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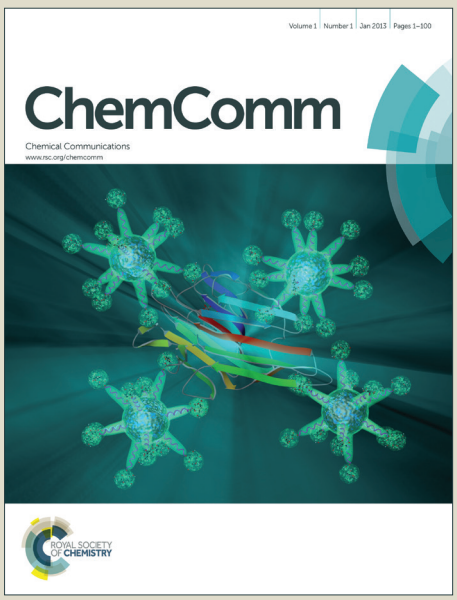

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Vinylogy in Nitronates: Utilization of α-Aryl Conjugated Nitroolefins as a Nucleophile for Highly Stereoselective Aza-Henry Reaction†

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Vinylogous reactivity of α,β-disubstituted nitroolefins was uncovered through the facile generation of the corresponding α-substituted vinylogous nitronates and their use for the development of a highly diastereo- and enantioselective aza-Henry reaction with N-Boc aldimines under the catalysis of chiral ammonium betaines. The novel vinylogous nitronates undergo the stereoselective bond formation at the sterically encumbered α-position exclusively, allowing the construction of contiguous tertiary-quaternary stereogenic carbon centers.

The principle of vinylogy was originally defined by Reynold C. Fuson in 1935 for both electrophiles and nucleophiles.[1] Interposing double bond(s) between an activating group and a parent reactive site of a substrate produces a conjugate π-system, through which the inherent electronic effects propagate, often shifting the reactive site. The extended conjugate system brings about multiple selectivity issues depending on the mode of transformations, but it also imparts additional yet useful functional handle to the products. Accordingly, a wide variety of studies into exploiting the characteristics of this principle in synthetic reaction development has recently been performed, leading to the establishment of highly selective catalytic methodologies.[2,3] However, most of the existing methods employ substrates bearing carbonyl-based activating groups and the potential utility of vinylogous reactivity associated with other functionalities such as nitro and sulfonyl groups is largely unexplored.[4] In particular, while simple nitronates of nitroalkanes have found extensive use as nucleophiles, especially in asymmetric catalysis, vinylogous nitronates remain underutilized in stereoselective transformations primarily because of the difficulty in selectively deprotonating the γ-carbon of nitroolefins using standard bases.[5] In 2012, we disclosed a highly stereoselective aza-Henry reaction of vinylogous nitronates generated from β,β-disubstituted nitroolefins with chiral ammonium betaine of type **1** as a catalyst, wherein the β-substituted vinylogous nitronate predominantly reacted at the sterically more *accessible* α-position with *N*-Boc aldimines.[6–11] It was assumed that the steric repulsion between the *cis*-oriented substituents, the nitro and alkyl groups, on the C=C moiety of the parent nitroolefin (allylic 1,3-strain[12]) would be relieved upon abstraction of the γ–proton, assisting the generation of the requisite vinylogous nitronate (Fig. 1). This notion led us to become interested in utilizing α,β-disubstituted nitroolefins **2** as the nucleophilic component, which feature similar steric congestion that would benefit the facile generation of the corresponding α-substituted vinylogous nitronates under the influence of **1**. Here, we report the realization of this possibility through the development of a highly diastereo- and enantioselective aza-Henry reaction of **2** with *N*-Boc imines **3** catalyzed by appropriately modified chiral ammonium betaine **1**. Notably, the novel vinylogous nitronate generated *in situ* from **2** undergoes bond formation at the sterically more *encumbered* α-position exclusively, thereby enabling the construction of adjacent tertiary-quaternary stereogenic carbon centers.

