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Multinuclear Cu-Catalysts Based on SPINOL-PHOS in Asymmetric Conjugate Addition of Organozinc Reagents

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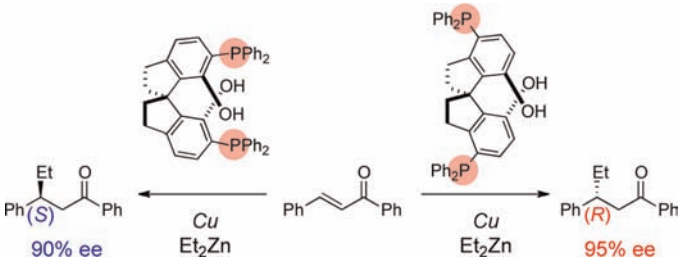
ABSTRACT



Multinuclear Cu/Zn complex-catalyzed efficient asymmetric conjugate addition of organozinc reagents to acyclic and cyclic enones has been developed in the presence of a wide variety of regioisomeric chiral diols bearing phosphorus moieties as ligands. The regioisomeric SPINOL-PHOS ligands based on a SPINOL architecture showed an unexpected inversion of stereoselectivity.

Multinuclear catalysts have recently attracted considerable attention due to their role in various asymmetric reactions as powerful tools for preparing chiral molecules.[1] We previously reported the self-assembled metal-linked phosphine ligands to generate multinuclear complexes (Figure 1). The deprotonation reaction of hydroxy protons using a dialkylzinc reagent and the subsequent addition of a Cu-salt gives oligomeric multinuclear Cu/Zn-complexes. Especially, the multinuclear catalysts derived from a

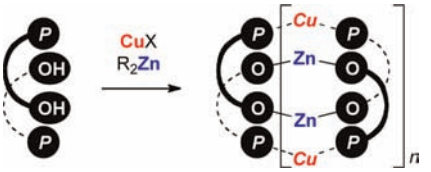


Figure 1. Metal-linked multinuclear complexes.

3,3′-diarylphosphino-2,2′-binol achieved the highly efficient Cu-catalyzed asymmetric conjugate addition of organozinc reagents to enones; the use of 0.05 mol % Cu catalyst was enough to give the product quantitatively and realized a turnover frequency (TOF) of 300 h^{-1} with excellent enantioselectivity.[2] Furthermore, the Pd/Zn-complexes

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(1) (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Majima, K.; Takita, R.; Okada, A.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837. (c) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (d) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494. (e) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (f) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170. (g) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438. (h) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117 and references cited therein.

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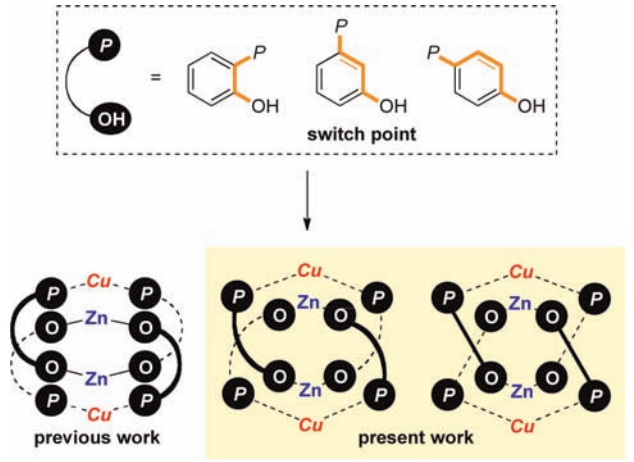


Figure 2. Switch-point strategy.

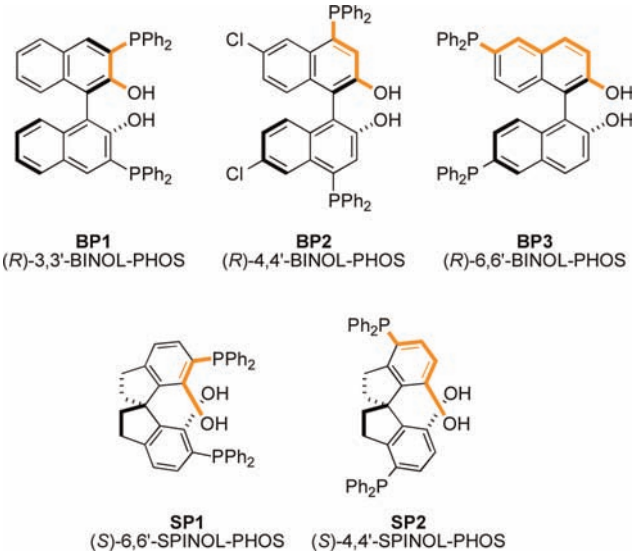


Figure 3. Representative regioisomeric ligands.

