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Highly Enantioselective 1,4-Addition of Diorganozinc Reagents to Cyclic Enones Using Chiral Diphosphite Ligands Derived from H_8-Binaphthol

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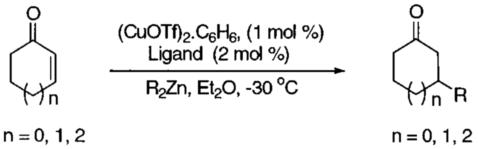
ABSTRACT



High enantioselectivities have been achieved in the 1,4-addition of dialkylzincs to 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone with ee values up to 99% by using chiral aryl diphosphite ligands derived from H_8-binaphthol.

The asymmetric nucleophilic 1,4-conjugate addition to α,β-unsaturated compounds is a highly useful method for generating a *C*-chiral center.[1] In the past few years, considerable efforts have been focused on the Cu-catalyzed enantioselective conjugate addition of organometallic reagents, particularly diorganozinc reagents, to α,β-unsaturated esters, lactones, acyclic, and cyclic enones. A number of chiral ligands such as chiral phosphoramidites,[2] phosphites,[3] aryl diphosphite,[4] and *P*,*N*-ligands[5] have been designed, synthesized, and applied in these reactions, and excellent results have been accomplished in some cases. Of particular interest are the conjugate additions of nucleophiles to cyclic enones since they can potentially furnish biologically active compounds after a subsequent diastereoselective, electrophilic trapping.[1,7] However, the development of an all-encompassing ligand effective in the conjugate addition of dialkylzincs

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(1) (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, (2), 171−196.

(2) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2620−2623. (b) Naasz, R.; Amold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc*. **1999**, *121*, 1104−1105. (c) Feringa, B. L. *Acc. Chem. Res*. **2000**, *33*, 346−353. (d) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2856−2878.

(3) (a) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3193−3196. (b) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett*. **1997**, *44*, 7745−7748. (c) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett*. **1998**, *39*, 7869−7872. (d) Pamies, O.; Net, G.; Ruiz, A.; Claver, C. *Tetrahedron: Asymmetry* **1999**, *10*, 2007−2014. (e) Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J.-M.; Maze F. *Eur. J. Org. Chem*. **2000**, 4011−4027.

(4) (a) Yan, M.; Yang, L. W.; Wong, K. Y.; Chan, A. S. C. *Chem. Commun*. **1999**, 11−12. (b) Yan, M.; Chan, A. S. C. *Tetrahedron Lett*. **1999**, *40*, 6645−4468. (c) Yan, M.; Zhou, Z.-Y.; Can, A. S. C. *Chem. Commun*. **2000**, 115−116.

(5) (a) Knöbel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429−1431. (b) Hu, X. Q.; Chen, H. L.; Zhang, X. M. *Angew. Chem., Int. Ed*. **1999**, *38*, 3518−3521. (c) Escher, Iris H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879−2888. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res*. **2000**, *33*, 336−345. (e) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 779−781.

(6) Krause N. *Angew. Chem., Int. Ed*. **1998**, *37*, 283−285.

(7) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2001**, *123*, 755−6.

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to all five-, six-, and seven-membered cycloalkenones has been less successful.[1,6,7] On the basis of our earlier studies in this area,[4] we herein report the successful synthesis and application of highly effective H_8-BINOL-based diphosphite ligands in the 1,4-addition of diethylzinc and dimethylzinc to cyclic enones. A chemical yield of 92% and an ee value of up to >98% have been achieved even when cyclopenten-2-one was used as a substrate.

