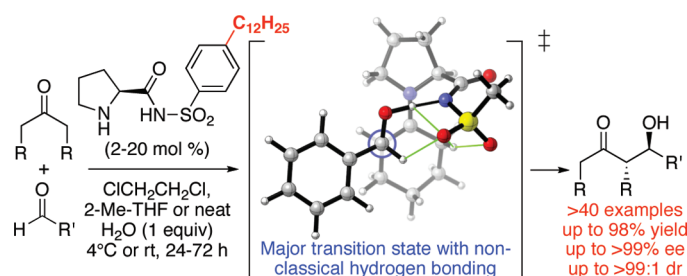
Highly Stereoselective and Scalable *anti*-Aldol Reactions Using *N*-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide: Scope and Origins of StereoselectivitiesHua Yang, Subham Mahapatra,[†] Paul Ha-Yeon Cheong,^{*,†} and Rich G. Carter*

Department of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, Oregon 97331.

[†]These researchers conducted the computational studies. Paul Ha-Yeon Cheong is the corresponding author for the computational portions of the article.

paul.cheong@oregonstate.edu; rich.carter@oregonstate.edu

Received July 30, 2010



A highly enantio- and diastereoselective *anti*-aldol process (up to > 99% ee, > 99:1 dr) catalyzed by a proline mimetic—*N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide—has been developed. Catalyst loading as low as 2 mol % can be employed. Use of industry-friendly solvents for this transformation as well as neat reaction conditions have been demonstrated. The scope of this transformation on a range of aldehydes and ketones is explored. Density functional theory computations reveal that the origins of enhanced diastereoselectivity are due to the presence of nonclassical hydrogen bonds between the sulfonyl group, the electrophile, and the catalyst enamine that favor the major *anti-Re* aldol TS in the Houk–List model.

Introduction

The aldol reaction has been a central focus of the chemical community since observed by Kane¹ and later by Borodin,² Kekulé,³ and Wurtz.⁴ Subsequent decades led to numerous advances that helped to address the stereoselectivity of the reaction process.⁵ These accomplishments have paved the way for modern polyketide and macrolide synthesis.⁶ In addition to these important discoveries, a wealth of effort has been directed to the development of alternate reaction

protocols, which generate a net aldol adduct but do not utilize traditional aldol starting materials.^{7–9} Zimmerman and Traxler proposed over 50 years ago that controlling *syn*- versus *anti*-aldol adducts may be explained through the use of cyclic, chairlike transition states.¹⁰ Alternate acyclic transition states have also been proposed to address stereochemical outcome of other aldol reactions.¹¹ Metal-based enolates have proven particularly useful in controlling both the enantio- and diastereoselectivity in aldol processes through

(1) Kane, R. *Ann. Phys. Chem., Ser. 2* **1838**, 44, 475.
(2) (a) Borodin, A. *J. Prakt. Chem.* **1864**, 93, 413–425. (b) Podlech, J. *Angew. Chem., Int. Ed.* **2010**, 49, 2010, DOI: 10.1002/anie.201002023.
(3) Kekulé, A. *Ber. Dtsch. Chem. Ges.* **1869**, 2, 365–368.
(4) Wurtz, A. *Bull. Soc. Chim. Fr.* **1872**, 17, 436–442.
(5) (a) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, 20, 131–173. (b) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.
(6) (a) Paterson, I. *Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2008; pp 293–298. (b) Brodmann, T.; Lorenz, M.; Schaeckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174–192.

(7) (a) Jung, M. E.; Salehi-Rad, R. *Angew. Chem., Int. Ed.* **2009**, 48, 8766–8769. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, 115, 12208–12209.
(8) Lohse-Frafel, N.; Carreira, E. M. *Chem.—Eur. J.* **2009**, 15, 12065–12081.
(9) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2005**, 127, 3694–3695.
(10) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, 79, 1920–1923.
(11) (a) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004. (b) Mahrwald, R. *Aldol Reactions*; Springer: New York, 2009.

the use of chiral directing groups.^{11,12} Metal-catalyzed, enantioselective protocols have also been developed which offer the ability to reduce the dependence on auxiliary-based approaches for accomplishing these transformations.¹³

Considerable recent excitement has been generated by the resurgence¹⁴ of organocatalysis as a practical and user-friendly method for facilitating these types of transformations.¹⁵ Many of the catalyst scaffolds are based on amino acid architecture with 2° amines proving particularly useful. Consequently, a large percentage of organocatalysts find their origins in proline. These organocatalyzed reactions often are performed at ambient or near-ambient temperatures and do not require the careful exclusion of moisture and oxygen. Organocatalyzed aldol reactions also tend to provide access to the *anti*-aldol adduct as the major product from the transformation. While alternate approaches to accessing enantioenriched *anti*-aldol adducts do exist,^{16,17} organocatalyzed protocols have often proven attractive based on stereoselectivity and practicality. The mechanistic underpinnings of the proline-catalyzed aldol reaction transformation have been previously explored;¹⁸ however, the divergent nature of the stereoselectivities based on catalyst modification and substrate scope is not fully understood. In this article, we

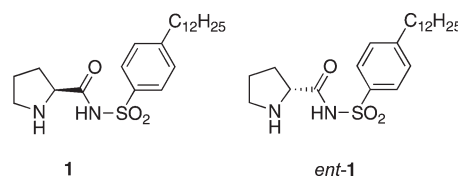


FIGURE 1. *N*-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide.

provide a full account of our organocatalyzed process for facilitating highly enantio- and diastereoselective aldol reactions using the practical proline mimetic *N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (**1**)¹⁹ and a detailed analysis of the enhanced stereoselectivities of this catalyst (Figure 1).

Results and Discussion

Proline and proline-derived organocatalysts have proven useful in a range of transformations.²⁰ Our interest in this field arose during our synthetic work toward the alkaloid lycopodine (Scheme 1).^{21,22} We required an organocatalyst for an intramolecular Michael addition which possessed both a 2° amine and an organic acid motif. These efforts ultimately resulted in the development of a catalyst scaffold based on a proline sulfonamide. A more detailed discussion of this transformation has been published elsewhere.²³

Solvent Effects. With our development of catalyst **1** for enantioselective, intramolecular keto-sulfone Michael reactions, we became intrigued by the possibility that this catalyst scaffold would have more widespread applicability. Given the considerable importance of the aldol reaction in modern synthetic organic chemistry, the application of our sulfonamide catalyst system in this setting seemed appropriate.²⁴ While numerous examples of organocatalyzed aldol reactions have

(12) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115.

(13) (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325–355. (b) Carreira, E. M.; Fettes, A.; Marti, C. *Org. React.* **2006**, *67*, 1–216. (c) Mlynarski, J.; Paradowska, J. *Chem. Soc. Rev.* **2008**, *37*, 1502–1511. (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600–1632.

(14) (a) Prelog, V.; Wihelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634–1660. (b) Yamada, S.-I.; Otani, G. *Tetrahedron Lett.* **1969**, 4237–3240. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496–497. (d) Hiroi, K.; Achiwa, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1972**, *20*, 246–257. (e) Hiroi, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 47–53. (f) Otani, G.; Yamada, S.-I. *Chem. Pharm. Bull.* **1973**, *21*, 2112–2118. (g) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621. (h) Hajos, Z. G.; Parrish, D. R. *Organic Syntheses*; Wiley & Sons: New York, 1990; Collect. Vol. 7, pp 363–368.

(15) For recent reviews, see: (a) Zlotin, S. G.; Kucherenko, A. S.; Belskaya, I. P. *Russ. Chem. Rev.* **2009**, *78*, 737–784. (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4338–4360. (d) Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichimica Acta* **2008**, *41*, 3–11. (e) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (g) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797–5815.

(16) Select auxiliary-based examples: (a) Oppolzer, W.; Marco-Contelles, J. *Helv. Chim. Acta* **1986**, *69*, 1699–1703. (b) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747–5750. (c) Gennari, C.; Hewkin, C. T.; Molinari, F.; Bernardi, A.; Comotti, A.; Goodman, J. M.; Paterson, I. J. *Org. Chem.* **1992**, *57*, 5173–5177. (d) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586–2587. (e) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652. (f) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392–393. (g) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. J. *Org. Chem.* **2003**, *68*, 8162–8169. (h) Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2003**, *5*, 1063–1066. (i) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591–594. (j) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569–2572. (k) Fanjul, S.; Humle, A. N. *J. Org. Chem.* **2008**, *73*, 9788–9791.

(17) Select transition-metal-mediated, catalytic asymmetric-based examples: (a) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860. (b) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292–3302. (c) Denmark, S. E.; Pham, S. M.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *J. Org. Chem.* **2006**, *71*, 3904–3922.

(18) (a) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475–2479. (c) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569. (d) Calderon, F.; Doyagez, E. G.; Cheong, P. H.-Y.; Fernandez-Mayoralas, A.; Houk, K. N. *J. Org. Chem.* **2008**, *73*, 7916–7920. (e) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766–5768. (f) Cheong, P. H.-Y.; Houk, K. N. *Synthesis* **2005**, 1533–1537.

(19) For a preliminary account of this work, see: Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4649–4652.

