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# Novel Diarylprolinol-Derived Amino Perfluoroalkanesulfonamide Catalysts: Highly Enantio- and Diastereoselective Aldol Reaction

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# Novel Diarylprolinol-Derived Amino Perfluoroalkanesulfonamide Catalysts: Highly Enantio- and Diastereoselective Aldol Reaction

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A new series of amino perfluoroalkanesulfonamide compounds derived from diarylprolinols has been developed and found to be efficient catalysts for the reaction of ethyl glyoxylate with 4-(benzyloxy)butanal. The aldol product, obtained in good yield with excellent enantio- and diastereomeric excess, is an intermediate for the synthesis of bis-THF alcohol, which is a commonly used unit in the design of HIV protease inhibitors such as Darunavir.

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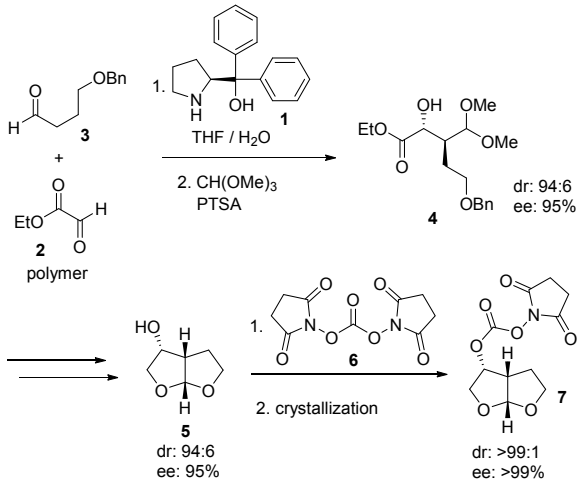
The aldol reaction is an important means of preparation of chiral β-hydroxy carbonyl compounds,[1] useful building blocks for pharmaceuticals and other biologically active products.[2] The enantioselective aldol reaction is achievable via metal catalysis,[3] bioorganic catalysis[4] and organocatalysis.[5] Although these three synthetic strategies are complementary, organocatalysis offers several advantages. For instance, organocatalysts generally tolerate air and water, possess a wider substrate scope than enzymes and are generally less expensive. Proline and its derivatives have been among the most used organocatalysts in the asymmetric aldol reaction.[6] Although remarkable progress has been accomplished in this field, the ever growing chiral drug industry and the strict requirements in optical purity of drug candidates necessitate the development of more efficient organocatalysts.[7]

(3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-ol, also known as bis-THF alcohol, is a commonly used unit in the design of HIV protease inhibitors.[8] Due to its importance, the synthesis of bis-THF alcohol has received considerable attention in recent years.[9] In order to obtain an optically pure product, most of the reported synthetic approaches require enzymatic resolution or the use of metal catalysts, which represent a drawback from an economical and ecological standpoint. In 2010, Hayashi et al. disclosed the diarylprolinol-catalyzed reaction of polymeric ethyl glyoxylate with aldehydes, giving preferentially anti-aldol products in high yields with excellent levels of enantiomeric excess.[10] In line with those findings, we have recently reported the synthesis of bis-THF alcohol **5** via the asymmetric aldol reaction of ethyl glyoxylate **2** with aldehyde **3** catalyzed by diphenylprolinol **1** (Scheme 1).[11] The diastereomeric ratio and the optical purity remained unchanged during the transformation of **4** to **5**. Therefore further steps of purification were necessary to obtain carbonate **7** with >99:1 diastereomeric ratio and >99% enantioselectivity. We speculated that a structural transformation of the initial catalyst would lead to an aldol reaction with higher enantio- and diastereoselectivity and, therefore, render extra steps of enhancement of the purity of **5** unnecessary. Herein, we wish to report the synthesis of novel diarylprolinol-derived amino perfluoroalkanesulfonamide catalysts and their application to the aldol reaction that serves as key step in the synthesis of bis-THF alcohol **5**.




**Scheme 1**. Synthesis of bis-THF alcohol via diphenylprolinol-catalyzed aldol reaction

We set out to design catalysts structurally related to **1** but with modified steric and electronic environment. In this regard, the Wang group has reported effective prolinol-derived amino perfluoroalkanesulfonamide catalysts.[12] The pronounced acidity of the N-H of the sulfonamide group allows a high catalytic activity. It occurred to us that replacing the O-H of the diphenylprolinol **1** with a $RSO_2N$-H group would lead to a more active catalyst. With this concept in mind, we embarked on the task of synthesizing diarylprolinol-derived amino perfluoroalkanesulfonamide compounds.

