

Chiral Lithium(I) Binaphtholate Salts for the Enantioselective Direct Mannich-Type Reaction with a Change of Syn/Anti and Absolute Stereochemistry

Manabu Hatano,[†] Takahiro Horibe,[†] and Kazuaki Ishihara^{*,†,‡}

Graduate School of Engineering, Nagoya University, and CREST, Japan Science and Technology Agency (JST), Furo-cho, Chikusa, Nagoya 464-8603, Japan

Received November 21, 2009; E-mail: ishihara@cc.nagoya-u.ac.jp

Acid–base combination chemistry, particularly with the use of chiral 1,1'-bis(2-naphthol) (BINOL) derivatives, has been widely accepted as an important concept in modern asymmetric catalysis.^{1,2} Chiral Li(I) BINOLate salts³ are among the simplest acid–base bifunctional catalysts, and Holmes and Kagan⁴ developed the trimethylsilylcyanation of aldehydes with the use of *dry* chiral Li(I) BINOLate salts. Later, we reported that *wet* or *alcoholic* Li(I) BINOLate salts showed dramatically improved catalytic activity as Lewis acid–Lewis base catalysts for trimethylsilylcyanation by activating both an aldehyde and Me₃SiCN.⁵ By taking advantage of the strong basicity of naphtholate oxygen, Li(I) BINOLate salts should be good Lewis acid–Brønsted base catalysts, which activate both a substrate and an acidic pronucleophile. In this paper, we describe a highly diastereo- and enantioselective direct Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds that involves a change of syn/anti and absolute stereochemistry, with the use of Li(I) BINOLate salts as the simplest chiral acid–base catalysts.

First we examined the enantioselective direct Mannich-type reaction of aldimine **1a** with acetylacetone (**2**) (Table 1).^{6,7} Mono- and dilithium salts of (*R*)-BINOL (5 mol %) gave (*R*)-**3** with poor enantioselectivities (entries 1 and 2). The monolithium salt of (*R*)-3,3'-Ph₂-BINOL improved the enantioselectivity to 38% ee (entry 3). The addition of *t*-BuOH significantly improved the catalytic activity, and (*R*)-**3** was obtained in 93% yield with 82% ee (entry 4). Moreover, the monolithium salt of (*R*)-3,3'-(3,4,5-F₃-C₆H₂)₂-BINOL (**4**) with *t*-BuOH was found to be more effective, and the catalyst loading could be decreased to 2.5 mol % (entries 5 and 6).

Table 1. Screening of Li(I) BINOLate Salts

entry	BINOL [mol %]	<i>n</i> -BuLi (mol %)	<i>t</i> -BuOH (mol %)	yield (%)	ee (%)
1	(<i>R</i>)-BINOL [5]	5	0	72	8
2	(<i>R</i>)-BINOL [5]	10	0	18	0
3	(<i>R</i>)-3,3'-Ph ₂ -BINOL [5]	5	0	40	38
4	(<i>R</i>)-3,3'-Ph ₂ -BINOL [5]	5	10	93	82
5	4 [5]	5	10	>99	80
6	4 [2.5]	2.5	5	>99	82

Under the optimized conditions using **4**, we next examined the reaction of a cyclic ketoester (**5**) with a variety of aryl aldimines with an electron-withdrawing or electron-donating group (**1a–f** and **1i**) and with heteroaryl aldimines (**1g** and **1h**) (Table 2). The reactions proceeded smoothly at –78 °C within 2 h, and the desired products **6** were obtained in high yields with high diastereoselectivities (syn/anti = 88:12–97:3). High enantioselectivities (87–95% ee) were observed

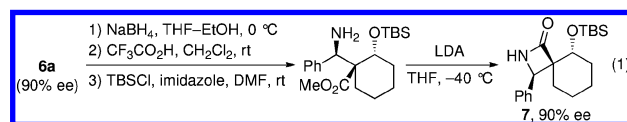
Table 2. Syn- and Enantioselective Reaction of **1** with **5**

entry	1	(<i>R</i> , Ar)	product	yield (%)	dr (syn/anti)	ee (%) ^a
1	1a	(Boc, Ph)	6a	98	88:12	91
2	1b	(Boc, 3-MeC ₆ H ₄)	6b	93	88:12	93
3	1c	(Boc, 4-MeC ₆ H ₄)	6c	93	88:12	93
4	1d	(Boc, 4-MeOC ₆ H ₄)	6d	95	96:4	95
5	1e	(Boc, 4-ClC ₆ H ₄)	6e	94	96:4	90
6	1f	(Boc, 2-Naph)	6f	96	91:9	91
7	1g	(Boc, 2-furyl)	6g	>99	95:5	87
8	1h	(Boc, 3-thienyl)	6h	>99	97:3	95
9 ^b	1a	(Boc, Ph)	6a	97	90:10	84
10 ^c	1a	(Boc, Ph)	6a	71	88:12	95
11 ^d	1a	(Boc, Ph)	6a	96	92:8	90
12	1i	(Cbz, Ph)	6i	91	95:5	87

