Modular Peptide-Based Phosphine Ligands in Asymmetric Catalysis: Efficient and Enantioselective Cu-Catalyzed Conjugate Additions to Five-, Six-, and Seven-Membered Cyclic Enones

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Peptide-based catalysts offer attractive and practical options in the development of asymmetric transformations. Peptides are easily prepared, consist of readily available chiral building blocks and are modular. Largely due to these attractive attributes, metal−peptide complexes have recently been demonstrated to initiate asymmetric C−C bond forming reactions.[1] Research in these laboratories, involving peptide-based phenolic Schiff bases as chiral ligands (e.g., **1**, Scheme 1), has led to the development of Ti-catalyzed additions of TMSCN to meso epoxides[2] and imines (Strecker amino acid synthesis),[3] and Zr-catalyzed addition of dialkylzincs to imines.[4] The effectiveness of peptidic ligands in the aforementioned programs led us to investigate their utility in promoting catalytic enantioselective olefin alkylations with alkylmetals.[5]

Herein, we report the results of our studies on catalytic enantioselective conjugate addition of dialkylzinc reagents to cyclic enones.[6,7] These transformations are promoted by $(CuOTf)_2 \cdot C_6H_6$ in conjunction with peptide-based chiral *phosphine* ligands (**2**, Scheme 1).[8] The method described allows for efficient, catalytic, and highly enantioselective (>95% ee) functionalization of not only six- and seven-membered ring enones, but also of cyclopentenones. It is worth noting that the catalytic asymmetric conjugate addition of alkylmetals to five-membered ring enones has previously been shown to be significantly less efficient and selective than reactions of the larger ring analogues.[7]

Scheme 1

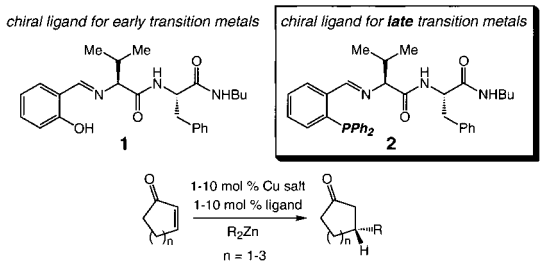

Table 1. Cu-Catalyzed Enantioselective Addition of Dialkylzinc Reagents to Cyclopentenones[a]

entry	substrate	alkylzinc	product	**2**, $(CuOTf)_2$ (mol %)	conv (%),[b] time (h)	yield[c] (%)	ee[d] (%)
1	**3**	Et_2Zn	**4a**	2.4, 1.0	90, 12	78[e]	97
2		Bu_2Zn	**4b**	2.4, 1.0	>98, 12	92[e]	98
3		$(i\text{-}Pr)_2Zn$	**4c**	2.4, 1.0	>98, 12	90	79
4		**5**	**4d**	2.4, 1.0	>98, 12	56	>98[f]
5	**6**	Et_2Zn	**7a**	2.4, 1.0	>98, 6	72[e]	>98
6		Bu_2Zn	**7b**	2.4, 1.0	95, 12	64[e]	>98
7		**5**	**7c**	6.0, 2.5	>98, 12	55	>98
8	**8**	Et_2Zn	**9**	17.5, 7.5	70, 24	56	97

[a] Conditions: indicated mol % **2** and $(CuOTf)_2 \cdot C_6H_6$, 3 equiv of dialkylzinc, toluene, −30 °C (−20 °C for entries 4 and 7). [b] Conversion determined by GLC. [c] Isolated yields after silica gel chromatography. [d] Enantioselectivities determined by chiral GLC (α-DEX for entries 1−2; CDGTA for entries 3, 5−8). [e] GLC yields (volatile products); representative isolated yields: 52% **4a** and 46% **7a**. [f] ee determined by GLC analysis of the acetal derived from (*R*,*R*)-dimethylethylene diol (CDGTA).

