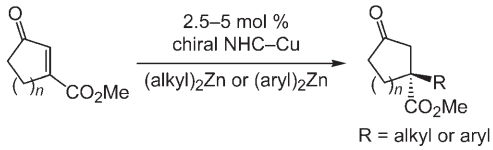
Chiral Carbenes

DOI: 10.1002/ange.200604511

All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene**

*M. Kevin Brown, Tricia L. May, Carl A. Baxter, and Amir H. Hoveyda**

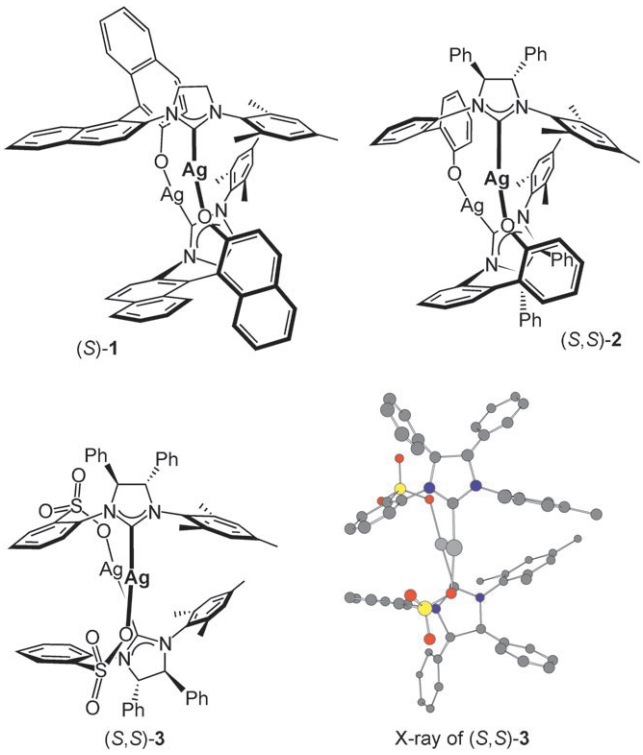
The design of new chiral catalysts for enantioselective synthesis of all-carbon quaternary stereogenic centers is a critical and challenging objective in modern chemistry.[1] Such catalysts must be enantio-differentiating but also especially active because the desired reactions involve additions of carbon nucleophiles to sterically congested electrophilic sites. Herein, we disclose a readily available chiral N-heterocyclic carbene (NHC) that can be used to promote the catalytic asymmetric conjugate addition (ACA)[2] of organozinc reagents to cyclic γ-keto esters [Eq. (1)]; these transformations give rise to the enantioselective formation of all-carbon



(1)

quaternary stereogenic centers that bear a readily functionalizable carboxylic ester substituent in up to 95% *ee*.[3–5] In nearly all of the catalytic ACA reactions (one exception), the new chiral NHC (Cu complex generated in situ) delivers significantly higher efficiency and asymmetric induction than the previously reported systems.

We began our investigation by examining the ability of Cu complexes generated from the reaction of **1**[5a] and **2**[5c] (Scheme 1) with $(CuOTf)_2{\cdot}C_6H_6$ in promoting the ACA of Me_2Zn to five- and six-membered ring γ-keto esters **4** and **5** (Table 1). With cyclopentenone **4a** as the substrate and in the presence of binaphthyl-based **1** and $(CuOTf)_2{\cdot}C_6H_6$ (2.5 mol%), less than 10% conversion is detected after 24 h (Table 1, entry 1). When biphenyl complex **2** is used, there is only 15% conversion and **6** is formed in 30% *ee* (Table 1, entry 2). With six-membered ring enone **5a**, Cu-based complexes derived from **1** and **2** (Table 1, entries 4–5) promote the ACA of Me_2Zn more efficiently (60% and >98% conversion) and with improved enantioselectivity (73% *ee* and 33% *ee*), but only in comparison to the reactions of cyclopentenone **4a** and not at synthetically useful levels.



Scheme 1. Previously reported **1** and **2** and the new chiral NHC complex **3**.

