Transition-Metal-Catalyzed Radical Cyclization: Copper-Catalyzed Cyclization of Allyl Trichloroacetates to Trichlorinated γ-Lactones

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Cuprous salts in acetonitrile catalyzed the cyclization of allyl trichloroacetates to trichlorinated γ-lactones by way of an intramolecular atom-transfer radical cyclization. Various trichlorinated γ-lactones having a variety of alkyl substituents were prepared by this method. γ-Lactones were generally obtained as a single product except the cyclization of methallyl trichloroacetate, which afforded a mixture of γ- and δ-lactones. The addition of a dichloroacetyl moiety and a chlorine atom to olefins was not stereospecific. Trichloroacetates of secondary allylic alcohols provided a mixture of diastereomers. The stereochemical outcome was dependent on the structure of the starting trichloroacetates; 2-cyclohexenyl trichloroacetate gave the corresponding cis-fused bicyclic lactone, whereas the reaction of acyclic trichloroacetates derived from 1-buten-3-ol and its analogues generally provided the trans-substituted lactones. A mechanism of this reaction based on the stereochemical outcome is discussed.

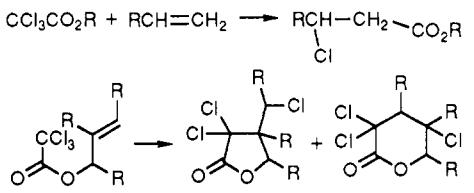
A number of radical cyclization reactions have been devised as a method of ring construction.[1] Especially, the reactions initiated by reductive methods, e.g., tin reduction of ω-haloolefins, are well-established process to promote carbon–carbon bond formations for the ring construction through formal intramolecular addition reactions of the carboradical moiety and the hydrogen atom to an olefinic bond.[2] In contrast, there is an another mode of radical cyclization reactions known as "atom-transfer radical cyclization",[3] in which ω-haloolefins underwent radical cyclization through cleavage of a carbon–halogen bond and subsequent intramolecular addition of the resulting carboradical species and the halogen atom to an olefinic bond. This type of reaction can introduce a halogen atom to the product, which is useful for further functionalization of the molecule. However, only limited processes belonging to the atom-transfer radical cyclization were reported so far, and thus, the development of this type of reactions is an interesting problem in organic synthesis.

In our previous communication,[4] we have reported an atom-transfer-type cyclization of allyl trichloroacetates by copper catalysts, which affords the corresponding α,α,γ-trichlorinated lactones as shown in eq 2 (Scheme I). It is known that intermolecular addition reactions of trichloroacetates to olefins as shown in eq 1 were promoted by radical initiators or transition-metal catalysts. The reaction in eq 2 is more than an intramolecular version of that in eq 1, providing stereochemical outcome that is useful for elucidation of the mechanisms of a wide range of metal-catalyzed addition reactions of polyhalogenated compounds to olefins. In this paper, we describe a detailed investigation on this intramolecular reactions emphasized on stereochemical studies and discussed the mechanistic aspects of the reactions.

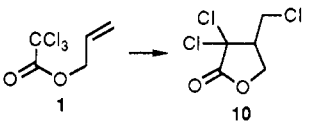
Results and Discussion

Screening of the Catalyst. Addition reactions of methyl or ethyl trichloroacetate to olefins were catalyzed by copper salts,[5] metal carbonyls,[6] a ruthenium–phosphine complex,[7] and a palladium salt.[8] Organic peroxides also promoted the reaction.[9] Although the cyclization of allyl trichloroacetates shown in eq 2 is an intramolecular version of these reactions, organic peroxides and many of the catalysts useful for the intermolecular reactions described in eq 2 did not provide the desired lactones. In most cases

Scheme I



Scheme II



we examined, mixtures of unidentified products were formed under the conditions involving allyl chloride and allyl dichloroacetates. Typically, an acetonitrile or toluene solution of allyl trichloroacetate (**1**) was heated at 110–140 °C in a sealed tube in the presence of a metal complex such as $RuCl_2(PPh_3)_3$, $RhCl(PPh_3)_3$, or $Cp_2Mo(CO)_6$ (1–2 mol %). All of **1** was consumed after 16 h to give tarry products. GLC analysis showed formation of some amounts of allyl dichloroacetate (**2**) and allyl chloride. The formation of **2** resulted from hydrogen abstraction of the dichloroacetyl radical intermediates, which were formed from **1** by transition-metal-promoted chlorine abstraction, whereas that of allyl chloride was attributed to the oxidative addition of the allylic C–O bond in allyl trichloroacetates to transition-metal complexes. The high molecular weight compounds may be formed by polymerization of **1** through the intermolecular addition reaction. Attempts to suppress the intermolecular polymerization under high dilution conditions failed.

As a result of the catalyst screening, we have found that γ-lactone **10** was obtained from **1** by several cuprous salts in acetonitrile (Scheme II). In Table I are summarized

† Tokyo Institute of Technology.

(1) For reviews, see: Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986. Curran, D. P. *Synthesis* **1988**, 417, 489.
(2) Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.
(3) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477.
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(5) Murai, S.; Sonoda, N.; Tsutsumi, S. *J. Org. Chem.* **1964**, *29*, 2104.
(6) Mori, Y.; Tsuji, J. *Tetrahedron* **1972**, *28*, 29.
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(8) Tsuji, J.; Sato, K.; Nagashima, H. *Chem. Lett.* **1981**, 1169.
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0022-3263/90/1955-0985$02.50/0

