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# A Readily Available Chiral Ag-Based N-Heterocyclic Carbene Complex for Use in Efficient and Highly Enantioselective Ru-Catalyzed Olefin Metathesis and Cu-Catalyzed Allylic Alkylation Reactions

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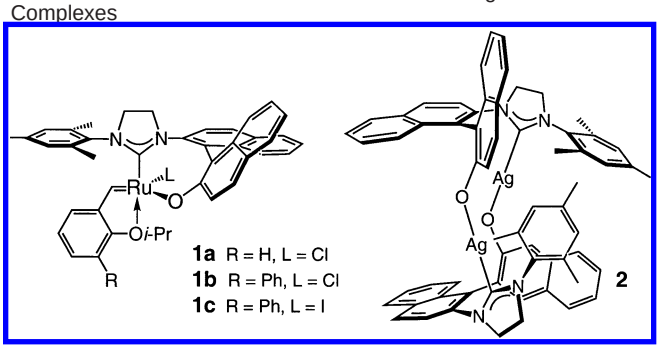
***Abstract:*** A new chiral bidentate N-heterocyclic carbene (NHC) ligand has been designed and synthesized. The NHC ligand bears a chiral diamine backbone and an achiral biphenol group; upon metal complexation (derived from Ag(I), Ru(II), or Cu(II)), the diamine moiety induces >98% diastereoselectivity such that the biaryl unit coordinates to the metal center to afford the desired complex as a single atropisomer. Because the ligand does not require optically pure biaryl amino alcohols, its synthesis is significantly shorter and simpler than the related first generation ligands bearing a chiral binaphthyl-based amino alcohol. The chiral NHC ligand can be used in the preparation of highly effective Ru- and Cu-based complexes (prepared and used in situ from the Ag(I) carbene) that promote enantioselective olefin metathesis and allylic alkylations with scope that is improved from previously reported protocols. In many cases, transformations promoted by the chiral NHC-based complexes proceed with higher enantioselectivity and reactivity than was observed with previously reported complexes.

## Introduction

The development of efficient and practical chiral ligands and catalysts is one of the most critical research objectives in modern organic synthesis.[1] Investigations in these laboratories during the past several years have been focused on the identification of various classes of optically pure chiral ligands that promote a range of enantioselective C−C bond forming reactions.[2] One area of investigation has resulted in the synthesis of chiral bidentate N-heterocyclic carbene (NHC) ligands,[3] which have led to Ru-based chiral complexes **1**,[2c] shown in Scheme 1. These chiral metal carbenes are noteworthy partly due to their ability to promote highly enantioselective ring-opening metathesis/cross-metathesis (AROM/CM) reactions[4] that cannot be effected with chiral Mo-based complexes;[2d] olefin metathesis reactions catalyzed by **1** can be performed under conditions that do not require rigorous exclusion of air, in the absence of solvent or without the need for purified solvents. We have also disclosed the synthesis of air-stable dimeric Ag(I) complex **2** (Scheme 1),[5] which, in the presence of various Cu salts, can be used to initiate enantioselective allylic alkylations with alkylzinc re-

***Scheme 1.*** First Generation Bidentate Ru- and Ag-NHC Complexes




(1) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999.

(2) For representative examples, see: (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) 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. (c) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018−4019. (f) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829−2832. (g) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. A. *Chem. Commun.* **2004**, 1779−1785.

(3) For additional examples of chiral NHC ligands in metal-catalyzed asymmetric catalysis, see: (a) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878−8879. (b) Ma, Y.; Song, C.; Ma, C.; Sun, Z.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871−5874. (c) Bonnet, L. C.; Douthwaite, R. E.; Kariuki, B. M.; *Organometallics* **2003**, *22*, 4187−4189. (d) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345−348. (e) Jensen, D. R.; Sigman, M. S. *Org. Lett.* **2003**, *5*, 63−65. (f) Gade, L. H.; Cesar, V.; Bellemin-Laponnaz, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014−1017. (g) Bappert, E.; Helmchen, G. *Synlett* **2004**, 1789−1793. (h) Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612−1613. (i) Tominaga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585−5588. For brief overviews, see: (j) Enders, D.; Gielen, H. *J. Organomet. Chem.* **2001**, *617*−*618*, 70−80. (k) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951−961.

