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Asymmetric Organocatalytic Double-Conjugate Addition of Malononitrile to Dienones: Efficient Synthesis of Optically Active Cyclohexanones

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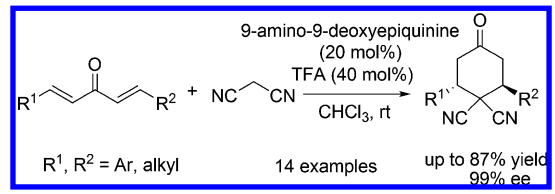
ABSTRACT



9-Amino-9-deoxyepiquinine efficiently catalyzed the double-conjugate addition of malononitrile to dienones. A number of 1,1,2,6-tetrasubstituted cyclohexanones were prepared in good yields, diastereoselectivities, and excellent enantioselectivities.

In the past decade, asymmetric organocatalysis has been developed to be a powerful tool for the synthesis of chiral compounds.[1] Organocatalytic conjugate addition of nucleophilic reagents to Michael acceptors is one of the most useful strategies.[2] A wide variety of nucleophilic reagents have been used successfully. While those nucleophilic reagents with potential Michael acceptors were adopted, cascade conjugate additions occurred and provided chiral cyclic compounds (Scheme 1, eq 1).[3,4] However, to our knowledge, the application of nucleophilic reagents with two active methylene protons in double asymmetric conjugate addition to dienones has not been developed. Such a transformation is valuable for the preparation of chiral hexanones (Scheme 1, eq 2). In previous studies, intramolecular double-conjugate additions were applied for the synthesis of polycyclic natural products.[5] Base-promoted double-conjugate additions of malononitrile, malonates, and isocyanoacetates to dienones,[6] divinyl esters,[7] and divinyl sulfone[8] were reported to give cyclic products. However asymmetric versions of the trans-

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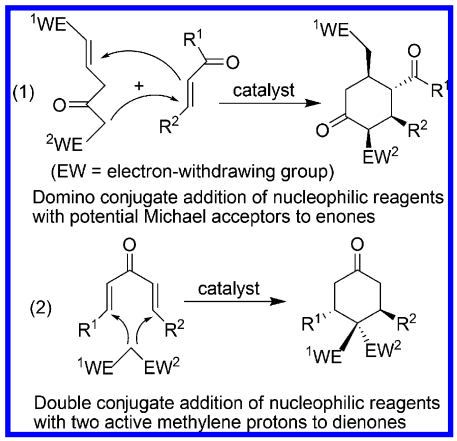
Scheme 1. Construction of Chiral Cyclic Compounds through Organocatalytic Asymmetric Conjugate Additions

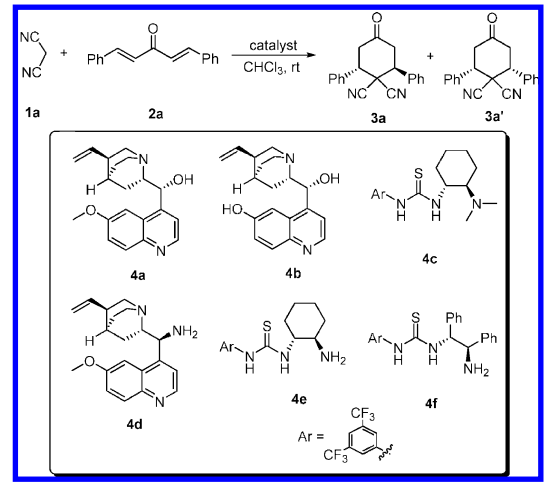


formations are still elusive. In this paper, we report our efforts in asymmetric organocatalytic double conjugate addition of malononitrile to dienones. The reaction provided 1,1,2,6-tetrasubstituted cyclohexanones in good yields and excellent enantioselectivities.