Table I. Transition-Metal-Catalyzed Cyclization of 1

run	catalyst (mol %)	solvent (M)	temp (°C)	time (h)	convn (%) of 1	yield (%) 10	yield (%) 11
1	$RuCl_2(PPh_3)_3$ (2)	MeCN (0.75)	110	16	90	0	13
2	$RhCl(PPh_3)_3$ (2)	MeCN (0.75)	110	16	92	0	24
3	$Cp_2Mo_2(CO)_6$ (2)	MeCN (0.75)	110	16	38	0	6
4	CuCl (2)	MeCN (0.75)	110	16	72	34	2
5	CuCl (2)	^{i}PrOH (0.75)	110	16	21	3	8
6	CuCl (2)	^{t}BuOH (0.75)	110	16	40	19	0
7	CuCl (20)	MeCN (0.75)	110	16	97	59	0
8	CuCl (30)	MeCN (0.25)	110	16	98	95	0
9	CuCl (30)	MeCN (0.13)	110	16	99	99	0
10	CuCl (30)	MeCN (0.13)	140	2.5	95	95	0
11	Cu_2O (2)	MeCN (0.75)	110	16	49	27	1
12	$Cu(NO_3)_2 \cdot H_2O$ (2)	MeCN (0.75)	110	16	68	47	1
13	Cu(CCPh) (2)	MeCN (0.75)	110	16	78	65	0
14	$Fe(CO)_5$ (2)	MeCN (0.75)	110	16	46	16	2
15	$Fe_2(CO)_9$ (2)	MeCN (0.75)	110	16	9	3	2
16	$Cp_2Fe_2(CO)_4$ (2)	MeCN (0.75)	110	16	15	1	2

[a] All reactions were carried out in a sealed tube according to the procedure of the Experimental Section. Conversion and yields were determined by GLC, using cyclododecanone as an internal standard.

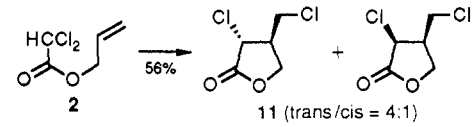
the results. Since allyl trichloroacetates are unstable at high temperatures, relatively large amounts of catalysts (10–30%) were required to attain high yields of the product. Use of acetonitrile under rather diluted conditions (4–8 mL per 1 mmol of **1**) is crucially important for the successful cyclization; higher concentration resulted in a decrease of the yield of **1** due to the intermolecular polymerization. Other solvents are generally ineffective, except alcohols, which gave **10** in low yields. Cupric salts are inactive except $Cu(NO_3)_2$, in which reduction to cuprous species might precede the reaction.

Addition of an equimolar amount of bipyridine to CuCl accelerated the formation of **10** from **1**.[10] The rates of the cyclization of **1** in acetonitrile were compared between CuCl and a 1:1 mixture of CuCl/bpy (5 mol % of the catalyst concentration to **1**); after 1.5 h of heating at 140 °C, the yields of **10** reached 83% with CuCl/bpy, which was four times as much as with CuCl. A 1:1 mixture of CuCl and bipyridine gave a yellow to brown solution in methylene chloride, which suggests the formation of a CuCl(bipyridine) complex. The solution was highly air-sensitive, and a trace of oxygen gave rise to green insoluble materials, probably Cu(II) compounds derived from the oxidation of copper. Under anaerobic conditions using high vacuum technique, the copper–bipyridine complex rapidly reacted with allyl trichloroacetate even at room temperature. However, the only product obtained was allyl dichloroacetate (**2**). An equimolar amount of **2** was obtained to the catalyst charged. Thus the addition of bipyridine apparently increased the rate of the chlorine abstraction, but the resulting radical species did not result in cyclization but hydrogen abstraction from the solvent. In sharp contrast, no reaction took place below 80 °C with CuCl/bpy catalyst in acetonitrile. Over 80 °C, lactone **10** was formed without contamination of dichloroacetate **2**. Thus, the cyclization preceded to hydrogen abstraction in acetonitrile. These results indicate that coordination of acetonitrile is crucially important for successful cyclization, though bipyridine accelerated the chlorine abstraction.

Several iron catalysts also afforded **10** from **1** in low yields. For example, $Fe(CO)_5$ (2 mol %) in acetonitrile gave 10–20% of **10**. However, side reactions to provide unidentified tars could not be suppressed by changing concentration of the substrate and the catalyst.

(10) A catalyst system consisting of Cu(I) salts and bipyridine resulted in successful addition of chloroacetonitrile to olefins: Julia, M.; Thuillier, G.; Saussine, L. *J. Organomet. Chem.* **1979**, *177*, 211.

Scheme III

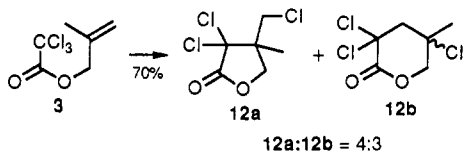


Nagai and co-workers reported an addition reaction of methyl dichloroacetate to olefins by $RuCl_2(PPh_3)_3$ in which a carbon–chlorine bond of the ester was cleaved and subjected to addition to the olefinic bond.[7] Interestingly, a similar reaction initiated by organic peroxides involves abstraction of hydrogen from the dichloroacetate, which forms a dichloroacetyl radical species. Thus, the products of this radical reaction were not α,γ-dichloroacetates but α,α-isomers.[7] Although neither the ruthenium catalysts nor the organic peroxides was effective for the cyclization of allyl dichloroacetate (**2**), use of CuCl/bipyridine catalyst successfully afforded the corresponding α,γ-dichlorolactone **13** as a single product. Without bipyridine, no reaction took place. Similarly, the cyclization of **2** was catalyzed by $Fe(CO)_5$ in the presence of a cocatalyst such as bipyridine and diphos to give **11** in 30–60% yields (Scheme III). This cyclization afforded the product as a diastereomeric mixture, and the stereochemical details are discussed later.

