

# Low Ligand Loading, Highly Enantioselective Addition of Phenylacetylene to Aromatic Ketones Catalyzed by Schiff-Base Amino Alcohols

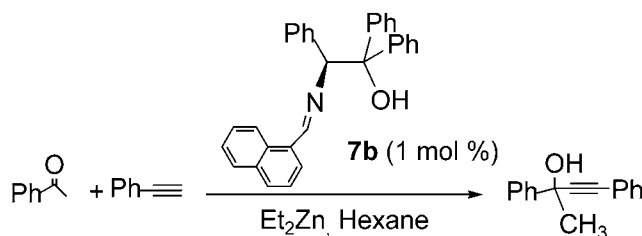
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## ABSTRACT



Schiff-base amino alcohols **7a,b** derived from L-phenylglycine through three simple steps are found to be highly effective for the enantioselective addition of phenylacetylene to aromatic ketones. When the loading of **7b** was 1 mol %, an ee value of up to 95% was obtained. However, when **7b** was lowered to 0.1 mol %, a high ee value of 85% was still achieved. A practical solution to synthesize the optically active tertiary propargylic alcohols was described.

The catalytic enantioselective formation of new C–C bonds is an important class of organic reactions.<sup>1</sup> Among them, the asymmetric addition of terminal alkynes to carbonyl compounds and formation of the chiral propargylic alcohols have been very intense research fields in recent years. Some excellent work has been reported in the field of the asymmetric addition of alkynes to aldehydes with high ee values.<sup>2</sup> However, the practical asymmetric alkylation of ketones to form optical tertiary propargylic alcohols is facing a challenge because of the reduced propensity of ketones to

coordinate to Lewis acids,<sup>3</sup> and few catalysts were found to be effective in promoting the asymmetric addition of alkynylzinc to ketones. P. G. Cozzi first reported that a Zn-

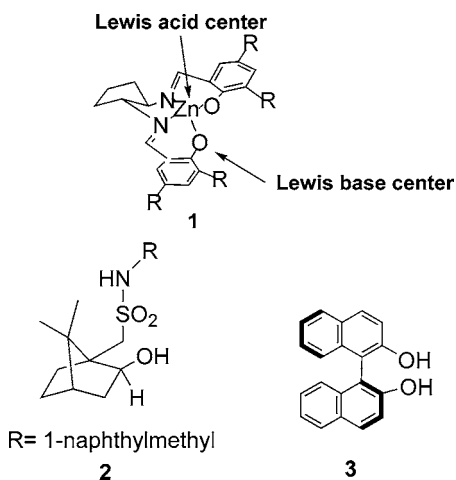
(2) (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (c) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688. (d) Frantz, D.; Fassler, E. R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807. (e) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172. (f) Li, X.; Lu, G.; Kwok, W. H.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636. (g) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606. (h) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855. (i) Gao, G.; Moore, D.; Xie, R. G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143. (j) Gao, G.; Xie, R. G.; Pu, L. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5417. (k) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (l) Gao, G.; Wang, Q.; Yu, X. Q.; Xie, R. G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122. (m) Trost, B. M.; Weiss, A. H.; Wangelin, J. v. *J. Am. Chem. Soc.* **2006**, *128*, 8. (n) Emmerson, D. P. G.; Hems, W. P.; Davis, B. G. *Org. Lett.* **2006**, *8*, 207.

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(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999.

(salen), **1**, promoted alkynylation of ketones with moderate enantioselectivities as a pioneering study.<sup>4</sup> He considered that the success of this addition ascribed to the salen–metal complex which could behave as a bifunctional Lewis acid–Lewis base catalyst. In the same year, Chan and co-workers described the alkynylzinc addition to ketones with very high ee values in the presence of chiral camphorsulfonamide ligand **2** and a stronger Lewis acid Cu(OTf)<sub>2</sub>.<sup>5</sup> Almost at the same time, Cozzi<sup>6</sup> and we<sup>7d</sup> developed an asymmetric addition of alkynylation of ketones in the presence of BINOL **3** and Ti (Figure 1). We found the 1:1 ratio of BIONL/Ti



