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Asymmetric Direct Vinylogous Michael Additions of Allyl Alkyl Ketones to Maleimides through Dienamine Catalysis

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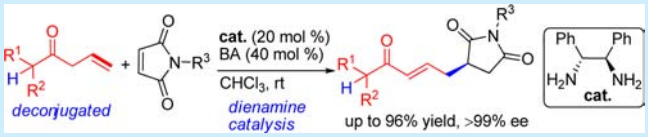
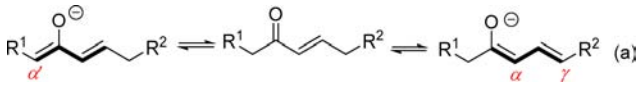
Supporting Information

ABSTRACT: A direct catalytic asymmetric γ-regioselective vinylogous Michael addition of allyl alkyl ketones to maleimides has been developed through dienamine catalysis of a simple chiral 1,2-diphenylethanediamine, giving multifunctional products in excellent enantioselectivity and with high yields. The success of this catalytic strategy relies on the unique inducing effect of deconjugated β,γ-C═C bond, which facilitates the formation of the otherwise unfavored extended dienamine species.

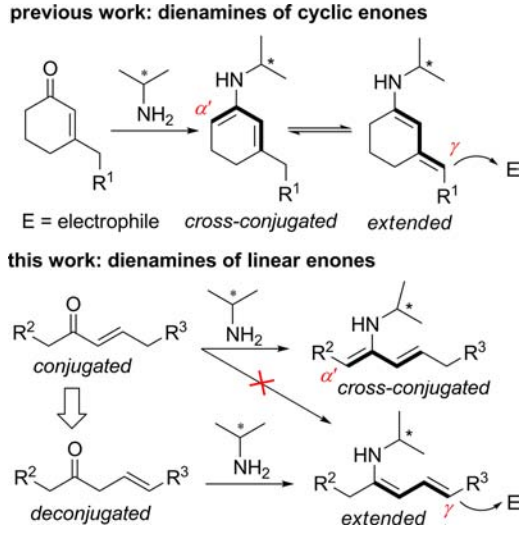


Vinylogous addition processes with unsaturated systems usually deliver extended carbon skeletons and multifunctional products in comparison with those of simple enolates; thus, efforts have been increasingly devoted to this field over the past decades.[1] Both regio- and stereoselectivity are among the most challenging problems of vinylogous reactions. Though asymmetric vinylogous reactions with previously modified Mukaiyama-type dienolates have been well investigated,[2] the corresponding direct versions would be more attractive in consideration of convenience and atom economy, and significant progress has also been made recently.[3] Nevertheless, for α,β-unsaturated ketones bearing an α′-CH group, chemists must deal with a more critical situation because there are two potential pathways of enolization and three potential nucleophilic sites in the molecules (a).[4] As a result, reports of direct asymmetric vinylogous additions of enone substrates are relatively rare. The Wang group developed stereoselective γ-functionalization of linear β,β-disubstituted α,β-unsaturated ketones by employing a chiral magnesium complex.[5] Jiang and co-workers realized the direct vinylogous aldol reaction of allyl ketones and isatins by using a bifunctional tertiary amine-thiourea catalyst,[6] but α′-substitutions were limited to non-enolizable aryl or *tert*-butyl groups.



On the other hand, dienamine catalysis has been established as a powerful protocol for the vinylogous activation of unmodified α,β-unsaturated carbonyl compounds.[7] Although cross-conjugated dienamines were preferably generated from 2-enones with a α′-CH group,[8] the Melchiorre group first succeeded in asymmetric direct vinylogous addition reactions with β-substituted 2-cyclohexenones via extended *exo*-dienamines catalyzed by a chiral primary amine (Scheme 1).[9] In contrast, cross-conjugated dienamines would be dominantly formed for linear 2-enones bearing α′-CH groups; thus, γ-regioselective vinylogous reactions of acyclic 2-enones via aminocatalysis remain to be solved. Inspired by our successful trienamine catalysis with interrupted 2,5-dienones or deconjugated 3,5-dienones,[10] we envisaged that previously positioned β,γ-C═C bond also could act as an inducing group for the formation of more stable extended dienamine species from deconjugated 3-enone substrates other than enamine inter-

Scheme 1. Dienamine Catalysis with Diverse Enone Substrates Bearing an α′-CH Group



