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Published on Web 08/07/2004

Cu-Catalyzed Asymmetric Allylic Alkylations of Aromatic and Aliphatic Phosphates with Alkylzinc Reagents. An Effective Method for Enantioselective Synthesis of Tertiary and Quaternary Carbons

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Abstract: Efficient enantioselective Cu-catalyzed allylic alkylations of aromatic and aliphatic allylic phosphates bearing di- and trisubstituted olefins are disclosed. Enantioselective C−C bond forming reactions are promoted in the presence of 10 mol % readily available chiral amino acid-based ligand (5 steps, 40% overall yield synthesis) and 5 mol % $(CuOTf)_2 \cdot C_6H_6$. Reactions deliver tertiary and quaternary stereogenic carbon centers regioselectively and in 78−96% ee. Data regarding the effect of variations in ligand structure on the efficiency and enantioselectivity of the alkylation process, as well as a mechanistic working model, are presented. The suggested model involves a dual role for the chiral Cu complex: association of the Cu(I) center to the olefin is facilitated by a two-point binding between the carbonyl of the ligand's amide terminus and the P═O of the substrate.

Introduction

Allylic alkylations are important C−C bond forming reactions that deliver synthetically versatile organic molecules. Although many related catalytic asymmetric protocols have been outlined involving stabilized carbon nucleophiles,[1] additions of alkyl nucleophiles are significantly less developed.[2] One recent example is in regards to Cu-catalyzed additions of alkylzincs to disubstituted olefins of allylic chlorides, where >90% ee can be obtained with the sterically bulky bis(neopentyl)zinc; reactions of less hindered alkylzinc reagents proceed with significantly lower enantioselectivity (≤72% ee).[3] Chiral phosphoramidites and phosphites have also been shown to promote additions of smaller alkylzinc reagents (predominantly Et_2Zn) to disubstituted alkenes of allylic chlorides in up to 77% ee.[4] Efforts concerning reactions of alkylmagnesium halides with allylic acetates and chlorides (also disubstituted olefins)[5] in the presence of chiral aryl[5a] and ferrocenyl[5b] thiols as well as P-based ligands[5c−e] have led to several regioselective and efficient catalytic asymmetric alkylations. High enantioselectivities (up to 96% ee) have been observed in the latter studies;[5e] however, substrate range is somewhat limited (a single aliphatic and two nearly identical aromatic allylic halides) and does not include trisubstituted olefins.

We recently disclosed Cu-catalyzed additions of alkylzinc reagents to allylic phosphates promoted by pyridyl Schiff bases **1a**−**c** (Scheme 1).[6,7] Selectivities of 78−90% ee were observed for reactions of trisubstituted olefins, leading to asymmetric formation of quaternary carbon centers; synthetic utility was demonstrated through a concise total synthesis of (−)-sporochnol in 82% overall yield (82% ee). However, several shortcomings detracted from the utility of our method. As with the previously mentioned protocols,[3−7] transformations involving disubstituted olefins often proceed with low enantioselectivity (66−87% ee). Moreover, highly enantioselective reactions of aliphatic substrates (di- or trisubstituted olefins), a synthetically important and challenging category of alkylations, continued to prove elusive. It should be noted that, except for two cases involving a single substrate,[3b,5e] catalytic alkylation of aliphatic substrates typically yield products with inferior levels of optical purity (<75% ee).[5]

After the above studies, we discovered that chiral dipeptide **2**, derived from a salicyl aldehyde, in the presence of $(CuOTf)_2 \cdot$

(1) For recent reviews, see: (a) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.
(2) For a review, see: Hoveyda, A. H.; Heron, N. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; pp 431−454.
(3) (a) Dubner, F.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 379−381. (b) Dubner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233−9237.
(4) (a) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169−1171. (b) Shi, W.-J.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 3867−3872. For related studies, see (products obtained in <65% ee): (c) Borner, C.; Gimeno, J.; Gladiali, S.; Goldsmith, P. J.; Ramazzotti, D.; Woodward, S. *Chem. Commun.* **2000**, 2433−2444.
(5) (a) Meuzelaar, G. J.; Karsltrom, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Backvall, J.-E. *Tetrahedron* **2000**, *56*, 2895−2903. (b) Karlstrom, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Backvall, J.-E. *Synlett* **2001**, 923−926. (c) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927−930. (d) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147−4149. (e) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426−2428.
(6) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1456−1460.
(7) For related studies, see: (a) Piarulli, U.; Daubos, P.; Claveric, C.; Roux, M.; Gennari, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 234−236. (b) Ongeri, S.; Piarulli, U.; Roux, M.; Monti, C.; Gennari, C. *Helv. Chim. Acta* **2002**, *85*, 3388−3399. (c) Piarulli, U.; Claverie, C.; Daubos, P.; Gennari, C.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 4493−4496.

