# Chelating Hydroxyalkyl NHC as Efficient Chiral Ligands for Room-Temperature Copper-Catalyzed Asymmetric Allylic Alkylation

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*Received 22 March 2010*

**Abstract:** The application of chiral chelating hydroxy NHC in copper-catalyzed asymmetric allylic alkylation (Cu-AAA) involving various dialkylzincs and allylic phosphate substrates is reported here. From a library of 11 chiral chelating hydroxyalkyl NHC, a fine-tuning has been done to identify the best architectural features enabling to produce the expected γ-adducts in total regioselectivity, good isolated yields, and excellent enantioselectivities (ranging from 93% to >98% ee).

**Key words:** chiral chelating diaminocarbene, asymmetric allylic alkylation, copper dialkylzinc

Belonging to the well-known class of N-heterocyclic carbene (NHC) ligands[1] discovered by Wanzlick[2] and Ofele,[3,4] chiral chelating hydroxyalkyl or hydroxyaryl NHC ($\mathbf{L_{alk}}$ and $\mathbf{L_{Ar}}$, respectively, Figure 1) have recently emerged as promising chiral ligands for asymmetric metal-catalyzed transformations.[5] Notably, in association with copper metal, they showed a remarkable activity in both asymmetric conjugated addition (ACA)[6] and asymmetric allylic alkylation (AAA, only for $\mathbf{L_{ar}}$),[7] two important C–C bond-formation reactions producing chiral useful building blocks.[8] As an important breakthrough in these areas, they allowed the formation of enantioenriched all-carbon quaternary centers in good yields and selectivities (up to 99% ee) surpassing in most cases phosphine-based ligands.[6c,d,f,7a,b]

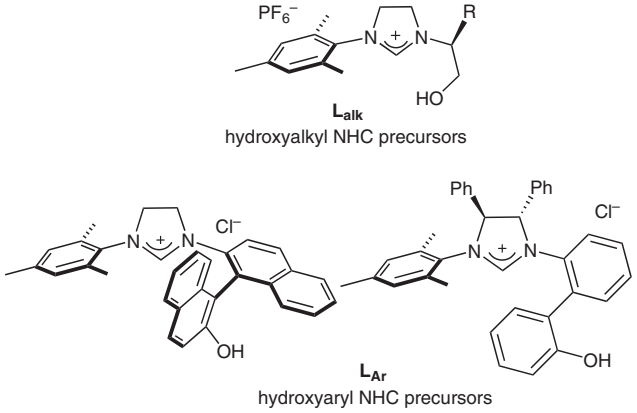



**Figure 1** Well-known chiral hydroxyalkyl and hydroxyaryl NHCs

*SYNLETT* 2010, No. 11, pp 1661–1665
Advanced online publication: 01.06.2010
DOI: 10.1055/s-0029-1220127; Art ID: G07910ST


Whereas hydroxyalkyl-chelating NHC $\mathbf{L_{alk}}$ designed by our team have been intensively studied in Cu-ACA,[6a–6e] their applications in Cu-AAA have not been yet studied. Herein, we report the evaluation of our library (Figure 2) of hydroxyalkyl imidazolium salts in Cu-AAA involving allylic diethylphosphates and dialkylzinc reagents. We started our investigation with the evaluation of **L1** (identified as the best designed $\mathbf{L_{alk}}$ ligand for previous applications)[6c,d] in a model Cu-AAA reaction involving cinnamylphosphate **P1** and diethylzinc (Table 1). NHC-Cu catalyst (1 mol%) was prepared in situ by reaction of *n*-BuLi (2.5 mol%) with the azolium **L1** in the presence of copper(I)-triflate-benzene complex.[9] After three hours at –20 °C in ethyl acetate, only the expected $SN_2'$-adduct **γ1** was formed in 71% isolated yield and 90% enantioselectivity (entry 1). At 0 °C, the yield was improved to reach 86% after 90 minutes with the same level of chiral induction (entry 2, 89% ee).

