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Organocatalytic Michael Addition of Aldehydes to Vinyl Sulfones: Enantioselective α-Alkylations of Aldehydes and Their Derivatives

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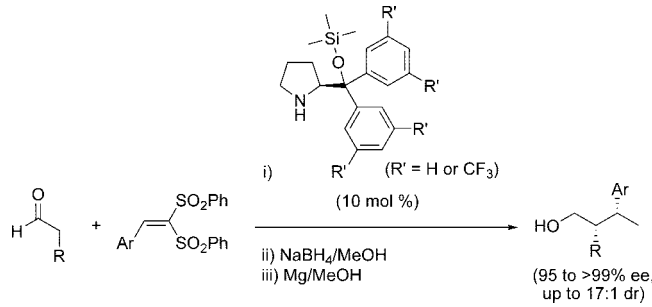
ABSTRACT



Organocatalytic asymmetric Michael reaction of unmodified aldehydes to vinyl sulfones catalyzed by silylated biarylprolinol afforded the desired Michael products with exceptional enantioselectivity. The described enantioselective addition to vinyl sulfones, in combination with desulfonation, offers a unique, asymmetric entry to α-alkylated aldehydes and their derivatives.

Sulfones are widely employed as valuable intermediates in organic synthesis.[1] Asymmetric Michael addition of carbon nucleophiles to vinyl sulfones represents an important carbon−carbon bond-forming reaction and provides an easy access to various optically pure sulfones. In a number of early reports,[2] enamines preformed from ketones were successfully added to vinyl sulfones; however, the additions were nonstereoselective. D'Angelo and co-workers later developed enantioselective additions of imines derived from cyclic ketones and chiral 1-phenyethylamine to vinyl sulfones.[3] Deng et al. reported elegant cinchona alkaloid-mediated enantioselective conjugate additions to vinyl sulfones for the construction of all-carbon quaternary stereocenters.[4] Recently, Alexakis and his co-workers described an asymmetric organocatalytic Michael addition of aldehydes to vinyl sulfones.[5] These reactions were promoted by their well-designed N-iPr-2,2′-bipyrrolidine catalysts, and the adducts were obtained with modest to good enantioselectivity. Despite all the aforementioned excellent advances, highly enantioselective catalytic Michael addition of carbonyl substrates to vinyl sulfones remains a challenging task, particularly with aldehyde substrates.

(1) (a) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951. (b) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

(2) (a) Risaliti, A.; Fatutta, S.; Forchiassin, M. *Tetrahedron* **1967**, *23*, 1451. (b) Benedetti, F.; Fabrissin, S.; Risaliti, A. *Tetrahedron* **1984**, *40*, 977. (c) Lucchi, O. D.; Pasquato, L.; Modena, G. *Tetrahedron Lett.* **1984**, *25*, 3643.

(3) (a) Pinheiro, S.; Guingant, A.; Desmaële, D.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1003. (b) Desmaële, D.; Delarue-Cochin, S.; Cave, C.; d'Angelo, J.; Morgant, G. *Org. Lett.* **2004**, *6*, 2421.

(4) Li, H.; Song, J.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2005**, *127*, 8948.

(5) (a) Mosse, S.; Alexakis, A. *Org. Lett.* **2005**, *7*, 4361. For an excellent recent report on organocatalytic addition of aldehyde to vinyl phosphonate, see: (b) Sulzer-Mosse, S.; Tissot, M.; Alexakis, A. *Org. Lett.* **2007**, *9*, 3749.

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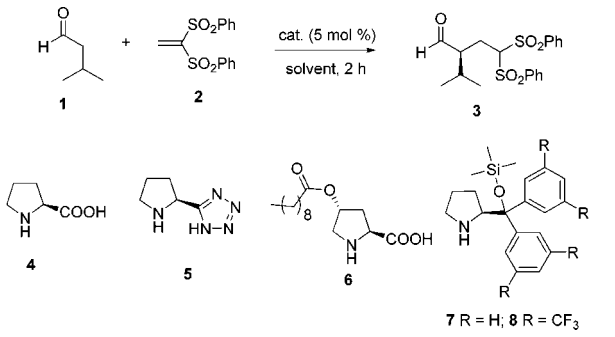
Asymmetric organocatalysis has attracted much attention in recent years.[6] In particular, proline and its various structural analogues have been shown to be efficient catalysts for a wide range of organic reactions. We became interested in developing an efficient and practical organocatalytic approach to access chiral sulfones. Herein, we disclose that silylated biarylprolinols promote addition of aldehydes to various vinyl sulfones with exceptional enantioselectivity.