10.1021/ja0478779 CCC: $27.50

Scheme 1. Chiral Ligands Used in Cu-Catalyzed Asymmetric Alkylations of Allylic Phosphates

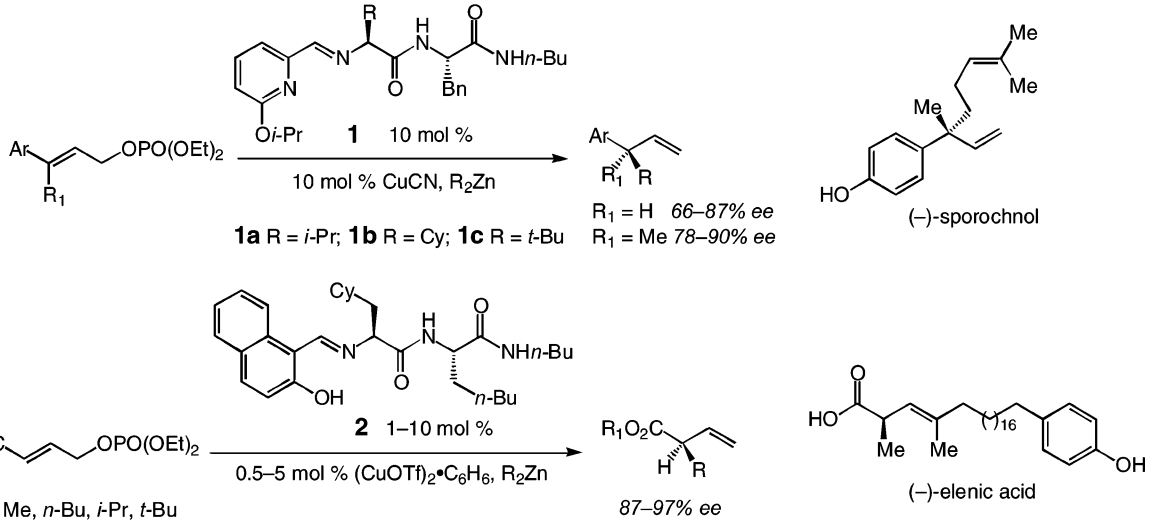
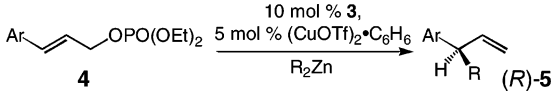


Table 1. Enantioselective Cu-Catalyzed Allylic Alkylations of Disubstituted Unsaturated Aryl Phosphates[a]

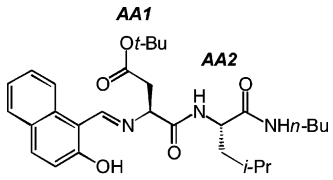


entry	Ar		alkylzinc	product	yield[b] (%)	$S_N2':S_N2$[c]	ee[d] (%)	ee with **1**[e] (%)
1	C_6H_5	**4a**	Et_2Zn	**5a**	61	90:10	95	66
2	C_6H_5	**4a**	$[Me_2CH(CH_2)_3]_2Zn$	**5b**	90	87:13	91	na
3	*p*-$CF_3C_6H_4$	**4b**	Et_2Zn	**5c**	73	90:10	94	na
4	*p*-$CF_3C_6H_4$	**4b**	$[AcO(CH_2)_4]_2Zn$	**5d**	62	81:19	84	na
5	*o*-$NO_2C_6H_4$	**4c**	Et_2Zn	**5e**	95	85:15	95	87
6	*o*-$NO_2C_6H_4$	**4c**	$[Me_2CH(CH_2)_3]_2Zn$	**5f**	82	87:13	95	na
7	*p*-$NO_2C_6H_4$	**4d**	Et_2Zn	**5g**	67	86:14	94	75
8	*o*-MeC_6H_4	**4e**	Et_2Zn	**5h**	66	50:50	96	72
9	2-naphth	**4f**	Et_2Zn	**5i**	64	40:60	93	na

[a] Conditions: 3 equiv of alkylzinc, THF, −15 °C, 24 h, N_2 atm. [b] Isolated yields. [c] Determined by 400 MHz ^1H NMR. [d] Determined by chiral GLC or HPLC (see Supporting Information for details). [e] See ref 6; >98% S_N2' in all cases. na = not available.

