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A Practical Method for Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers through NHC-Cu-Catalyzed Conjugate Additions of Alkyl- and Arylzinc Reagents to β-Substituted Cyclic Enones

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Catalytic asymmetric conjugate addition (ACA) of carbon-based nucleophiles to unsaturated carbonyls provides a direct route for synthesis of enantiomerically enriched organic molecules.[1] Progress has been achieved in connection with catalytic ACA of alkylmetals to different classes of unsaturated carbonyl compounds. Such advances include the development of amino acid-based chiral phosphines in these laboratories for Cu-catalyzed ACA of alkylzinc reagents to cyclic[2] and acyclic enones,[3] nitroalkenes,[4] and *N*-acyloxazolidinones.[5] A related approach involves Cu- and Rh-catalyzed hydride conjugate additions to β-substituted enones.[1,6]

The significant majority of the above investigations involve catalytic enantioselective synthesis of tertiary C−C bonds. The more challenging problem of catalytic ACAs that afford all-carbon quaternary stereogenic centers,[7] a task that cannot be addressed by enantioselective hydride additions, has been the subject of only a small cluster of disclosures. Alexakis reported in 2005 that chiral phosphoramidite·Cu complexes can be utilized to catalyze ACA of Me_3Al and Et_3Al to β-alkyl-substituted cyclohexenones.[8] Catalytic ACA of the less reactive but more functional group-tolerant dialkylzinc reagents have been limited to highly electrophilic (activated) substrates. We showed in 2005 that chiral amino acid-based ligands may be employed for Cu-catalyzed ACA of acyclic trisubstituted nitroalkenes[9] and cyclic tetrasubstituted alkylidene β-ketoesters.[10] Carretero has used Rh-catalyzed ACA of alkenylboronic acids to unsaturated pyridyl sulfones (chiraphos as ligand).[11] Most recently, Fillion has outlined a method for Cu-catalyzed ACA of dialkylzinc reagents to acyclic aryl-substituted alkylidene β-ketoesters that are derived from Meldrum's acid (phosphoramidites again used as ligands).[12] Our initial focus on reactions of the more activated systems (nitroalkenes and unsaturated β-ketoesters) stemmed from the fact that peptide·Cu complexes are ineffective in catalyzing ACAs of alkylzincs to simple β-substituted enones (<50% conv and <20% ee). To address the above reactivity and selectivity problems, we turned our attention to chiral bidentate *N*-heterocyclic carbenes (Scheme 1), entities developed in these laboratories for Ru-catalyzed enantioselective olefin metathesis[13] and later applied to Cu-catalyzed allylic alkylations.[14]

Herein we report the first examples of Cu-catalyzed ACAs of alkyl- *and* arylzinc reagents to simple unactivated β-substituted cyclic enones. Transformations are promoted with of 2.5−15 mol % of a readily available chiral NHC-based Cu complex,[15] and afford products that bear all-carbon quaternary stereogenic centers in 67−98% yield and up to 97% ee. Catalytic reactions can be carried out on a benchtop, with undistilled solvent and commercially available (not purified) Cu salts and in reasonable scale. Tentative mechanistic models, accounting for the observed levels and trends in enantioselectivity, are provided.

Preliminary investigations focused on chiral NHC complexes **1**−**4** (Scheme 1); conversion of cyclohexenone **5** to ketone **6** served as the representative process (Table 1). These studies indicated that, although inefficient (32% conv, 48 h, −30 °C), Cu(II) complex **1** promotes the ACA with appreciable enantioselectivity (72% ee; entry 1, Table 1). The "second-generation" NHC·Cu complex **2** proved to be more effective (53% conv, 48 h), delivering **6** in 59% ee. Next, we investigated NHC·Ag(I) complex **4**, which is precursor to **2**,[14] and the ability of the derived in situ generated NHC·Cu complexes to promote ACA. As illustrated in entries 3−7 (Table 1), in all cases, including air-stable CuOAc and CuTC salts (entries 5−6), reactions proceed readily (93−98% conv in 6 h), and the desired product is isolated with high asymmetric induction. The highest enantioselectivity is obtained with $(CuOTf)_2{\cdot}C_6H_6$, used in conjunction with **4**, affording **6** efficiently (94% conv in 6 h; 92%