The Michael addition of isovaleraldehyde **1** to vinyl sulfone **2** was selected as our model reaction, and a few common organocatalysts were screened (Table 1). Proline

Table 1. Screening of Organocatalysts for the Asymmetric Michael Addition of Isovaleraldehyde to Vinyl Sulfone[a]



entry	catalyst	solvent	T (°C)	yield[b] (%)	ee[c] (%)
1	**4**	$CHCl_3$	rt	56	2
2	**5**	$CHCl_3$	rt	41	31
3	**6**	$CHCl_3$	rt	76	9
4	**7**	$CHCl_3$	rt	92	89
5	**8**	$CHCl_3$	rt	93	98
6	**8**	CH_3CN	rt	87	79
7	**8**	CH_2Cl_2	rt	94	96
8	**8**	Toluene	rt	95	98
9	**8**	DMSO	rt	71	79
10	**8**	CH_3OH	rt	88	91
11	**8**	THF	rt	95	96
12	**8**	**$CHCl_3$**	**0**	**94**	**>99**

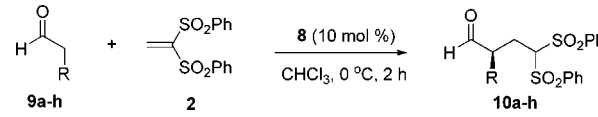
[a] The reactions were performed with isovaleraldehyde (0.5 mmol), vinyl sulfone (0.05 mmol), and catalyst (0.005 mmol) in anhydrous solvent (0.1 mL) at room temperature, unless otherwise specified. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

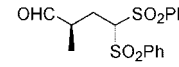
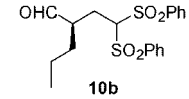
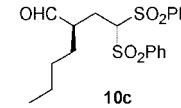
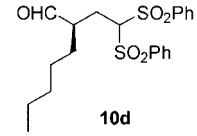
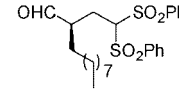
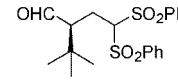
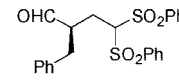
4, tetrazole **5**, and proline derivative **6** were not very effective, affording the desired adducts with poor enantioselectivites (entries 1−3). Prolinol silyl ethers,[7] independently developed by the groups of Hayashi and Jørgensen, were found to be very effective. The trifluoromethyl-substituted silylated diphenylprolinol catalyst **8** was more effective than the diphenylprolinol silyl ether **7** (entries 4 and 5). Solvent screening revealed that a number of solvents were suitable (entries 6−11), and chloroform was chosen for synthetic convenience. When the reaction was carried out at 0 °C, essentially enantiomerically pure adduct was obtained (entry 12).

After the reaction conditions were optimized, the generality of the reaction was then examined, and the results are summarized in Table 2. A wide range of aliphatic aldehydes were tested as Michael donors. In all the examples studied, very high yield and excellent enantioselectivity were attainable.

To make our methodology synthetically more useful, we extended our reactions to include 2-aryl-substituted vinyl

Table 2. Addition of Various Aldehydes to Vinyl Sulfone **2** Catalyzed by Prolinol Silyl Ether **8**[a]



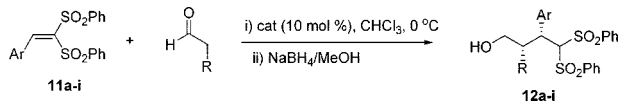
entry	product	yield[b] (%)	ee[c] (%)
1	 **10a**	93	97
2	 **10b**	94	99
3	 **10c**	95	99
4	 **10d**	94	>99
5	 **10e**	97	>99
6	 **10f**	93	94
7	 **10g**	94	95

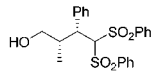
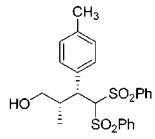
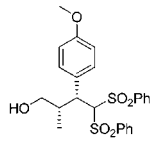
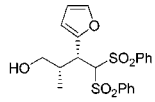
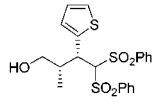
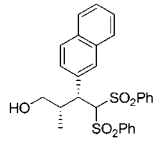
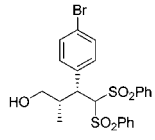
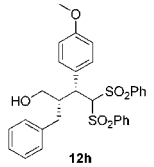
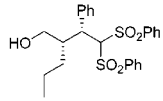
[a] The reactions were performed with aldehyde (0.5 mmol), vinyl sulfone (0.05 mmol), and catalyst (0.005 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 °C. [b] Isolated yield. [c] The ee value was determined by chiral HPLC analysis.

(6) (a) Dalko, P. I.; Moisan, L. *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (c) *Enantioselective Organocatalysis, Reactions and Experimental Procedures*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007.