Malononitrile is an active nucleophilic reagent. It had been used in asymmetric organocatalytic conjugate additions by several research groups. Lattanzi and co-workers reported the enantioselective conjugate addition of malononitrile to chalcones.[9] Quinine was identified as the best catalyst for the reaction. Takemoto and co-workers applied chiral thiourea−tertiary amines for the conjugate addition of malononitrile to α,β-unsaturated imides.[10] Lately, Zhao and co-workers expanded Takemoto's catalyst for asymmetric conjugate addition of malononitrile to α,β-unsaturated ketoesters. 4*H*-Pyran derivatives were obtained in moderate yields and good enantioselectivities.[11] On the other hand, secondary and primary amines proved to be highly efficient catalysts for the activation of α,β-unsaturated aldehydes and ketones toward conjugate additions.[12] A LUMO lowering activation mechanism was proposed by Macmillan and other researchers. Along this road, Deng and co-workers used 9-amino-9-deoxyepiquinine as an efficient chiral catalyst for the conjugate addition of malononotrile to α,β-unsaturated ketones.[13]

Initially, we chose conjugate addition of malononitrile (**1a**) to dibenzylidene acetone (**2a**) as the model reaction. A number of organocatalysts were screened, and the results are summarized in Table 1. Quinine (**4a**) showed low catalytic

Table 1. Screening of Catalysts[a]



entry	catalyst	time (h)	yield[b] (%)	**3a/3a′**[c]	ee[d] (%)
1	**4a**	72	35	17/1	(−) 60
2	**4b**	72	37	16/1	(+) 22
3	**4c**	72	25	1/1	(−) 60
4[e]	**4d**	72	53	18/1	(+) 94
5	**4e**	72	n.r.[f]		
6	**4f**	72	n.r.		
7[g]	**4d**	48	80	6/1	(+) 96
8[h]	**4d**	48	80	20/1	(+) 99
9[i]	**4d**	48	76	19/1	(+) 96

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (0.02 mmol), and $CHCl_3$ (0.5 mL) at room temperature. [b] Isolated yields of **3a**. [c] The ratios of **3a/3a′** were determined by ^1H NMR analysis of the crude reaction mixture. [d] The ee values of **3a** were determined by chiral HPLC. [e] CF_3COOH (TFA) (0.04 mmol) was used as the additive. [f] No reaction. [g] 0.2 mmol of **2a** and 0.04 mmol of TFA were used. [h] 0.15 mmol of **2a** and 0.04 mmol of TFA were used. [i] 0.12 mmol of **2a** and 0.04 mmol of TFA were used.

activity. The desired *trans*-product **3a** was obtained in low yield and moderate enantioselectivity (Table 1, entry 1). Only a trace of *cis*-isomer **3a′** was observed. 6′-Demethylquinine (**4b**) gave **3a** in low yield and enantioselectivity (Table 1, entry 2).[14] In addition, the enantiofacial selection was reversed in comparison with quinine. Takemoto's catalyst (**4c**) was less efficient in the reaction. Low yield and moderate enantioselectivity were obtained. The diastereoselectivity was extremely low (Table 1, entry 3). To our delight, 9-amino-9-deoxyepiquinine (**4d**) provided much better results.[15] Product **3a** was obtained in moderate yield, good diastereoselectivity, and good enantioselectivity (Table 1, entry 4). Bifunctional primary amine catalysts **4e** and **4f** were completely inefficient (Table 1, entries 5 and 6),

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although **4f** was found to be an efficient catalyst for the conjugate addition of bromonitromethane to enones.[16] Interestingly, changing the ratio of **1a** to **2a** significantly affected the yield and diastereoselectivity. When 2 equiv of **2a** were used, better yield was obtained, however with inferior diastereoselectivity (Table 1, entry 7). Further studies indicated that 1.5 equiv of **2a** was optimal concerning the yield, diastereoselectivity, and enantioselectivity (Table 1, entries 8−9).

The effect of reaction solvents was also examined, and the results are summarized in Table 2 (entries 1−9).