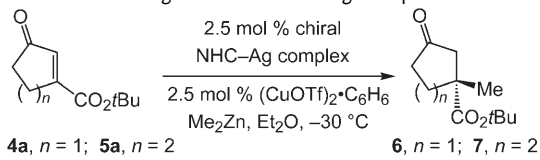
Faced with the inferior activity and asymmetric induction provided by the Cu complexes of **1** and **2**, we set out to identify a more effective chiral catalyst. This initiative led us to discover that complex **3**,[6] a sulfonate-containing chiral NHC (Table 1, entry 3), promotes the addition of Me_2Zn to **4a** with substantially higher efficiency (>98% conversion, 17 h versus <15% conversion with **1** and **2**) and superior enantioselectivity (84% *ee* versus ≤30% *ee* with **1** and **2**). Furthermore, catalytic ACA of Me_2Zn to cyclohexenone **5a** proceeds efficiently with the Cu complex generated in situ from **3**, which affords **7** in 75% *ee*. Thus, in one case (compare

[*] M. K. Brown, T. L. May, Dr. C. A. Baxter, Prof. A. H. Hoveyda
Department of Chemistry
Merkert Chemistry Center
Boston College
Chestnut Hill, MA 02467 (USA)
Fax: (+1) 617-552-1442
E-mail: amir.hoveyda@bc.edu

[**] We are grateful to the NIH (GM-47480) and the NSF (CHE-0213009) for financial support. We thank Professor A. Alexakis (University of Geneva) for generously sharing unpublished results with us (reference [10]). M.K.B. and C.A.B. are recipients of an ACS Graduate Fellowship in Organic Chemistry (sponsored by Schering-Plough) and a Fulbright Distinguished Scholarship, respectively. The X-ray facility at Boston College is supported by Schering-Plough; Dr. R. J. Staples provided valuable assistance in obtaining X-ray structures.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Initial screening of various NHC–Ag^{I} complexes.[a]

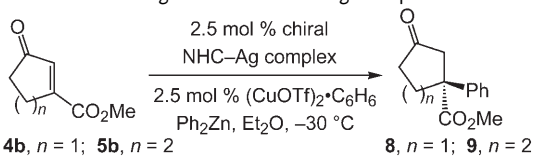


4a, $n = 1$; **5a**, $n = 2$ — **6**, $n = 1$; **7**, $n = 2$

Entry	n	NHC–Ag^{I}	t [h]; Conversion [%][b]	*ee* [%][c]
1	1	(*S*)-**1**	24; <10	n.d.
2	1	(*S*,*S*)-**2**	24; 15	30
3	1	(*S*,*S*)-**3**	17; >98	84
4	2	(*S*)-**1**	16; 60	73
5	2	(*S*,*S*)-**2**	18; >98	33
6	2	(*S*,*S*)-**3**	15; >98	75

[a] Reaction performed under N_2. [b] Conversions determined by analysis of the 400 MHz ^{1}H NMR spectra. [c] Enantioselectivities determined by chiral GLC analysis; see the Supporting Information for details. n.d. = not determined.

Table 2: Initial screening of various NHC–Ag^{I} complexes.[a]



4b, $n = 1$; **5b**, $n = 2$ — **8**, $n = 1$; **9**, $n = 2$

Entry	n	NHC–Ag^{I}	t [h]; Conversion [%][b]	*ee* [%][c]
1	1	(*S*)-**1**	15; <2	n.d.
2	1	(*S*,*S*)-**2**	42; 26	25
3	1	(*S*,*S*)-**3**	42; >98	81
4	2	(*S*)-**1**	21; 43	46
5	2	(*S*,*S*)-**2**	21; >98	93
6	2	(*S*,*S*)-**3**	18; >98	−17

[a]–[c] See Table 1.

