Communication

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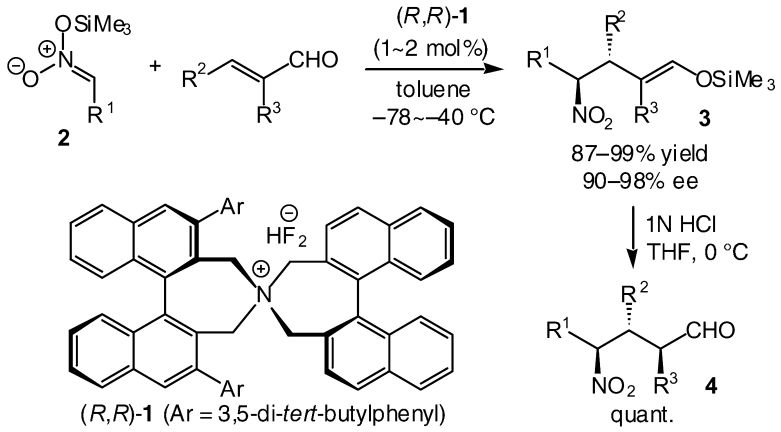

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Highly Enantioselective Michael Addition of Silyl Nitronates to α,β-Unsaturated Aldehydes Catalyzed by Designer Chiral Ammonium Bifluorides: Efficient Access to Optically Active γ-Nitro Aldehydes and Their Enol Silyl Ethers

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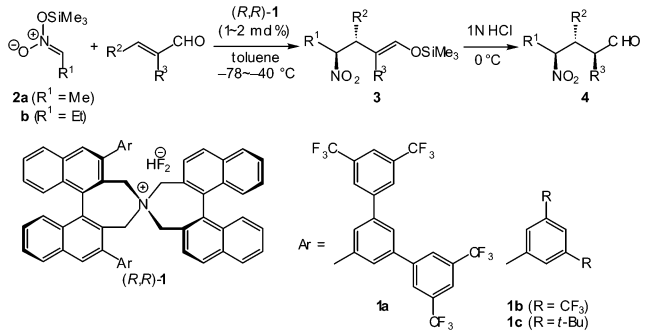
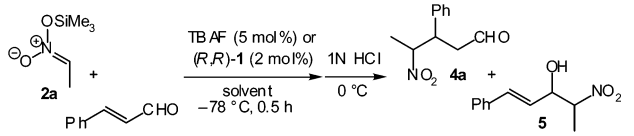
Michael addition to α,β-unsaturated systems is one of the fundamental bond-forming processes in organic chemistry and offers an extremely powerful tool for the synthesis of highly functionalized organic molecules.[1] Therefore, extensive studies have been done on the development of catalytic asymmetric Michael technology for various useful donor−acceptor combinations.[2] Despite the considerable progress in this field, however, asymmetric Michael addition to α,β-unsaturated aldehydes has remained a difficult task mainly because of the ready participation of aldehyde carbonyls in 1,2-addition reactions.[3] MacMillan and co-workers recently demonstrated the effectiveness of an iminium activation strategy for achieving stereoselective 1,4-olefin addition as exemplified by the elegant asymmetric synthesis of γ-butenolide architecture.[4] In conjunction with our recent efforts to develop chiral ammonium bifluoride-catalyzed asymmetric carbon−carbon bond-forming reactions,[5] we here report our own approach to this problem; that is, regio- and stereochemistry of the fluoride-catalyzed addition of silyl nitronates to α,β-unsaturated aldehydes can be precisely controlled by designer chiral quaternary ammonium bifluoride of type **1** via the in situ formation of chiral ammonium nitronates, thereby enabling direct access to both optically active γ-nitro aldehydes and their enol silyl ethers (Scheme 1).[6]