To initiate our studies, we examined the potential utility of chiral peptidic ligands represented by **1** (Scheme 1). Under a variety of conditions, however, conjugate additions deliver racemic products. Treatment of cyclopentenone (**3**) with 10 mol % **1**, a variety of Cu salts,[9] and 3 equiv of Et_2Zn (toluene, −30 °C) leads to the formation of the expected ketone product in >98% conv but in <5% ee. Similar results were obtained with cyclohexenone and cycloheptenone.

At this point we reasoned that, whereas the phenol Schiff base may be suitable for association with early transition metals (e.g., Ti or Zr), the corresponding P-containing chiral ligand **2** should provide a "softer" site of binding and may be more appropriate for late transition metals (e.g., Cu or Zn). Accordingly, we prepared **2** from commercially available 2-(diphenylphosphino)-benzaldehyde and performed screening of conditions to establish the optimum Cu salt and solvent. As illustrated in entry 1 of Table 1, treatment of cyclopentenone **3** with 1.0 mol % $(CuOTf)_2 \cdot C_6H_6$,[10] 2.4 mol % **2**[11] and 3 equiv of Et_2Zn leads to 90% conv[12]

(1) (a) Mori, A.; Nitta, H.; Kudo, M.; Inoue, S. *Tetrahedron Lett.* **1991**, *32*, 4333−4336. (b) Abe, H.; Nitta, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1992**, 2443−2446. (c) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969−7975. (d) Mori, A.; Abe, H.; Inoue, S. *Appl. Organomet. Chem.* **1995**, *9*, 189−197. For representative reports, where peptides serve as chiral catalysts (without a metal salt), see: (e) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638−11643. (f) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed., Engl.* **2000**, *39*, 1279−1281.

(2) (a) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668−1671. (b) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704−1707.

(3) (a) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284−4285. (b) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658.

(4) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, in press.

(5) Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; p 431−454.

(6) Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649−7650.

(7) (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) Strangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503−16510. (c) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104−1105. (d) Alexakis, A.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Leveque, J.-M.; March, S.; Rosset, S. *Synlett* **1999**, 1811−1813. (e) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518−3521. (f) Yamanoi, Y.; Imamoto, T. *J. Am. Chem. Soc.* **1999**, *64*, 2988−2989. (g) Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879−2888. (h) Chataigner, I.; Gennari, C.; Piarulli, U.; Ceccarelli, S. *Angew. Chem., Int. Ed., Engl.* **2000**, *39*, 916−918.

(8) For a recent report in connection with a peptide-based phosphine ligand (Pd-catalyzed allylic substitution), see: Gilbertson, S. R.; Collibee, S. E.; Agarkov, A. *J. Am. Chem. Soc.* **2000**, *122*, 6522−6523.

(9) The following Cu salts were examined: CuCN, CuCl, $CuBr \cdot Me_2S$, CuI, CuOAc, $Cu(OTf)_2$, and $(CuOTf)_2 \cdot C_6H_6$. Solvents screened were THF, Et_2O, toluene, CH_2Cl_2, and $ClCH_2CH_2Cl$. Among various possible combinations, $Cu(OTf) \cdot C_6H_6$ in toluene proved to be the most efficient combination.

(10) (a) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 1889−1897. (b) Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300−3310.

(11) Approximately 20% excess ligand (vs CuOTf) is used to avoid competing background reactions.

(12) Complete conversion and identical enantioselection is observed at higher catalyst loading. For example, with 2.8 mol % $(CuOTf)_2 \cdot C_6H_6$ and 7.0 mol % **2**, >98% conv is achieved in 6 h.

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Table 2. Cu-Catalyzed Enantioselective Addition of Dialkylzinc Reagents to Cyclohexenones and Cycloheptenones[a]

entry	substrate	alkylzinc	product		conv[b] (%)	yield[c] (%)	ee[d] (%)
1		Me_2Zn		**11a**	>98	71	>98
2		Et_2Zn		**11b**	>98	98	98
3		Bu_2Zn		**11c**	>98	93	95
4		$(i\text{-Pr})_2Zn$		**11d**	>98	98	72
5	**10**	 **5**	**11**	**11e**	>98	76	95
6		Me_2Zn		**13a**	>98	80	>98
7		Et_2Zn		**13b**	>98	98	98
8		Bu_2Zn		**13c**	>98	81	95
9		$(i\text{-Pr})_2Zn$		**13d**	88	78	62
	12		**13**				

