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Asymmetric Direct Vinylogous Michael Reaction of Activated Alkenes to Nitroolefins Catalyzed by Modified Cinchona Alkaloids

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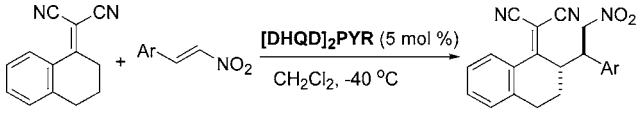
ABSTRACT



13 examples, 87-95% yield, up to 94% ee

The first organocatalytic and asymmetric direct vinylogous Michael reaction that employs the electron-deficient vinyl malononitriles as the nucleophilic species has been reported. The novel transformations exhibit exclusive γ-selectivity and high diastereo- and enantioselectivity in the addition to nitroolefins, which give the multifunctional products with two vicinal chiral centers.

The development of novel carbon−carbon bond construction methods is very important to organic synthesis. However, most of the usually applied protocols to generate the nucleophilic carbanion are limited to the deprotonation of an acidic C−H adjacent to one or more functional group-(s).[1] In 1935, Fuson[2] formulated the principle of vinylogy to provide a better understanding of the "anomalous" reactivity of some unsaturated compound and recognized that when a functional group is attached to an unsaturated moiety, "the influence of (that) functional group might sometimes be propagated along the chain and make itself apparent at some remote point in the molecule". Since then, fruitful results have been reported in vinylogous aldol[3] and Mannich[4] reactions by employing previously masked dienol ethers derived from γ-enolizable α,β-unsaturated carbonyl compounds.

However, the direct vinylogous reactions would be more desirable in regard to the development of green chemistry and atom economy. It could be envisioned that the acidity of γ-C−H might be greatly enhanced when strong electron−withdrawing groups are attached to C=C bond, which allows the easy generation of nucleophilic species by in situ deprotonation under mild conditions. Indeed, in our recent studies[5] on the transfer hydrogenation of vinyl malononitriles catalyzed by Noyori's diamine-Ru(II) catalysts, it was found that the γ-C−H of the vinyl malononitriles could be easily

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(1) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Kluwer: New York, 2000; p 57.
(2) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.
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(5) (a) Chen, Y.-C.; Xue, D.; Deng, J.-G.; Cui, X.; Zhu, J.; Jiang, Y.-Z. *Tetrahedron Lett.* **2004**, *45*, 1555. (b) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584.

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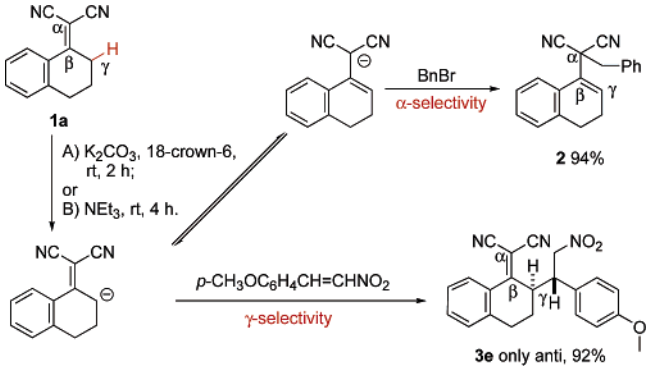
deuterated in the presence of NEt_3. It is noteworthy that the Hammett substituent constant for α,α-dicyanovinyl group [−CH=C(CN)$_2$] is even higher than that of nitro group ($\sigma_p = 0.84$ cf $\sigma_p = 0.78$).[6] Thus, as illustrated in Scheme 1,

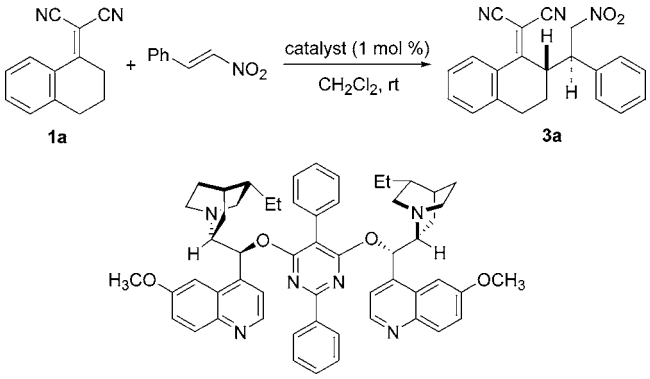
Scheme 1. Regioselectivity in the C−C Bond Formation Reaction of Vinyl Malononitrile under Mild Basic Conditions



facile deprotonation of **1a** could occur to generate the vinylogous carbanion under mild basic conditions. It is interesting that high regioselectivity was observed for different C−C bond forming reactions.[7,8] Only the α-alkylated product **2** was detected in alkylation reaction (condition A).[7a] However, the site selectivity completely changed to γ-position using *p*-methoxynitrostyrene as the Michael addition acceptor, with excellent diastereoselectivity (condition B).[7b] Here we present for the first time an asymmetric direct vinylogous Michael addition to nitrostyrenes with high regio- and stereoselectivity, employing the electron-deficient vinyl malononitriles as the vinylogous necleophiles.[8,9]

