Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 277–280

A new organocatalyst for 1,3-dipolar cycloadditions of nitrones to α,β-unsaturated aldehydes

San San Chow, Marta Nevalainen,* Catherine A. Evans and Charles W. Johannes

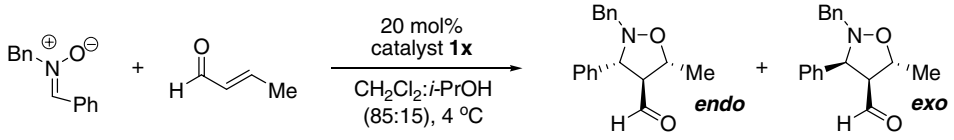
Infinity Pharmaceuticals, Inc., 780 Memorial Drive, Cambridge, MA 02139, USA

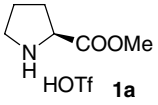
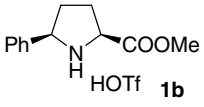
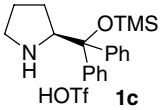
Received 29 September 2006; revised 2 November 2006; accepted 5 November 2006
Available online 27 November 2006

Abstract—The triflate salt resulting from the treatment of diphenyl-*S*-prolinol with trimethylsilyl triflate, catalyzes the addition of nitrones to α,β-unsaturated aldehydes to provide isoxazolidines in high yields and excellent diastereo- and enantioselectivities.

In the past few years organocatalysis has emerged as a powerful approach for the preparation of important optically active building blocks.[1] The LUMO-lowering activation of α,β-unsaturated aldehydes using the reversible formation of iminium ions with chiral imidazolidinones was reported by MacMillan and co-workers as a valuable platform for the development of various enantioselective organocatalytic cycloadditions.[2] We decided to apply that strategy to the [3+2] cycloaddition of α,β-unsaturated aldehydes to nitrones[2b] using catalysts that could be synthesized in one step from commercially available starting materials. As

Table 1. Catalyst screen for the cycloaddition of *N*-benzylidenebenzylamine *N*-oxide and crotonaldehyde



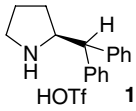
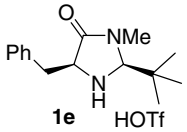
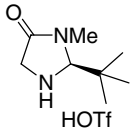
Entry	Catalyst	Time (days)	*endo*:*exo*[a]	% ee (*endo*)[b]
1	 **1a**	1	78:22	37
2	 **1b**	0.5	78:22	26
3	 **1c**	2	—	—
4[c]	**1c**	3	93:7	96
5[d]	**1c**	1	98:2	93
6[e]	**1c**	3.5	96:4	83

(*continued on next page*)

Keywords: Enantioselectivity; [3+2] Cycloadditions; Organocatalysis; Nitrones; Isoxazolidines; Diphenyl-prolinol; Asymmetric catalysis.
* Corresponding author. Tel.: +1 6174531248; fax: +1 6174531001; e-mail: Marta.Nevalainen@ipi.com

0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.11.029

Table 1 (*continued*)

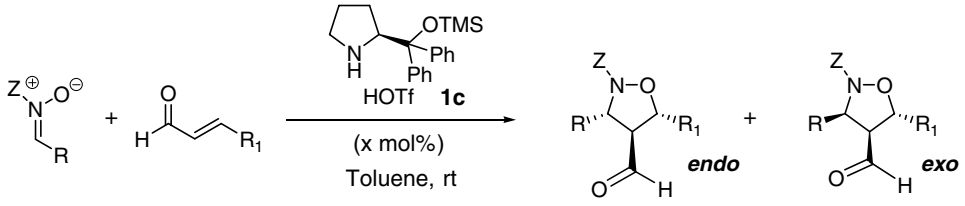
Entry	Catalyst	Time (days)	*endo*:*exo*[a]	% ee (*endo*)[b]
7	 **1d**	>7	84:16	14
8	 **1e**	0.5	98:2	97
9	 **1f**	1	91:9	42

