### All-Carbon Quaternary Stereogenic Centers by Enantioselective Cu-Catalyzed Conjugate Additions Promoted by a Chiral N-Heterocyclic Carbene<sup>\*\*</sup>

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The design of new chiral catalysts for enantioselective synthesis of all-carbon quaternary stereogenic centers is a critical and challenging objective in modern chemistry.<sup>[1]</sup> 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)<sup>[2]</sup> of organozinc reagents to cyclic  $\gamma$ -keto esters [Eq. (1)]; these transformations give rise to the enantioselective formation of all-carbon

quaternary stereogenic centers that bear a readily functionalizable carboxylic ester substituent in up to 95% *ee*.<sup>[3-5]</sup> 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  $\mathbf{1}^{[5a]}$  and  $\mathbf{2}^{[5c]}$  (Scheme 1) with (CuOTf)<sub>2</sub>·C<sub>6</sub>H<sub>6</sub> in promoting the ACA of Me<sub>2</sub>Zn to five- and six-membered ring  $\gamma$ -keto esters **4** and **5** (Table 1). With cyclopentenone **4a** as the substrate and in the presence of binaphthyl-based **1** and (CuOTf)<sub>2</sub>·C<sub>6</sub>H<sub>6</sub>

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



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

(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<sub>2</sub>Zn 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.

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**,<sup>[6]</sup> a sulfonate-containing chiral NHC (Table 1, entry 3), promotes the addition of Me<sub>2</sub>Zn to **4a** with substantially higher efficiency (>98% conversion, 17 h versus <15% conversion with **1** and **2**) and superior enantioselectivity (84% *ee* versus  $\leq$  30% *ee* with **1** and **2**). Furthermore, catalytic ACA of Me<sub>2</sub>Zn 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

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

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*).<sup>[7]</sup>

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–



[a]–[c] See Table 1.

3. In contrast to the monomeric Cu<sup>I</sup> complexes derived from 1 and 2,<sup>[8]</sup> in which the bidentate ligand gives rise to an eightmembered 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).<sup>[13]</sup> The unique attribute of the sulfonate unit is further highlighted by the finding that the related NHC-AgI 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  $\gamma$ -keto esters promoted with NHC complex 3.<sup>[a]</sup>

$ \begin{array}{c} 0\\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	2.5 mol % NHC-Ag complex 2.5 mol % (CuOTf) <sub>2</sub> •C <sub>6</sub> H <sub>6</sub> , R <sub>2</sub> Zn, -30 °C	O $()_n = R^2$ $CO_2 R^1$
4, // - 1, 5, // - 2		002K

Entry	Substrate (R <sup>1</sup> )	$R_2Zn$	Solvent; <i>t</i> [h]	Chiral NHC complex	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1 <sup>[d]</sup>	<b>4b</b> (Me)	Me <sub>2</sub> Zn	tBuOMe; 15	(S,S)- <b>3</b>	61	91
2	<b>4a</b> (tBu)	Me <sub>2</sub> Zn	tBuOMe; 42	(S,S)- <b>3</b>	68	90
3	<b>4b</b> (Me)	Et₂Zn	tBuOMe; 1	(S,S)- <b>3</b>	83	88
4	4b (Me)	[(Me) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> Zn	tBuOMe; 18	(S,S)- <b>3</b>	53	87
5	<b>4a</b> (tBu)	(iPr) <sub>2</sub> Zn	tBuOMe; 15	(S,S)- <b>3</b>	80	95
6	<b>4b</b> (Me)	Ph <sub>2</sub> Zn	Et <sub>2</sub> O; 42	(S,S)- <b>3</b>	72	81
7	<b>4a</b> (tBu)	Ph <sub>2</sub> Zn	Et <sub>2</sub> O; 42	(S,S)- <b>3</b>	98	82
8	5 b (Me)	Me <sub>2</sub> Zn	tBuOMe; 15	(S,S)- <b>3</b>	89	89
9	5 a (tBu)	Me <sub>2</sub> Zn	tBuOMe; 15	(S,S)- <b>3</b>	86	84
10 <sup>[e]</sup>	5 b (Me)	( <i>i</i> Pr)₂Zn	tBuOMe; 15	(S,S)- <b>3</b>	57	73
11	5 b (Me)	Ph <sub>2</sub> Zn	Et <sub>2</sub> O; 21	(S,S)- <b>2</b>	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 tBuOMe is used as the solvent (versus Et<sub>2</sub>O). For example, as shown in Table 3, entry 8, catalytic ACA of Me<sub>2</sub>Zn to 5b leads to the formation of the desired product in 89% ee (versus 75% ee in Et<sub>2</sub>O). Several additional points are noteworthy: 1) In all cases, with the addition of Ph<sub>2</sub>Zn 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.<sup>[10]</sup> 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  $\beta$ , $\beta'$ -dialkyl ketones,<sup>[3b,c,g,h]</sup> 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:



thus, the need for protection/deprotection of the more reactive ketone carbonyl is obviated.<sup>[11]</sup> 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  $\beta$ -substituted cyclic enones with **1–3** are either inefficient and/or proceed with low selectivity. For example, Cu-catalyzed ACA of Me<sub>2</sub>Zn (to afford benzyl-protected **10**) and Ph<sub>2</sub>Zn to  $\beta$ -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  $\beta$ , $\beta$ '-disubstituted ketones. As shown in Equation (3), Ph<sub>2</sub>Zn, prepared in situ from the less expensive commercial grade PhLi,<sup>[12]</sup> can be employed directly (see Table 3, entry 11). Cu-catalyzed ACA processes

### In situ generation/catalytic ACA of organozinc reagent:



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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.



Chiral NHCs, relative newcomers on the scene, have had a notable influence on enantioselective synthesis.<sup>[13]</sup> A new chiral NHC impacts asymmetric catalysis involving a variety of metals<sup>[13]</sup> and can facilitate the utility of such carbenes as catalysts.<sup>[14]</sup> 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.

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