**Figure 1.** Structure of ligands for the asymmetric addition of alkynylation of ketones.

was necessary for a stronger Lewis acid. Although advances have been achieved, high loadings of ligands (usually 20 mol %) had to be used to achieve good to excellent enantioselectivities. Therefore, we report here an example of a highly efficient chiral ligand which could catalyze the enantioselective addition of alkynylzinc to simple ketones

(3) Selected references on the enantioselective organozinc addition to ketones: (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284. (b) Betancort, J. M.; García, C.; Walsh, P. J. *Synlett* **2004**, 749. (c) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (d) Ramón, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239. (e) Ramón, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (f) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (g) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544. (h) García, C.; Walsh, P. J. *J. Org. Chem.* **2003**, *68*, 3641. (i) Li, H.; García, C.; Walsh, P. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5425. (j) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538. (k) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448. (l) Saito, B.; Katsuki, T. *Synlett* **2004**, 1557.

(4) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895.

(5) Lu, G.; Li, X. S.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5057.

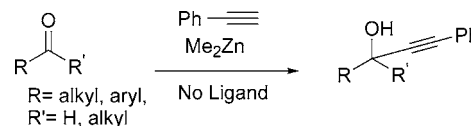
(6) Cozzi, P. G.; Alessi, S. *Chem. Commun.* **2004**, 2448.

(7) Selected recent examples of our group: (a) Xu, Z. Q.; Wang, R.; Xu, J. K.; Da, C. S.; Yan, W. J.; Chen, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5747. (b) Xu, Z. Q.; Chen, C.; Xu, J. K.; Miao, M. B.; Yan, W. J.; Wang, R. *Org. Lett.* **2004**, *6*, 1193. (c) Kang, Y. F.; Liu, L.; Wang, R.; Zhou, Y. F.; Yan, W. J. *Adv. Synth. Catal.* **2005**, *347*, 243. (d) Zhou, Y. F.; Wang, R.; Xu, Z. Q.; Yan, W. J.; Liu, L.; Kang, Y. F.; Han, Z. J. *Org. Lett.* **2004**, *6*, 4147. (e) Ni, M.; Wang, R.; Han, Z. J.; Mao, B.; Da, C. S.; Liu, L.; Chen, C. *Adv. Synth. Catal.* **2005**, *347*, 1659. (f) Liu, L.; Wang, R.; Kang, Y. F.; Chen, C.; Xu, Z. Q.; Zhou, Y. F.; Ni, M.; Cai, H. Q.; Gong, M. Z. *J. Org. Chem.* **2005**, *70*, 1084.

with high ee values and good yields in low loading of the ligand, and to the best of our knowledge, 1 mol % was the lowest amount reported in this reaction.

It is well-known that alkyl<sub>2</sub>Zn does not react with simple ketones without another Lewis acid's assistance because of the low activity of the carbonyl in ketones. Recently, Cozzi reported that MeZnC≡CPh could be directly added to the simple ketones without a ligand (Scheme 1).<sup>8</sup> It was because

**Scheme 1.** Alkynylation of Ketones in the Presence of Alkynylzinc

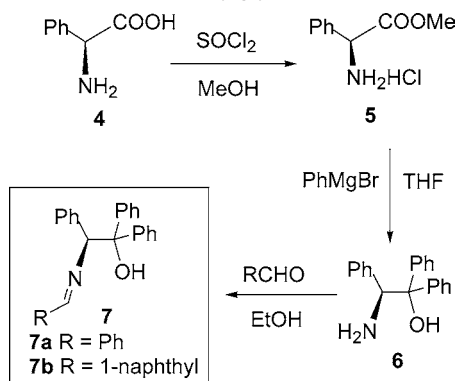


the electron-withdrawing nature of the alkynyl affected the zinc center in MeZnC≡CPh, thus increasing the polarity of the C–Zn bond and the Lewis acidity of the metal to a great extent. This kind of zinc complex has enough Lewis acidity to activate the carbonyl group in the ketone. Therefore, it can make this kind of addition work successfully. On the basis of the facts mentioned above, we attempted to perform the enantioselective addition of phenylacetylene to ketones without adding any other stronger Lewis acid except zinc.