We previously prepared the aryl diphosphite ligands **1** (Figure 1), featuring a general structure in which two units of binolate is bridged with a 2,2′-biarylate scaffold, and demonstrated their effectiveness in the catalytic 1,4-additions to give moderate to high enantioselectivities.[4] Our consistent observation, where partial hydrogenation of the binaphthlene rings as part of the ligand moiety often gave better enantioselectivies in various catalytic asymmetric reactions,[8] provided us the impetus to expand on this successful lead by replacing the binolate end groups with H_8-binolate units. Thus, in a one-pot reaction, **2** and **3** were synthesized from the precursor chlorophosphite of (*S*)-H_8-binaphthol **5** with (*S*)- or (*R*)-2,2′-binaphthol (Scheme 1).

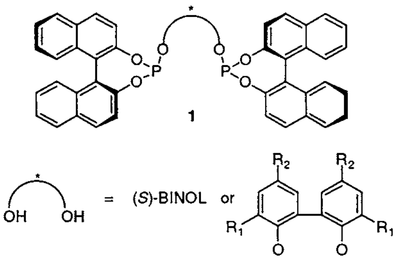
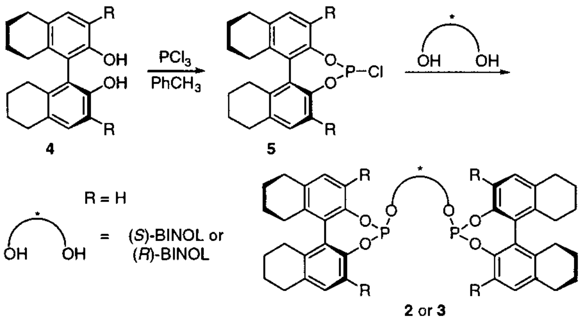


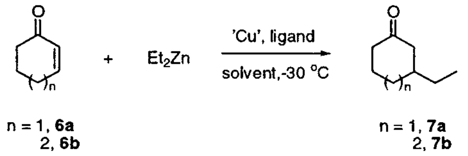
Figure 1.

Scheme 1. Synthesis of Diphosphites (*S*,*S*,*S*)-**2** and (*S*,*R*,*S*)-**3**



At the outset of our studies, cyclohexen-2-one (0.5 mmol) was treated with 1.0−1.5 equiv of diethylzinc (neat, −30 °C) in the presence of (*S*,*S*,*S*)-**2** (2 mol %) and the copper source (1 mol %) in various solvents (Table 1, entries 2−5).

Table 1. Asymmetric Addition of Diethylzinc to 2-Cyclohexen-1-one and 2-Cyclohepten-1-one Employing **2** and **3** as Ligands[a]



entry	*n*	ligand	solvent	yield (%),[b,c] time (h)	ee (%)[b] (configuration)[d]
1[e]	1	(*S*,*S*,*S*)-**2**	$PhCH_3$	>99, 3	84 (*S*)
2[f]	1	(*S*,*S*,*S*)-**2**	$PhCH_3$	>99, 3	92 (*S*)
3[f]	1	(*S*,*S*,*S*)-**2**	CH_2Cl_2	>99, 15	87 (*S*)
4[f]	1	(*S*,*S*,*S*)-**2**	Et_2O	>99, 15	97 (*S*)
5[f]	1	(*S*,*R*,*S*)-**3**	Et_2O	>99, 3	96 (*S*)
6[e]	2	(*S*,*S*,*S*)-**2**	$PhCH_3$	75, 15	37
7[f]	2	(*S*,*S*,*S*)-**2**	$PhCH_3$	>99, 15	83
8[f]	2	(*S*,*S*,*S*)-**2**	CH_2Cl_2	>99, 18	63
9[f]	2	(*S*,*S*,*S*)-**2**	Et_2O	>99, 18	89
10[f]	2	(*S*,*R*,*S*)-**3**	Et_2O	>99, 3	97

[a] Reactions were performed on a 0.5 mmol scale at −30 °C (molar ratio of copper/ligand/substrate/Et_2Zn = 0.01/0.02/1/1.0∼1.5). [b] Yields and ee values of **7a** and **7b** were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm) or a Chrompack Diol column (25 m × 0.25 mm) by using dodecane as an internal standard. [c] No 1,2-addition product was observed. [d] Absolute configuration was assigned by comparison with a literature report.[4a] [e] Cu = $Cu(OTf)_2$. [f] Cu = $(CuOTf)_2{\cdot}C_6H_6$.

