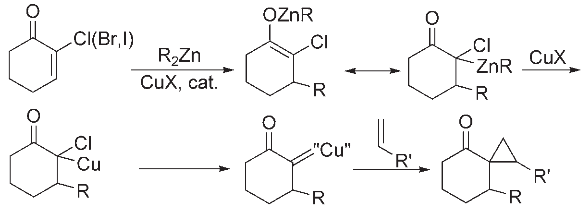
Asymmetric Catalysis

DOI: 10.1002/ange.200602417

Asymmetric Conjugate Addition to α-Halo Enones: Dramatic Effect of Styrene on the Enantioselectivity**

*Kangying Li and Alexandre Alexakis**

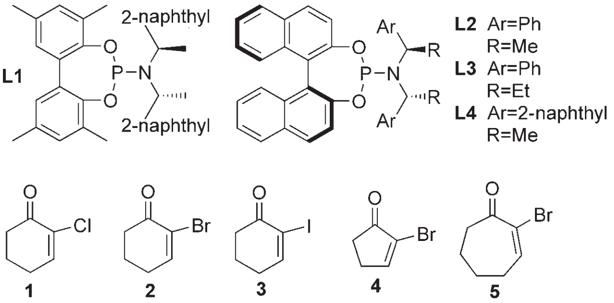
Aiming to enlarging the scope of potential Michael acceptors in the copper-catalyzed asymmetric conjugate addition,[1,2] we regarded the class of α-halo enones as being attractive, because the resulting α-halo ketones are versatile intermediates that are widely used in organic synthesis, for example, in the synthesis of a variety of heterocycles,[3] in cross aldol condensations,[4] in the synthesis of enaminoketones,[5] and in Favorskii rearrangements.[6] Of particular interest was the reactivity of the resulting α-halogenated enolate, which could be seen as a carbenoid that might undergo inter- or intramolecular cyclopropanation reactions in the presence of a copper catalyst (Scheme 1).[7]



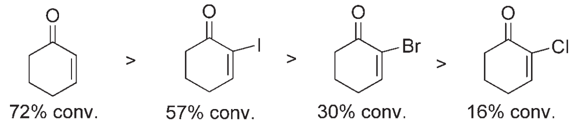
Scheme 1. Potential pathway for cyclopropanation.

There are scarce examples of the conjugate addition of allyllithium,[8] cuprates,[9] or organometallic reagents that react under copper catalysis, such as Grignard[10e] and organozinc reagents,[11] to α-halogenated Michael acceptors. However, no results have been reported so far for the asymmetric conjugate addition of dialkyl zinc or trialkyl aluminum reagents to α-halo enones, despite all the recent progress in this research area.[1b] We describe herein the results of our research on this topic, including an interesting observation of an improvement in enantioselectivity when styrene is employed as a radical scavenger.

With respect to the proposed reaction in Scheme 1, there were three main points to address: 1) the reactivity of α-halo enones, 2) the level of enantioselectivity that could be attained in an enantioselective process, and 3) the feasibility of the cyclopropanation. First, we compared the reactivity of the α-halo cyclohexenones **1**–**3** (Scheme 2) with that of cyclohexenone. The conjugate addition reactions carried out in parallel in the presence of Et_2Zn and ligand **L4** (see details in the Supporting Information) showed that α-halogenated enones were less reactive than cyclohexenone and that the reactivity of the three substrates **1**, **2**, and **3** decreased mildly with increasing electronegativity of the halogen (Scheme 3).



Scheme 2. Chiral ligands and substrates used in this study.



Scheme 3. Relative reactivity of **1**–**3**: % conversion after a reaction time of 10 min at −30 °C in diethyl ether.

A variety of reaction conditions was tested for their effect on the enantioselectivity of the reaction (Table 1). The ligand

Table 1: Asymmetric conjugate addition of diethylzinc to compounds **1**–**3** in diethyl ether.

Entry	Substrate	CuX[d]	Ligand	*trans*/*cis*[a]	*ee* [%][b]	Config.[c]
1	**1**	CuTC	**L1**	71:29	77 (77)	(2*R*,3*S*)
2	**1**	CuTC	*ent*-**L2**	70:30	80 (84)	(2*S*,3*R*)
3	**1**	CuTC	**L4**	70:30	83 (83)	(2*R*,3*S*)
4[e]	**1**	CuTC	**L4**	69:31	87 (80)	(2*R*,3*S*)
5[f]	**1**	CuTC	**L4**	71:29	78 (69)	(2*R*,3*S*)
6	**1**	$Cu(OTf)_2$	**L4**	70:30	90 (92)	(2*R*,3*S*)
7	**2**	CuTC	**L1**	68:32	77 (76)	(2*R*,3*S*)
8	**2**	CuTC	*ent*-**L2**	69:31	63 (64)	(2*S*,3*R*)
9	**2**	CuTC	**L4**	70:30	88 (88)	(2*R*,3*S*)
10	**2**	$Cu(OTf)_2$	**L4**	71:29	86 (86)	(2*R*,3*S*)
11	**3**	CuTC	**L1**	18:82	73 (65)	(2*S*,3*S*)
12	**3**	CuTC	*ent*-**L2**	18:82	79 (74)	(2*R*,3*R*)
13	**3**	CuTC	**L4**	18:82	84 (83)	(2*S*,3*S*)
14	**3**	$Cu(OTf)_2$	**L4**	18:82	84 (83)	(2*S*,3*S*)