(20) (a) *Chem. Rev.* **2007**, Issue 12, 5413–5883. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660. (c) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308. (d) Merino, P.; Marques-Lopez, E.; Tejero, T.; Herrera, R. P. *Tetrahedron* **2009**, *65*, 1219–1234. (e) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807–1821. (f) Palomo, C.; Oiarbide, M.; Lopez, R. *Chem. Soc. Rev.* **2009**, *38*, 632–653. (g) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583–1614. (h) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178–2189. (i) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. *Curr. Org. Chem.* **2009**, *13*, 1431–1474. (j) Liu, X.; Lin, L. *Feng, X. Chem. Commun.* **2009**, 6145–6158. (k) Raj, M.; Singh, V. K. *Chem. Commun.* **2009**, 6687–6703. (l) Merino, P.; Marques-Lopez, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1–26. (m) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167–178. (n) Xu, L.-W.; Li, L.; Shi, Z. H. *Adv. Synth. Catal.* **2010**, *252*, 243–279.

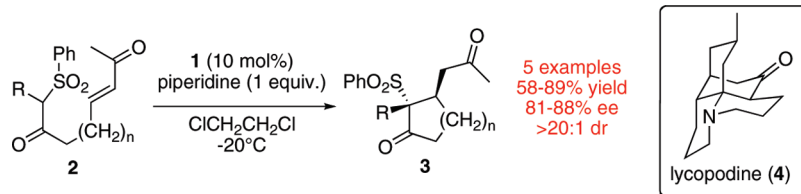
(21) (a) Kobayashi, J.; Morita, H. *Alkaloids* **2005**, *61*, 1–57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(22) (a) Bödeker, K. *Justus Liebig's Ann. Chem.* **1881**, *208*, 363. (b) Achmatowicz, O.; Uzieblo, W. *Rocz. Chem.* **1938**, *18*, 88–95. (c) Ayer, W. A.; Iverach, G. G. *Tetrahedron Lett.* **1962**, 87–92. (d) Rogers, D.; Quick, A.; Hague, M. *Acta Crystallogr.* **1974**, *B30*, 552–553. (e) Hague, M.; Rogers, D. J. *Chem. Soc., Perkin Trans. 2* **1975**, 93–98.

(23) Yang, H.; Carter, R. G. *J. Org. Chem.* **2010**, *75*, 4929–4938.

(24) (a) Berkessel, A.; Koch, B.; Lex, J. *Adv. Synth. Catal.* **2004**, *346*, 1141–1146. (b) Dahlin, N.; Boegevig, A.; Adolfsen, H. *Adv. Synth. Catal.* **2004**, *346*, 1101–1105. (c) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96. (d) Sundén, H.; Dahlin, N.; Ibrahim, I.; Adolfsen, H.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3385–3389. (e) Bellis, E.; Vasiatou, K.; Kokotos, G. *Synthesis* **2005**, 2407–2413. (f) Wu, Y.; Zhang, Y.; Yu, M.; Zhao, G.; Wang, S. *Org. Lett.* **2006**, *8*, 4417–4420. (g) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417–5419. (h) Vogt, H.; Baumann, T.; Nieger, M.; Braese, S. *Eur. J. Org. Chem.* **2006**, 5315–5338. (i) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961. (j) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem.—Eur. J.* **2007**, *13*, 10246–10256. (k) Huang, J.; Zhang, X.; Armstrong, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 9073–9077. (l) For related series, see: Wang, X.-J.; Zhao, Y.; Liu, J.-T. *Org. Lett.* **2007**, *9*, 1343–1345. (m) Zu, L.; Xie, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211–1214.

SCHEME 1. Development of an Organocatalyzed, Intramolecular Michael Addition and Application to Lycopodine



been reported based on proline, we were struck by the fact that the vast majority of these catalyst systems employed polar, aprotic solvent systems (e.g., DMSO, DMF). This solvent choice is primarily based on the poor solubility of proline and related derivatives in nonpolar, aprotic solvents. We reasoned that if improved levels of stereoselectivity could be realized in nonpolar media, it would allow for the more subtle differentiation between competing transition states.

While use of these polar aprotic solvents (e.g., MeCN, DMF, DMSO) are common in academic research laboratories, their polarity poses serious challenges in industrial settings with aqueous phase miscibility, product isolation issues,²⁵ and solvent reclamation.²⁶ DMSO is a particularly challenging solvent, as solvent recycling on an industrial scale is typically impossible.²⁷ The development of new catalysts and processes that use relatively inexpensive, nonpolar solvents is crucial, due to the specific industrial advantages associated with efficient aqueous phase splits and ease of recycle at scale.²⁸ Alternatively, the development of synthetic processes performed in the absence of solvents (or minimal solvent volumes) can effectively eliminate chemical waste in industrial processes (in some cases, solvent is always required to effectively dissipate exotherms and ensure even heat transfer throughout the medium).²⁹

The proline dodecylphenylsulfonamide **1** has greatly improved solubility properties in nonpolar solvents, as compared to proline, as illustrated in Figure 2. Comparable weights (300 mg) of proline and our sulfonamide **1** were mixed with 1.0 mL of dichloromethane at ambient temperature. Proline is essentially insoluble in this solvent (calculated solubility < 5 mg/mL in CH₂Cl₂), as were proline tetrazole and proline phenylsulfonamide. In contrast, dodecylphenylsulfonamide **1** is completely soluble under these conditions.



FIGURE 2. Solubility comparison of organocatalysts in CH₂Cl₂. The left image illustrates that 300 mg of sulfonamide **1** is soluble in 1 mL of CH₂Cl₂, and the right image demonstrates that 300 mg of proline is not readily soluble in 1 mL of CH₂Cl₂.

(25) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2003; p 653.

(26) P. J. Dunn, P. G. 10th Annual Green Chemistry and Engineering Conference, Abstract 184 [see also *Chem. Eng. News* **2006**, 84 (30), 36].

We first explored the optimization of the catalyst on the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde (Table 1). This reaction has become the standard reaction explored in most organocatalyzed aldol publications and provided us with a good metric for analysis. We were primarily interested in developing a protocol that preformed well in nonpolar organic solvents. Given the high solubility of the sulfonamide catalyst in dichloromethane (DCM), we started our screening process using it as the baseline solvent (entry 1). While the reaction performed reasonably well in that solvent, we observed dramatic improvements in yield by switching the solvent to 1,2-dichloroethane (DCE) (entry 2). We^{23,30} and others³¹ have observed similar results by replacement of DCM with DCE. Reduction of catalyst loading led to a reduction in chemical efficiency (entry 3). Use of ethanol as a potential proton source had minimal impact on the transformation (entries 4–6). Fortunately, the addition of a single equivalent of water had a dramatic positive impact on the rate and selectivity of the transformation (entry 7). Pihko and others have observed the significant importance of water in the rate, yield, and stereoselectivity of the reaction.³² Excess water did not appear to have a significant additional impact on the transformation (entry 8). Use of DCE as solvent continued to be preferred to DCM for achieving optimum levels of diastereoselectivity (entries 7 and 9). The reaction could alternatively be performed in water as solvent (entry 10) at reduced catalyst loading or in 2-methyltetrahydrofuran (2-Me-THF, entry 11) with excellent levels of selectivity. Reduction in the reaction temperature to 4 °C led to the outstanding levels of chemical

(27) Vinci, D.; Donaldson, M.; Hallett, J. P.; John, E. A.; Pollet, P.; Thomas, C. A.; Grilly, J. D.; Jessop, P. G.; Liotta, C. L.; Eckert, C. A. *Chem. Commun.* **2007**, 1427–1429.

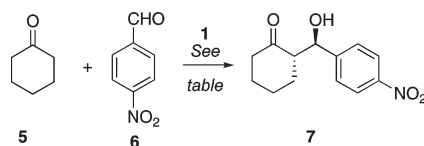
(28) (a) Aycock, D. F. *Org. Process Res. Dev.* **2007**, 11, 156–159. (b) Butters, M.; Catterick, D.; Craig, A.; A. Curzons, A.; Dale, D.; Gillmore, A.; Green, S. P.; Marziano, I.; Sherlock, J.-P.; White, W. *Chem. Rev.* **2006**, 106, 3002–27. (c) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. *Org. Process Res. Dev.* **2007**, 11, 133–137. (d) Delhaye, L.; Ceccato, A.; Jacobs, P.; Kottgen, C.; Merschaert, A. *Org. Process Res. Dev.* **2007**, 11, 160–164. (e) Fuenfschilling, P. C.; Hoehn, P.; Mutz, J.-P. *Org. Process Res. Dev.* **2007**, 11, 13–18. (f) Anderson, N. G. *Practical Process Research & Development*; Academic Press: New York, 2000.

(29) (a) Metzger, J. O. *Org. Synth. Highlights V* **2003**, 82–92. (b) Varma, R. S.; Ju, Y. *Green Sep. Processes* **2005**, 53–87. (c) Walsh, P. J.; Li, H.; de Parrodi, C. A. *Chem. Rev.* **2007**, 107, 2503–2545.

(30) Carlson, E. K.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, 73, 5155–5158.

(31) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 50, 7–509.

(32) Water effects in organocatalyzed aldol reactions: (a) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891–1896. (b) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, 62, 317–328. (c) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, 45, 958–961. (d) Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem.—Eur. J.* **2007**, 13, 10246–10256. (e) Li, X.-J.; Zhang, G.-W.; Wang, L.; Hu, M.-Q.; Ma, J.-A. *Synlett* **2008**, 1255–1259. Effects of water on organocatalyzed Mannich reactions: (f) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, 5, 4301–4304. (g) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Cat.* **2004**, 346, 1131–1140.

