Multinuclear Catalyst

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Multinuclear Catalyst for Copper-Catalyzed Asymmetric Conjugate Addition of Organozinc Reagents**

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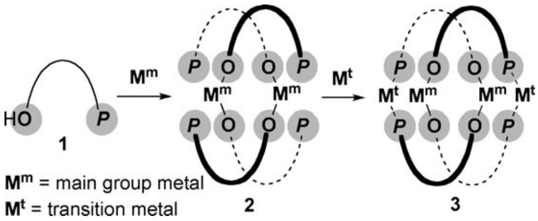
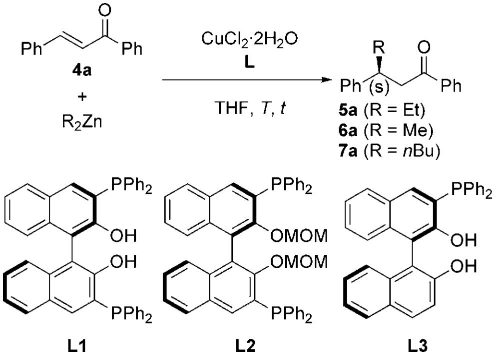
Recent progress in metal catalysis has arisen from dramatic improvements in catalytic performance using multinuclear complexes. There has been great interest in controlling the synergistic and cooperative effects between the metal centers in such complexes; however, the complicated nature and restriction of the ligand framework make it difficult to design tri-, tetra-, and multinuclear complexes.[1] For example, there are excellent reports concerning rhodium- or ruthenium-linked oligomeric complexes for heterogeneous asymmetric hydrogenation; the improvement of catalytic activity and stereoselectivity remains untouched.[2] Therefore, the design of ligand architectures and the demonstration of excellent catalytic activity using multinuclear complexes, including oligomeric complexes, are the next challenge in organic chemistry. We describe herein the dramatic effect of a multinuclear complex, having both copper and zinc centers, upon catalytic performance. The catalytic performance achieved was much higher than that of previous systems in the copper-catalyzed asymmetric conjugate addition of organozinc reagents to acyclic enones. Our working hypothesis is shown in Scheme 1. The deprotonation reaction of the phosphorus ligand **1**, which bears a hydroxy moiety, by an organometallic reagent generates metal-linked ligand **2**, the phosphorus moieties of which coordinate to transition-metal centers to form the tetranuclear complex **3**. Such a pliable ligand scaffold as **1** makes it possible to tune the structural and electronic features.



Scheme 1. Working hypothesis for the formation of multinuclear complexes.

The metal-linked scaffold prompted us to examine the copper-catalyzed asymmetric conjugate addition of organozinc reagents to enones using (*R*)-3,3′-bis(diphenylphosphino)-[1,1′-binaphthalene]-2,2′-diol (**L1**).[3] To identify the optimal ligand structure, binol derivatives **L1**–**L3** were examined (Table 1). The reaction of Et_2Zn and (*E*)-chalcone (**4a**) was conducted in the presence of $CuCl_2{\cdot}2H_2O$ and the ligand in THF at either 0 °C or −20 °C.[4,5] The reaction using simple (*R*)-binol (binol = 1,1′-binaphthol) at 0 °C was examined but it did not proceed at all (Table 1, entry 1). In contrast, the reaction using Et_2Zn (1.5 equiv) in the presence of **L1** was complete in 1 hour at 0 °C to give the product **5a** in 67 % yield with 92 % *ee* (Table 1, entry 2). The mixture of $CuCl_2{\cdot}2H_2O$ and **L1** in THF gave a white suspension, and when this was treated with Et_2Zn a homogeneous solution resulted. How-

Table 1: Screening of reaction conditions.[a]



Entry	L (mol %)	R (equiv)	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*R*)-binol (5)	Et (1.5)	0	24	–	–
2	**L1** (5)	Et (1.5)	0	1	67	92
3	**L1** (10)	Et (1.5)	0	48	23	68
4	**L2** (5)	Et (1.5)	0	72	12	10
5	**L1** (5)	Et (3.0)	0	0.5	96	91
6	**L1** (5)	Et (3.0)	−20	0.5	> 98	94
7	**L3** (5)	Et (3.0)	−20	24	21	65
8	**L3** (10)	Et (3.0)	−20	24	30	71
9	(*R*)-binol (5)[d]	Et (3.0)	−20	16	89	< 1
10	**L1** (5)	Me (3.0)	RT	16	68	95
11	**L1** (5)	*n*Bu (3.0)	−20	16	93	87

[a] $CuCl_2{\cdot}2H_2O$ (5 mol %) used in all cases. [b] Yields determined based on NMR spectra. [c] The enantiomeric excess (*ee*) was determined by HPLC analysis on a chiral stationary phase (see the Supporting Information for details). [d] PPh_3 (10 mol %) was employed. MOM = methoxymethyl.