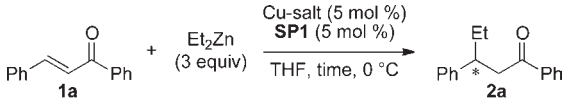
derived from 3,3′-diphenylphosphino-2,2′-binol (**BP1**) achieved the highly enantioselective ring-opening reaction of oxabicyclic alkenes.[3]

We further focused on the novel "switch-point" strategy in ligand architectures (Figure 2). Our hypothesis based on a phosphinophenol moiety would manipulate the global structures of multinuclear complexes. Hence, the representative ligand architectures based on a BINOL or a SPINOL are new entries to the novel design of multinuclear complexes (Figure 3). In this work, we report the dramatic influence of regioisomeric ligands as pillars of multinuclear complexes, which are highly versatile catalysts for the asymmetric conjugate addition of organozinc regents.

(3) Endo, K.; Tanaka, K.; Ogawa, M.; Shibata, T. *Org. Lett.* **2011**, *13*, 868.

We embarked on the development of novel architectures for the design and construction of multinuclear complexes. The Cu-catalyzed asymmetric conjugate addition of Et_2Zn to (*E*)-chalcone (**1a**) was carried out in THF at 0 °C as a model reaction in the presence of **SP1** ligand based on a SPINOL architecture as a novel **BP1** analogue.[4] The screening of Cu-salts showed that $Cu(acac)_2$ was suitable to give the product **2a** in excellent yield with high enantioselectivity (Table 1, entry 2). Notably, the use of $Cu(OAc)_2$ as a Cu-salt gave the opposite major enantiomer (entry 4). Alexakis et al. reported that Cu-salts affected the yields and enantioselectivities in the asymmetric conjugate addition of organozinc reagents to enones due to the incorporation of a counteranion derived from a Cu-salt in the C−C bond forming process.[5] However, the reversal of enantioselectivity with Cu-salts in the conjugate addition of organozinc reagents seems to be rare.[6]

Table 1. Screening of Reaction Conditions for **SP1**



entry	Cu-salt	time (h)	yield, ee (%)[a]
1	$CuCl_2 \cdot 2H_2O$	3	27, 48 (*S*)
2	$Cu(acac)_2$	1	>98, 90 (*S*)
3[b]	$Cu(acac)_2$	3	>98, 73 (*S*)
4	$Cu(OAc)_2$	2	95, 41 (*R*)
5	$Cu(NO_3)_2 \cdot 3H_2O$	6	86, 27 (*S*)
6	$Cu(OTf)_2$	19	83, 30 (*S*)
7	CuBr·SMe_2	19	49, 28 (*S*)
8	CuTC[c]	19	79, 5 (*R*)

[a] NMR yields. Ee was determined by chiral HPLC analysis. [b] **SP1** (10 mol %) was used. [c] Copper(I) (thiophene-2-carboxylate).

Further examination of the regioisomeric ligands based on a BINOL or SPINOL as novel architectures revealed an unexpected influence on the catalytic performance (Table 2). We previously reported that the reaction in the presence of $CuCl_2 \cdot 2H_2O$ and **BP1** gave the product **2a** in more than 98% yield with 94% ee (*S*) (entry 1).[2] The regioisomer of **BP1**, namely (*R*)-4,4′-BINOL-PHOS **BP2**, decreased the yield and ee; notably, the major enantiomer of the product **2a** was *R* (entry 2). Furthermore, the use of (*R*)-6,6′-BINOL-PHOS **BP3** gave the product **2a** in low yield with poor enantioselectivity (entry 3). Further screening of ligand effect clarified the characteristic features of SPINOL-PHOS derivatives. The reaction using

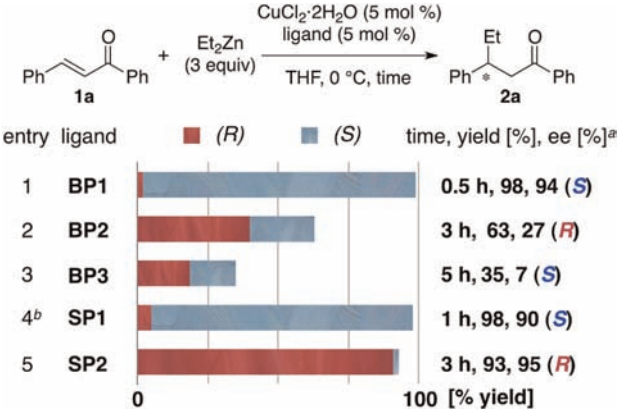
(4) For reviews of Cu-catalyzed asymmetric addition: (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796.