The Schiff-base amino alcohols<sup>9</sup> were easily prepared from L-phenylglycine in three simple steps with overall yields of up to 70% and 73%, respectively (Scheme 2). At first, 5 mol % of **7a** and **7b** was employed in the asymmetric addition of phenylacetylene to acetophenone in the presence of diethylzinc. The reaction was completed in 14 h at room temperature. Ligand **7b** which has a much bulkier substitute gave a better result. Then, the solvent effect on this process using **7b** was probed. Low enantioselectivity and a slow reaction time were found in CH<sub>2</sub>Cl<sub>2</sub>. Hexane gave the best ee and yield. In the reaction, we found that the ligand was not completely dissolved in hexane, and perhaps, a smaller amount of ligand could serve as a catalyst with the same result. Therefore, we attempted to decrease the loading of the ligand to 1 mol %. To our surprise, the ee was up to

(8) Cozzi, P. G.; Rudolph, J.; Bolm, C.; Norrby, P. O.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 5733.

(9) Selected references for the salen-schiff base as chiral catalysts: (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668–12669. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781–3784. (c) Li, Z. B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065–1068. (d) Dahmen, S. *Org. Lett.* **2004**, *6*, 2113–2116. (e) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2145. (f) Belokon, Y. R.; Cavada-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tassinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968–3971. (g) Belokon, Y. R.; North, M.; Parsons, T. *Org. Lett.* **2000**, *2*, 1617. (h) Cameron, P. A.; Gibson, V. C.; Irvine, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2141–2144. (i) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704. (j) Yun, H. Y.; Wu, Y. J.; Wu, K. L.; Zhou, D. Y. *Tetrahedron Lett.* **2000**, *41*, 10263–10266. (k) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–1317.

**Scheme 2.** Preparation of Schiff-Base Amino Alcohols from L-Phenylglycine

81% at room temperature (Table 1, entry 5). Encouraged by these results, we studied the effects of the temperature. Lowering the reaction temperature from room temperature to 0 °C led to an increasing ee (Table 1, entry 6), and at -18 °C, the best result was obtained (Table 1, entry 7). When the amount of diethylzinc was increased from 1.2 to 5 equiv, the ee was slightly influenced (entries 8–11).

Under the optimized conditions, catalyst **7b** loading as low as 1 mol % has been successfully used for the asymmetric addition of phenylacetylene to various aromatic ketone reactions. Acetophenone and related derivatives were excellent substrates for the catalyst (Table 2). Moreover, 2-naphthacetophenone gave the best enantiomeric excess (95% ee, Table 2, entry 3). When the  $\alpha,\beta$ -unsaturated ketone was used as the substrate, a moderate enantiomeric excess was

**Table 1.** Asymmetric Addition of Phenylacetylene to Acetophenone Catalyzed by Schiff-Base Amino Alcohols<sup>a</sup>

		<b>7a or 7b</b>							
		$\text{Et}_2\text{Zn, Hex}$							
entry	ligand	mol %	solvent	<i>T</i> (°C)	time (h)	$\text{Et}_2\text{Zn}^b$ (mL)	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)	
1	<b>7a</b>	5	toluene	rt	14	0.5	90	78	
2	<b>7b</b>	5	toluene	rt	14	0.5	92	83	
3	<b>7b</b>	5	$\text{CH}_2\text{Cl}_2$	rt	14	0.5	67	47	
4	<b>7b</b>	5	hexane	rt	14	0.5	94	86	
5	<b>7b</b>	1	hexane	rt	48	0.5	75	81	
6	<b>7b</b>	1	hexane	0	48	0.5	71	84	
7	<b>7b</b>	1	hexane	-18	48	0.5	70	90	
8	<b>7b</b>	1	hexane	-18	48	0.3	63	87	
9	<b>7b</b>	1	hexane	-18	48	0.75	75	88	
10	<b>7b</b>	1	hexane	-18	48	1.0	73	85	
11	<b>7b</b>	1	hexane	-18	48	1.25	70	84	
12 <sup>e</sup>	<b>7b</b>	1	hexane	-18	48	0.5	71	83	

<sup>a</sup> Unless otherwise specified, the substrate of acetophenone was run on a 0.25 mmol scale in 1 mL of hexane under argon. <sup>b</sup> 1 M  $\text{Et}_2\text{Zn}$  in hexane. <sup>c</sup> Yield of isolated product. <sup>d</sup> The enantiomeric excess was determined by HPLC on a chiralcel OD-H column. <sup>e</sup> The reaction was performed in 0.5 mL of 1 M  $\text{Et}_2\text{Zn}$  in hexane.