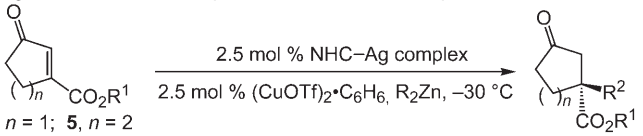
Table 1, entries 4 and 6), the new NHC delivers the appreciable enantioselectivity offered by **1** (75% *ee* versus 73% *ee*) together with higher reaction efficiency (>98% conversion versus 60% conversion). In another case (compare Table 1, entries 5 and 6), **3** provides the high activity of **2** (>98% conversion) but also a significantly higher product enantiopurity (75% *ee* versus 33% *ee*).[7]

Similar studies were performed with commercially available Ph_2Zn. As illustrated in Table 2, entries 1 and 2, with **4b** as the substrate, reactions involving **1** and **2** are inefficient (<2% and 26% conversion in 15 h and 42 h, respectively). In the presence of **3**, however, ACA of Ph_2Zn to cyclopentenone **4b** is promoted with significantly higher efficiency (>98% conversion, 81% *ee* in 42 h versus <30% conversion and <30% *ee* with **1** and **2**). The catalytic ACA of Ph_2Zn to cyclohexenone **5b** (Table 2, entries 4–6) is the only instance in which **3** is not superior to **1** or **2**.

The differences in the reactivity and selectivity levels mentioned above are substantial, and they likely arise from significant steric and electronic differences between NHCs **1**–**3**. In contrast to the monomeric Cu^{I} complexes derived from **1** and **2**,[8] in which the bidentate ligand gives rise to an eight-membered chelate, the sulfonate-bearing system contains a more geometrically constrained seven-membered ring. The chelating heteroatom in complexes derived from **3** is less basic. The latter difference is underlined by the chemical shift values for the benzylic protons (proximal to biphenyl and aryl sulfonate) of complexes **2** ($\delta = 5.36$ ppm) and **3** ($\delta = 6.55$ ppm), as well as variations in the C–Ag coupling constant values ($J_{C-Ag} = 267.1$ and 231.5 Hz for complex **2** versus $J_{C-Ag} = 186.8$ and 182.5 Hz for complex **3**).[13] The unique attribute of the sulfonate unit is further highlighted by the finding that the related NHC–Ag^{I} complex that bears a carboxylate group (versus a sulfonate), similar to **1** and **2**, is ineffective in promoting the present class of ACA reactions (<30% *ee*).[9]

With the availability of complex **3**, a variety of cyclic ketones bearing carboxylic ester substituted all-carbon quaternary stereogenic centers can be synthesized efficiently and in high enantiomeric purity (Table 3). The improved selectivities in Table 3 (versus those in Table 1) are due to subsequent studies that led us to establish that the addition of dialkylzinc

Table 3: Catalytic ACA of organozinc reagents to γ-keto esters promoted with NHC complex **3**.[a]



4, $n = 1$; **5**, $n = 2$

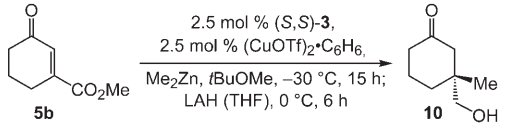
Entry	Substrate (R^1)	R_2Zn	Solvent; t [h]	Chiral NHC complex	Yield [%][b]	*ee* [%][c]
1[d]	**4b** (Me)	Me_2Zn	*t*BuOMe; 15	(*S*,*S*)-**3**	61	91
2	**4a** (*t*Bu)	Me_2Zn	*t*BuOMe; 42	(*S*,*S*)-**3**	68	90
3	**4b** (Me)	Et_2Zn	*t*BuOMe; 1	(*S*,*S*)-**3**	83	88
4	**4b** (Me)	$[(Me)_2CH(CH_2)_2]_2Zn$	*t*BuOMe; 18	(*S*,*S*)-**3**	53	87
5	**4a** (*t*Bu)	$(iPr)_2Zn$	*t*BuOMe; 15	(*S*,*S*)-**3**	80	95
6	**4b** (Me)	Ph_2Zn	Et_2O; 42	(*S*,*S*)-**3**	72	81
7	**4a** (*t*Bu)	Ph_2Zn	Et_2O; 42	(*S*,*S*)-**3**	98	82
8	**5b** (Me)	Me_2Zn	*t*BuOMe; 15	(*S*,*S*)-**3**	89	89
9	**5a** (*t*Bu)	Me_2Zn	*t*BuOMe; 15	(*S*,*S*)-**3**	86	84
10[e]	**5b** (Me)	$(iPr)_2Zn$	*t*BuOMe; 15	(*S*,*S*)-**3**	57	73
11	**5b** (Me)	Ph_2Zn	Et_2O; 21	(*S*,*S*)-**2**	82	93