TABLE 1. Optimization of Reaction Conditions^a

entry	conditions ^a	mol % (1)	temp	time (h)	yield (%)	ee % ^b	dr ^c
1	CH ₂ Cl ₂	20	rt	36	51	97	15:1
2	DCE	20	rt	46	92	95	12:1
3	DCE	10	rt	36	55	95	11:1
4	DCE/EtOH (99:1)	20	rt	36	96	97	14:1
5	DCE/EtOH (99:1)	10	rt	36	60	95	18:1
6	EtOH	20	rt	36	82	80	6:1
7	DCE, H ₂ O (1 equiv)	20	rt	14	96	97	36:1
8	DCE, H ₂ O (10 equiv)	20	rt	16	96	98	31:1
9	CH ₂ Cl ₂ , H ₂ O (1 equiv)	20	rt	16	95	97	18:1
10	H ₂ O	10	rt	36	95	95	20:1
11	2-Me-THF, H ₂ O (1 equiv)	20	rt	16	85	94	30:1
12	DCE/EtOH (99:1)	20	4 °C	36	97	97	53:1
13	DCE, H ₂ O (1 equiv)	20	4 °C	30	95	99	> 99:1 ^c
14 ^d	neat, H ₂ O (1 equiv)	2	rt	36	96	96	> 99:1

^aAll reactions were performed at 2 M concentration of 6 in solution and with 5 equiv of 5. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis. ^dPerformed using 2 equiv of 5. ^e¹H NMR expansions are provided in the Supporting Information to demonstrate the diastereomeric selectivity for product 7.

yield and stereoselectivities with 99% ee, > 99:1 dr, and 95% chemical yield (entry 12). It is important to note that 1 equiv of water is not readily soluble under the DCE, 4 °C reaction conditions. Immiscible phases can be visually observed, indicating that far less than 1 equiv of water is actually present in the organic phase under these reaction conditions. It is possible that the organocatalyst is acting in part as a phase transfer catalyst between the aqueous and organic phases. We have also developed an alternative procedure requiring just 2 mol % of catalyst loading and reduced equivalents of the cyclohexanone (entry 14). This protocol was performed in the absence of solvent at room temperature with a single of equivalent of water and again provides excellent levels of chemical yield and stereoselectivity.

Catalyst Structure Effects on Stereoselectivities. Next, we screened a range of known organocatalysts under our optimized reaction conditions to provide a comparative analysis. We recognize that each catalyst structure may have reaction parameters which are favorable for optimum performance, but a standardized set of conditions were important to gauge how much of the high diastereoselectivity is a function of the unique structural characteristics of the new sulfonamide catalyst 1. We chose to look at reaction conditions containing 1% ethanol or 1 equiv of water to provide two separate data sets for evaluation. With each catalyst we screened, conditions B (which employed 1 equiv of water) provided higher levels of diastereoselectivity than the ethanol conditions (conditions A). The increased chemical yield with proline under conditions A is likely due to the improved solubility of proline with 1% ethanol present in the reaction mixture. As mentioned previously, immiscible phases are readily formed under conditions B. From the data collected, it appears that the long alkyl chain on the sulfonamide is acting principally to improve solubility in the transformations, leading to improved chemical yields. That said, proline sulfonamides as a group provided superior levels of diastereoselectivity as compared to both proline and proline tetrazole.

We have developed a model to explain the considerable improvements in diastereoselectivity that are uniquely observed

with proline-sulfonamide-catalyzed aldol reactions (Table 2). The intermolecular aldol reaction between the proline sulfonamide enamine of cyclohexanone and benzaldehyde was explored computationally using DFT (B3LYP/6-31G*) geometries and thermochemistries,³³ augmented with SCS-MP2 energies extrapolated to infinite basis (extrapolated from cc-pVTZ and cc-pVQZ results).³⁴ The use of the two-point extrapolation to infinite basis addresses the problem of basis set truncation, a major source of error in computations. Solvation single points were computed for DCM at the B3LYP/6-31+G** level, using the PCM solvation model and UAKS radii.

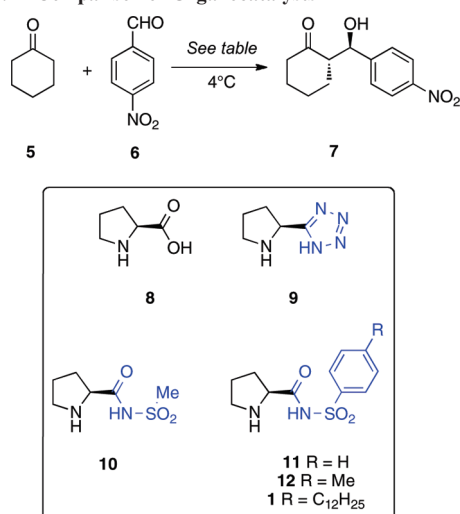
The mechanism of the aldol reaction catalyzed by proline has been reported previously by Houk and co-workers.¹⁸ A strong hydrogen-bonding network between the carboxylic acid and the aldehyde oxygen in the stereodetermining C–C bond-forming transition state (TS) is key for stereocontrol and catalysis. In addition, staggering of the substituents around the forming C–C bond minimizes steric repulsions in the TS. There are four possible diastereomeric enamine aldol transition states that meet these two requirements: TS-*anti-Re*, TS-*anti-Si*, TS-*syn-Re*, and TS-*syn-Si*. *anti/syn* refers to the arrangement of the enamine with respect to the organic acid moiety while *Re/Si* denotes the

(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford CT, 2004.

(34) (a) Weigend, F.; Köhn, A.; Hättig, C. *J. Chem. Phys.* **2002**, *116*, 3175. (b) Helgaker, T.; Klopper, W.; Koch, H.; Noga, J. *J. Chem. Phys.* **1997**, *106*, 9639–9646.

facial attack of the aldehyde electrophile. The most stable transition structures are shown in Figure 3.

TABLE 2. Comparison of Organocatalysts^a



entry	conditions ^a	catalyst	yield (%)	ee % ^b	dr ^c
1	A	8	84	96	6:1
2	B	8	22	98	13:1
3	A	9	81	96	2:1
4	B	9	91	98	7:1
5	A	10	34	97	24:1
6	B	10	42	99	65:1
7	A	11	55	99	40:1
8	B	11	49	98	83:1
9	A	12	54	98	35:1
10	B	12	52	99	92:1
11	A	1	97	97	53:1
12	B	1	95	99	> 99:1

^aConditions A: DCE/EtOH (99:1), 4 °C, 36 h. Conditions B: DCE, H₂O (1 equiv), 4 °C, 30 h. All reactions were performed at 2 M concentration of **6** in solution and with 5 equiv of **5**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis.

The major diastereomer arises from the TS-*anti-Re* and the minor isomer from the TS-*anti-Si*. All theoretical methods employed (B3LYP/6-31G*, B3LYP/6-31G*//SCS-MP2/∞, and B3LYP/6-31G*//MP2/∞) agree in the substantial energetic preference for TS-*anti-Re*. Our calculations indicate that the energetic difference between these two TSs is > 4.5 kcal/mol (or > 3.7 with solvation corrections). It should be noted that the computed difference in this series is 3 kcal/mol more selective than observed for proline.¹⁸

The greatly enhanced diastereoselectivity of proline sulfonamide catalysts over proline is due to two nonclassical hydrogen bonds: between the sulfonamide oxygens and (1) the hydrogens of the aldehyde electrophile (distance O–HCOPh = 2.9 Å) and (2) the cyclohexyl enamine (distance O–enamineH = 3.9 and 2.6 Å) that stabilize the TS-*anti-Re* C–C bond-forming TS. In the disfavored TS-*anti-Si*, these favorable interactions are replaced by steric repulsions from the intercalating phenyl ring (analogous distance O–enamineH = 4.9 and 4.0 Å). This loss of stabilizing electrostatic interactions and gain of repulsive steric interactions in the TS-*anti-Si* cause the proline sulfonamide catalysts to be ~3 kcal/mol more selective than other simpler proline-type catalysts.

An extensive conformational analysis was performed in order to determine the most stable nonclassical hydrogen-bonding pattern by the sulfonamide. Three such arrangements for the TS-*anti-Re* are shown in Figure 4. The sulfonamide conformation found in TS-*anti-Re*, in which the sulfonamide oxygens are in close proximity to the aldehyde hydrogen and the cyclohexyl protons, were found to be much more stable than TS-*anti-Re'* or TS-*anti-Re''*, in which one of these stabilizing nonclassical hydrogen-bonding interactions is missing. This preference is somewhat diminished with solvation corrections (DCE results shown in Figure 4), as expected for any electrostatic interactions.

