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Chiral Primary Amine Catalyzed Asymmetric Michael Addition of Malononitrile to α-Substituted Vinyl Ketone

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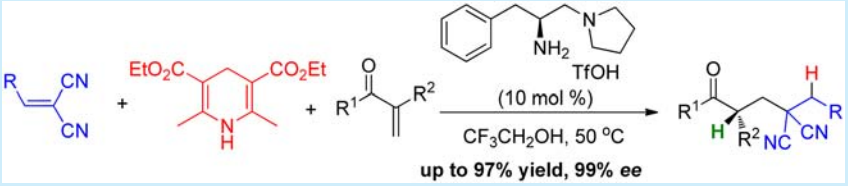
Supporting Information

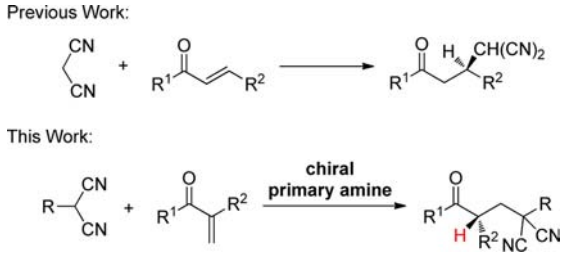


ABSTRACT: The first efficient and highly enantioselective Michael addition−protonation reaction of malononitriles to α-substituted vinyl ketones has been developed by using a chiral primary amine as the organocatalyst. With a Hantzsch ester as the hydride source, an enantioselective tandem reduction, Michael addition−protonation reaction of benzylidenemalononitrile has also been achieved with good yields and high enantioselectivities.

The catalytic asymmetric Michael addition reaction is undoubtedly one of the most powerful transformations in organic synthesis. The capability of this reaction is exponentially increased by a wide variety of substrates that can serve as either nucleophiles or Michael acceptors, and consequently, a diverse array of products can be generated.[1] Among various nucleophiles, malononitrile, a classic equivalent of a 1,3-dicarbonyl compound, is a valuable candidate that can be conveniently transformed into carboxylic acid, ester, amine, or amide groups.[2] However, the asymmetric malononitrile addition reactions are generally limited to the parent unsubstituted malononitrile.[3] Explorations on substituted malononitirile have been much less successful so far. In 2011, the asymmetric Michael addition of 2-methylmalononitrile to ethyl 2-phenyl acrylate was attempted using chiral diamine as the catalyst, but with rather poor enantioselectivity, pinpointing the difficulties of this type of transformation.[4] With respect to Michael acceptors, previous examples are mostly with β-stereogenic α,β-unsaturated carbonyls. A catalytic asymmetric manolonitrile addition to α-substituted vinyl carbonyls that features α-stereogenic protonation steps remains elusive (Scheme 1).[5]

Our group demonstrated recently that chiral primary−tertiary diamines are effective catalysts for the iminium activation of α-substituted acroleins and vinyl ketones with good activity and high enantioselectivity.[6] These reactions feature enamine protonation as the key stereogenic step, and further mechanistic studies have disclosed Curtin−Hammett stereocontrol for the reactions of α-substituted vinyl ketones, which infers that successful extensions to other nucleophiles in the reactions with vinyl ketones may be readily achieved.[6e] Recently, this control mode has been successfully tested by

Scheme 1. Asymmetric Michael Addition of Malononitrile



using azoles, thiols, and alkenes as nucleophiles.[6f−h] The extension of this catalysis to other nucleophiles has been further pursued. Herein, we document the first highly enantioselective Michael addition−enamine protonation reactions of malononitriles to α-branched vinyl ketones. The current protocol encompasses a number of vinyl ketones as well as malononitriles bearing different 2-substitutions, thus providing convenient accesses to chiral α-alkylated ketones, a long-standing challenge in asymmetric alkylation chemistry.[7]

Our initial studies on Michael addition−protonation reactions with malononitriles were carried out using 2-benzylmalononitrile **4a** as the nucleophile. Compared with simple malononitrile (pK_a 11.1 in DMSO), 2-alkyl-substituted malononitrile has a less acidic C−H bond (e.g., 2-methyl-malononitrile, pK_a 12.4 in DMSO), which means this type of substrates would be less reactive. In this context, we were quite delighted to find out that the vicinal primary−tertiary diamine catalysts derived from L-phenylalanine could promote the