[a] Determined by GC-MS and/or NMR spectroscopy. [b] Determined by GC on a chiral phase; the *ee* value of the minor diastereomer is given in parentheses. [c] Configuration of the major product. [d] CuTC stands for copper thiophene carboxylate, Tf for trifluoromethanesulfonyl. [e] Toluene was used as the solvent. [f] CH_2Cl_2 was used as the solvent.

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[*] Dr. K. Li, Prof. Dr. A. Alexakis
Département de chimie organique
Université de Genève
30 quai E. Ansermet, 1211 Genève 4 (Switzerland)
Fax: (+41) 223-793-215
E-mail: alexandre.alexakis@chiorg.unige.ch

[**] The authors thank the Swiss National Research Foundation (no. 200020-105368) and COST Action D24/003/01 (OFES contract no. C02.0027) for financial support, and BASF for their generous gift of chiral amines.

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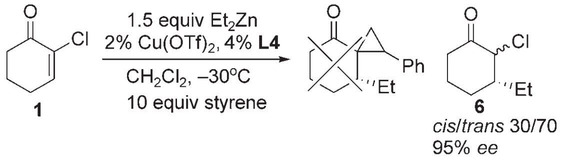
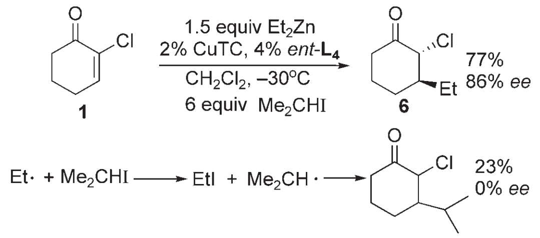
L4 was slightly better than **L1** and **L2**. All reactions were carried out to full conversion. (The mixture was maintained at −30°C for 2 h, then warmed to room temperature.) The reactions were very clean, and all products were isolated in greater than 85% yield. The only by-product detected (5–10%) was 3-ethylcyclohexanone, which results from an iodine–zinc exchange with 2-iodocyclohexenone (**3**).[12] After quenching the reaction with an acid, two diastereomers were obtained. The major diastereomer was the *trans* diastereomer in the case of the α-chloro and α-bromo products **6** and **7**.[10a] Isomerization with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave the *cis* isomer as the thermodynamically more stable (*cis*/*trans* 63:37 for **6** and 79:21 for **7**). This isomerization is not unexpected in view of the favored axial orientation of the halo substituent of α-halo cyclohexanones.[10b–d] In the case of the α-iodo product **8**, the more stable *cis* isomer was obtained directly.[10e]

As seen in Table 1, the enantioselectivity is good in most cases. In CH_2Cl_2, however, a clear drop in enantioselectivity was observed (78% *ee*; Table 1, entry 5). This was an unfortunate result because CH_2Cl_2 is the best solvent for copper-catalyzed cyclopropanations, which we intended to investigate next. Nevertheless, we proceeded to examine the behavior of the resulting enolate. When the copper-catalyzed conjugate addition was carried out with 10 equivalents of styrene, cyclopropanation was observed neither at room temperature, nor after prolonged heating at reflux (Scheme 4). Only the hydrolyzed conjugate adduct **6** was obtained, but its *ee* value had jumped from 78% to 95%! This remarkable effect of the addition of styrene may have two causes. First, π coordination of Cu to the double bond of styrene results in a favorable modification of the environment of the organometallic species. Such an effect has been observed by Knochel and co-workers,[13] who reported that *para*-trifluorostyrene is helpful in a Ni-catalyzed cross-coupling reaction. The second possibility is that styrene may prevent an alternative non-asymmetric conjugate-addition pathway.



Scheme 4. Attempted cyclopropanation.

Indeed, it was demonstrated by Bertrand et al. that ethyl radicals could be generated from diethylzinc in the presence of oxygen and added to cyclohexenone.[14a] They also showed that when *i*PrI or *t*BuI were added, the ethyl radical reacted to generate the more stable isopropyl or *tert*-butyl radical, which underwent the conjugate addition instead. Therefore, a simple way to detect a possible radical pathway was to run the copper-catalyzed reaction in the presence of *i*PrI (6 equiv). The presence of the isopropyl conjugate adduct would provide evidence that such a radical pathway exists (Scheme 5). In our case, the radical process could be initiated by traces of oxygen, but also by the reduction of a Cu^{II} salt to Cu^{I} by diethylzinc. We also could not exclude an SET mechanism in the reaction of α-halo enones.[14b,c]



Scheme 5. Reaction sequence in the presence of *i*PrI that is indicative of a radical pathway with **1**.

