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Copper(I)-Catalyzed Chlorine Atom Transfer Radical Cyclization Reactions of Unsaturated α-Chloro β-Keto Esters

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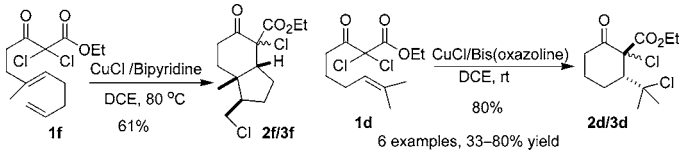
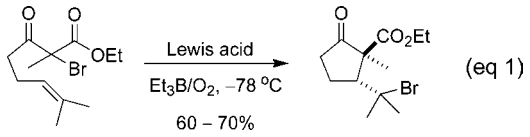
ABSTRACT



Copper(I) chloride catalyzed chlorine atom transfer radical cyclization reactions of a series of olefinic α-chloro β-keto esters were investigated. It was found that α-dichlorinated β-keto esters were suitable substrates; the chlorine transfer mono or tandem radical cyclization reactions catalyzed by CuCl complex with bis(oxazoline) or bipyridine proceeded smoothly in dichloroethane at room temperature or 80 °C, providing cyclic and bicyclic compounds in moderate to high yield.

Atom or group transfer radical cyclization reaction has become a powerful tool for the synthesis of cyclic compounds.[1] Previously, we have reported the Lewis acid catalyzed bromine atom transfer radical cyclization reactions of olefinic α-bromo β-keto esters for the construction of mono- and polycylic ketones (eq 1).[2] Our interest in atom



(eq 1)

transfer radical cyclization reactions led to the study of radical cyclization reactions of substrates with a chlorine atom as the transfer group. In comparison with their bromo counterparts, chloro compounds have the advantage that they are more stable and easier to handle. The C−C bond-forming reactions involving chlorine transfer of halocarbons were among the earliest observed atom transfer radical reactions,[3] but this type of reaction was not as extensively explored and utilized as other types of atom transfer processes because of the low reactivity of alkyl chlorides.[4] Here we report our investigation on the chlorine transfer radical carbocyclization reactions of unsaturated α-chloro β-keto esters.[5]

The optimal reaction conditions developed in the Lewis acid catalyzed bromine transfer radical cyclization reactions of olefinic α-bromo β-keto esters were first applied in the chlorine transfer radical cyclization reaction of substrate **1a** (Table 1). It was found that neither $Yb(OTf)_3/Et_2O$ nor $Mg(ClO_4)_2$/toluene promoted the chlorine transfer radical cyclization of **1a** at −78 °C (entries 1 and 2).

At room temperature, the expected atom transfer radical cyclization reaction proceeded with $Mg(ClO_4)_2$ in toluene or CH_2Cl_2 and product **2a** was obtained in 10−20% yield. The major byproducts **3a** and **4a** were also isolated as an inseparable mixture in 10−20% yield, and substrate **1a** was

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(2) (a) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612−8613. (b) Yang, D.; Gu, S.; Yan, Y.-L.; Zhao, H.-W.; Zhu, N.-Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3014−3017.

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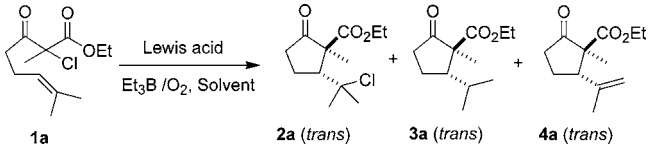
Table 1. Chlorine Transfer Radical Cyclization Reactions of 1a Catalyzed by Lewis Acids Initiated by Et_3B/O_2[a]



1a — **2a** (*trans*) — **3a** (*trans*) — **4a** (*trans*)

entry	Lewis acid (1.2 equiv)	solvent	Et_3B[b] (equiv)	temp (°C)	time (h)	isolated yield **2a** (%)
1	$Yb(OTf)_3$	Et_2O	5	−78	20	*c*
2	$Mg(ClO_4)_2$	toluene	4	−78	14	*c*
3[d]	$Mg(ClO_4)_2$	toluene	4	rt	>30	21
4[d]	$Mg(ClO_4)_2$	CH_2Cl_2	4	rt	>30	13
5[d]	$Mg(ClO_4)_2$	$ClCH_2CH_2Cl$	4	80	24	15
6[d]	$Mg(ClO_4)_2$	toluene	4	80	24	17