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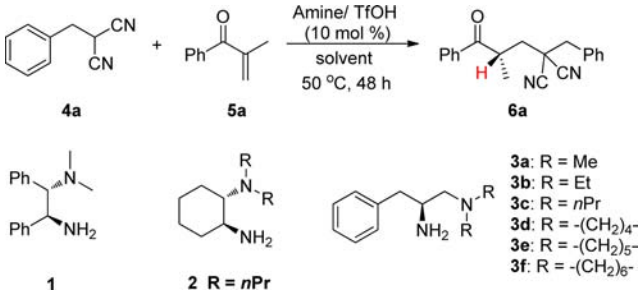
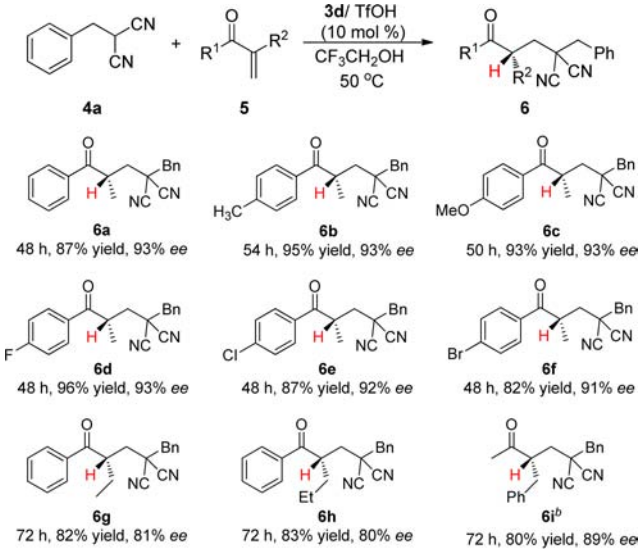
Table 1. Optimization of the Reaction Conditions[a]



entry	amine	solvent	yield (%)[b]	*ee* (%)[c]
1	**1**	toluene	trace	–
2	**2**	toluene	trace	–
3	**3a**	toluene	15	84
4	**3b**	toluene	11	81
5	**3c**	toluene	10	68
6	**3d**	toluene	22	84
7	**3e**	toluene	20	50
8	**3f**	toluene	10	77
9	**3d**	$CHCl_3$	48	87
10	**3d**	EtOH	90	81
11	**3d**	*i*PrOH	85	82
12	**3d**	CF_3CH_2OH	87	93
13	**3d**	HFIP[d]	92	77

[a]General conditions: **4a** (0.15 mmol), **5a** (0.30 mmol), amine/TfOH (10 mol %) in solvent (0.50 M) at 50 °C, 48 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]HFIP: Hexafluoroisopropanol.

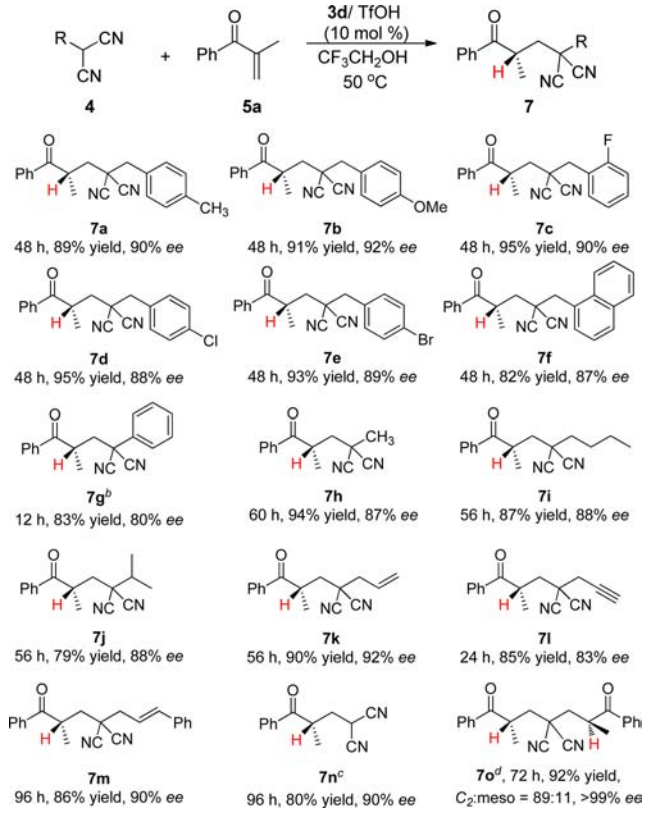
Scheme 2. Substrate Scope for α-Substituted Vinyl Ketones[a]



