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Bifunctional 3,3′-Ph_2-BINOL-Mg Catalyzed Direct Asymmetric Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam

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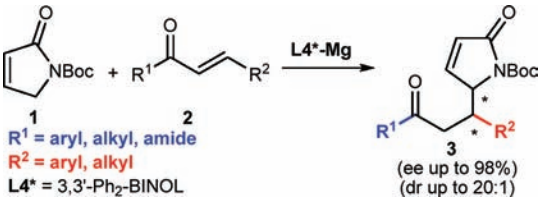
ABSTRACT



Bifunctional 3,3′-Ph_2-BINOL-Mg catalyzed direct asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam has been developed. The catalytic activity of this protocol was slightly affected by different types of Michael acceptors, such as a variety of enones as well as α,β-unsaturated *N*-acylpyrroles. The Michael products were obtained with high diastereoselectivities (up to 20:1) and excellent enantioselectivities (up to 98%).

Chiral γ-butyrolactams as well as γ-butyrolactones are present in a variety of natural products as well as bioactive compounds. These frameworks are also very important synthetic intermediates to many organic compounds. Among several of the synthetic protocols to the chiral γ-butyrolactams/lactones synthesis, the most attractive one is vinylogous addition which has always attracted chemists' interests.[1] Although asymmetric vinylogous Mukaiyama additions have been well established,[2] the more practical direct asymmetric vinylogous additions were less developed until recent years. The present reports mainly focused on the organocatalytic direct vinylogous additions.[3,4] However, these strategies seriously suffer from not only a limited substrate scope but also low catalytic activity. Most reactions always proceeded over days. In contrast, organometallic catalysis has many advantages such as being more easily tunable and exhibiting

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higher catalytic efficiency and a broader application scope.[5] B. M. Trost's group and M. Shibasaki's group have reported their pioneering works on the organometallic catalytic direct vinylogous additions to imines as well as nitroolefins, respectively. Unfortunately, enones as the more challenging substrates were not explored in these studies, maybe due to the poor reactivity as well as difficulty in stereocontrol. Besides Shibasaki's dinuclear nickel catalytic system, there were only three organocatalytic systems which were developed for the direct asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactams to α,β-unsaturated aldehydes[4f] as well as enones[4g,h] (Figure 1). It must be noted that these three organocatalysts were critically required for different Michael acceptors due to their greatly varied activity affected by the substituents of the carbonyl. Accordingly, a highly efficient bifunctional catalytic system is eagerly required.

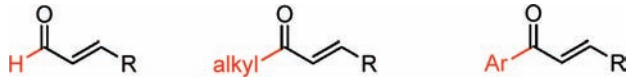
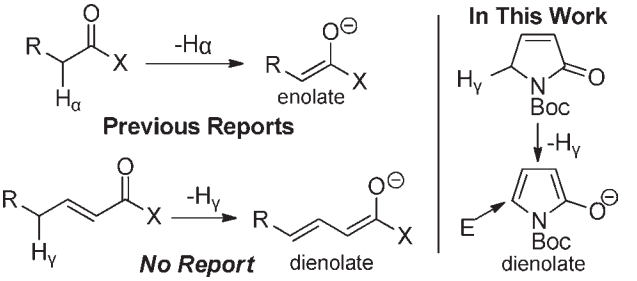


Figure 1. α,β-Unsaturated carbonyls explored in title reaction.

Unlike the transition metal, the alkaline earth metal has been well recognized for its vast abundance and being inexpensive as well as relatively nontoxic. However, application of these catalysts, especially the magnesium catalyst,[6] to novel transformations has been rarely revealed.[7] Although alkaline earth metal catalysis has received growing attention very recently, these studies mainly focused on the 1,3-dicarbonyl compound addition[8] and the activated ester-Aldol type reaction (Scheme 1).[9] In general, these processes underwent an α-deprotonation pathway, which involved deprotonating H_α of the carbonyl to generate the enolate or dienolate intermediate. Alkaline earth metal catalyzed direct γ-deprotonation of the carbonyl to generate a dienolate for related transformations still remains unexplored.[10] Herein, we report a bifunctional 3,3′-Ph_2-BINOL-Mg catalyzed direct asymmetric vinylogous Michael addition of α,β-unsaturated γ-butyrolactam to a variety of enones and α,β-unsaturated *N*-acylpyrrole.