Scheme 1

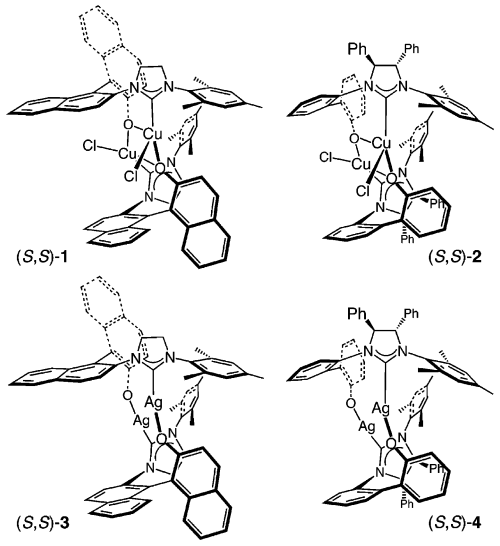
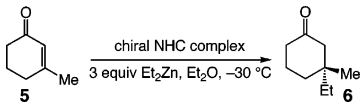


Table 1. Initial Screening Studies[a]



entry	catalyst	mol (%)	time (h)	conv (%)[b]	ee (%)[c]
1	(*S*,*S*)-**1**	2.5	48	32	72
2	(*S*,*S*)-**2**	2.5	48	53	59
3	(*S*,*S*)-**4**; $CuCl_2{\cdot}2H_2O$	2.5; 5	48	56	48
4	(*S*,*S*)-**4**; $Cu(OTf)_2$	2.5; 5	48	45	78
5	(*S*,*S*)-**4**; CuOAc	2.5; 5	6	98	89
6	(*S*,*S*)-**4**; CuTC	2.5; 5	6	93	91
7	(*S*,*S*)-**4**; $(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	**6**	**94**	**93**
8	(*S*,*S*)-**3**; $(CuOTf)_2{\cdot}C_6H_6$	2.5; 2.5	48	85	96

[a] Reactions performed under N_2 atm. [b] Determined by ^1H NMR analysis. [c] Determined by chiral GLC analysis (see the SI for details).

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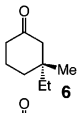
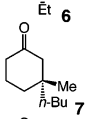
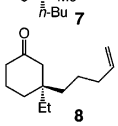
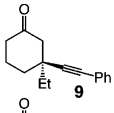
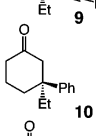
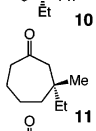
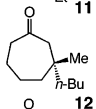
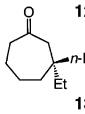
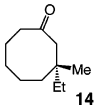
Table 2. Cu-Catalyzed ACA of Dialkylzinc Reagents to β-Substituted Cyclic Enones[a]

entry	product	R_2Zn	mol % **4** and Cu Salt	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	 **6**	Et_2Zn	2.5	94	92	93
2	 **7**	$(n\text{-Bu})_2Zn$	2.5	91	83	86
3	 **8**	Et_2Zn	5	93	92	84
4[e]	 **9**	Et_2Zn	2.5	81	78	74
5	 **10**	Et_2Zn	10	85	85	90
6	 **11**	Et_2Zn	2.5	84	83	85
7	 **12**	$(n\text{-Bu})_2Zn$	5	67	67	77
8	 **13**	Et_2Zn	15	86	81	76
9	 **14**	Et_2Zn	10	35	34	54

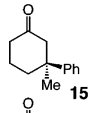
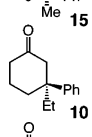
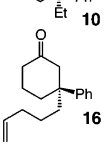
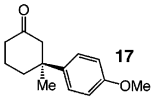
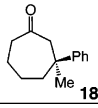
[a] See Table 1 for conditions; 6 h for entry 1, 24−48 h otherwise. [b] By ^{1}H NMR analysis. [c] Isolated yields. [d] Determined by chiral GLC analysis (see the SI for details). [e] Reaction performed at −15 °C.

yield) and in 93% ee. Use of NHC−Ag(I) complex **3** and $(CuOTf)_2\cdot C_6H_6$ also leads to improvement in reactivity and selectivity (entry 8 vs with NHC−Cu(II) complex **1** in entry 1); the combination in entry 7, however, delivers a more facile ACA. The data summarized in Table 1 indicate that, when Cu(I) salts are used to generate the chiral complex (entries 5−6), higher catalyst efficiency is achieved (vs Cu(II) salts; >98% conv for entries 5−6 vs 45−55% conv for entries 3−4). This difference in reactivity may arise from the slow rate of Cu(II) → Cu(I) reduction under the reaction conditions, or could be due to low solubility of Cu(II) salts in Et_2O.