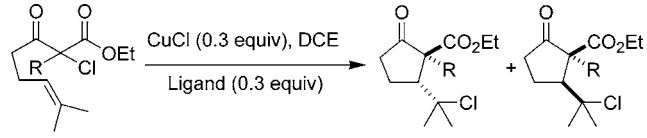
[a] The reactions were carried out with 0.4 mmol of substrate **1a** in 10 mL of anhydrous solvent. [b] Et_3B (1 M in *n*-hexane)/O_2 was added twice, and the second addition was 10 h after the reaction. [c] No reaction. [d] A mixture of **3a** and **4a** was isolated in 13−20% yield with about 1:2 ratio, and substrate **1a** was recovered in 40−46% yield.

recovered in 40−46% yield (entries 3 and 4). Similar results were obtained at higher temperature (entries 5 and 6). The cyclization product **2a** was found to be the *trans* product (2-ester group and 3-chloro alkyl group were in a *trans* relationship). The low yields of cyclization product **2a** reflected the low reactivity of the substrate, because the bond dissociation energy of C−Cl bond (365 kJ/mol) is much higher than that of C−Br bond (297 kJ/mol).[6]

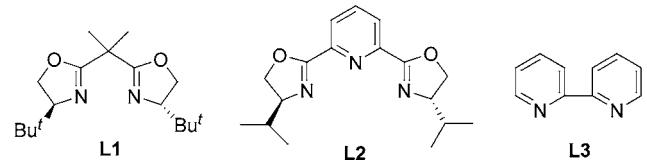
These disappointing results led us to search for a new reaction system for chlorine transfer radical cyclization. It has been reported that metal catalysts can significantly promote the chlorine transfer radical reactions.[7] Inspired by the studies on the lactone[7,8] and lactam[7,9] syntheses via chlorine transfer radical cyclization with copper(I) chloride as the catalyst, we selected copper(I) chloride as the catalyst to promote our carbocyclization reactions.

In order to develop optimal reaction conditions, substrates **1a**−**c** were first investigated with CuCl (0.3 equiv) as the catalyst. 1,2-Dichloroethane (DCE) was selected as the solvent because of its high boiling point and good substrate solubility. The results are summarized in Table 2.

Table 2. CuCl-Catalyzed Chlorine Transfer Radical Cyclization Reactions of 1a−c [a]



1 (**a**: R = Me; **b**: R = Cl; **c**: R = H) — **2** — **3**



entry	substrate	additives (equiv)[b]	temp (°C)	time (h)	conv (%)	yield (%) ratio[c] (**2/3**)
1	**1b**		rt	15	0	
2	**1b**	**L1** (0.3)	rt	17	>95	74 (1/2.1)
3	**1b**	**L1** (0.3)	0	48	57	15 (1/2.0)
4	**1b**	**L1** (0.6)/ $Mg(ClO_4)_2$ (0.3)	rt	23	74	11 (1/1.8)
5	**1b**	**L1** (0.3)/ $Yb(OTf)_3$ (0.3)	rt	40	44	33 (1/1.9)
6	**1b**	**L1** (0.3)/ $Ti(O\text{-}^iPr)_4$ (0.3)	rt	28	75	56 (1/1.2)
7	**1b**	**L1** (0.3)/ CuOTf (0.3)[d]	rt	25	22	13 (1/1.6)
8	**1b**	**L2** (0.3)	rt	25	56	17 (1/1.8)
9	**1b**	**L2** (0.3)	80	19	>95	76 (1/1.5)
10	**1b**	**L3** (0.3)	rt	24	52	29 (1/1.9)
11	**1b**	**L3** (0.3)	80	24	96	67 (1/1.5)
12	**1a**	**L1** (0.3)	80	24	23	3 (**2a**)[e]
13	**1c**	**L1** (0.3)	rt	17	0	
14	**1c**	**L1** (0.3)	80	24	*f*	26 (**2b**)[g]

[a] The reactions were carried out with 0.3 mmol of substrate in 10 mL of deoxygenated 1,2-dichloroethane at indicated temperature. [b] The amount of additives was indicated in parentheses. [c] When chiral ligand **L1** or **L2** was used, product enantioselectivity (ee) was measured by chiral HPLC analysis with chiral AD column and the ee values were all below 10%. [d] CuOTf was added instead of CuCl. [e] Only product **2a** was isolated. [f] Not determined. [g] Only product **2b** was obtained instead of expected **2c** and **3c**.

