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Identification of Modular Chiral Bisphosphines Effective for Cu(I)-Catalyzed Asymmetric Allylation and Propargylation of Ketones

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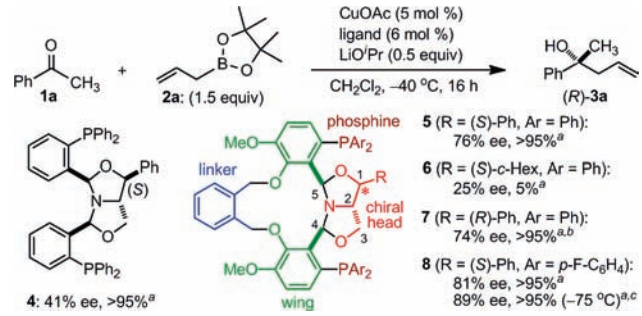
Chiral phosphines play pivotal roles in asymmetric catalysis.[1] Many privileged chiral phosphines have been developed. Continuous structural improvement and diversification are still necessary, however, to achieve high asymmetric induction in difficult-to-control C−C bond formations, such as construction of tetrasubstituted carbons.[2] Synthesis of chiral phosphines is generally labor-intensive, which has hampered their intensive structural optimization. A modular approach would facilitate chiral phosphine development, as it would allow for rapid and systematic synthesis of molecules with structurally diverse arrays.[3] We report herein the discovery of new modular chiral phosphines that produce excellent enantioselectivity in Cu(I)-catalyzed asymmetric allylation and propargylation of ketones.

We previously reported an asymmetric allylboration of ketones using a catalytic combination of a CuX−^{i}Pr-DuPHOS complex (X = F, OR) and hard-metal (La, Li, K) alkoxides.[4,5] The active nucleophile was an allylcopper species generated through transmetalation of an allylboronate.[6] Although the products were obtained in high yield, the enantioselectivity was not necessarily satisfactory, even after intensive screening of commercially available chiral phosphines. For example, product **3a** from acetophenone (**1a**) was produced in 94% yield with 82% ee. To improve the enantioselectivity, we started a program to develop chiral phosphine ligands with a completely new scaffold. Our basic ligand design concept was to construct chiral phosphines through the facile assembly of independent modules.

We first synthesized diphosphine **4** via bisaminal formation using an air-stable triarylphosphine module and an inexpensive chirality-introducing aminodiol. Its function was assessed by Cu-catalyzed asymmetric allylation of **1a** (Scheme 1). Despite the simple and flexible structure of **4**, a CuOAc−**4** complex[7] produced (*R*)-**3a** in quantitative yield with a promising 41% ee. To improve the enantioselectivity, we designed **5** containing a conformationally constrained 13-membered macrocycle. Ligand **5** comprised four modules (linker, wing, chiral head, and phosphine) and was synthesized on a gram scale in three steps from commercially available starting materials (overall yield 70%).[8] As expected, the use of **5** improved the enantioselectivity to 76% ee.

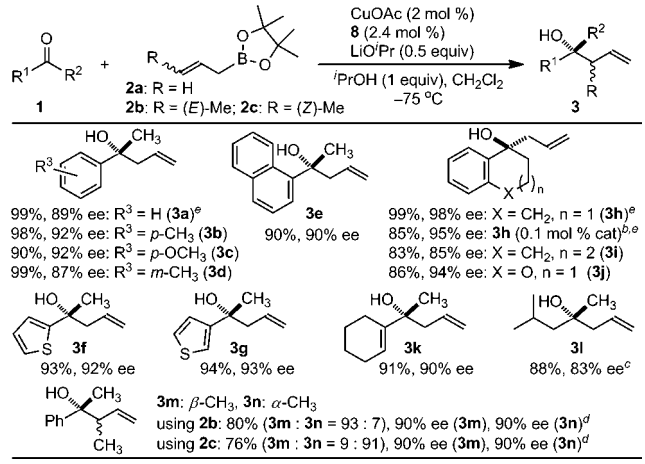
The effects of the structural modification of each module of **5** were then systematically investigated.[8] Four significant trends were observed (Scheme 1): (1) As a substituent of the chiral head (R), aromatic groups were essential (**5** vs **6**). (2) The chirality of C2 had almost no effect on the enantioselectivity (**5** vs **7**). (3) A specific rigid conformation of the core macrocycle defined by the linker and wing modules was critical.[8] (4) Introduction of electron-withdrawing substituents at the para position of the phosphine part (Ar) improved the enantioselectivity (**5** vs **8**). Addition of 1 equiv of ^{i}PrOH effectively enhanced the reactivity,[5f,l] allowing the reaction temperature to be decreased to −75 °C; product **3a** was obtained with 89% ee using 2 mol % catalyst.