Scheme 1



Reaction of trimethylsilyl nitronate **2a** with *trans*-cinnamaldehyde in the presence of TBAF (5 mol %) in THF at −78 °C for 0.5 h followed by treatment with 1 N HCl at 0 °C gave rise to a mixture of 1,4-adduct **4a** and 1,2-adduct **5** in a ratio of 1.1:1 (76% combined yield, anti/syn of **4a** = 61:39), revealing the intrinsic regiochemical preference of this fluoride-catalyzed reaction (entry 1 in Table 1). Interestingly, however, use of chiral *N*-spiro ammonium bifluoride **1a**, a promising catalyst for asymmetric nitro aldol reactions,[5] as a fluoride ion source (2 mol %) resulted in the predominant formation of **4a** (**4a**/**5** = 17:1) with an anti/syn ratio of 85:15, although the enantiomeric excess of the major anti isomer was only 4% ee (entry 2). On the basis of the initial observation, we thoroughly examined the substituent (Ar) effect of the catalyst on the reactivity and

Table 1. Regio- and Stereochemical Outcome of the Chiral Quaternary Ammonium Bifluoride **1**-Catalyzed Addition of Silyl Nitronate **2a** to *trans*-Cinnamaldehyde[a]



entry	catalyst	solvent	% yield[b]	**4a**/**5**[c]	anti/syn[c,d]	% ee[e] anti	% ee[e] syn
1	TBAF	THF	76	1.1:1	61:39		
2	**1a**		72	17:1	85:15	4	25
3	**1b**		99	19:1	80:20	86	49
4	**1c**		99	24:1	78:22	85	81
5[f]	**1c**	toluene	99	32:1	81:19	97	79
6[f,g]	**1c**		99	32:1	82:18	97	78

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of **2a** in the presence of either 5 mol % of TBAF or 2 mol % of (*R*,*R*)-**1** in the given solvent (0.1 M substrate concentration) at −78 °C for 0.5 h followed by treatment with 1 N HCl at 0 °C. [b] Combined isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Diastereomeric ratio of **4a**. Assignment of the relative configuration was deduced from that of **4c**. [e] Enantiopurity was determined by GLC analysis using a chiral column [Astec Chiradex Γ-TA (30 m × 0.25 mm)]. [f] Stirring at −78 °C for 1 h. [g] With 1 mol % of **1c** at 0.3 M substrate concentration.

selectivity of this reaction, which eventually revealed that the sterically less congested **1b**[5] exerted high catalytic activity, affording the products quantitatively with high regio- and diastereoselectivity (**4a**/**5** = 19:1, anti/syn of **4a** = 80:20), and the enantioselectivity of *anti*-**4a** was dramatically improved to 86% ee (entry 3). Further, **4a** was obtained with even higher regioselectivity and comparable stereoselectivity when the catalyst **1c**[7a] possessing a 3,5-di-*tert*-butylphenyl substituent was employed (entry 4). Moreover, we found that the use of toluene as solvent led to almost exclusive formation of **4a** (**4a**/**5** = 32:1) with similar diastereoselectivity (anti/syn = 81:19), and critical enhancement of the enantioselectivity was attained (97% ee) (entry 5).[8] It should be noted that the catalyst loading can be reduced to 1 mol % without loss of regio- and stereoselectivity by performing the reaction under more concentrated conditions (enrty 6).

The significant synthetic advantage of this chiral ammonium bifluoride-catalyzed Michael addition of silyl nitronates to α,β-unsaturated aldehydes is the isolation of enol silyl ethers of optically active γ-nitro aldehydes as an attractive Mukaiyama donor, not readily accessible by ordinary asymmetric methodologies. For instance, after the reaction of **2a** with *trans*-cinnamaldehyde under the optimized conditions, the resulting mixture can be directly subjected to purification by silica gel column chromatography to give optically active enol silyl ether **3a** in 90% yield (entry 1 in Table 2).[9] Here, we confirmed that the subsequent treatment of **3a**

