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Asymmetric Catalysis

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Highly Diastereo- and Enantioselective Formal Conjugate Addition of Nitroalkanes to Nitroalkenes by Chiral Ammonium Bifluoride Catalysis**

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The conjugate addition of reactive nucleophiles to electrondeficient alkenes (the Michael addition reaction) is an important and reliable tool for the construction of highly functionalized carbon skeletons. Among the various candidates for this bond-forming process, nitro compounds are particularly attractive because of the strong electron-withdrawing property of the nitro group and their versatility as a masked functionality.^[11] Indeed, it is well documented that nitroalkenes serve as excellent Michael acceptors^[2] and the

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anions of nitroalkanes (nitronates) as prominent Michael donors.^[3] Surprisingly, however, despite its potential use for the synthesis of optically active 1,3-diamines, carbon–carbon coupling between nitroalkanes and nitroalkenes is extremely rare,^[4] and catalytic enantioselective systems have so far been limited to the recent contribution reported by Du and coworkers^[5]. This is partly because of the inherent difficulty of controlling the addition of nitronate **3** to nitroalkene **4**. The initial product formed is the nitronate **5**, which is sufficiently reactive to also undergo conjugate addition to **4**, thus resulting in a mixture of oligomerization products [Eq. 1].



Our strategy toward overcoming this methodological deficiency involves the use of chiral ammonium bifluoride catalysis in combination with silyl nitronates (6, Scheme 1).^[6] The chiral ammonium nitronate 8, generated in situ from 6, and chiral ammonium bifluoride of type $1^{[7]}$ or 2 would be responsible for controlling the relative and absolute stereo-chemistry in the addition to the nitroalkene 4, to afford the corresponding chiral nitronate 9 of the stereochemically defined conjugate adduct. If the reaction of 9 with residual 6 is



Scheme 1. Selective conjugate addition of silyl nitronates to nitroalkenes under chiral ammonium bifluoride catalysis.



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faster than its further addition to **4**, the requisite chiral nucleophile **8** would be regenerated along with derivatization of the desired product **7** as the silyl nitronate **10**. This process would thereby allow the asymmetric formal conjugate addition of nitroalkanes to nitroalkenes with ideal stoichiometry. Herein, we describe the realization of this hypothesis by using the N-spiro C_2 -symmetric chiral quaternary ammonium bifluoride **2b**.

We began our studies by examining the reaction of nitropropane-derived silyl nitronate 6a with β -nitrostyrene (4a) using the chiral quaternary ammonium bifluoride 1a.^[7b,c] When 4a was treated with 6a (1.2 equiv) in the presence of 1a (2 mol%) in toluene (0.1M substrate concentration) at -78°C, an almost instantaneous consumption of 4a was observed along with the formation of totally insoluble white precipitate, and the one-to-one adduct 7a was isolated in only 7% yield. This finding implied the predominant intervention of the rapid oligomerization process under the reaction conditions. However, we were encouraged by the fact that 7a thus obtained was diastereomerically homogeneous and it was determined to have 58% ee (entry 1, Table 1). We next screened reaction variables and found initially that switching the solvent to THF under otherwise similar conditions significantly augmented the desired pathway to furnish 7a in 73% yield, although the enantioselectivity decreased to 29% ee (entry 2, Table 1). On the basis of this result, we evaluated the effect of the catalyst structure mainly on the enantioselectivity. Although the electron-withdrawing 3,5bis(trifluoromethyl)phenyl-substituted 1b^[7a,b] exhibited comparable chiral efficiency to that of 1a, modification of the 3,3'aromatic substituent to the meta-terphenyl-type structure $1c^{[7]}$ led to a dramatic improvement in selectivity (entries 3) and 4, Table 1). Furthermore, we assembled the chiral ammonium bifluoride 2a, which consisted of a chiral octahydrobinaphthyl subunit, with the expectation that its steric and

electronic effects would help control stereoselectivity. Fortunately, the conjugate addition of **6a** to **4a** proceeded smoothly under the influence of **2a** in a highly diastereoselective manner, affording syn-7a in 78% yield with 89% ee (entry 5, Table 1). Moreover, introduction of a trifluoromethyl group in the 6,6' position of the binaphthyl core of 2b delivered even higher enantioselectivity (91% ee, entry 6, Table 1).^[8] Here, the use of two equivalents of silyl nitronate 6a allowed near quantitative production of 7a, and the slight erosion in enantiomeric excess was recovered by performing the reaction at a lower substrate concentration (entries 7 and 8, Table 1). It should be noted that the catalyst loading can be reduced to 0.5 mol% without substantial loss of reactivity and stereoselectivity (entries 9 and 10, Table 1).