C_6H_6 effectively promotes catalytic alkylations of unsaturated esters bearing γ-phosphates to deliver α-alkyl-β,γ-unsaturated carbonyls with excellent levels of optical purity (Scheme 1).[8] The synthetic utility of this latter catalytic asymmetric protocol was demonstrated through application to a concise enantioselective total synthesis of topoisomerase II inhibitor (−)-elenic acid. These observations prompted us to examine the ability of the salicyl-based peptidic chiral ligands in effecting Cu-catalyzed asymmetric alkylations of the previously mentioned class of allylic phosphates (first equation in Scheme 1). Our aim was to enhance the enantioselectivity levels of the C−C bond forming reactions as well as expand the scope of the catalytic asymmetric method to include additions to the more difficult aliphatic substrates.

In this article, we report a new method for Cu-catalyzed enantioselective alkylations of allylic phosphates with alkylzinc reagents that is significantly more general and effective than the approaches mentioned above. Transformations are promoted by dipeptide Schiff base **3** and $(CuOTf)_2{\cdot}C_6H_6$ and afford products in up to 96% ee. A wide range of substrates can be effectively alkylated: *aromatic and aliphatic phosphates that bear di- or trisubstituted olefins undergo highly enantioselective alkylations*. Unlike the previously reported dipeptide **1**,[6] access to which requires synthesis of a functionalized pyridyl aldehyde, chiral ligand **3** is readily obtained in gram quantities in five reliable steps from a commercially available salicyl aldehyde and optically pure protected amino acids (40% overall yield; unoptimized).



3

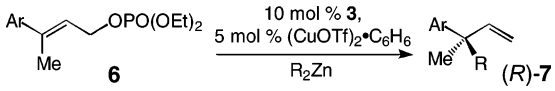
Results and Discussion

I. Cu-Catalyzed Asymmetric Allylic Alkylations of Aromatic Phosphates. As illustrated in Table 1, in the presence of 10 mol % chiral Schiff base **3**[9] and 5 mol % $(CuOTf)_2{\cdot}C_6H_6$ (THF, −15 °C, 24 h), aromatic disubstituted allylic phosphates **4a**−**f** undergo highly enantioselective (84−96% ee) allylic alkylations with various alkylzinc reagents. The regioselectivities

(8) Murphy, K. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4690−4691.

(9) A brief initial screening with selected di- and trisubstituted olefinic substrates (see Tables 1 and 2, below) indicated that although chiral ligand **2** is typically as effective in promoting catalytic alkylations, in a few instances dipeptide **3** promotes more efficient and/or enantioselective C−C bond forming reactions.

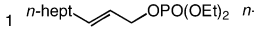
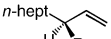
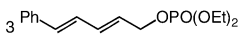
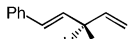
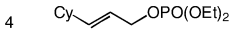
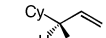
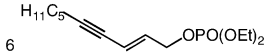
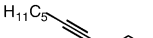
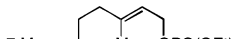
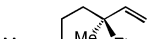
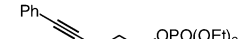
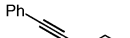
Table 2. Enantioselective Cu-Catalyzed Allylic Alkylations of Trisubstituted Unsaturated Aryl Phosphates[a]



entry	Ar		alkylzinc	product	yield[b] (%)	$S_N2':S_N2$[c]	ee[d] (%)	ee with **1**[e] (%)
1	C_6H_5	**6a**	Et_2Zn	**7a**	64	>30:1	92	78
2	*p*-$CF_3C_6H_4$	**6b**	Et_2Zn	**7b**	58	>30:1	88	81
3	*p*-$NO_2C_6H_4$	**6c**	Et_2Zn	**7c**	79	>30:1	87	86
4	*p*-$NO_2C_6H_4$	**6c**	$[Me_2CH(CH_2)_3]_2Zn$	**7d**	86	>30:1	83	na
5	*p*-$OTsC_6H_4$	**6d**	Et_2Zn	**7e**	92	>30:1	88	90

