**Asymmetric Conjugate Additions**

Enantioselective Synthesis of All-Carbon Quaternary Stereogenic Centers by Catalytic Asymmetric Conjugate Additions of Alkyl and Aryl Aluminum Reagents to Five-, Six-, and Seven-Membered-Ring β-Substituted Cyclic Enones**

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Dedicated to Professor Elias J. Corey

Catalytic asymmetric conjugate addition (ACA) reactions of carbon-based nucleophiles to β,β-disubstituted enones present an efficient approach to enantioselective synthesis of all-carbon quaternary stereogenic centers[1] that reside adjacent to synthetically versatile enolates [Eq. (1)]. In spite of recent
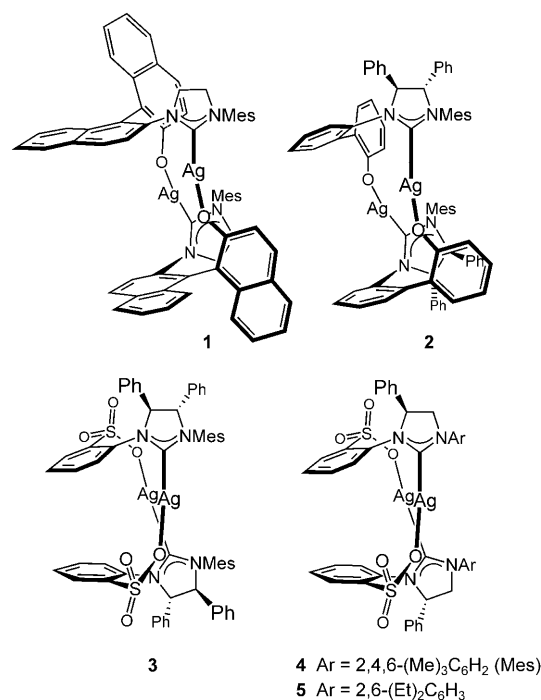

$$(1)$$
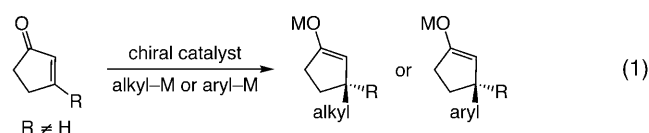
advances involving catalytic ACA reactions of alkyl metal (mostly dialkyl zinc) reagents,[2–5] a number of critical shortcomings remain unaddressed. One noteworthy challenge concerns transformations of β-substituted cyclopentenones, processes that are often less efficient[6,7] (vs. reactions of larger rings) but can deliver products that may be used in enantioselective syntheses of a variety of biologically active natural products.[8] Previously reported approaches, involving zinc-based reagents, are only effective with five-membered-ring substrates when the enone bears an additional activating substituent.[4] Additions of trialkyl aluminum reagents to β-substituted cyclopentenones catalyzed by chiral copper phosphoramidites have been shown to proceed in three cases. In only a single instance, however, is high selectivity observed (ACA with Et₃Al; 96.5:3.5 e.r., 93% *ee*).[5a] Herein, we disclose an efficient set of protocols for catalytic ACA reactions of alkyl and aryl aluminum reagents with a range of unactivated β-substituted cyclic enones, including cyclopentenones. Reactions, promoted in the presence of a chiral bidentate N-heterocyclic carbene (NHC) copper complex

(5 mol%), are efficient (up to 97% yield) and highly selective (up to >99:<1 e.r., greater than 98% *ee*). In the case of transformations involving additions of aryl units, the requisite aluminum-based reagents are prepared in situ from commercially available dimethylaluminum chloride and the corresponding aryl lithium compounds.

We began our investigations by examining the ability of NHC complexes 1–4 (Scheme 1), previously developed in our laboratories,[9] to promote ACA of trialkyl aluminum reagents to cyclic enones. As the main objective of these studies is reactions of β-substituted cyclopentenones, we selected **6a** to serve as the representative substrate (Table 1). Our focus on aluminum-based reagents[10] is partly due to the higher reactivity as well as the significantly lower cost of this class of alkylating agents (vs. dialkyl zinc reagents).