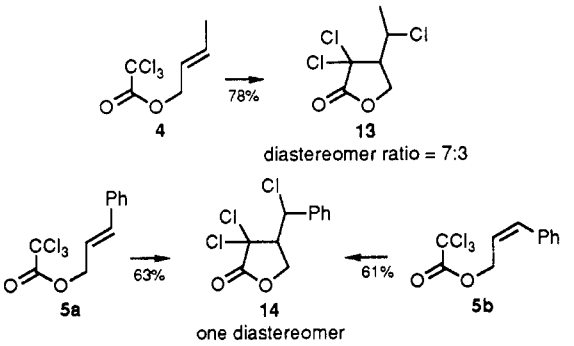
Regio- and Stereoselectivity of the Cyclization. Regio- and stereoselectivity of free-radical cyclization has been widely investigated in terms of the development of synthetic methods to build-up various five- or six-membered ring skeletons.[1] The copper-catalyzed cyclization of allyl trichloroacetates involves three unique features on the regio- and stereochemical outcome. The first is the regioselectivity of the cyclization, in which γ-lactones were generally obtained as a single product. The second is nonstereospecificity of the addition mode of the carbon and chlorine moieties to the olefinic bond. The last is high 1,2-asymmetric induction observed in the cyclization of trichloroacetates derived from secondary allylic alcohols.

The regioselectivity of the radical cyclization was extensively studied on various systems. In a typical example, the 5-hexenyl radical was cyclized via exo and endo transition states to give methylcyclopentane and cyclohexane, respectively, in a ratio of 98:2. Higher exo selectivity was observed in the cyclization of the 3-oxa-5-hexenyl radical in which the 3-methyltetrahydrofuran was predominantly formed over the tetrahydropyran (100:0). The cyclization of allyl trichloroacetates generally provided selective for-

Scheme IV



Scheme V

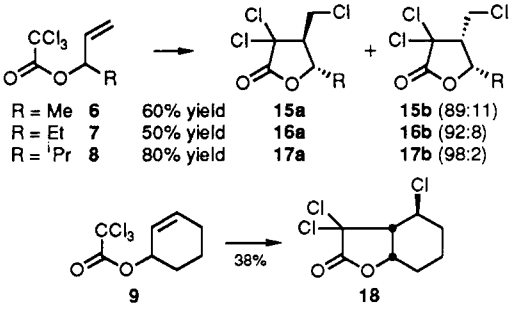


mation of γ-lactones. δ-Lactones were never observed except for the reaction of methallyl trichloroacetate (**3**), in which the ratio between γ- and δ-lactones **12a** and **12b** was approximately 4:3, respectively[11] (Scheme IV).

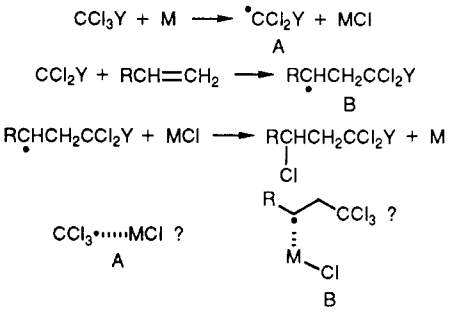
In sharp contrast to the reductive radical cyclization, the atom-transfer radical cyclization essentially involves addition of carbon moieties and a halogen atom to the olefinic bond. Copper-catalyzed cyclization of *trans*-crotyl trichloroacetate (**4**) was examined in order to investigate the stereochemical course of the addition. The obtained lactone was a mixture of diastereomers **13** derived from the chirality of the β-carbon and the carbon attached to chlorine in a ratio of 7:3 (Scheme V). The reactions of *trans*- and *cis*-cinnamyl trichloroacetates **5a** and **5b** independently prepared from the corresponding alcohols provided the identical diastereomer **14** either from **5a** or from **5b**. These results apparently suggest that the addition of the carbon moiety and the chlorine atom is nonstereospecific.

The cyclization of trichloroacetates derived from secondary allylic alcohols essentially involves diastereoselection reflecting the relative stereochemistry of β- and γ-substituents on the lactone ring. 1-Buten-3-yl trichloroacetate (**6**) provided the corresponding β-(chloromethyl)-γ-methyl lactone **15** as a mixture of diastereomers in which the trans isomer was predominantly formed over the cis isomer (9:1).[12] Thus, 1,2-asymmetric induction by

Scheme VI



Scheme VII



the methyl group adjacent to the oxygen function in **6** occurred during the cyclization. The stereoselectivity was dependent on the steric bulkiness of the adjacent alkyl group; the ratio of trans to cis was increased by changing the substituents from methyl to ethyl and isopropyl as shown in Scheme VI. In contrast to the trans selectivity generally observed in the cyclization of acyclic trichloroacetates, the reaction of 2-cyclohexenyl trichloroacetate (**9**) gave the cis-fused bicyclic lactone **18**.[16] Although a diastereomer from relative stereochemistry of the introduced carbon moiety and chlorine atom may be formed in this cyclization, NMR evidence in which the coupling constant between ClC*H* and C*H*CCl$_2$ was 7.7 Hz suggests that this reaction proceeded with high trans selectivity.

The other stereochemical problem was derived from the cyclization of allyl dichloroacetate (**2**), in which the relative stereochemistry between the α-chlorine atom and β-chloromethyl group was determined (Scheme III). The ratio of the isomers was 1:4 based on NMR and GLC. The chloromethyl protons of the major isomer appeared at 2.55 ppm in C_6D_6 as a sharp doublet. In contrast, that of the minor isomer split into AA′BB′X patterns and appeared at 2.58 and 2.85 ppm. These splitting patterns suggest the presence of restricted rotation of the chloromethyl group. Since the restricted rotation of the chloromethyl group by α-chlorine occurs in the cis isomer rather than in the trans isomer, the major isomer obtained by the cyclization of **2** would be the trans form. NOE studies irradiating the chloromethyl protons of the major isomer revealed strong correlations to the α-hydrogen, supporting the above assignments.