Chiral tertiary amines, especially Cinchona alkaloids and their derivatives, have been successfully applied in various organocatalytic asymmetric transformations,[10,11] for example, acting as chiral base catalysts.[12] However, this concept has not yet been applied to the vinylogous Michael reaction.[8b] Thus, a series of chiral modified cinchona alkaloids were investigated in the asymmetric reaction of vinyl malononitrile **1a** to nitrostyrene. The results are shown in Table 1. The

Table 1. Optimization of Reaction Conditions for the Vinylogous Michael Addition of Vinyl Malononitrile **1a** with Nitrostyrene[a]



entry	catalyst	T (h)	yield (%)[b]	ee (%)[c]
1	NEt_3	7	88	
2	quinine	3	90	19
3	quinidine	3	90	26
4	$(DHQ)_2AQN$	3	92	54
5	$(DHQD)_2AQN$	3	90	52
6	$(DHQ)_2PHAL$	5	92	63
7	$(DHQ)_2PYR$	5.5	90	75
8	$(DHQD)_2PYR$	4	93	81
9[d]	$(DHQD)_2PYR$	48	26	82
10[d,e]	**$(DHQD)_2PYR$**	**48**	**72**	**90**
11[d,f]	$(DHQD)_2PYR$	48	87	88
12[e,g]	$(DHQD)_2PYR$	80	62	88

[a] Reactions performed at 0.1 mmol scales. Method: 1.1 equiv nitrostyrene, in 0.5 mL of DCM at room temperature. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] At −40 °C. [e] 5 mol % catalyst. [f] 10 mol % catalyst. [g] At −60 °C.

reaction exhibited high diastereoselectivity, and only the *anti*-product was obtained in all reactions despite the various catalysts used. Of the cinchona alkaloids and the derivatives tested (for the structure of catalysts, see Supporting Information), the commercially available $[DHQD]_2PYR$ proved to be the most promising catalyst, giving the addition product **3a** with 93% yield and 81% ee at room temperature (Table 1, entry 8). Several solvents have been investigated, and DCM was selected as the best one. Temperature and catalyst loading had obvious influence on enantioselectivity. The best result (90% ee) was obtained with 5 mol % catalyst loading at −40 °C (entry 10). Slightly low enantioselectivity was afforded with higher catalyst loading at the same temperature (entry 11). In addition, lower temperature also slightly diminished the enantioselectivity with 5 mol % catalyst loading (entry 12). With the optimized reaction conditions in hand, the scope of the enantioselective vinylogous Michael reaction was investigated (Table 2). A wide range of

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(8) For recent examples of vinylogous Michael reactions, see: (a) Christoffers, J. *Synlett* **2001**, 723 and references therein. (b) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3397.

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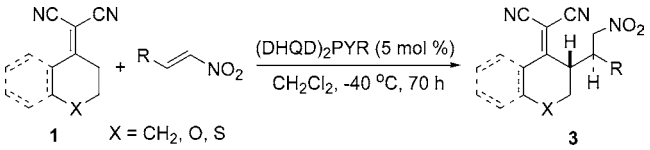
Table 2. Enantioselective Vinylogous Michael Addition of Vinyl Malononitriles **1a**−**e** to Nitroolefins Catalyzed by $[DHQD]_2PYR$[a]



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entry	substrate	R	product	yield (%)[b]	ee (%)[c]
1	**1a**	Ph	**3a**	87	90
2	**1a**	*p*-$CH_3C_6H_4$	**3b**	90	90
3	**1a**	*p*-ClC_6H_4	**3c**	91	90
4	**1a**	*p*-BrC_6H_4	**3d**	90	91
5	**1a**	*p*-$CH_3OC_6H_4$	**3e**	93	94
6	**1a**	*p*-$(CH_3)_2NC_6H_4$	**3f**	91	93
7	**1a**	2-furanyl	**3g**	85	91
8	**1a**	2-thiophenyl	**3h**	93	94
9	**1b**	*p*-$CH_3OC_6H_4$	**3i**	93	70
10	**1c**	Ph	**3j**	95	86
11	**1d**	*p*-$CH_3OC_6H_4$	**3k**	89	81
12	**1d**	Ph	**3l**	91	76
13	**1e**	Ph	**3m**	95	66

[a] Reactions performed at 0.068 mmol scales. Method: 1.0 equiv nitroolefin, in 0.3 mL of DCM. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

nitroolefins bearing aryl and heteroaryl groups were reacted with vinyl malononitriles **1a**−**e** (Figure 1) derived from