Table 2. Effect of Reaction Conditions[a]

entry	solvent	acid	yield (%)	**3a/3a′**	ee (%)
1	$CHCl_3$	TFA	80	20/1	99
2	CH_2Cl_2	TFA	80	20/1	97
3	$(CH_2Cl)_2$	TFA	64	10/1	97
4	Et_2O	TFA	71	20/1	96
5	THF	TFA	74	10/1	97
6	PhMe	TFA	71	8/1	98
7	MeCN	TFA	60	13/1	70
8	MeOH	TFA	40	14/1	74
9	DMF	TFA	50	20/1	33
10	$CHCl_3$	PhCOOH	13	10/1	89
11	$CHCl_3$	*p*-TSA	37	7/1	95
12	$CHCl_3$	AcOH	33	5/1	90
13	$CHCl_3$	TfOH	n.r.		
14[b]	$CHCl_3$	TFA	60	17/1	90
15[c]	$CHCl_3$	TFA	68	3/1	96

[a] Reactions were performed with **1a** (0.10 mmol), **2a** (0.15 mmol), **4d** (0.02 mmol), acid (0.04 mmol), and solvent (0.5 mL) at room temperature for 48 h. [b] 20 mol % of TFA was used. [c] 60 mol % of TFA was used.

Dichloromethane provided similar result with chloroform. 1,2-Dichloroethane, ether, THF, and toluene afforded **3a** with excellent enantioselectivities, however in lower yields. More polar solvents, such as acetonitrile, methanol, and DMF, were detrimental for both the yield and enantioselectivity.

A significant effect of acid additives was observed (Table 2, entries 10−15). Benzoic acid, *p*-toluenesulfonic acid (*p*-TSA), and acetic acid (AcOH) led to low yield and inferior enantioselectivity (Table 2, entries 10−12). Trifluoromethanesulfonic acid (TfOH) generated insoluble salt with catalyst **4d** and completely inhibited the reaction (Table 2, entry 13). The use of 40 mol % of TFA was optimal for the reaction. the use of less or more TFA decreased the yield and enantioselectivity (Table 2, entries 14 and 15).

Furthermore, the reactions of penta-1,4-dien-3-ones (**2a**−**m**) with **1a** were examined, and the results are summarized in Table 3. 4-MeO-substituted dienone **2b** gave **3b** exclusively with excellent enantioselectivity (Table 3, entry 2). 4-Me-substituted dienone **2c** also

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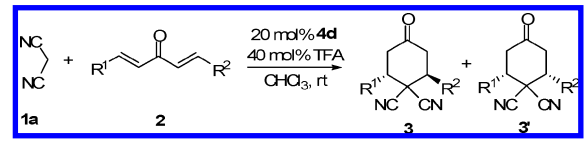
Table 3. Asymmetric Double-Conjugate Addition of Malonitrile **1a** to Penta-1,4-dien-3-ones (**2a**−**m**)[a]