[a] Determined by ^{1}H NMR.
[b] Determined by chiral SFC on the corresponding alcohol.
[c] Reaction conducted in toluene at 4 °C.
[d] Reaction conducted in toluene at rt.
[e] Reaction conducted in CH_2Cl_2 at rt.

revealed in Table 1, the reaction of *N*-benzylidenebenzylamine *N*-oxide with (*E*)-crotonaldehyde was successful with a variety of amine catalysts[3] (entries 1–9, 14–97% ee) in CH_2Cl_2–IPA (85:15) at +4 °C. This solvent system was unsuitable for catalyst **1c**, as presumably its sensitive trimethylsilyl moiety was cleaved under those conditions. A solvent screen revealed that toluene was optimal for that catalyst (Table 1, entries 4 and 5). Catalyst **1e** (second generation MacMillan catalyst)[4–6] performed best (Table 1, entry 8) in terms of rate, diastereo- and enantioselectivity. To our delight the performance of catalyst **1c** was comparable to that of **1e** (Table 1, entries 5 and 8), with the advantage that it is prepared in one step from commercially available diphenyl-*S*-prolinol;[3] the synthesis of second generation MacMillan catalyst **1e** requires multiple synthesis steps from phenylalanine methyl ester.[6] All other catalysts screened (entries 1, 2, 7 and 9), promoted the desired [3+2] cycloaddition, albeit in lower enantioselectivities. The free base of **1c** has been used in previous organocatalytic studies,[7] but to the best of our knowledge this is the first report on the organocatalytic properties of triflate salt **1c**.[8]

The scope of the organocatalytic 1,3-dipolar cycloaddition between α,β-unsaturated aldehydes and various

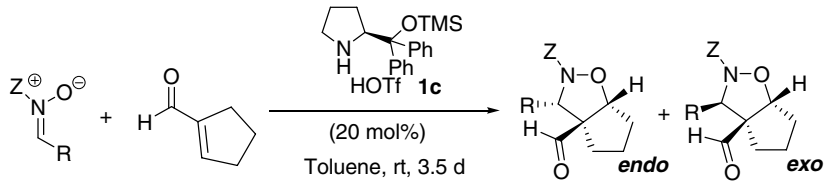
Table 2. [3+2] Cycloaddition of α,β-unsaturated aldehydes and nitrones: substract generality



Entry	Z	R	R_1	*x* (mol %)	Time (h)	% Yield[a]	*endo*:*exo*[b]	% ee (*endo*)[c]
1	Bn	Ph	Me	20	22	75	98:2	93
2	Bn	Ph	Me	10	24	86	97:3	95
3	Bn	Ph	Me	5	33	92	96:4	95
4[d]	Bn	Ph	H	10	24	79	93:7	86
5	Bn	Ph	CO_2Et	10	24	80	99:1	96
6	Me	Ph	Me	10	24	61	96:4	94
7[d]	Me	Ph	H	10	24	47	93:7	88
8	Me	Ph	CO_2Et	10	24	66	99:1	93
9	Bn	Naph	Me	10	24	96	97:3	91
10[d]	Bn	Naph	H	10	24	70	92:8	66

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral SFC on the corresponding alcohol.
[d] Reaction conducted at 40 °C.

Table 3. [3+2] Cycloaddition of cyclopentene carboxaldehyde and various nitrones



Entry	Z	R	% Yield[a]	*endo*:*exo*[b]	% ee (*endo*)[c]
1	Bn	Ph	66	80:20	46
2	Me	Ph	75	79:21	83
4	Bn	Naph	75	90:10	37

[a] After column chromatography.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral SFC on the corresponding alcohol.

