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Enantioselective Organocatalytic Mukaiyama–Michael Addition of Silyl Enol Ethers to α,β-Unsaturated Aldehydes

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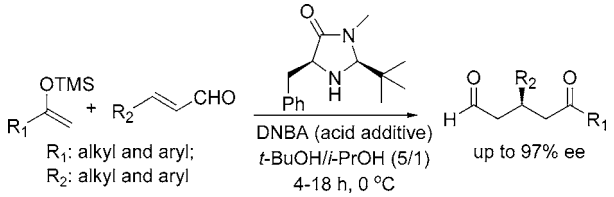
ABSTRACT



A highly enantioselective, organocatalytic Mukaiyama–Michael addition reaction of silyl ethers and α,β-unsaturated aldehydes has been developed. The process, catalyzed by MacMillan's chiral imidazolidinone, affords δ-keto aldehydes in high yields (56–87%) and high enantioselectivities (85–97% ee). Moreover, the reaction is applicable to a wide range of silyl ethers and α,β-unsaturated aldehydes and, as such, provides access to a range of important synthetic building blocks.

The Mukaiyama−Michael addition reaction is a powerful tool for the preparation of synthetically useful 1,5-dicarbonyl compounds.[1,2] Consequently, considerable attention has been given to the development of a catalytic asymmetric version of this process. Although significant progress has been made for α,β-unsaturated ketone, ester, amide, and nitrostyrene substrates,[2,3] the development of a catalytic method to promote enantioselective Michael additions to α,β-unsaturated aldehydes has proven to be more challenging. One of the main reasons for this is the greater susceptibility of α,β-unsaturated aldehydes to 1,2-addition reactions as compared to other unsaturated systems. Thus, it is not surprising that only a few successful examples of these reactions have been presented.[3f,4] Recent studies of organocatalysts have uncovered methods to achieve 1,4- rather than 1,2-additions to conjugated aldehydes. MacMillan reported that chiral imidazolidinones serve as effective catalysts for 1,4-addition of electron rich aromatic systems to α,β-unsaturated aldehydes.[5]

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.

(2) For recent reviews on the catalytic asymmetric Michael reactions, see: (a) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (d) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1.

(3) For leading references on the catalytic asymmetric Michael reactions, see: (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (b) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480. (c) Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. *Org. Lett.* **2001**, *3*, 2101. (d) Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. (e) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Fukuzumi, S. *J. Am. Chem. Soc.* **1991**, *113*, 4028. (f) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (g) Wang, X.; Adachi, S.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A.; Harada, T. *J. Org. Chem.* **2003**, *68*, 10046. (h) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (i) Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (j) Halland, N.; Hansen, T.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955. (k) Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272.

(4) (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176. (b) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2000**, 1851. (c) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589. (d) Kumaraswamy, G.; Sastry, M. N. V.; Jena, N. *Tetrahedron Lett.* **2001**, *42*, 8515.

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In addition, Maruoka demonstrated the utility of chiral ammonium bifluorides as catalysts for silyl nitronate Michael addition reactions with unsaturated aldehydes.[6] Despite these advances, catalysts which promote the classic asymmetric Mukaiyama−Michael addition reaction between silyl enol ethers and α,β-unsaturated aldehydes have not yet been developed. In this paper, we describe the first highly enantioselective version of this process, which employs MacMillan's chiral imidazolidinone catalyst and provides δ-keto aldehydes in high yields and high enantioselectivities.

Chiral pyrrolidine and pyrrolidinone derivatives have been shown to be effective organocatalysts for asymmetric reactions.[7] Consequently, in initial exploratory efforts directed at the development of chiral amine-catalyzed asymmetric Michael addition reactions, we screened five chiral pyrrolidines and pyrrolidinones (Figure 1). These substances were

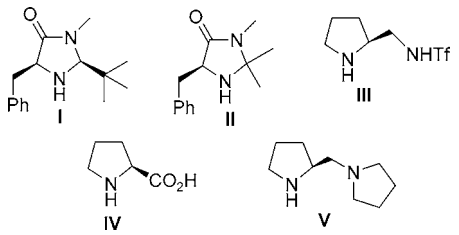
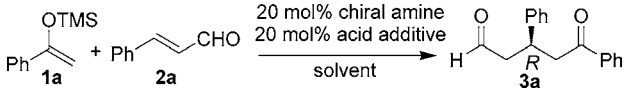


Figure 1. Chiral amine organocatalysts.