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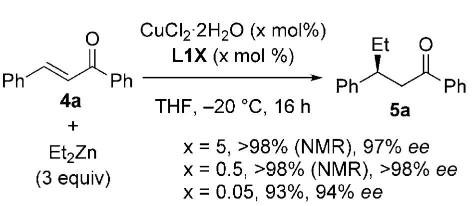
ever, the use of twice the amount of **L1** (10 mol %) relative to $CuCl_2{\cdot}2H_2O$ resulted in a clear yellow solution and a dramatically decreased reaction rate; the reaction was quenched after 48 hours and gave the product **5a** in 23 % yield with 68 % *ee* (Table 1, entry 3). The reaction using MOM-protected **L2**, bearing diphenylphosphino moieties at the 3,3′-positions, gave a notable result: $CuCl_2{\cdot}2H_2O$ and **L2** generated an oligomeric gel in THF, and the addition of diethylzinc did not give soluble complexes. The subsequent addition of (*E*)-chalcone (**4a**) gave an insoluble gel, and the desired product **5a** was obtained in 12 % yield and 10 % *ee* along with large amounts of unknown by-products after 72 hours (Table 1, entry 4). The reaction with **L1** using diethylzinc (3 equiv) at 0 °C improved the yield to 96 % with 91 % *ee* (Table 1, entry 5). The same reaction at −20 °C gave better results, and product **5a** was obtained in greater than 98 % yield with 94 % *ee* (Table 1, entry 6). In contrast, the monophosphine ligand **L3** decreased the reaction rate (homogeneous solution) and the reaction was not complete within 24 hours, but the product **5a** was produced in low yields with moderate *ee* values (Table 1, entries 7 and 8). These results are similar to those of the reaction using 10 mol % **L1** (Table 1, entry 3). Accordingly, the phosphorus moiety at the 3′-position in **L1** is important for the generation of the multicopper complex as the dramatic increase in catalytic activity and enantioselectivity relative to **L3** is notable. These findings clarified that the metal centers of the Cu/Zn/**L1** catalyst provided unique catalytic activity which was not present for the monocopper complex. As shown in entry 9 of Table 1, the reaction in the presence of PPh_3 (10 mol %) and (*R*)-binol (5 mol %) gave the product **5a** after 16 hours in 89 % yield with less than 1 % *ee*, thereby indicating that the phosphine and the (*R*)-binol moieties must be part of the same molecule to achieve selectivity in the conjugate addition reaction. The use of other dialkylzincs, such as Me_2Zn and $n{\rm Bu}_2Zn$, gave the products **6a** and **7a**, respectively, in high yield with high enantioselectivity (Table 1, entries 10 and 11). Surprisingly, the reaction proceeded in the presence of 0.05 mol % of the copper complex with **L1X** [Eq. (1); see Table 2 for **L1X** structure].[6] The reaction took place at −20 °C to give the product **5a** in 99 % yield (isolated) with 96 % *ee*. A previously reported catalyst system requires 1 mol % to achieve greater than 80 % yield and greater than 80 % *ee* in the copper-catalyzed asymmetric conjugate addition of organozinc reagents to acyclic enones, since the organocopper intermediates are generally unstable at lower temperatures for a long period of time.[7a,b] Therefore, we have succeeded in achieving the highest catalytic conjugate addition of alkylzinc reagents to acyclic enones to date.[7a,b]

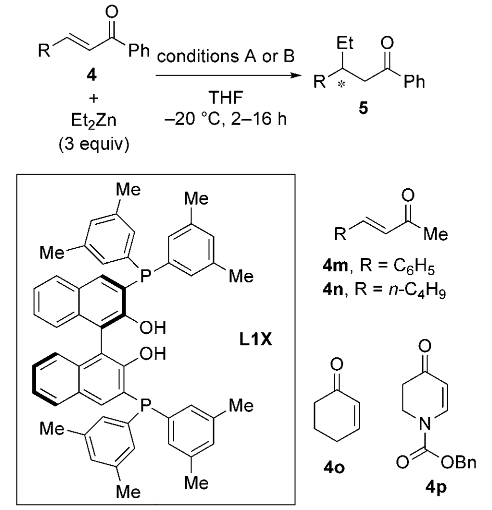


x = 5, >98% (NMR), 97% *ee*
x = 0.5, >98% (NMR), >98% *ee*
x = 0.05, 93%, 94% *ee*

(1)