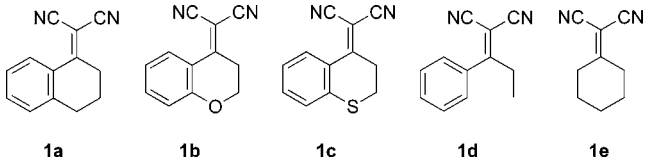


Figure 1. Structure of Vinyl Malononitriles.

corresponding ketones and malononitrile in CH_2Cl_2 at −40 °C in the presence of 5 mol % $[DHQD]_2PYR$, and only the *anti*-products were observed in all reactions. Reaction of aryl and heteroaryl nitroalkenes with vinyl malononitrile **1a** was found to cleanly produce the corresponding adducts **3a**−**h** in high enantioselectivities (90−94% ee) and good yields (85−93% range) (entries 1−8). High yield but decreased enantioselectivity was obtained for **1b** and **1c** bearing heteroatom (entries 9 and 10). For substrate **1d** derived from acyclic aromatic ketone, moderate enantioselectivities were observed (entries 11 and 12). Cyclic aliphatic substrate **1e** also exhibited good reactivity, although the ee (66%) was not satisfying (entry 13).

Enantiopure **3c** (>99% ee), which contains a chlorine atom, was obtained by crystallizing slowly from a mixture of ethyl acetate and petroleum ether and the crystals were suitable for X-ray structural analysis. Thus, the stereochemistry of the two newly created stereocenters of **3c** was revealed to possess (10*S*,11*R*)-configuration as shown in Figure 2.

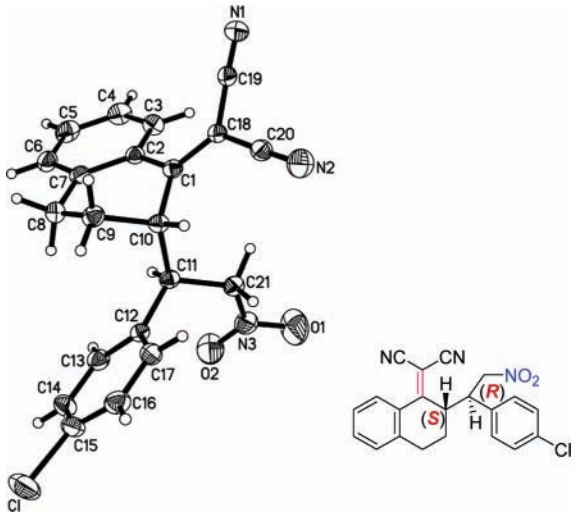
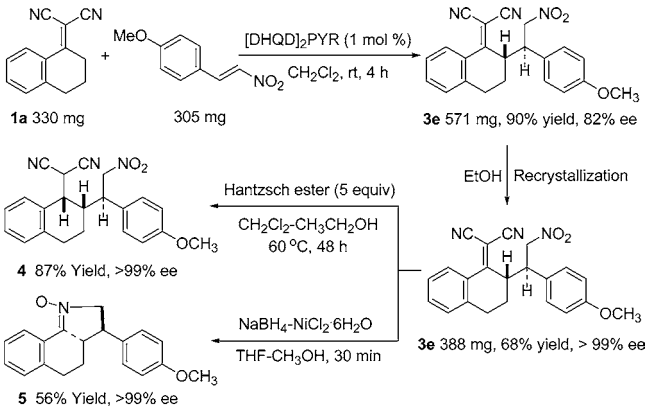


Figure 2. X-ray Crystallographic Structure of **3c**.

The scaling-up experiment verified the potential application of this methodology (Scheme 2). Enantiopure **3e** could

Scheme 2. Selective Transformation of the Addition Product



be obtained by a single recrystallization from EtOH. In addition, chemo- and stereoselective reduction of the double bond could be achieved using Hantzsch ester as the hydrogen source, which gave compound **4** with continuous three chiral carbon centers. The stereochemistry was determined to be *cis*,*trans*-form by NMR analysis. Interestingly, enantiopure nitrone compound **5** was accidentally obtained when $NaBH_4$-$NiCl_2$ was used as the reductive reagent. Moreover, it should be noted that 1-tetralone did not react with nitroolefins under our conditions. This implies that malononitrile can serve as a masking group[7a,13] as well as an activating group.[13]

In summary, to the best our knowledge, this paper represents the first organocatalytic and asymmetric direct

vinylogous Michael addition that employs the electron-deficient vinyl malononitriles as the nucleophilic species. The novel transformations exhibit exclusive γ-selectivity and high diastereo- and enantioselectivity in the addition to nitroolefins, which give the multifunctional products with two vicinal chiral centers. It is noticeable that vinyl malononitriles had served as Michael acceptor for successful transfer hydrogenation of carbon−carbon double bonds catalyzed by Noyori's diamine-Ru(II) catalysts[5] and in this work, vinyl malononitriles were applied as Michael donor for successful carbon−carbon bond construction. Current studies are actively underway to extend this strategy to alkyl-substituted nitroolefins and other asymmetric vinylogous reactions.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds, including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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