Having established the optimized conditions,^[9] the scope of the reaction was investigated using silyl nitronate 6a and a variety of nitroalkenes (Table 2). With **Table 1:** Screening of the reaction variables in the conjugate addition reaction of silyl nitronate **6a** to β -nitrostyrene **(4a)**, catalyzed by chiral quaternary ammonium bifluoride.^[a]

OSil N ⁺ Et 6a	Me ₃ 5 ⁺ P 1	h 4a	2 (R,R)- 5 -78	1 or (<i>R</i> , <i>R</i>)- solvent 3 °C, 1 h	2 H ₃ O ⁺	Et Ph	NO ₂ NO ₂ 7a
Entry	6a (equiv)	Catalyst	mol%	Solvent	Conc. [M]	Yield [%] ^[b]	[%] ee ^[c]
1	1.2	(R,R)- 1 a	2	toluene	0.1	7	58
2		(R,R)- 1 a		THF		73	29
3		(R,R)- 1b				67	32
4		(R,R)- 1c				80	80
5		(R,R)- 2 a				78	89
6		(R,R)- 2b				85	91
7	2.0	(R,R)- 2b				97	85
8		(R,R)- 2b			0.04	97	91
9		(R,R)- 2b	1			99	90
10		(R,R)- 2b	0.5			86	90

[a] The reaction was carried out at -78 °C for 1 h using (*R*,*R*)-1 or (*R*,*R*)-2 as catalyst. [b] Yield of isolated product. The ratio *syn/anti* was determined by ¹H NMR analysis to be >95:5, which means that the minor isomer could not be detected by NMR analysis (the authentic sample of *anti* isomer was prepared by a literature procedure^[4a]). [c] The enantiopurity of **7a** was determined by HPLC analysis on a chiral stationary phase using hexane-2-propanol as the solvent. The relative and absolute configurations were assigned by ¹H NMR analysis after derivatization to the corresponding cyclic thiourea and diamide compounds. For further details, see the Supporting Information.

aromatic nitroalkenes, the reaction efficiency and diastereoselectivity were relatively insensitive to the electronic properties of the aromatic ring, although the presence of electronwithdrawing substituents seemed to be associated with slightly lower enantioselectivity (entries 1–4, Table 2). This protocol proved to be compatible with heteroaromatic nitro-

Table 2: Stereoselective conjugate addition of silyl nitronates **6** to nitroalkenes **4** catalyzed by chiral quaternary ammonium bifluoride (R,R)-**2b**.^[a]

	OSiMe	+ R ² No	D ₂ (<i>R</i> , <i>R</i>)- 2b (0.5-2) THF, -78 °C,	$\frac{\text{mol}\%)}{1 \text{ h}} \frac{\text{H}_{3}\text{O}^{\dagger}}{\text{H}_{3}}$		D ₂ NO ₂	
	R ¹ 6	4			7		
Entry	R ¹ (6)	R ² (4)	(R,R)- 2b [mol%]	Yield [%] ^[b]	syn/anti ^[c]	ee [%] ^[d]	Prod.
1	Et (6 a)	p-MeO-C ₆ H₄	1	99	> 95:5	91	7 b
2		o-MeO-C ₆ H ₄	0.5	99	>95:5	87	7 c
3		o-Cl-C ₆ H ₄	0.5	98	> 95:5	80	7 d
4			0.5	95	>95:5	89	7 e
5			2	92	> 95:5	93	7 f
6		S	2	85	> 95:5	91	7 g
7		<i>c</i> -Hex	1	99	> 95:5	92	7 h
8		$CH_3(CH_2)_5$	1	93	> 95:5	76	7 i
9	Pr (6b)	Ph	1	99	> 95:5	91	7j
10	MeOCH ₂ (6c)	Ph	1	99	82:18	83	7 k

[a] The reaction was carried out using 2 equiv of silyl nitronate **6** in the presence of (R,R)-**2b** in THF (0.04 M substrate concentration) at -78 °C for 1 h. [b] Yield of isolated product. [c] Determined by ¹H NMR analysis. [d] The enantiopurity of major product syn-**7** was determined by HPLC analysis on a chiral stationary phase using hexane-2-propanol or ethanol as the solvent. *c*-Hex = cyclohexyl.

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alkenes and the corresponding 1,3-dinitro compounds were obtained in high yield with excellent diastereo- and enantioselectivities by employing 2 mol% of **2b** (entries 5 and 6, Table 2). Aliphatic nitroalkenes also appeared to be good acceptors, further expanding the generality of the substrates (entries 7 and 8, Table 2). The present method was applicable to other silyl nitronates derived from simple nitroalkanes, where eminent catalytic activity and a high level of stereo-selectivity were attained (entries 9 and 10, Table 2).

The resulting 1,3-dinitro compounds with two consecutive stereochemically defined stereocenters can be readily converted into the corresponding 1,3-diamines, which are versatile chiral building blocks from synthetic as well as pharmaceutical viewpoints.^[10] For example, exposure of a mixture of **7a** in THF to a hydrogen atmosphere in the presence of a catalytic amount of Raney Nickel at 45 °C for 36 h resulted in the formation of **11** in 75 % yield with complete preservation of the stereochemical integrity (Scheme 2).^[11]



Scheme 2. Derivatization of 1,3-dinitroalkane syn-7a into the corresponding 1,3-diamine syn-11.

In conclusion, we have achieved an efficient, highly diastereo- and enantioselective formal conjugate addition of nitroalkanes to nitroalkenes by the catalysis with the novel chiral quaternary ammonium bifluoride **2b** in combination with silyl nitronates. This strategy greatly expands the use of conjugate addition chemistry involving organonitro compounds and provides a reliable route to optically active 1,3-dinitro compounds, which are synthetically useful intermediates for a wide range of valuable 1,3-difunctionalized organic molecules.

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