[a] Conditions: 3 equiv of alkylzinc, THF, −15 °C, 24 h, N_2 atm. [b] Isolated yields. [c] Determined by 400 MHz ^{1}H NMR. [d] Determined by chiral GLC or HPLC (see Supporting Information for details). [e] See ref 6; >98% S_N2' in all cases. na = not available.

Table 3. Enantioselective Cu-Catalyzed Allylic Alkylations of Unsaturated Alkyl, Alkenyl, and Alkynyl Allylic Phosphates[a]

entry	substrate	product		yield[b] (%)	$S_N2':S_N2$[c]	ee[d] (%)
1			**a** R = Me	76	>30:1	78
2	**8**	**9**	**b** R = Et	73	>30:1	92
3	 **10**	 **11**		74	85:15	89
4			**a** R = Me	68	>30:1	87
5	**12**	**13**	**b** R = Et	77	>30:1	95
6	 **14**	 **15**		76	82:18	96
7	 **16**	 **17**		87	>30:1	82
8	 **18**	 **19**		77	>30:1	91

[a] Conditions: 10 mol % **3**, 5 mol % $(CuOTf)_2{\cdot}C_6H_6$, 3 equiv of Et_2Zn or 6 equiv of Me_2Zn, THF, −15 °C, 24 h for Et_2Zn and 48 h for Me_2Zn, THF, N_2 atm. [b] Isolated yields. [c] Determined by 400 MHz ^{1}H NMR. [d] Determined by chiral GLC (see Supporting Information for details).

shown in Table 1, although synthetically useful, are lower than some of the previously reported cases.[3−7] However, the enantioselectivites are by far the highest reported for allylic alkylations with small alkylmetal reagents. In all cases, the increase in asymmetric induction is significant compared to reactions promoted by **1** (entries 1, 5, 7, and 8, Table 1).

The findings summarized in Table 2 illustrate that chiral ligand **3** also catalyzes alkylations of trisubstituted allylic phosphates with high regioselectivity (>30:1 $S_N2':S_N2$) to afford products bearing quaternary carbon centers in 83−92% ee. Optical purities obtained through the use of **3** are either nearly identical or higher than observed with pyridyl ligand **1** (92% vs 78% ee in entry 1, Table 2).[10]

II. Cu-Catalyzed Asymmetric Allylic Alkylations of Aliphatic Phosphates. One of the more important and unique attributes of the present method is that it can be used for alkylations of di- and trisubstituted aliphatic phosphates efficiently and with unprecedented enantioselectivity and excellent regioselectivity (Table 3). Facile alkylations of aliphatic substrates **8** and **12** with the less reactive Me_2Zn (vs Et_2Zn) stands in stark contrast to the significantly lower reactivity of aromatic phosphates shown in Table 1 (<10% conversion in most cases). Catalytic alkylation of alkenyl allylic phosphate **10** proceeds regioselectively (85:15 $S_N2':S_N2'$) to afford 1,4-diene **11** in 89% ee. Cu-catalyzed addition of Et_2Zn to alkynyl substrate **14** (entry 6) is less regioselective but delivers enyne **15** in 96% ee. *Efficient catalytic enantioselective alkylations of the trisubstituted allylic phosphates **16** and **18**, leading with high regiocontrol to the formation of a quaternary carbon stereogenic centers in diene **17** and enyne **19** in 82% and 91% ee, respectively, underline the significant potential of the present protocol in organic synthesis.*

III. Effect of the Chiral Ligand Structure on Efficiency and Enantioselectivity of Alkylations. The data illustrated in Table 4 shed light on the inner workings of the Cu-catalyzed transformations. As suggested by the alkylation in entry 1 (**20**, Table 4), the AA2 moiety (amino acid forming Schiff base is AA1) is necessary for high enantioselectivity but not for efficient alkylation. It is important to note that there is <2% conversion in the absence of a chiral ligand. The inability of ligand **21** (entry 2) to promote addition together with effectiveness of its diastereomer **3** indicates that the presence of an AA2 is not sufficient for high selectivity; the AA2 unit must also carry the proper stereochemical identity. The data in entries 3 and 4 show that, whereas chirality at AA1 raises the efficiency of a catalytic alkylation (reaction of **22**), it is not nearly as critical as the chirality resident within AA2 (reaction of **23**). Data in entries 3 and 4 demonstrate that asymmetric induction mainly originates at the AA2 site.