(7) (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem.* **2005**, *117*, 42824; *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (b) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (c) Palomo, C.; Mielgo, A. *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

Table 3. Organocatalytic Michael Addition of Aldehydes to 2-Aryl-Substituted Vinyl Sulfones[a]



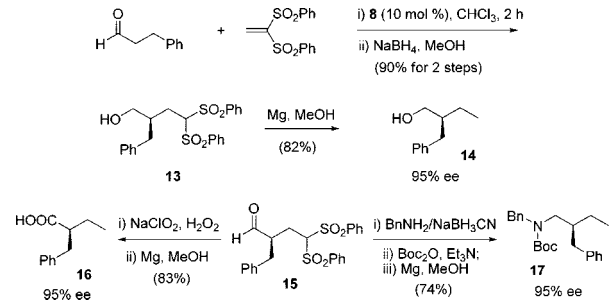
entry	product	catalyst	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	 12a	**8**	12	91	15:1	98
2	 12b	**8**	12	88	10:1	95
3	 12c	**8**	20	94	10:1	>99
4	 12d	**8**	14	86	4:1	98
5	 12e	**8**	16	90	3:1	98
6	 12f	**8**	24	82	10:1	99
7	 12g	**8**	15	92	12:1	99
8	 12h	**7**	12	91	17:1	99
9	 12i	**7**	16	94	6:1	99

[a] The reactions were performed with aldehyde (0.5 mmol), vinyl sulfone (0.05 mmol), and catalyst (0.005 mmol) in anhydrous $CHCl_3$ (0.1 mL) at 0 °C. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude product. [d] The ee value of the *syn*-isomer was determined by chiral HPLC analysis.

sulfones **11**[8] as acceptors (Table 3). The aryl component of vinyl sulfone can be either electron rich or neutral; however, electron-poor aryl-substituted vinyl sulfones were too unstable to be prepared. The addition of aldehydes to various vinyl sulfones proceeded very efficiently, yielding the desired adducts in excellent yield, good diastereoselectivity, and nearly perfect enantioselectivity.

The Michael adduct of an aldehyde to vinyl sulfone is a versatile intermediate in organic synthesis. The facile conversion of aldehyde into a number of important functional groups, in combination with well-established desulfonylation methods,[9] offers a unique asymmetric entry to α-alkylated aldehydes and their derivatives. To illustrate the value of our highly enantioselective Michael additions of aldehydes to vinyl sulfones, we prepared a number of chiral building blocks, as shown in Scheme 1. Following the prolinol silyl

Scheme 1. Conversion of the Michael Adduct into Synthetically Useful Chiral Building Blocks



ether **8**-medicated Michael addition, reduction with $NaBH_4$ then afforded **13**, and the subsequent reductive removal of the sulfone groups yielded chiral alcohol **14**[10] in high yield and with 95% ee. Chiral acid **16** and amine **17** could also be readily prepared, in overall good yield and with excellent enantioselectivity.

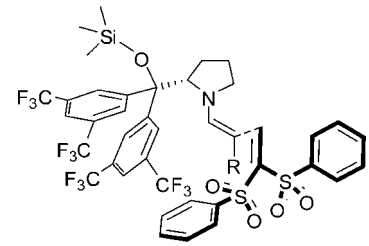


Figure 1. Proposed transition-state model.

Based on the observed stereochemistry of the Michael product, a plausible transition-state model is proposed in

(8) Ziegler, E.; Ruef, W.; Zwainz, J. G. *Anorg. Chem., Org. Chem.* **1975**, *30*, 755.

(9) (a) Najera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547. (b) Kundig, E. P.; Cunningham, A. F., Jr. *Tetrahedron* **1988**, *44*, 6855.

Figure 1. The bulky biaryl silyl ether moiety exerts steric shielding, resulting in the formation of observed stereoisomer.

In conclusion, we have disclosed highly efficient organocatalytic Michael additions of aldehydes to vinyl sulfones mediated by trifluoromethyl-substituted diphenylprolinol silyl ether. Our results represent the only example in the literature showing that remarkable enantioselectivity can be achieved for this type of reaction. The excellent enantioselectivity described in this report makes the utilization of vinyl sulfone as valuable synthetic intermediates highly practical and desirable, and we anticipate that these synthetic methods will find wide application in organic synthesis.

Acknowledgment. We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112) for generous financial support.

Supporting Information Available: Representative experimental procedure for Michael addition to vinyl sulfone, procedures to convert Michael adduct into chiral alcohol, acid, and amine, determination of absolute configurations of Michael products, HPLC chromatogram, and analytical data and NMR spectra of the Michael adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) (a) Absolute configuration of the Michael adduct **10g** was assigned by comparing the optical rotation of its derivative **14** with the literature data; see: Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc.* **1996**, *118*, 1577. (b) For the assignment of absolute configurations of **12a-I**, see the Supporting Information.