Nonclassical hydrogen bonds, or electrostatic interactions, are prevalent in literature. Corey was one of the pioneers to propose formyl $\delta^+\text{CH}-\text{O}^{\delta-}$ nonclassical hydrogen bonds as

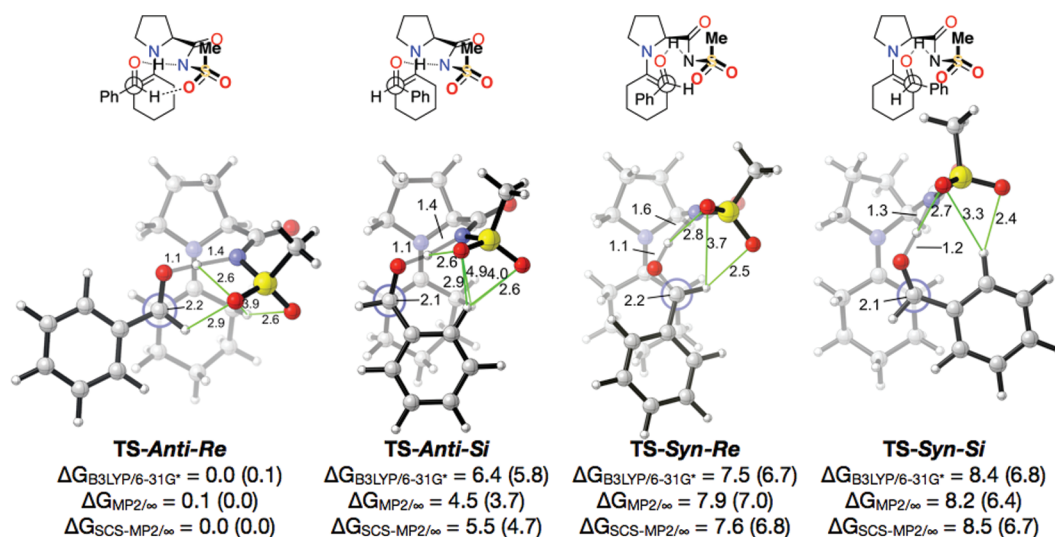


FIGURE 3. Lowest energy transition structures for the aldol reaction between cyclohexanone enamine of proline-sulfonamide and benzaldehyde leading to the formation of each of the diastereomeric products;³⁵ *anti/syn* refers to the arrangement of the enamine with respect to the organic acid moiety while *Re/Si* denotes the facial attack of the aldehyde electrophile. Distances are in angstroms, energies in kcal/mol. Green lines designate possible stabilizing electrostatic interactions. Structures and thermodynamic corrections computed using B3LYP/6-31G* in the gas phase. Numbers in parentheses include solvation corrections for DCE; ∞ designates infinite basis set extrapolation from the Dunning cc-pVTZ and cc-pVQZ basis sets.

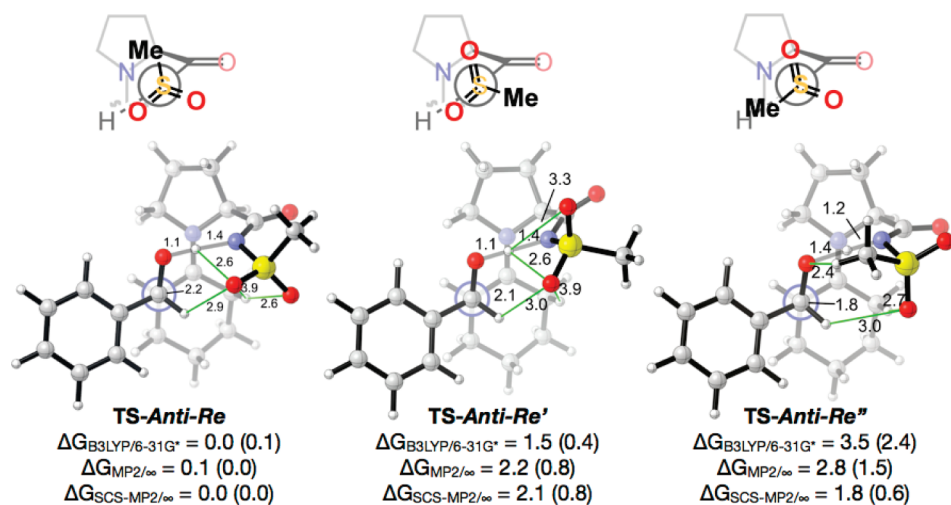


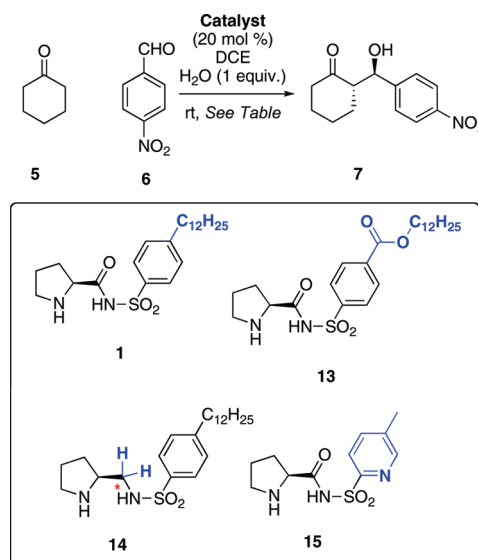
FIGURE 4. Three *anti-Re* transition structures for the aldol reaction between cyclohexanone enamine of proline sulfonamide and benzaldehyde, showing three different conformations of the sulfonamide.³⁵ Distances are in angstroms, energies in kcal/mol. Green lines designate possible stabilizing electrostatic interactions. Structures and thermodynamic corrections computed using B3LYP/6-31G* in the gas phase. Numbers in parentheses include solvation corrections for DCE; ∞ designates infinite basis set extrapolation from the Dunning cc-pVTZ and cc-pVQZ basis sets.

stabilizing interactions.³⁶ Nonclassical hydrogen bonds have been subsequently invoked by other groups to explain stabilizing relationships.³⁷ With respect to organocatalysis, Houk and co-workers pointed out that stabilizing electrostatic interactions between the CH vicinal to the forming iminium and the forming alkoxide (referred to as the $\delta^+\text{NCH}-\text{O}^{\delta-}$ interactions) contributes to the stereoselectivity of proline-catalyzed aldol reactions.^{18a} These nonclassical hydrogen-bonding electrostatic interactions were also demonstrated as stabilizing interactions in stereoselective additions of chiral alcohols to ketenes.³⁸ The magnitude of these stabilizing interactions has also been quantified and has been demonstrated to be significant even in the solution.³⁹

We did consider the possibility that the enhanced diastereoselectivity of the proline sulfonamide catalysts over proline may be due to increased torsional strain around the forming bond that stabilizes the TS-*anti-Re* over other transition states. Interestingly, juxtaposing the proline sulfonamide transition structures with those published for proline,^{18b} we find no evidence that proline sulfonamide transition structures exhibit drastically different torsional strain than proline transition structures. The torsional differences that do exist cannot explain the > 3 kcal/mol greater selectivity exhibited by proline sulfonamides compared to proline.

Variation of Sulfonamide Scaffold. We also explored additional modification of the sulfonamide scaffold (Table 3). For this series, the aldol reaction was conducted at room

TABLE 3. Comparison of Proline Sulfonamides^a



entry	catalyst	time (h)	yield (%)	ee % ^b	dr ^c
1	1	16	96	97	36:1
2	13	60	97	97	26:1
3	14	18	96	<i>d</i>	1.5:1
4	15	24	88	<i>d</i>	2.4:1

^aAll reactions were performed at 2 M concentration of **6** in solution and with 5 equiv of **5**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis. ^dNot determined due to poor diastereoselectivity.

temperature. The baseline experiment with the sulfonamide **1** provides high chemical yield, diastereoselectivity, and enantioselectivity (entry 1). Recently, we reported the development of a second generation (compound **13**) of our catalyst system in which a dodecyl ester is placed on the aromatic ring.⁴⁰ This catalyst proved more effective than catalyst **1** in

(35) Legault, C. Y. *CYLview BETA 1.0*, Copyright 2006–2010.
 (36) (a) Corey, E. J.; Rohde, J. J.; Fischer, A.; Azimioara, M. D. *Tetrahedron Lett.* **1997**, 38, 33–36. (b) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, 38, 37–40. (c) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, 38, 1699–1702. (d) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, 38, 4351–4354.
 (37) For a selected subset of examples, see: (a) Gung, B. W.; Xue, W.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, 124, 10692–10697. (b) Fujiyama, R.; Goh, K.; Kiyooka, S. I. *Tetrahedron Lett.* **2005**, 46, 1211–1215. (c) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, 7, 4299–4302. (d) Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, 73, 1253–1263.
 (38) Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, 126, 10992–11008.
 (39) Cannizzaro, C. E.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, 124, 7163–7169.

(40) Yang, H.; Carter, R. G. *Org. Lett.* **2010**, 12, 3108–3111.

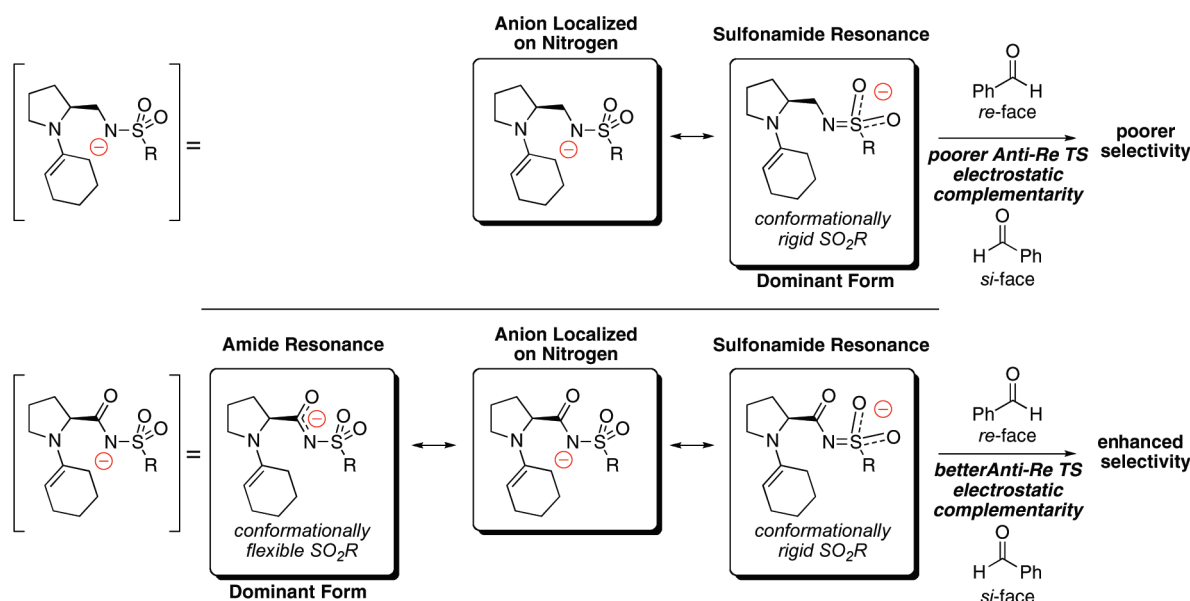


FIGURE 5. Effect of carbonyl motif on catalyst performance.