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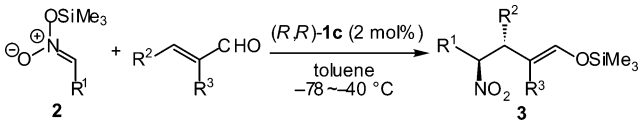
Table 2. Asymmetric Michael Addition of Silyl Nitronates to α,β-Unsaturated Aldehydes Catalyzed by Chiral Quaternary Ammonium Bifluoride **1c**: Isolation of Optically Active Enol Silyl Ether **3**[a]



entry	**2** (R^1)	aldehyde (R^2, R^3)	condition (°C, h)	% yield[b] (anti/syn)[c]	% ee[d]	prod.
1	Me (**2a**)	Ph, H	−78, 1	90 (83:17)	97	**3a**
2		*n*-Pr, H	−78, 1	92 (81:19)	93	**3b**
3		Ph, Me	−78, 1; −40, 1	90 (95:5)	95	**3c**
4		$-(CH_2)_4-$	−78, 1; −40, 1	99 (97:3)	90	**3d**
5	Et (**2b**)	Ph, H	−78, 1	87 (90:10)	98	**3e**
6		*n*-Pr, H	−78, 1	99 (76:24)	97	**3f**

[a] Unless otherwise noted, the reaction was conducted with 1.2 equiv of **2** and α,β-unsaturated aldehyde in the presence of 2 mol % of (*R*,*R*)-**1c** in toluene (0.1 M substrate concentration) under the given reaction conditions. The olefin geometry of **3** was confirmed by a NOE experiment. [b] Isolated yield.[9] [c] Determined by ^{1}H NMR analysis, and stereochemical assignment was deduced from that of **3c**. [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) or GL Science CP-CHIRASIL-DEX CB (25 m × 0.25 mm)] either directly or after conversion to the corresponding aldehyde **4**. Optical purity of the minor *syn*-**3** was generally lower (5−89% ee).

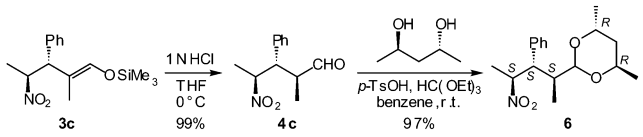
with 1 N HCl in THF at 0 °C afforded γ-nitro aldehyde **4a** quantitatively with a degree of relative and absolute stereoinduction similar to that of the case of one-pot derivatization.

Other selected examples are summarized in Table 2. High levels of catalytic efficiency and stereoselectivity were also available in the reaction of **2a** with the aliphatic Michael acceptor 2-hexenal, implying the general applicability of the present method (entry 2). The introduction of an alkyl substituent at the α-carbon of enals can be well accommodated, as is demonstrated in the case of an acyclic as well as a cyclic system where excellent diastereo- and enantiofacial differentiation have been achieved (entries 3 and 4). A similar tendency was observed in the Michael addition of silyl nitronate **2b** to representative aromatic and aliphatic α,β-unsaturated aldehydes (entries 5 and 6).

An additional distinct feature of our approach was highlighted by the highly diastereoselective protonation of optically active enol silyl ether having an α-substituent, which established three consecutive acyclic stereocenters. Quite surprisingly, simple treatment of enol silyl ether **3c** with 1 N HCl in THF at 0 °C furnished **4c** exclusively, whose absolute configuration was unequivocally determined by X-ray crystallographic analysis after conversion to the corresponding acetal **6** with (2*R*,4*R*)-pentanediol as shown in Scheme 2.[10]

In conclusion, the unique ability of designer *N*-spiro C_2-symmetric chiral quaternary ammonium bifluoride **1c** to efficiently catalyze the addition of silyl nitronates to α,β-unsaturated aldehydes with excellent regio- and stereoselectivity has been illuminated. The present method provides direct access to both optically active γ-nitro aldehydes, a very useful precursor to various complex organic molecules including aminocarbonyls, and their enol silyl ethers, a Mukaiyama donor of potential synthetic utility for further selective transformations. Intensive investigations on the application of this new asymmetric Michael strategy are currently being conducted in our laboratory.

Scheme 2



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Supporting Information Available: Representative experimental procedures and spectroscopic characterization of all new compounds including stereochemical assignment (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Unfortunately, the catalytic and chiral efficiency of **1b** was significantly decreased in toluene mainly due to its solubility problem.
(9) For the purification, silanized silica gel purchased from Merck was used to minimize the protonation.
(10) For details, see the Supporting Information.

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