(4) (a) Reference 2c. (b) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502−12508. (c) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288−12290.

agents with unprecedented levels of generality (in terms of both substrate and alkylzincs) and enantioselectivity.[6]

As a result of the promising developments mentioned above in connection with Ru- and Cu-catalyzed transformations, and because N-heterocyclic carbenes are effective in initiating a range of organic transformations as ligands[7] or catalysts,[8] we set out to design, synthesize, and develop a new generation of the chiral bidentate NHCs that can be prepared more readily. Specifically, a significant drawback regarding the general utility of the first generation ligands (cf., Scheme 1) arises from the level of efficiency and practicality with which the requisite optically pure axially chiral amino alcohols are typically prepared.[4]

Herein, we describe the synthesis, structure, and utility of a significantly more easily accessible chiral bidentate NHC and the utility of the corresponding Ag(I) complex in promoting Ru-catalyzed asymmetric olefin metathesis and Cu-catalyzed allylic alkylations. We also demonstrate that metal complexes derived from the new bidentate NHC often provide higher reactivity and enantioselectivity in comparison to the chiral complexes depicted in Scheme 1.

## Results and Discussion

**1. A Readily Available Chiral Imidazolinium Salt and Its Derived Ag(I) Complex. Chiral Ligand Design Considerations.** To obviate the requirement for the use of an optically pure binaphthyl-based amino alcohol, we decided to employ a readily available optically pure chiral diamine backbone as the source of chirality. Thus, we surmised that the asymmetric diamine structure could allow us to employ an achiral biphenyl-based amino alcohol: diastereoselectivity would be induced once the transition metal is inserted within the structure of the bidentate ligand.[9,10]

**Synthesis of Chiral NHC Ligand and the Derived Ag(I) Complex.** The above hypothesis was brought to fruition in the manner illustrated in Scheme 2. Treatment of commercially available optically pure diamine **3**[11] with aryliodide **4**[12] in the presence of 5 mol % $Pd(OAc)_2$ and *rac*-BINAP with NaO*t*-Bu (toluene, 110 °C, 24 h) leads to the formation of secondary arylamine **5**.[13] At this point, the reaction mixture is charged with 2 equiv of mesityl bromide (for 12 h), leading to the formation of the desired diamine **6** in 65% overall yield for the two-step, one-vessel procedure. Conversion of the methyl ether to the corresponding phenol, followed by treatment with HCl and triethylorthoformate, results in the generation of optically pure imidazolinium salt **7** in 45% overall yield. Subjection of **7** to $Ag_2O$ at reflux for 3 h in a 1:1 mixture of THF and $C_6H_6$ leads to facile generation of Ag(I) complex **8** in >98% isolated yield as a single diastereomer (>98% de, as judged by 400 MHz $^1$H NMR analysis). Thus, the diamine chirality is readily transferred to the biphenol moiety, such that metal complexation proceeds with complete control of stereoselectivity. The diastereomer that is formed exclusively is one where the chelating phenol moiety points away from the proximal phenyl unit of the chiral diamine backbone. The structural assignment for complex **8** is supported by an X-ray crystal structure, illustrated in Scheme 2 (details in the Supporting Information).

**2. Chiral Ru-Based Complexes Bearing Readily Available Bidentate NHC Ligands as Efficient Catalysts for Enantioselective Olefin Metathesis. Synthesis of Chiral Ru-Chloride and Iodide Complexes.** As illustrated in Scheme 3, treatment of chiral Ag(I) complex **8** with 1 equiv of achiral Ru complex **9** at 70 °C in THF leads to the formation of chiral Ru-chloride **10** in 42% isolated yield after silica gel chromatography. The low isolated yield is due to partial decomposition of complex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(9) For application of a related strategy, see: Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225−3228.

