Asymmetric Synthesis

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Highly Asymmetric Michael Addition to α,β-Unsaturated Ketones Catalyzed by 9-Amino-9-deoxyepiquinine**

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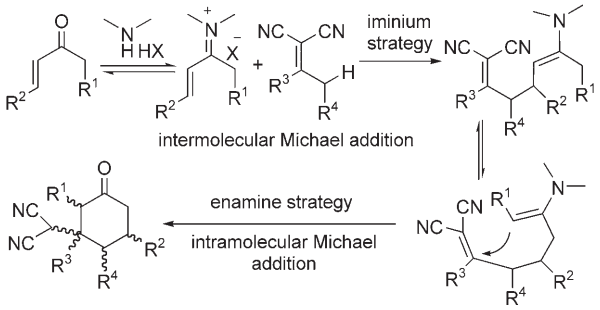
Dedicated to Prof. Yao-Zhong Jiang on the occasion of his 70th birthday

The in situ generation of an iminium ion from a chiral aminocatalyst and a carbonyl compound is thought to lower the LUMO energy of the system and is a powerful strategy for a range of asymmetric transformations.[1] The commonly applied catalysts are ammonium salts of secondary amines derived from chiral α-amino acids or 1,2-diphenylethylenediamine. Highly efficient asymmetric reactions, including conjugate addition and pericyclic reactions, have been described for α,β-unsaturated aldehydes, even at very low temperatures.[2] However, the reactions of α,β-unsaturated ketones catalyzed by secondary amine salts usually suffer from a sluggish reaction rate at room temperature,[3] and some reactions could not be promoted at all, probably because of poor generation of the corresponding iminium cations. Therefore, an alternative catalyst with stronger activating ability, broader applicability, and improved enantioselectivity would be highly desirable.

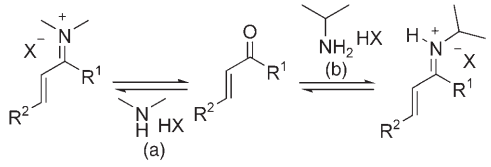
Recently, we reported that the electron-deficient α,α-dicyanoalkenes could act as versatile direct vinylogous donors in asymmetric Michael addition reactions of nitroalkenes and α,β-unsaturated aldehydes with excellent chemo- and stereoselectivity.[4] These activated alkenes also behave as good hydride acceptors in conjugate reduction reactions.[4a–b,5] It is intriguing to consider that α,α-dicyanoalkenes might be applied successively as Michael donors and Michael acceptors in some domino sequences. Inspired by the recent reports on tandem iminium–enamine activation of α,β-unsaturated aldehydes by chiral secondary aminocatalysts,[6] we envisaged that sequential Michael–Michael addition reactions would be possible between α,α-dicyanoalkenes and α,β-unsaturated ketones, as outlined in Scheme 1, to provide a straightforward protocol for the synthesis of chiral cyclic products with multiple substituents.



Scheme 1. Proposed domino Michael–Michael addition reactions based on iminium–enamine activation.

Unfortunately, we found that the secondary-amine catalysts, such as L-proline and its analogues, that have been used successfully in the asymmetric Michael reactions of Jørgensen and co-workers,[3d–f] were completely inert for the vinylogous Michael reactions of α,α-dicyanoalkenes and α,β-unsaturated ketones. As the relative bulkiness of secondary amines might be unfavorable for the formation of iminium ions with α,β-unsaturated ketones [Eq. (a)], we envisaged that the generation of a ketimine cation from a primary amine salt and a ketone would be more feasible and lead to the activation of the α,β-unsaturated system [Eq. (b)]. Moreover, the application of primary amines as iminium catalysts for α,β-unsaturated ketones has rarely been explored.[7]

The vinylogous Michael addition of α,α-dicyanoalkene **2a** to benzylideneacetone (**3a**) was indeed promoted by the