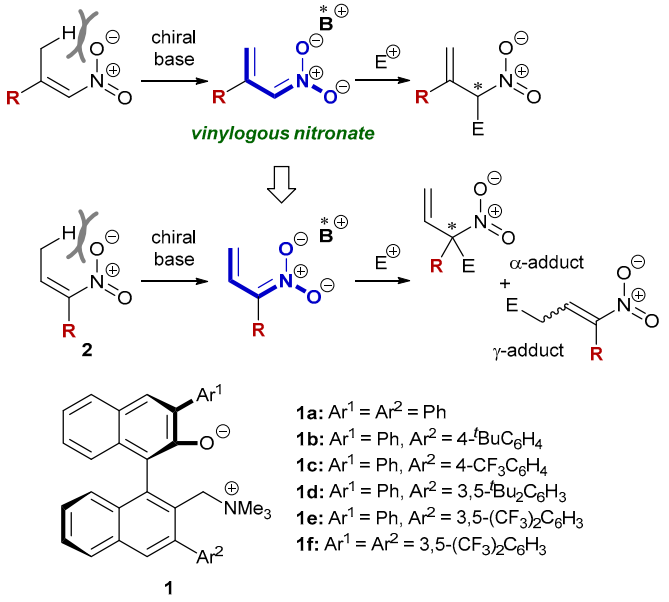
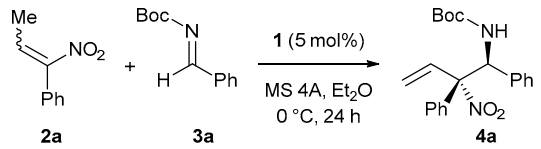


Figure 1. Generation of Vinylogous Nitronates from Conjugated Nitroolefins and Structures of C_1-Symmetric Chiral Ammonium Betaine **1**.

Table 1 Effect of Substituents at 3-Position of Each Naphthyl Unit of Chiral Ammonium Betaine **1**[a]



2a **3a** **4a**

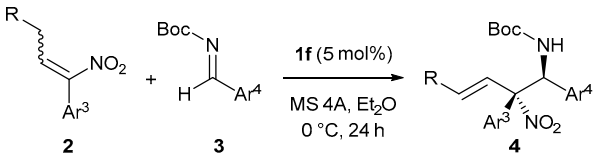
Entry	**1**	Yield (%)[b]	d.r. (*anti*/*syn*)[c]	ee (%)[d]
1	**1a**	21	13:1	77
2	**1b**	trace	-	-
3	**1c**	52	15:1	87
4	**1d**	52	14:1	87
5	**1e**	69	19:1	90
6	**1f**	90	>20:1	96

[a] Reactions were carried out with 0.11 mmol of **2a**, 0.10 mmol of **3a**, and 0.005 mmol of **1** in 0.3 mL of Et_2O with 100 mg of MS 4A at 0 ºC under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^1H NMR (400 MHz) analysis of crude aliquots. [d] Enantiomeric excesses of product **4a** were analyzed by chiral HPLC using DAICEL CHIRALPAK IA with a hexane/2-propanol solvent system. Absolute and relative stereochemistries of **4a** were determined by comparison with known α,β-diamino acid after derivatization (Scheme 1).