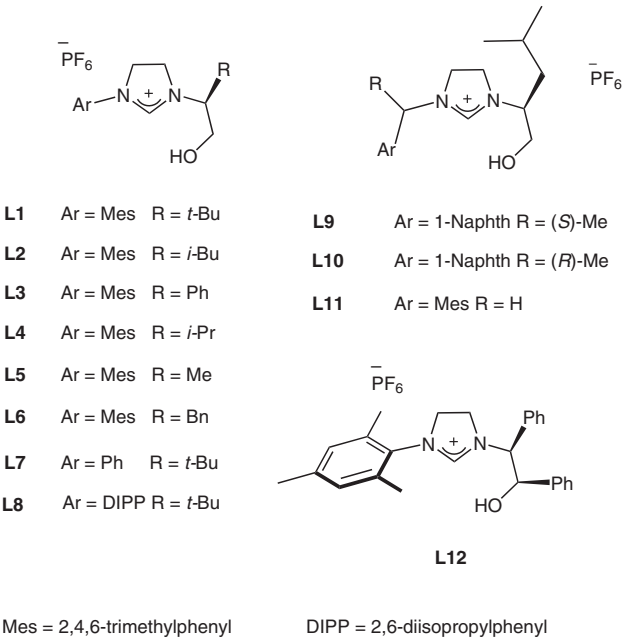
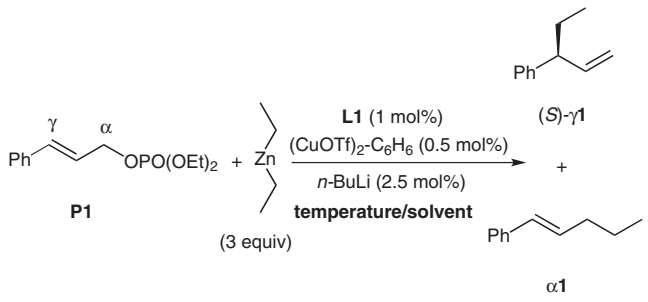



**Figure 2** Library of chiral chelating hydroxyalkyl NHC

Interestingly, at room temperature, the alkylation was finished within 30 minutes without any loss of the enantioselectivity (entry 3, 91% of ee). Then other solvents were investigated, however, only slight variations in yields and

**Table 1** Optimization of Conditions in Cu-**L1**-Catalyzed AAA Using $Et_2Zn$ and Cinnamylphosphate **P1** as Reagents




| Entry | Solvent | Temp (°C) | Time (h) | Yield (%)[a] | γ/α | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | EtOAc | –20 | 3 | 71 | 100:0 | 90 |
| 2 | EtOAc | 0 | 1.5 | 86 | 100:0 | 89 |
| 3 | EtOAc | 20 | 0.5 | 90 | 100:0 | 91 |
| 4 | THF | 20 | 0.5 | 86 | 100:0 | 89 |
| 5 | DEC | 20 | 0.5 | 90 | 100:0 | 91 |
| 6 | DMC | 20 | 0.5 | 88 | 100:0 | 92 |

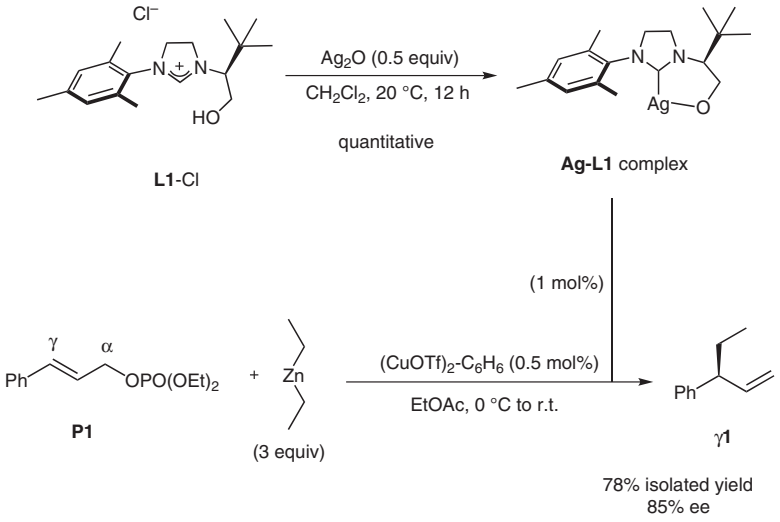
[a] Isolated yield.
[b] Determined by GC on a chiral stationary phase (see ESI).

selectivities were observed (86–90% of yields and 89–92% of ee, entries 5–7).