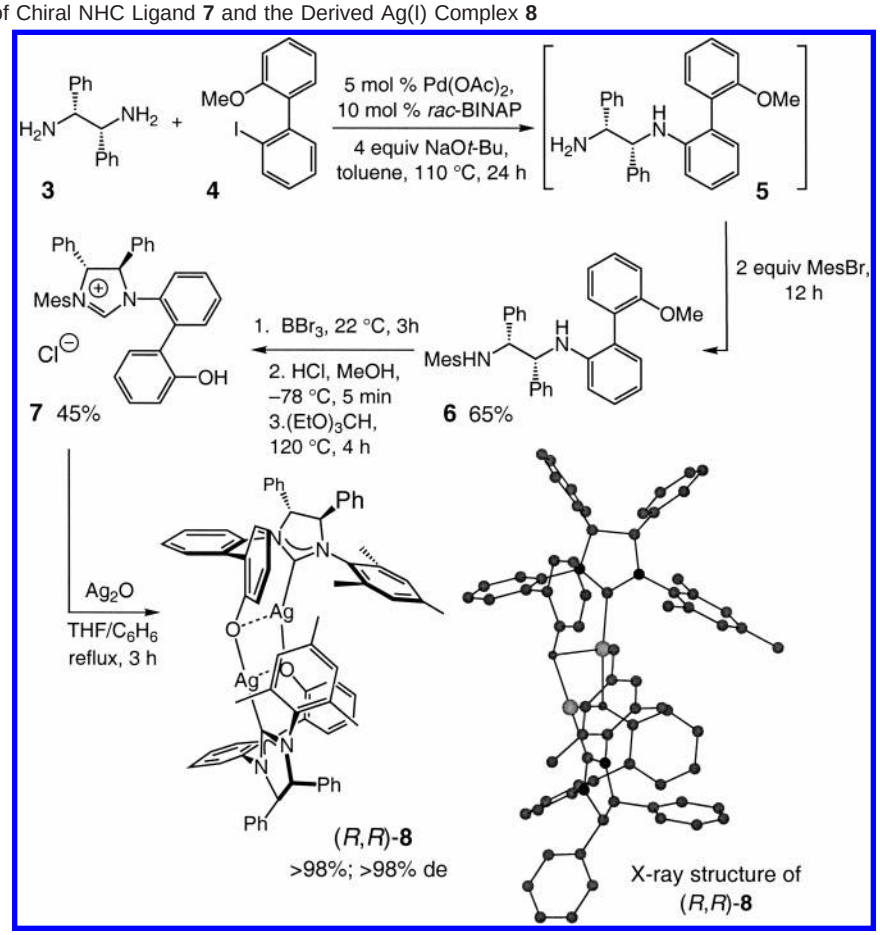
(10) A chiral ligand may induce asymmetry in the coordination of a second (and achiral in the absence of metal coordination) ligand, see: (a) Ringwald, M.; Sturmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, *121*, 1524−1527. (b) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495−497. (c) Becker, J. J.; White, P. S.; Gagne, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 9478−9479. (d) Mikami, K.; Aikawa, K. *Org. Lett.* **2001**, *3*, 243−245. (e) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91−94. (f) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95−97. (g) Mikami, K.; Aikawa, K.; *Org. Lett.* **2002**, *4*, 99−101. (h) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5458−5461. (i) Aikawa, K.; Mikami, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5455−5458. (j) Pelz, K. A.; White, P. S.; Gagne, M. R. *Organometallics* **2004**, *23*, 3210−3217.

(11) Diamine **3** can be prepared in the optically pure form (both antipodes) in multigram quantities in ∼20% overall yield (five steps from benzaldehydes). Procedures leading to the preparation of optically pure diamine **3** were obtained from: (a) Kupfer, R.; Brinker, U. H. *J. Org. Chem.* **1996**, *61*, 4185−4186. (b) Williams, O. F.; Bailar, J. C. *J. Am. Chem. Soc.* **1959**, *81*, 4464−4469. (c) Corey, E. J.; Kuhnle, F. N. M. *Tetrahedron Lett.* **1997**, *38*, 8631−8634. (d) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 22−29.

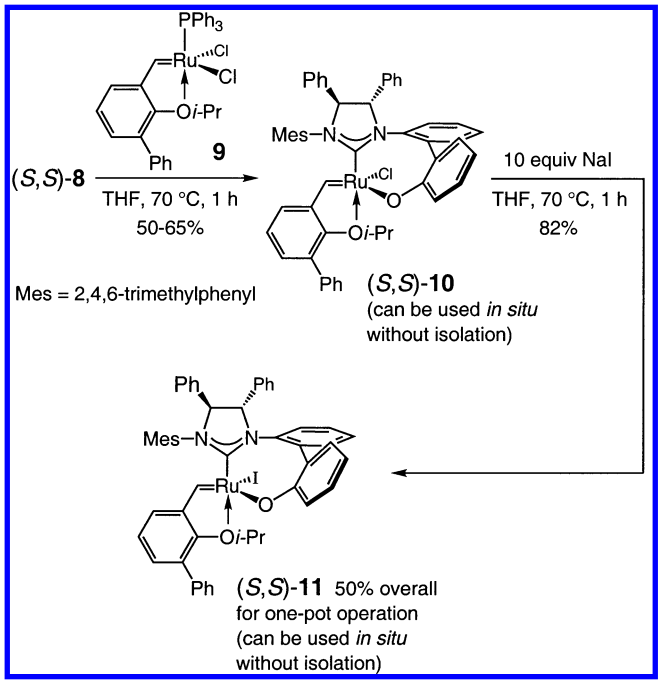
(12) Multigram quantities of aryl iodide **4** can be prepared in four steps, based on modified published procedures, in 66% overall yield. See: (a) Collette, J.; McGreer, D.; Crawford, R.; Chubb, F.; Sandin, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3819−3820. (b) Fuson, R. C.; Albright, R. L. *J. Am. Chem. Soc.* **1959**, *81*, 487−490.

