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Asymmetric Michael addition of silyl nitronates to cyclic α,β-unsaturated ketones catalyzed by chiral quaternary ammonium bifluorides: isolation and selective functionalization of enol silyl ethers of optically active γ-nitro ketones

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Abstract—Highly enantioselective Michael addition of silyl nitronates to cyclic α,β-unsaturated ketones has been accomplished by the utilization of *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride **1** as an efficient catalyst, offering a new route to the enol silyl ethers of optically active γ-nitro ketones. The synthetic utility of this transformation has been demonstrated by the diastereoselective derivatizations of the optically active enol silyl ethers to the corresponding α-substituted cyclic ketones having three consecutive stereochemically defined stereocenters.

We recently communicated that *N*-spiro chiral quaternary ammonium bifluoride **1a** catalyzes the Michael addition of silyl nitronates to α,β-unsaturated aldehydes with high diastereo- and enantioselectivities, providing a direct access to both optically active γ-nitro aldehydes and their enol silyl ethers.[1,2] This achievement prompted us to further examine the scope of the efficient catalysis of the chiral ammonium bifluoride, particularly with respect to the Michael acceptors. Herein, we report that the unique Michael addition protocol can be successfully extended to cyclic α,β-unsaturated ketones, which allows the isolation of enol silyl ethers of the corresponding γ-nitro ketones with excellent stereoselectivities (Scheme 1). In addition, synthetic advantage of the present approach over the precedent strategies[3–5] has been clearly demonstrated by the facile one-pot functionalization of the optically active enol silyl ethers.

Initially, we attempted the addition of silyl nitronate **2a** derived from nitropropane to cyclohexenone in the presence of (*R*,*R*)-**1a**[1] (2 mol %) in toluene. The reaction was found to proceed smoothly at −40 °C to give a diastereomeric mixture of the desired enol silyl ether **3a** ($n = 1$) in 90% isolated yield with *anti*/*syn* ratio of 98:2. The enantiomeric excess of the major *anti* isomer was determined to be 87% ee after quantitative conversion to the corresponding γ-nitro ketone **4a** ($n = 1$) by treatment with 1 N HCl in THF (entry 1 in Table 1). Encouraged by this promising result, we thoroughly evaluated the effect of the catalyst structure mainly on the enantioselectivity, which revealed that chiral ammonium bifluoride **1b**[6,7] possessing 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl group exhibited a superior level of asymmetric induction to afford *anti*-**3a** ($n = 1$) almost exclusively in 91% yield (*anti*/*syn* = 99:1) with 96% ee (entry 2).

The results of experiments to probe the scope of this optimized asymmetric Michael addition system are also summarized in Table 1. Cyclopentenone and cycloheptenone were employable as a useful acceptor, though moderate stereoselectivity was observed in the case of the former (entries 3 and 4). As a Michael donor, a series of different silyl nitronates **2b–f** were examined with cyclohexenone as a representative electrophilic partner. High levels of catalytic efficiency and stereocontrol were available in the additions of **2b** and **2c** regardless of the length of carbon chain in the silyl nitronates (entries 5

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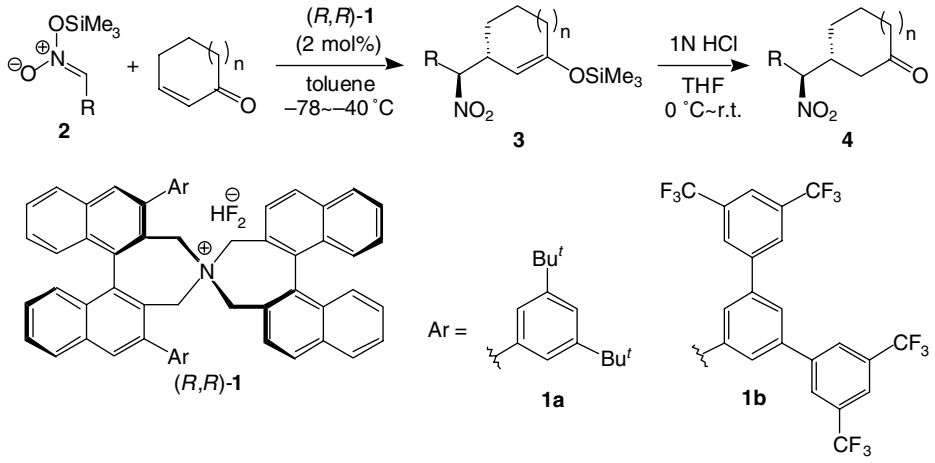
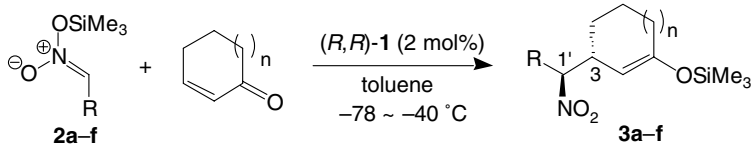