[a] Conditions: 1.0 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % **2**, 3 equiv of alkylzinc, toluene, −30 °C (−20 °C for entry 5). All reactions required 12 h, except for entries 2 and 7. [b] Conversion determined by GLC. [c] Isolated yields after silica gel chromatography. [d] Enantioselectivities were determined by chiral GLC (CDGTA for entries 1−5, 7, 9; β-DEX for entries 6, 8). See Supporting Information for details.

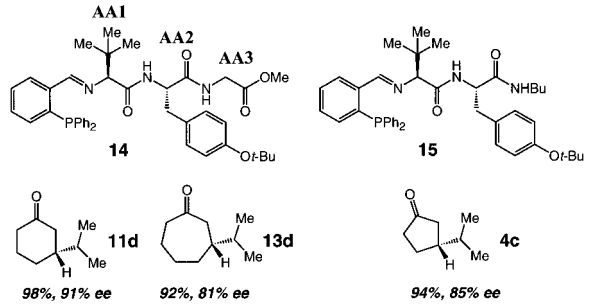
after 12 h (toluene, −30 °C), where ketone **4a** is obtained in 78% yield and 97% ee (chiral GLC).[13] Addition of Bu_2Zn (**3**→**4b**) and functionalized alkylzinc **5** (→**4d**) takes place smoothly with 98% and >98% ee, respectively (entries 2 and 4, Table 1). With the sterically more hindered $(i\text{-Pr})_2Zn$ as the alkylating agent (entry 3, Table 1), the catalytic addition proceeds to completion (>98% conv) but is less enantioselective (79% ee; see below for ligand optimization).

As depicted in entries 5−7 of Table 1, Cu-catalyzed conjugate additions of dimethyl-cyclopentenone **6** are equally efficient. In the presence of 1−2.5 mol % $(CuOTf)_2 \cdot C_6H_6$ and 2.4−6 mol % **2** reactions are complete within 12 h and deliver the desired products in ≥98% ee.[14] In contrast, the sterically more hindered alkene of **8** (entry 8) undergoes conjugate addition reluctantly: higher catalyst loadings are required for appreciable conversion (7.5 mol % Cu salt and 17.5 mol % **2**). The desired product **9** is however obtained in 97% ee (56%).[15]

Chiral phosphine **2** and CuOTf promote enantioselective conjugate additions to larger ring enones as well. As illustrated in Table 2, cyclohexenone **10** undergoes Cu-catalyzed conjugate additions in the presence of 1.0 mol % $(CuOTf)_2 \cdot C_6H_6$ and 2.4 mol % **2** (>98% conv in all cases). Entries 1−3 and 5 of Table 2 indicate that when *n*-alkylzinc reagents are used, chiral ketones **11a**−**11c** and **11e** are isolated in >70% yield and ≥95% ee. As before (entry 3, Table 1), reaction with $(i\text{-Pr})_2Zn$ occurs with lower enantioselectivity (72% ee). A similar trend is observed with reactions of cycloheptenone **12** (entries 6−9, Table 2); most *n*-alkylzincs, except for $(i\text{-Pr})_2Zn$ (entry 9), participate in facile and highly enantioselective transformations.

To address the issue of lower enantiocontrol in additions involving $i\text{-Pr}_2Zn$, we set out to identify an improved chiral ligand through the positional optimization strategy,[2a] with cyclohexenone **10** serving as the substrate. As illustrated in Scheme 2, we have established that reactions promoted by phosphine **14** (*t*-Leu at AA1, *t*-Bu-Tyr at AA2 and Gly at AA3) deliver **11d** in 91% ee (vs 72% ee with **2** as catalyst). Ligand **14** also provides a better selectivity in reaction of cycloheptenone **12** with $i\text{-Pr}_2Zn$ (81% ee vs 62% ee with **2**). In contrast, with cyclopentenone **3** as