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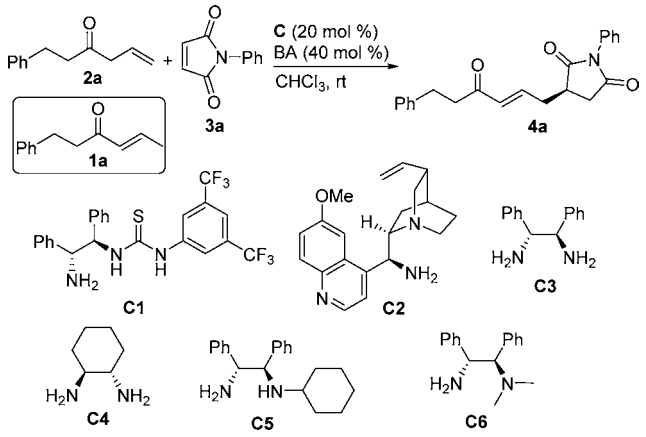
mediates, thus activating the γ-site and furnishing the following vinylogous addition process.

The initial study on the reaction of deconjugated 3-enone **2a** and *N*-phenylmaleimide[11] **3a** was not successful under the catalysis of bifunctional primary amine−thiourea compound[12] **C1** in combination with benzoic acid (BA) (Table 1, entry 1).

Table 1. Screening Conditions of Asymmetric Vinylogous Michael Addition[a]



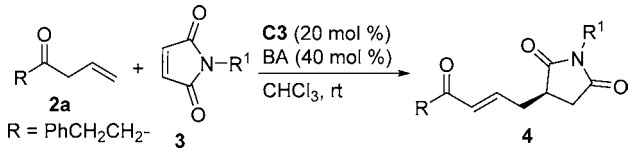
entry	cat.	solvent	acid	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**C1**	$CHCl_3$	BA	48		
2[d]	**C2**	$CHCl_3$	BA	48		
3	**C3**	$CHCl_3$	BA	24	90	>99
4	**C4**	$CHCl_3$	BA	24	88	−94
5	**C5**	$CHCl_3$	BA	24	89	99
6	**C6**	$CHCl_3$	BA	24	<20	
7	**C3**	DCM	BA	24	86	>99
8	**C3**	toluene	BA	24	76	>99
9	**C3**	THF	BA	48	29	80
10	**C3**	CH_3CN	BA	48	26	87
11	**C3**	$CHCl_3$	AcOH	24	68	94
12	**C3**	$CHCl_3$	OFBA	24	81	92
13	**C3**	$CHCl_3$	SA	24	84	>99
14	**C3**	$CHCl_3$	TsOH	24	<20	
15[e]	**C3**	$CHCl_3$	BA	36	82	>99
16[f]	**C3**	$CHCl_3$	BA	48	69	97

[a]Unless noted otherwise, reactions were performed with **2a** (0.15 mmol), **3a** (0.1 mmol), amine **C** (20 mol %), and acid (40 mol %) in solvent (0.5 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis (E/Z > 19:1 by ^{1}H NMR analysis). [d]At 50 °C. [e]With 10 mol % of **C3** and 20 mol % of BA. [f]With 5 mol % of **C3** and 10 mol % of BA at 45 °C.

9-Amino-9-deoxyepiquinine[13] **C2** also failed though it can effectively activate β-substituted cyclohexenones and furnish the γ-regioselective addition (entry 2).[9a] Pleasingly, commercially available (*R*,*R*)-1,2-diphenylethanediamine[14] **C3** exhibited high catalytic activity even at ambient temperature, and the desired γ-regioselective vinylogous Michael addition product **4a** was obtained in an enantiomerically pure form and with excellent yield (entry 3). It should be noted that the conjugated 2-enone substrate **1a** (Table 1) showed inert reactivity under the same catalytic conditions, indicating that the inducing effect of β,γ-C=C bond is crucial for the success of the current extended dienamine catalysis. (*S*,*S*)-1,2-Cyclohexanediamine **C4** also delivered good results, though a slightly lower enantioselectivity was observed (entry 4). In addition, the similar outstanding data could be obtained with amine **C5** bearing a secondary amine moiety (entry 5), while amine **C6** with a tertiary amine group still produced poor results, as that of catalyst **C2** (entry 6 vs entry 2). Moreover, other reaction parameters, such as solvents and acid additives, were investigated but generally provided inferior results (entries 7−14). Finally, it was found that the reaction could occur smoothly with 10 mol % of catalyst **C3** without affecting the enantiocontrol, while a longer time was required to gain a better conversion (entry 15). Using 5 mol % of **C3** still produced high enantioselectivity even at 45 °C, though with a modest yield after 48 h (entry 16).