(13) (a) Beletskaya, I. P.; Bessmertnykh, A. G.; Guillard, R. *Tetrahedron Lett.* **1997**, *38*, 2287−2290. (b) Canabal-Duvillard, I.; Mangeney, P. *Tetrahedron Lett.* **1999**, *40*, 3877−3880. (c) Beletskaya, I. P.; Bessmertnykh, A. G.; Guillard, R. *Synlett* **1999**, 1459−1461. (d) Frost, C. G.; Mendonca, P. *Tetrahedron: Asymmetry* **1999**, *10*, 1831−1834.

***Scheme 2.*** Synthesis of Chiral NHC Ligand **7** and the Derived Ag(I) Complex **8**




***Scheme 3.*** Synthesis of Chiral Ru-Based Complexes **10** and **11**



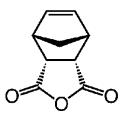
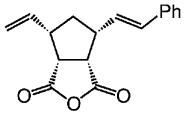
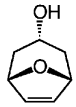
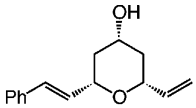
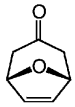
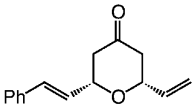
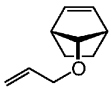
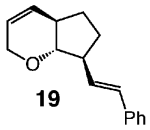

**10** during chromatography; to minimize such loss, the purification procedure was carried out under $N_2$ atmosphere. It should also be noted that lower stability of Ru-chloride **10** is in contrast to the robustness of the first generation complexes **1a**,**b**; the exact reason for this difference in stability is unclear at the present time.

Our previous studies show that chiral Ru-iodide **1c** is more stable than the corresponding chlorides **1a**,**b**. Accordingly, when[4c] the unpurified mixture derived from treatment of Ag(I) complex **8** and Ru complex **9** is directly (without isolation of sensitive **10**) subjected to 10 equiv of NaI in THF at 70 °C for 1 h, chiral iodide complex **11** is isolated in 50% yield. Unlike chloride **10**, iodide complex **11** is stable to silica gel chromatography in air.

**Catalytic Activity of Ru-Based Chiral Complexes 10 and 11.** As the data summarized in Table 1 illustrate, Ru carbene **10** is a generally effective chiral catalyst for olefin metathesis (data for chiral complex **1b** and **1c** are provided for comparison). Reactions promoted by complex **10** deliver similar (entry 3) or higher (entries 1 and 4) enantioselectivity as compared to the first generation Ru chloride **1b**; reactions are typically complete within a shorter period of time with **10**. It is important to note that the relatively sensitive (see above) chiral Ru complex **10** can be prepared and used in situ (without isolation) to promote efficient enantioselective olefin metathesis. Control experiments generally indicate that the catalyst prepared and used in situ[14] affords reactivity and enantioselectivity similar to that obtained with the isolated complex. As an example, when isolated and purified Ru chloride **10** is employed in the AROM/CM reaction in entry 1 of Table 1, anhydride **13** is

(14) For other examples, where chiral olefin metathesis catalysts are prepared and used in situ, see: (a) Aeilts, S. L.; Cefalo, D. R.; Bonitatebus, P. J.; Houser, J. H.; Hoveyda, A. H.; Schrock, R. R. *Angew. Chem., Int. Ed.* **2001**, *40*, 1452−1456. (b) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991−6997. (c) Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779−10784.

***Table 1.*** Catalytic Enantioselective Ring-Opening Metathesis/Cross-Metathesis (AROM/CM) with Various Ru-Based Chiral Complexes[a]

| entry | substrate | product | *in situ* complex **10** conv (%);[b] t (h), ***yield (%);[c] ee (%)[d]*** | complex **1b** conv (%);[b] t (h), ***yield (%);[c] ee (%)[d]*** | *in situ* complex **11** conv (%);[b] t (h), ***yield (%);[c] ee (%)[d]*** | complex **11** conv (%);[b] t (h), ***yield (%);[c] ee (%)[d]*** | complex **1c** conv (%);[b] t (h), ***yield (%);[c] ee (%)[d]*** |
|---|---|---|---|---|---|---|---|
| 1 |  **12** |  **13** | >98; 0.1 ***59; 84*** | >98; 0.3 ***60; 70*** | >98; 2 ***62; 89*** | >98; 2 ***50; 90*** | >98; 4 ***72; >98*** |
| 2 |  **14** |  **15** | >98; 0.5 ***82; 74*** | >98; 1.5 ***80; 94*** | >98; 0.5 ***89; >98*** | >98; **1** ***71; 93*** | >98; 2 ***81; 97*** |
| 3 |  **16** |  **17** | >98; 1 ***84; 71*** | 50; 48 ***66; 67*** | >98; 1 ***87; 83*** | >98; 1.5 ***73; 84*** | <2; 48 |
| 4[e] |  **18** |  **19** | >98; 1 ***57; 84*** | >98; 1 ***20; 46*** | >98; 1 ***66; 93*** | >98; 1 ***52; 90*** | >98; 1 ***71; 43*** |