In summary, the regio- and stereochemical outcome of the cyclization of various allyl trichloroacetates and an allyl dichloroacetate was illustrated in Schemes III–VI. *It is of importance that all of these stereochemical results did not vary by the catalysts used. Addition of bipyridine*

(11) Interestingly, an ^{1}H NMR spectrum of the formed δ-lactone showed the existence of two conformational isomers. Two methyl signals appeared at 1.85 and 1.87 ppm in $CDCl_3$, and at 1.18 and 1.20 ppm in C_6D_6, respectively. Two methylene protons, which were split to AB patterns, were also observed as two sets. Coupled and decoupled spectra of ^{13}C NMR also showed two sets of signals, which have close chemical sifts. These conformational isomers derived from β-chlorine, which is located at the axial and equatorial positions in equal amounts. No collapse was observed on ^{1}H NMR signals between room temperature to 100 °C in toluene-d_8, which suggests a high energy barrier for the interconversion of these two isomers.

(12) **15** and **16** were misassigned in our primary report.[4] The stereochemistry of these lactones was determined by analyzing the corresponding reductive dechlorinated lactones. However, Stork[15] et al. reported that the stereochemistry of one of them[13] was misassigned in the literature. We confirmed these misassignments by preparation of authentic samples of the corresponding trans isomers of the dechlorinated lactones by conjugate addition of Me_2CuLi to the corresponding γ-alkyl-α,β-unsaturated lactones. Thus, the lactones from **15a** and **16a** assigned to cis in the original papers[13,14] were the corresponding trans isomers, whereas the trans isomer from **17a** was correctly assigned by Stork.[15]

(13) Kanetsuna, H.; Nonaka, T. *Denki Kagaku* **1979**, *47*, 422.

(14) Tokuda, M.; Yokoyama, T.; Taguchi, T.; Suzuki, A.; Itoh, M. *J. Org. Chem.* **1972**, *37*, 1859.

(15) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741.

(16) The stereochemistry was determined after reductive dechlorination.

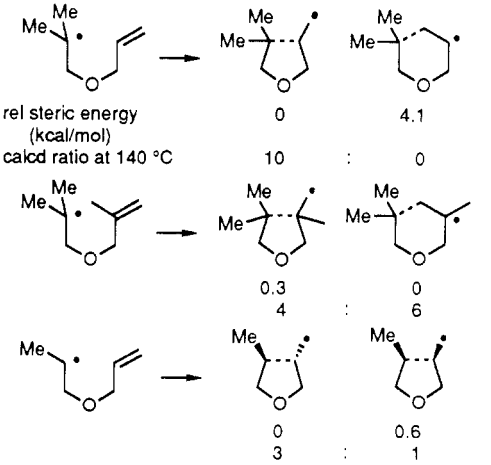
as the cocatalyst accelerated the reactions but did not affect the diastereomer ratios. These findings are very important for the mechanistic consideration described in the following section.

Mechanistic Consideration. It is known that addition reactions of polyhalogenated compounds such as carbon tetrachloride and trichloroacetates to olefins are initiated by organic peroxides, proceeding through free-radical chain mechanisms. Although the same reactions were attained with transition-metal catalysts, the radical chain mechanism was excluded in the metal-catalyzed systems from the solvent effects, inhibition studies, and kinetics.[17] Furthermore, several unique reactions that cannot be achieved with free-radical reactions were developed by certain transition-metal catalysts. In typical examples, facile coaddition of CCl_4 and CO to olefins are catalyzed by palladium salts[18] and binuclear metal carbonyls,[19] and asymmetric addition of $BrCCl_3$ to styrene was attained with chiral rhodium catalysts.[20] These reactions were generally explained by the redox mechanism shown in Scheme VII.[17,21] If strong interaction of metallic species to the alkyl radical intermediates B, which may provide a carbon–metal bond in extreme cases, is assumed, the facile CO insertion and the asymmetric induction could be explained. There is another potential metal–radical interaction between the metal species and polyhalogenomethyl radical intermediates A, of which the possibility has not been well-investigated. In this regard, the successful construction of new chiral centers in either carbon–carbon or carbon–chlorine bonds in the present cyclization of allyl trichloroacetates followed by the redox mechanism provides strong evidence on the radical–metal interaction. In other words, potential metal–radical interactions in the addition of carboradical species and chlorine atom to the olefinic bonds could be deduced from the relative stereochemistry between the substituents on the resulting lactones.

As described above, the present cyclization provided the stereochemical features shown in Scheme III–VI. Interestingly, many of these features are consistent with those observed in the tin-mediated radical cyclization, which has been established to proceed through free-radical chain mechanisms. A closely related example of this copper-catalyzed process is the β-alkoxy radical cyclization, in which reduction of allyloxy acetals of bromoacetaldehyde afforded tetrahydrofuran derivatives.[15,22] Regioselectivity of this cyclization is generally excellent for the predominant formation of five-membered ring products over six-membered ones. It was also reported that high 1,2-asymmetric induction was possible in the cyclization of bromo acetals prepared from secondary allylic alcohols; trans-selective cyclization was observed in the reactions of bromo acetals from 1-alken-3-ols, whereas cis-fused bicyclic ring products were obtained from that of 2-cyclohexen-1-ol. The ratios of cis to trans in each case are comparable to those obtained in the cyclization reactions of allyl trichloroacetates described above. Transition states for the tin-mediated radical cyclization have been extensively studied.[1,2] Recent studies by Beckwith[23] and Houk[24] eventually realized the prediction of regio- and stereochemical outcome by using MM2 force field calculations based on the model transition states determined by MNDO-UHF[23] or ab initio calculations.[24] If these transition states are close to those of the copper-catalyzed process, the above-described selective γ-lactone formation and high 1,2-asymmetric induction could be explained. The formation of δ-lactone **12b** in a high ratio in the cyclization of methallyl trichloroacetate (**2**) is also consistent with the radical transition states, because carbon–carbon bond formation reactions are attained by addition of a bulky dichloroacetyl or chloroacetyl radical to the olefinic bond in the copper-catalyzed process, and thus, the five-membered ring formation in the cyclization of methallyl trichloroacetate is disfavored because of larger steric hindrance between the dichloroacetyl radical and the methyl substituents on the olefin than in the six-membered ring formation. Similarly, in the cyclization of dichloroacetate, carbon–carbon bond formation took place in such a way as to avoid the repulsion between the chlorine and terminal carbon on the olefin to give the trans product.[25] The nonstereospecificity for the introduction of the dichloroacetyl moiety and the chlorine atom to the olefinic bond suggests that stereochemically feasible radical intermediates are involved in the copper-catalyzed cyclization of allyl trichloroacetates.

