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Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex

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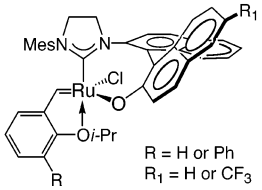
N-Heterocyclic carbenes (NHCs) readily promote a variety of organic transformations.[1] Accordingly, development of *chiral* NHCs for use in enantioselective synthesis has emerged as a critical objective. To date, however, there are only a few reports regarding NHC−metal complexes that have been effectively used in asymmetric catalysis.[2] One instance is a disclosure from these laboratories regarding asymmetric ring-opening/cross metathesis reactions that are catalyzed by chiral Ru complexes shown below (up to 96% ee).[3] In light of the above findings, we initiated a program to prepare additional members of this new class of chiral NHCs and examine their ability to effect other useful enantioselective transformations.



Herein, we disclose the synthesis, structure, and catalytic activity of an optically pure NHC−Ag(I) complex that can be used to effect Cu-catalyzed enantioselective formation of tertiary and quaternary carbon centers in up to 97% ee. Synthesis and structure of an isolable, air-stable, and catalytically active chiral NHC−Cu(II) complex are reported as well. Data are presented indicating that the *bidentate* nature of the NHC ligand is required for effective asymmetric C−C bond formation. The NHC-promoted alkylations can be carried out under less stringent conditions than related former methods;[4,5] levels of regio- and enantioselectivity, as well as efficiency and substrate generality, are superior to previous methods.[4]

We initiated our investigations by examining the ability of chiral NHC ligands **1**−**4** (Chart 1) to promote Cu-catalyzed asymmetric alkylations. Addition of Et_2Zn to phosphate **5** (Table 1) to afford **6** served as the representative transformation. We selected $(CuOTf)_2 \cdot C_6H_6$ for comparison with related protocols involving amino acid-based ligands.[4f]

As shown in entry 1 of Table 1, alkylation of **5** in the presence of 10 mol % **1a** affords **6** in 82% ee. When 1 mol % **1a** is used, reaction proceeds to >98% conv in 1 h but affords the desired product in 65% ee (entry 2); there is <2% conv at −78 °C (entry 3). As the data in entries 4 and 5 indicate, electron-deficient **1b** is less effective than NHC ligand **1a** (36 h needed for 87% conv at −15 °C). The significantly lower activity of methyl ether **2** (entry 6) indicates that formation of a covalent O-metal bond (vs dative MeO → metal) is critical for effective catalysis. Results in entries 7 and 8 show that if the mesityl unit is replaced by a 2,6-(*i*-Pr)$_2$C$_6$H$_3$ or an adamantyl group, conversion and enantioselectivity suffer significantly.

To enhance efficiency and selectivity, we prepared Ag(I) complex of **1a**, a decision that was based on disclosures pointing to facile exchange between Ag-based complexes of heterocyclic carbenes and Cu salts.[6] We obtained Ag(I) complex of **7** as an air-stable tan-colored solid in 97% yield by treatment of **1a** with Ag_2O (22 °C). As indicated by the X-ray crystal structure (Scheme 1), **7** exists as a dimer. NOE experiments indicate that the Ag complex remains largely as a dimer in solution; a representative nOe is shown in Scheme 1. It should be noted that, as expected, such enhancements are not observed with the monomeric Ru complexes shown above.

When complex **7** (5 mol %) is used to promote Cu-catalyzed alkylation of allylic phosphate **5** with Et_2Zn (entry 1, Table 2), **6** is formed in 84% ee within 15 min (>98% S_N2'; <2% conv without Cu salt). Even 0.25 mol % **7** is sufficient for >98% conv; unlike **1a** (entry 2, Table 1), enantioselectivity does not suffer with lower catalyst loading (84% ee). With 0.5 mol % **7** at −78 °C (entry 2), conditions that result in <2% conv with **1a** (cf. entry 3, Table 1), >98% conv is observed in 1 h to afford **6** in 89% ee. The data in entries 3−5 (Table 2) illustrate that the Ag(I) complexes of **2** and **3** (Chart 1) are more effective than their parent ligands, but alkylations are significantly less effective and selective than with **7**.

