Enantioselective Aza-Michael Addition to Conjugated Nitroenynes Catalyzed by Chiral Arylaminophosphonium Barfates

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Abstract: Enantioselective aza-Michael addition to conjugated nitroenynes has been developed. *P*-Spiro heterochiral arylaminophosphonium barfate **1b**·BArF effectively catalyzes the reaction, and the corresponding conjugate adducts, β-amino homopropargylic nitro compounds, are obtained in good chemical yields with high enantioselectivities.

Key words: phosphonium salt, Brønsted acid, aza-Michael addition, propargyl amine, asymmetric synthesis

The catalytic asymmetric conjugate addition to extended Michael acceptors occupies a unique place in the realm of the stereoselective conjugate addition chemistry.[1,2] With rigorous control of both regio- and stereoselectivities, this Michael technology serves as an expedient means for the facile synthesis of functionalized chiral building blocks, which are not readily accessible by other asymmetric methodologies. As one of the suitable acceptors, nitroenynes possess their own attractive features because the conjugate addition to this class of substrate generally proceeds in a 1,4-manner and hence the corresponding adducts, homopropargylic nitro compounds, could enjoy the rich chemistry of functional-group transformations associated with the nitro[3] and alkynyl[4] moieties.[5–7] In 2006, the first example of this type of bond-forming reaction was reported by Trost et al. as a part of their study on the conjugate addition of α-hydroxy ketones to nitroolefins catalyzed by a chiral heterodinuclear metal complex.[5] More recently, Alexakis et al. developed highly enantioselective conjugate additions of carbonyl compounds and organometallic reagents to nitroenynes in the context of catalytic regio- and stereocontrols with extended nitro-Michael acceptors.[6] However, these pioneering research efforts have focused on the use of carbon nucleophiles, and thus heteroatom-centered nucleophiles have never been employed in combination with nitroenynes despite the significant synthetic potential of the corresponding conjugate adducts, namely, chiral β-hetero-substituted homopropargylic nitro compounds. In this situation, we have been interested for some time in developing asymmetric conjugate addition of aniline derivatives to extended nitro-Michael acceptors using chiral ionic Brønsted acid[8,9] of type **1**·BArF[10] as a catalyst on the basis of its effectiveness in aza-Michael reaction of simple conjugated nitroolefins.[11–13] Here, we present the results of this study by describing the highly enantioselective conjugate addition of 2,4-dimethoxyaniline to various nitroenynes efficiently catalyzed by *P*-spiro chiral arylaminophosphonium barfate **1b**·BArF.

We initiated our investigations by evaluating the ability of the chiral arylaminophosphonium barfates **1**·BArF and **2**·BArF as a Brønsted acid catalyst in the Michael donor–acceptor combination of 2,4-dimethoxyaniline and nitroenyne **3a** having a terminal phenyl substituent. The focus was then directed toward the relationship between the catalyst structure and the profile of reactivity and selectivity (Table 1). When **3a** was treated with 2,4-dimethoxyaniline in toluene at 0 °C under the influence of homochiral **2a**·BArF with a phenyl group at 3,3′-positions of one binaphthyl subunit (Ar), aza-Michael addition took place smoothly, and the desired β-amino homopropargylic nitro compound **4a** was isolated in 89% yield (Table 1, entry 1). Because the enantiomeric excess of **4a** thus obtained was revealed to be only 30%, we applied arylaminophosphonium barfate **2b**·BArF bearing a 3,4,5-trifluorophenyl moiety to this reaction under similar conditions (Table 1, entry 2). Although notable rate enhancement was attained, the facial discrimination of prochiral **3a** remained insufficient, indicating that the structural modification on the aromatic substituents may not have a major impact on the enantioselectivity. This selectivity issue was fortunately solved by switching the axial chirality of unsubstituted binaphthyl unit (right side of the drawing structures in Figure 1), as we previously observed.[10] In fact, heterochiral arylaminophosphonium barfate **1**·BArF catalyzed the present aza-Michael addition with high efficiency and good enantioselectivity (78% ee) irrespective of the electronic property of the pendant aromatic groups (Table 1, entries 3 and 4). Finally, we found that performing the reaction with **1b**·BArF at a lower temperature resulted in a critical improvement in enantioselectivity (92% ee, Table 1, entry 5).