It was found that the catalyst prepared in situ from $(CuOTf)_2{\cdot}C_6H_6$ was more effective than that from $Cu(OTf)_2$ (Table 1, entries 2−5 vs entry 1), giving the desired 1,4-addition product in over 99% yield in all cases as determined by quantitative GC-analysis using dodecane as an internal standard. Contrary to the common notion where the use of a coordinating solvent is detrimental to either the yield or the ee in most asymmetric catalytic reactions involving the use of diethylzinc as a reagent, diethyl ether proved to be more effective than the noncoordinating toluene and dichloromethane, affording 3-ethylcyclohexanone in 97% ee (Table 1, entry 4 vs entries 2 and 3). When the ligand was switched to (*S*,*R*,*S*)-**3**, enhanced activity was observed with the enantiopurity of **7a** remaining largely unchanged (Table 1, entry 5 vs 4). Interestingly, the same product configuration was obtained irrespective of the absolute configuration of the bridging binolate (Table 1, entries 4 and 5). These results suggested that the asymmetric induction was mainly influenced by the end groups of the chiral ligands. Identical trends were noted when cyclohepten-2-one was treated with diethylzinc in different solvents, except where the use of (*S*,*R*,*S*)-**3** instead of (*S*,*S*,*S*)-**2** as a ligand increased the enantioselectivity of **7b** from 89 to 97% (Table 1, entries 9 and 10).

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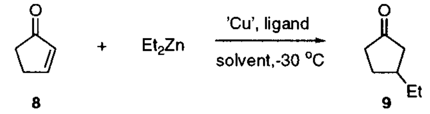
(8) (a) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 585−589. (b) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080−4081. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651−3655. (d) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179−1182. (e) Zhang, F.-Y.; Pai, C.-C.; Chan, A. S. C.. *J. Am. Chem. Soc.* **1998**, *120*, 5808−5809. (f) Zhang, F.-Y.; Kwok, W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 2337−2342. (g) Zeng, Q.; Liu, H.; Cui, X.; Mi, A.; Jiang, Y.; Li, X.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2002**, *13*, 115−117. (h) Lu, G.; Li, X.; Chan, W. L.; Chan, A. S. C. *Chem. Commun.* **2002**, 172−173.

Next, we turned our attention to the more problematic substrate cyclopenten-2-one.[2a,9] Studies similar to those carried out above were applied here (see Table 2). Again, the combination of (*S*,*S*,*S*)-**2** and a noncoordinating solvent afforded the 1,4-addition compound in relatively inferior yields and lower ees (Table 2, entries 1−3).

Table 2. Asymmetric Addition of Diethylzinc to 2-Cyclopenten-1-one Using **2** and **3** as Ligands[a]



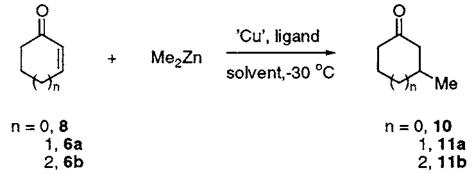
entry	ligand	solvent	yield (%)[b,c]	ee (%)[b] (configuration)[d]
1[e]	(*S*,*S*,*S*)-**2**	$PhCH_3$	50	90 (*S*)
2[f]	(*S*,*S*,*S*)-**2**	$PhCH_3$	68	89 (*S*)
3[f]	(*S*,*S*,*S*)-**2**	CH_2Cl_2	87	89 (*S*)
4[f]	(*S*,*S*,*S*)-**2**	Et_2O	90	90 (*S*)
5[f]	(*S*,*R*,*S*)-**3**	Et_2O	92	>98 (*S*)