We have examined the utility of Ag(I) complex **7** in promoting Cu-catalyzed asymmetric alkylations of a wide range of allylic phosphates (Table 3). Noteworthy features of these findings are: (i) Catalyst loading is significantly lower than required with amino acid-based ligands (2 vs 10 mol %). (ii) Enantioselective additions can be catalyzed with air-stable, moisture-insensitive, commercially

Chart 1. Chiral Bidentate NHC Ligands

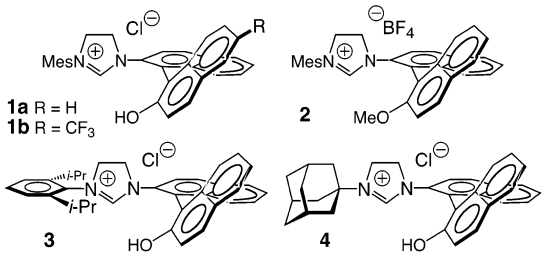
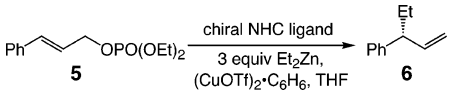


Table 1. Initial Screening of Various Chiral NHC Ligands



entry	NHC ligand mol %[a]	*T* (°C); time (h)	conv (%)[b]	$S_N2':S_N2$[b]	ee (%)[c]
1	**1a**; 10	−15; 1	>98	>98:2	82
2	**1a**; 1	−15; 1	>98	>98:2	65
3	**1a**; 1	−78; 1	<2	−	nd
4	**1b**; 10	−15; 36	87	>98:2	80
5	**1b**; 1	−78; 36	<2	−	−
6	**2**; 10	−15; 10	20	>98:2	21
7	**3**; 10	−15; 24	18	>98:2	64
8	**4**; 10	−15; 24	70	>98:2	52

[a] 5 mol % (10 mol % ligand) and 0.5 mol % (1 mol % ligand) $(CuOTf)_2 \cdot C_6H_6$ were used. [b] Determined by ^{1}H NMR analysis. [c] See Supporting Information for details.

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Scheme 1. Synthesis and Structure of NHC·Ag Complex **7**

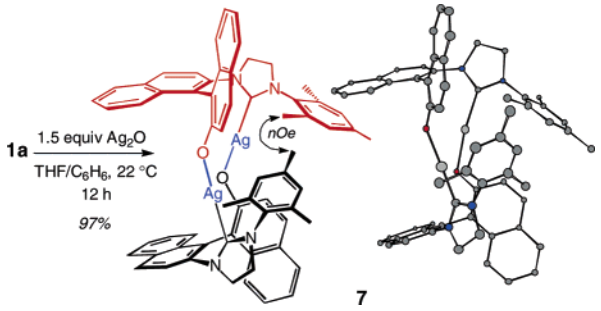
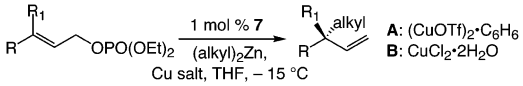


Table 2. Cu-Catalyzed Alkylations (**5** → **6**) with Chiral NHC·Ag Complexes

entry	NHC ligand mol %[a]	*T* (°C); time (h)	conv (%)[b]	$S_N2':S_N2$[b]	ee (%)[b]
1	**7**; 5	−15; 0.2	>98	>98:2	84
2	**7**; 0.5	−15; 1	>98	>98:2	89
3	**2·Ag**; 5	−15; 1	>98	>98:2	34
4	**2·Ag**; 0.5	−78; 36	29	>98:2	39
5	**3·Ag**; 0.5	−15; 24	>98	>98:2	70

[a,b] See corresponding footnotes for Table 1.

Table 3. Cu-Catalyzed Asymmetric Allylic Alkylations[a]