Scheme 1. Alkaline Earth Metal Catalyzed Enolate Addition



Primarily, alkoxyl alkaline earth metals in combination with various BINOL derivatives were explored in the direct asymmetric vinylogous addition of α,β-unsaturated γ-butyrolactone. However, these catalysts displayed very poor catalytic activity as well as stereoselectivity, which might be caused by the nature of the reactants and the intermediates (Figure 2). First, the alkoxyl alkaline earth metals were moisture and air sensitive. This led to poor repetition either for the reaction activity or for the reaction stereoselectivity. Second, the rotatable monochelated bond in the generated complex **A** might lead to difficulty in stereocontrol. While using an α,β-unsaturated γ-butyrolactam with an *N*-Boc protection group, stereocontrol would be much more favorable with the contribution of the bidentate chelation between the intermediate and the catalyst in complex **B**. Thereby, *N*-Boc-α,β-unsaturated γ-butyrolactam **1** was exploited in the subsequent investigation.

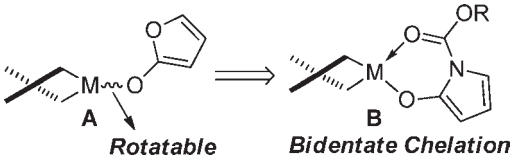


Figure 2. Reaction intermediate of γ-butyrolactone (**A**) vs γ-butyrolactam (**B**).

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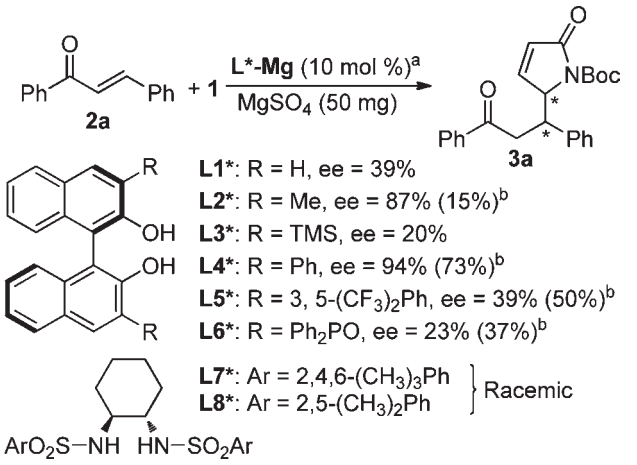
Scheme 2. Ligand Screening for the Model Addition[a]



[a] The reactions were carried out with **1** (0.24 mmol, 1.2 equiv) and **2a** (0.2 mmol) in 1 mL DCM at 0 °C overnight. (a) Prepared *in situ* by stirring 1:1 of **L*** and Bu_2Mg (1 M in heptane) for 2 h in 1 mL solvent. (b) ee value in parentheses referred to the reaction carried out in toluene.

Although the BINOL–metal complex has been widely used in asymmetric catalysis, applications of the typical BINOL-Mg were less disclosed.[11] This type of complex can be easily obtained by combining *in situ* the ligand and Bu_2Mg. Using $MgSO_4$ as the additive, a series of BINOL derivatives and disulfonamides was explored in the model reaction with results summarized in Scheme 2. Generally speaking, 3,3′-substituted BINOL exhibited different catalytic activities with an obvious solvent effect. The enantioselectivity of the model reaction decreased sharply by changing the 3,3′-substituents of the BINOL derivatives with either larger or smaller groups. An excellent ee (94%) for **3a** was observed under the catalysis of an **L4***–Mg complex. Unfortunately, disulfonamide–Mg complexes[12] did not work in controlling the stereoselectivity of the model reaction.