Scheme 1.

Table 1. Asymmetric Michael addition of silyl nitronates **2** to cyclic α,β-unsaturated ketones catalyzed by chiral quaternary ammonium bifluoride **1**: Isolation of optically active enol silyl ethers **3**[a]



Entry	Silyl nitronate (R)	Enone ($n = 0$, 1, and 2)	Catalyst (*R*,*R*)-**1**	Yield[b] (%) (*anti*/*syn*)[c]	ee[d] (%) (config)[e]	Product
1	Et (**2a**)	$n = 1$	**1a**	90 (98:2)	87 (3*R*,1′*S*)	**3a** ($n = 1$)
2			**1b**	91 (99:1)	96 (3*R*,1′*S*)	**3a** ($n = 1$)
3		$n = 0$		81 (71:29)	70	**3a** ($n = 0$)
4		$n = 2$		70 (95:5)	90	**3a** ($n = 2$)
5	Me (**2b**)	$n = 1$		74 (97:3)	96 (3*R*,1′*S*)	**3b**
6	$CH_2CH_2CH{=}CH_2$ (**2c**)			81 (99:1)	94	**3c**
7[f]	*i*-Pr (**2d**)			90 (99:1)	88	**3d**
8[f]	CH_2OCH_3 (**2e**)			75 (92:8)	97	**3e**
9[f]	$CH_2CH_2CO_2CH_3$ (**2f**)			75 (94:6)	92	**3f**

[a] Unless otherwise noted, the reaction was conducted with 1.2 equiv of **2** and cyclic α,β-unsaturated ketone in the presence of 2 mol % of (*R*,*R*)-**1** in toluene (0.1 M substrate concentration) at −78 °C for 0.5 h and at −40 °C for 2 h.

[b] Isolated yield.

[c] Determined by ^{1}H NMR analysis.

[d] Enantiomeric excess of the major *anti*-**3** was determined by GLC analysis using a chiral column [Astec Chiradex Γ-TA (30 m × 0.25 mm)] after conversion to the corresponding ketone **4**. Optical purity of the minor *syn*-**3** was generally lower (13–63% ee).

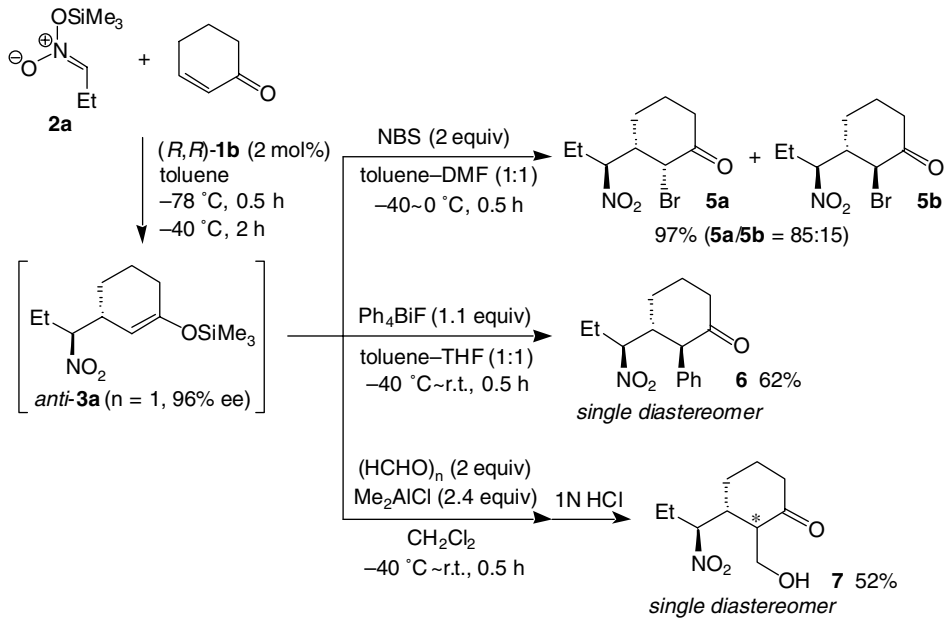
[e] The absolute configuration of **3a** ($n = 1$) was confirmed, after hydrolysis to **4a** ($n = 1$), by comparison of the GLC retention time with the reported value.[5] The absolute configuration of **3b** was assigned, after conversion to the acetal of the corresponding α-brominated ketone with (2*R*,3*R*)-(−)-2,3-butanediol, by X-ray crystallographic analysis.[8]