As suspected, the experiment in dichloromethane afforded the *i*Pr adduct and the desired ethylated product in the ratio 23:77, respectively. However, most striking was the observation that the desired product **6** was formed with 86% *ee*, as opposed to 78% *ee* in the absence of *i*PrI (Table 1, entry 5), whereas the *i*Pr adduct was racemic. Thus, the copper-catalyzed conjugate addition might actually proceed with higher enantioselectivity than that usually observed.

It seems clear that the role of styrene is to inhibit a non-asymmetric conjugate addition by trapping the initial Et radical. The radical polymerization of styrene is a well-known process.[15] The high enantioselectivity of the reaction shown in Scheme 4 implies that the addition of an ethyl radical to styrene is faster than its addition to 2-chlorocyclohexenone (**1**). Furthermore, the resulting phenylbutyl radical appears to be sufficiently inert not to add to **1**. To check this point, we repeated the experiment of Bertrand et al. (Et_2Zn, air, no copper, substrate **1**) in the presence of styrene. Only traces of adduct **6** were found, along with a visible cloud of polymerized styrene.

This "styrene effect" was investigated more thoroughly with 2-bromocyclohexenone (**2**; Table 2). In CH_2Cl_2, in the absence of styrene, the *ee* value of the product was 85%. In the presence of styrene (10 equiv), the *ee* value increased to 95%; complete conversion was observed, and the reaction was not slower. The high enantioselectivity was maintained even with just 0.1 equivalents of styrene. This is a remarkable effect, which shows the true enantioselectivity of the copper-catalyzed pathway. It may be assumed that many results in the literature on this topic could be improved just by adding styrene! Indeed, several reports point to "slightly improved"

Table 2: Effect of styrene on the enantioselectivity in the reaction of **2**.[a]

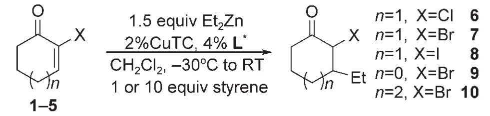
Entry	Styrene [equiv]	*trans*/*cis*[b]	*ee* %[c]
1	–	70:30	85 (87)
2	10	70:30	95 (95)
3	5	71:29	96 (95)
4	1	76:24	97 (94)
5	0.5	75:25	98 (96)
6	0.1	74:26	96 (94)

[a] The reaction conditions were the same as those given in Scheme 5. [b] Determined by GC-MS. [c] Determined by GC on a chiral phase; *ee* value of the minor diastereomer is given in parentheses.

enantioselectivity when a Cu^I salt, such as $[CuOTf]_2$·benzene, is employed instead of a Cu^{II} salt, such as $Cu(OTf)_2$.[16] The reduction of the Cu^{II} catalyst, present in 2 mol %, with diethylzinc generates 2 mol % of ethyl radical and corresponds to at least a 2 % loss in enantioselectivity. If the radical propagation is not stopped, the loss in enantioselectivity may be much higher. Thus, it is only the initial radical-formation step that has to be prevented. Nevertheless, most other experiments were run with 1–10 equivalents of styrene.

We repeated our experiments with all enones **1**–**5** under these new conditions (Table 3). The results clearly show the beneficial effect of added styrene on the reactions of the three α-halo cyclohexenones **1**–**3**, whatever the solvent (see Table 3, entry 2, footnote [c]). With 2-bromocyclopentenone (**4**), this “styrene effect” is even more spectacular: In the absence of styrene, the adduct **9** was formed in almost racemic form, whereas it was formed with 79 % *ee* in the presence of styrene![17] In the reaction of 2-bromocycloheptenone (**5**), the ligand **L4** was not as good as **L2**, and the “styrene effect” was not so pronounced when the reaction was performed in Et_2O in the presence of **L2**.

Table 3: Asymmetric conjugate addition of diethylzinc to compounds **1**–**5**.