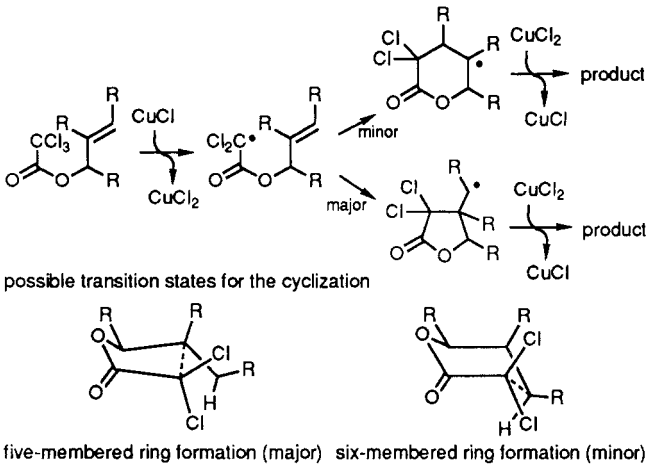
The copper-catalyzed process was not inhibited by radical scavengers such as hydroquinone. Thus, the radical chain mechanism was excluded. However, the stereochemical results are quite similar to the free-radical reactions. These results indicated that the transition states of the carbon–carbon bond-forming step do not involve any

(17) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978.
(18) Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* **1985**, *41*, 5003.
(19) Susuki, T.; Tsuji, J. *J. Org. Chem.* **1970**, *35*, 2982.
(20) Murai, S.; Sugie, R.; Sonoda, N. *Angew. Chem.* **1981**, *93*, 481.
(21) Original reports to propose the redox mechanism: Asscher, M.; Vofsi, D. *J. Chem. Soc.* **1961**, 2261; **1963**, 1887, 3921. Minisci, F. *Acc. Chem. Res.* **1975**, *8*, 165.
(22) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.
(23) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.
(24) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
(25) We assume that chlorine substituents on the allyl trichloroacetates would be important for the facile chlorine abstraction by cuprous species. However, they would contribute simply as a steric factor in the transition states. In this context, we carried out a rough estimation of regio- and stereochemical results obtained by the cyclization of polychloroacetates by MM2 calculation according to the procedure by Houk in the following tetrahydrofuran or pyran ring formation, in which chlorine atoms were replaced by methyl groups. As shown below, the β-allyloxy radical substituted by two methyl groups was predicted to form no six-membered ring products because of high energy difference between the two transition states (4.1 kcal/mol). On the other hand, its methallyl analogue rather preferred the formation of a pyran ring to that of a furan derivative. Calculation of the transition states in the cyclization of the monomethyl-substituted β-allyloxy radical suggests selective formation of furan products in which the trans-substituted isomer was formed predominantly. Calculated ratios at 140 °C roughly resembles the diastereomer ratios observed in the cyclization of **2** and **3**, suggesting that the regio- and stereochemical results in the copper-catalyzed cyclization could be qualitatively predicted in a similar way to the usual free-radical cyclization.



(26) Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1984**, 949.

Scheme VIII



participation of metallic species. At the initial stage, the abstraction of chlorine atom from the trichloroacetates generates the dichloroacetyl radical moiety. There is no strong interaction between this radical species and the metallic species. Then the formed radical moiety adds to olefins to form a new carbon–carbon bond via five-membered transition states similar to the free-radical cyclization, and then a new carboradical moiety is generated on the exo-substituted carbon. This carbon radical then abstracts the chlorine atom from the metallic species. Although the interaction of the latter radical species with the metallic species plays an important role in avoiding the radical chain process, it is weak enough to promote facile racemization. The overall scheme involving the redox process is shown in Scheme VIII.

The important findings through these stereochemical studies are that the carbon–carbon bond-forming step of the copper-catalyzed cyclization of allyl trichloroacetates would not involve any contribution of the metallic species. In other words, the stereochemical outcome of this metal-catalyzed system also considered by a general five-membered transition states similar to the free-radical cyclization.

Conclusion

The copper-catalyzed cyclization of allyl trichloroacetates is a new mode of radical cyclization to provide γ-lactones in one step.[27] The reactions involve excellent regio- and stereoselectivities that are advantageous for the preparation of substituted lactones in a highly stereoselective manner. It is important that the catalyst gives no influence in determining the stereochemistry, which can be predicted by the usual free-radical cyclization mechanism. This suggests that transition state of the copper-catalyzed cyclization is relevant to those of the free-radical reactions, though the reaction does not involve a chain process. This report is the first clear example to exclude the interaction of metallic species to the initially formed radical species from the stereochemical views, providing a new mechanistic insight in the problematic mechanistic aspects of the transition-metal-catalyzed reactions of polyhalogenated compounds.

In view of organic synthesis, this cyclization is a simple synthetic method for β-substituted or β,γ-disubstituted lactones. Especially, the excellent regio- and stereoselectivities described above are attractive as a stereoselective synthesis of these compounds. This reaction was eventually applied to syntheses of pyrethroids by Takano and co-workers.[26] A limitation of this reaction that we should mention is derived from the thermal instability of the starting materials. The trichloroacetoxy group is a better leaving group than other carboxylates, leading to a facile elimination reaction of trichloroacetic acid at elevated temperatures. The low yields of bicyclic lactone 18 were attributed to this elimination to form cyclohexadiene. Several allyl trichloroacetates induce 3,3-sigmatropic rearrangement; for example, trichloroacetates from 1-phenyl-2-propen-1-ol or 2-methyl-3-buten-2-ol gave the corresponding rearranged products, cinnamyl trichloroacetate and prenyl trichloroacetate, upon distillation, respectively. Except for these thermally unstable trichloroacetates, the reactions proceeded smoothly to give the corresponding lactones in reasonable yields.