Scheme 1. Systematic Optimization of the Modular Ligand



[a] Enantiomeric excess and yield of **3a**. [b] (*S*)-**3a** was obtained. [c] Using 2 mol % catalyst at −75 °C in the presence of 1 equiv of ^{i}PrOH.

Table 1. Catalytic Asymmetric Allylation of Ketones[a]



[a] Standard conditions are shown in the scheme. Isolated yields and enantiomeric excesses determined by chiral HPLC or GC are summarized. [b] Using 0.1 mol % CuOAc and 0.12 mol % **8**. [c] At −60 °C. [d] Using 5 mol % CuOAc and 6 mol % **8** with 1 equiv of LiO^{i}Pr at −60 °C. [e] The absolute configuration was determined as shown.

The substrate scope was then studied under the optimized conditions (Table 1). In general, the enantioselectivity and catalytic activity were significantly higher than in our previous reaction using ^{i}Pr-DuPHOS.[4,9] The crotylation reaction also proceeded with improved diastereo- and enantioselectivity (**3m** and **3n**). In comparison with the organocatalyzed reaction recently reported by Schaus,[5l] the enantio- and diastereoselectivity were slightly inferior. The high catalytic activity and applicability to saturated aliphatic ketones (e.g., **1l**), however, are advantages of our reaction. In an ideal case, the catalyst loading was reduced to 0.1 mol % (**3h**).

To expand the utility of ligand **8**, we applied the CuOAc−**8** catalyst to an enantioselective propargylation of ketones[10] using allenylboronate **9** (Table 2). Homopropargyl tertiary alcohols **10**

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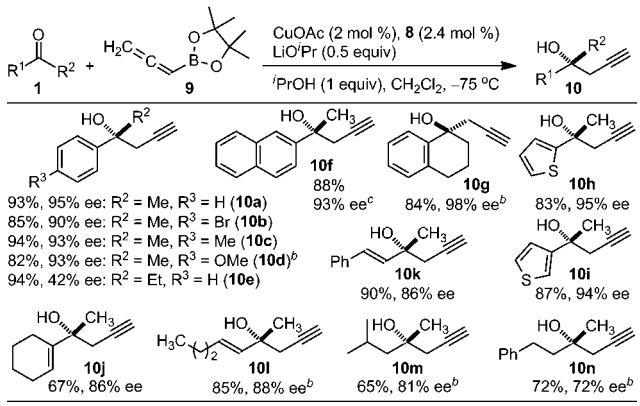
Table 2. Catalytic Asymmetric Propargylation of Ketones[a]



[a] Standard conditions are shown in the scheme. Isolated yields and enantiomeric excesses determined by chiral HPLC are summarized. [b] Using 5 mol % catalyst. [c] The absolute configuration was determined as shown.

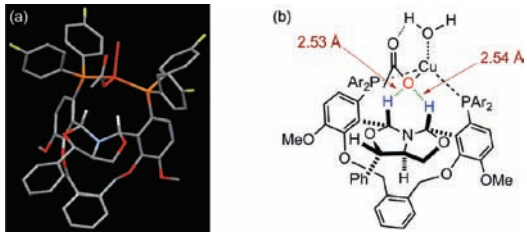


Figure 1. (a) X-ray crystal structure of the CuOAc·H_2O−**8** complex. (b) Its chemical description.

were produced with high enantioselectivity from a range of ketones. The reaction proceeded with perfect regioselectivity (γ-addition), and the corresponding allenyl alcohol isomers (α-adducts) were not detected in any case. Because of the synthetic versatility of terminal alkynes, various product conversions, such as Sonogashira coupling and one-pot Huisgen cycloaddition with azides (using the same Cu catalyst),[11] were possible.[8] Therefore, this reaction produces a synthetically independent family of chiral building blocks for allylation. To our knowledge, this is the first catalytic enantioselective propargylation of ketones.

To gain preliminary insight into the origin of the high catalytic activity and enantioselectivity of the CuOAc−**8** complex, we elucidated the X-ray crystal structure of the complex (Figure 1).[12] The central 13-membered macrocycle forms a conformationally rigid folded structure in which the linker aromatic group overhangs the chiral bisaminal bicyclo[3.3.0] system. The observed bite angle is extraordinarily wide ($\angle$P−Cu−P = 137.8°), resulting in the stabilization of the catalytically active monomeric Cu complex.[8,13] In addition, the oxygen atom of the acetate ligand forms nonconventional C−H···O hydrogen bonds with the bisaminal protons,[14] leading to a distortion of the tetrahedral geometry around the copper atom. The relevance of this distorted geometry and hydrogen-bonding ability to the enantioselectivity and high catalytic activity is currently under investigation.