In front of these results, we decided to keep ethyl acetate as the solvent[10] and perform the reaction at room temperature. The corresponding silver NHC complex can be generated by just mixing an equimolar amount of azolium salt and silver oxide.[11] The new formed silver complex can lead to the copper active species by transmetalation. It is worth to note that the use of chiral silver NHC in both Cu-ACA and Cu-AAA allowed to improve the selectivity of the alkylation and the reproductibility.[6f,7] Thus, the **Ag-L1** complex was isolated in quantitative yield from **L1**-Cl and evaluated in the model AAA reaction (Scheme 1). Unfortunately, both the yield and the selectivity were lower than when the hydroxyalkylate NHC was in situ formed through deprotonation (78% and 85% ee, respectively). Moreover, the **Ag-L1** complex is less stable than the corresponding azolium salt, which could be stored some years without any degradation. Additionally, all attempts to isolate and characterize the corresponding copper hydroxyalkylate NHC complex from **Ag-L1** failed.

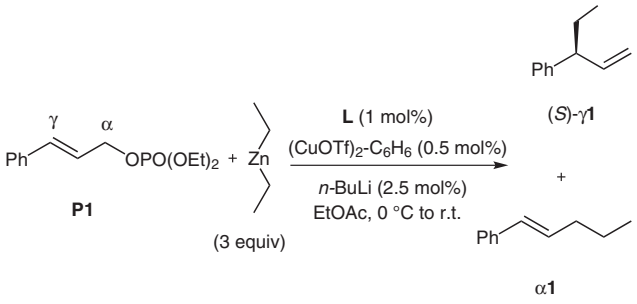
Having established the best conditions to perform the Cu-AAA with **L1**, we focused our attention in the architectural modification of the azolium salt to find the best enantiodiscriminating candidate. A library of 12 azolium salts[12] has been evaluated in Cu-AAA using **P1** and $Et_2Zn$ as reagents. The reaction was performed at room temperature in ethyl acetate (Table 2). With the mesityl serie (**L1**–**L6**), the variation of the stereogenic center did not allow to improve the enantioselectivity of the alkylation (ranging between 86–91%, entries 1–5) except for **L6** (81% ee, entry 6). The modification of the nonchelating unit was more critical, both in term of regio- and enantioselectivity. Indeed, while **L7**, bearing a phenyl group, led to a dramatic decrease of ee (32%, entry 7), the presence of the DIPP unit allowed to improve significantly the ee up to 96%, while the yield remained high (90%, entry 8). Curiously, this last result was completely opposite to this observed in Cu-ACA in which the DIPP group promoted only bad ee.[6b] This shows again the importance to dispose of a wide library of ligands with various structural features.

We have also considered nonchelating CH(R)-aryl groups[6e] (R = H or Me; **L9**–**11**, entries 9–11). Unfortunately, the presence of either (*R*)- or (*S*)-α-methyl-1-naphthyl group did not allow to improve the enantioinduction (84% and 82% ee, respectively, entries 9 and 10) while important losses of regio- and enantioselectivity were observed with the $CH_2Mes$ unit (entry 11). Finally, as last structural variation, the presence of an additional stereo-




**Scheme 1** Synthesis of silver NHC complex **Ag-L1** from **L1**-Cl and its evaluation in Cu-AAA

**Table 2** Evaluation of a Library of Chelating Hydroxyalkyl NHC in the Cu-Catalyzed AAA Using $Et_2Zn$ and Cinnamylphosphate **P1** as Reagents




| Entry | Ligand | Time (h) | Yield (%)[a] | γ/α | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | **L1** | 0.5 | 90 | 100:0 | 91 |
| 2 | **L2** | 0.5 | 87 | 100:0 | 89 |
| 3 | **L3** | 0.5 | 75 | 100:0 | 87 |
| 4 | **L4** | 0.5 | 81 | 100:0 | 89 |
| 5 | **L5** | 0.5 | 85 | 100:0 | 86 |
| 6 | **L6** | 0.5 | 83 | 100:0 | 81 |
| 7 | **L7** | 0.5 | 82 | 100:0 | 32 |
| 8 | **L8** | 0.5 | 90 | 100:0 | 96 |
| 9 | **L9** | 0.5 | 76 | 98:2 | 84 |
| 10 | **L10** | 0.5 | 82 | 98:2 | 82 |
| 11 | **L11** | 0.5 | 78 | 88:12 | 47 |
| 12 | **L12** | 24 | 82 | 100:0 | 23 |

[a] Isolated yield.
[b] Determined by GC on a chiral stationary phase (see ESI).

