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Magnesium(II)-Binaphtholate as a Practical Chiral Catalyst for the Enantioselective Direct Mannich-Type Reaction with Malonates

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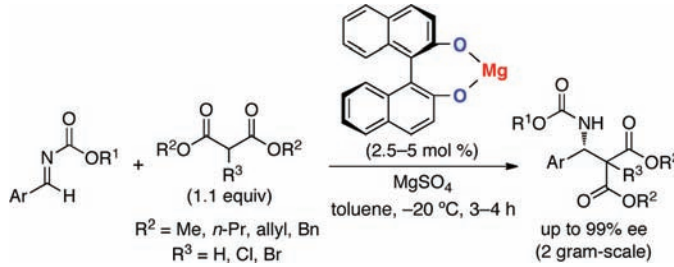
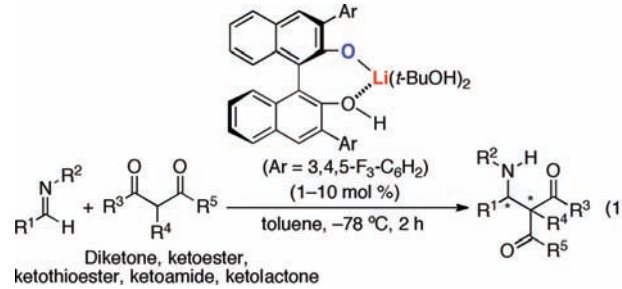
ABSTRACT



A highly enantioselective direct Mannich-type reaction of aldimines with dialkyl malonates was developed with the use of a Mg(II)-BINOLate salt, which was designed as a cooperative acid—base catalyst that can activate both aldimines and malonates. Optically active β-aminoesters and α-halo-β-aminoesters could be synthesized in high yields and with high enantioselectivities. This inexpensive and practical Mg(II)-BINOLate salt could be used in gram-scale catalysis.

A catalytic enantioselective direct Mannich-type reaction between aldimines and carbonyl compounds is highly useful for the synthesis of chiral building blocks of β-amino carbonyl compounds.[1] As a result of the importance of these enantioenriched derivatives, particularly in biological and pharmaceutical chemistry, over the past decade considerable effort has been devoted to establishing a methodology for the direct Mannich-type reaction with chiral metal catalysts[2] or organocatalysts.[3] In this regard, we have recently developed chiral Li(I)-BINOLate [BINOL = 1,1′-bi-2-naphthol] salts[4] as effective acid—base catalysts[5] for the direct Mannich-type reaction with 1,3-diketone, 1,3-ketoester, 1,3-ketolactone, 1,3-ketothioester, and 1,3-ketoamide (eq 1).[6] However, less-reactive malonates could not be used in the Li(I)-catalysis, unlike other favored 1,3-dicarbonyl compounds.



Among 1,3-dicarbonyl compounds, the inherent difficulty of the direct Mannich-type reaction with malonates[2a,d,e,3c−f,i,l] is due to their weak acidity[7] and stronger chelation to the metal center without the generation of an activated metal-

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Figure 1. Expected Mg(II)-malonate BINOLate salt in situ.

enolate. To overcome these problems, we designed a cooperative acid−base catalyst with divalent group II elements. In particular, an uncommon but easily prepared chiral Mg(II)-BINOLate salt[8,9] is attractive because it should have enough Brønsted basicity to generate Mg(II)-enolate in situ without the release of BINOL (Figure 1). Therefore, when this cooperative acid−base Mg(II)-salt catalyst activates both aldimine and malonate, a *divalent* Mg(II) center would be firmly bound to both BINOL and malonate through ionic and coordinate bonds. In sharp contrast to previous metal catalysts and organocatalysts, we report here that the extremely simple and inexpensive Mg(II)-BINOLate salt is highly effective for the catalytic enantioselective direct Mannich-type reaction of aldimines with dialkyl malonates. Smooth conversion was established within 3−4 h at −20 °C with the use of a smaller amount of catalyst loading (2.5−5 mol %) of the Mg(II)-BINOLate salt compared to the reactions with many previous catalysts, which often needed a catalyst loading of 10−20 mol % and/or a longer reaction time (sometimes >12 h).[2a,d,e,3c−f,i,l]

First, we examined the enantioselective direct Mannich-type reaction of aldimine **1a** with dimethyl malonate (**2a**) (Table 1).

Table 1. Screening of Catalysts

entry	MX (mol %)	conditions	yield (%)	ee (%)
1[a]		rt, 24 h	0	
2	*n*-BuLi (5)	−40 °C, 6 h	<3	
3[b]	*n*-BuLi (5) + *t*-BuOH (10)	−40 °C, 6 h	98	0
4	*n*-BuLi (10)	−40 °C, 6 h	>99	28
5[b]	*n*-BuLi (10) + *t*-BuOH (20)	−40 °C, 6 h	99	0
6	*n*-Bu_2Mg (2.5)	−40 °C, 6 h	14	
7	*n*-Bu_2Mg (5)	−40 °C, 6 h	98	92
8	*n*-Bu_2Mg (10)	−40 °C, 6 h	97	80

[a] 5 mol % of (*R*)-BINOL was used without a metal complex. [b] In the absence of $MgSO_4$.