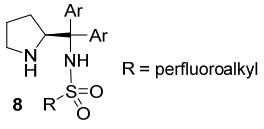
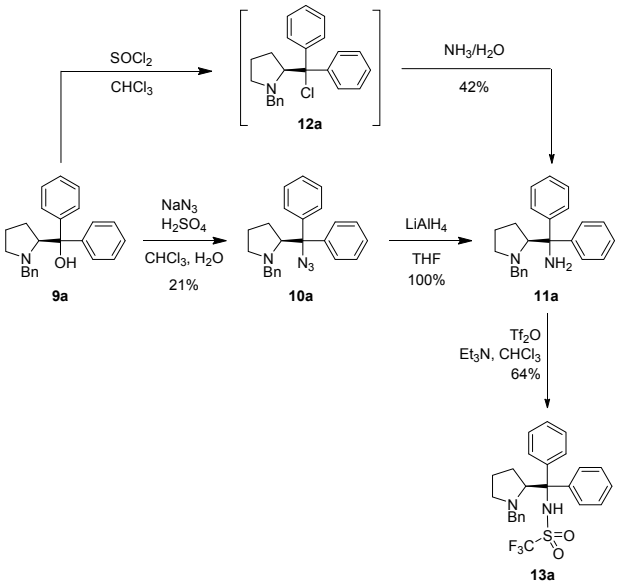


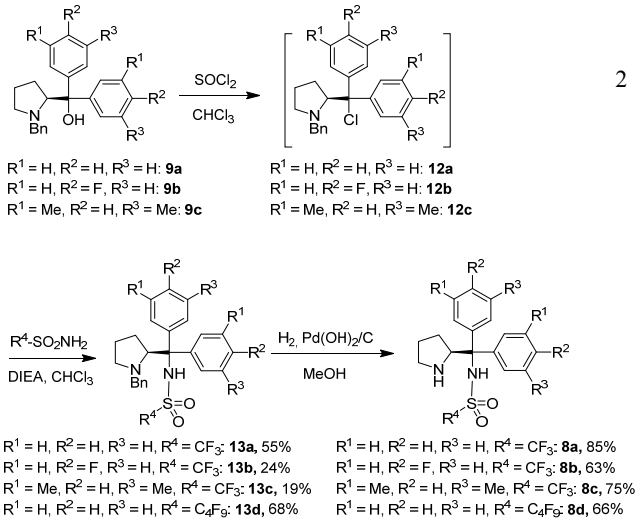

**Figure 1**. Diarylprolinol-derived amino perfluoroalkanesulfonamides

Diarylprolinol intermediate **9a** was prepared from L-proline following reported procedures.[13b] The replacement of the tertiary hydroxyl group in **9a** by an amino group was first attempted following known methods[14] (Scheme 2). Namely, **9a** was treated with sodium azide under strongly acidic conditions at reflux to give azide **10a** in 21% yield. Subsequent reduction with lithium aluminum hydride afforded amine **11a** quantitatively. Regrettably, despite numerous trials, we were unable to reproduce the high yield of azide **10a** reported in the above-mentioned literature. The poor yield of **10a** coupled with concerns over the toxicity and explosive nature of azido compounds, especially in case of large scale syntheses, led us to seek an alternative approach. Thus, diphenylprolinol **9a** was treated with $SOCl_2$ and the resulting chloride **12a** was reacted with a 28% aqueous solution of ammonia, giving the intended amino compound **11a** in 42% over two steps. Subsequent treatment of **11a** with trifluoromethanesulfonic anhydride led to sulfonamide **13a** in 64%.



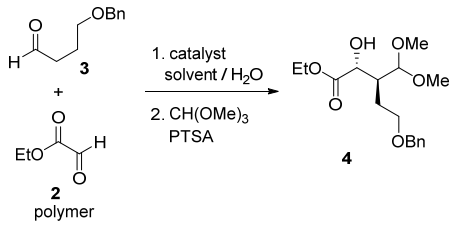

**Scheme 2**. Amination of diphenylprolinol and formation of sulfonamide

A better outcome was reached by chlorinating **9a** with thionyl chloride and treating intermediate **12a** with trifluoromethanesulfonamide, which afforded the sulfonamide product **13a** in 75% over two steps (Scheme 3). Palladium catalyzed hydrogenation of **13a** led to the target amino trifluoromethanesulfonamide **8a** in 95%. Under similar conditions, amino trifluoromethanesulfonamide analogs **8b** and **8c** were synthesized starting from known **9b**[13a] and **9c**,[13c] respectively. The reaction of **12a** with nonafluorobutanesulfonamide instead of trifluoromethanesulfonamide afforded the sulfonamide derivative **13d**, which upon hydrogenation in the presence of palladium hydroxide on carbon gave the bulkier and more acidic amino nonafluorobutanesulfonamide **8d**.




