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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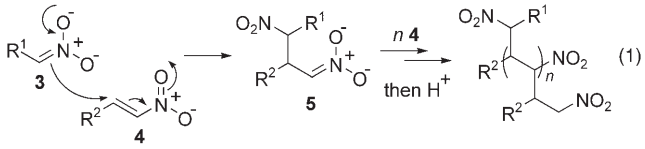
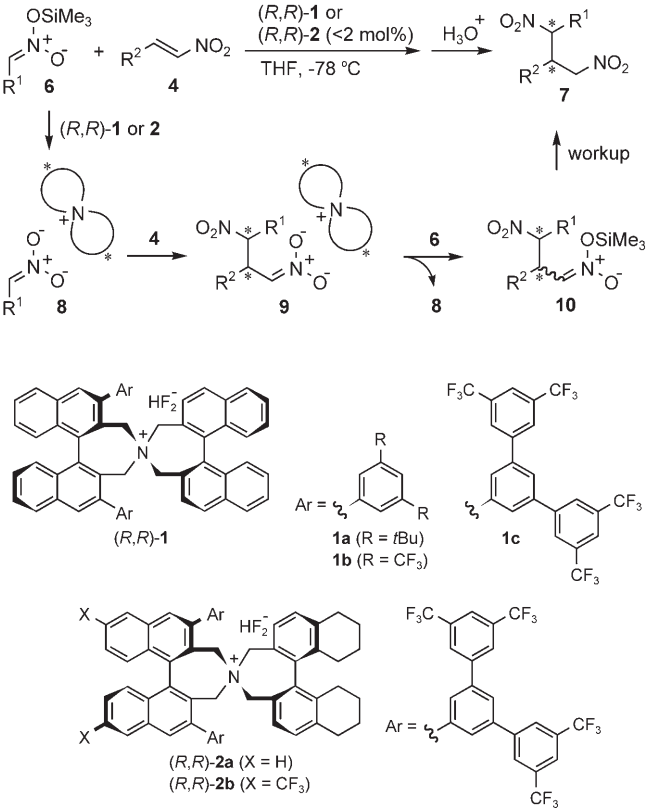
The conjugate addition of reactive nucleophiles to electron-deficient alkenes (the Michael addition reaction) is an important and reliable tool for the construction of highly functionalized carbon skeletons. Among the various candidates for this bond-forming process, nitro compounds are particularly attractive because of the strong electron-withdrawing property of the nitro group and their versatility as a masked functionality.[1] Indeed, it is well documented that nitroalkenes serve as excellent Michael acceptors[2] and the 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 co-workers[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 stereochemistry 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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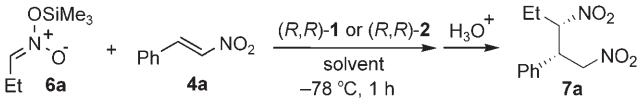
faster than its further addition to **4**, the requisite chiral nucleophile **8** would be regenerated along with derivatization of the desired product **7** as the silyl nitronate **10**. This process would thereby allow the asymmetric formal conjugate addition of nitroalkanes to nitroalkenes with ideal 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 3,5-bis(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 aromatic nitroalkenes, the reaction efficiency and diastereoselectivity were relatively insensitive to the electronic properties of the aromatic ring, although the presence of electron-withdrawing substituents seemed to be associated with slightly lower enantioselectivity (entries 1–4, Table 2). This protocol proved to be compatible with heteroaromatic nitro-

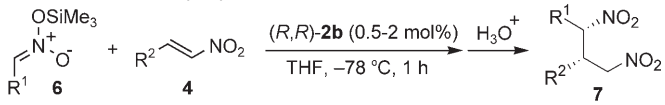
Table 1: Screening of the reaction variables in the conjugate addition reaction of silyl nitronate **6a** to β-nitrostyrene (**4a**), catalyzed by chiral quaternary ammonium bifluoride.[a]

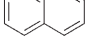


Entry	**6a** (equiv)	Catalyst	mol%	Solvent	Conc. [M]	Yield [%][b]	[%] *ee*[c]
1	1.2	(*R*,*R*)-**1a**	2	toluene	0.1	7	58
2		(*R*,*R*)-**1a**		THF		73	29
3		(*R*,*R*)-**1b**				67	32
4		(*R*,*R*)-**1c**				80	80
5		(*R*,*R*)-**2a**				78	89
6		(*R*,*R*)-**2b**				85	91
7	2.0	(*R*,*R*)-**2b**				97	85
8		(*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 ^{1}H 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 ^{1}H NMR analysis after derivatization to the corresponding cyclic thiourea and diamide compounds. For further details, see the Supporting Information.