These optimized reaction conditions were used for further experiments to probe the substrate scope.[14] As shown in Table 2, a series of conjugated nitroenynes **3** with substituents of different electronic and steric properties on the alkyne terminus were employable, demonstrating the general applicability of this asymmetric aza-Michael protocol. In detail, slight electronic effect on enantioselectivity was observed in the reactions with **3b** and **3c** having *p*-methoxy- and *p*-chlorophenyl moieties, respectively

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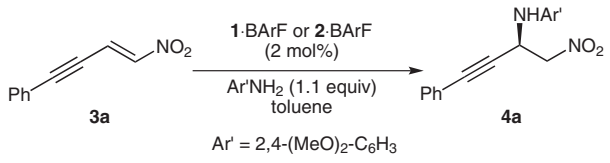
Table 1 Optimization of the Structure of Chiral Arylaminophosphonium Barfate **1**·BArF and **2**·BArF for Aza-Michael Reaction of Nitroenyne **3a**[a]



Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	0	15	89	30
2	**2b**	0	6	93	32
3	**1a**	0	15	97	78
4	**1b**	0	5.5	89	78
5	**1b**	–20	14	92	92

[a] All reaction was performed on a 0.1 mmol scale in 1.0 mL of toluene.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC analysis. Absolute stereochemistry was determined as described in Scheme 1.

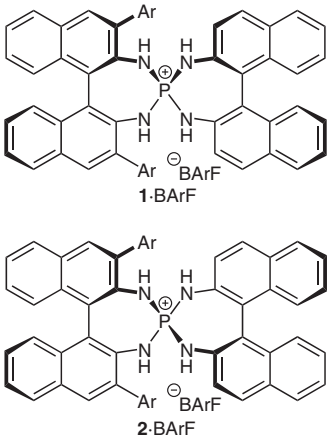
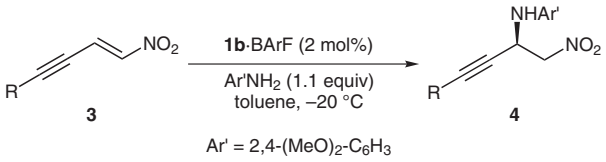


Figure 1 *P*-Spiro chiral arylaminophosphonium barfates **1**·BArF and **2**·BArF; BArF = $[3,5\text{-}(CF_3)_2C_6H_3]_4B$

(Table 2, entry 1 vs. 2). The substrates with liner and branched saturated alkyl chains (**3d–f**) were effectively converted into the corresponding β-amino homopropargylic nitroalkanes **4d–f** with uniformly high levels of enantiomeric excess (Table 2, entries 3–5). The present system was compatible with primary alkyl chloride, as the reaction with **3g** led to the quantitative formation of **4g** with 95% ee (Table 2, entry 6). Further, incorporation of an ethereal functionality such as benzyl and *tert*-butyldimethylsilyl ethers (**3h**,**i**) was also tolerated without any detrimental effects on the reactivity and selectivity (Table 2, entries 7 and 8).

Absolute configuration of the conjugate adduct **4a** was determined after the derivatization to known *N*-monoacetyl diamine **6a**,[15] which was performed via the straightforward processes illustrated in Scheme 1. The catalytic

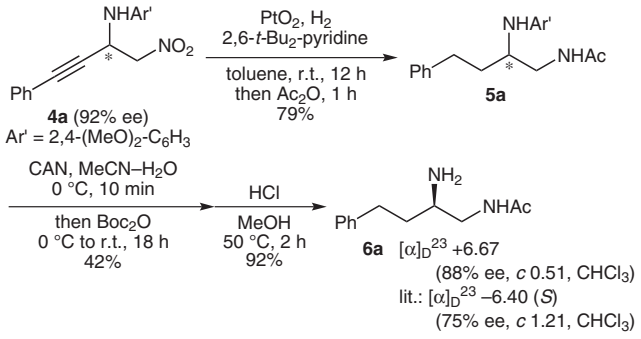
Table 2 Substrate Scope[a]