[f] The reaction was performed at −78 °C for 0.5 h and then at −20 °C for 2 h.

and 6). Although the use of β-branched **2d** caused rate retardation, it was overcome by raising the reaction temperature to −20 °C (entry 7). Silyl nitronates bearing an additional oxygen-containing functional group such as **2e** and **2f** were also tolerated, and the corresponding Michael adducts **3e** and **3f** were obtained with excellent diastereo- and enantioselectivities (entries 8 and 9).

The versatility of the optically active enol silyl ethers **3** in synthetic chemistry serves as a stimulus for exploration of the potential application of this methodology. Accordingly, we established one-pot, stereoselective transformation of **3** to the corresponding α-substituted γ-nitro ketones having three consecutive stereocenters as illustrated in Scheme 2.

The generation of *anti*-**3a** ($n = 1$) by the chiral quaternary ammonium bifluoride **1b**-catalyzed Michael addition of **2a** to cyclohexenone at −40 °C, followed by the addition of *N*,*N*-dimethylformamide as a polar co-solvent and *N*-bromosuccinimide and continuous stirring at 0 °C for 0.5 h resulted in the production of α-brominated product **5** in 97% yield. Here, **5a** with cis-disposition of α-bromo and β-nitroalkyl substituents was formed preferentially to another trans isomer **5b**.[9] The one-pot α-phenylation was also achieved with



Scheme 2.

fluorotetraphenylbismuth (Ph_4BiF)[10] to afford **6** in 62% yield with complete diastereocontrol.[11] Furthermore, dimethylaluminum chloride-mediated reaction with paraformaldehyde appeared feasible, giving rise to α-hydroxymethylcyclohexanone derivative **7** as a single diastereomer (52%).[12]

In summary, we have developed highly diastereo- and enantioselective Michael addition of various prochiral silyl nitronates to cyclic α,β-unsaturated ketones under mild conditions by the use of *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride **1b** as an efficient catalyst; this allows the isolation of enol silyl ethers of optically active γ-nitro ketones. The synthetic utility of this new asymmetric transformation has been highlighted by the diastereoselective functionalizations of the optically active enol silyl ethers to the corresponding α-substituted γ-nitro ketones bearing three consecutive stereochemically defined stereogenic carbon centers.