[a] Reactions carried out with 5 mol % Ru catalyst in THF (except entry 3 performed in the absence of solvent) in the presence of 5 equiv of styrene at 22 °C. See the Supporting Information for detailed conditions. [b] Conversions determined by analysis of 400 MHz $^1$H NMR spectra of unpurified product mixtures. [c] Isolated yield after silica gel chromatography. [d] Enantioselectivities determined by chiral HPLC (see the Supporting Information for details). [e] Reaction performed through slow addition of substrate to a solution of the catalyst and styrene in THF.

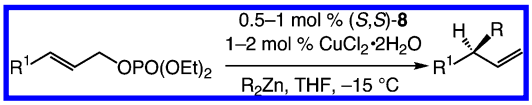
isolated in identical optical purity and yield as when the catalyst is prepared and used in situ (84% ee and 59% isolated yield; >98% conv in 0.1 h).

Data shown in Table 1 illustrate that the more robust chiral Ru complex **11** can serve as a highly effective catalyst for enantioselective olefin metathesis. Several important points regarding asymmetric olefin metatheses initiated by Ru iodide **11** are worthy of note: (a) Similar yields and enantioselectivities are observed when chiral complex **11** is prepared in situ or used after isolation and purification. Interestingly, in two cases, the catalyst prepared in situ delivers a higher level of enantioselectivity (entries 2 and 4). (b) Biphenyl-based Ru complex **11** exhibits higher levels of reactivity (vs **1c**), as is clearly demonstrated by the data shown in entry 3 of Table 1.

**3. Chiral Cu-Based Complexes Bearing Readily Available Bidentate NHC Ligands as Efficient Catalysts for Enantioselective Allylic Alkylations. Cu-Catalyzed Asymmetric Alkylations of Disubstituted Olefins. Enantioselective Synthesis of Tertiary Carbon Stereogenic Centers.** As the data summarized in Table 2 illustrate, 0.5−1 mol % chiral Ag(I) complex **8** can be used to promote efficient and enantioselective alkylations of allylic phosphates bearing a disubstituted olefin with aryl (entries 1−6, Table 2) as well as alkyl substituents (entries 7−12, Table 2). Reactions are readily effected in the presence of air-stable $CuCl_2 \cdot 2H_2O$,[15] and achiral products from the $S_N2$ mode of addition are not observed (<2% by 400 MHz $^1$H NMR analysis).

Several additional points regarding the data in Table 2 merit specific mention: (a) Not only is the new chiral complex, derived from carbene **7** (Scheme 2), as effective as the first generation Ag(I) complex **2**, the desired products can be obtained in significantly higher optical purity. For example, the products from transformations shown in entries 1 and 2 of Table 2 were obtained in 71% and 86% ee when **2** was used (vs 90% ee in both cases with complex **8**).[5] (b) A key attribute of the present method is that Cu-catalyzed asymmetric alkylations with larger alkylzincs such as *n*-$Bu_2Zn$ (entries 3 and 11) and even (*i*-Pr)$_2$Zn (entries 4 and 12) are catalyzed in the presence of 0.5−1 mol % of Ag(I) complex **8**.

***Table 2.*** Cu-Catalyzed Asymmetric Allylic Alkylations with Ag(I)-Complex **8**; Enantioselective Synthesis of Tertiary Carbons[a]