In the cyclization of substrate **1b**, CuCl alone was found to be insufficient to promote the chlorine transfer radical cyclization reaction at room temperature (entry 1, Table 2). Chelation of ligands to Cu(I) has been known to lower the redox potential of Cu(I)/Cu(II) complexes.[9d,e,10] With the addition of ligand **L1**, **L2**, or **L3**, chlorine transfer radical cyclization reaction proceeded and cyclization products **2b** and **3b** were obtained (entries 2, 8, and 10). **L1** was the most efficient ligand for Cu(I) at room temperature. Cyclization of **1b** catalyzed by 0.3 equiv of CuCl/**L1** provided cyclization products **2b** and **3b** in 74% total yield (ratio 1/2.1, entry 2). Moreover, the reaction rate was increased by increasing the reaction temperature (entry 2 vs 3; 9 vs 8; 11 vs 10). When the temperature was raised to 80 °C, cyclization of **1b** catalyzed by CuCl/**L2** and CuCl/**L3** also provided products (**2b** and **3b**) in 76% and 67% total yields (entries 9 and 11), respectively.

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(9) (a) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682−1689. (b) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464−470. (c) Seijas, J. A.; Vazquez-Tato, M. P.; Castedo, L.; Estevez, R. J.; Onega, M. G.; Ruiz, M. *Tetrahedron* **1992**, *48*, 1637− 1642. (d) Clark, A. J.; Campo, F. D.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671−680. (e) Clark, A. J.; Battle, G. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 1999−2001.

(10) Bernhardt, P. V. *J. Am. Chem. Soc.* **1997**, *119*, 771−774.

Note that in the CuCl-catalyzed chlorine transfer radical cyclization reaction of **1b**, two 5-*exo* cyclization products, **2b** and **3b**, were obtained. The stereochemistry of the major product **3b** had a *cis* relationship between the 2-ester group and 3-chloro alkyl group as shown by X-ray analysis (see Supporting Information). This outcome was different from the case for Lewis acid catalyzed bromine transfer radical cyclization of olefinic α-bromo *β*-keto esters, in which exclusive *trans* cyclization product was obtained.[2a] When chiral ligand **L1** or **L2** was employed as the catalyst, enantioselectivity of the products **2b** and **3b** was found to be very low (less than 10% ee), but it does provide evidence that it may be possible to design asymmetric reactions. An attempt to control the diastereoselectivity of the reaction was made with substrate **1b** by adding Lewis acids $Mg(ClO_4)_2$ and $Yb(OTf)_3$, as well as Lewis base $Ti(O\text{-}^iPr)_4$. Unfortunately, low reaction rates and yields were observed in the presence of these Lewis acids or base (entries 4−6), and the diastereomeric ratios changed little (entries 4 and 6 vs 2 and 3). Changing Cu(I) catalyst from CuCl to CuOTf did not provide any improvement (entry 7). Under the optimal conditions, cyclization reactions of **1b** were generally completed in around 20 h (entries 2, 9, and 11). In other reaction systems, substrate **1b** was recovered in 20−80% yield as a result of incomplete reactions.

The reactivity of the substrates **1a**−**c** was found to depend largely on their structures. Whereas α-dichlorinated *β*-keto ester substrate **1b** underwent chlorine transfer radical cyclization reaction with reasonable rate, cyclizations of α-monochlorinated *β*-keto ester substrate **1a** was found to be sluggish. In the cyclization of **1a** under the optimized conditions, product **2a** was only obtained in 3% yield (entry 12). Interestingly, the atom transfer radical cyclization of substrate **1c** catalyzed by CuCl/**L1** at 80 °C gave product **2b** in 26% yield but not products **2c** and **3c** (entry 14).

On the basis of the above studies, α-dichlorinated *β*-keto ester **1b** was found to be a suitable substrate for chlorine transfer radical cyclization; the optimal reaction systems included CuCl/**L1** at room temperature and CuCl/**L2** or **L3** at 80 °C in 1,2-dichloroethane.

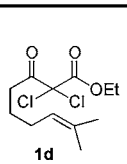
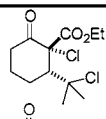
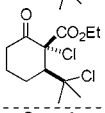
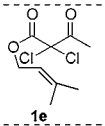
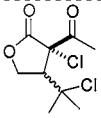
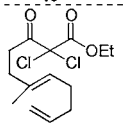
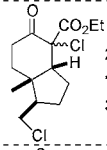
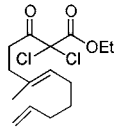
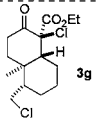
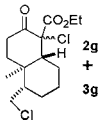
Substrates **1d**−**g** were subjected to the optimal conditions for **1b** (Table 3). Cyclization of substrate **1d** with 0.3 equiv of catalyst CuCl/**L1** or CuCl/**L3** exclusively gave the 6-*exo* cyclization products **2d** and **3d** in 79−80% total yields with **3d** as the major product (entries 1 and 2, Table 3). The optimal reaction system was also applied to the synthesis of a *β*-keto lactone. Cyclization of substrate **1e** provided lactones **2e** and **3e** in 44% and 57% total yields, respectively (entries 3 and 4).