Through an initial screening study (Table 1), we established that the first two generations of aryloxide-containing NHC copper complexes derived from 1 and 2[9a–b] do not

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802910.

Scheme 1. Air-stable chiral NHC silver(I) complexes that serve as precursors to the corresponding copper-based catalysts.

4 Ar = 2,4,6-(Me)₃C₆H₂ (Mes)
5 Ar = 2,6-(Et)₂C₆H₃

Table 1: Initial screening of various NHC silver(I) complexes.[a]

Entry	NHC–Ag[I]	Conversion [%][b]	e.r.[c]	ee [%][c]
1	**1**	<2	–	–
2	**2**	<2	–	–
3	**3**	56	71.5:28.5	43
4	**4**	72	83.5:16.5	67
5	**5**	88	94.5:5.5	89

[a] Reactions were performed under N_2 atmosphere. [b] Conversions were determined by analysis of 400 MHz ^{1}H NMR spectra of product mixtures prior to purification. [c] Enantiomeric ratios and excesses were determined by chiral gas–liquid chromatography (GLC) analysis; see the Supporting Information for details.

promote the reaction of Me$_3$Al with **6a** at −78°C (entries 1 and 2, Table 1).[11] In contrast, under identical conditions, the copper complex derived from NHC sulfonate **3**[4b] generates 56% conversion, affording **7a** in 43% *ee* (71.5:28.5 e.r., entry 3, Table 1). Deletion of one of the phenyl groups of the chiral NHC compound (complex **4**, entry 4, Table 1), a previously utilized ligand alteration[9g] that we surmised would enhance the effective size of a less geometrically constrained mesityl substituent, improves enantioselectivity (83.5:16.5 e.r., 67% *ee*). To explore whether reaction efficiency and enantiopurity of products can be further enhanced, we prepared NHC–Ag[I] complex **5**, which carries the more sterically demanding diethylphenyl substituent (entry 5, Table 1). Copper-catalyzed ACA in the presence of 2.5 mol% **5** proceeds to 88% conversion to furnish **7a** in 89% *ee* (94.5:5.5 e.r.; entry 5, Table 1).

In the presence of 2.5 mol% NHC–Ag[I] complexes **3–5** and 5 mol% Cu(OTf)$_2$, an assortment of β-substituted cyclopentenones undergo efficient ACA with three commercially available trialkyl aluminum reagents (Table 2). These catalytic transformations deliver the desired products in 86–97% *ee* (93:7–98.5:1.5 e.r.) and up to 97% yield after purification. Five-membered-ring enones that bear an alkyl (entries 1–7, Table 2), an alkynyl (entry 8, Table 2), an aryl (entry 9, Table 2), or a carboxylic ester (entry 10, Table 2) substituent can

be used effectively. The reactions in entries 8 and 9 of Table 2 are particularly noteworthy: the derived ACA products represent β,β-disubstituted cyclopentanones that would be obtained from ACA with alkynyl (not yet reported) and aryl metal reagents (see below) to β-alkyl-substituted cyclic enones, respectively.

Copper-catalyzed ACA of trialkyl aluminum reagents can be extended to larger size cyclic enones (Table 3). Thus, under the conditions described for the transformations in Table 2 (2.5 mol% NHC–Ag[I] complex), β-substituted cyclohexenones **8a–8c** (entries 1–3, Table 3) as well as seven-membered-ring enone **9a** (entries 4–5, Table 3) are transformed to the corresponding β,β-disubstituted cyclohexanones or cycloheptanones efficiently (85–91% yield after purification) and with high enantioselectivity (91.5:8.5–95:5 e.r., 83–90% *ee*). It is noteworthy that, compared to the previously reported transformations involving bidentate NHC complex **2** and dialkyl zinc reagents (up to 15 mol% **2** required), the present method offers a more efficient approach to enantioselective synthesis of β,β-disubstituted cyclohexanones and cycloheptanones.[3g] Three additional points in connection with the data in Tables 2 and 3 merit mention: 1) Although **5** is optimal

Table 2: Catalytic ACA reactions of trialkyl aluminum reagents to cyclopentenones promoted by NHC copper complexes.[a]