| entry | $R^1$ | alkylzinc | mol % **8**; mol % Cu salt | conv (%);[b] time (h) | yield (%);[c] ee (%)[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $Me_2Zn$ | 1 | >98; 24 | 68; 90 |
| 2 | $C_6H_5$ | $Et_2Zn$ | 0.5 | >98; 2 | 80; 90 |
| 3 | $C_6H_5$ | *n*-$Bu_2Zn$ | 0.5 | >98; 20 | 94; 89 |
| 4 | $C_6H_5$ | *i*-$Pr_2Zn$ | 0.5 | >98; 2 | 80; 86 |
| 5 | *o*-$NO_2C_6H_4$ | $Me_2Zn$ | 1 | >98; 24 | 92; 91 |
| 6 | *o*-$NO_2C_6H_4$ | $Et_2Zn$ | 0.5 | >98; 2 | 78; 90 |
| 7 | $C_7H_{15}$ | $Me_2Zn$ | 1 | >98; 24 | 75; 88 |
| 8 | $C_7H_{15}$ | $Et_2Zn$ | 0.5 | >98; 15 | 72; 88 |
| 9 | Cy | $Me_2Zn$ | 1 | >98; 24 | 60; 95 |
| 10 | Cy | $Et_2Zn$ | 0.5 | >98; 15 | 80; 95 |
| 11 | Cy | *n*-$Bu_2Zn$ | 1 | >98; 24 | 52; 96 |
| 12 | Cy | *i*-$Pr_2Zn$ | 1 | >98; 24 | 68; 97 |

[a] See the Supporting Information for further details; >98% regioisomeric excess (re; $S_N2'$:$S_N2$) in all cases. [b] Determined by GLC analysis; details in the Supporting Information. [c] Isolated yield of purified products. [d] Determined by chiral GLC analysis; details in the Supporting Information.

**Cu-Catalyzed Asymmetric Alkylations of Trisubstituted Olefins. Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers.** As the data in Table 3 indicate,

(15) Ag-based complexes of heterocyclic carbenes readily undergo exchange with a variety of late transition metals. See: (a) Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972−975. (b) Arnold, P. L. *Heteroat. Chem.* **2002**, *13*, 534−539 and references therein.

***Scheme 4.*** Synthesis, X-ray Structure, and Catalytic Activity of Cu Complex **24**

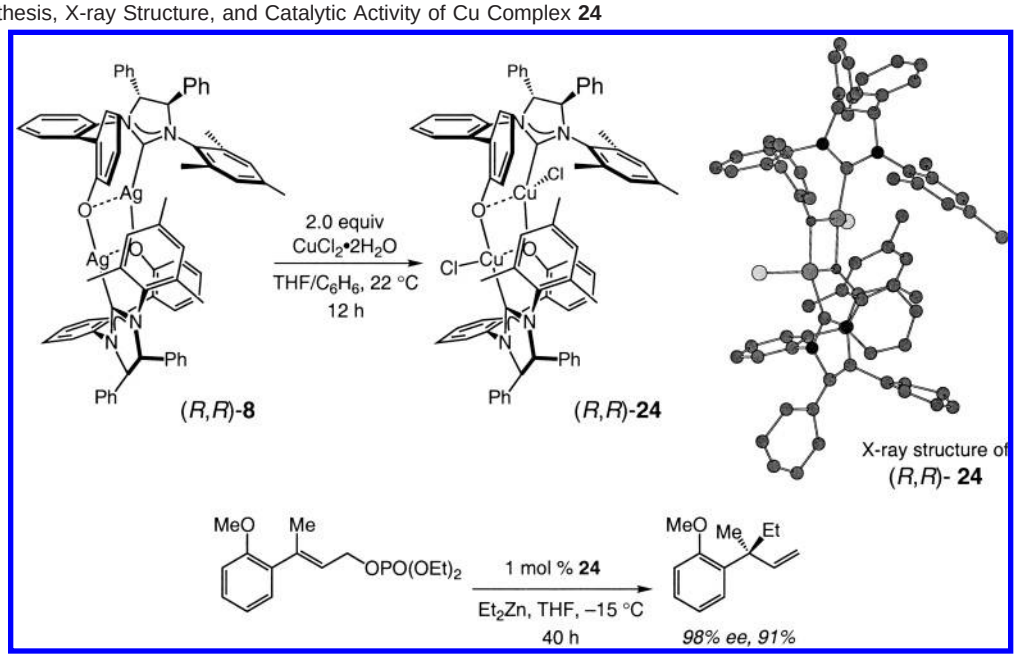
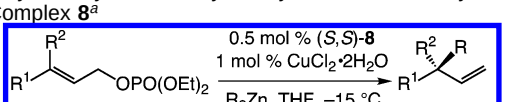
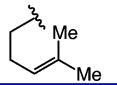



***Table 3.*** Enantioselective Synthesis of Quaternary Carbons by Cu-Catalyzed Asymmetric Allylic Alkylation Promoted by Ag(I)-Complex **8**[a]