the formation of cyclohexanones containing a stereogenic all-carbon quaternary center. Interestingly, this catalyst **13** proved significantly less reactive than its parent **1** in the aldol reaction (entry 2). While the enantioselectivity and diastereoselectivity were comparable to catalyst **1**, a nearly 4-fold decrease in reactivity was observed. This difference is likely due to the presumed increased acidity of the sulfonamide N–H in the modified catalyst **13**. In addition to this electronic impact, catalyst **13** is also less soluble than catalyst **1**. This solubility difference may be explained by the difference in the dodecyl chain—linear, homogeneous $\text{C}_{12}\text{H}_{25}$ chain in catalyst **13** and a mixture of branched and linear isomers (e.g., 1-dodecyl, 2-dodecyl, etc.) in catalyst **1**. As a complement to this study, we also explored the removal of the carbonyl of the amide carbon (catalyst **14**). This previously unknown catalyst **14** led to dramatically lower levels of diastereoselectivity (entry 3). Removal of the amide carbonyl should decrease the sulfonamide N–H acidity. Finally, we also probed the placement of an additional Lewis base on the sulfonamide scaffold through pyridyl sulfonamide **15**. While catalyst **15** had not been previously prepared, a closely related desmethyl version was utilized by Nakamura and co-workers in an aldol reaction between acetaldehyde and 4,6-dibromoisatin with modest success (77% yield, 80% ee).⁴¹ In our system, pyridyl catalyst **15** gave greatly reduced diastereoselectivity in the aldol reaction (entry 4). These experiments point to the delicate balance between the nature of the sulfonamide moiety and reaction rate and diastereoselectivity.

We hypothesize that the sulfonamide conformation is key for stereocontrol. The electronics of the sulfonamide moiety is critical in determining this conformation of the sulfonamide (Figure 5). In catalysts **1** and **13**, the attenuation of the developing negative charge on the nitrogen via conjugation to the carbonyl allows the sulfonamide conformational freedom to electrostatically complement the incoming electrophile in the critical C–C bond-forming TS (bottom, Figure 5). The exposure of the aldehyde hydrogen to the catalyst organic base

moiety in the *anti-Re* TS is ideally suited to benefit energetically from this conformational freedom. This is in contrast to the *Re*-face approach, in which the sterically bulky phenyl group is universally poorly accommodated by the any conformation of the sulfonamide (Figure 3). Thus, sulfonamides in catalysts **1** and **13** are conformationally more flexible and can change conformations to better electrostatically suit the *anti-Re* TS, leading to high selectivity. The sulfonamide in catalyst **14** is more conformationally rigid (the double bond between N=S makes the sulfonamide more rigid; top, Figure 5) and poorly stabilizes the *anti-Re* TS, leading to the observed poor selectivity.

The lower diastereoselectivities observed with catalysts **14** and **15** can be rationalized through analysis of their structural features. In catalyst **14**, the sulfonamide is the only functional group stabilizing the nitrogen anion. We hypothesize that the remarkable degradation in diastereoselectivity of catalyst **14** is due to the sulfonamide conformation being locked to achieve this conjugation. This in effect results in the loss of electrostatic distinction between the *anti-Re* and *anti-Si* TS and leads to loss of selectivity. The change from sp^2 to sp^3 hybridization at the starred carbon in catalyst **14** likely introduces flexibility in the sulfonamide group that may decrease the differentiation between the *anti-Re* and *anti-Si* TS, leading to lower selectivities. Wang and co-workers have shown that further increase in the electron-withdrawing capacity of the sulfonamide scaffold by incorporation of a trifluoromethyl moiety can counterbalance this effect.²⁴ⁿ In catalyst **15**, we believe the additional internal base may participate in the key proton transfer event of the critical C–C bond-forming transition state, as previously suggested by Nakamura.⁴¹ Such participation will impart conformational rigidity to the sulfonamide moiety, leading to poor selectivity.

Alternate explanations for the differences in selectivities between the various sulfonamide catalysts are possible. One alternative is based on the pK_a differences between the various catalysts. The pK_a values of sulfonamides are generally viewed as similar to those of carboxylic acids^{24c} and can conceivably be modulated through either the addition of electron-withdrawing or electron-donating moiety on the

(41) (a) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2009**, *15*, 6790–6793. (b) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem.—Eur. J.* **2008**, *14*, 8079–8081.

TABLE 4. Scope of Aldehyde Moiety at 4 °C^a

entry	R	time (h)	yield % (product)	ee % ^b	dr ^c
a	pentafluorophenyl-	36	91 (17a)	> 99	> 99:1
b	2,4-dinitrophenyl-	72	51 (17b)	97	> 99:1
c	2,6-dichlorophenyl-	72	94 (17c)	99	> 99:1
d	4-chlorophenyl-	48	68 (17d)	99	> 99:1
e	2-nitrophenyl-	72	91 (17e)	99	> 99:1
f	2-chlorophenyl-	72	79 (17f)	98	> 99:1
g	4-methoxyphenyl-	72	16 (17g)	98	80:1
h	phenyl-	60	60 (17h)	99	> 99:1
i	4-pyridyl-	24	98 (17i)	99	29:1
j	1-naphthyl-	72	19 (14j)	99	> 99:1
k	2-naphthyl-	72	51 (14k)	> 99	> 99:1

^aAll reactions were performed at 2 M concentration of **16** in solution and with 5 equiv of **5**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis.

sulfonamide aromatic ring⁴⁰ or modification of the carbonyl moiety. Wu and co-workers have previously postulated that the repulsive interaction between the proton being transferred and the electrophile substituent destabilize the *anti-Si* TS and could contribute to the enhanced selectivity of proline-amide-catalyzed aldol reactions.⁴² The modulation of the sulfonamide pK_a could effect this interaction and may be a factor in the resulting differential selectivities.

Substrate Scope. We next set out to screen a range of aromatic aldehydes to probe the scope of this transformation (Table 4). In the vast majority of cases, the transformation performed remarkably well. High levels of enantioselectivity, diastereoselectivity, and chemical yield were observed in most cases. Aldol reactions on even sterically congested aldehydes **16b** and **16c** proved reasonably effective. Single *ortho* substitution did not appear to adversely impact reactivity (entries b,c and e,f). Current limitations to the protocol appear to include electron-rich aldehydes, which showed sluggish reactivity (entry g).

We also wanted to screen the scope of these reactions performed at room temperature (Table 5). While it was expected that increased reaction temperature would increase reactivity while possibly reducing stereoselectivity, the added practicality of avoiding externally cooling a reaction was attractive. Fortunately, the overall stereoselectivities in most cases at room temperature were still high. In fact, the dinitrophenyl case gave significantly higher yields at room temperature than at 4 °C (entry 2). One substrate class that was ineffective at lower temperatures was aliphatic aldehydes. Fortunately, it appears that improved reactivity provided by conducting the experiment at room temperature did facilitate a modestly effective transformation with 59% ee and 32% chemical yield (entry 6). These types of aldehydes are particularly challenging as self-aldol condensation is often a major competing transformation.⁴³ Currently, 4-hydroxyproline derivatives have proven most effective at facilitating related aldol reactions with aliphatic aldehydes.^{32c,d}

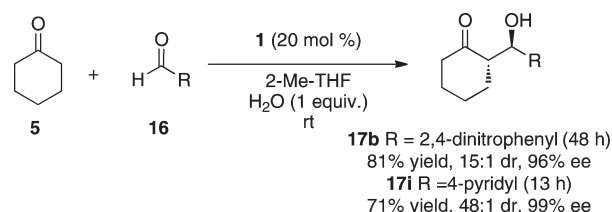
(42) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A. Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263.

(43) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573–575.

TABLE 5. Scope of Aldehyde Moiety at Room Temperature^a

entry	R	time (h)	yield % (product)	ee % ^b	dr ^c
1	pentafluorophenyl-	13	97 (17)	> 99	> 99:1
2	2,4-dinitrophenyl-	40	99 (17)	96	57:1
3	2,6-dichlorophenyl-	48	99 (17)	99	> 99:1
4	4-pyridyl-	12	92 (17)	99	50:1
5	2-naphthyl-	48	63 (17k)	> 99	> 99:1
6	phenylethyl-	72	32 (17l)	59	29:1

^aAll reactions were performed at 2 M concentration of **16** in solution and with 5 equiv of **5**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis.

SCHEME 2. Scope of Aldehyde Moiety at 2-Methyltetrahydrofuran as Solvent^a

^aAll reactions were performed at 2 M concentration of **16** in solution and with 5 equiv of **5**. Enantiomeric excess was determined by chiral HPLC analysis. Diastereomeric ratios (dr) were determined by ¹H NMR analysis.