Entry	Substrate [R]	(alkyl)$_3$Al	NHC–Ag[I]	T [°C]	t [h]	Yield [%][b]	e.r.[c]	ee [%][c]
1	**6a** [CH$_2$CH$_2$Ph]	Me$_3$Al	**5**	−78	24	71	94.5:5.5	89
2	**6a** [CH$_2$CH$_2$Ph]	Et$_3$Al	**5**	−78	4	97	96:4	92
3	**6a** [CH$_2$CH$_2$Ph]	iBu$_3$Al	**5**	−30	21	74	93.5:6.5	87
4	**6b** [nBu]	Me$_3$Al	**5**	−78	15	80	94:6	88
5	**6b** [nBu]	Et$_3$Al	**4**	−78	6	86	93:7	86
6	**6c** [Me]	Et$_3$Al	**4**	−78	4	97	98.5:1.5	97
7	**6c** [Me]	iBu$_3$Al	**4**	−30	15	83	94.5:5.5	89
8	**6d** [C≡C-$n$hep]	Me$_3$Al	**5**	−78	24	71[d]	95.5:4.5	91
9	**6e** [Ph]	Et$_3$Al	**5**	−78	15	87	98.2	96
10	**6f** [CO$_2$Me]	Et$_3$Al	**3**	−78	6	76	94.5:5.5	89

[a] Reactions were performed under N_2 atmosphere; greater than 98% conversion in all cases. [b] Yields of isolated, purified products. [c] Determined by chiral GLC analysis; see the Supporting Information for details. [d] 5 mol% NHC and 10 mol% Cu salt was used to ensure complete conversion.

Table 3: Catalytic ACA reactions of trialkyl aluminum reagents with cyclohexenones and cycloheptenones promoted by NHC copper complexes.[a]

Entry	Substrate [R]	(alkyl)$_3$Al	NHC–Ag[I]	T [°C]	t [h]	Yield [%][b]	e.r.[c]	ee [%][c]
1[d]	**8a** [Me]	iBu$_3$Al	**4**	22	0.25	89	95:5	90
2	**8b** [5-hexenyl]	Me$_3$Al	**5**	−78	12	85	95:5	90
3	**8c** [CO$_2$Me]	Et$_3$Al	**3**	−78	6	91	91.5:8.5	83
4	**9a** [nBu]	Me$_3$Al	**5**	−78	12	90	92.5:7.5	85
5	**9a** [nBu]	Et$_3$Al	**5**	22	0.25	87	94.5:5.5	89

[a–c] See Table 2. [d] 5 mol% CuCl$_2$·2H$_2$O was used.