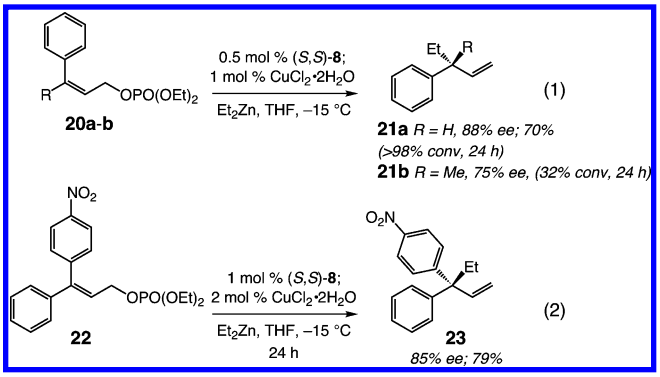

| entry | $R^1$ | $R^2$ | alkylzinc | conv (%);[b] time (h) | yield (%);[c] ee (%)[d] |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | Me | $Et_2Zn$ | >98; 2 | 94; 97 |
| 2[e] | $C_6H_5$ | Me | *i*-$Pr_2Zn$ | >98;12 | 74; 98 |
| 3 | Cy | Me | $Et_2Zn$ | >98; 24 | 76; 97 |
| 4 |  | Me | $Et_2Zn$ | >98; 16 | 82; 94 |

[a] See the Supporting Information for details. >98% regioisomeric excess (re; $S_N2'$:$S_N2$) in all cases. [b] Determined by GLC analysis; details in the Supporting Information. [c] Isolated yield of purified product. [d] Determined by chiral GLC analysis; details in the Supporting Information. [e] 1 mol % (*S*,*S*)-**8** and 2 mol % Cu salt were used.

complex **8** is particularly effective when used to promote Cu-catalyzed alkylations that lead to enantioselective synthesis of all-carbon quaternary stereogenic centers (94−98% ee).[16] In all cases, >98% regioisomeric excess (re) in favor of the $S_N2'$ mode of addition is observed. Even when the sterically demanding (*i*-Pr)$_2$Zn is used, formation of the quaternary carbon stereogenic center proceeds efficiently (1 mol % **8** in 12 h at −15 °C) to afford the desired product in 98% ee and >98% re. It should be noted that higher asymmetric induction can be obtained with the new complex; Cu-catalyzed alkylations in entries 1 and 3 of Table 3 proceed to afford the desired alkylation products in 91% and 93% ee when chiral complex **2** is used in the presence of $CuCl_2•2H_2O$ (vs 97% ee in both cases with **8**).[5]

(16) For reviews on enantioselective 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. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363−6367.

Several additional points regarding the Cu-catalyzed allylic alkylations in the presence of Ag(I) complex **8** are worthy of note:

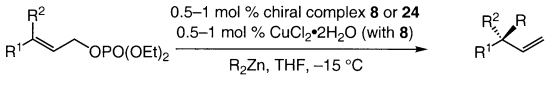



(a) As shown in eq 1, when the corresponding cis and *Z* allylic phosphates (e.g., **20a**,**b**) are used as the substrate, Cu-catalyzed allylic alkylations are slower and proceed with lower enantioselectivity to afford the opposite product enantiomer (as compared to trans and *E* substrates). It should however be noted that, as indicated by the example in eq 1, even in instances where a trisubstituted olefin bears sterically hindered substituents, appreciable reactivity and high asymmetric induction are attained. The Cu-catalyzed asymmetric synthesis of the quaternary carbon stereogenic center in eq 2 is especially noteworthy, as it constitutes stereodifferentiation of two aryl groups in **22**[17] that differ almost exclusively in their electronic properties.

(b) As illustrated in Scheme 4, treatment of Ag(I) complex **8** with $CuCl_2•2H_2O$ leads to the formation of air-stable Cu(II) complex **24** in 95% yield; the X-ray structure of **24** is depicted in Scheme 4.[18] As the representative examples in Scheme 4 and Table 4 indicate, the Cu(II) complex can be employed directly to catalyze highly enantioselective allylic alkylation reactions.

(17) For stereoselective synthesis of **22**, see: Havranek, M.; Dvorak, D. J. *J. Org. Chem.* **2002**, *67*, 2125−2130.
(18) For a related dimeric Cu complex, see: Arnold, P. L.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2001**, 2340−2341.