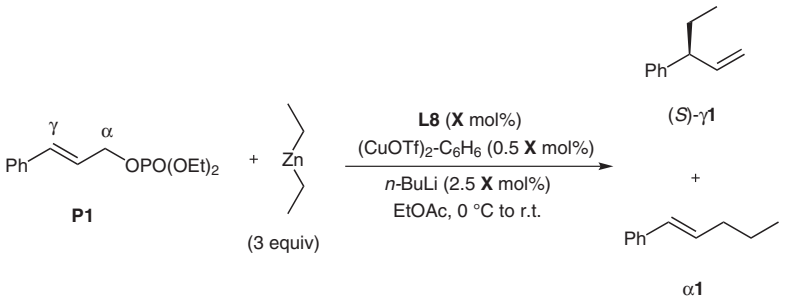
genic center on the chelating side chain (in α-position to the hydroxy function) in **L12**[6b] led to a dramatic decrease in enantioselectivity (23% ee, entry 12). The catalyst loading was then tried to be decreased (Table 3). We were pleased to see that the enantioselectivity and the yield remained satisfactory at 0.1 mol% (91% vs. 96% and 81% vs. 90%, respectively, entry 2) but a longer reaction time was required (6 h). At 0.01 mol%, the effect was more pronounced as the ee was decreased to 86% while only 75% of yield was obtained after 24 h of reaction.

In order to keep a reasonable reaction time and a maximum of chiral induction, we decided to continue our study with a catalyst loading of 1 mol%. Having in our hands the optimized catalytic system (1 mol% of **L8**,[13,14] EtOAc, r.t.), we evaluated the allylic alkylation of dimethyl- and dibutylzinc reagents on three different allylic phosphates **P1**–**3** (Table 4). Considering **P1**, dibutylzinc led to a good isolated yield of γ**2** adduct with a same level of enantioselectivity than for γ**1** adduct (85% and 95%, respectively, entry 2).

In the case of Cu-AAA involving the more sterically hindered 1-naphthyl substrate **P2** and $Me_2Zn$, beside 12 hours was required to complete the addition, the regioselectivity remained excellent (entry 3). The expected γ**3** adduct was isolated in good yield and very high ee (69% and >98%, respectively). Considering, the cyclohexyl allylic substrate **P3**, the chiral transfer of ethyl group was also efficient (entry 4). The resulting γ**4** adduct was obtained in 82% yield and 93% ee.

In conclusion, we have widened the field of application of chiral hydroxyalkyl NHC $\mathbf{L_{alk}}$ in asymmetric catalysis using copper complexes. Through their high synthetic tunability, we identified the best scaffold for the Cu-AAA involving various dialkylzinc reagents and allylic phosphates. The critical structural feature appears to be the aryl nonchelating fragment of the ligand. The regioselectivity of the alkylation was always complete, the expected γ-adducts were obtained in good isolated yields and excellent enantioselectivities. Our study will be extended to the formation of chiral all-carbon quaternary centers and reported in due course.

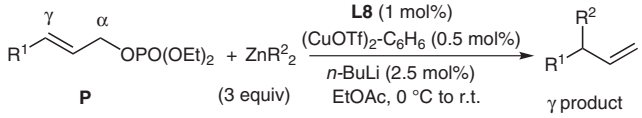
**Table 3** Effect of the Catalyst Loading [**L8**/$(CuOTf)_2$-$C_6H_6$] in AAA Involving $Et_2Zn$ and Cinnamylphosphate **P1**



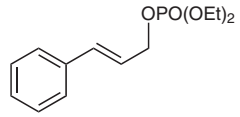
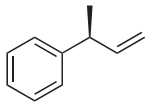
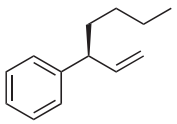
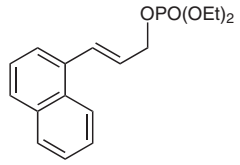
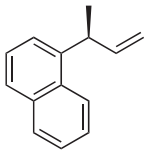
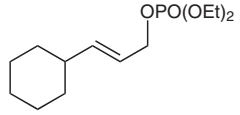
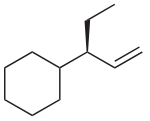

| Entry | Catalyst loading (mol%) | Time (h) | Yield (%)[a] | γ/α | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | 1 | 0.5 | 90 | 100:0 | 96 |
| 2 | 0.1 | 6 | 81 | 100:0 | 91 |
| 3 | 0.01 | 24 | 75 | 100:0 | 86 |

[a] Isolated yield.
[b] Determined by GC on a chiral stationary phase (see ESI).