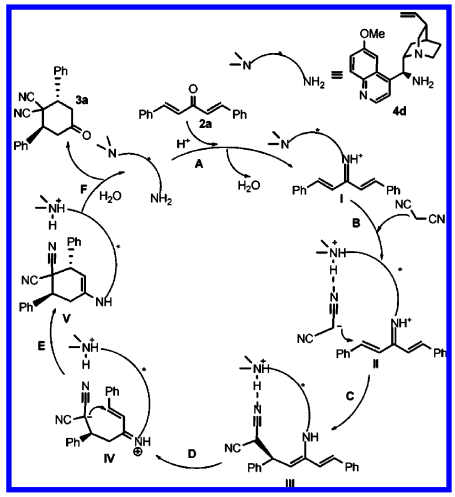
entry	**2**	time (h)	yield (%)[b]	**3/3′**[c]	ee[d] (%)
1	$R^1 = R^2 =$ Ph, **2a**	48	80	20/1	99
2	$R^1 = R^2 = p$-$OMeC_6H_4$, **2b**	48	78	>99/1	99
3	$R^1 = R^2 = p$-MeC_6H_4, **2c**	48	75	30/1	98
4	$R^1 = R^2 = p$-ClC_6H_4, **2d**	72	79	8/1	97
5	$R^1 = R^2 = p$-$CF_3C_6H_4$, **2e**	96	40	6/1	97
6	$R^1 = R^2 = p$-$NO_2C_6H_4$, **2f**	168	7	*e*	*e*
7	$R^1 = R^2 = m$-ClC_6H_4, **2g**	72	87	10/1	95
8	$R^1 = R^2 = o$-ClC_6H_4, **2h**	48	71	6/1	99
9	$R^1 = R^2 =$ furan-2-yl, **2i**	144	79	10/1	99
10	$R^1 = R^2 =$ thiophene-2-yl, **2j**	144	35	10/1	99
11	$R^1 =$ Ph, $R^2 = p$-$NO_2C_6H_4$, **2k**	36	70	4/1	98
12	$R^1 = R^2 =$ isopropyl, **2l**	48	*f*		
13	$R^1 =$ Ph, $R^2 =$ Me, **2m**	144	8	*e*	*e*

[a] Reactions were performed with **1a** (0.10 mmol), **2a**−**m** (0.15 mmol), **4d** (0.02 mmol), TFA (0.04 mmol), and $CHCl_3$ (0.5 mL) at room temperature. [b] Isolated yield of **3**. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] ee values of **3** were determined by chiral HPLC. [e] Not determined. [f] No reaction.

provided the product **3c** with excellent enantioselectivity and diastereoselectivity (Table 3, entry 3). Excellent enantioselectivity was kept for 4-Cl-substituted dienone **2d**; however, lower diastereoselectivity was observed (Table 3, entry 4). 4-Trifluoromethyl-substituted dienone **2e** provided the product **3e** in low yield and diastereoselectivity (Table 3, entry 5). 4-Nitro-substituted dienone **2f** only gave a trace of the product after 7 days (Table 3, entry 6), probably due to its extremely low solubility in chloroform. The results imply that electron-donating substitutents are favorable for both the yield and the diastereoselectivity of the reaction. *3*-Chloro and 2-chloro substitutions are well tolerated (Table 3, entries 7 and 8). The products were obtained in good yields and enantioselectivities. 1,5-Diheteroarylpenta-1,4-dien-3-ones (**2i**−**j**) are applicable in this reaction (Table 3, entries 9 and 10). After an extended reaction time, **3i** and **3j** were obtained with excellent enantioselectivities; however, the yield of **3j** was low. Unsymmetric dienone **2k** was also examined. The product **3k** was obtained in good yield and excellent enantioselectivity, but the diastereoselectivity significantly decreased in comparison with symmetric dienones (Table 3, entry 11). 1,5-Diisopropylpenta-1,4-dien-3-one **2l** was found to be unreactive (Table 3, entry 12). Unsymmetric dienones with R^1 as aromatic group and R^2 as aliphatic group, such as 1-phenylhexa-1,4-dien-3-one **2m**, was also examined. It showed very low reactivity, and only a trace of the product was obtained (Table 3, entry 13). A single crystal of product **3f** was obtained. X-ray diffraction analysis showed unambiguously (2*S*,6*S*)-configuration.[17] The enantiofacial selection is identical with the reaction of benzylidene acetone and malononitrile catalyzed by **4d**.[13]

The reaction is proposed to proceed through a stepwise mechanism (Scheme 2). The formation of iminium cation **I**

