Letter

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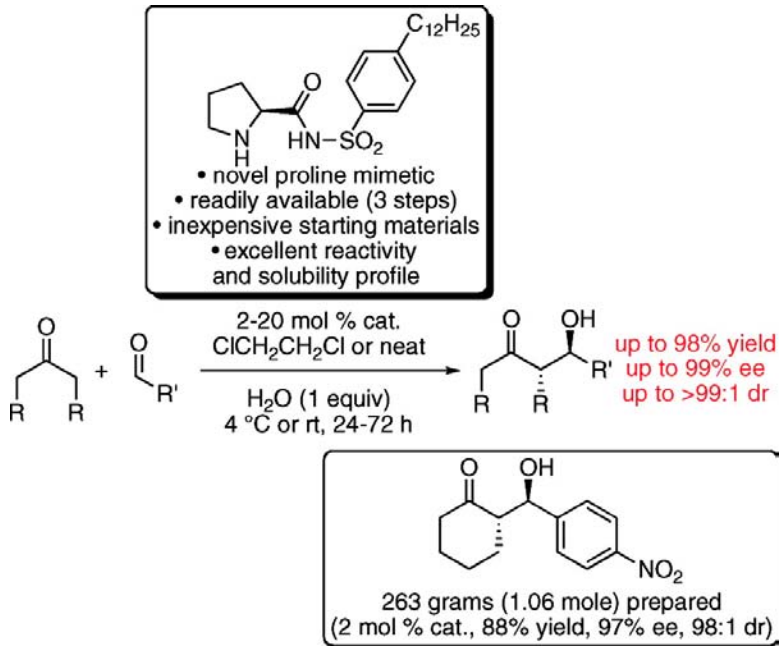
Org. Lett., **2008**, 10 (20), 4649-4652• DOI: 10.1021/ol801941j • Publication Date (Web): 23 September 2008



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ORGANIC LETTERS

2008
Vol. 10, No. 20
4649−4652

N-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide: A Practical Proline Mimetic for Facilitating Enantioselective Aldol Reactions

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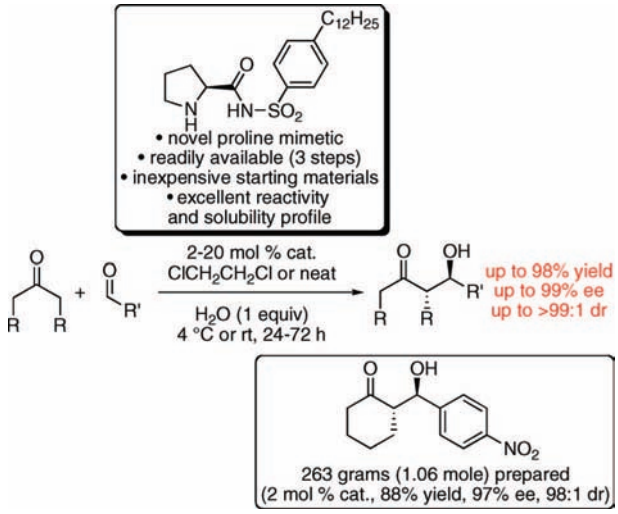
Received August 19, 2008

ABSTRACT



A highly practical and readily available proline surrogate has been developed with improved solubility properties in common, nonpolar organic solvents. This sulfonamide-based catalyst has proven highly effective at facilitating enantioselective and diastereoselective aldol reactions with a range of substrates in nonpolar organic solvents in the presence of a single equivalent of water. Additionally, catalyst loading as low as 2 mol % can be employed in the absence of any organic solvent with continued high levels of selectivity.

Since the early days of enantioselective Robinson annulations facilitated by proline,[1] organocatalysis has garnered the attention of the synthetic community. The explosion of research in this area in recent years has been fueled by the general mildness of the conditions, the relative ease of execution, and the wide variety of chemical transformations that are possible.[2] Proline **1** has attracted significant attention in this area—particularly in the role of facilitating aldol reactions (Figure 1).[3−5] Despite proline's utility in facilitating an organocatalyzed process, it is not without its short-

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10.1021/ol801941j CCC: $40.75
Published on Web 09/23/2008

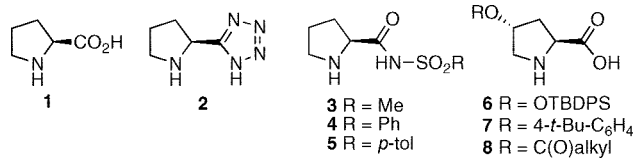
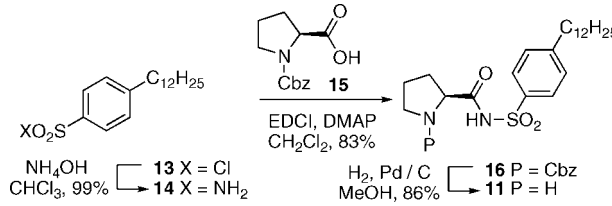