The combination of NHC·Ag(I) complex **4** and $(CuOTf)_2\cdot C_6H_6$ can be utilized to promote catalytic ACAs of commercially available (not purified) dialkylzinc reagents to β-alkyl- and β-aryl-substituted cyclic enones in 54−95% ee (Table 2).

Several points regarding the data in Table 2 are noteworthy: (1) Transformations typically proceed to >80% conv after 6−48 h (−30 °C); comparison between percent conversion and isolated yield demonstrates that there is minimal formation of byproducts (e.g., 1,2-addition). (2) Rates of reactions and levels of enantioselectivity are sensitive to steric factors. There is <5% conversion when $(i\text{-Pr})_2Zn$ is used. Catalytic ACA of Me-substituted enone (**6**) in entry 1 (Table 2) requires 2.5 mol % **4** (94% conv), affording the desired product in 93% ee; 5 mol % catalyst is needed for *n*-alkenyl-substituted enone in entry 3 to proceed to 93% conversion, delivering **8** in 84% ee. Consistent with this trend, enantioslective synthesis of β-phenyl-substituted **10** (90% ee, 85% conv) must be performed with 10 mol % **4**. (3) Catalytic ACAs of cycloheptenones (entries 6−8, Table 2) deliver cyclic enones **11**−**13** in 76−85% ee and 67−83% isolated yield. However, these transformations are slower than their six-membered ring analogues. (4) Reactions of eight-membered rings are slower and less selective than β-substituted cyclohexenones and cycloheptenones; the example provided in entry 9 (Table 2) is illustrative. The relatively unreactive Me_2Zn cannot be used (<5% conv, 48 h), and there is <5% conversion with cyclopentenones (after 48 h).

Table 3. Cu-Catalyzed ACA of Diarylzinc Reagents to β-Substituted Cyclic Enones[a]

entry	product	mol % **4** and Cu Salt	conv (%)[b]	yield (%)[c]	ee (%)[d]
1	 **15**	2.5	96	95	97
2	 **10**	2.5	92	89	94
3[e]	 **16**	5	88	88	89
4[f]	 **17**	5	93	89	90
5[g]	 **18**	5	88	88	96

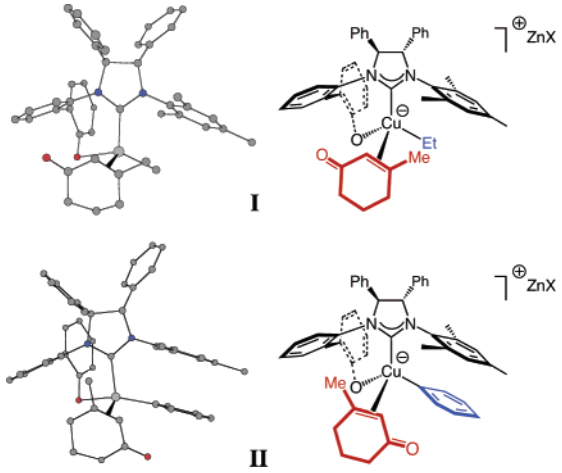
[a−d] See Table 2; 48 h. [e] At −15 °C. [f] At −15 °C, in toluene, 72 h. [g] Time = 72 h.

The Cu-catalyzed protocol can be used to promote ACA of diarylzinc reagents; desired cyclic ketones are obtained in 88−95% isolated yield and 89−97% ee (Table 3). Transformations with Ph_2Zn proceed less readily than those involving dialkylzinc reagents, but with higher enantioselectivity (e.g., compare entries 1−3 of Table 3 with entries 1−3 of Table 2). Cu-catalyzed ACA can be extended to an electron-rich diarylzinc reagent (entry 4 of Table 3), albeit with lower enantioselectivity (90% ee vs 97% ee in entry 1). Attempts to effect addition with the corresponding $(p\text{-}CF_3C_6H_4)_2Zn$[16] gave rise to <5% conversion (e.g., with enone **5**). As the example in entry 5 of Table 3 indicates (**18** formed in 96% ee), ACA of Ph_2Zn to β-substituted cycloheptenones proceeds with enantioselectivity levels similar to those observed with cyclohexenones. To the best of our knowledge, catalytic ACA transformations of an arylmetal to afford an all-carbon quaternary stereogenic center have not been reported previously.[17]