^a Values are for *syn*-**6**. ^b **4** (1 mol %), *n*-BuLi (1 mol %), and *t*-BuOH (2 mol %) were used. ^c **4** (5 mol %), *n*-BuLi (5 mol %), and *t*-BuOH (10 mol %) were used. The reaction time was 3 min. ^d LiOH (2.5 mol %) was used in place of *n*-BuLi and *t*-BuOH.

for *syn*-**6** as the major product, with the formation of a chiral quaternary carbon center (entries 1–8). A catalyst loading of 1 mol % was still effective, and **6a** was obtained in 97% yield with high diastereo- and enantioselectivity (entry 9). Since the observed turnover frequency was 284 h^{–1} (71% yield at 3 min) (entry 10), the high reactivity of this catalyst is quite unlike those of other previous catalysts.^{6,7} Moreover, another advantage is that inexpensive LiOH can be used as the lithium precursor in place of *n*-BuLi/*t*-BuOH (entry 11). When *N*-Cbz-aldimine **1i** was used, *syn*-**6i** was obtained as the major product with 87% ee (entry 12). Notably, we found that a dramatic changeover of the absolute configuration at the amino carbon center took place in going from **3** to **6** (see below).

To demonstrate the synthetic utility of this approach, adduct **6a** (90% ee) was transformed to the useful spiro β-lactam **7** with three consecutive chiral carbon centers in a highly diastereo- and enantioselective manner (eq 1):



Furthermore, we explored the scope of the diastereo- and enantioselective direct Mannich-type reaction with a class of 1,3-dicarbonyl compounds (Table 3). Consequently, the Li(I) BINOLate salt was shown to be one of the most efficient catalysts and, unlike previous catalysts, showed high catalytic activity (at –78 °C within 2 h) toward cyclic and acyclic 1,3-dicarbonyl compounds. Cyclic ketoesters, acyclic ketoesters, a ketothioester, and a ketoamide gave the corresponding

[†] Nagoya University.[‡] Japan Science and Technology Agency.

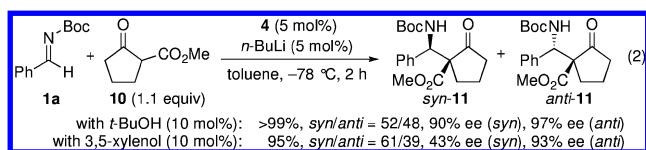
Table 3. Diastereo- and Enantioselective Reaction

product (9),	yield,	diastereoselectivity,	and enantioselectivity
	96%		
<i>syn/anti</i> = 96/4			97% ee (<i>syn</i>)
	94%		
<i>syn/anti</i> = 96/4			97% ee (<i>syn</i>)
	>99%		
<i>syn/anti</i> = 97/3			88% ee (<i>syn</i>)
	97%		
<i>syn/anti</i> = 5/95			85% ee (<i>anti</i>)
	>99%		
<i>syn/anti</i> = 4/96			91% ee (<i>anti</i>)
	97%		
<i>syn/anti</i> = 10/90			86% ee (<i>anti</i>)
	97%		
<i>syn/anti</i> = 4/99			84% ee (<i>anti</i>)
	93%		
<i>syn/anti</i> = 9/91			97% ee (<i>anti</i>)
	>99%		
<i>syn/anti</i> = 39/61			41% ee/85% ee
	97% ^b		
<i>dr</i> = 61/39			82% ee/99% ee
	90%		
<i>syn/anti</i> = 88/12			93% ee (<i>syn</i>)

^a Using 10 mol % catalyst. ^b The temperature was -40°C .

products (**9a–h**) with high enantioselectivities (85–97% ee).⁹ Notably, anti products (**9d–h**) were selectively obtained from acyclic reagents without epimerization at the α - 3° -carbon center, and these are valuable since previous catalysts often gave *syn/anti* mixtures or the stereochemistry has not yet been determined.^{6,7} A ketolactone and a cyclic diketone also gave the adducts (**9i** and **9j**) in high yields with up to 99% ee. From an S-heterocyclic ketoester, the desired adduct (**9k**) was obtained in 90% yield with a *syn/anti* ratio of 88:12 in 93% ee. Subsequent reduction and desulfurization of **9k** with Raney Ni gave the valuable acyclic β -amino dicarbonyl compound **9l** having three consecutive chiral carbons and involving a methyl-substituted quaternary center.

Interestingly, *syn*-**9a–c,k** and *anti*-**9d–h** from cyclic and acyclic pronucleophiles, respectively, offered opposite absolute configurations at the amino carbon center (Table 3). However, during our investigation of these unexpected changes in stereochemistry (see above), we found that cyclic ketoester **10** gave a mixture of *syn*-**11** and *anti*-**11** at a diastereomeric ratio of 52:48 with high enantioselectivities (90 and 97% ee, respectively) (eq 2): Moreover, when 3,5-xylenol was used



in place of *t*-BuOH, **11** was obtained with similar diastereoselectivity, but the enantioselectivity of *syn*-**11** was significantly decreased to 43% ee.¹⁰ Overall, these results strongly suggest that the *syn* and *anti* isomers were obtained through different reaction pathways.