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for most processes, in certain cases, the related NHC–Ag^I complexes **3** and **4** deliver higher selectivity; such differences are, however, not significant (not more than 10% *ee*). 2) In some instances, ACA reactions proceed faster and deliver slightly higher enantioselectivity when performed at relatively elevated temperatures; the processes in entries 1 and 5 of Table 3 are notable in this regard. For example, ACA of β-substituted cycloheptenone **9a** (entry 5, Table 3) proceeds to greater than 98% conversion at 22°C within fifteen minutes to afford the desired product in 89% *ee* (94.5:5.5 e.r.), whereas at −78°C, 12 h is required and the desired product is obtained in 85% *ee* (92.5:7.5 e.r.). 3) In the reaction shown in entry 1 of Table 3, involving *i*Bu$_3$Al and performed at 22°C, significant amounts of the [1,2]-hydride addition product (10–15%) is isolated when Cu(OTf)$_2$ is used. When CuCl$_2$·2H$_2$O is used instead, the aforementioned byproduct is not observed (less than 2% by ^{1}H NMR spectroscopic analysis), while **10a** is generated with the same selectivity as obtained with Cu(OTf)$_2$. It should be noted that for reactions carried out at −78°C, use of CuCl$_2$·2H$_2$O (along with a chiral NHC) leads to less than 10% conversion.
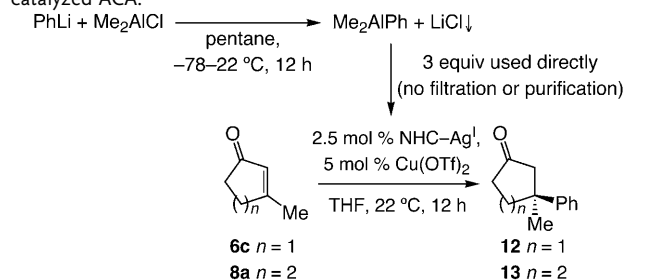
Next, we turned our attention towards developing a procedure for catalytic ACA of aryl-based aluminum reagents. Since only one triaryl aluminum compound[12] is commercially available (Ph$_3$Al), and use of such reagents would not be particularly atom-economical, an alternative procedure that provides access to a wider range of aryl metal reagents is required. To address this problem, as shown in Table 4, we envisioned that reaction of a readily accessible aryl lithium reagent with a commercially available and inexpensive dialkyl aluminum halide, such as Me$_2$AlCl, could lead to the formation of the corresponding dialkyl aryl aluminum species.[13] It is well-established that transfer of the sp^2-hybridized carbon-based substituents of aluminum-based reagents is significantly more facile than of those that are sp^3-hybridized.[9g] Accordingly, as illustrated in Table 4, treatment of phenyllithium with one equivalent of commercially available Me$_2$AlCl in pentane (−78 to 22°C, 12 h) affords a solution of Me$_2$PhAl containing LiCl, which can be used directly—without filtration or purification—in copper-catalyzed ACA reactions of β-substituted cyclic enones (e.g., cyclopentenone **6c** and cyclohexenone **8a**).

Due to the substantially different nature of the aluminum-based reagent derived from phenyllithium (vs. trialkyl aluminum compounds),[3g] we decided to probe the ability of copper complexes derived from **1–5** in promoting the addition of the in situ generated reagent to **6c** and **8a**. As the results summarized in Table 4 indicate, reactions performed at 22°C in the presence of 2.5 mol% NHC–Ag^I complex **2** (entries 2 and 7, Table 4) furnish the highest degrees of asymmetric induction. When the catalytic ACA is carried out at −50°C (48 h; see entry 1, Table 5), **12c** is obtained in 66% yield and 72% *ee* (86:14 e.r.).

As the additional data summarized in Table 5 illustrate, catalytic ACA with aryl aluminum reagents, generated in situ,

Table 4: Synthesis and in situ use of aryl aluminum reagents in copper-catalyzed ACA.[a]

PhLi + Me$_2$AlCl $\xrightarrow{\text{pentane,} \ -78\text{–}22\,°\text{C, 12 h}}$ Me$_2$AlPh + LiCl↓

↓ 3 equiv used directly (no filtration or purification)

6c n = 1
8a n = 2

2.5 mol% NHC–Ag^I, 5 mol% Cu(OTf)$_2$ / THF, 22°C, 12 h →

12 n = 1
13 n = 2

Entry	NHC–Ag^I	Substrate	Conversion [%][b]	e.r.[c]	ee [%][c]
1	**1**	**6c**	>98	68.5:31.5	37
2	**2**	**6c**	>98	73.5:26.5	47
3	**3**	**6c**	>98	50:50	<2
4	**4**	**6c**	>98	34:66	−32
5	**5**	**6c**	>98	46.5:53.5	−7
6	**1**	**8a**	>98	64:36	28
7	**2**	**8a**	>98	89:11	78
8	**3**	**8a**	>98	38:62	−24
9	**4**	**8a**	>98	26:74	−48
10	**5**	**8a**	>98	42.5:57.5	−15

[a–c] See Table 1. Three equivalents of the aluminum-based reagent were used.