[a] Reactions performed under a N_2 atmosphere; all conversion >98%. [b] Yield of isolated product after purification. [c] Enantioselectivities determined by chiral GLC analysis (see the Supporting Information for details). [d] In this reaction, 5 mol% catalyst and 6 equiv Me_2Zn was used. [e] Reaction was carried out with 5 equiv styrene.

reagents affords higher *ee* values when *t*BuOMe is used as the solvent (versus Et_2O). For example, as shown in Table 3, entry 8, catalytic ACA of Me_2Zn to **5b** leads to the formation of the desired product in 89% *ee* (versus 75% *ee* in Et_2O). Several additional points are noteworthy: 1) In all cases, with the addition of Ph_2Zn to cyclohexenone **5b** (Table 3, entry 11) being the only exception, NHC-sulfonate **3** delivers the highest enantioselectivity. 2) Methyl ester (**4b** and **5b**) and the more sterically hindered *tert*-butyl ester (**4a** and **5a**) substrates can be used. Typically, catalytic ACA of cyclopentenones **4a**–**b** (Table 3, entries 1–7) proceed to furnish products in higher enantiomeric purity than those of cyclohexenones **5a**–**b** (Table 3, entries 8–11). 3) The effect of added styrene as a radical scavenger in the reactions of organozinc reagents was investigated.[10] In one case (Table 3, entry 10), the selectivity improves to 73% *ee* from 60% *ee*; in other instances, minimal (< 5%) alteration of the enantioselectivity is observed.

The special versatility of the enantiomerically enriched product obtained by the Cu-catalyzed protocol is partly because, in contrast to β,β′-dialkyl ketones,[3b,c,g,h] the carboxylic ester unit provides a convenient handle for many structural manipulations. As the enantioselective synthesis of alcohol **10** illustrates [Eq. (2)], the carboxylic ester can be reduced while the ketone group is masked as a Zn enolate;

Site-selective ester reduction with ketone protected as a Zn enolate:

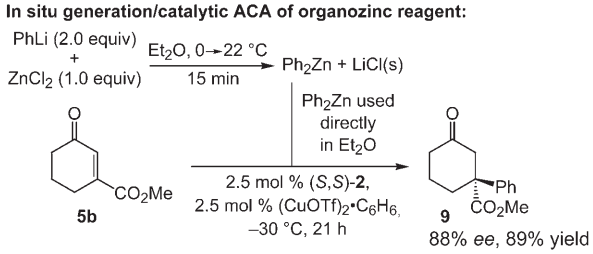


(2)

76% yield (89% *ee*)

thus, the need for protection/deprotection of the more reactive ketone carbonyl is obviated.[11] On the basis of initial studies, enantioselective synthesis of **10** and its protected variants through catalytic ACA of dialkyl- and diarylzinc reagents to the corresponding β-substituted cyclic enones with **1**–**3** are either inefficient and/or proceed with low selectivity. For example, Cu-catalyzed ACA of Me_2Zn (to afford benzyl-protected **10**) and Ph_2Zn to β-benzyloxymethyl cyclohexenone in the presence of 2.5 mol% **1**–**3** proceeds to less than 30% conversion. The above findings underline the unique ability of the present protocol to allow access to enantiomerically enriched β,β′-disubstituted ketones. As shown in Equation (3), Ph_2Zn, prepared in situ from the less expensive commercial grade PhLi,[12] can be employed directly (see Table 3, entry 11). Cu-catalyzed ACA processes

In situ generation/catalytic ACA of organozinc reagent:

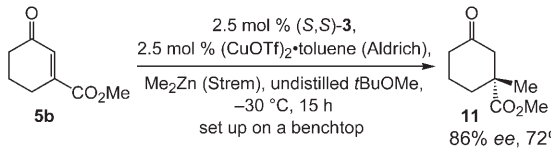


(3)

88% *ee*, 89% yield

are simple to perform: as depicted in Equation (4), reactions can be set up on a benchtop and performed with commercially available $(CuOTf)_2$·toluene (Aldrich, not purified), in undistilled solvent, and with commercial grade organozinc reagents.