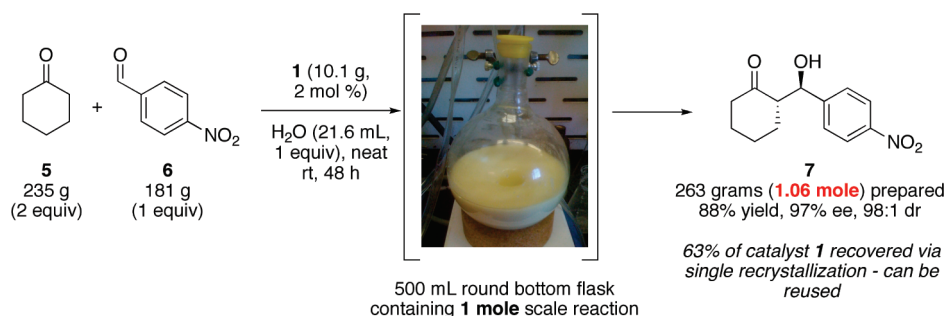
While DCE proved to be an excellent solvent for facilitating highly stereoselective aldol reactions, it has been designated a class 1 genotoxin.^{44,45} Consequently, we sought to explore alternative solvent choices, which might be viewed as more industrial friendly (Scheme 2). 2-Methyltetrahydrofuran (2-Me-THF) is rapidly becoming an industrially friendly alternative to chlorinated solvents.⁴⁶ The cost of production of this solvent has come down significantly in recent years. Unlike THF, 2-Me-THF provides good phase splits with water, which can facilitate easier solvent recycling. We were pleased to see that 2-Me-THF can be substituted for DCE with only minimal disruption in the levels of enantioselectivity. The experiments were conducted at room temperature and provided high levels of chemical yield, enantioselectivity, and diastereoselectivity. These examples coupled with the entry detailed in Table 1 indicate that there is significant promise in utilizing the catalyst **1** in nonchlorinated solvents such as 2-Me-THF.

We also explored the utility of neat reaction conditions using the low catalyst loading conditions (2 mol % of **1**, neat, rt) on a range of aldehyde substituents (Table 6). Please note that these

(44) Müller, L.; Mauthe, R. J.; Riley, C. M.; Andino, M. M.; De Antonis, D.; Beels, C.; DeGeorge, J.; De Knaep, A. G. M.; Ellison, D.; Fagerland, J. A.; Frank, R.; Fritschel, B.; Galloway, S.; Harpur, E.; Humfrey, C. D. N.; Jacks, A. S.; Jagota, N.; Mackinnon, J.; Mohan, G.; Ness, D. K.; O'Donovan, M. R.; Smith, M. D.; Vudathala, G.; Yotti, L. *Regul. Toxicol. Pharmacol.* **2006**, *44*, 198–211.

(45) (a) Robinson, D. I. *Org. Process Res. Dev.* **2010**, *14*, 946–959. (b) McGovern, T.; Jacobson-Kram, D. *Trends Anal. Chem.* **2006**, *25*, 790–795.

(46) Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 157–159.

SCHEME 3. Large-Scale Example of Aldol Reaction^a

^aEnantiomeric excess was determined by chiral HPLC analysis. Diastereomeric ratios (dr) were determined by ¹H NMR analysis.

TABLE 6. Scope of Aldehyde Moiety under Low Catalyst Loading^a

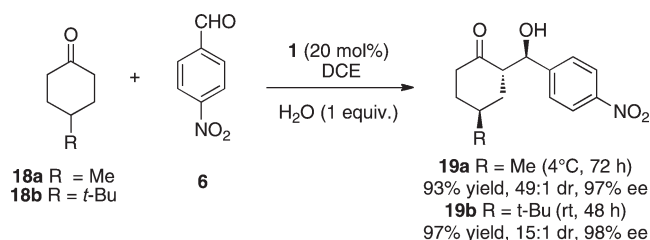
entry	R	time (h)	yield % (product)	ee % ^b	dr ^c
1	2,4-dinitrophenyl-	48	50 (17b)	93	> 99:1
2	4-chlorophenyl-	48	49 (17d)	92	> 99:1
3	2-chlorophenyl-	72	67 (17f)	99	> 99:1
4	4-hydroxyphenyl-	72	22 (17m)	90	26:1
5	phenyl-	48	75 (17h)	99	55:1
6	4-pyridyl-	36	91 (17i)	91	7:1
7	1-naphthyl-	72	36 (17j)	88	96:1

^aAll reactions were performed with 2 equiv of **5**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis.

2 mol % catalyst experiments were performed with a reduced loading of **5** (2 equiv) and only a single equivalent of both the aldehyde and water. These transformations generally performed well, with enantioselectivities greater than 90% ee in each case. The diastereoselectivity in neat reactions was somewhat reduced as compared to the experiments conducted in an organic solvent. We attribute that result to the impact of the solvent's polarity on the diastereomeric transition states as compared to the neat component reactions. It should be noted that, in most cases, both **5** and the aldehyde **16** were not readily miscible with the 1 equiv of water. We hypothesize that the polar pyrrolidine portion and the aliphatic side arm of the sulfonamide catalyst may function as a phase transfer agent for this transformation.

Given the procedural ease for accomplishing these aldol reactions, we thought it would be valuable to demonstrate the utility of this protocol for conducting a mole scale reaction (Scheme 3). The experiment was conducted in a single 500 mL round-bottom capped flask using 235 g of cyclohexanone and 181 g of 4-nitrobenzaldehyde with just 2 mol % (10.1 g) of the sulfonamide catalyst **1** and a single equivalent of water (21.6 mL). Shown in Scheme 3 is the photograph of the experiment. The solid stirring around in the reaction is the product **7**, which was filtered and washed with hexanes to isolate. Over 60% of the catalyst **1** could be recovered via simple purification of the mother liquor through a plug of silica gel followed by a single recrystallization in methanol.

We investigated the impact of substitution of the cyclohexanone ring in the aldol process (Scheme 4). This reaction worked similarly well with either the methyl or *tert*-butyl-substituted

SCHEME 4. Use of Substituted Cyclohexanones in Aldol Reactions^a

^aAll reactions were performed at 2 M concentration of **6** in solution and 5 equiv of ketone **18**. Enantiomeric excess was determined by chiral HPLC analysis. Diastereomeric ratios (dr) were determined by ¹H NMR analysis.

cyclohexanones. In each case, high levels of stereoselectivity and chemical yield were observed. In each experiment, a total of three stereogenic centers are established.

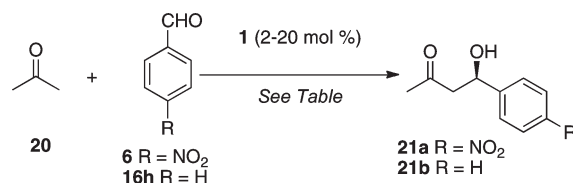
The use of acetone as a potential nucleophile in the aldol process was also screened (Table 7). This reaction appeared to work most effectively using our optimized conditions [DCE, H₂O (1 equiv), 4 °C] to provide 66% yield of the desired product in a reasonable (84% ee) enantioselectivity. Performing the transformation at room temperature led to reduced chemical yields and enantioselectivity. Interestingly, the same reaction performed in the absence of added water gave comparable levels of enantioselectivity to the optimized conditions. We are unsure as to the rationale of this result, but this outcome may be in part due to the hydroscopic nature of acetone, which was not rigorously dried prior to use.

We explored the impact of utilizing cyclopentanone instead of cyclohexanone in the aldol process (Table 8). Interestingly, the level of diastereoselectivity (*anti/syn*) was greatly eroded as compared to the cyclohexanone examples. This diastereoselectivity difference between cyclopentanone and cyclohexanone was first observed by Gong⁴⁷ and Zhao⁴⁸ independently; however, we are unaware of a mechanistic explanation for the difference outside of the increased reactivity of cyclopentanone-derived enamines.⁴⁹ We screened both the low catalyst loading conditions [2 mol % **1**, H₂O (1 equiv), neat] and the optimized 20 mol % catalyst loading

(47) 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*, 9285–9289.

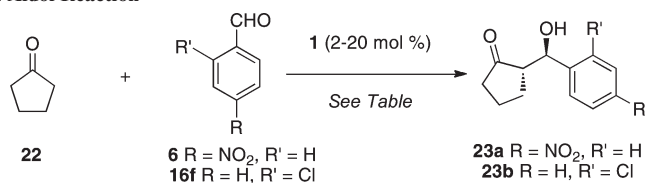
(48) Samanatha, S.; Liu, J.; Dodda, R.; Zhao, C.-G. *Org. Lett.* **2005**, *7*, 5321–5323.

(49) Shechter, H.; Collis, M. J.; Dessy, R.; Okuzumi, Y.; Chen, A. *J. Am. Chem. Soc.* **1962**, *84*, 2905–2910.

TABLE 7. Use of Acetone in Organocatalyzed Reaction^a

entry	aldehyde	mol % of 1	conditions	time (h)	yield (%)	ee % ^b
1	6	20	DCE, H ₂ O (1 equiv), 4 °C	62	66	84
2	6	20	DCE/EtOH (99:1), 4 °C	72	64	82
3	6	20	DCE, rt	30	80	80
4 ^c	6	2	neat, H ₂ O (1 equiv), rt	48	52	71
5	16h	20	DCE/EtOH (99:1), 4 °C	72	42	87

^aAll reactions were performed at 2 M concentration of aldehyde in solution and with 5 equiv of **20** unless otherwise noted. ^bDetermined by chiral HPLC analysis. ^cThis reaction was performed with 2 equiv of **20**.