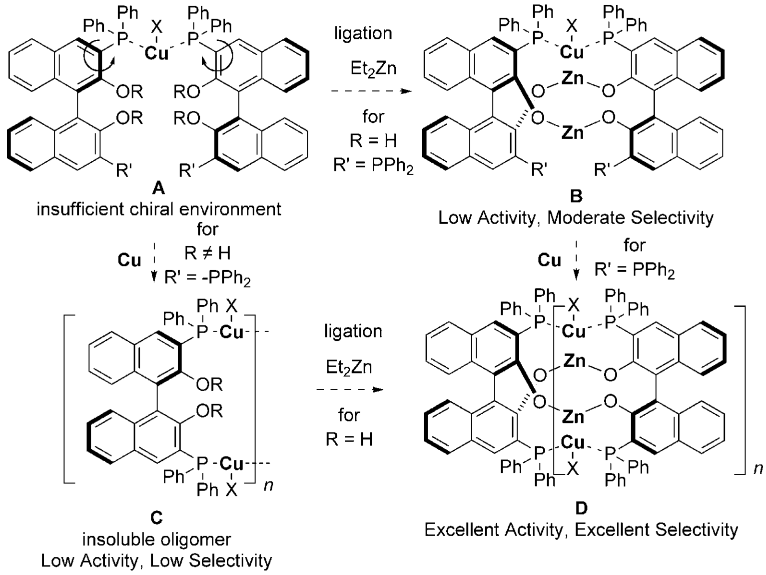
Additional investigations showed that **L1X** gave the best catalytic performance and achieved the highest catalytic activity (Table 2). The **L1X** ligand can be used under two different sets of reaction conditions to promote the asymmetric conjugate addition of diethylzinc to enones **4a**–**p**. The results of chalcones bearing electron-donating or electron-withdrawing groups showed high to excellent yields and excellent *ee* values under reaction conditions A (Table 2), which is superior to existing catalyst systems. Literature precedent has stated that the electronic nature of the substituents dramatically affects the catalysis and decreases the reaction rate.[7c] Modest catalytic performance when electron-rich chalcones are used is a typical disadvantage of

Table 2: Asymmetric conjugate addition to various enones.[a]



Entry	Enone, R	5	Conditions A Yield [%][b]	 *ee* [%][c]	Conditions B Yield [%][b]	 *ee* [%][c]
1	**4a**, C_6H_5	**5a**	91	> 98 (*S*)	99	96 (*S*)[d]
2	**4b**, $4\text{-}FC_6H_4$	**5b**	95	98 (+)	93	94 (+)
3	**4c**, $4\text{-}ClC_6H_4$	**5c**	99	98 (*S*)	88	93 (*S*)
4	**4d**, $4\text{-}F_3CC_6H_4$	**5d**	97	96 (*S*)	91	90 (*S*)
5	**4e**, $4\text{-}MeC_6H_4$	**5e**	94	> 98 (+)	90	95 (+)
6	**4f**, $4\text{-}PhC_6H_4$	**5f**	93	98 (−)	90	94 (−)
7	**4g**, $4\text{-}MeOC_6H_4$	**5g**	98	> 98 (*S*)	82	94 (*S*)
8	**4h**, naphthalene-2-yl	**5h**	99	> 98 (−)	91	97 (−)
9	**4i**, furan-2-yl	**5i**	97	> 98 (−)	90	96 (−)
10	**4j**, thiophen-2-yl	**5j**	93	98 (+)	82	91 (+)
11	**4k**, cyclohexyl	**5k**	91	89 (*R*)	52	72 (*R*)
12	**4l**, $n\text{-}C_5H_{11}$	**5l**	85	96 (+)	91	97 (+)
13	**4m**	**5m**	94	93 (*S*)	48	81 (*S*)
14	**4n**	**5n**	92	92 (+)	91	81 (+)
15	**4o**	**5o**	(90)	86 (*R*)	(60)	13 (*R*)
16[e]	**4p**	**5p**	67 (88)	97 (*S*)	–	–

[a] Reaction conditions A: enone (0.5 mmol), $CuCl_2{\cdot}2H_2O$ (0.5 mol%), **L1X** (0.5 mol%); reaction conditions B: enone (0.5 mmol), $CuCl_2{\cdot}2H_2O$ (0.05 mol%), **L1X** (0.05 mol%). [b] Yields of the isolated products. NMR yields are given within the parentheses. [c] The *ee* values were determined by HPLC analysis or GC analysis on chiral stationary phases (see the Supporting Information for details). The absolute configuration was determined by comparing the reported specific rotation data or retention time from HPLC analyses. The + or − signs refer to the optical rotation. [d] (*E*)-Chalcone (5 mmol) was used. [e] $CuBr{\cdot}SMe_2$ (12 mol%) and **L1X** (12 mol%) in toluene. Bn = benzyl.