Table 5: Copper-catalyzed ACA of aryl aluminum reagents to β-substituted cyclic enones.[a]

2.5 mol% **2**, 5 mol% Cu(OTf)$_2$ → 3 equiv Me$_2$(Ar)Al, THF

6c n = 1
8a n = 2

12 n = 1
13 n = 2

Entry	Substrate	Ar	T [°C]	t [h]	Yield [%][b]	e.r.[c]	ee [%][c]
1	**6c**	C$_6$H$_5$	−50	48	66	86:14	72
2	**6c**	oMeC$_6$H$_4$	−15	48	85	99:1	98
3	**6c**	pOMeC$_6$H$_4$	−50	48	67	85.5:14.5	71
4	**6c**	oOMeC$_6$H$_4$	−15	48	55	97.5:2.5	95
5	**8a**	C$_6$H$_5$	−30	36	71	95:5	90
6	**8a**	oMeC$_6$H$_4$	+4	42	49	98:2	96
7	**8a**	pOMeC$_6$H$_4$	−50	36	61	92:8	84
8	**8a**	pCF$_3$C$_6$H$_4$	−30	36	52	93:7	86
9	**8a**	oOMeC$_6$H$_4$	+4	48	60	88:12	83

[a–c] See Table 2. [c] Determined by chiral GLC or HPLC analysis (see the Supporting Information for additional details).

can be performed on five- as well as six-membered β-substituted cyclic enones, affording the desired products in up to 98% *ee* (entry 2, Table 5). Examination of the findings depicted in Table 5 indicates that aryl lithium species bearing electron-donating (e.g., entries 3, 4, 7 and 9, Table 5) and electron-withdrawing (entry 8, Table 5) substituents can be used effectively.[14] Enantioselectivities appear to be highest, however, when the aryl unit is sterically more encumbered (i.e., carries an *ortho* group: entries 2, 4, and 6, Table 5). Two additional points are noteworthy: 1) All aryl lithium reagents (except for commercially available PhLi) were easily obtained by treatment of commercially available aryl bromides with *n*BuLi.[15] 2) Not only can the aryl aluminum reagents be used

directly (without removal of LiCl),[16] the solution generated from reaction of aryl lithium compounds with Me$_2$AlCl can be stored under N$_2$ for more than two months and used in catalytic ACA reactions without any noticeable diminution in efficiency or enantioselectivity.

The catalytic ACA reactions of β-substituted cyclopentenones outlined herein put forth an additional example of the ability of bidentate NHC metal complexes in promoting processes that are not effectively initiated by alternative catalytic systems.[4b,9d,f] We demonstrate that this recently developed class of chiral carbenes, prepared in five or six steps,[17] can be structurally modified for achieving optimal results (e.g., 3–5).[18] Although the transformations involving cyclohexenones and cycloheptenones (i.e., Table 3), in some cases, are slightly less selective than those performed in the presence of other catalysts,[3c,5b] the present approach is more general, since it offers an effective solution to the important problem of ACA of five-membered-ring substrates. The protocols presented are attractive from the practical point of view, as they require the use of inexpensive and/or readily available trialkyl aluminum reagents, aryl halides, or dialkyl aluminum chlorides. In the case of ACA reactions of aryl aluminum reagents, the requisite aryl metal reagent is conveniently prepared and used in situ. The above attributes render the catalytic enantioselective methods presented herein of significant potential utility in enantioselective chemical synthesis.[19] Development of additional catalytic asymmetric protocols involving aluminum-based reagents and application of the present processes to the total synthesis of complex molecule natural products are among the objectives being pursued in our laboratories.

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[14] The somewhat moderate yields for the reactions in Table 5, which are in spite of conversions greater than 98%, are partly due to difficulties associated with removal of biphenyl formed in

the course of the transformation. Modified procedures that address this complication are under development.

[15] See the Supporting Information for additional details.

[16] Control experiments involving filtered solutions of aryl aluminum reagents or those where excess LiCl is added to the mixture indicate that the presence of LiCl does not have any favorable or deleterious effects on the catalytic ACA reactions when chiral complex derived from **2** is used.

[17] NHC–Ag^I complexes **4** and **5** are not yet commercially available but can be prepared on a multigram scale in six steps from commercially available *tert*-butoxycarbonylphenylglycinol (ca. 20% overall yield of isolated product). See the Supporting Information for experimental and spectral details. In our experience, the required sequences do not require any significant experimental expertise. It should be noted that NHC complex **3** has already been used in a key step at an early stage of a complex-molecule total synthesis: K. M. Peese, D. Y. Gin, *Chem. Eur. J.* **2007**, *14*, 1645–1665.

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