Ease of operation:



(4)

86% *ee*, 72% yield

Chiral NHCs, relative newcomers on the scene, have had a notable influence on enantioselective synthesis.[13] A new chiral NHC impacts asymmetric catalysis involving a variety of metals[13] and can facilitate the utility of such carbenes as catalysts.[14] With its distinct steric and electronic attributes, complex **3** enhances the possibility to achieve higher reactivities and selectivities in catalytic asymmetric processes. Realization of such goals, study of the mechanistic details of the present class of ACA reactions, and applications to target-oriented synthesis are the subjects of ongoing investigations.

Received: November 3, 2006
Published online: January 3, 2007

Keywords: asymmetric catalysis · asymmetric synthesis · carbenes · conjugate addition · quaternary centers

[1] J. Christophers, A. Baro (Eds.), *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

[2] a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196; b) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221–3236; c) B. L. Feringa, R. Naasz, R. Imbos, L. A. Arnold in *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 224–258.

[3] For previous studies regarding Cu-catalyzed ACA to afford all-carbon quaternary stereogenic centers, see: a) J. Wu, D. Mampreian, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 4584–4585; b) A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 14988–14989; c) M. d'Augustin, L. Palais, A. Alexakis, *Angew. Chem.* **2005**, *117*, 1400–1402; *Angew. Chem. Int. Ed.* **2005**, *44*, 1376–1378; d) P. Mauleon, J. C. Carretero, *Chem. Commun.* **2005**, 4961–4963; e) E. Fillion, A. Wilsily, *J. Am. Chem. Soc.* **2006**, *128*, 2774–2775; f) R. Shintani, W.-L. Duan, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 5628–5629; g) K. Lee, M. K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182–7184; h) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416–8417.

[4] For Cu-catalyzed asymmetric allylic alkylations that afford all-carbon quaternary stereogenic centers, see: a) M. A. Kacprzynski, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 10676–10681; b) A. O. Larsen, W. Leu, C. Nieto-Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 11130–11131; c) J. J. Van Veldhuizen, J. E. Campbell, R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882; for NHC-catalyzed asymmetric allylic alkylations with alkyl Grignard

reagents, see: d) Y. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 15604 – 15605.
[5] For examples of Cu-catalyzed enantioselective reactions that deliver all-carbon quaternary stereogenic centers and involve catalysts bearing a chiral NHC, see references [3g,h] and [4b,c].
[6] Ag complex **3** is obtained in 98% yield (> 98% *de*) by treatment of the imidazolium salt with Ag_2O (THF/C_6H_6; 80 °C). The chiral imidazolium salt is prepared in four steps from commercially available starting materials. See the Supporting Information for all details.
[7] For details regarding the proof of the stereochemical identities of catalytic ACA products, see the Supporting Information.
[8] On the basis of steric considerations, it is likely that it is the derived monomeric chiral NHC complexes that serve as active catalysts; also see reference [3g].
[9] We are grateful to K.-s. Lee for carrying out these experiments. Details will be disclosed in a separate account.
[10] K. Li, A. Alexakis, *Angew. Chem.* **2006**, *118*, 7762 – 7765; *Angew. Chem. Int. Ed.* **2006**, *45*, 7600 – 7603.
[11] For functionalization of enolates derived from catalytic ACA reactions, see: O. Knopff, A. Alexakis, *Org. Lett.* **2002**, *4*, 3835 – 3837.
[12] a) D. Peña, F. López, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *Chem. Commun.* **2004**, 1836 – 1837; b) J. G. Kim, P. J. Walsh, *Angew. Chem.* **2006**, *118*, 4281 – 4284; *Angew. Chem. Int. Ed.* **2006**, *45*, 4175 – 4178.
[13] For a review regarding synthesis, catalytic activity, and structural characteristics of NHC complexes, see: J. C. Garrison, W. J. Youngs, *Chem. Rev.* **2005**, *105*, 3978 – 4008.
[14] For an enantioselective NHC-catalyzed protocol that affords all-carbon quaternary stereogenic centers, see: M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876 – 8877.