Scheme 2. Proposed structures of the multinuclear complexes.

the copper-catalyzed asymmetric conjugate addition of organozinc reagents. In contrast, the present catalysis using binol derivatives provides versatile catalytic performance to give the desired products, even in the presence of 0.5 mol % catalyst. A notable characteristic of the present catalysis is that 0.05 mol % catalyst ($S/Cu = 2000$, conditions B) is enough to efficiently catalyze the reaction without any inhibition of the catalytic activity. These results suggest that additional modification of the diol architecture and phosphorus substituents could improve the catalysis. The reaction of **4k** bearing a cyclohexyl moiety required 18 hours to give the product **5k** in 91 % yield with 89 % *ee* (Table 2, entry 11; conditions A). The reaction of **4k** under reaction conditions B unfortunately delivered the product **5k** in 52 % yield with 72 % *ee*. The less hindered enone **4l**, bearing an alkyl chain, gave the product **5l** in 85 % yield with 96 % *ee* after 3 hours (Table 2, entry 12; conditions A). To date, these results for **4k** and **4l** are the best reported thus far with respect to the yield and enantioselectivity. Furthermore, the reaction of **4l** under conditions B for 24 hours delivered **5l** in 91 % yield with 97 % *ee* (Table 2, entry 12; conditions B). The reaction using (*E*)-4-phenylbut-3-en-2-one (**4m**) under reaction conditions A gave the desired product **5m** in 94 % yield with 93 % *ee*, and under reaction conditions B, **5m** was isolated in 48 % yield with 81 % *ee* (Table 2, entry 13). Furthermore, the use of the dialkyl-substituted enone (*E*)-oct-3-en-2-one (**4n**) resulted in 92 % yield of the product having a 92 % *ee* (Table 2, entry 14; conditions A). The lower catalyst loading could afford the corresponding product **5n** in 91 % yield with 81 % *ee* (Table 2, entry 14; conditions B). The reaction of cyclohex-2-enone (**4o**) gave the product **5o** in 90 % yield and 86 % *ee* (Table 2, entry 15; conditions A). Under the reaction conditions B **4o** yielded product with a dramatically decreased enantioselectivity. The reaction of **4p** using **L1X** gave **5p**, which was isolated in 67 % yield, with superior stereoselectivity; this is the highest enantioselectivity of **5p** reported to date (Table 2, entry 16). Previously developed ligands can typically not facilitate high catalytic performance for both cyclic and acyclic enones; for example, the phosphoramidite ligand generally gives much higher stereoselectivity in reactions of cyclic enones than in those of acyclic enones.[5] Consequently, the present ligand system has a potential advantage of providing the generality for the asymmetric conjugate addition of organozinc reagents to a variety of acyclic enones, which might be attributed to the effect of the multinuclear system.

The MOM-protected **L2** showed poor catalytic performance (Table 1, entry 4), which suggests that complexes derived form **L2**-type ligands, such as complexes **A** and **C** (Scheme 2), are not active catalysts.[8] Since **L3** showed poor catalytic performance (Table 1, entries 7 and 8), and a 1:2 ratio of $CuCl_2 \cdot 2H_2O$ and **L1** gave a similarly poor catalytic performance, it appears that the formed complexes, for example **B**, bearing uncoordinated phosphorus moieties are probably not the active catalysts. Therefore, the coordination of complex **B** with an additional copper center to give a complex such as **D** is important for achieving excellent catalytic performance. We propose that the active catalyst is formed upon generation of complex **D**.

The ESI MS analyses of **D** showed the presence of [**D**-$(CuBr)_2Zn_2 + SMe_2 + H]^+$ (*m*/*z* 1784.5, 100 %) and [**B**-$(CuBr)Zn_2 + SMe_2 + H]^+$ (*m*/*z* 1640.8, 22 %) as major fragments of the complexes formed in solution (see the Supporting Information for details).[9] Although the ESI MS analyses did not indicate oligomeric complexes, their formation cannot be ruled out. This data suggest that multinuclear complexes serve as the predominant species in the described catalysis.

In conclusion, we discovered and demonstrated the promising behavior of binol derivatives, which established the efficient copper-catalyzed asymmetric conjugate addition of organozinc reagents to enones. The highest catalytic performance was achieved relative to the previously developed ligand systems for acyclic enones. The experimental results indicated that the **L3**–Cu complex was not suitable for the high catalytic performance; therefore, the **L1**-type scaffolds coordinated to multiple metal centers result in effective chiral catalysts. We are now investigating the utility of the present catalyst system for various types of catalytic reactions, as well as studying the mechanism. The influence of the combined copper and zinc centers, and the exact structure of complex in both the solid and liquid states will be disclosed in due course.

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Keywords: alkylation · synthetic methods · copper · Michael addition · zinc

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