Scheme 2[a]

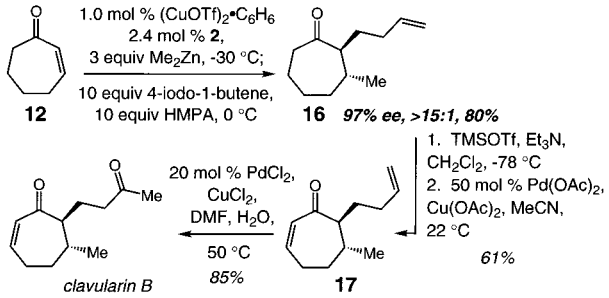


[a] Conditions: 1.0 mol % $(CuOTf)_2 \cdot C_6H_6$, 2.4 mol % chiral ligand, 3 equiv of $(i\text{-Pr})_2Zn$, −30 °C.

substrate, **4c** is obtained in 65% ee when **14** is used (vs 79% ee with **2**). When phosphine **15** (Gly replaced by *n*-Bu)[16] is employed in the reaction of **3**, however, cyclopentanone **4c** is isolated in 85% ee (94%). The above observations imply that if complete ligand screening is carried out specifically for each substrate, a different optimal chiral phosphine construct may emerge for that particular enone.[2]

The present catalytic asymmetric method delivers Zn−enolate intermediates that can be functionalized in situ. For example, sequential catalytic addition/alkylation of **12** provides **16** in 97% ee, 80% yield, and with >15:1 diastereoselectivity (Scheme 3). Pd-mediated regioselective oxidation (→**17**),[17] followed by Wacker oxidation[18] completes a four-step enantioselective synthesis of anti-cancer clavularin B[19] (42% overall from commercially available **12**).

Scheme 3



In brief, we disclose an effective protocol for the enantioselective addition of dialkylzincs promoted by catalysts that are composed of commercially available components and can be easily modified.[20] Future studies are aimed at deciphering various mechanistic issues and the application of peptidic phosphine ligands to enantioselective additions involving acyclic substrates. Development of other asymmetric C−C bond forming transformations with this class of chiral ligands is in progress as well.[21]

Supporting Information Available: Experimental procedures and spectral and analytical data for all recovered starting materials and reaction products (PDF). This material is available free of charge via the Internet at http//:www.acs.pubs.org.

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(13) Reactions proceed with equal facility in the absence of **2**. This suggests that a rapidly generated chiral phosphine•Cu complex promotes the enantioselective addition.

(14) Reaction of **6** with dialkylzinc **5** proceeds to ~80% conv with 2.4 mol % **2** and 1.0 mol % of the Cu salt (48% yield and >98% ee).

(15) Once the identity of the optimum ligand (e.g., **2**) and Cu salt $(CuOTf)_2 \cdot C_6H_6$ were established, a brief screening of various solvents was again performed; toluene remained the most effective medium. Representaive data from this study (**8** as substrate and Et_2Zn): CH_2Cl_2 (20% conv, 21% ee); $ClCH_2CH_2Cl$ (32% conv, 42% ee), THF (<5% conv), Et_2O (31% conv, 92% ee), 50% hexanes in toluene (<5% conv).

(16) In all screenings, two sets of ligands involving Gly and *n*-Bu as AA3 were examined. Structural modifications thus involved variations at AA1 and AA2. Further details will be disclosed in the full account of this work.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(18) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, *34*, 2975−2976.

(19) (a) Tamura, R.; Watabe, K.; Ono, N.; Yamamoto, Y. *J. Org. Chem.* **1993**, *58*, 4471−4472. (b) Hiroya, K.; Zhang, H.; Ogasawara, K. *Synlett* **1999**, 592−532.

(20) For an alternative approach to similar products through catalytic asymmetric hydride addition, see: Moritani, Y.; Apella, D. H.; Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 6797−6798.

(21) This research was supported by the NIH (General Medical Sciences) and DuPont. We are grateful to Professor M. L. Snapper and C. A. Luchaco-Cullis for helpful discussions.