The inability of tertiary amide **24** to promote reaction points to the significance of peptide conformation preferences that accompany secondary amide structures.[11] The lack of reactivity with unsaturated ligand **25** and the inability of methyl ester **26** and dialkyl amide **27** to promote efficient or enantioselective reactions imply that the requirement for the terminal secondary amide moiety is conformational as well as steric: the presence of a sufficiently Lewis basic and sterically accessible amide is critical to a high yielding and enantioselective alkylation.

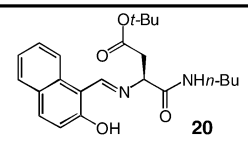
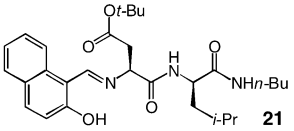
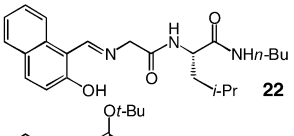
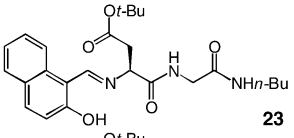
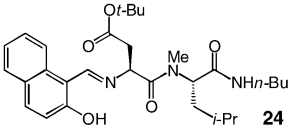
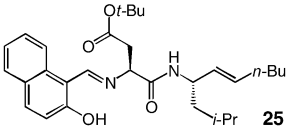
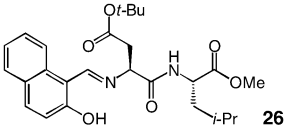
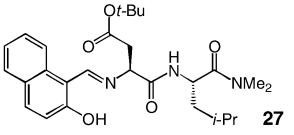
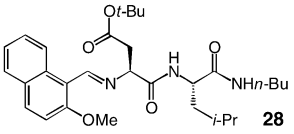
IV. Mechanistic Working Model. A working model (Scheme 2) is proposed based on the above data and recent mechanistic studies regarding other C−C bond forming reactions promoted by this class of chiral ligands.[12] Complex **I**, bearing a pseudo-tetrahedral Cu(I), represents the resting state of the chiral complex. Upon association of an unsaturated phosphate, complex **II** is generated. Catalytic alkylations likely proceed through

(10) Allylic phosphates with aryl units that bear *o*- or *p*-electron donating substituents are typically unstable. However, such substrates do undergo highly enantioselective catalytic alkylations. As an example, reaction of allylic phosphate **6** with an *o*-$OMeC_6H_4$ group proceeds to 50% conversion after 30 h to afford the desired product in 80−85% ee (>30:1 S_N2').

(11) For a general discussion, see: Creighton, T. E. In *Proteins. Structures and Molecular Properties*; Freeman: New York, 1984; pp 159−197.

(12) Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 11594−11599.

Table 4. Ligand Structure and Cu-Catalyzed Alkylation of **4a** with Et_2Zn[a]

entry	ligand	conv (%)[b]	$S_N2':S_N2$ (%)[b]	ee (%)[b]
1	 **20**	93	96:4	11
2	 **21**	18	77:23	–62
3	 **22**	63	85:15	88
4	 **23**	5-10	72:28	26
5	 **24**	<2	–	–
6	 **25**	5-10	60:40	17
7	 **26**	5	93:7	<2
8	 **27**	21	88:12	<2
9	 **28**	5-10	82:18	11

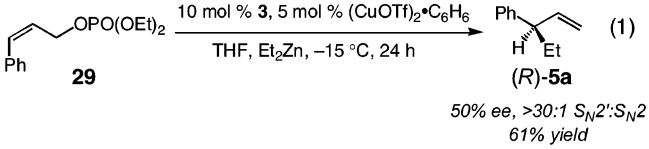
[a] Conditions: 10 mol % ligand, 5 mol % $(CuOTf)_2 \cdot C_6H_6$, 3 equiv of Et_2Zn, THF, −15 °C, 24 h, THF, N_2 atm. [b] Determined by GLC (see Supporting Information for details).