Typical experimental procedure is as follows (Table 1, entry 2): To a solution of chiral quaternary ammonium bifluoride (*R*,*R*)-**1b** (9.6 mg, 0.006 mmol) in toluene (3 mL) was added cyclohexenone (29.0 μL, 0.3 mmol) at room temperature and the mixture was cooled to −78 °C with methanol-dry ice bath under argon atmosphere. Then, silyl nitronate **2a** (58.1 mg, 0.36 mmol) was introduced. Then, this mixture was stirred for 0.5 h at that temperature followed by additional stirring at −40 °C for 2 h. The resulting mixture was directly purified by column chromatography on silica gel 60 silanized (ether/hexane = 1:2 as eluant) to afford the corresponding enol silyl ether **3a** ($n = 1$) (70.1 mg, 0.272 mmol, 91% yield, *anti*/*syn* = 99:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.60 (1H, br s, CH=COSi), 4.19 (1H, ddd, $J = 3.2$, 7.9, 11.1 Hz, $CHNO_2$), 2.77–2.70 (1H, m, $CHCNO_2$), 2.04–1.92 (3H, m, CH_2COSi, CH_2), 1.87–1.72 (3H, m, CH_2), 1.64–1.54 (1H, m, CH_2), 1.28–1.19 (1H, m, CH_2), 0.95 (3H, t, $J = 7.4$ Hz, CH_3), 0.17 (9H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.03, 102.34, 95.00, 38.48, 29.40, 24.78, 23.86, 21.01, 10.23, 0.00; IR (liquid film) 2941, 2866, 1665, 1549, 1458, 1373, 1254, 1211, 1196, 930, 899, 870, 847, 808, 756 cm^{-1}. To a stirred solution of **3a** ($n = 1$) (70.1 mg, 0.272 mmol) in THF (3 mL) was added 1 N HCl (1 mL) at 0 °C. After vigorous stirring at room temperature for 0.5 h, the whole mixture was extracted with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane = 1:1 as eluant) afforded γ-nitro ketone **4a** ($n = 1$)[5] quantitatively. The enantiomeric excess of **4a** ($n = 1$) was determined to be 96% ee by GLC analysis; conditions: Astec Chiradex Γ-TA (30 m × 0.25 mm) column (120 °C isotherm), retention time; *syn* isomer: 55.8 min (3*S**,1′*S**) and 58.1 min (3*R**,1′*R**), *anti* isomer: 62.3 min (3*S*,1′*R*) and 91.5 min (3*R*,1′*S*).

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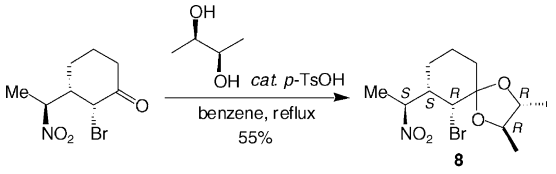
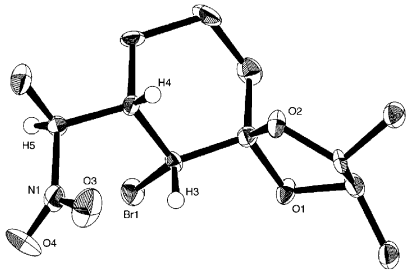
References and notes

1. Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.
2. For an account of our contributions to this area, see: Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526.

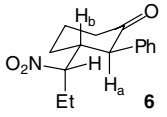
3. (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233; (b) Yamaguchi, M.; Igarashi, Y.; Reddy, R. S.; Shiraishi, T.; Hirama, M. *Tetrahedron* **1997**, *53*, 11223; (c) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975; See also: (d) Schionato, A.; Paganelli, S.; Botteghi, C.; Chelucci, G. *J. Mol. Catal.* **1989**, *50*, 11; (e) Tsogoeva, S. B.; Jagtap, S. B. *Synlett* **2004**, 2624; For a recent excellent review on conjugate addition of nitroalkanes to electron deficient olefins, see: (f) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.
4. For reviews on catalytic asymmetric conjugate addition of stabilized carbanions, see: (a) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.2, (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; p 151.
5. For our recent contribution, see: Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143.
6. Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2054.
7. For the use of this type of ammonium bromide as chiral phase-transfer catalyst, see: (a) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542; (b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685; (c) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790.
8. The acetal **8** was recrystallized from ether/hexane. Crystal structure data for **8** collected at 123 K: $C_{12}H_{20}BrO_4N$, $M_w = 322.20$, monoclinic, space group $P2_1$ (#4), $a = 10.097(14)$ Å, $b = 6.784(11)$ Å, $c = 10.104(14)$ Å, $\beta = 80.31(13)$ °, $V = 682.2(17)$ Å^3, $Z = 2$, $D_{calcd} = 1.568$ g/cm^3, $R_1 = 0.0595$, $R_w = 0.1280$.





ORTEP diagram of **8**

9. The relative configuration was assigned by ^{1}H NMR analysis, which was also supported by the crystal structure of acetal **8**. See Ref. 8.
10. Ooi, T.; Goto, R.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 10494.
11. The coupling constant between H_a and H_b of the α-phenylation product **6** was 13.0 Hz, indicating their 1,2-diaxial alignments.



12. The relative stereochemistry was not determined.