[a]General conditions: **4a** (0.15 mmol), **5** (0.30 mmol), **3d**/TfOH (10 mol %) in CF_3CH_2OH (0.50 M) at 50 °C. [b] At 40 °C, with $CHCl_3$ (0.50 M) as solvent.

targeted reaction, with not unexpectedly very low activity even when carried out at 50 °C (Table 1, entries 3–8). However, the enantioselectivity of the product was reasonably good (84% *ee*) when using **3d**/TfOH as the catalyst (Table 1, entry 6). Further screening of reaction mediums indicated that the solvents had a pronounced effect on both the yields and enantioselectivities. The use of alcohol solvent, especially trifluoroethanol, can

Scheme 3. Substrate Scope for Malononitriles[a]



[a]General conditions: **4** (0.15 mmol), **5a** (0.30 mmol), **3d**/TfOH (10 mol %) in CF_3CH_2OH (0.50 M) at 50 °C. [b] At 35 °C, with $CHCl_3$ (0.10 M) as solvent. [c] At 40 °C, **5a** (0.15 mmol), malononitrile (0.45 mmol), with $CHCl_3$ (0.10 M) as solvent. [d] Malononitrile (0.15 mmol), **5a** (0.45 mmol).

greatly improve the result, affording the desired product **6a** in 87% isolated yield and with 93% *ee* (Table 1, entry 12).

With the optimized conditions in hand, the scope of the catalytic system was explored. An array of α-substituted vinyl ketones were tested in this reaction, resulting in high yields of products **6a–i** with good to excellent enantioselectivity (Scheme 2). Aromatic α-substituted vinyl ketones were identified as one class of preferred substrates, and phenyl groups bearing either electron-rich (**6b**, **6c**) or electron-deficient (**6d–6f**) substituents are equally applicable. However, it was found that increasing the bulkiness of α-substituents turned out to be detrimental to the enantioselectivity. When an α-substituent was changed to an ethyl or *n*-propyl group, the enantioselectivity dropped to 80% *ee* (Scheme 2, **6g**, **6h**). Lastly, an aliphatic enone, such as methyl enone, can also be applied to this reaction system with good enantioselectivity (Scheme 2, **6i**).

The scopes of the reaction with respect to different types of malononitriles were also investigated (Scheme 3). As seen from the results in Scheme 3, a series of 2-benzyl substituted malononitriles with different substituents at the phenyl group were generally good nucleophiles in this catalytic system. The desired products **7a–f** were obtained in high yields and with high enantioselectivities. 2-Phenylmalononitrile (pK_a 4.2 in DMSO) is a highly reactive substrate, with chloroform as the solvent at 35 °C, the reaction still proceeded smoothly to furnish the desired product **7g** with good activity and enantioselectivity. To our delight, an alkyl substituent can be