TABLE 8. Use of Cyclopentanone in Aldol Reaction^a

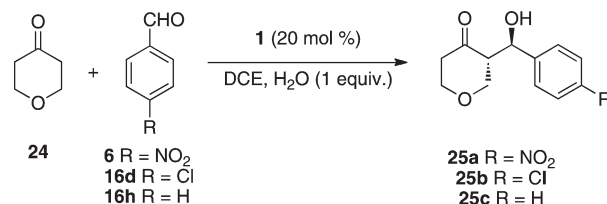
entry	aldehyde	mol % (1)	conditions	yield (%)	ee % ^b	dr ^c
1 ^d	6	2	neat, H ₂ O (1 equiv), 15 h, rt	87	77 (<i>syn</i>), 91 (<i>anti</i>)	1.05:1
3	6	2	neat, 24 h, rt	63	73 (<i>syn</i>), 74 (<i>anti</i>)	3.2:1
4	6	20	DCE, H ₂ O (1 equiv), 16 h, 4 °C	94	87 (<i>syn</i>), 95 (<i>anti</i>)	1.35:1
5	6	20	DCE/EtOH (99:1), 36 h, 4 °C	87	85 (<i>syn</i>), 92 (<i>anti</i>)	2:1
6	16f	20	DCE, H ₂ O (1 equiv), 48 h, 4 °C	51	81 (<i>syn</i>), 93 (<i>anti</i>)	1.5:1

^aAll reactions were performed at 2 M concentration of aldehyde in solution and with 5 equiv of **22** unless otherwise noted. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis. ^dThis reaction was performed with 2 equiv of **22**.

conditions [DCE, H₂O (1 equiv), 4 °C]. Under both sets of conditions, similar results were obtained.

We explored the potential use of 4-pyranone in the aldol reaction process with a series of aromatic aldehydes (Table 9). 4-Pyranones are present in a wide range of natural product scaffolds.⁵⁰ Xiao and co-workers have focused specifically on exploiting the utility of organocatalysis for the heteroatom-containing cyclic ketone substrates.⁵¹ In each case, our optimized reaction conditions [DCE, H₂O (1 equiv), 4 °C] provided superior results to alternative procedures performed at room temperature or using alternative additives. Aldehyde **16d** was particularly effective as excellent levels of enantioselectivity and diastereoselectivity were achieved (entry 4).

The potential use of 4-thiopyranone in the aldol reaction process was also explored (Scheme 5). Thiopyranones have been exploited as polyproprioate surrogates through

TABLE 9. Use of 4-Pyranone in Aldol Reactions^a

entry	aldehyde	conditions	time (h)	yield (%)	ee % ^b	dr ^c
1	6	DCE/EtOH (99:1), rt	16	16	88	4:1
2	6	DCE, H ₂ O (1 equiv), 4 °C	52	92	96	5:1
3	16d	DCE, H ₂ O (1 equiv), rt	16	52	94	13:1
4	16d	DCE, H ₂ O (1 equiv), 4 °C	72	60	97	>99:1
5	16h	DCE, H ₂ O (1 equiv), rt	16	27	90	41:1
6	13h	DCE, H ₂ O (1 equiv), 4 °C	72	47	94	41:1

^aAll reactions were performed at 2 M concentration of aldehyde in solution and with 5 equiv of **24**. ^bDetermined by chiral HPLC analysis. ^cDetermined by ¹H NMR analysis.

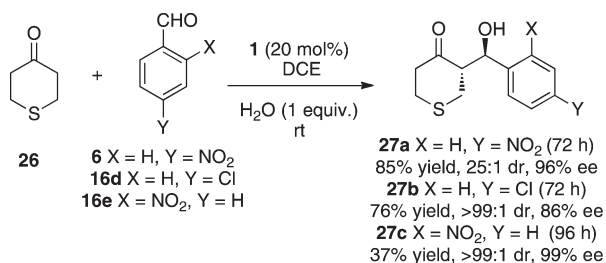
Raney-Ni removal of the carbon–sulfur bonds after coupling.⁵² The aldol reaction proved sufficiently effective that they could be performed at room temperature with high levels of stereo-selectivity. We attribute the difference between pyranone and thiopyranone to the modulated reactivity imparted by the presence of the sulfur moiety.

Glycolate aldol reactions have proven particularly significant for construction of 1,2-*anti*- and 1,2-*syn*-diol functionality.⁵³

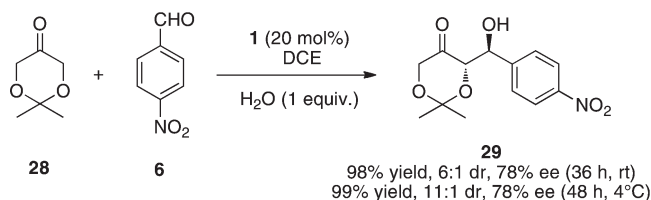
(50) (a) Turner, W. B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1621. (b) Goehrt, A.; Grabley, S.; Thiericke, R.; Zecek, A. *Liebigs Ann.* **1996**, 627–634. (c) Pittayakhajonwut, P.; Suvannakad, R.; Thienhirun, S.; Prabpai, S.; Kongsaree, P.; Tanticharoen, M. *Tetrahedron Lett.* **2005**, 46, 1341–1344. (d) Lopez, S. N.; Sierra, M. G.; Gattuso, S. J.; Furlan, R. L.; Zacchino, S. A. *Phytochem.* **2006**, 67, 2152–2158. (e) Krick, A.; Kehraus, S.; Gerhaeuser, C.; Klimo, K.; Nieger, M.; Maier, A.; Fiebig, H.-H.; Atodiresi, I.; Raabe, G.; Fleischhauer, J.; Koenig, G. M. *J. Nat. Prod.* **2007**, 70, 353–360. (f) Ahmed, S. A.; Ross, S. A.; Slade, D.; Radwan, M. M.; Khan, I. A.; ElSohly, M. A. *Tetrahedron Lett.* **2008**, 49, 6050–6053. (g) Tantray, M. A.; Shawl, A. S.; Ali, N.; Khuroo, M. A. *Chem. Nat. Prod.* **2008**, 44, 424–426.

(51) Chen, J.-R.; Li, X.-Y.; Xing, X.-N.; Xiao, W.-J. *J. Org. Chem.* **2006**, 71, 8198–8202.

(52) (a) Jheengut, V.; Ward, D. E. *J. Org. Chem.* **2007**, 72, 7805–7808. (b) Beye, G. E.; Goodman, J. M.; Ward, D. E. *Org. Lett.* **2009**, 11, 1373–1376.

SCHEME 5. Use of 4-Thiopyranone in Aldol Reactions^a

^aAll reactions were performed at 2 M concentration of aldehyde in solution and with 5 equiv of **26**. Enantiomeric excess was determined by chiral HPLC analysis. Diastereomeric ratios were determined by ¹H NMR analysis.

SCHEME 6. Use of Glycolates in Aldol Reactions^a

^aAll reactions were performed at 2 M concentration of **6** in solution and with 5 equiv of **24**. Enantiomeric excess was determined by chiral HPLC analysis. Diastereomeric ratios (dr) were determined by ¹H NMR analysis.

We were pleased to see that our organocatalyzed process could again provide reasonable levels of stereoselectivity in this type of transformation (Scheme 6). While the chemical yield and enantioselectivity appear for this transformation to be insensitive to reaction temperature, the diastereoselectivity was improved when the reaction was carried out at lower temperatures.

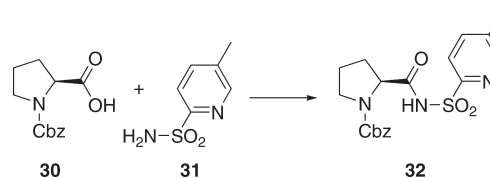
Conclusion

A practical asymmetric aldol process has been developed based on the proline aryl sulfonamide scaffold. These reactions have been shown to be effective on a wide range of substrates in generally high levels of enantioselectivity. The presence of a single equivalent of water was shown to be beneficial to the reaction yield, enantioselectivity, and diastereoselectivity. Particular utility has been showcased in nonpolar organic solvents such as DCE and 2-Me-THF. Nonpolar solvents increase the practicality of the chemistry for applications in industrial settings as the solvents are more readily recyclable. Alternatively, the sulfonamide-catalyzed aldol reaction was also shown to be effective in aqueous media with generally good levels of stereoselectivity. We hypothesized that the proline sulfonamide organocatalyst may be acting as a phase transfer catalyst between the aqueous and nonpolar media. Catalyst loading as low as 2 mol % was demonstrated using neat reaction conditions

with generally high levels of stereoselectivity. The practicality of this protocol has been demonstrated on a 1 mol scale reaction conducted in a single 500 mL round-bottom flask. Detailed computational analysis established that nonclassical hydrogen bonds to the sulfonamide lead to improved stereoselectivity in this system. We anticipate that this catalyst system will find application in natural product synthesis and industrial processes.