**Scheme 3**. Synthesis of amino perfluoroalkanesulfonamides **8a-d**.

**Table 1**. Aldol Reaction of aldehydes **2** and **3** catalyzed by amino perfluoroalkanesulfonamides **8a-d**[a]




| entry | catalyst | solvent | yield (%)[b] | anti : syn | ee (%) |
|---|---|---|---|---|---|
| 1 | **1** | MeCN | 83[c] | 90:10 | 97 |
| 2 | **8a** | MeCN | 87[c] | 98:2 | 98 |
| 3 | **8a** | DMF | 78 | 98:2 | 99 |
| 4 | **8a** | NMP | 83[c] | >99:1 | >99 |
| 5 | **8a** | MeOH | 68 | 90:10 | 76 |
| 6 | **8a** | toluene | 75 | 95:5 | 97 |
| 7 | **8a** | $CHCl_3$ | 79 | 94:6 | 96 |
| 8 | **8a** | THF | 84 | 97:3 | 96 |
| 9 | **8b** | NMP | 83 | >99:1 | >99 |
| 10 | **8c** | NMP | 85 | >99:1 | >99 |
| 11 | **8d** | NMP | 87[c] | >99:1 | >99 |

[a]Reaction conditions: 1) aldehyde **3** (2 mmol), aldehyde **2** (3 mmol), solvent (2 mL), $H_2O$ (2 mmol), catalyst (0.2 mmol), 25°C. 2) $CH(OMe)_3$ (20 mmol), PTSA (0.2 mmol), rt. [b]Unless otherwise noted, yields were determined using biphenyl as internal standard. [c]Isolated yield.

With the target catalysts in hands, our attention shifted to the application to the reaction of polymeric aldehyde **2** with aldehyde **3**. The product was examined as an acetal to prevent epimerization (Table 1). First, the catalytic activity of amino trifluoromethanesulfonamide **8a** was compared to that of diphenylprolinol **1**. Good yields and excellent enantioselectivities were achieved with both catalysts tested. However, **8a** gave significantly better results in terms of

diastereoselectivity. Next, the present reaction was investigated under various conditions. Using **8a** as catalyst, a number of solvents were surveyed (entries 2-8) and 1-methylpyrrolidone (NMP) gave the best combination of diastereo- and enantioselectivity (entry 4). Furthermore, the reactions catalyzed by **8b** and **8c** in NMP also gave the product in good yield with excellent diastereo- and enantioselectivity regardless of the substitution pattern on the phenyl rings of the catalysts, indicating that the electronic density and the substitution pattern on the phenyl rings have no significant bearing on the outcome of the reaction (entries 9 and 10). It is noteworthy that under similar conditions catalyst **8d** with a larger sulfonyl moiety equally led to the product with excellent optical purity and a slightly superior chemical yield (entry 11). This fact may be attributed to the increased acidity of the N-H proton of the sulfonamide group, which allows a more effective activation of the electrophile through a stronger bonding with its carbonyl group.

Based on the proline model,[15] the assumed transition state shown in Figure 2 is proposed to account for the diastereo- and enantioselectivity observed in the present reaction. Accordingly, the strongly acidic proton of the N-H bond of the perfluoroalkanesulfonamide group activates the aldol acceptor through hydrogen bonding and plays a key role in positioning the acceptor for the attack by the enamine. The re attack is preferred since the interaction with the bulky sulfonyl group is avoided and leads to the formation of (2*R*,3*S*)-**4**.

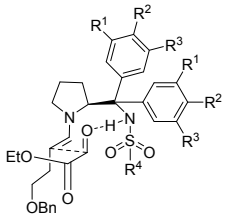



**Figure 2**. Possible transition state for the reaction of ethyl glyoxylate **2** with aldehyde **3** catalyzed by amino perfluoroalkanesulfonamides **8a-d**.

In conclusion, we have developed a novel type of amino perfluoroalkanesulfonamide catalysts that are easily accessible from naturally occurring proline. The unique structural and electronic character of these organocatalysts provided a remarkable efficiency in the direct aldol reaction of ethyl glyoxylate with 4-(benzyloxy)butanal. The product can conveniently be transformed to bis-THF alcohol with excellent diastereoselectivity and enantioselectivity. Efforts to expand the use of these catalysts to reactions involving other substrates are underway.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

## References and Notes


1 R. Mahrwald, *Chem. Rev*. **1999**, *99*, 1095–1120.

2 a) B. Schetter, R. Mahrwald, *Angew. Chem. Int. Ed. Engl*. **2006**, *45*, 7506-7525. b) I. Paterson, M. M. Mansuri, *Tetrahedron* **1985**, *41*, 3569-3624. c) S. Masamune, G. S. Bates, J. W. Corcoran, *Angew. Chem. Int. Ed. Engl.***1977**, *16*, 585-607.