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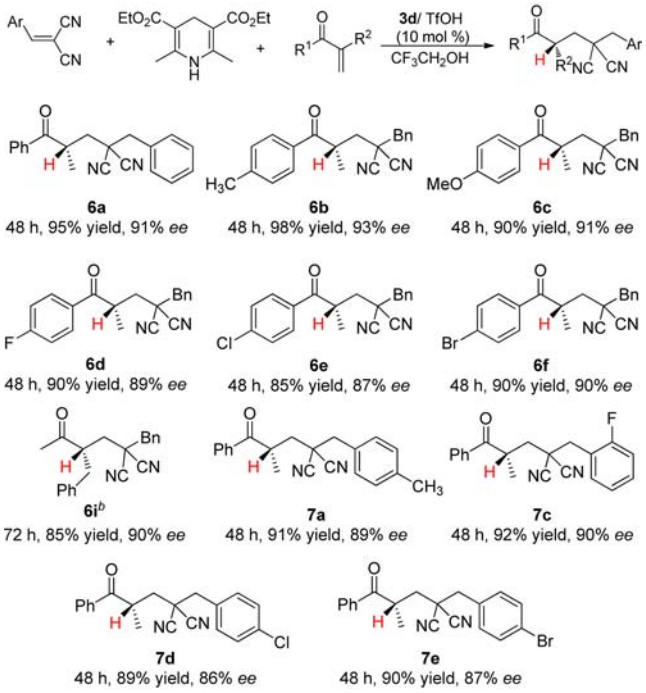
Scheme 4. Substrate Scope for One-Pot Reductive Michael Addition–Protonation Reaction[a]



[a]General conditions: Benzylidenemalononitrile (0.15 mmol), Hantzsch ester (0.18 mmol), **5** (0.30 mmol), **3d**/TfOH (10 mol %) in CF_3CH_2OH (0.50 M) at 50 °C. [b] At 40 °C, with $CHCl_3$ (0.50 M) as solvent.

altered to methyl, *n*-butyl, or a bulky isopropyl moiety to give the desired adducts with good yields and high enantioselectivities (Scheme 3, **7h**–**7j**). Additionally, propargyl and allyl-type groups can also be very compatible with the present catalytic system (Scheme 3, **7k**–**7m**). Furthermore, with excess malononitrile, mono-Michael addition of malononitrile to **5a** can be realized (Scheme 3, **7n**). On the other hand, in the presence of excess **5a**, double Michael addition was observed to give the C_2-symmetric adduct **7o** with 99% *ee*. The determined C_2:*meso* ratio (89:11) is close to the theoretical value (90.5:9.5) based on the enantioselectivity of the monoaddition (**7n**), verifying that both addition steps are catalyst controlled. We expect this enantioselective double Michael addition–protonation technology to be of particular value for the construction of chiral spiro-compounds. Finally, the absolute configurations of **7e** and **7f** were determined by X-ray analysis. The configurations of the Michael addition products can be assigned to be *S* accordingly.[8]

Recently, the capacity of Hantzsch esters and related organic hydride donors in transfer hydrogenation reactions has been successfully explored in iminium-based and hydrogen bonding catalysis.[9] We reasoned that Hantzsch esters may serve as a chemoselective hydride source to reduce 2-benzylidenemalononitrile and its derivatives;[10] thus, a one-pot enantioselective tandem reduction/Michael addition–protonation reaction can be achieved in the present catalytic system. Of note is that although intramolecular asymmetric reductive Michael addition is known, an intermolecular version is very limited.[11c]

When we treated 2-benzylidenemalononitrile, Hantzsch esters, and α-methyl vinyl ketone **5a** in the presence of **3d**/TfOH, a clean reductive Michael addition–protonation reaction to the desired product was observed. To our gratification, an excellent yield and enantioselectivity can still be obtained in this one-pot three-component procedure (Scheme 4, **6a**). Different α-substituted vinyl ketones, including aromatic and aliphatic enones, were then examined, giving the reductive Michael addition–protonation products with equally good results compared with the normal Michael addition procedure (Scheme 4, **6b**–**6f**, **6i**). Moreover, different substituents at the phenyl group of 2-benzylidenemalononitrile did not result in a significant effect on the reaction results (Scheme 4, **7a**, **7c**–**7e**).

In summary, we have developed highly efficient Michael addition–protonation reactions of malononitriles to α-substituted vinyl ketones by chiral primary amine catalysis. The one-pot three-component reactions with a Hantzsch ester as a hydride source have also been realized with the same catalytic system. Additional investigations into the mechanism of the asymmetric induction and the extension of the methodology to other types of additions are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) CCDC 1037039 (**7e**) and CCDC 1037038 (**7f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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