Experimental Section

General. ^1H NMR spectra were taken on a Hitachi R-24a spectrophotometer in CCl_4 or on a JEOL-PMX60, JEOL FX-90Q, or GX-270 spectrophotometer in $CDCl_3$. The chemical shifts were recorded as δ values in ppm from TMS. IR spectra were recorded on a Jasco-IRA-2 spectrometer in wavenumber. Mass spectra were taken on a JEOL-D300 spectrometer. Melting points are uncorrected.

All manipulations were carried out under a nitrogen or argon atmosphere. CuCl was freshly prepared from $CuCl_2$ hydrate according to the known procedure and stored under nitrogen.[28] MeCN was dried over P_2O_5 and distilled before use. Anhydrous ether was prepared by distillation from benzophenone–ketyl. Column chromatography was carried out on silica gel (Merk 7740) eluted by hexane–ether. We had some trouble in performing TLC analysis of the chlorinated compounds. Many of them are not active to UV, iodine, and anisaldehyde–H_2SO_4 in ethanol. The best way to identify the spot of the starting materials and the products was atomizing 5–10% of *p*-toluidine in ethanol to the silica gel TLC plate, drying and then irradiating by low pressure UV lamp. Brown to violet spots appeared.

General Procedure for the Preparation of Allyl Trichloroacetates. Freshly distilled allyl alcohol (14 mmol) and Et_3N (23 mmol) were dissolved in dry ether (30 mL). CCl_3COCl (17 mmol) was added dropwise through a syringe at 0 °C. After stirring for 3 h, usual workup provided the corresponding ester in 70–90% yields.

1: ^1H NMR (CCl_4, 60 MHz) 4.78 (dd, 2 H, J = 1.8, 5.2 Hz, OCH_2), 5.1–6.15 (m, 2 H, olefinic); IR (neat) 1770; bp 80.5–82 °C/20 mmHg.

2: ^1H NMR (CCl_4, 60 MHz) 4.32 (d, 2 H, J = 5 Hz, OCH_2), 5.2–6.5 (m, 3 H, olefinic), 6.0 (s, 1 H, Cl_2CH); IR (neat) 1750; bp 71–71.5 °C/18 mmHg.

3: ^1H NMR ($CDCl_3$, 270 MHz) 1.86 (s, 3 H, CH_3), 4.77 (s, 2 H, CH_2), 5.05 (s, 1 H, olefinic), 5.12 (s, 1 H, olefinic); IR (neat) 1765; bp 88–89 °C/20 mmHg.

4: ^1H NMR (CCl_4, 60 MHz) 1.78 (d, 3 H, J = 6 Hz, Me), 4.76 (d, 2 H, J = 6 Hz, OCH_2), 5.35–6.35 (m, 2 H, olefinic); IR (neat) 1760; HRMS calcd for $C_6H_7O_2Cl_3$ 215.9510, found 215.9506; bp 49.5–53 °C/5 mmHg.

5a: ^1H NMR ($CDCl_3$, 270 MHz) 4.99 (dd, 2 H, J = 0.98, 6.35 Hz, OCH_2), 6.32 (dt, 1 H, J = 6.35, 16.11 Hz, PhCH=C*H*), 6.78 (d, 1 H, J = 16.11 Hz, PhC*H*), 7.28–7.43 (m, 5 H, Ph); IR (neat) 1760; MS m/e 278 (M), 280 (M + 2).

5b: ^1H NMR ($CDCl_3$, 270 MHz) 5.07 (dd, 2 H, J = 1.46, 6.84 Hz, OCH_2), 5.87 (dt, 1 H, J = 6.84, 11.72 Hz, PhCH=C*H*), 6.82 (d, 1 H, J = 11.72 Hz, PhC*H*), 7.22–7.45 (m, 5 H, Ph); IR (neat) 1765; MS m/e 278 (M), 280 (M + 2).

6: ^1H NMR (CCl_4, 60 MHz) 1.45 (t, 3 H, J = 6 Hz, Me), 5.0–6.2 (m, 4 H, olefinic and OCH); IR (neat) 1760; HRMS calcd for $C_6H_7O_2Cl_3$ 215.9510, found 215.9506; bp 82.5–85.5 °C/21 mmHg.

7: ^1H NMR (CCl_4, 60 MHz) 0.98 (t, 3 H, J = 7 Hz, Me), 1.78 (q, 2 H, J = 7 Hz, CH_2), 5.0–6.2 (m, 4 H, olefinic and OCH); IR

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(neat) 1760; HRMS calcd for $C_7H_9O_2Cl_3$ 229.9670, found 229.9658; bp 68–70 °C/16 mmHg.

8: ^{1}H NMR (270 MHz, $CDCl_3$) 0.98 (d, 3 H, J = 6.8 Hz, Me), 1.00 (d, 3 H, J = 6.8 Hz, Me), 2.05 (oct, 1 H, J = 6.8 Hz, $CHMe_2$), 5.13 (t, 1 H, J = 6.8 Hz, C*H*O), 5.33–5.82 (m, 3 H, olefinic); IR (neat) 1765; MS m/e (CI) 245 (M + 1), 247 (M + 3), 249 (M + 5); (EI) 202, 204, 206 (M – C_3H_6 and its isotope peaks); HRMS calcd for $C_5H_5O_2Cl_3$ (M – C_3H_6) 201.9356, found 201.9361; bp (Kugel-lore) 45–65 °C/2 mmHg.

9: ^{1}H NMR (270 MHz, $CDCl_3$) 1.65–2.23 (m, 6 H, cyclohexene ring), 5.38 (d, 1 H, J = 5 Hz), 5.80 (dd, 1 H, J = 5, 11 Hz), 5.80 (dd, 1 H, J = 5, 11 Hz), 6.12 (m, 1 H); IR (neat) 1760; HRMS calcd for $C_8H_9O_2Cl_3$ 241.9670, found 241.9657; bp 72 °C/0.9 mmHg.