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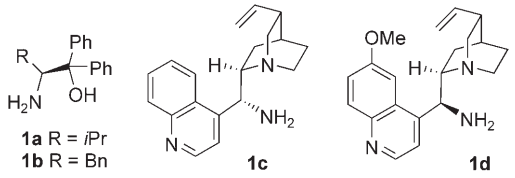
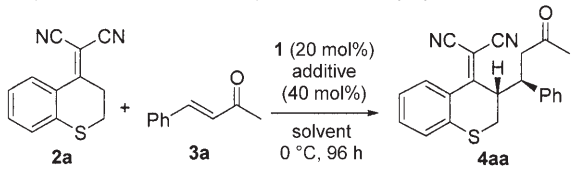
trifluoroacetic acid (TFA) salt of the primary aminoalcohol **1a** (20 mol%; Scheme 2) derived from L-valine. The addition product **4aa** was formed with complete *anti* selectivity and isolated in 40% yield with 69% *ee* after 96 h at room



Scheme 2. Structures of the chiral primary amine catalysts used. Bn = benzyl.

temperature (Table 1, entry 1).[8] However, the expected intramolecular Michael reaction through enamine activation did not occur, probably because of steric reasons. A slightly higher *ee* value was attained in the presence of **1b**–TFA (Table 1, entry 2). Subsequently, we found that a combination of TFA (40 mol%) and 9-amino-9-deoxyepicinchonine (**1c**; 20 mol%), which is readily accessible from natural cinchonine,[9] exhibited much higher catalytic activity, and **4aa** was obtained in 75% yield with 70% *ee* after 96 h at 0 °C (Table 1, entry 3). Gratifyingly, the addition product was formed with excellent enantioselectivity (93% *ee*) and in 88% yield when the TFA salt of 9-amino-9-deoxyepiquinine **1d** was used. This catalyst afforded the desired product with the opposite configuration to that obtained with **1c** (Table 1, entry 4).

Table 1: Screening of primary amine catalysts in the Michael reaction of α,α-dicyanoalkene **2a** with benzylideneacetone (**3a**).[a]

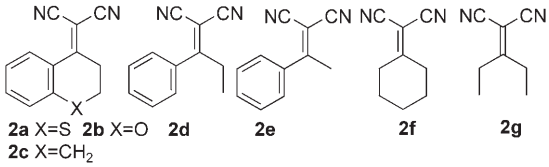


Entry	Catalyst	Solvent	Additive	Yield [%][b]	*ee* [%][c]
1[d,e]	**1a**	THF	CF_3COOH	40	−69
2[d,e]	**1b**	THF	CF_3COOH	36	−76
3	**1c**	THF	CF_3COOH	75	−70
4	**1d**	THF	CF_3COOH	88	93
5[e]	**1d**	THF	CF_3COOH	83	78
6	**1d**	THF	CF_3SO_3H	13	65
7	**1d**	THF	$HClO_4$	83	87
8	**1d**	THF	HCl	80	92
9	**1d**	CH_2Cl_2	CF_3COOH	90	85
10	**1d**	toluene	CF_3COOH	50	88
11	**1d**	ethanol	CF_3SO_3H	50	69
12	**1d**	ether	CF_3COOH	53	84
13[f]	**1d**	THF	CF_3COOH	99	91

[a] Reaction conditions, unless otherwise noted: **2a** (0.1 mmol), **3a** (0.2 mmol), catalyst (20 mol%), THF (1 mL), 0 °C, 96 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase. [d] Reaction was carried out at room temperature. [e] TFA: 20 mol%. [f] **2a**/**3a** = 1.5:1.

The *ee* value was dramatically decreased when TFA and **1d** were used in a 1:1 ratio (Table 1, entry 5). A variety of other acid additives and solvents were screened; however, inferior results to that with **1d** were observed (Table 1, entries 6–12). The product **4aa** was formed with slightly lower enantioselectivity but in excellent yield when an excess of the α,α-dicyanoalkene **2a** was used (Table 1, entry 13).

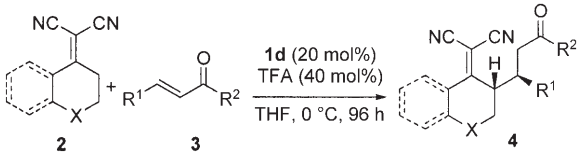
Having established the optimal reaction conditions, we then examined a range of α,α-dicyanoalkenes (Scheme 3) and



Scheme 3. Structures of the α,α-dicyanoalkenes used.