The solvent effect as well as additive effect was further studied in more detail (Table 1). It was found that the enantioselectivity of the model reaction was not well repeated when using $MgSO_4$ as the additive due to its moisture sensitivity. More easily handled 4 Å molecular sieve was used instead of $MgSO_4$, and the reaction gave a higher enantioselectivity (entry 2 vs 1). The enantioselectivity of the model reaction was intensively affected by using ether solvent due to its negative coordination with the magnesium (entry 4). Chloride hydrocarbon solvents were more favorable. The highest enantioselectivity (ee up to 94%) was observed while the model reaction was carried out in DCM (entry 7). Lowering the reaction temperature to −40 °C caused a sharp decrease of the reaction enantioselectivity (only 10% ee) (entry 8). The ee value of **3a** also decreased markedly to 80% while reducing the catalyst loading to 5 mol % (entry 9).

Table 1. Reaction Condition Optimization of Model Reaction[a]

entry	**L4*-Mg** (mol %)[b]	additive[c]	solvent	ee (%)[d]
1	10	$MgSO_4$	Tol	73
2	10	4 Å MS	Tol	89
3	10	4 Å MS	Xylene	84
4	10	4 Å MS	THF	78
5	10	4 Å MS	$CHCl_3$	90
6	10	4 Å MS	DCE	88
7	10	4 Å MS	DCM	94
8	10	4 Å MS	DCM	10[e]
9	5	4 Å MS	DCM	80

[a] Unless otherwise noted, reactions were carried out with **1** (0.24 mmol, 1.2 equiv) and **2a** (0.2 mmol) in 1 mL of solvent at 0 °C overnight (about 8 h). [b] Prepared *in situ* by stirring 1:1 of **L4*** and Bu_2Mg (1 M in heptane) for 2 h in 1 mL of solvent. [c] 50 mg of the freshly dried $MgSO_4$ or 4 Å MS were used. [d] Determined by HPLC analysis. [e] Reaction was performed at −40 °C.

Under the optimal conditions, varieties of aryl enones were compatible with the present protocol. The reaction activity as well as the enantioselectivtiy was minimally affected by either the aryl substituents of the carbonyl or the γ-aryl substituents of the enone (Table 2). Either electron-deficient or electron-rich γ-aryl substituted **2** could be transferred to **3** favorably with ee up to 98% and dr up to over 20:1. With a γ-(*o*-substituted)-phenyl substituent, hindered enones underwent the direct asymmetric vinylogous Michael addition successfully to afford products **3** with 92–95% ee, respectively (entries 2, 5, 7). The Michael addition of γ-butyrolactam **1** to γ-(4-CN-phenyl) substituted **2k** afforded **3k** with an excellent ee up to 98% (entry 11). Either α- or β-naphthyl substituted **2** also proceeded favorably to give **3l**–**m** with a high ee of 91% and 93%, respectively (entries 12–13). With *p*-substituted-phenyl substituents, adducts **3o**–**p** were obtained with excellent ee values of 91% and 97% (entries 15–16). Even heteroaromatic substituted **3q** was also favorably afforded with a high yield of 81% and 94% ee (entry 17). The relative configuration of **3** was confirmed by comparison with the literature ^1H NMR spectra, and the absolute configuration of **3** was confirmed by comparison with the literature optical rotation.[4h]

It was well recognized that either the substituent of the carbonyl or γ-substituent of the enone significantly affected the reactivity of the enone substrate, which is the main limitation in the reported catalytic systems. However, we were very pleased to find that our present protocol is

(10) Generation of dienolate *via* an alkaline-earth metal catalyzed α-deprotonation pathway was reported: (a) Yamaguchi, A.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 3387. (b) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842.

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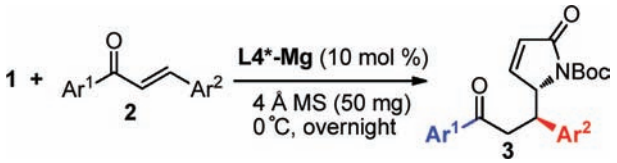
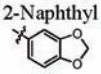
Table 2. Catalyzed Direct Asymmetric Vinylogous Michael Addition of α,β-Unsaturated γ-Butyrolactam to Aryl Enones[a]