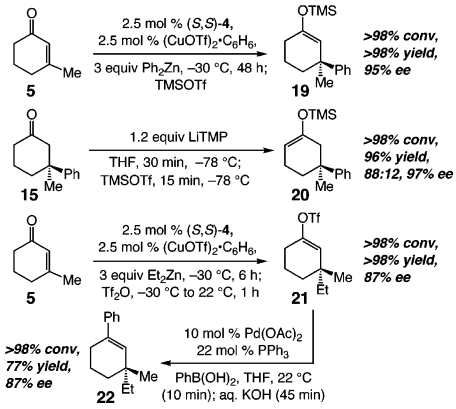
Cu-catalyzed ACA of dialkylzinc reagents (Table 2) proceed in the *opposite* sense compared to reactions with diarylzinc reagents (e.g., compare entry 5 of Table 2 and entry 2 of Table 3). Preliminary mechanistic models that account for the observed enantioselectivity, as well as the aforementioned reversal in the sense of asymmetric induction, are presented in Scheme 2.[18] Alkyl-cuprate NHC complexes may undergo ACA through **I**; unfavorable steric interaction involving the enone substituent (Me) and the NHC's biphenol moiety is therefore avoided. In contrast, with aryl-cuprate complexes, the steric interaction between the enone's β-substituent and the aryl-Cu unit might be the dominant factor, giving rise to preference for complex **II**.

The optically enriched Zn-enolate intermediates can be converted to versatile enolsilane or enoltriflate derivatives for further functionalization.[19] Representative cases are depicted in Scheme 3.

Scheme 2. Proposed Mechanistic Models

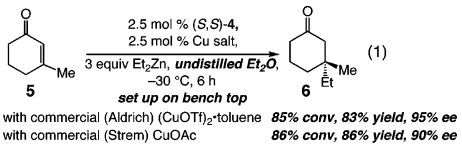


Scheme 3. Representative Functionalizations of ACA Products



Enolsilane **19** is obtained with >98% regioselectivity and in >98% yield when the mixture from Cu-catalyzed ACA of Ph_2Zn to **5** is treated with TMSOTf. Regioselective deprotonation of **15** with LiTMP delivers enolsilane **20** in 96% isolated yield and with 88:12 regioselectivity. Similarly, **5** is converted to enoltriflate **21** (>98% yield), which can be subjected to Pd-catalyzed cross-coupling reactions.[20] Conversion to cyclohexene **22** in 87% isolated yield serves as a case in point (Scheme 3).

The present class of transformations can be performed under operationally simple conditions. As illustrated in eq 1, *reactions can be carried out with undistilled solvent and set up on benchtop* (Schlenck-ware not needed).Catalytic ACA can be effected with commercially available $(CuOTf)_2$·toluene; nonetheless, use of freshly prepared $(CuOTf)_2$·C_6H_6 leads to higher conversion. Although this study was focused on ACA with $(CuOTf)_2$·C_6H_6 (for maximum activity), as the examples in entries 5−6 of Table 1 indicate, more user-friendly Cu salts are effective. When the catalytic ACA in eq 1 is carried out with commercially available and air stable CuOAc, **6** is isolated in 86% yield and 90% ee. Cu-catalyzed additions can be performed on reasonable scale; the transformation in eq 1, at 0.5-g scale ($(CuOTf)_2$·C_6H_6; −40 °C, 8−12 h), delivers **6** in 87% ee and in quantitative yield.



In summary, we have developed the first Cu-catalyzed ACA of alkyl- and arylzinc reagents to unactivated β-substituted cyclic enones; the catalytic protocol is operationally straightforward and delivers cyclic ketones that bear all-carbon quaternary stereogenic centers in excellent yields and 54−97% ee. This is the first application of this class of chiral bidentate NHC ligands to catalytic ACA reactions.

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

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(15) For catalytic ACAs of Et_2Zn to *di*substituted enones with NHC ligands, see: (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083−2086. (b) Pytkowicz, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087−2089. (c) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345−348. (d) Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612−1613. (e) Clavier, H.; Coutable, L.; Guillemin, J.-C.; Mauduit, M. *Tetrahedron: Asymmetry* **2005**, *16*, 921−924.
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(18) Although rigorous evidence is not yet available, due to consideration of steric factors, it is likely that monomeric NHC complex is the active catalyst. The models proposed herein are preliminary and tentative; related high-level calculations are being carried out, the results of which will be reported in due course.
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