Scheme 2. Proposed Reaction Mechanism



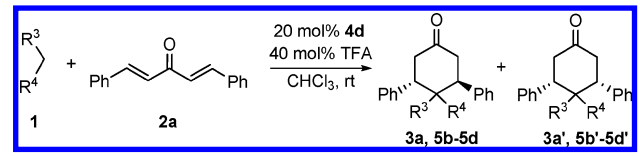
from **2a** and **4d** increases the electrophilic reactivity of **2a**. Malononitrile is deprotonated by the tertiary amine group in **4d**. The resulting ammonium cation generates a hydrogen bond with the malononitrile anion. The attack of the malononitrile anion from *re*-face of the double bond gives the intermediate **III**. The tautomerization of **III** results in a new iminium intermediate **IV**. The second conjugate addition of the malononitrile anion gives the intermediate **V**, which is hydrolyzed to provide the product **3a**. It should be noted that the enantiofacial selection of second conjugate addition is affected by both the chirality of **4d** and the first established chiral center, so the enantioselectivity is higher than the corresponding reaction of malonontrile and benzylidene acetone.[13] Monitoring the reaction mixture of **1a** and **2**a with ^{1}H NMR in $CDCl_3$ indicated the existence of only trace of single conjugate addition product. It is expected that the transformation of **IV** to **V** proceeds faster than the first conjugate addition because of its advantage of intramolecular reaction.

Besides malononitrile, several nucleophilic reagents were also examined and the results are summarized in Table 4. The reaction of ethyl nitroacetate **1b** with **2a** occurred smoothly and gave the product **5b** in good yield and excellent enantioselectivity (Table 4, entry 2). Ethyl 2-cyanoacetate **1c** gave low yield of product **5c**, but with excellent enantioselectivity (Table 4, entry 3). Nitro acetophenone **1d** was also applicable, and the yield was moderate (Table 4, entry 4). Methyl malonate **1e** and nitromethane **1f** were found to be unreactive in this reaction (Table 4, entries 5 and 6).

Product **3a** could be reduced with $NaBH_4$ according to the reported procedure.[6b] The imidic ester was formed first

(17) CCDC 795057 contains 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. An ORTEP drawing of **3f** is also provided in the Supporting Information.

Table 4. Asymmetric Double-Conjugate Addition of **1a**−**f** to **2a**[a]

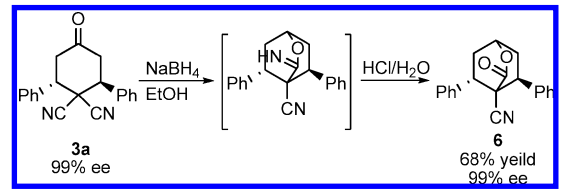


entry	R^3, R^4	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	CN, CN (**1a**)	48	**3a**, 80	20/1	99
2	NO_2, COOEt (**1b**)	48	**5b**, 76	6/1	99
3	CN, COOEt (**1c**)	72	**5c**, 41	3/1	97
4	NO_2, PhCO (**1d**)	36	**5d**, 55	3/1	*e*
5	COOMe, COOMe (**1e**)	48	*f*		
6	NO_2, H (**1f**)	48	*f*		

[a] Reactions were performed with **1a** (0.1 mmol), **2** (0.15 mmol), **4d** (0.02 mmol), TFA (0.04 mmol), and $CHCl_3$ (0.5 mL) at room temperature. [b] Isolated yields of **5**. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] ee values of the major diastereoisomers were determined by chiral HPLC. [e] Not determined. [f] No reaction.

and was hydrolyzed with aqueous hydrogen chloride to provide chiral lactone **6** (Scheme 3).

Scheme 3. Elaboration of Product **3a**



In conclusion, we have developed an asymmetric double-conjugate addition of malononitrile to dienones. Readily available 9-amino-9-deoxyepiquinine was identified as the superior catalyst. A number of 1,1,2,6-tetrasubstituted cyclohexanones were obtained in good yields, good diastereoselectivities, and excellent enantioselectivities. The results demonstrate organocatalytic asymmetric double-conjugate addition is an efficient method to prepare chiral cyclic compounds.

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Supporting Information Available: Experimental procedures, product characterization, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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