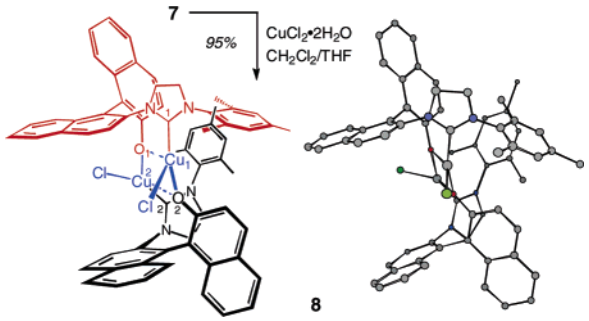
entry	R	R_1	$(alkyl)_2Zn$	Cu salt; mol %	time (h); conv (%)[b]	yield (%);[c] ee (%)[d]
1	C_6H_5	H	Me_2Zn	**A**; 1	24; >98	42; 74
2	C_6H_5	H	Me_2Zn	**B**; 2	24; >98	58; 71
3	C_6H_5	H	Et_2Zn	**B**; 2	4; >98	68; 86
4	C_6H_5	Me	Et_2Zn	**A**; 2.5[e]	24; >98	88; 91
5	C_6H_5	H	$(PivOCH_2)_2Zn$	**B**; 2	24; >98	94; 76
6	*o*-$NO_2C_6H_4$	H	Et_2Zn	**A**; 1	1; >98	73; 82
7	*o*-$NO_2C_6H_4$	H	Et_2Zn	**B**; 2	4; >98	89; 97
8	*p*-$NO_2C_6H_4$	H	Me_2Zn	**A**; 1	24; 96	80; 72
9	*p*-$NO_2C_6H_4$	Me	Et_2Zn	**A**; 2.5[e]	24; >98	72; 89
10	*p*-$NO_2C_6H_4$	Me	Et_2Zn	**B**; 2	4; >98	62; 98
11	1-naphth	H	Me_2Zn	**A**; 1	12; >98	69; 75
12	1-naphth	H	Et_2Zn	**A**; 1	3; >98	80; 89
13	Cy	H	Et_2Zn	**A**; 1	3; >98	53; 94
14		Me	Et_2Zn	**B**; 2	24; >98	54; 96
15	Cy	Me	Et_2Zn	**B**; 2	12; >98	73; 93

[a] >98% S_N2'. [b] Determined by 400 MHz ^1H NMR. [c] Isolated yields; some low yields due to volatility. [d] See Supporting Information for details. [e] 2.5 mol % **7** and 2.5 mol % **A**.

available and unpurified $CuCl_2·2H_2O$; this is in contrast to the rigorously inert conditions required with CuOTf salts.[4,5] In several cases where comparison studies were carried out, Cu(II) salts deliver faster reactions (entries 9 and 10) and higher enantioselectivities (entries 6, 7, 9, and 10). (iii) Unlike previous methods,[4] additions of heteroatom-bearing $(PivOCH_2)_2Zn$ and the less reactive Me_2Zn proceed efficiently with aromatic and aliphatic substrates (entries 1, 2, 4, 5, 8, 11). (iv) High selectivities extend to formation of quaternary carbon stereogenic centers (entries 4, 9, 10, 14, and 15) with 2 mol % catalyst (vs 10 mol % peptidic ligands);[4c,f] asymmetric induction in alkylations of trisubstituted olefins (aromatic and aliphatic) is higher than previously reported.[4c,f] (v) Adventitious S_N2 addition does not occur. Overall, the present protocol is one of the most general, efficient, regio- and enantioselective methods reported for allylic alkylations involving hard alkylmetals.

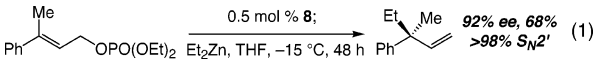
To gain insight to the identity of the active catalyst, **7** was treated with $CuCl_2·2H_2O$ at 22 °C (Scheme 2). The resulting air-stable

Scheme 2. Synthesis and X-ray Structure of NHC·Cu(II) Complex **8**[a]



[a] Selected bond lengths (Å): $Cu_1-C_1 = 1.926(8)$, $Cu_1-O_1 = 1.986(6)$, $Cu_1-O_2 = 1.950(6)$, $Cu_2-C_2 = 1.964(8)$, $Cu_2-O_1 = 1.933(6)$, $Cu_2-O_2 = 1.975(6)$.

dimeric Cu complex **8** (X-ray, Scheme 2) was isolated as a dark red solid in 95% yield.[7] Importantly, **8** gives rise to enantioselective alkylation: as shown in eq 1, treatment of the trisubstituted olefin in entry 4 of Table 3 with 0.5 mol % **8** and Et_2Zn affords the desired product in 92% ee (48 h; 68% yield).



In conclusion, the present study extends the utility of chiral NHC ligands to highly enantioselective Cu-catalyzed allylic alkylations with alkylzincs. Development of new chiral NHC ligands and applications to other catalytic asymmetric methods, as well as mechanistic studies (e.g., monomeric vs dimeric active catalytic complex) are in progress.

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

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