used by us and others as catalysts for the different versions of the Michael addition reactions.[5,8−10] Reaction of 1-phenyl-1-(trimethylsilylox)ethylene **1a** with *trans*-cinnamaldehyde **2a** and 20 mol % of chiral imidazolidinone **I** in CH_2Cl_2 at room temperature (rt) in the presence of 2,4-dinitrobenzenesulfonic acid (DNBA) (20 mol %) proceeded very slowly in low yield (14%, 12 h) (Table 1, entry 1). A survey of solvents revealed that the reaction media had a significant

Table 1. Results of Exploratory Studies of Catalytic Asymmetric Mukaiyama−Michael Addition Reactions of Silyl Enol Ether and *trans*-Cinnamaldehyde[a]



entry	catalyst	solvent	T (°C)	yield[b] (%)	ee[c] (%)
1	**I** + DNBA	CH_2Cl_2	rt	14	*d*
2	**I** + DNBA	*i*-PrOH	rt	58	76
3	**I** + DNBA	*i*-PrOH	0	68	86
4	**I** + DNBA	*t*-BuOH	rt	55	87
5	**I** + DNBA	mixture[e]	0	60	90
6	**I** + HCl	mixture[e]	0	<10	*d*
7	**I** + TFA	mixture[e]	0	*d*	*d*
8	**I** + DNBA[f]	mixture[e]	0	75	90
9	**II** + DNBA	mixture[e]	0	40	47
10	**III** + DNBA	mixture[e]	0	16	83[g]
11	**IV** + DNBA	mixture[e]	0	*d*	*d*
12	**V** + DNBA	mixture[e]	0	*d*	*d*

[a] Unless otherwise specified, the reaction was carried out with 5 equiv of **1a** and 1 equiv of **2a** in the presence of 20 mol % chiral amine and acid (20 mol %) in 0.5 mL of solvent at rt or 0 °C for 12 h. [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H, hexane/2-propanol = 90:10). [d] Not determined. [e] A mixture of *t*-BuOH/*i*-PrOH (5:1 v/v) used. [f] 30 mol % of **I** and 30 mol % of DNBA used. [g] *S* configuration.

effect on the rate of this process (Table 1, entries 1−5).[11] For example, the reactions carried out in *i*-PrOH and *t*-BuOH gave higher yields (58% and 55%, respectively, Table 1, entries 2 and 4). More importantly, reactions in these solvents were highly enantioselective (87% ee in *t*-BuOH and 76% ee in *i*-PrOH). The major enantiomer of product, 1,5-diketoaldehyde **3a**, has the *R* configuration.[12] By lowering the temperature to 0 °C for reaction in *i*-PrOH, both the enantioselectivity (86% ee) and the yield (68%) were significantly improved (Table 1, entry 3). Optimization studies showed that a solvent system consisting of 5:1 (v/v) mixture of *t*-BuOH and *i*-PrOH at 0 °C was ideal for this process.

An acid additive is required for this reaction in which an aldiminium ion serves as a key intermediate.[5] Evaluation of three acids revealed that strong acids, such as HCl and TFA, caused decomposition of silyl ether **1a**. In contrast, **1a** tolerated DNBA (Table 1, entries 5−7), and subsequently, the acid was used in further studies of this process.

Studies showed that the catalytic activities of five organocatalysts **I**−**V** differed significantly (Table 1, entries 5 and 9−12). Under identical reaction conditions (0 °C in *t*-BuOH and *i*-PrOH (5/1, v/v) with DNBA), reaction of silylenol ether **1a** with *trans*-cinnamaldehyde **2a** catalyzed by **I** afforded adduct **3a** with excellent enantioselectivity (90% ee) and

(5) For MacMillan catalyst-catalyzed reactions, see: (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (d) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (e) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 3958.

(6) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.

(7) For selected reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580.

(8) Recently we have found pyrrolidine amides/sulfonamides as effective organocatalysts for asymmetric reactions: (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (b) Wang, W.; Wang, J.; Li, H. *Org. Lett.* **2004**, *6*, 2817. (c) Wang, W.; Mei, Y.-J.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601. (d) Wang, W.; Wang, J.; Li, H.; Liao, L.-X. *Tetrahedron Lett.* **2004**, *45*, 7235. (e) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.

(9) For L-proline-catalyzed Michael reactions, see: (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (c) Ender, D.; Seki, A. *Synlett* **2002**, 26.

(10) For diamine-catalyzed Michael reactions, see: (a) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527. (c) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611.

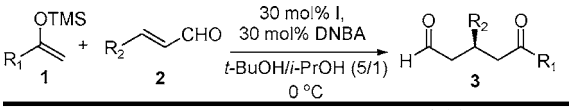
(11) More solvents were screened: THF, 16% yield; DMF, <10% yield; DMSO, <10% yield; 1,4-dioxane, 24% yield; CH_3NO_2, 32% yield; CH_3CN, 37% yield.