Entry	R	3	Time (h)	Yield (%)[b]	ee (%)[c]	Product 4
1	4-$MeOC_6H_4$	**3b**	15	94	94	**4b**
2	4-ClC_6H_4	**3c**	14	91	86	**4c**
3	*n*-Hex	**3d**	14	93	92	**4d**
4	*i*-Bu	**3e**	14	90	96	**4e**
5	*c*-Hex	**3f**	13	91	92	**4f**
6	$Cl(CH_2)_3$	**3g**	12	99	95	**4g**
7	$BnO(CH_2)_2$	**3h**	13	99	90	**4h**
8	*t*-$BuMe_2SiO(CH_2)_2$	**3i**	10	99	90	**4i**

[a] All reaction was performed on a 0.1 mmol scale in 1.0 mL of toluene.
[b] Isolated yield.
[c] Determined by chiral stationary phase HPLC analysis. Absolute configuration of **4** was assigned on the analogy of **4a**.

hydrogenation of **4a** with Adam's catalyst followed by acetylation of the primary amino functionality gave N-protected, saturated diamine **5a** in 79% yield. Oxidative removal of the dimethoxyphenyl moiety using ceric ammonium nitrate (CAN) and a subsequent protection–deprotection sequence furnished essentially pure **6a** without significant loss of its enantiomeric excess. The absolute configuration of **6a** was assigned to be *R* by comparison of its observed optical rotation with that reported in literature.[15]



Scheme 1 Procedure for the determination of the absolute configuration of **4a**

In conclusion, we have achieved highly enantioselective aza-Michael addition to conjugated nitroenynes for the first time using *P*-spiro chiral arylaminophosphonium barfate **1b**·BArF as a catalyst. The chemistry described here expands the synthetic utility of weakly acidic aryl-

aminophosphonium cation and also underscores the potential of the asymmetric catalysis of chiral ionic Brønsted acids.

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(14) **Representative Procedure for 1b·BArF Catalyzed Aza-Michael Addition to Nitroenyne 3**
To a solution of nitroenyne **3a** (17.3 mg, 0.10 mmol) and chiral arylaminophosphonium barfate **1b**·BArF (3.44 mg, 2.0 μmol) in toluene (0.80 mL) was slowly added a solution of 2,4-dimethoxyaniline (16.8 mg, 0.11 mmol) in toluene (0.20 mL) at –20 °C. After being stirred for 14 h, the reaction mixture was directly subjected to purification by column chromatography on silica gel (hexane–EtOAc = 20:1 to 3:1 as eluent) to afford β-amino nitroalkyne **4a** (30.0 mg, 92% yield). The ee of **4a** was determined by chiral stationary phase HPLC.
Analytical Data for Compound 4a
HPLC (DICEL CHIRALPAK IA, hexane–2-PrOH = 10:1, flow rate = 1.0 mL/min, λ = 210 nm): t_R = 17.3 min (*R*), 18.9 min (*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (2 H, dd, *J* = 7.8, 1.6 Hz), 7.35–7.24 (3 H, m), 6.81 (1 H, d, *J* = 8.6 Hz), 6.48 (1 H, d, *J* = 2.4 Hz), 6.44 (1 H, dd, *J* = 8.6, 2.4 Hz), 5.05 (1 H, t, *J* = 6.6 Hz), 4.76 (1 H, dd, *J* = 12.4, 6.6 Hz), 4.69 (1 H, dd, *J* = 12.4, 6.6 Hz), 4.38 (1 H, br), 3.82 (3 H, s), 3.77 (3 H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.1, 149.6, 132.0, 128.9, 128.8, 128.4, 121.9, 114.2, 104.0, 99.5, 85.8, 84.5, 78.1, 55.8, 46.3, one carbon was not found, probably due to overlapping. IR (neat): 3363, 2939, 2834, 1555, 1514, 1463, 1378, 1291, 1258, 1206, 1157, 1033, 917, 835, 758 cm^{-1}. HRMS–FAB: *m/z* calcd for $C_{18}H_{19}N_2O_4^+$ [M + H]$^+$: 327.1339; found: 327.1329.

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