2-Phenyl-1-nitroprop-1-ene (**2a**, *E*/*Z* = 10:1) was selected as a model pronucleophile to assess the validity of our hypothesis on the applicability of α,β-disubstituted nitroolefins as precursors for α-substituted vinylogous nitronates. Thus, an initial attempt was made by treating **2a** with *N*-Boc benzaldimine (**3a**) in the presence of 4A molecular sieves (MS 4A) and chiral ammonium betaine **1a** (5 mol%) in Et_2O at 0 ºC (Table 1, entry 1).[13] Although the rate was insufficient, bond formation took place within 24 h of stirring; intriguingly, ^1H NMR (400 MHz) analysis of the crude mixture showed product signals corresponding only to aza-Henry adduct **4a** that was formed through the exclusive α-addition of the expected vinylogous nitronate to **3a** despite the significant steric constraints. It should be noted that the *E*/*Z* ratio of the recovered **2a** was virtually unchanged. This observation suggested that the vinylogous nitronate was generated from both isomers, probably because the relief of the allylic 1,3-strain through the deprotonation of the γ-carbon could be appreciated by either geometrical isomer.[14] Since a promising level of stereoselectivity was attained with betaine **1a** as the catalyst, we pursued the optimization of **1** by altering the structural features of the aryl appendages at the 3,3'-positions of the binaphthyl backbone (Ar^1 and Ar^2). As revealed in Table 1 (entries 2-6), introduction of electron-deficient substituents such as a trifluoromethyl group, rather than a sterically demanding alkyl group, to the aromatic nucleus had a positive impact on the catalytic efficiency and stereocontrolling ability of **1** (entries 2,4 vs 3,5). Eventually, compounds **1f** possessing 3,5-bis(trifluoromethyl)phenyl groups as Ar^1 and Ar^2 was identified as the optimal catalyst that allowed the production of **4a** in 90% yield with rigorous stereochemical control of the vicinal tertiary-quaternary stereocenters (entry 6).

With the optimized reaction conditions in hand, the substrate generality of this asymmetric aza-Henry protocol was investigated and the representative results are summarized in Table 2. As the electrophilic component, various *N*-Boc aromatic aldimines **3** were employable irrespective of their steric and electronic attributes (entries 1-9). When an electron-withdrawing group was introduced at the *para*-position of the aromatic ring, certain decrease in chemical yield was detected, while high diastereoselectivity and excellent enantioselectivity were generally observed (entries 2 and 4). The imines **3i** and **3j** derived from 1-naphthyl- and 2-furylaldehydes, respectively,

Table 2 Substrate Scope in **1f**-Catalyzed Aza-Henry Reaction of α,β-Disubstituted Nitroolefins **2** with *N*-Boc Imines **3**[a]



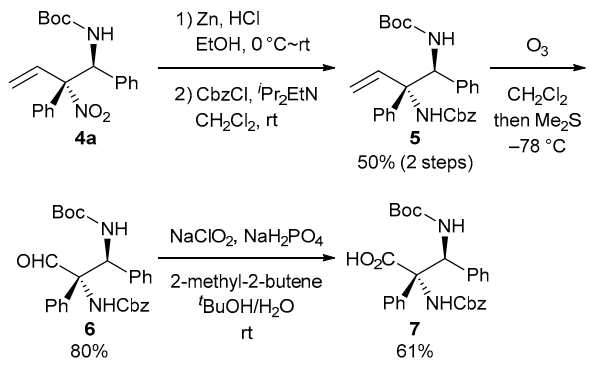
2 **3** **4**

Entry	R, Ar^3 (**2**)	Ar^4 (**3**)	Yield (%)[b]	d.r. (*anti*/*syn*)[c]	ee (%)[d]	Prod (**4**)
1	H, Ph (**2a**)	4-MeC_6H_4 (**3b**)	82	>20:1	92	**4b**
2	H, Ph (**2a**)	4-FC_6H_4 (**3c**)	64	>20:1	96	**4c**
3	H, Ph (**2a**)	4-ClC_6H_4 (**3d**)	97	15:1	93	**4d**
4	H, Ph (**2a**)	4-$CF_3C_6H_4$ (**3e**)	70	>20:1	99	**4e**
5	H, Ph (**2a**)	3-BrC_6H_4 (**3f**)	80	13:1	93	**4f**
6	H, Ph (**2a**)	3-$MeOC_6H_4$ (**3g**)	94	16:1	94	**4g**
7	H, Ph (**2a**)	2-FC_6H_4 (**3h**)	91	>20:1	96	**4h**
8	H, Ph (**2a**)	1-naphthyl (**3i**)	66	14:1	91	**4i**
9	H, Ph (**2a**)	2-furyl (**3j**)	68	5:1	94	**4j**
10	H, 4-MeC_6H_4 (**2b**)	Ph (**3a**)	85	>20:1	95	**4k**
11	H, 4-FC_6H_4 (**2c**)	Ph (**3a**)	73	10:1	92	**4l**
12	H, 3-$MeOC_6H_4$ (**2d**)	Ph (**3a**)	99	18:1	98	**4m**
13	Me, Ph (**2e**)	Ph (**3a**)	90	>20:1	99	**4n**
14	$Me(CH_2)_6$, Ph (**2f**)	Ph (**3a**)	86	>20:1	98	**4o**