α,β-unsaturated ketones to explore the generality of this novel catalytic system (Table 2). The reaction scope proved to be quite broad with respect to both the α,α-dicyanoalkene and the substitution pattern of the electrophile. Excellent diastereoselectivity was observed for all the reactions tested. High *ee* values were observed in the vinylogous Michael reactions of α,α-dicyanoalkene **2a** and the variously substituted enones **3a**–**3h** (Table 2, entries 1–8), and the product was formed with over 99% *ee* in the case of the cyclic enone substrate **3h** (Table 2, entry 8). Although low reactivity was observed for the other nucleophiles **2b**–**2g**, the Michael

Table 2: Asymmetric vinylogous Michael addition of α,α-dicyanoalkenes **2** to α,β-unsaturated ketones **3**.[a]

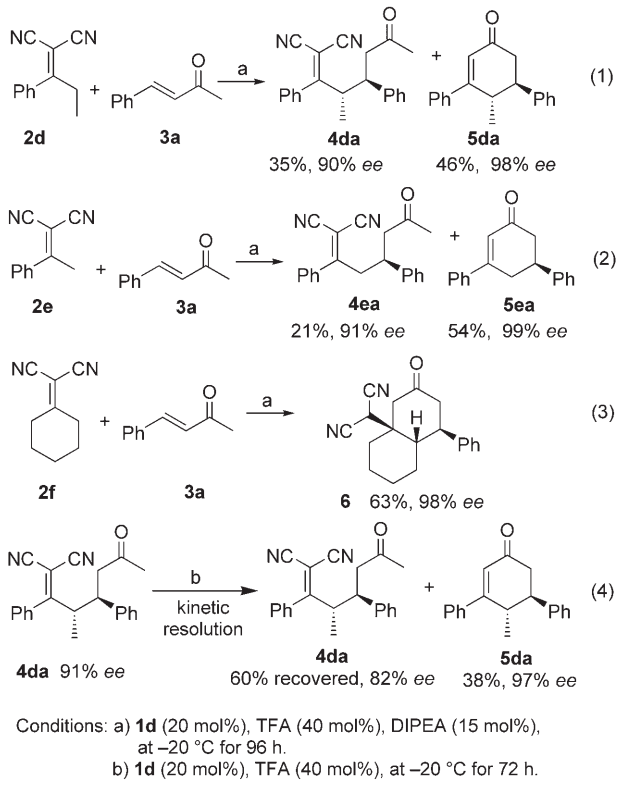


Entry	**2**	R^1	R^2	**3**	**4**	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph	Me	**3a**	**4aa**	88	93
2	**2a**	*p*-ClC_6H_4	Me	**3b**	**4ab**	85	90
3	**2a**	*p*-(MeO)ClC_6H_4	Me	**3c**	**4ac**	83	91[d]
4	**2a**	2-furanyl	Me	**3d**	**4ad**	82	97
5	**2a**	Ph	Et	**3e**	**4ae**	78	95
6	**2a**	Ph	*n*Pr	**3f**	**4af**	81	98[d]
7	**2a**	*n*Pr	Me	**3g**	**4ag**	76	98
8	**2a**	$-(CH_2)_3-$		**3h**	**4ah**	80	>99
9[e]	**2b**	Ph	Me	**3a**	**4ba**	69	89
10[e]	**2c**	Ph	Me	**3a**	**4ca**	60	91
11[e]	**2g**	Ph	Me	**3a**	**4ga**	51	95
12[e,f]	**2a**	*n*Pr	Me	**3g**	**4ag**	78	−87
13[e,f]	**2a**	$-(CH_2)_3-$		**3h**	**4ah**	98	−99

[a] Reaction conditions, unless otherwise noted: **2** (0.1 mmol), **3** (0.2 mmol), **1d** (20 mol%), TFA (40 mol%), THF (1 mL), 0 °C, 96 h. [b] Yield of the isolated product. [c] Determined by HPLC analysis on a chiral phase. [d] The absolute configuration was determined to be C_8: *S*, C_{13}: *R* by X-ray crystallographic analysis.[10] [e] DIPEA (15 mol%) was added, and the reaction was conducted at −20 °C. [f] Amine **1c** was used as the organocatalyst.

reactions could be greatly accelerated by adding DIPEA (diisopropylethylamine; 15 mol%), even at −20°C. The products were obtained with high *ee* values and in good yields when the cyclic substrates **2b** and **2c** were used (Table 2, entries 9 and 10). Excellent enantioselectivity was also observed for the simple α,α-dicyanoalkene **2g**, although the yield of the isolated product was only moderate after this period of time (Table 2, entry 11). Furthermore, the desired adducts with the opposite configuration could be obtained with high enantioselectivity upon catalysis by **1c** at −20°C (Table 2, entries 12 and 13).