Experimental Section

Sulfonamide 14: To a solution of **1** (0.422 g, 1.00 mmol) in THF (10 mL) was added lithium aluminum hydride (0.190 g, 5.0 mmol) slowly at 0 °C. After stirring at 0 °C for 2 h, the solution was quenched with H₂O (10 mL) and extracted with CH₂Cl₂ (3 × 25 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% MeOH/dichloromethane, to give **14** (0.346 g, 0.848 mmol, 85%) as a colorless oil: [α]_D²³ = +21.4 (*c* = 1.9, CHCl₃); IR (neat) 3276, 2954, 2916, 2856, 1451, 1408, 1331, 1146, 1097, 825, 645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.27–7.33 (m, 2H), 3.87 (br s, 2H), 3.31–3.33 (m, 1H), 2.57–3.04 (m, 4H), 0.75–1.86 (m, 28H); ¹³C NMR (100 MHz, CDCl₃) δ 137.3, 128.3, 127.7, 127.0, 57.2, 47.2, 46.3, 40.0, 38.9, 38.2, 36.7, 36.4, 31.9, 29.7, 29.3, 28.9, 27.5, 27.2, 25.8, 22.7, 22.0, 20.6, 14.1, 12.1; HRMS (EI⁺) calcd for C₂₃H₄₀N₂O₂S (M⁺) 408.2811, found 408.2787.



(Z)-L-Sulfonamide 32: To a solution of (Z)-L-proline **30** (1.25 g, 5.0 mmol) in CH₂Cl₂ (50 mL) were added sulfonamide **31** (1.04 g, 6.0 mmol), EDCI (0.96 g, 5.0 mmol), and DMAP (0.122 g, 1.0 mmol). The reaction mixture was stirred at room temperature for 48 h before being partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with half-saturated brine (2 × 50 mL). The dried (Na₂SO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20–70% EtOAc/CH₂Cl₂, to give **32** (1.59 g, 3.95 mmol, 79%) as a white solid: mp 136–137 °C; [α]_D²³ = –129.7 (*c* = 3.1, CHCl₃); IR (neat) 3069, 2953, 2871, 1704, 1684, 1455, 1420, 1357, 1190, 1132, 1108, 739, 700, 665 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆, two rotamers) δ 8.37 (s, 1H), 8.30 (s, 1H), 7.59–7.76 (m, 2H), 7.21–7.35 (m, 5H), 4.78–5.03 (m, 2H), 4.02–4.06 (m, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 1.71–2.10 (m, 3H); ¹³C NMR (100 MHz, MeOD, two rotamers) δ 181.3, 155.9, 155.6, 154.9, 148.9, 148.7, 139.5, 139.3, 137.9, 137.8, 136.6, 128.2, 128.0, 127.7, 127.3, 127.2, 126.2, 127.7, 66.7, 66.2, 62.5, 62.1, 47.1, 46.7, 31.1, 30.3, 23.8, 23.1, 17.2; HRMS (EI⁺) calcd for C₁₉H₂₁N₃O₅S (M⁺) 403.1202, found 403.1219.

Sulfonamide 15: To a solution of (Z)-L-sulfamide **32** (0.12 g, 0.298 mmol) in MeOH (3 mL) was added Pd/C (12 mg, 10%). The mixture was stirred at rt under an atmosphere of hydrogen. After 13 h, the reaction was filtered through Celite and a silica gel pad, and the filtrate was concentrated in vacuo to give a white solid. The crude product was purified by chromatography over silica gel, eluting with 10% MeOH/CH₂Cl₂, to give the product **15** (71.2 mg, 0.265 mmol, 89%) as a white solid: mp 192–194 °C; [α]_D²³ = –44.5 (*c* = 0.2, EtOH); IR (neat) 3432, 3070, 3031, 2992, 1610, 1564, 1455, 1381, 1315, 1264, 1248, 1151, 1089, 789, 696, 649, 560 cm⁻¹; ¹H NMR (400 MHz, MeOD) δ 8.41 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 7.2 Hz, 1H),

(53) (a) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790–12791. (b) Vaughn, J. F.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2005**, *15*, 3449–3455. (c) Davies, S. G.; Nicholson, R. L.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 348–359. (d) Andrus, M. B.; Liu, J.; Ye, Z.; Cannon, J. F. *Org. Lett.* **2005**, *7*, 3861–3864. (e) Denmark, S. E.; Chung, W.-J. *J. Org. Chem.* **2008**, *73*, 4582–4595. (f) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788–9791. (g) Gawas, D.; Kazmaier, U. *J. Org. Chem.* **2009**, *74*, 1788–1790.

4.02–4.06 (m, 1H), 3.21–3.39 (m, 2H), 2.45 (s, 3H), 1.93–2.42 (m, 4H); ^{13}C NMR (100 MHz, MeOD) δ 173.3, 157.3, 148.9, 137.8, 136.5, 121.9, 62.3, 45.8, 29.2, 23.4, 16.9; HRMS (ES⁺) calcd for $\text{C}_{11}\text{H}_{16}\text{N}_3\text{O}_3\text{S}$ ($M + 1$) 270.0895, found 270.0912.

General Procedure for Aldol Reaction. Procedure A (DCE, 20 mol % of Catalyst, 4 °C): To a solution of aldehyde (0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE (0.24 mL) were added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at 4 °C. After stirring at the same temperature, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the corresponding aldol product.

General Procedure for Aldol Reaction. Procedure B (DCE, 20 mol % of Catalyst, Room Temperature): To a solution of aldehyde (0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE (0.24 mL) were added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After stirring at the same temperature, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the corresponding aldol product.

General Procedure for Aldol Reaction. Procedure C (Neat, 2 mol % of Catalyst, Room Temperature): To a solution of aldehyde (0.5 mmol) and cyclohexanone (0.098 g, 0.1 mL, 1.0 mmol, 2 equiv) were added sulfonamide **1**²³ (4.2 mg, 0.01 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After stirring at the same temperature, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the corresponding aldol product.

General Procedure for Aldol Reaction. Procedure D (DCE/EtOH (99:1), 20 mol % of Catalyst, Room Temperature): To a solution of aldehyde (0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE/EtOH (99:1, 0.24 mL) was added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) at room temperature. After stirring at the same temperature, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the corresponding aldol product.

General Procedure for Aldol Reaction. Procedure E (2-Methyltetrahydrofuran, 20 mol % of Catalyst, Room Temperature): To a solution of aldehyde (0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in 2-methyltetrahydrofuran (0.24 mL) were added sulfonamide **1** (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After stirring at the same temperature, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the corresponding aldol product.

2-[Hydroxy-(4-nitrophenyl)methyl]cyclohexan-1-one (7): Procedure A: To a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE (0.24 mL) were added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at 4 °C. After stirring at the same temperature for 30 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30%

EtOAc/hexanes, to give the known aldol product **7**⁵⁴ (118 mg, 0.474 mmol, 95%, 99% ee, > 99:1 dr). **Procedure B:** To a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE (0.24 mL) were added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After 14 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the aldol product **7** (119 mg, 0.478 mmol, 96%, 97% ee, 36:1 dr). **Procedure C:** To a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and cyclohexanone (98.0 mg, 0.1 mL, 1.0 mmol, 2 equiv) were added sulfonamide **1**²³ (4.2 mg, 0.01 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After 36 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the aldol product **7** (119 mg, 0.478 mmol, 96%, 96% ee, > 99:1 dr). **Procedure D:** To a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in DCE/EtOH (99:1, 0.24 mL) was added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) at room temperature. After 36 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the aldol product **7** (119 mg, 0.478 mmol, 96%, 97% ee, 14:1 dr). **Procedure E:** To a solution of *p*-nitrobenzaldehyde (75.5 mg, 0.5 mmol) and cyclohexanone (0.245 g, 0.26 mL, 2.5 mmol, 5 equiv) in 2-Me-THF (0.24 mL) were added sulfonamide **1**²³ (42.2 mg, 0.1 mmol) and water (0.5 mmol, 9 mg, 1 equiv) at room temperature. After stirring at the same temperature for 16 h, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10–30% EtOAc/hexanes, to give the known aldol product **7** (106 mg, 0.425 mmol, 85%, 94% ee, 30:1 dr): $[\alpha]_{\text{D}}^{25} = +8.0$ ($c = 1.3$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 4.92 (dd, $J = 8.4$, 3.2 Hz, 1H), 4.10 (d, $J = 3.2$ Hz, 1H), 2.38–2.62 (m, 3H), 2.11–2.16 (m, 1H), 1.38–1.87 (m, 5H); ^{13}C NMR (100 MHz, CDCl_3) δ 214.8, 148.4, 147.6, 127.9, 123.6, 74.0, 57.2, 42.7, 30.8, 27.7, 24.7; HPLC (Daicel Chiralpak AD) hexanes/*i*-PrOH, 90:10, 1.0 mL min^{−1}, 254 nm: t_{R} (major) = 41.1 min; t_{R} (minor) = 32.7 min.

Acknowledgment. Financial support was provided by the National Institutes of Health (NIH) (GM63723) and Oregon State University. National Science Foundation (CHE-0722319) and the Murdock Charitable Trust (2005265) are acknowledged for their support of the NMR facility. The authors would like to thank Professor Max Deinzer and Dr. Jeff Morré (OSU) for mass spectra data and Synthetech, Inc. for the generous gift of Cbz-proline. Finally, the authors are grateful to Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for helpful discussions. We acknowledge Christopher M. Sullivan and Matthew Peterson of the Center for Genome Research and Biocomputing (CGRB), Oregon State University, for computing cluster management.

Supporting Information Available: Complete experimental procedures are provided, including ^1H and ^{13}C spectra, of all new compounds. Cartesian coordinates and energies for structures present in Figures 3 and 4 are also provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(54) Wang, C.; Jiang, Y.; Zhang, X.; Huang, Y.; Li, B.; Zhang, G. *Tetrahedron Lett.* **2007**, 48, 4281–4285.