formation of Cu(III)-alkyl intermediates,[13] followed by reductive elimination to afford the desired products.[14]

Catalyst−substrate complex **II** reserves an activating, as well as a directing role, for the terminal amide carbonyl (cf. entries 1 and 5−8 in Table 4).[15] The substrate is delivered preferably to one face of the ligand•Cu complex by the carbonyl group of the amide terminus[16] if it is sterically unencumbered (cf. entry 8, Table 4) and sufficiently Lewis basic (cf. entry 7, Table 4).[17] The preferred ligand face is predicated on the identity of the minimized peptide structure (cf. entry 5),[11] including the conformational preorganization induced by the stereogenic center at AA2 (cf. entries 2 and 4, Table 4).[12] A preorganized peptide structure is critical as it minimizes the entropic cost associated with a macrocyclic transition structure, as shown in **I**.

The presence of an AA1 substituent (R in Scheme 2) is not required for a highly enantioselective process (cf. entry 3 in Table 4; 88% ee with Gly as AA1). Nonetheless, the alternative diastereomer (cf. entry 2 in Table 4) would position the AA1 substituent (R) at a less favorable pseudoaxial position, raising the energy of the requisite catalyst−substrate complex. Mode of addition **II** is sterically favored: the larger olefin substituent (R_L) points away from the bulk of the ligand structure. The presence of an O−Cu bond in **II** is suggested by the observation that the methyl ether derived **28** (entry 9, Table 4) promotes <10% alkylation.

As illustrated in eq 1, catalytic alkylation of **29**, the cis isomer of **4a** (cf. Table 1), with Et_2Zn under identical conditions as those in Table 1, proceeds to completion but affords (*R*)-**5a** in only 50% ee (>30:1 $S_N2':S_N2$, 61% yield). It is plausible that



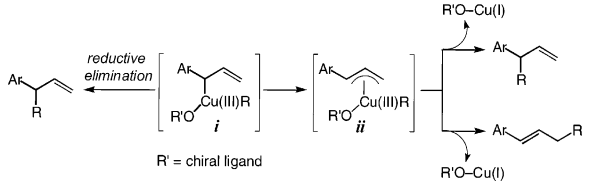
(1)

positioning of the large Ph group at the R_S site leads to destabilization of **II** (steric interaction with ligand's Schiff base moiety) and lowers enantioselectivity as a result of addition through other energetically competitive catalyst−substrate complexes. The increase in regioselectivity, however, is difficult to explain at this time.

Further evidence for the substrate−catalyst complexes shown in Scheme 2 is found in Cu-catalyzed alkylations of chiral nonracemic phosphate **30**. As illustrated in Scheme 3, catalytic alkylation of **30**, generated by Ru-catalyzed cross metathesis of **5e**,[18] in the presence of 10 mol % **3** leads to the formation of **31** as a single diastereomer (>98% conversion, 48 h). In contrast, when (D,D)-**3** is used, 10−15% conversion is observed

(13) For representative relevant experimental and theoretical studies, see: (a) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721−724. (b) Backvall, J.-E.; Sellen, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615−6621 and references therein. (c) Dorigo, A. E.; Wanner, J.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476−478. (d) Mori, S.; Hirai, A.; Nakamura, M.; Nakamura, E. *Tetrahedron* **2000**, *56*, 2805−2809. (e) Karlstrom, A. S. E.; Backvall, J. E. *Chem.—Eur. J.* **2001**, *7*, 1981−1989.

(14) Generation of the products derived through the S_N2 process in reactions shown in Table 1 may arise from collapse of the initial η^1 Cu complex ***i*** to π-allyl ***ii*** which then can afford the undesired product. The reason for the propensity of aromatic disubstituted phosphates (Table 1) to afford achiral alkylation byproducts is not clear at the present time. See ref 13 for related discussions.