Although the role of the alcoholic Li(I) salt is not completely clear, two major mechanisms can be considered (Figure 1).¹¹ On one hand, the aldimine would be activated by the Lewis acidic Li(I) center (**path a**). On the other hand, the pronucleophile would be activated as a Li enolate (**path b**). In both paths, the addition of alcohols such as *t*-BuOH would promote the dissociation to a monomeric precursor, Li(I) BINOLate·(ROH)_n (Figure 1, left).⁵ Since an acyclic 1,3-dicarbonyl compound would have a rather flexible conformation, activation of the aldimine on the Li(I) center would be likely (**path a**). In **path a**, alcohols (*t*-BuOH or 3,5-xylenol) would still coordinate to the Li(I) center, which would not strongly affect the enantioselectivity (eq 2, *anti*). In sharp contrast, a cyclic 1,3-dicarbonyl compound would be preferentially activated as a Li enolate because the conformationally rigid structure could promote chelation to the Li(I) center (**path b**). Ligand **4** protonated via Li enolization would activate the aldimine through hydrogen bonding. However, 3,5-xylenol, which is more acidic than *t*-BuOH, might compete with **4** and could trigger a nonselective

pathway (eq 2, *syn*). Therefore, we rationalized that *syn* isomers would be obtained via **path b** while *anti* isomers would be obtained via **path a**. In **path a**, a pronucleophile would be activated by coordination with a Brønsted basic naphtholate oxygen, after which attack of the Li-coordinated aldimine on the *re* face would occur. In **path b**, the aldimine would be activated by a resulting Brønsted acidic naphthol proton, and the Li enolate would attack the aldimine on the *si* face.

**Figure 1.** Proposed precursor and transition states.

In summary, we have developed a highly enantioselective direct Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds. A simple Li(I) BINOLate salt was effective for selectively synthesizing both *syn* adducts from cyclic reagents and unprecedented *anti* adducts from acyclic reagents with an interesting change in absolute stereochemistry.

Acknowledgment. Financial support for this project was provided by JSPS KAKENHI (20245022), MEXT KAKENHI (21750094, 21200033), and the Global COE Program of MEXT. We greatly thank the referees for helpful suggestions regarding the mechanistic aspects.

Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- Reviews of acid–base chemistry: (a) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (b) Ishihara, K.; Sakakura, A.; Hatano, M. *Synlett* **2007**, 686.
- Reviews of BINOL chemistry: (a) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (b) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (c) Brunel, J. M. *Chem. Rev.* **2007**, *107*, PR1.
- Chiral Li(I) BINOLate catalysts: (a) Schiffrers, R.; Kagan, H. B. *Synlett* **1997**, 1175. (b) Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, *10*, 2411. (c) Nakajima, M.; Orito, Y.; Ishizuka, T.; Hashimoto, S. *Org. Lett.* **2004**, *6*, 3763. (d) Ichibakase, T.; Orito, Y.; Nakajima, M. *Tetrahedron Lett.* **2008**, *49*, 4427.
- Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7453.
- (a) Hatano, M.; Ikeno, T.; Miyamoto, T.; Ishihara, K. *J. Am. Chem. Soc.* **2005**, *127*, 10776. (b) Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *Adv. Synth. Catal.* **2008**, *350*, 1776.
- Reviews of direct Mannich-type reactions: (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102. (b) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29.
- Asymmetric direct Mannich-type reactions of aldimines with 1,3-dicarbonyl compounds: (a) Uruguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (b) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (c) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (d) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (e) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (f) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043. (g) Yamaoka, Y.; Miyabe, H.; Yasui, Y.; Takemoto, Y. *Synthesis* **2007**, 2571. (h) Lou, S.; Dai, P.; Schaus, S. E. *J. Org. Chem.* **2007**, *72*, 9998. (i) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (j) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (k) Kang, Y. K.; Kim, D. Y. *J. Org. Chem.* **2009**, *74*, 5734. (l) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604.
- Bhalla, A.; Venugopalan, P.; Bari, S. S. *Eur. J. Org. Chem.* **2006**, 4943.
- The reaction of PMPN=CCO₂Et with **10** gave the corresponding products in 76% yield (*dr* = 71:29) with 91/26% ee.
- We can exclude a pathway with achiral 3,5-Me₂C₆H₃OLi in eq 2 because the *dr* ratios in eq 2 were nearly the same even though the reaction of **1a** and **10** with 3,5-xylenol/*n*-BuLi (5 mol%) gave *syn*-**11** in 98% yield.
- A more detailed mechanism is discussed in the Supporting Information.

JA909874B