Consequently, we examined the substrate scope and limitations of this new vinylogous Michael reaction. At first, different *N*-substituted maleimides **3** were investigated in reactions with 3-enone **2a** in $CHCl_3$ by the catalysis of **C3** (20 mol %) and benzoic acid (40 mol %) at room temperature. As summarized in Table 2, acceptors **3** with diverse *N*-aryl or

Table 2. Scope of Maleimides 3[a]



entry	R^1 (**3**)	time (h)	yield[b] (%)	ee[c] (%)
1	Ph (**3a**)	24	**4a**, 90	>99
2	4-Me-Ph (**3b**)	24	**4b**, 95	>99
3	4-MeO-Ph (**3c**)	24	**4c**, 90	95
4	4-Br-Ph (**3d**)	24	**4d**, 84	97
5	Bn (**3e**)	24	**4e**, 85	>99
6	Me (**3f**)	36	**4f**, 96	>99
7	H (**3g**)	48	**4g**, 92	99

[a]Reactions were performed with **2a** (0.3 mmol), **3** (0.2 mmol), amine **C3** (20 mol %), and BA (40 mol %) in $CHCl_3$ (1.0 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis (E/Z > 19:1 by ^{1}H NMR analysis).

alkyl groups could be well tolerated, and excellent results were obtained efficiently (Table 2, entries 1−6). Notably, maleimide **3g** possessing a free NH group still delivered the vinylogous adduct **4g** in 92% yield and with 99% ee, while a longer time was needed, probably due to the relatively poor solubility of **3g** in $CHCl_3$ (entry 7).

Subsequently, a series of allyl ketones bearing diversely structured α'-alkyl groups were explored in reactions with maleimide **3a**. As summarized in Table 3, a number of either linear or branched alkyl-substituted allyl ketones **2b−i** exhibited the similar high reactivity, and the corresponding vinylogous Michael adducts **4h−o** were effectively produced in excellent yields and enantioselectivity (Table 3, entries 1−8). In addition, allyl ketones **2j−l** with various benzylic substitutions showed the same γ-regioseletivity, affording products **4p−r** in remarkable data (entries 9−11).

To further demonstrate the generality of the vinylogous Michael addition through dienamine catalysis, more allyl ketones bearing various functionalized groups, such as indole, alkene, ketal, amide, or ether, were explored. As outlined in Scheme 2, all of the reactions proceeded smoothly under the established catalytic conditions, and the desired products **4s−x** were attained in high yields and with excellent enantioselectivity. It was noteworthy that an allyl crotyl substrate also

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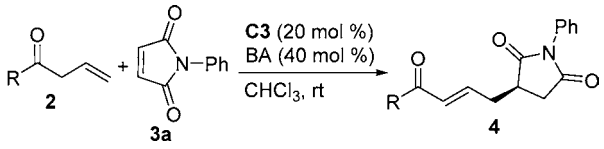
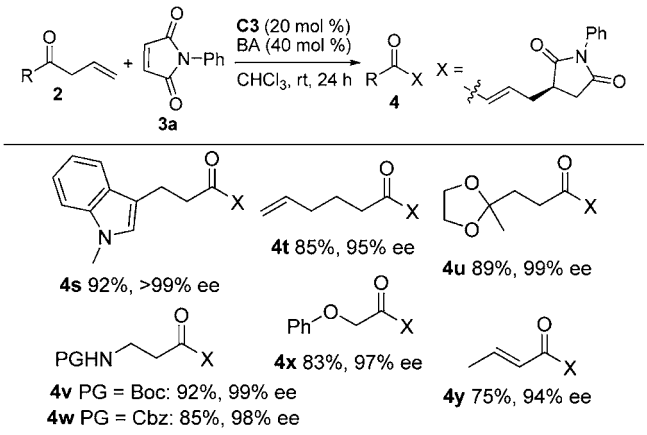
Table 3. Scope of Allyl Ketones with Diverse Alkyl Groups[a]



entry	R (2)	t (h)	yield[b] (%)	ee[c] (%)
1	*n*-C_5H_{11} (**2b**)	24	**4h**, 90	99
2	*n*-C_7H_{15} (**2c**)	24	**4i**, 95	>99
3	 (**2d**)	24	**4j**, 93	>99
4	 (**2e**)	24	**4k**, 90	>99
5	*i*-butyl (**2f**)	36	**4l**, 96	99
6	*i*-propyl (**2g**)	48	**4m**, 89	>99
7	*c*-pentyl (**2h**)	24	**4n**, 88	>99
8[d]	*c*-hexyl (**2i**)	24	**4o**, 95	>99
9	benzyl (**2j**)	24	**4p**, 92	97
10	1-naphthylmethyl (**2k**)	24	**4q**, 89	99
11	3-thienylmethyl (**2l**)	24	**4r**, 96	99

[a]Unless noted otherwise, reactions were performed with **2** (0.3 mmol), **3a** (0.2 mmol), **C3** (20 mol %), and BA (40 mol %) in $CHCl_3$ (1.0 mL) at rt. [b]Isolated yield. [c]Determined by chiral HPLC analysis (*E*/*Z* > 19:1 by ^{1}H NMR analysis). [d]Maleimide **3d** was used. The absolute configuration of enantiopure **4o** was determined by X-ray analysis. The other products were assigned by analogy.