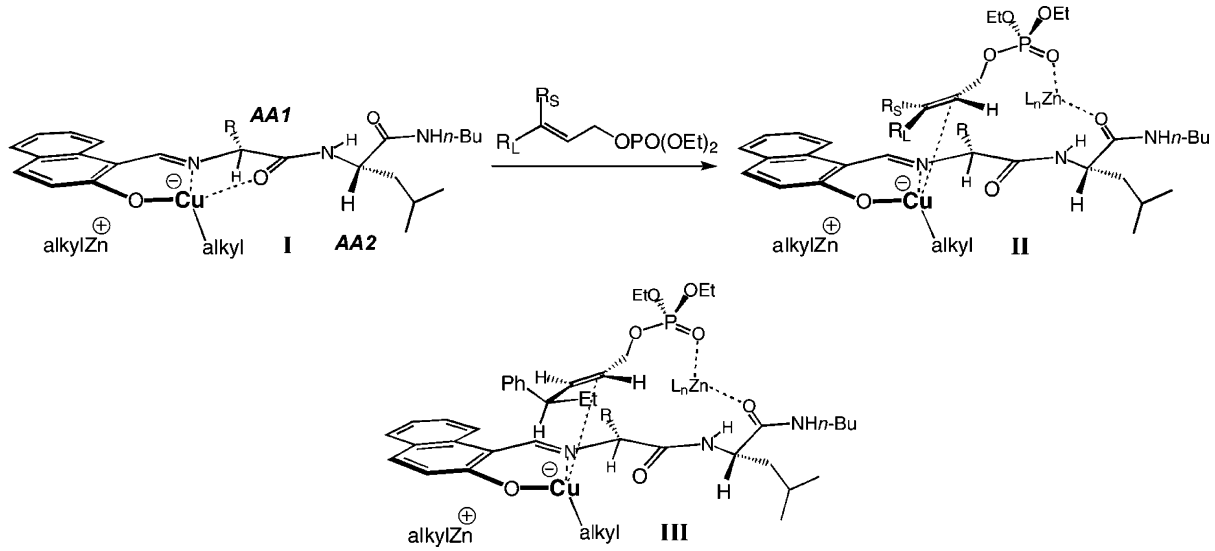


(15) For a related proposal involving two-point association between catalyst and substrate in a Cu-catalyzed allylic alkylation reaction, see ref 5a.

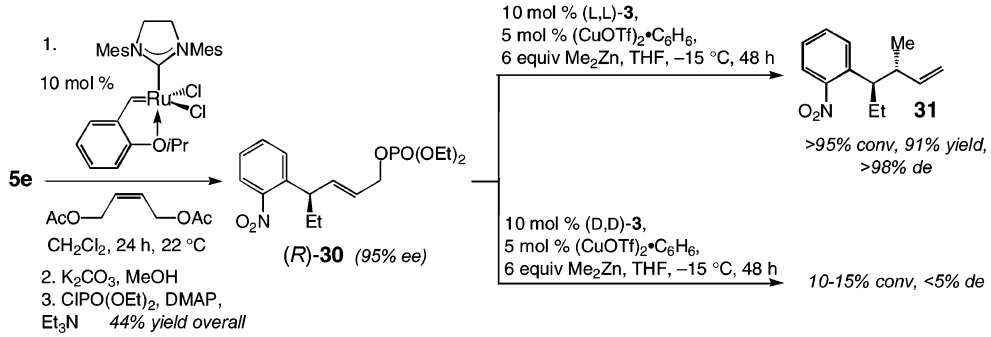
(16) Although a Zn chelate involving the amide C=O is shown in **II** and **III**, it is possible that the amide N participates in this chelation. It is also feasible that H-bonding between the secondary amide and the P=O of the substrate leads to the second point of contact between catalyst and substrate.

(17) Several observations point to the significance of the P=O bond in establishing an organized substrate-catalyzed complex that translates to high asymmetric induction. For example, catalytic alkylations of the derived allylic bromides proceed to afford the desired products (77% S_N2') in <2% ee. Moreover, alkylation of the thiophosphate derivative of substrate **4a** (P=S instead of P=O) with Et_2Zn (under conditions described for Table 1) leads to only ~20% conversion and <2% ee. The latter observation may underscore the significance of specific Lewis base−Lewis acid distances for effective generation of substrate−catalyst complexes.

Scheme 2. Proposed Modes of Reaction for Cu-Catalyzed Allylic Alkylations



Scheme 3. Cu-Catalyzed Alkylations of Optically Enriched Allylic Phosphate (*R*)-**30**



(<5% de). As illustrated in Scheme 2 (**III**), it may be proposed that association of (*R*)-**30** with **3** occurs through a complex where the small H points toward the catalyst structure and the large phenyl is oriented away from the chiral complex. Alkylation of (*S*)-**30**[19] would require the large phenyl to occupy the "inside" position (the position Et holds in **III**), engendering a higher degree of steric repulsion within the catalyst−substrate complex.