nitrones catalyzed by **1c** was investigated (Table 2).[9] The amount of catalyst used was 10 mol %, as higher or lower catalyst loadings seemed to be detrimental either for yield or reaction rate (compare entries 1–3). The lower yield attained with 20 mol % catalyst (Table 2, entry 1) could be attributed to greater aldehyde polymerization or nitrone decomposition in the presence of a higher amount of catalyst, but that experimental result is not totally understood at this time. The cycloaddition was quite general with respect to the nitrone structure. Variation in the *N*-alkyl group (Z = Bn, Me) was possible without loss in enantioselectivity (i.e., entries 2 and 6, 95% and 94% ee). Changes in the structure of the dipolarophile were also well tolerated; acrolein (Table 2, entries 4, 7 and 10) and ethyl oxobutenoate (Table 2, entries 5 and 8) provided isoxazolidines in high diastereo- and enantioselectivities. In the case of acrolein, best results were attained at 40 °C instead of rt. Indeed the *endo*:*exo* ratio was better at a higher temperature (Table 2, entry 4, 93:7 at 40 °C vs 75:25 at rt and 69:31 at +4 °C), while the ee remained essentially the same. Even 1-cyclopentene-1-carboxaldehyde reacted to provide fused isoxazolidines (Table 3) in an *endo* fashion. In this instance, the smaller *N*-methyl group on the nitrone afforded a better enantioselectivity (entry 2). This method is complementary to a previous report using a different organocatalyst,[10] which afforded selectively the *exo* adducts. *Endo* adducts from 1-cyclopentene-1-carboxaldehyde and *N*-benzylidenephenylamine *N*-oxide had been obtained earlier via a Lewis acid catalyzed approach.[11]

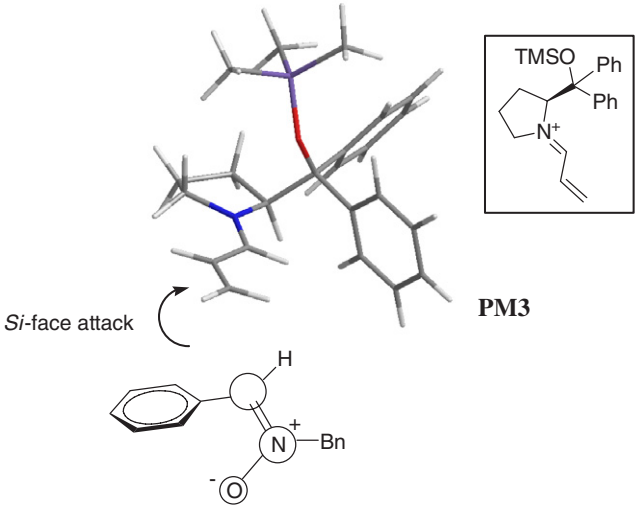


Figure 1. Postulated *Si*-face attack of the nitrone on the *E*-iminium formed from acrolein and catalyst **1c**.

Enantioselective formation of the *endo*-(4*S*)-isoxazolidine adduct was observed in all cases involving catalyst (*S*)-**1c** (determined by comparison of their optical rotation with values reported in the literature).[2b] Formation of the (*E*)-iminium isomer (Fig. 1) was found to be preferential (PM3-optimized structure). The position of one of the phenyl groups and the silyl substituent on the catalyst scaffold effectively shield the *Re*-face of the dipolarophile, thus promoting cycloaddition from its open *Si*-face.

In summary, a new chiral pyrrolidine derivative synthesized in one step from commercially available reagents has been found to be an excellent organocatalyst for [3+2] cycloadditions. This catalyst is now available to the scientific community to further investigate its scope and utility in asymmetric reactions.

Acknowledgements

We thank Dr. Michael A. Foley for his insight and fruitful comments. S. Chow is indebted to the Economic and Development Board (EDB) of Singapore for a Training and Attachment Program stipend.

References and notes

1. For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH Weinheim: Germany, 2004; (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (d) List, B. *Chem.*

Commun. **2006**, 819–824; (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011.