(5) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262.

(6) Okamoto, M.; Yamamoto, Y.; Sakaguchi, S. *Chem. Commun.* **2009**, 7363.

(*S*)-6,6′-SPINOL-PHOS **SP1** (5 mol %) gave the product **2a** in more than 98% yield with 90% ee (*S*) (entry 4). To our surprise, the use of (*S*)-4,4′-SPINOL-PHOS **SP2** (5 mol %) showed a dramatic inversion of stereoselectivity (entry 5).[6] Imamoto et al. reported the use of P-chiral *ortho*-phosphinophenol derivatives as a ligand for Cu-catalyzed asymmetric conjugate addition of organozinc reagents to enones, where the P,O-bidentate coordination to the Cu-center seems to be essential. In contrast, our ligand system, especially for **SP2**, indicated that the P,O-bidentate coordination should not be necessary.[7]

Table 2. Remarkable Effect of Switch-Point Strategy

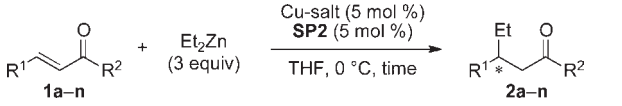


[a] NMR yields. Ee was determined by chiral HPLC analysis. [b] Cu(acac)$_2$ was used.

The reaction of a wide variety of acyclic enones is described in the presence of a Cu-salt and **SP1** or **SP2** (Table 3). Alexakis reported that the substituents, such as aromatic and aliphatic or sterically hindered and less hindered, in acyclic enones required an appropriate Cu-salt and solvent, respectively.[5] In contrast, we found that the reaction of various acyclic enones in the presence of $CuCl_2 \cdot 2H_2O$ and **SP1** or **SP2** gave the opposite major enantiomers as products respectively with high enantioselectivities. The reaction of **1a**−**e** gave the products in high yields with high enantioselectivities (entries 1−10). The reaction of **1f**−**i** in the presence of **SP1** diminished the yields and/or enantioselectivities (entries 11, 13, 15, 17, and 19). In contrast, the use of **SP2** gave good to high yields with high enantioselectivities (entries 12, 14, 16, 18, and 20). The aliphatic enones gave the desired products in moderate to good yields with moderate to high enantioselectivities, respectively (entries 21−28). Furthermore, the asymmetric conjugate addition to cyclohexenone **1o** was also investigated. The use of **SP1** gave a better enantioselectivity of product **2o** than **SP2**; the use of **SP1** (10 mol %) was effective (entries 29−32). The opposite major enantiomer was obtained in low enantioselectivity when **SP2** (10 mol %) was used (entry 32).

The ESI-MS analyses of the complexes derived from SPINOL-PHOS ligands were performed. The treatment of **SP1** with Et_2Zn in THF gave the mixture, the ESI-MS analysis of which suggested the presence of $[(\mathbf{SP1}-2H)_2Zn_2 + H]^+$ (m/z = 1369.3) as a major fragment formed in solution; the proposed structure is shown (Figure 4).[8]

Table 3. Screening of Acyclic Enones



entry[a]	R^1, R^2	ligand	time (h)	yield, ee (%)[b]
1	**1a**, Ph, Ph	**SP1**	1	**2a**, 98, 90 (*S*)
2		**SP2**	3	**2a**, 93, 95 (*R*)
3	**1b**, 4-F-Ph, Ph	**SP1**	2	**2b**, 87, 75 (+)
4		**SP2**	4	**2b**, 86, 94 (−)
5	**1c**, 4-Cl-Ph, Ph	**SP1**	2	**2c**, 90, 85 (*S*)
6		**SP2**	2	**2c**, 98, 95 (*R*)
7	**1d**, 4-F_3C-Ph, Ph	**SP1**	2	**2d**, 88, 84 (*S*)
8		**SP2**	3	**2d**, 95, 92 (*R*)
9	**1e**, 4-Me-Ph, Ph	**SP1**	1	**2e**, 95, 83 (+)
10		**SP2**	2	**2e**, 78, 96 (−)
11	**1f**, 4-biphenyl, Ph	**SP1**	1	**2f**, 79, 59 (−)
12		**SP2**	3	**2f**, 90, 94 (+)
13	**1g**, 4-MeO-Ph, Ph	**SP1**	5	**2g**, 51, 73 (*S*)
14		**SP2**	6	**2g**, 54, 93 (*R*)
15	**1h**, 2-Np, Ph	**SP1**	1	**2h**, 63, 76 (−)
16		**SP2**	3	**2h**, 96, 94 (+)
17	**1i**, furan-2-yl, Ph	**SP1**	5	**2i**, 33, 79 (−)
18		**SP2**	5	**2i**, 79, 90 (+)
19	**1j**, thiophen-2-yl, Ph	**SP1**	1	**2j**, 88, 78 (+)
20		**SP2**	13	**2j**, 72, 90 (−)
21	**1k**, cyclohexyl, Ph	**SP1**	4	**2k**, 73, 91 (*R*)
22		**SP2**	13	**2k**, 77, 96 (*S*)
23	**1l**, *n*-pentyl, Ph	**SP1**	2	**2l**, 69, 75 (+)
24		**SP2**	24	**2l**, 44, 96 (−)
25	**1m**, Ph, Me	**SP1**	4	**2m**, 55, 64 (*S*)
26		**SP2**	24	**2m**, 59, 85 (*R*)
27	**1n**, *n*-butyl, Me	**SP1**	4	**2n**, 62, 78 (+)
28		**SP2**	24	**2n**, 54, 88 (−)
29	 **1o**	**SP1**	6	**2o**, 50, 47 (*R*)
30		**SP1**	15	**2o**, 95, 92 (*R*)
31		**SP2**	24	**2o**, 98, 32 (*R*)
32		**SP2**	24	**2o**, 98, 17 (*S*)