As expected, the exclusive use of (*R*)-BINOL without a metal precursor did not promote the reaction, even at room temperature for 24 h (entry 1). Unlike in the reaction with diketones, ketoesters, etc.,[6] lithium salts of (*R*)-BINOL (5 mol %) in the presence of *t*-BuOH (10−20 mol %) showed low enantioselectivity for **3a** despite high reactivity at −40 °C for 6 h (entries 3 and 5). However, a *dry* dilithium salt of (*R*)-BINOL (5 mol %) in the absence of *t*-BuOH improved the enantioselectivity up to 28% ee (entry 4), whereas a corresponding monolithium salt scarcely provided **3a** (entry 2).[10] In sharp contrast, *dry* magnesium salts of (*R*)-BINOL greatly improved the enantioselectivity of **3a**. After optimization of the amount of *n*-Bu_2Mg (entries 6− 8), (*R*)-**3a** was obtained in 98% yield with 92% ee when 5 mol % each of (*R*)-BINOL and *n*-Bu_2Mg were used in the presence of $MgSO_4$[11] (entry 7). Interestingly, modification of the skeleton of (*R*)-BINOL (e.g., substitution at the 3,3′-positions, etc.) gave **3a** in low reactivity and/or low enantioselectivity. Therefore, to our delight, we selected simple and inexpensive nonmodified (*R*)-BINOL for subsequent experiments.

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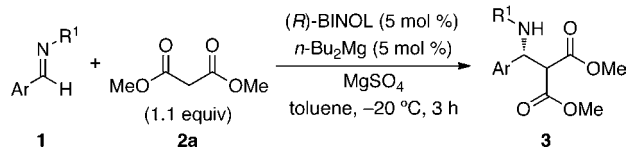
(10) During the preliminary investigation with lithium salt catalysts, we found that previously optimized 3,3′-(3,4,5-$F_3C_6H_2$)$_2$-BINOL did not promote the reaction between **1a** and **2a** at −78 to −20 °C. Also see ref 6.

(11) $MgSO_4$ was not an actual source of the catalyst. While it was not essential, it was used as a drying agent to remove adventitious water in situ. Powdered MS 4Å was also effective in place of $MgSO_4$.

Table 2. Direct Mannich-Type Reaction with *N*-Boc Aldimines and Dimethyl Malonate



1 **2a** **3**

entry	1	Ar	R^1	3	yield (%)	ee (%)
1	**1a**	Ph	CO_2t-Bu (Boc)	**3a**	>99	92
2	**1b**	Ph	CO_2Bn (Cbz)	**3b**	98	81
3	**1c**	4-ClC_6H_4	Boc	**3c**	98	93
4	**1d**	3-MeC_6H_4	Boc	**3d**	94	87
5	**1e**	3,4-(MeO)$_2C_6H_3$	Boc	**3e**	55, [91][a]	87, [90][a]
6	**1f**	2-furyl	Boc	**3f**	>99	90
7	**1g**	3-thienyl	Boc	**3g**	>99	95
8	**1h**	3-pyridyl	Boc	**3h**	>99	89
9	**1i**	1-naphthyl	Boc	**3i**	98	88

[a] 5 mol % of (*R*)-BINOL and 7.5 mol % of *n*-Bu$_2$Mg were used.

We further found that the reactions proceeded at −20 °C for 3 h without any loss of enantioselectivity (Table 2). With regard to the protecting group in the *N*-moiety of aldimines, *tert*-butoxycarbonyl (Boc) showed better enantioselectivity than benzyoxycarbonyl (Cbz) (entries 1 and 2). A variety of aryl aldimines with an electron-withdrawing or electron-donating group and heteroaryl aldimines could be applied, and the desired products **3c**−**i** were obtained in high yields and with high enantioselectivities (entries 3−9).[12] For **1e** with a 3,4-(MeO)$_2C_6H_3$ moiety, an optimal 1/1 ratio of (*R*)-BINOL/*n*-Bu$_2$Mg (5 mol % each) provided **3g** in moderate yield (55%) (entry 5). Interestingly, however, a slight excess of *n*-Bu$_2$Mg (7.5 mol %) to (*R*)-BINOL (5 mol %) improved the yield and enantioselectivity (91% with 90% ee) (entry 5, data in brackets). A chelatable moiety such as an *o*-dimethoxy group may partially ligate the Mg(II) center, and this may prevent the generation of the active catalyst.