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

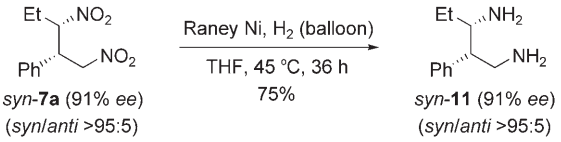


Entry	R^1 (**6**)	R^2 (**4**)	(*R*,*R*)-**2b** [mol%]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%] [d]	Prod.
1	Et (**6a**)	*p*-MeO-C_6H_4	1	99	>95:5	91	**7b**
2		*o*-MeO-C_6H_4	0.5	99	>95:5	87	**7c**
3		*o*-Cl-C_6H_4	0.5	98	>95:5	80	**7d**
4			0.5	95	>95:5	89	**7e**
5			2	92	>95:5	93	**7f**
6			2	85	>95:5	91	**7g**
7		*c*-Hex	1	99	>95:5	92	**7h**
8		$CH_3(CH_2)_5$	1	93	>95:5	76	**7i**
9	Pr (**6b**)	Ph	1	99	>95:5	91	**7j**
10	$MeOCH_2$ (**6c**)	Ph	1	99	82:18	83	**7k**

[a] The reaction was carried out using 2 equiv of silyl nitronate **6** in the presence of (*R*,*R*)-**2b** in THF (0.04M substrate concentration) at −78°C for 1 h. [b] Yield of isolated product. [c] Determined by ^{1}H 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.

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 stereoselectivity 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]



syn-**7a** (91% *ee*) (*syn*/*anti* >95:5)

syn-**11** (91% *ee*) (*syn*/*anti* >95:5)

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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[1] a) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, **2001**, chaps. 4 and 6; for a recent example of facile transformations of optically active organonitro compounds, see: b) C. Czekelius, E. M. Carreira, *Angew. Chem.* **2005**, *117*, 618; *Angew. Chem. Int. Ed.* **2005**, *44*, 612.

[2] a) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877; for recent examples, see: b) D. J. Dixon, R. D. Richardson, *Synlett* **2006**, 81; c) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; d) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454; e) P. J. Nichols, J. A. DeMattei, B. R. Barnett, N. A. LeFur, T.-H. Chuang, A. D. Piscopio, K. Koch, *Org. Lett.* **2006**, *8*, 1495; f) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170, and references therein.

[3] a) M. Yamaguchi in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 31.2; b) M. Yamaguchi in *Comprehensive Asymmetric Catalysis Supplement 1* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**, p. 151; c) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* **2005**, *105*, 933.

[4] For a few examples of non-stereoselective reactions, see: a) M. D. Alcántara, F. C. Escribano, A. Gómez-Sánchez, M. J. Diánez, M. D. Estrada, A. López-Castro, S. Pérez-Garrido, *Synthesis* **1996**, 64; b) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Synthesis* **2004**, 1938.

[5] S.-F. Lu, D.-M. Du, J. Xu, S.-W. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 7418.

[6] For an account of chiral ammonium fluoride catalysis, see: T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526.

[7] a) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054; b) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 9022; c) T. Ooi, K. Doda, S. Takada, K. Maruoka, *Tetrahedron Lett.* **2006**, *47*, 145.

[8] When the reaction was quenched with an excess amount of D_2O, approximately 60% of deuterium incorporation was observed at the C1 methylene center of *syn*-**7a**, thereby suggesting the intervention of a silyl nitronate intermediate of type **10**. We assume that the low deuterium incorporation could be ascribed to the high susceptibility of the silyl nitronate, generated in situ, to protonation from a small amount of water or methanol.

[9] Although 1.2 equiv of silyl nitronate **6** seemed to be sufficient, we decided to use 2 equiv of **6** at 0.04 M substrate concentration for further investigations to constantly attain excellent yields.

[10] For selected examples, see: a) C. F. Bigge, J.-P. Wu, J. T. Drummond, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 207; b) G. H. P. Roos, A. R. Donovan, *Tetrahedron: Asymmetry* **1999**, *10*, 991; c) S. E. Denmark, J.-H. Kim, *Can. J. Chem.* **2000**, *78*, 673; d) M. M. Kabat, *Tetrahedron Lett.* **2001**, *42*, 7521; e) F. Cohen, L. E. Overman, *J. Am. Chem. Soc.* **2001**, *123*, 10782.

[11] The *ee* value of *syn*-**11** was confirmed by HPLC analysis after derivatization to the corresponding cyclic thiourea. See the Supporting Information.