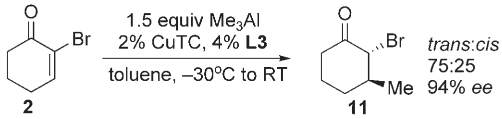


1–5

Entry	Substrate	L*	Styrene [equiv]	Product	*trans/cis*[a]	*ee* [%][b]
1	**1**	**L4**	–	**6**	71:29	78 (69)
2[c]	**1**	**L4**	10	**6**	70:30	98 (97)
3	**2**	**L4**	–	**7**	70:30	85 (87)
4	**2**	**L4**	1	**7**	76:24	97 (94)
5	**3**	**L4**	–	**8**	18:82	88 (87)
6	**3**	**L4**	1	**8**	19:81	95 (92)
7	**4**	**L4**	–	**9**	71:29	05 (05)
8	**4**	**L4**	10	**9**	70:30	79 (78)
9	**5**	**L4**	–	**10**	2:98	21
10[d]	**5**	*ent*-**L2**	–	**10**	5:95	75 (74)
11[d]	**5**	*ent*-**L2**	10	**10**	5:95	78 (78)

[a] Determined by GC-MS and/or NMR spectroscopy. [b] Determined by GC on a chiral phase; the *ee* value of the minor diastereomer is given in parentheses. [c] The same results were obtained in toluene and in Et_2O. [d] Et_2O was used as the solvent.

The successful application of diethylzinc in this reaction prompted us to try another dialkyl zinc reagent. Unfortunately, no reaction took place between **2** and dimethylzinc under the same conditions, probably as a result of the low reactivity of the latter. Recently, triorganoaluminum reagents have been shown to be good replacements for dialkyl zinc reagents in asymmetric copper-catalyzed conjugate additions.[2a,b,18] To our pleasure, the addition of Me_3Al to **2** proceeded very well (Scheme 6). The desired 1,4-adduct **11** was formed with moderate diastereoselectivity and excellent enantioselectivity. In this case, the best ligand appeared to be **L3**. The addition of styrene did not improve this result.



2 **11**

Scheme 6. Addition of Me_3Al to **2**.

In summary, we have shown that high enantioselectivities can be attained in the copper-catalyzed conjugate addition of Et_2Zn and Me_3Al to α-halogenated enones. We also found evidence of an achiral radical pathway by carrying out the reaction with isopropyl iodide, and demonstrated that it is possible to stop this radical process by adding styrene, which acts as a radical scavenger. It may be assumed that many conjugate addition reactions described previously could be improved if they were carried out in the presence of styrene.

Experimental Section

Typical procedure: Dry diethyl ether (2 mL) was added to a mixture of copper thiophene carboxylate (CuTC; 1.9 mg, 0.01 mmol) and ligand **L4** (12.8 mg, 0.02 mmol) under nitrogen. The solution was stirred at room temperature for 30 min and was then cooled to −30 °C. Diethylzinc (1 M in hexane, 0.75 mL) was added dropwise, with the temperature maintained below −30 °C. The resulting solution was stirred for 5 min, and a solution of 2-bromocyclohexenone (**2**; 0.5 mmol) in diethyl ether (0.5 mL) was then added dropwise. The reaction mixture was stirred at −30 °C for 2 h and then allowed to warm up to room temperature. The reaction mixture was stirred at room temperature until all the starting material had been consumed. The solution was then diluted with diethyl ether (20 mL) and washed successively with 2 N HCl and brine. The organic layer was dried over anhydrous sodium sulfate. Removal of the solvent gave the crude product, which was subjected to flash chromatography. The product was then analyzed by GC on a chiral stationary phase (or supercritical fluid chromatography) and NMR spectroscopy to determine the ratio of diastereomers and the *ee* values.

7: *trans*/*cis* 76:24 (crude), 72:28 (after chromatography), light-yellow oil; Mixture of isomers: ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.88$–0.95 (dt, 3 H, CH_3), 1.36–1.80 (m, 5 H, $2CH_2$, CH), 1.99–2.07 (m, 2 H, CH_2), 2.27–2.34 (m, 1 H, CH), 2.84–3,15 (m, 1 H, CH), 4.25 (d, $^3J_{H,H} =$ 7.6 Hz, 0.73 H, CH), 4.28–4.29 ppm (d, $^3J_{H,H} = 1.28$ Hz, 0.27 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.82$, 23.55, 25.18, 25.92, 26.46, 26.99, 35.58, 38.69, 44.66, 47.64, 58.89, 59.61, 203.29, 204.87 ppm; IR (neat): $\tilde{\nu} = 2962$, 2936, 2874, 1715, 1458, 1424, 1313, 1221, 1174, 1093, 962, 927, 757, 668 cm^{-1}; MS (ESI): *m*/*z* (%): 206 (8), 204 (8), 125 (34), 107 (13), 81 (19), 69 (16), 55 (100); HRMS (EI): $[M+Na]^+$ calcd for $C_8H_{13}BrO$: 227.0047; found: 227.0049.

Received: June 15, 2006
Revised: September 7, 2006

Keywords: asymmetric synthesis · conjugate addition · copper · homogeneous catalysis · radicals

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[17] A similar experiment to that in Scheme 5 with 2-bromocyclopentenone (**4**) afforded the ethylated product along with the racemic isopropylated product in a 16:84 ratio.

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