2. (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; (b) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.
3. Catalysts **1a**, **1b** and **1d**–**f** were synthesized from the corresponding commercially available Boc-protected amines (free amine in the case of **1e**) upon treatment with 3% solution of triflic acid in dichloromethane. Catalyst **1c** was obtained as follows: To a suspension of diphenyl-*S*-prolinol (1.0 g, 3.95 mmol) (purchased from 3B Medical Systems; both enantiomers available at $9/g) in DCM (10.0 mL) at 0 °C under argon atmosphere was added triethylamine (825 μL, 1.5 equiv, 5.92 mmol). TMSOTf (857 μL, 1.2 equiv, 4.74 mmol) followed dropwise, the resulting mixture was stirred at 0 °C for 1.5 h and was concentrated under reduced pressure. The residual oil was dried under vacuum overnight, and the resulting solid was recrystallized from diethylether to provide **1c** as white needles (80% yield). Mp = 146.5–148.5 °C; $[\alpha]_D^{20}$ −8.7 (*c* 1.0, toluene). ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.44 (br s, 1H), 7.40–7.30 (m, 10H), 6.50 (br s, 1H), 4.81 (br s, 1H), 3.25 (br s, 1H), 2.69 (br s, 1H), 2.40–2.25 (m, 1H), 2.10–1.90 (m, 2H), 1.60–1.48 (m, 1H), −0.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 141.7, 140.8, 128.9, 128.9, 128.6, 128.6, 128.5, 128.5, 128.2, 128.2, 128.1, 128.1, 81.7, 67.3, 47.0, 27.0, 24.1, 1.6. Anal. ($C_{21}H_{28}F_3NO_4SSi$): C, 53.00; H, 6.02; N, 2.96; F, 11.66; S, 6.65; Si, 4.18.
4. A full account of the scope of catalyst **1e** has not been reported (Wiener, J. J. M. Ph.D. Thesis, California Institute of Technology, 2004).
5. MacMillan, D. W. C.; Ahrendt, K. A. Chemical synthesis using nonmetallic organic catalyst compositions. PCT Int. Appl., 2001, 81pp. CODEN: PIXXD2 WO 2001053241 A1 20010726 CAN 135:122022 AN 2001:545646.
6. MacMillan, D. W. C. Enantioselective transformations of α,β-unsaturated aldehydes by a wide variety of reactions using imidazolidinone enantiomers as chiral organic catalysts. PCT Int. Appl., 2003, 67pp. CODEN: PIXXD2 WO 2003002491 A2 20030109. Only the 2*S*,5*S* configuration of second generation MacMillan catalyst (as a free base) is currently available from Aldrich.
7. (a) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861–863; (b) Ibrahem, I.; Zhao, G.; Sunden, H.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 4659–4663; (c) Sunden, H.; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2006**, *47*, 99–103; (d) Ibrahem, I.; Cordova, A. *Chem. Commun.* **2006**, *16*, 1760–1762; (e) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029; (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215; (g) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797.
8. Two reports have recently appeared in which they use respectively acetic acid (a) and benzoic acid (b) as additives along with the free base of **1c** (a) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355; (b) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804–6805.
9. *General procedure for [3+2] cycloadditions*: To a vial containing the nitrone (1.0 mmol) in toluene (8.0 mL) was added the catalyst (0.1 equiv) followed by crotonaldehyde (4.0 equiv). The resulting mixture was stirred at rt (or otherwise indicated, Table 2) for 24 h, filtered through a plug of silica gel with the aid of EtOAc and the filtrate concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/hexane as eluant) to render the cycloadducts as oils. A portion of crude cycloadducts was reduced to the corresponding alcohol with $NaBH_4$ (3.0 equiv) in EtOH for ee determination via chiral supercritical fluid chromatography (SFC) using Daicel Chiralcel OD-H or Chiralpak AD-H columns (IPA/hexane, 1.0 mL/min flow rate).
10. Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782–2791.
11. Kezuka, S.; Ohtsuki, N.; Mita, T.; Kogami, Y.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197–2207.