Figure 1. Proline and select proline mimetics.

comings.[6] Consequently, a range of proline mimetics has been created to provide an improved reactivity profile. Two commonly employed classes are the tetrazole **2**[7] and sulfonamides **3**−**5**.[8] Derivatives of 4-*trans*-hydroxyproline (e.g., **6**−**8**) have been utilized in organocatalysis;[9] however, these substrates suffer from the fact that only one enantiomer of *trans*-hydroxyproline is readily available. More substantially different structures have also been introduced by Mauroka,[6b,10] Jørgensen,[11] and others.[12] It is important to note that the vast majority of organocatalyzed processes involving proline or proline surrogates employ polar solvents such as DMF and DMSO.[7a,8c] While these solvents are commonly used in research laboratories, their polarity creates added hurdles for product isolation. Nonpolar solvents have industrial advantages by providing good phase splits with water and are more easily recycled on scale.[13] We were also cognizant of the need for any proline mimetic to be readily accessible for inexpensive starting materials in both enantiomeric forms. In this Letter, we disclose the development of a practical solution for these challenges.

To explore the effects of solvent polarity, the solubility of catalysts **1**−**5** in methylene chloride was screened. Surprisingly, the solubility properties for each of these compounds were quite poor (<5 mg/mL). The absence of a significant nonpolar region to molecules **1**−**5** is one possible hypothesis to explain the origin of this poor solubility. Consequently, we developed a new sulfonamide catalyst **11** that possessed a sizable hydrocarbon chain in the para position of the aromatic ring. This sulfonamide **11** is readily accessible from the commercially available *p*-dodecylsulfonyl chloride (**13**)[14,15] and Cbz-protected proline **15** in 3 steps (Scheme 1; Table 1). Sulfonamides are ideal choices for proline mimetics as their pK_a has been documented to nicely match that of proline.[8c,16] In contrast to catalysts **1**−**5**, sulfonamide **11** displays impressive solubility in methylene chloride (300 mg/mL). The aldol reaction between cyclohexanone (**9**) and *p*-nitrobenzaldehyde (**10**) in methylene chloride with sulfonamide **11** provided the desired product **12** in reasonable ee and dr (entry 1); however, the yield of this transformation was somewhat disappointing (51%). Use of dichloroethylene (DCE) led to an appreciable rate increase (entry 2).[17] Further improvement was found by using a DCE/EtOH mixed solvent system (99:1) (entry 3). Alternatively, a single equivalent of water had a similar rate accelerating effect[9a,b] and with the added benefit of increased diastereo-

Scheme 1. Synthesis of Sulfonamide **11**



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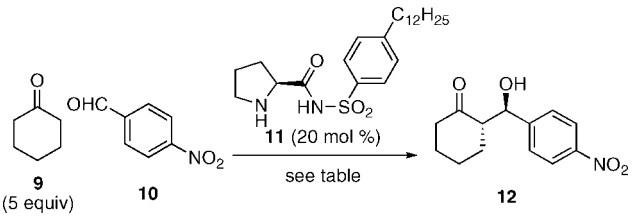
(14) Wako Chemicals Catalog Number 040-19872.

(15) Compound **13** is sold as a mixture of isomers on the $C_{12}H_{25}$ alkyl chain. No attempt was made to separate the isomers in this sequence and the isomeric mixture does not appear to adversely affect the reactivity.

(16) It is important to note that Hayashi and co-workers recently published the synthesis of two long alkyl chain (nonaromatic) sulfonamides; however, these sulfonamides did not provide optimum results in their analysis. We attribute the divergent reactivity to a likely difference in the pK_a of a alkyl sulfonamide versus an aryl sulfonamide. Aratake, S.; Itoh, T.; Okano, T.; Nagae, N.; Sumiya, T.; Shoji, M.; Hayashi, Y. *Chem. Eur. J.* **2007**, *13*, 10246–10256.

(17) (a) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, *50*, 7–509. (b) Carlson, E. K.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158.