entry	Ar^1	Ar^2	product[b]	yield[c]	dr[d]	ee[e]
1	Ph	Ph	**3a**	83%	10:1	94%
2	Ph	2-MeO-Ph	**3b**	85%	>20:1	95%
3	Ph	3-MeO-Ph	**3c**	78%	>20:1	92%
4	Ph	4-MeO-Ph	**3d**	91%	12:1	97%
5	Ph	2-F-Ph	**3e**	72%	>15:1	92%
6	Ph	4-F-Ph	**3f**	94%	>15:1	92%
7	Ph	2-Cl-Ph	**3g**	82%	>15:1	92%
8	Ph	4-Cl-Ph	**3h**	85%	>15:1	92%
9	Ph	3-Me-Ph	**3i**	74%	>15:1	97%
10	Ph	4-Br-Ph	**3j**	81%	>15:1	95%
11	Ph	4-CN-Ph	**3k**	86%	8:1	98%
12	Ph	1-Naphthyl	**3l**	88%	8:1	91%
13	Ph	2-Naphthyl	**3m**	76%	7:1	93%
14	Ph		**3n**	87%	>15:1	93%
15	4-Br-Ph	Ph	**3o**	89%	>15:1	91%
16	4-Me-Ph	Ph	**3p**	80%	>15:1	97%
17	2-Furyl	Ph	**3q**	81%	>15:1	94%

[a] **L4*-Mg** was prepared *in situ* by stirring **L4*** (10 mol %) and Bu_2Mg (10 mol %, 1 M in heptane) for 2 h in 1 mL of DCM before **1** (0.24 mmol, 1.2 equiv) and **2** (0.2 mmol) being added. Then the reaction was performed at 0 °C overnight (about 8 h). [b] The absolute configuration of **3** was confirmed by comparison with literature ^{1}H NMR spectra and optical rotation.[4h] [c] Isolated yield of the major diastereomer. [d] Determined by ^{1}H NMR analysis of the crude product. [e] Determined by HPLC analysis.

also applicable to different Michael acceptors possessing a similar nature to enone (Figure 3). It is noteworthy that direct asymmetric vinylogous Michael addition of **1** to an inert aliphatic enone afforded **3r** with a very high ee of 92% and a moderate yield of 62%. Replacing the γ-aryl moiety with a methyl group resulted in the enantioselectivity of the catalytic process dramatically decreasing to a moderate level, and only 54% ee for **3s** was observed. This may be because it is too hard for the intermediate to construct a highly selective chiral center with the aid of a γ-methyl group of the enone that is too small. It was of great significance to find that α,β-unsaturated *N*-acylpyrrole is also a compatible substrate to the catalytic system.[13] The Michael adduct **3t** was favorably afforded with a high ee of 92%. Moreover, the versatile **3t** possessed far more synthetic utilities due to the *N*-acylpyrrole being easily transformed into esters, acids, and amides.

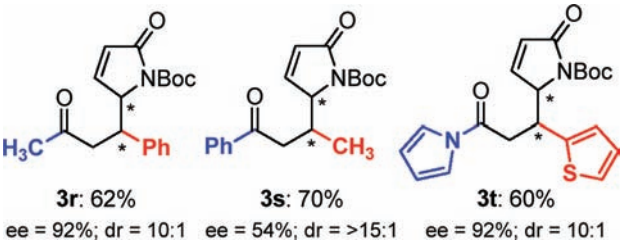


Figure 3. Versatility of the present protocol.

In summary, we developed direct asymmetric vinylogous Michael additions of α,β-unsaturated γ-butyrolactams using a bifunctional 3,3′-Ph_2-BINOL-Mg catalyst. The addition to a variety of enones afforded the products with high yields (70−94%), high diastereoselectivities (up to over 20:1), and excellent enantioselectivities (up to 98%). The stereoselectivity of the reaction was slightly affected by the substituent of the enone carbonyl but highly affected by its γ-substituent. We also disclosed the first highly enantioselective direct vinylogous Michael addition of α,β-unsaturated γ-butyrolactams to α,β-unsaturated *N*-acylpyrroles. The versatility of the *N*-acylpyrrole moiety makes this protocol a powerful tool for synthetic chemistry as well as new drug discovery. Further investigation of the present bifunctional catalyst in bioactive compound synthesis is underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectral data for isolated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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