Scheme 2. Scope of Allyl Ketones with Diverse Functionalized α′-Alkyl Groups[a]−[c]

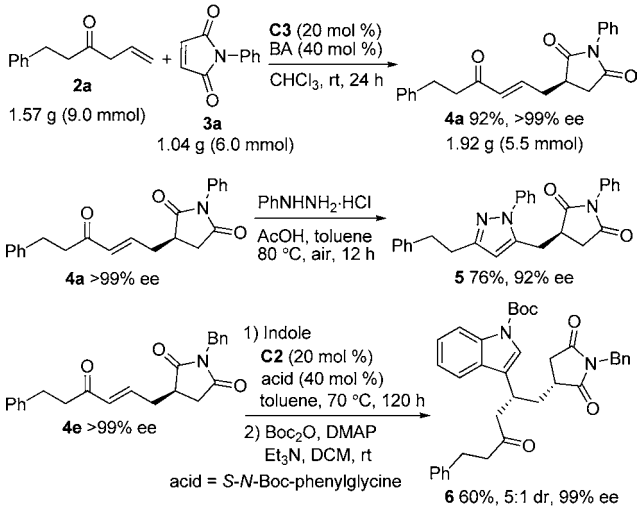


[a]Reactions were performed with **2** (0.3 mmol), **3a** (0.2 mmol), **C3** (20 mol %), and BA (40 mol %) in $CHCl_3$ (1 mL) at rt for 24−48 h. [b]Isolated yield. [c]Ee was determined by chiral HPLC analysis (*E*/*Z* > 19:1 by ^{1}H NMR analysis).

effectively produced the γ-regioselective adduct **4y** in a moderate yield and with high enantioselectivity through forming cross-conjugated trienamine intermediate.[15] Nevertheless, some alkyl ketones with other allylic groups failed to participate in reactions with maleimide **3a**.[16]

The catalytic vinylogous Michael addition of 3-enone **2a** to maleimide **3a** is highly reliable, and the same excellent results were efficiently obtained on a gram scale, as illustrated in Scheme 3. Moreover, the multifunctional features of vinylogous adducts enable further transformations to construct more

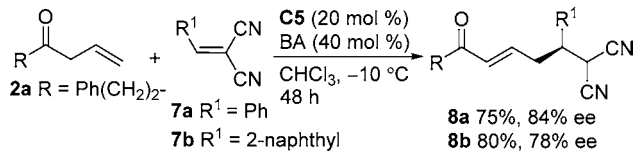
Scheme 3. Transformations of Vinylogous Adducts



complicated chiral molecules. A chiral pyrazole **5** was attained in 76% yield with a slightly decreased ee value by condensation of adduct **4a** with phenylhydrazine under air conditions.[17] In addition, amine **C2**-catalyzed Friedel−Crafts alkylation of indole with **4e** delivered **6** after *N*-protection of indole, while with a moderate dr value (Scheme 3).[18]

On the other hand, the vinylogous Michael additions of 3-enone **2a** to other electron-deficient alkenes were also explored. Alkylidenemalononitriles **7** were suitable acceptors, and better enantioselectivity was obtained at −10 °C by using amine **C5** as the catalyst (Scheme 4). Nevertheless, nitroolefins could not be successfully applied under current catalytic systems.[9a]

Scheme 4. Asymmetric Vinylogous Michael Additions to Alkylidenemalononitriles



In summary, we have developed the asymmetric direct vinylogous Michael additions of allyl alkyl ketones to maleimides through dienamine catalysis based on an inducing strategy. These reactions exhibited exclusive γ-regioselectivity, and remarkable enantioselectivity was generally achieved by using a commercially available chiral diamine as the catalyst, even at a gram scale. We believe that this catalytic strategy would enable development of more asymmetric reactions with unsaturated ketone substrates bearing enolizable α′-CH groups. More results will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products, X-ray data for enantiopure product **4o** (CIF), NMR spectra, and HPLC chromatograms. 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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