[a] Cu(acac)$_2$ was used (entries 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, and 30). $CuCl_2 \cdot 2H_2O$ (entries 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 31, and 32). Ligand (10 mol %) was used (entries 30 and 32). [b] Isolated yields. Ee was determined by chiral HPLC analysis or chiral GC analysis.

(7) Takahashi, Y.; Yamamoto, Y.; Katagiri, K.; Danjo, H.; Yamaguchi, K.; Imamoto, T. *J. Org. Chem.* **2005**, *70*, 9009.

(8) Examples of multinuclear Zn-complexes based on BINOL for the reaction of enones, see: (a) Minatti, A.; Dötz, K. H. *Synlett* **2004**, 1634. (b) Minatti, A.; Dötz, K. H. *Eur. J. Org. Chem.* **2006**, 268. (c) Wang, H.; Wang, Z.; Ding, K. *Tetrahedron Lett.* **2009**, *50*, 2200.

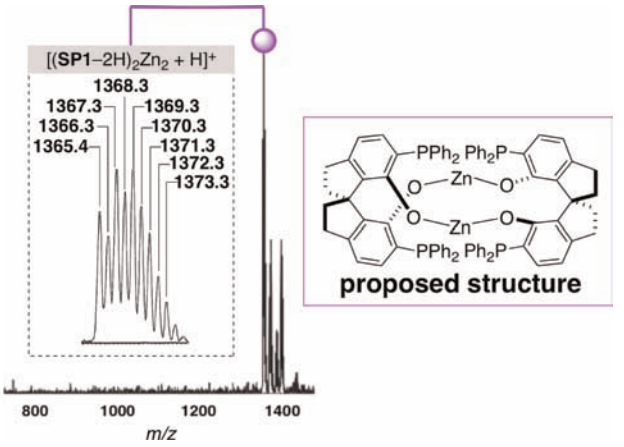


Figure 4. ESI-MS analysis of Zn/**SP1**-complexes.

The complicated isotope pattern of the detected peak suggests the incorporation of Zn-atoms. The subsequent treatment of the Zn-complexes with a Cu-salt predominantly gave oligomers, the ESI-MS analysis of which showed a complicated spectrum with various unidentified peaks. Furthermore, **SP2** also was not a suitable ligand to find identical Zn- and Cu/Zn-complexes; the ESI-MS spectra gave many unidentified peaks. The reaction using Et_2Zn and a Cu-salt with SPINOL-PHOS derivatives generates insoluble precipitates in the reaction mixture, which seem to be oligomeric complexes. This information suggests the incorporation of multinuclear Cu- and Zn-atoms in equilibrium between molecular and oligomeric complexes. To elucidate the structures of active complexes, further investigation would be required.

In conclusion, we discovered a dramatic effect of regioisomeric ligands for the construction of multinuclear Cu/Zn-complexes in the asymmetric conjugate addition of organozinc reagents to enones. The regioisomeric ligands gave the opposite major enantiomer of products, respectively. The present results based on our original strategy of multinuclear complexes would contribute to the design of new ligand architectures for asymmetric catalysis. Further examination of the influence of regioisomeric ligands on various asymmetric reactions is underway in our laboratory.

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Supporting Information Available. The experimental procedure and physical property of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.