General Procedure for the Cyclization. CuCl (30 mg, 1 mmol) was measured in a Pyrex tube fitted with a screw cap. Allyl trichloroacetate (1 mmol) dissolved in acetonitrile (8 mL) was added. The resulting mixture was heated at 110–140 °C for 1–3 h. The initial suspension changed from yellow to a brown homogeneous solution. The cooled solution was passed through a short silica gel column to remove metallic species. The eluents were collected and concentrated to give the corresponding lactone. Further purification was carried out by recrystallization from hexane–ether or column chromatography.

10: ^{1}H NMR (270 MHz, $CDCl_3$) 3.32–3.41 (m, 1 H, CCl_2CH), 3.75 (dd, 1 H, J = 9.5, 11.5 Hz, C*H*Cl), 3.99 (dd, 1 H, J = 4.6, 11.5 Hz, C*H*Cl), 4.23 (dd, 1 H, J = 8.8, 9.3 Hz, C*H*O), 4.65 (dd, 1 H, J = 7.1, 9.3 Hz, C*H*O); ^{13}C NMR ($CDCl_3$) 39.6 (*C*Cl), 53.1 (*C*CCl_2), 68.6 (*C*Cl_2), 78.6 (*C*O), 167.1 (*C*=O); IR ($CHCl_3$) 1810, 700; mp 71.6–72 °C. Anal. Calcd for $C_5H_5Cl_3O_2$: C, 29.52; H, 2.48. Found: C, 29.73; H, 2.47.

11: mixture of two isomers, which were hardly separated. Assignment of the ^{1}H NMR spectra was carried out unambigueously by ^{1}H–^{1}H decoupling techniques: ^{1}H NMR major isomer (270 MHz, C_6D_6) 1.86 (m, 1 H, C*H*CCl_2), 2.55 (d, 2 H, J = 5.3 Hz, ClC*H*$_2$), 3.11 (dd, 1 H, J = 8.3, 9.3 Hz, C*H*O), 3.42 (dd, 1 H, J = 7.3, 9.3 Hz, C*H*O), 3.52 (d, 1 H, J = 9.3 Hz, COClC*H*); minor isomer 1.65 (m, 1 H, $ClCH_2CH$), 2.58 (dd, 1 H, J = 8.1, 12.2 Hz, ClC*H*), 2.84 (dd, 1 H, J = 6.3, 11.2 Hz, ClC*H*), 3.27 (dd, 1 H, J = 7.9, 9.9 Hz, C*H*O), 3.32 (dd, 1 H, J = 7.2, 9.9 Hz, C*H*O), 3.55 (d, 1 H, J = 6.8 Hz, COC*H*Cl). IR ($CHCl_3$): 1795. Anal. Calcd for $C_5H_6O_2Cl_2$: C, 35.53; H, 3.58. Found: C, 35.51; H, 3.73.

12a: ^{1}H NMR (270 MHz, $CDCl_3$) 1.48 (s, 3 H, Me), 3.70 (d, 1 H, J = 11.7 Hz, C*H*Cl), 3.77 (d, 1 H, J = 11.7 Hz, C*H*Cl), 4.18 (d, 1 H, J = 9.3 Hz, C*H*O), 4.47 (d, 1 H, J = 9.3 Hz, C*H*O); IR (Nujol) 1820; mp 117–123 °C. Anal. Calcd for $C_6H_7O_2Cl_3$: C, 33.14; H, 3.25. Found: C, 33.25; H, 3.18.

12b: ^{1}H NMR (270 Mz, $CDCl_3$) 1.85 (s, 3 H), 1.87 (s, 3 H), 3.23 (d, 1 H, J = 7.3 Hz, C*H*CCl_2), 3.28 (d, 1 H, J = 7.3 Hz, C*H*CCl_2), 3.40 (d, 1 H, J = 15.6 Hz, C*H*CCl_2), 3.52 (d, 1 H, J = 15.6 Hz, C*H*CCl_2), 4.06 (d, 1 H, J = 12.7 Hz, C*H*O), 4.12 (d, 1 H, J = 12.7 Hz, C*H*O), 4.27 (d, 1 H, J = 4.4 Hz, C*H*O), 4.31 (d, 1 H, J = 4.4 Hz, C*H*O); ^{13}C NMR (67.8 Hz, $CDCl_3$) 28.8, 29.5 (q, J = 131 Hz, *C*H_3), 53.4 (t, J = 139 Hz, *C*CCl_2), 64.6, 65.2 (s, *C*Cl), 71.4, 71.8 (t, J = 154 Hz, *C*O), 80.7 (s, *C*Cl_2), 164.0, 164.2 (s, *C*=O); IR (Nujol) 1760; mp 164–165.5 °C. Anal. Calcd for $C_6H_7O_2Cl_3$: C, 33.14; H, 3.25. Found: C, 33.33; H, 3.14.

13. Two isomers were seperated easily by column chromatography.

Major isomer: TLC R_f 0.44 (hexane/ether = 1/1); ^{1}H NMR (90 MHz, $CDCl_3$) 1.85 (d, 3 H, J = 6 Hz, Me), 3,.20 (ddd, J = 7.5, 9.5, 10.0 Hz, CCl_2CH), 4.20 (dd, J = 9.5, 10 Hz, C*H*O), 4.43 (dq, 1 H, J = 7, 9.5 Hz, C*H*Cl), 4.73 (dd, 1 H, J = 7.5, 9.5 Hz, C*H*O); IR (neat) 1805; MS m/e calcd for $C_6H_7O_2Cl_3$ 215.9510, found 215.9506.

Minor isomer: TLC R_f 0.16 (hexane/ether = 1/1); ^{1}H NMR (90 MHz, $CDCl_3$) 1.56 (d, 3 H, J = 6 Hz, Me), 3.25 (q, 1 H, J = 9 Hz, CCl_2CH), 4.16 ndd, 1 H, J = 7.5, 10 Hz, C*H*O), 4.1–4.5 (m, 1 H, C*H*Cl), 4.53 (dd, 1 H, J = 7, 10 Hz, C*H*O); IR (neat) 1810; HRMS calcd for $C_6H_7O_2Cl_3$ 215.9510, found 215.9506.