[a] Reactions were carried out with 0.11 mmol of **2**, 0.10 mmol of **3**, and 0.005 mmol of **1f** in 0.3 mL of Et_2O with 100 mg of MS 4A at 0 ºC under argon atmosphere. [b] Isolated yields were reported. [c] Diastereomeric ratios were measured by ^1H NMR (400 MHz) analysis of crude mixtures. [d] Enantiomeric excesses were analyzed by chiral stationary phase HPLC. Absolute and relative configurations of aza-Henry adducts **4** were assigned by analogy to **4a**.

were also amenable to this catalytic system, although diastereoselectivity was moderate in the reaction with **3j** (entries 8 and 9). With respect to nitroolefin nucleophile **2**, varying the α-aromatic substituent subtly affected the efficiency and stereocontrol (entries 10-12). Furthermore, elongation of the β-alkyl chain was tolerated, which suggested the smooth generation of the vinylogous nitronates from 1-nitro-1-phenylbutene (**2e**) and 1-nitro-1-phenyloctene (**2f**) under the present conditions, leading to afford the aza-Henry adducts **4n** and **4o** in high yield in an essentially stereochemically pure form (entries 13 and 14).

The absolute stereochemistry of the major diastereomer of **4a** was determined by derivatization into known α,β-diamino acid **7** (Scheme 1). Reduction of the nitro functionality of **4a** followed by protection of the resulting primary amine with benzyl chloroformate (CbzCl) afforded differentially protected chiral diamine **5** in good yield. Its vinyl group was oxidatively cleaved via ozonolysis to give α,β-diamino aldehyde **6** and subsequent Pinnick oxidation of the aldehyde moiety furnished α,β-diamino acid **7**. The conservation of the enantiomeric excess in **7** was confirmed by chiral HPLC analysis of its methyl ester[15] and the absolute configuration was assigned as 1*S*,2*S* by comparison with the literature data.[7b]



Scheme 1. Derivatization of **4a** to the Corresponding α,β-Diamino Acid **7** to Determine Its Absolute and Relative Configuration

In conclusion, we have demonstrated the feasibility and synthetic utility of catalytically generating α-substituted vinylogous nitronates from α,β-disubstituted nitroolefins through the development of a highly stereoselective aza-Henry reaction using chiral ammonium betaines as organic base catalysts. The relief of the steric repulsion between *cis*-oriented substituents of the nitroolefins appeared to assist the facile generation of the vinylogous nitronates, which reacted with *N*-Boc aldimines at the sterically more congested α-position exclusively, thus establishing the contiguous tertiary-quaternary stereocenters. We believe that the present study significantly expands the potential of the vinylogous reactivity of nitroolefins and its utilization for developing selective carbon-carbon bond-forming reactions.

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Notes and references

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data of **2** and **4~7**. See DOI: 10.1039/c3cc00000x/

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13 The addition of MS 4A was effective to improve catalytic efficiency probably because of suppressing protonation of the ammonium nitronate by a small amount (<5%) of water, which was contaminated from slightly hygroscopic onium salt **1**.

14 There would be a similar degree of steric repulsion between methyl and phenyl groups in *E*-**2a** to that between methyl and nitro groups in *Z*-**2a**.
15 See Electronic supplementary information (ESI) for details.

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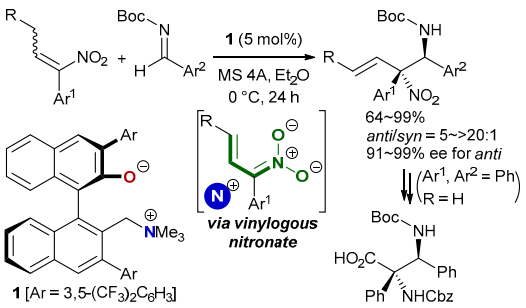

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