In conclusion, we have identified new modular chiral phosphines that are effective for Cu(I)-catalyzed asymmetric allylation and propargylation of ketones. Studies directed toward obtaining a more detailed understanding of the enantiodifferentiation mechanism and extending the utility of the new phosphines to other catalytic asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedures, characterization of the products, ligand optimization, and theoretical support for the nonconventional hydrogen bonding. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008.
(2) (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (c) Hatano, M.; Ishihara, K. *Synthesis* **2008**, 1647.
(3) For examples, see: (a) Reetz, M.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (b) van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539. (c) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792. (d) Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (e) Takacs, J. M.; Reddy, D. S.; Moteki, S. A.; Wu, D.; Palencia, H. *J. Am. Chem. Soc.* **2004**, *126*, 4494. (f) Chen, W.; Mbafor, W.; Roberts, S. M.; Whittall, J. *J. Am. Chem. Soc.* **2006**, *128*, 3922. (g) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188. (h) Liu, Y.; Sandoval, C. A.; Yamaguchi, Y.; Zhang, X.; Wang, Z.; Kato, K.; Ding, K. *J. Am. Chem. Soc.* **2006**, *128*, 14212. (i) Hattori, G.; Hori, T.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12930. (j) Wakabayashi, K.; Aikawa, K.; Kawauchi, S.; Mikami, K. *J. Am. Chem. Soc.* **2008**, *130*, 5012. (k) Yu, J.; RajanBabu, T. V.; Parquette, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 7845. (l) Patureau, F. W.; de Boer, S.; Kuil, M.; Meeuwissen, J.; Breuil, P. R.; Siegler, M. A.; Spek, A. L.; Sandee, A. J.; de Bruin, B.; Reek, J. N. H. *J. Am. Chem. Soc.* **2009**, *131*, 6683.
(4) (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (b) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055.
(5) For other examples of catalytic asymmetric allylation of ketones, see: (a) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061. (b) Hanawa, H.; Kii, S.; Maruoka, K. *Adv. Synth. Catal.* **2001**, *343*, 57. (c) Cunningham, A.; Woodward, S. *Synlett* **2002**, 43. (d) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697. (e) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (f) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556. (g) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (h) Zhang, X.; Chen, D.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 5227. (i) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752. (j) Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824. (k) Itoh, J.; Han, S. B.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6313. (l) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679. (m) Huang, X.-R.; Chen, C.; Lee, G.-H.; Peng, S.-M. *Adv. Synth. Catal.* **2009**, *351*, 3089.
(6) Russo, V.; Herron, J. R.; Ball, Z. T. *Org. Lett.* **2010**, *12*, 220.
(7) Cu(I) salts conjugated with a hard anion (e.g., F^-, RO^-, RCO_2^-) generally promoted the allylation reaction without affecting the enantioselectivity. Preparation of the asymmetric catalyst was simpler using CuOAc (simple mixing with an approximately equimolar amount of the chiral phosphine) than CuF [reduction of CuF_2 using 2 equiv of the chiral phosphine relative to Cu (see ref 4a)]. The catalytic activity of CuF, however, was generally higher than that of CuOAc.
(8) See the Supporting Information (SI) for details.
(9) When ^{i}Pr-DuPHOS and xantphos were used under the current optimized conditions, the product yields were markedly lower (less than 5% for **1a**) than when **8** was used. Moreover, no detectable amount of product was obtained in propargylation using CuOAc−^{i}Pr-DuPHOS or −xantphos catalyst.
(10) Enantioselective propargylation of ketones depended on the use of stoichiometric amounts of chiral sources. See: (a) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal.* **2009**, *351*, 2295. (b) Hernandez, E.; Burgos, C. H.; Alicea, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 4089.
(11) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(12) Use of the crystal as an asymmetric catalyst produced results comparable to those for the in situ-prepared CuOAc−**8** complex.
(13) (a) A clear dependence of the catalytic activity on the aggregation state of the Cu−bisphosphine (**8**, ^{i}Pr-DuPHOS, xantphos) complexes was observed (see the SI for details). (b) Sterically bulky phosphines markedly enhance the reactivity of Cu-catalyzed hydrosilylation reactions by stabilizing active monomeric catalysts. For examples, see: Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916.
(14) For examples of C−H···O hydrogen bonding, see: (a) Vargas, R.; Garza, J.; Dixon, D. A.; Hay, B. P. *J. Am. Chem. Soc.* **2000**, *122*, 4750. (b) Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321. (c) C−H···O hydrogen-bond formation in the CuOAc−**8** complex was also supported by density functional theory calculations (see the SI). (d) The crystal structure of the CuOAc−**5** complex did not contain H_2O, but the C−H···O hydrogen bond still existed (see the SI).

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