14: ^{1}H NMR (90 MHz, $CDCl_3$) 3.60 (ddd, 1 H, J = 7, 9, 10 Hz, CCl_2CH), 4.29 (t, 1 H, J = 9 Hz, C*H*O), 4.78 (dd, 1 H, J = 7, 9 Hz, C*H*O), 5.25 (d, 1 H, J = 10 Hz, ClC*H*), 7.25–7.60 (m, 5 H, Ph); IR ($CHCl_3$) 1810; mp 90.5–91.5 °C. Anal. Calcd for $C_{11}H_9Cl_3O_2$: C, 47.25; H, 3.24. Found: C, 47.23; H, 3.32.

15a: ^{1}H NMR (90 MHz, $CDCl_3$) 1.65 (d, 3 H, J = 6.4 Hz, Me), 2.90 (ddd, 1 H, 5.4, 7.6, 9.1 Hz, CCl_2CH), 3.74 (dd, 1 H, J = 7.6, 12 Hz, ClC*H*), 4.02 (dd, 1 H, J = 5.4, 12.1 Hz, ClC*H*), 4.50 (dq, 1 H, J = 6.4, 9.1 Hz, C*H*O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 19.4 (Me), 38.8 (*C*Cl), 60.0 (CCl_2CH), 78.4 (*C*HO), 80.1 (Cl_2C), 166.3 (*C*=O); IR (neat) 1800; HRMS calcd for $C_6H_7O_2Cl_3$ 215.9510, found 215.9536.

15b: ^{1}H NMR ($CDCl_3$) 1.59 (d, 3 H, J = 6.8 Hz, Me), 3.42 (ddd, 1 H, J = 4.9, 7.1, 8.6 Hz, CCl_2CH), 3.81 (dd, 1 H, J = 8.6, 11.6 Hz, ClC*H*), 4.01 (dd, 1 H, J = 4.9, 11.6 Hz, ClC*H*), 4.50 (quint., 1 H, J = 7 Hz, C*H*O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 14.7 (Me), 54.8 (CCl_2CH, *C*lC), 76.7 (*C*HO), 77.7 (Cl_2C), 167.1 (*C*=O); IR (neat) 1800.

16a: ^{1}H NMR (90 MHz, $CDCl_3$) 1.10 (t, 3 H, J = 7.5 Hz, Me), 1.5–2.4 (m, 2 H, MeC*H*$_2$), 2.93 (ddd, 1 H, J = 5.7, 7.5, 9.2 Hz, CCl_2CH), 3.70 (dd, 1 H, J = 8.0, 11.3 Hz, ClC*H*), 4.00 (dd, 1 H, J = 5.7, 11.3 Hz, ClC*H*), 4.32 (ddd, 1 H, J = 3.8, 8, 9.2 Hz, C*H*O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 9.4 (Me), 26.3 (*C*H_2Me), 39.0 (*C*lC), 57.4 (CCl_2CH), 80.3 (Cl_2C), 83.0 (*C*HO), 166.4 (*C*=O); IR (neat) 1800; HRMS calcd for $C_7H_9Cl_3O_2$ 229.9670, found 229.9658.

16b: ^{1}H NMR (90 MHz, $CDCl_3$) 1.15 (t, 3 H, J = 7.5 Hz, Me), 1.5–2.2 (m, 2 H, C*H*$_2$Me), 3.27–3.57 (m, 1 H, CCl_2CH), 3.67–4.10 (m, 2 H, ClC*H*$_2$), 4.55–4.83 (m, 1 H, C*H*O); ^{13}C NMR (22.5 MHz, $CDCl_3$) 10.6 (Me), 22.3 (*C*H_2Me), 38.5 (*C*lC), 54.9 (CCl_2CH), 78.4 (Cl_2C), 82.0 (*C*HO), 167.2 (*C*=O); IR ($CHCl_3$) 1800.

17: (trans isomer) ^{1}H NMR (270 MHz, $CDCl_3$) 1.02 (d, 3 H, J = 6.8 Hz, Me), 1.16 (d, 3 H, J = 6.8 Hz, Me), 2.23 (d septet, J = 3.4, 6.8 Hz, 1 H, C*H*Me$_2$), 3.06 (ddd, 1 H, J = 5.4, 6.8, 9.3 Hz, CCl_2CH), 3.72 (dd, 1 H, J = 6.8, 11.7 Hz, C*H*Cl), 3.99 (dd, 1 H, J = 5.4, 11.7 Hz, C*H*Cl), 4.27 (dd, 1 H, J = 3.4, 9.3 Hz, C*H*O); IR (CH_2Cl_2) 1800 cm^{-1}. Anal. Calcd for $C_8O_{11}O_2Cl_3$: C, 39.13; H, 4.52. Found: C, 39.00; H, 4.51.

18: ^{1}H NMR (270 MHz, $CDCl_3$) 1.58 (m, 1 H), 1.80 (m, 3 H), 2.20 (m, 1 H), 2.34 (m, 1 H), 3.21 (dd, 1 H, J = 5.4, 7.8 Hz, C*H*CCl_2), 3.99 (m, 1 H, C*H*Cl), 5.00 (dd, 1 H, J = 4.6, 9.5 Hz); IR (Nujol) 1790; mp 97–97.5 °C. Anal. Calcd for $C_8H_9O_2Cl_3$: C, 39.46; H, 3.73. Found: C, 39.57; H, 3.78.

Reductive Dechlorination of Trichorinated Lactones. A mixture of trichlorolactone (1 mmol) and Bu_3SnH (3 mmol) was heated at 140 °C for 3 h. AIBN was used as the radical initiator. Chromatography to remove tin products gave the corresponding lactone.

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