[a] Reactions were performed on a 0.5 mmol scale at −30 °C (molar ratio of copper/ligand/substrate/Et_2Zn = 0.01/ 0.02/1/1.0∼1.5). [b] Yields and ee values of **7a** and **7b** were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm) or a Chrompack Diol column (25 m × 0.25 mm) by using dodecane as an internal standard. [c] No 1,2-addition product was observed. [d] Absolute configuration was assigned by comparison with a literature report.[4a] [e] Cu = $Cu(OTf)_2$. [f] Cu = $(CuOTf)_2{\cdot}C_6H_6$.

Deploying $(CuOTf)_2{\cdot}C_6H_6$ as the metal source, (*S*,*R*,*S*)-**3** as the ligand, and diethyl ether as the solvent delivered the desired 3-ethylcyclopentanone in excellent yield (92%) and enantiomeric excess (>98%) (Table 2, entry 5). This result compares very favorably with the best literature value hitherto reported.[7]

Finally, we tested the optimal conditions established above in Cu-catalyzed dimethylzinc addition to cyclic enones. As illustrated in Table 3, cyclopenten-2-one reacted very slowly with dimethylzinc to give the 1,4-addition product in low ee (entry 2), while larger ring analogues showed substantially higher reactivity toward the organometallic reagent, leading to the desired product in near quantitative yield and high ee (entries 4 and 6). In light of the poor performance of $(CuOTf)_2{\cdot}C_6H_6$ on **8**, we sought to investigate the effect of a different metal source. Interestingly, the best result for cyclohepten-2-one came from the use of $Cu(OTf)_2$ as the catalytic metal with a slight reduction in yield but a remarkable boost of enantioselectivity to >99% (entry 5). Again, these values are comparable with the best literature result so far obtained, and the reaction represents a key step en route to anticarcinogenic clavularin B.[7] Nevertheless, $Cu(OTf)_2$ appeared to work less efficiently when smaller ring analogues were used as substrates (entries 1 and 3). The strong dependence of ee on the reconciliation between the Cu source and the dialkylzinc reagent reflects the requirement of matching conditions for this reaction.

Table 3. Asymmetric Addition of Dimethylzinc to 2-Cyclopenten-1-one, 2-Cyclohexen-1-one, and 2-Cyclohepten-1-one Employing **3** as a Ligand[a]



entry	*n*	solvent	yield (%),[b,c] time (h)	ee (%)[b] (configuration)
1[d]	0	Et_2O	20, 24	68
2[e]	0	Et_2O	22, 16	21
3[d]	1	Et_2O	87, 24	66
4[e]	1	Et_2O	>99, 12	93
5[d]	2	Et_2O	85, 24	>99
6[e]	2	Et_2O	98, 15	91

[a] Reactions were performed on a 0.5 mmol scale at −30 °C (molar ratio of copper/ligand/substrate/Et_2Zn = 0.01/ 0.02/1/1.0∼1.5). [b] Yields and ee values of **7a** and **7b** were determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm) or a Chrompack Diol column (25 m × 0.25 mm) by using dodecane as an internal standard. [c] No 1,2-addition product was observed. [d] Cu = $Cu(OTf)_2$. [e] Cu = $(CuOTf)_2{\cdot}C_6H_6$.

To summarize, aryl diphosphite ligands derived from the H_8-binaphthoxy moiety can be easily prepared and are very efficient in the Cu-catalyzed 1,4-conjugate addition of diorganozinc reagents to cyclic enones. The selection of anhydrous diethyl ether as the reaction solvent is crucial to achieving both high reactivity and enantioselectivity. Further studies directed toward the expansion of the scope of substrates and ligands by modifications at the 3,3′-positions will be reported in due course.

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Supporting Information Available: Full characterization and detailed experimental procedures for the synthesis of diphosphites **2** and **3** and the chromatograms of 1,4-addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999−1014.