**Table 4** Screening of Allylic Diethylphosphate **P1**–**3** and Dialkyzincs in Cu-**L8**-Catalyzed AAA




P γ product

| Entry | Allylic substrates | $ZnR^2_2$ | Time (h) | γ Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  **P1** | $Et_2Zn$ | 0.5 | γ**1**  | 90 | 96 (*S*) |
| 2 | | $n$-$Bu_2Zn$ | 2 | γ**2**  | 85 | 95 (*S*) |
| 3 |  **P2** | $Me_2Zn$ | 12 | γ**3**  | 69 | >98 (*S*) |
| 4 |  **P3** | $Et_2Zn$ | 2 | γ**4**  | 82 | 93 (*R*) |

[a] Isolated yield.
[b] Determined by GC on a chiral stationary phase (see ESI).

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

This work was supported by the CNRS, the Région-Bretagne and the Ministère de la Recherche et de la Technologie (grants to J.W. and D.R.).

## References and Notes

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(9) Other copper sources have been evaluated such as $Cu(OTf)_2$, CuTC (TC = thiophene 2-carboxylate) or $(CuOTf)_2$-toluene, however, lower yields and enantioselectivities were observed.

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(12) Azolium salts **L1**–**11** are easily accessible in four steps from enantiopure β-amino alcohols, see ref. 6b and 6e.

(13) **Analytical and Spectral Data of L8**
$^1$H NMR (400 MHz, $CD_2Cl_2$): δ = 7.73 (s, 1 H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.22–7.19 (m, 2 H), 4.31–4.10 (m, 4 H), 3.93 (dd, *J* = 11.9, 3.8 Hz, 1 H), 3.73 (dd, *J* = 1.09, 10.4 Hz, 1 H), 3.62 (dd, *J* = 10.4, 3.8 Hz, 1 H), 2.86–2.73 (m, 2 H), 2.03 (s, 1 H), 1.22 (d, *J* = 6.8 Hz, 3 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 1.13 (d, *J* = 5.2 Hz, 3 H), 1.11 (d, *J* = 5.2 Hz, 3 H), 0.99 (s, 9 H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): δ = 159.9 (CH), 147.1 (C), 146.8 (C), 131.7 (CH), 129.9 (C), 125.4 (CH), 125.2 (CH), 70.7 (CH), 57.6 ($CH_2$), 48.5 ($CH_2$), 37.8 ($CH_2$), 31.0 (C), 29.2 (CH), 29.0 (CH), 27.4 (3 $CH_3$), 24.9 ($CH_3$), 24.8 ($CH_3$), 24.0 ($CH_3$), 23.9 ($CH_3$). $^{31}$P NMR (162 MHz, $CD_2Cl_2$): δ = –144.5 (sept, *J* = 711 Hz, 1 P). $^{19}$F NMR (376 MHz, $CD_2Cl_2$): δ = –71.53 (d, *J* = 711 Hz, 6 F). $[\alpha]_D^{20}$ +5.4 (*c* 1, acetone). Anal. Calcd (%) for $C_{21}H_{35}F_6N_2OP$ (476.24): C, 52.94; H, 7.40; N, 5.88. Found: C, 52.97; H, 7.54; N, 5.89.

(14) **Representative Procedure for the Copper-Catalyzed Allylic Alkylation of Dialkylzinc Reagents to Allylic Phosphates**
A dried Schlenk tube, under an argon atmosphere, was charged with $(CuOTf)_2 \cdot C_6H_6$ (0.005 mmol) and ligand **L8** (0.01 mmol). Then, 0.5 mL of freshly distillated EtOAc was added, followed by the addition of *n*-BuLi (0.025 mmol). After stirring at r.t. for 10 min, the dialkylzinc reagent (3.0 mmol) was added dropwise at this temperature. After cooling the reaction vessel to 0 °C, the phosphate (1 mmol) was added. As soon as the addition of the substrate was completed, the ice bath was removed, and the reaction mixture was stirred at r.t. Upon completion of the reaction, 1 N HCl was added, and the compound was extracted with $Et_2O$. The combined organic layers were then washed with sat. $NaHCO_3$ aq solution, brine, and dried over $MgSO_4$. The solvents were carefully removed under vacuo. The crude product was purified by silica gel chromatography (100% pentane) to afford the corresponding product as a colorless oil.