Alkylation of (*R*)-**30** with 10 mol % CuCN (without chiral ligand, otherwise identical conditions as in Scheme 3) affords **31** in 81% isolated yield and only 80% de (>98% conversion). The "matched" chiral ligand thus imposes higher degrees of transition state organization to enhance the diastereoselectivity of the alkylation.[20] It should also be noted that the significant differences in the rates of allylic alkylations of (*R*)-**30** (Scheme 3) suggest that related racemic substrates can be subjected to efficient Cu-catalyzed kinetic resolutions as well.[21]

(18) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (b) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Garber, S. B.; Kataoka, O.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biol. Chem.* **2004**, *2*, 8−23.

(19) The substrate/catalyst complex derived from (*S*)-**24** and (L,L)-**3** is energetically equivalent to that arising from (*R*)-**24** and (D,D)-**3** and is therefore used here for the sake of clarity of discussion.

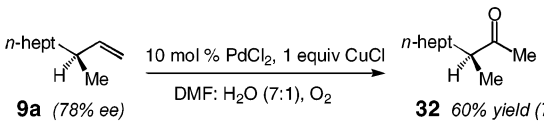
(20) For another example, where, in the presence of a chiral amino acid-based ligand, diastereoselectivities are enhanced significantly, see: Cesati, R. R.; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96−101.

(21) For recent reviews of metal-catalyzed kinetic resolutions, see: (a) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537−574. (b) Cook, G. R. *Curr. Org. Chem.* **2000**, *4*, 869−885. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5−26.

Conclusions

In summary, we disclose an efficient and highly enantioselective method for catalytic alkylations of allylic phosphates with various alkylzinc reagents. Special features of the present protocol include efficient asymmetric additions to di- and trisubstituted *aliphatic* substrates that deliver tertiary and quaternary carbon centers;[22] the derived optically enriched products cannot be accessed readily by other methods. Moreover, we propose a plausible working model that explains the origin of the observed selectivities.

The Cu-catalyzed enantioselective alkylations presented herein are of high synthetic potential. The products obtained can be readily functionalized in a large variety of ways. The Ru-catalyzed cross metathesis[23] shown in Scheme 3 is a case in point; related reactions with α,β-unsaturated carbonyls can deliver optically enriched chiral substrates for subsequent diastereoselective conjugate addition reactions.[24] Another example is illustrated in eq 2; Wacker oxidation[25] of optically enriched **9a** (cf. entry 1, Table 3) leads to formation of methyl ketone **32** in 60% isolated yield.[26]



(2)

The salicyl-based peptidic chiral ligands have been shown previously to be effective for a variety of early transition metal-

catalyzed reactions.[27] The present catalytic asymmetric protocol further expands the utility of this emerging class of readily available chiral ligands to include late transition metal catalysis as well.[8] Future studies will focus on the design and development of additional chiral ligands, development of new catalytic asymmetric C−C bond forming reactions, and applications to the synthesis of biologically significant molecules.

Acknowledgment. This paper is dedicated to our colleague and friend, Professor Lawrence T. Scott, on the occasion of his sixtieth birthday. Financial support was provided by the NIH (GM-47480). We are grateful to Kerry E. Murphy for many helpful discussions.

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

JA0478779

(22) For a review of catalytic enantioselective methods for the synthesis of quaternary carbon stereogenic centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591−4597. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105−10146.

(23) For a recent review on catalytic cross metathesis, see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923.

(24) For example, see: Breit, B.; Demel, P. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; pp 188−223.

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

(26) For a related approach to enantioselective synthesis of ketones through Cu-catalyzed conjugate additions to cyclic nitroalkenes, see: Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192−8193.

(27) (a) Nitta, H.; Yu, D.; Kudo, M.; Mori, A.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 7969−7975. (b) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1668−1671. (c) 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. (d) 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. (e) Porter, J. R.; Wirschun, W. G.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2657−2658. (f) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984−985. (g) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410. (h) Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 1009−1012. (i) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273−3275. (j) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247.