Tandem cyclization reactions were also studied using substrates **1f** and **1g**. In both cases, four stereocenters of the products were established in one step. Cyclization of substrate **1f** catalyzed by CuCl/**L3** occurred via 6-*endo* and then 5-*exo* cyclization to give 6,5-*cis* tandem cyclization products **2f** and **3f** as an inseparable mixture in 61% total yield (entry 5). The structures of products **2f** and **3f** were confirmed by converting this mixture to a single product **4f** via α-dechlorination with Zn powder in acetic acid (Scheme 1). The structure of compound **4f** was established by 2D NMR experiments.[11]

Cyclization of substrate **1g** catalyzed by CuCl/**L3** provided the 6,6-*cis* tandem cyclization products **2g** and **3g** in low yields (20−30%) (entries 6 and 7). At 65 °C, only one tandem cyclization product **3g** was isolated (entry 6), and its structure was confirmed by X-ray analysis. When the temperature was raised to 80 °C, the two products **2g** and **3g** were obtained as an inseparable mixture (entry 7). Their structures were determined by converting this mixture to the single product **4g** with Zn powder in acetic acid (Scheme 2). The *trans* relationship between protons H_a and H_b of **4g** was assigned on the basis of their large coupling constant (J = 12.9 Hz) (Scheme 2).

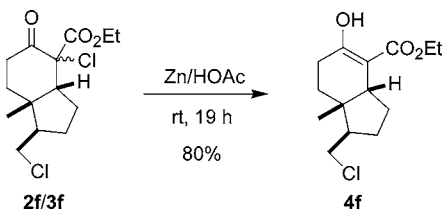
A mechanism for the CuCl-catalyzed chlorine transfer radical cyclization reaction of substrate **1b** is proposed in Scheme 3. CuCl abstracts a chlorine atom from substrate **1b** to generate radical **r1** and $CuCl_2$. Because of the weak chelation ef-

Table 3. CuCl-Catalyzed Chlorine Transfer Cyclization of Substrates 1d−g[a]

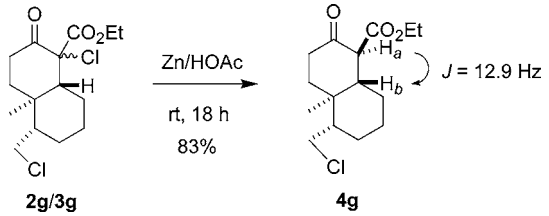
entry	substrate	ligand	temp (°C)	time (h)	products **2** and **3**	yield (%) (ratio)
1	 **1d**	**L1**	rt	18	 **2d** +  **3d**	80 (**2d/3d** = 1/3.4)
2		**L3**	80	21		79 (**2d/3d** = 1/2.8)
3	 **1e**	**L1**	rt	18	 **2e** + **3e**	44 (1/1.3) [b]
4		**L3**	80	18		57 (1/1.6) [b]
5	 **1f**	**L3**	80	18	 **2f** + **3f**	61 (1/2.3) [c]
6		**L3**	65	16	 **3g**	22 [d]
7	**1g**	**L3**	80	16	 **2g** + **3g**	33 (**2g/3g** = 1/1.5) [c]

[a] The reactions were carried out with 0.4 mmol of substrate in 10 mL of anhydrous solvent. [b] Products **2e** and **3e** could be separated, but their stereochemistries were not determined. [c] The two isomers could not be separated by column chromatography. [d] Only one tandem cyclization product **3g** was isolated along with monocyclization products.