**Table 2.** Asymmetric Addition of Phenylacetylene to Various Ketones Promoted by Ligand **7b**<sup>a-c</sup>

entry	ketones	ligand (mol %)	yield <sup>d</sup> (%)	ee <sup>e</sup> (%)
1	acetophenone	1	70	90
2	2'-fluoroacetophenone	1	83	94
3	2'-naphthacetophenone	1	77	95
4	1'-naphthacetophenone	1	62	94
5	2'-methoxyacetophenone	1	70	94
6	4'-methylacetophenone	1	76	92
7	4'-fluoroacetophenone	1	70	90
8	4'-chloroacetophenone	1	63	90
9	3'-methylacetophenone	1	76	90
10	benzalacetone	1	80	77

<sup>a</sup> Ligand/ketones/ $\text{Et}_2\text{Zn}$ /phenylacetylene = 0.01:1:2:2. <sup>b</sup> All the reactions were conducted at -18 °C in 1 mL of hexane. <sup>c</sup> All the reactions were carried out for 48–60 h for aromatic ketones and for 24 h for  $\alpha,\beta$ -unsaturated ketones. <sup>d</sup> Yield of isolated product. <sup>e</sup> The enantiomeric excess was determined by HPLC on a chiralcel OD-H column.

achieved (Table 2, entry 10). In contrast to aromatic ketones, aliphatic ketones are reactive using the catalyst **7b** and a moderate enantiomeric excess was obtained.<sup>10</sup>

In addition, to test the power of the ligand **7b**, we further lowered the loading of **7b** to 0.1 mol % and up to 85% ee was achieved (Table 3, entry 8). Studies of the mechanism

**Table 3.** Asymmetric Addition of Phenylacetylene to Ketones Promoted by the Ligand **7b** with Lower Loading<sup>a,b</sup>

entry	ketones	ketones/ligand	yield <sup>c</sup> (%)	ee <sup>d</sup> (%)
1	acetophenone	100	70	90
2	acetophenone	1000	67	80
3	2'-fluoroacetophenone	100	83	94
4	2'-fluoroacetophenone	1000	80	80
5	2'-naphthacetophenone	100	77	95
6	2'-naphthacetophenone	1000	70	84
7	1'-naphthacetophenone	100	62	94
8	1'-naphthacetophenone	1000	65	85

<sup>a</sup> Unless otherwise specified, the reaction was run in 1 mL of hexane under argon for 48 h with 1 M  $\text{Et}_2\text{Zn}$  in hexane. <sup>b</sup> Ketones/ligand = 1000 were performed at room temperature. <sup>c</sup> Yield of isolated product. <sup>d</sup> The enantiomeric excess was determined by HPLC on chiralcel OD-H column.

of the reaction and the application of this catalyst system in other asymmetric catalytic reactions are in progress.

In summary, we have reported that an easily prepared Schiff-base amino alcohol is highly efficient for asymmetric addition of phenylacetylene to aromatic ketones when the loading of **7b** is 1 mol %. This system does not need to add any other stronger Lewis acid except zinc, and the alkylzinc must be prepared in advance. To the best of our knowledge, **7b** is the most efficient chiral ligand for the

(10) Methyl isobutyl ketone (-18 °C in 1 mL of hexane, **7b**/ketone/ $\text{Et}_2\text{Zn}$ /phenylacetylene = 0.01:1:2:2, 61% ee).

enantioselective addition of alkynylzinc to simple ketones from the standpoint of low loading of ligands.

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**Supporting Information Available:** The characterizations of ligand **7** and the products are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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