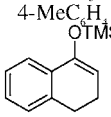
(12) The absolute (*R*) configuration of compound **3a** was determined by comparing the optical rotation with a known compound, which has been reported in: Barluenga, J.; Montserrat, J. M.; Florez, J.; Garcia-Granda, S.; Martin, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1392.

good yield (60%, Table 1, entry 5). Moreover, increasing the loading of **I** up to 30 mol % significantly improves the yield of this reaction without sacrificing enantioselectivity (75% yield, 90% ee, entry 8). However, the reaction promoted by catalyst **II**, which has a similar structure to **I**, took place with a much lower enantioselectivity (47% ee, entry 9). Interestingly, a highly enantioselective reaction (83% ee, entry 10) occurred when our pyrrolidine trifluoromethanesulfonamide catalyst **III** was used, but unfortunately the rate of this process was very low. L-Proline **IV** and diamine **V** did not serve to catalyze the formation of product **3a** even after a 12 h period (entries 11 and 12).

Having established the optimal reaction conditions, we next probed the generality of this asymmetric catalytic variant of the Mukaiyama−Michael addition reaction with a variety of silyl ethers **1** and α,β-unsaturated aldehydes **2** (Table 2).

Table 2. Catalytic Asymmetric Mukaiyama−Michael Addition of Silyl Enol Ethers **1** to α,β-Unsaturated Aldehydes **2**[a]



entry	R_1	R_2	yield (%)[b]	ee (%)[c]
1	Ph	Ph	75	90
2	4-BrC_6H_4	Ph	58	86
3	4-MeC_6H_4	Ph	62	95
4	4-$MeOC_6H_4$	Ph	56	97
5[c]	4-MeC_6H_4	4-FC_6H_4	71	92
6	4-$MeOC_6H_4$	4-FC_6H_4	63	95
7	Ph	4-CNC_6H_4	59	90
8	4-$MeOC_6H_4$	4-CNC_6H_4	61	94
9	4-$MeOC_6H_4$	4-$MeOC_6H_4$	63	90
10	4-MeC_6H_4	Me	60	87
11[d,e]		Ph	87	85

[a] See footnote in Table 1. [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or Chialcel OJ-H). [d] Reaction run at −20 °C. [e] dr determined by ^{1}H NMR.

The results showed that the reactions took place efficiently (56−87%), and high to excellent levels of enantioselectivity (85−97%) with all of the silyl enol ethers and unsaturated aldehyde were achieved. As revealed by inspecting the results given in Table 2, high to excellent enantioselectivities were obtained with silyl ethers that possess both electron-withdrawing (4-Br, Table 2, entry 2) and electron-donating substituents (4-Me and 4-MeO, Table 2, entries 3 and 4). It was noted that reactions with electron-withdrawing group substituted aldehydes tended to give lower enantioselectivities (e.g., 4-Br, 86% ee, entry 2), whereas those with electron-donating group substituted substrates (4-Me and 4-MeO, entries 3 and 4) proceeded with higher enantioselectivities (95 and 97% ee).

Significant structural variation in the α,β-unsaturated aldehydes was tolerated in this reaction, which occurred efficiently, independent of the nature of substituents on the phenyl ring (Table 2, entries 5−9, 59−71% yields, 90−95% ee). In all cases, excellent levels (≥90% ee) of enantioselectivity were observed. Moreover, based on preliminary results, it appeared that the catalytic process was applicable to β-alkyl substituted α,β-unsaturated aldehydes (e.g., acreloin) and cyclic (e.g., tetralone) silylenol ethers (entries 10 and 11, 60% yield, 87% ee and 87% yield and 85% ee, respectively). In the latter case, two stereogenic centers were produced in the reaction with high enantioselectivity (85% ee) and diastereoselectivity (30:1 dr) (Table 2, entry 11).[13]

In summary, we have developed a catalytic variant of the asymmetric Mukaiyama−Michael addition reaction between silyl enol ethers and α,β-unsaturated aldehydes. The reactions are effectively catalyzed by the organocatalyst **I**, affording synthetically useful 1,5-dicarbonyl compounds in high yields and high to excellent levels of enantioselectivity. Further investigations of the mechanistic features and scope of this reaction are underway.

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Supporting Information Available: Experimental procedures and ^{1}H, ^{13}C NMR and/or MS data for Mukaiyama−Michael addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) We could not determine the absolute configurations of the compound because of the quick racemization.