Table 1. Optimization of Reaction Conditions with Sulfonamide **11**



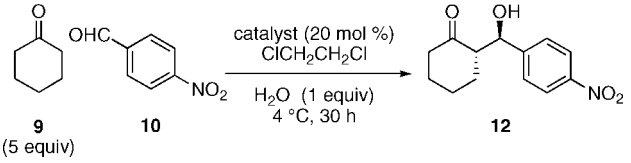
entry	conditions[a]	additive	% yield (dr[b])	% ee[c]
1	CH_2Cl_2, rt, 36 h		51 (15:1)	97
2	$ClCH_2CH_2Cl$, rt, 46 h		92 (12:1)	95
3	$ClCH_2CH_2Cl$, rt, 36 h	EtOH (1%)	96 (14:1)	97
4	$ClCH_2CH_2Cl$, rt, 36 h	H_2O (1 equiv)	96 (36:1)	97
5	$ClCH_2CH_2Cl$,4 °C, 30 h	H_2O (1 equiv)	95 (>99:1)	99

[a] All reactions were performed at 1 M. [b] dr was determined by ^{1}H NMR. [c] ee was determined by chiral HPLC, using a Daicel AD column.

selectivity (entry 4). The optimum reaction conditions included cooling of the reaction to 4 °C with a 30 h reaction time (entry 5).

A direct comparison between sulfonamide **11** and a series of commonly used organocatalysts is provided in Table 2.

Table 2. Comparison of Select Proline Mimetics



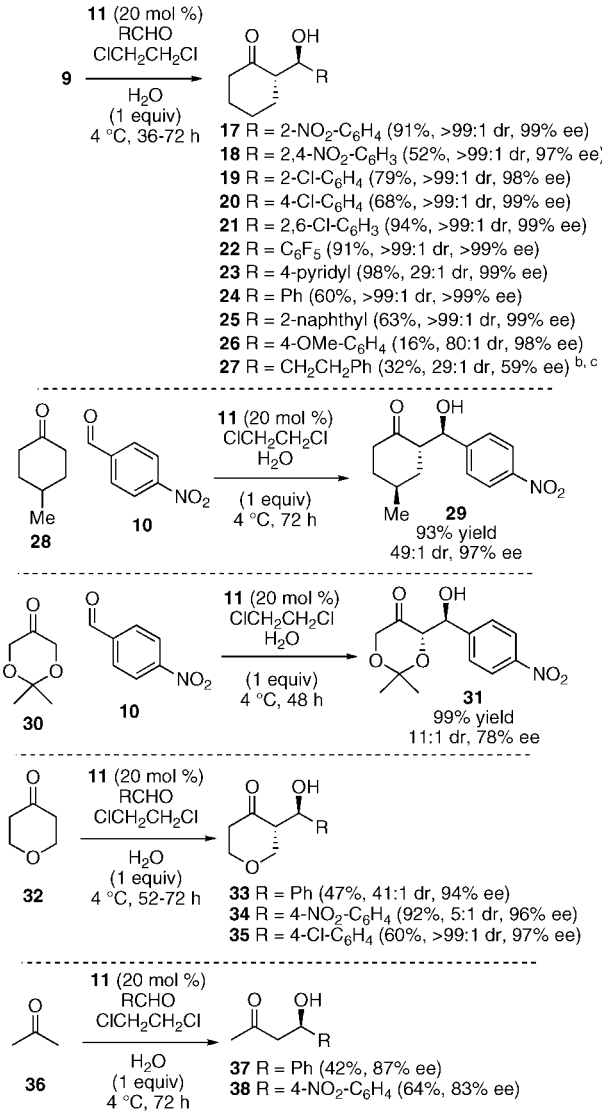
entry	catalyst	% yield	% ee[a]	dr[b]
1	**1**	22	98	13:1
2	**2**	91	98	7:1
3	**3**	42	99	65:1
4	**4**	49	98	83:1
5	**5**	52	99	92:1
6	**11**	95	99	>99:1

[a] ee was determined by chiral HPLC, using Daicel AD column. [b] dr was determined by ^{1}H NMR.

Each of the known catalysts **1**−**5** facilitated the transformation with good enantioselectivity (98−99% ee); however, only the tetrazole **2** is able to provide a reasonable yield (91%) for this transformation (entry 2). Unfortunately, the diastereoselectivity with the tetrazole catalyst **2** (7:1 dr) is significantly below that of the sulfonamides (entries 3−6). In contrast, our *p*-dodecylphenylsulfonamide catalyst **11** provided excellent diastereoselectivity, enantioselectivity, and chemical yield for this transformation (entry 6). It is important to note that the standard proline-based conditions for this transformation (DMSO, rt) have been shown to perform less effectively [65%, 1.7:1 dr, 67% ee (*syn*), 89% ee (*anti*)].[4]

Next, focus was shifted to screening the utility of our sulfonamide catalyst **11** for facilitating aldol reactions across a range of substrates (Scheme 2). We were able to access

Scheme 2. Exploration of Substrate Scope with Sulfonamide Catalyst **11**[a]