Interestingly, under the same conditions as above, the reaction of the acyclic β-phenyl-α,α-dicyanoalkenes **2d** and **2e** with **3a** gave not only the vinylogous Michael products **4da** and **4ea**, but also the 2-cyclohexen-1-one derivatives **5da** and **5ea**,[11] respectively, with higher optical purity (Scheme 4,

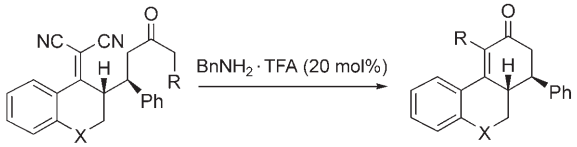


Conditions: a) **1d** (20 mol%), TFA (40 mol%), DIPEA (15 mol%), at –20 °C for 96 h.
b) **1d** (20 mol%), TFA (40 mol%), at –20 °C for 72 h.

Scheme 4. Domino Michael–Michael reactions based on iminium–enamine activation.

Eq. (1) and (2)). Apparently the expected domino Michael–Michael reactions occurred and were followed by a further retro-Michael reaction to generate the observed enone products. Moreover, a kinetic resolution was associated with the intramolecular Michael reaction of the enamine intermediate, as verified through a cyclization experiment with the isolated adduct **4da** (Scheme 4, Eq. (4)). As direct organocatalytic asymmetric Michael reactions of unmodified ketones, especially aryl ketones, with α,β-unsaturated ketones have not been feasible to date,[12,13] readily available and easily handled α,α-dicyanoalkenes could act as versatile and highly reactive precursors of ketones in such reactions. Finally, the reaction of the aliphatic cyclic substrate **2f** gave the annulated product **6** with three contiguous chiral centers, including a quaternary center surrounded by four carbon atoms,[14] with excellent enantioselectivity; in this case the elimination of malononitrile did not take place under these conditions [Scheme 4, Eq. (3)].[15]

Although the straightforward intramolecular Michael addition of the products in Table 2 was not successful in the presence of bulky chiral primary amines, such reactions could be promoted in a separate step. As illustrated in Scheme 5,



Scheme 5. Domino Michael–retro-Michael reactions promoted by an achiral primary aminocatalyst.

the vinylogous product **4ba** could be converted cleanly into the annulated compound **5ba** by catalysis with achiral benzylamine without affecting the *ee* value. Slightly forcing conditions were needed for the conversion of **4ae**, in which the carbonyl group has an ethyl substituent. Thus, this methodology provides a versatile protocol for the construction of a variety of chiral 2-cyclohexen-1-ones with multiple substituents.

In conclusion, we have presented the first asymmetric direct vinylogous Michael addition of α,α-dicyanoalkenes and α,β-unsaturated ketones. The reaction scope is quite substantial and excellent stereoselectivity was generally observed with a chiral primary aminocatalyst derived from quinine. Moreover, enantiomerically pure polysubstituted 2-cyclohexen-1-one derivatives, which have not been readily accessible to date, could be prepared smoothly through the novel organocatalytic Michael–Michael–retro-Michael reaction cascade. This domino reaction sequence is highly efficient, and two reagents act alternately and selectively as the Michael donor and acceptor under readily controllable conditions. To the best of our knowledge, this is the first example of asymmetric domino reactions catalyzed by chiral primary amines. We also believe that the strategy applied in this study may lead to the design and application of primary aminocatalysts in other asymmetric transformations of α,β-unsaturated ketones. The investigation of potential transformations of this type is well underway in our laboratory, and the results will be reported in due course.

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