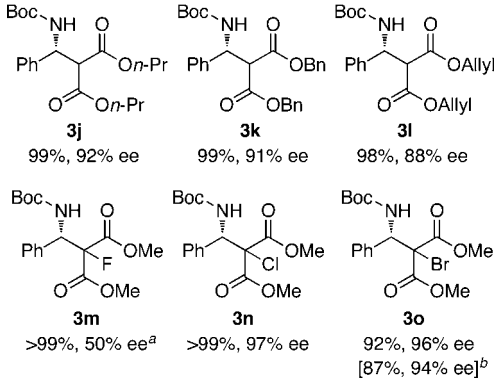
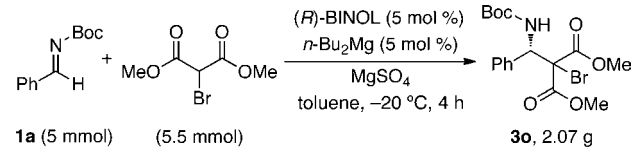


Figure 2. Scope of malonates. The reactions were performed in toluene at −20 °C for 3 h in the presence of 5 mol % each of (*R*)-BINOL and *n*-Bu$_2$Mg, unless otherwise noted. (a) Yield and enantioselectivity when 10 mol % each of (*R*)-BINOL and *n*-Bu$_2$Mg were used. (b) Yield and enantioselectivity when 2.5 mol % of (*R*)-BINOL and 3.75 mol % of *n*-Bu$_2$Mg were used.

We next explored the scope of malonates (Figure 2). Not only dimethyl malonate (**2a**) but also di(*n*-propyl) malonate, dibenzyl malonate, and diallyl malonate were applied successfully, and the corresponding products were obtained from **1a** in almost quantitative yields with 88−92% ee (see **3j**−**l**). The reaction of dimethyl α-halomalonates was also examined.[13] Although dimethyl 2-fluoromalonate gave the corresponding adduct (**3m**) with moderate enantioselectivity (50% ee), the reaction of dimethyl 2-chloromalonate and dimethyl 2-bromomalonate proceeded smoothly with the formation of a chiral quaternary carbon center, and the desired α-halo-*β*-aminoesters (**3n** and **3o**) were obtained in high yields (92−>99%) and with high enantioselectivities (96−97% ee). The reaction proceeded smoothly even in the presence of 2.5 mol % of (*R*)-BINOL and 3.75 mol % of *n*-Bu$_2$Mg,[14] and **3o** was obtained in 87% yield with 94% ee.

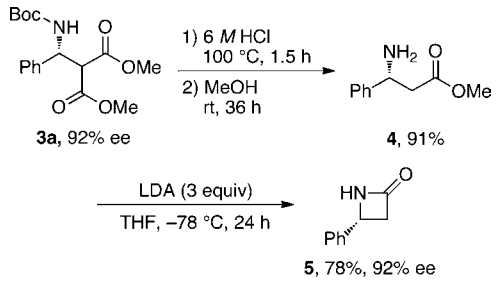
To evaluate the tolerance of this catalyst, a 2-g-scale (5 mmol) synthesis of **3o** was examined in the reaction of **1a** with dimethyl 2-bromomalonate (Scheme 1). The reaction proceeded smoothly with the use of 5 mol % each of (*R*)-BINOL and *n*-Bu$_2$Mg in toluene at −20 °C for 4 h, and the desired product (**3o**) was obtained in quantitative yield (>99%) with 99% ee.

Scheme 1. Catalytic Gram-Scale Synthesis of Mannich Adduct



With regard to the utility of the resulting Mannich product, we transformed **3a** (92% ee) to the corresponding *β*-lactam **5** (Scheme 2).[15,16] Without any loss of enantioselectivity

Scheme 2. β-Lactam Synthesis



(92% ee), β-phenyl-substituted β-lactam **5** was obtained in 71% yield in three steps via the synthetically useful optically active β-aminoester (**4**).

In summary, we have developed a catalytic enantioselective direct Mannich-type reaction of aldimines with dialkyl malonates in the presence of a simple Mg(II)-BINOLate salt. Smooth conversion was established within 3−4 h at −20 °C with 2.5−5 mol % catalyst loading of the Mg(II)-BINOLate salt. This was in sharp contrast to the reactions with previous catalysts, which often needed 5−10 mol % loading and a longer reaction time. Although a mechanistic investigation of the actual catalysts (Brønsted acid−Brønsted base or Lewis acid−Brønsted base) will be necessary in the future, this inexpensive and practical Mg(II)-BINOLate salt catalyst should be highly attractive in academic and industrial process chemistry. Further applications of BINOL-alkali and alkaline earth metal (group I and II elements) complexes to other catalytic enantioselective reactions are now underway.

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Supporting Information Available: Experimental procedures, spectral data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The compatibility of this catalysis with aliphatic aldimines would need further examinations due to their lower reactivity. However, we examined the preliminary reaction of PMPN=CCO_2Et (PMP = *p*-methoxyphenyl) as a non-aromatic aldimine with dimethyl 2-bromomalonate, and the corresponding product was obtained in 81% yield with 60% ee.

(13) Recently, some research groups have reported the catalytic asymmetric direct Mannich-type reaction with 2-halo-1,3-dicarbonyl compounds. See refs 2f and 3j−l

(14) Poor conversion (<5%) was observed when 2.5 mol % each of (*R*)-BINOL and *n*-Bu_2Mg were used, probably due to the incomplete formation of Mg(II)-BINOLate salt.

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