3 a) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.*, **2002**, 1989-2183 and references therein. b) N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2169-2178. c) B. M. Trost, H. Ito, E. R. Silcoff, *J. Am. Chem. Soc.* **2001**, *123*, 3367-3368.

4 a) Z. Guan, J-P. Fu, Y-H. He, *Tetrahedron Lett*. **2012**, *53*, 4959-4961. b) X. Garrabou, J. A. Castillo, C. Guerard-Helaine, T. Parella, J. Joglar, M. Lemaire, P. Clapes, *Angew. Chem. Int. Ed*. **2009**, *48*, 5521-5525. c) J. Mlynarski, J. Paradowska, *Chem. Soc. Rev*. **2008**, *37*, 1502–1511.

5 a) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475-2479. b) L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16-17. c) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260-5267. d) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. e) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

6 a) G. Guillena, C. Najera, D. J. Ramon, *Tetrahedron: Asymmetry* **2007**, *18*, 2249 – 2293. b) S. K. Panday, *Tetrahedron: Asymmetry* **2011**, *22*, 1817-1847.

7 a) L. A. Nguyen, H. He, P-H. Chuong, *Int. J. Biomed. Sci.* **2006**, *2*, 85-100. b) Y. Gao, E. Boschetti, L. Guerrier, *Ann. Pharm. Fr*. **1994**, *52*, 184-203.

8 a) E. De Clercq, *Int. J. Antimicrob. Agents* **2009**, *33*, 307–320. b) K. McKeage, C. M. Perry, S. J. Keam, *Drugs* **2009**, *69*, 477–503. c) A. K. Ghosh, S. Leshchenko-Yashchuk, D. D. Anderson, A. Baldridge, M. Noetzel, H. B. Miller, Y. Tie, Y-F. Wang, Y. Koh, I. T. Weber, H. Mitsuya, *J. Med. Chem.* **2009**, *52*, 3902–3914. d) M. H. Hanlon, D. J. T. Porter, E. S. Furfine, A. Spaltenstein, H. L. Carter, D. Danger, A. Y. L. Shu, I. W. Kaldor, J. F. Miller, V. A. Samano, *Biochemistry* **2004**, *43*, 14500–14507.

9 a) M. G. Kulkarni, Y. B. Shaikh, A. S. Borhade, A. P. Dhondge S. W. Chavhan, M. P. Desai, D. R. Birhade, N. R. Dhatrak, R. Gannimani, *Tetrahedron: Asymmetry* **2010**, *21*, 2394–2398. b) D. M. Black, R. Davis, B. D. Doan, T. C. Lovelace, A. Millar, J. F. Toczko, S. Xie, *Tetrahedron: Asymmetry* **2008**, *19*, 2015–2019. c) A. K. Ghosh, J. Li, R. S. Perali, *Synthesis* **2006**, 3015–3018. d) A. K. Ghosh, W. J. Thompson, W. J.; P. M. D. Fitzgerald, J. C. Culberson, M. G. Axel, S. P. McKee, J. R. Huff, P. S. Anderson, *J. Med. Chem.* **1994**, *37*, 2506–2508.

10 T. Urushima, Y. Yasui, H. Ishikawa, Y. Hayashi, *Org. Lett*. **2010**, *12*, 2966-2969.

11 Y. Hayashi, T. Aikawa, Y. Shimasaki, H. Okamoto, Y. Tomioka, T. Miki, M. Takeda, T. Ikemoto, *Org. Process Res. Dev.* **2016**, *20*, 1615−1620.

12 a) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Org. Lett.* **2008**, *10*, 1211-1214. b) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077-3079. c) W. Wang, H. Li, J. Wang, *Tetrahedron Lett.* **2005**, *46*, 5077-5079. d) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235-7238.

13 a) U. Osorio-Nieto, D. Chamorro-Arenas, L. Quintero, H. Hopfl, F. Sartillo-Piscil, *J. Org. Chem*. **2016**, *81*, 8625-8632. b) C. Sparr, E-M. Tanzer, J. Bachmann, R. Glimour, *Synthesis* **2010**, (8), 1394-1997. c) K. Nakano, K. Nozaki, T. Hiyama, *J. Am. Chem. Soc*. **2003**, *125*, 5501-5510.

14 (a) N. Hosoda, H. Kamito, M. Takano, Y. Takebe, Y. Yamaguchi, M. Asami, *Tetrahedron* **2013**, *69*, 1739-1746. b) O. Gleeson, Y. K. Gun'ko, S. J. Connon, *Synlett* **2013**, *24*, 1728-1734. c) J. L. Olivares-Romero, E. Juaristi, *Tetrahedron* **2008**, *64*, 9992–9998.

15 S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc*. **2003**, *125*, 2475-2479.