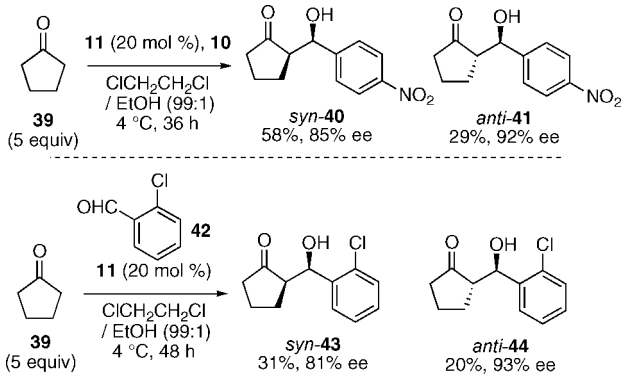
[a]The ratio of ketone to aldehyde was 5:1. [b]This reaction was conducted at room temperature. [c]This reaction was performed without the addition of H_2O.

aldol adducts **17**−**27** derived from their corresponding aldehydes and cyclohexanone. Additionally, 4-methylcyclohexanone (**28**) proved to be a competent substrate for these conditions.[18] Dihydroxyacetone equivalent **30** and pyran-4-one (**32**) also were effective in this transformation to provide aldol adducts **31** and **33**−**35**. Finally, we were pleased to find that this transformation is effective with acetone (**36**) to provide adducts **37**−**38** in reasonable enantioselectivities.

(18) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Mi, X.; Zheng, X.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 11307–11314.

Extension to cyclopentanone (**39**) revealed some interesting results (Scheme 3). The optimized 1 equiv of water

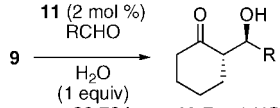
Scheme 3. Select Examples with Cyclopentanone



conditions gave poor diasteroselectivity in the transformation [94%, 1.35:1 (**40**:**41**), 87−95% ee]. In contrast, the DCE/EtOH (99:1) solvent system gave improved levels of diastereoselectivity favoring the *syn* product **40**. Limited prior examples of *syn* selective aldol reactions with cyclopentanone have been reported.[8c,19] Interestingly, slightly improved levels of *syn* selectivity are observed at room temperature (*syn*-**40**: 71%, 77% ee; *anti*-**41**: 26%, 80% ee), but with reduced enantioselectivity.

Finally, we have found that we can perform aldol reactions with catalyst loading as low as 2 mol % if the reaction is performed neat (Scheme 4). Under these conditions, a single

Scheme 4. Select Aldol Reactions Using Low Catalyst Loading[a]

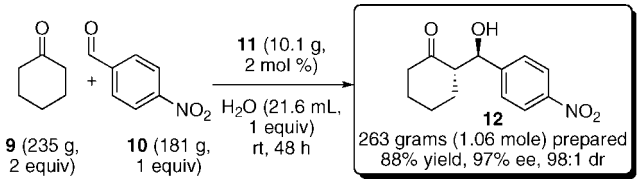


12 R = 4-NO_2-C_6H_4 (96%, >99:1 dr, 96% ee)
19 R = 2-Cl-C_6H_4 (67%, >99:1 dr, 99% ee)
20 R = 4-Cl-C_6H_4 (49%, >99:1 dr, 92% ee)
23 R = 4-pyridyl (91%, 7:1 dr, 91% ee)
24 R = Ph (75%, 55:1 dr, 99% ee)

[a]The ratio of ketone to aldehyde was 2:1.

equivalent of water was still added to the reaction to improve reaction rate and selectivity.[9a,b] As seen in the previous examples, these transformations generally proceeded in good to excellent diastereoselectivity and enantioselectivity. We have demonstrated the practicality of this process by preparing *1 mol* of the aldol adduct **12** (Scheme 5) using a 500 mL round-bottomed flask in excellent diastereoselectivity and enantioselectivity (88% yield, 97% ee, 98:1 dr). We were also able to recover over 60% of the catalyst **11** via a single crystallization.

Scheme 5. Large Scale Example of Enantioselective Aldol Reaction



In conclusion, a highly practical and readily available proline mimetic **11** has been developed. The sulfonamide **11** can be prepared from commercially available and inexpensive D- or L-proline. This important attribute is not shared by 4-*trans*-hydroxyproline derivatives where only one of the two enantiomers is commercially available at a reasonable price. This catalyst **11** has been shown to be effective at facilitating a range of aldol reactions with some of the highest levels of diastereoselectivity and enantioselectivity reported for many of these transformations.[3,4,7−12] Further applications of this catalyst **11** will be reported in due course.

Acknowledgment. Financial support was provided in part by the National Institutes of Health (NIH) (GM63723) and the Oregon State University (OSU) Venture Fund. 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 compound **15**. Finally, the authors are grateful to Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for his helpful discussions.

Supporting Information Available: Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801941J

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