***Table 4.*** Comparison of Enantioselective Cu-Catalyzed Asymmetric Allylic Alkylation Promoted by Ag(I)-Complex **8** and Cu(II)-Complex **24**[a]




| | | | | | with Ag(I) complex **8** | | with Cu(II) complex **24** | |
|---|---|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | alkylzinc | mol (%) | conv (%);[b] time (h) | ee (%)[c] | conv (%);[b] time (h) | ee (%)[c] |
| 1 | Cy | H | $Me_2Zn$ | 1 | >98; 24 | 93 | >98; 24 | 92 |
| 2 | Cy | H | *i*-$Pr_2Zn$ | 1 | >98; 24 | 90 | >98; 24 | 90 |
| 3 | Ph | Me | *i*-$Pr_2Zn$ | 1 | >98; 12 | 98 | >98; 12 | 97 |
| 4 | *o*-$OMeC_6H_4$ | Me | $Et_2Zn$ | 1 | 75; 24 | 95 | >98; 40 | 98 |
| 5 |  | Me | $Et_2Zn$ | 0.5 | 84; 16 | 95 | 95; 16 | 95 |

[a] See the Supporting Information for details. [b] Determined by GLC analysis; details in the Supporting Information. [c] Determined by chiral GLC analysis; details in the Supporting Information.

As shown by the data summarized in Table 4, Cu(II) complex **24** delivers levels of reactivity and enantioselectivity similar to those observed with the combination of Ag(I) complex **8** and $CuCl_2 \cdot 2H_2O$. These findings support the contention that similar (if not identical) Cu-based NHC complexes are involved in initiating C−C bond formation when Ag(I) complexes such as **8** are used in the presence of various Cu salts.

**Comparison with Cu-Catalyzed Alkylations Promoted by Amino Acid-Based Ligands.** Recent reports from these laboratories have introduced various peptide-based ligands that promote Cu-catalyzed asymmetric allylic alkylations involving the same allylic phosphate substrates that are discussed above.[6m] In general, in cases involving di- and trisubstituted olefins, the NHC-based catalysts presented herein are significantly more effective in promoting enantioselective alkylations (0.5−1 mol % vs 10 mol % catalyst loading required with peptidic ligands).

It should be noted that with chiral Ag(I) complex **8** and $CuCl_2 \cdot 2H_2O$, catalyst loading may be as low as 0.25 mol %. As an example, Cu-catalyzed alkylation shown in entry 2 of Table 2 proceeds to >98% conv within 15 h in the presence of 0.25 mol % **8** to afford the desired product in 89% ee and 67% isolated yield; with 0.05 mol % **8**, alkylation proceeds to 80% conv after 24 h (desired product formed in 86% ee).

In contrast to peptidic systems, NHC-based catalysts readily promote highly enantioselective reactions with the less reactive alkylzinc reagents such as $Me_2Zn$ and *i*-$Pr_2Zn$. It is particularly important to note that complexes **8** and **24** are by far the most efficient chiral catalysts for enantioselective synthesis of all-carbon quaternary stereogenic centers through allylic alkylations with (hard) alkylmetal reagents.[19] Finally, NHC-based catalysts require the use of air-stable (and commercially available) $CuCl_2 \cdot 2H_2O$, whereas peptidic ligands demand the presence of air-sensitive $(CuOTf)_2 \cdot C_6H_6$.

## Conclusions

We report the design, synthesis, characterization, and development of a new class of chiral NHC ligand. Preparation of the ligand does not require the availability of an optically pure binaphthyl-based amino alcohol, the synthesis of which would require longer synthesis routes and inefficient resolution procedures.[4] Chirality is transferred by the stereogenic centers in the diamine backbone that in turn induce the achiral biphenyl amino alcohol moiety to coordinate to the metal center to form a single atropisomer. The resulting enantiomerically and diastereomerically pure Ag(I) complex **8**, the X-ray structure of which is disclosed, can be used in the preparation of the corresponding Ru-based and Cu-based complexes that readily promote efficient enantioselective olefin metathesis and allylic alkylation reactions. In all cases, whether it is the Cu complex **24**, the sensitive but reactive chiral Ru-chloride **10**, or the more robust Ru-iodide **11**, chiral catalysts can be prepared and employed in situ to promote highly enantioselective C−C bond forming reactions.

In the presence of air-stable $CuCl_2 \cdot 2H_2O$, the optically pure NHC−Ag(I) complex can be utilized to generate a Cu(I) complex that serves as an exceptionally effective chiral alkylation catalyst. Particularly noteworthy is the facility and enantioselectivity with which even sterically hindered alkylzincs are induced to add to trisubstituted olefins to generate all-carbon quaternary stereogenic centers with high optical purity. The derived Cu(II) complex (**24**) has been synthesized and characterized by X-ray crystallography; this air-stable Cu complex can be used to effect catalytic alkylations.

The readily available chiral NHC ligand **7** as well as the corresponding Ag(I) complex **8** are expected to give rise to a range of chiral complexes that promote other synthetically useful C−C bond forming reactions. Studies toward the development of such catalytic asymmetric methods, as well as mechanistic studies elucidating the mode of action of this class of bidentate NHC ligands and the related applications to target-oriented synthesis, are in progress.

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

JA050179J

(19) 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.