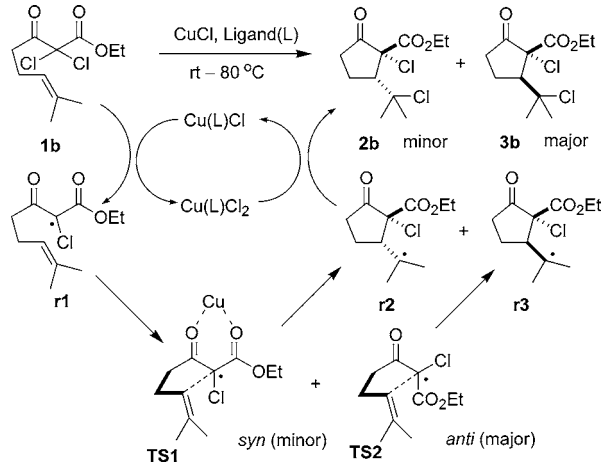
Scheme 1



Scheme 2



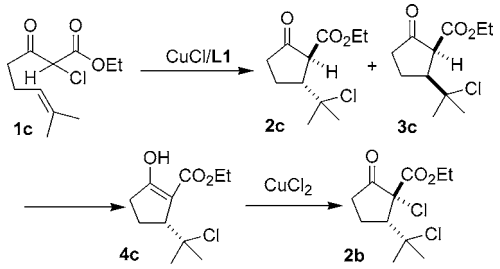
Scheme 3



fect of copper Lewis acid under the reaction conditions, radical **r1** preferentially cyclizes to form **r3** via transition state **TS2** rather than **TS1** in order to minimize the dipole repulsion and steric repulsion between the two carbonyl groups of the radical intermediate. Then radicals **r2** and **r3** abstract a chlorine atom from $CuCl_2$ to give the chlorine transfer cyclization products **2b** and **3b**, respectively, with **3b** as the major product. The chlorine abstraction regenerates the catalyst CuCl to complete the catalytic cycle. The weak chelation may also be responsible for the low enantioselectivity (<10% ee) of the products when chiral ligand **L2** or **L3** was employed.

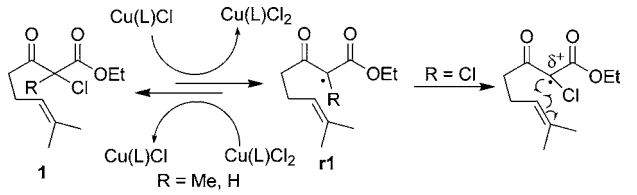
The formation of product **2b** instead of **2c** and **3c** in the cyclization of substrate **1c** (entry 14, Table 2) could be explained as shown in Scheme 4. The chlorine atom transfer radical cyclization reaction of substrate **1c** provides cyclization products **2c** and **3c**, which are further chlorinated via the enol intermediate **4c** by $CuCl_2$ to give **2b** as the final product.[12]

Scheme 4



The different reactivity of β-keto ester substrates **1a**−**c** may be explained by the electron density difference at the α-carbons of the substrates (Scheme 5). An electron-with-

Scheme 5



drawing α-substituent such as Cl (**1b**) makes the α-carbon of **r1** more electron-deficient, resulting in rapid intramolecular attack of the α-radical on the electron-rich olefin (Schemes 3 and 5). In contrast, an electron-donating α-substituent such as a methyl group (**1a**) makes the α-radical more electron-rich, slowing down its addition to the olefin. As a result, with R = Me, radical **r1** abstracted a chlorine atom from $CuCl_2$ much faster and became the recovered substrate. According to the order of electron-withdrawing effect of the α-substituents (Cl > H > Me), the reactivity of the substrates should be in the order of **1b** (R = Cl) > **1c** (R = H) > **1a** (R = Me), which is consistent with the experimental results (entries 2, 12, and 14, Table 2).

In summary, the chlorine transfer radical carbocyclization reactions of a series of olefinic α-chloro β-keto esters were investigated. It was found that the α-dichlorinated β-keto esters were suitable substrates; the chlorine transfer mono or tandem radical cyclization reactions catalyzed by CuCl complexed with ligand **L1**, **L2**, or **L3** proceeded smoothly in 1,2-dichloroethane at room temperature or 80 °C. As the products are highly functionalized and versatile in organic transformation, this method should be useful in the construction of natural products and other biologically important cyclic compounds.

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Supporting Information Available: Preparation and characterization of compounds **1**−**4** and X-ray structural analysis of **3b** and **3g**, containing tables of atomic coordinates, thermal parameters, bond lengths, and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Similar skeletons have been reported to exist in enol forms, see: (a) Collins, D. J.; Tomkins, C. W. *Aust. J. Chem.* **1977**, *30*, 443−450. (b) Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, 112, 2759−2767.

(12) For an example of using $CuCl_2$ in the α-chlorination of β-keto esters, see: Shi, X. X.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4596−4598.