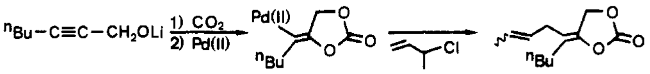
Scheme IV



1c 5

mmol of (trimethylsilyl)ethyne and 5.0 mmol of BuLi in THF solution) was added cyclopentanone (420 mg, 5.0 mmol) at −78 °C, and the whole was stirred at 0 °C for 1 h. Carbon dioxide (gas) was blown through the reaction mixture for 30 min at −78 °C. Allyl chloride (8.3 mL, 100 mmol) and $PdCl_2(MeCN)_2$ (65 mg, 0.25 mmol) were added to the reaction mixture maintained at −78 °C, and then the whole was stirred at 0 °C for 4 h. Water was added to the reaction mixture and the whole was extracted with ether. Ethereal solution was washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography of the residue (silica gel/hexane–ethyl acetate) afforded cyclic carbonate **3u** (R,R′ = $-(CH_2)_4-$, 710 mg, 53% yield) and 1-[(trimethylsilyl)ethynyl]-1-cyclopentanol (210 mg, 23% yield). Alkaline hydrolysis of the carbonate **3u** afforded the corresponding keto alcohol **4u** (Scheme III). Analogously, cyclic carbonates **3** were prepared: **3v** (R,R′ = $-(CH_2)_5-$, 19% from cyclohexanone),[15] **3w** (R = Ph, R′ = H, 78% from benzaldehyde),[16] **3x** (R = R′ = H, 47% from paraformaldehyde).

In contrast to the above results with 3-(trimethylsilyl)-2-propynolate, cyclized coupling of lithium 2-alkynyl carbonates with substituted allyl chlorides gave unsatisfactory results: reaction of lithium 2-heptyn-1-olate (**1c**) with 3-chloro-1-butene gave **5**[17] as an *E*/*Z* mixture in 10% yield and reaction with 1-chloro-2-butene did nott give any coupling product (Scheme IV).

The above described palladium-catalyzed three-component reaction of 2-alkyn-1-olates **1**, carbon dioxide, and allyl chloride opens both a novel access to cyclic carbonates **3** and use of lithioalkynes as acyl anion equivalents.

Acknowledgment. We thank The Ministry of Education, Science and Culture for Grant-in-Aid for Developmental Scientific Research (61850153).

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[15] 1-[(Trimethylsilyl)ethynyl]-1-cyclohexanol was obtained in 59% yield. Carboxylative coupling of the above lithio alcoholate with allyl chloride gave **3v** in 59% yield.

[16] The corresponding keto alcohol was obtained in 58% yield by the hydrolysis in aqueous sodium carbonate.

[17] Structures of the two isomers were determined by ^1H NMR (200 MHz) and the ratio of the two isomer was determined by GLC as a well as NMR.

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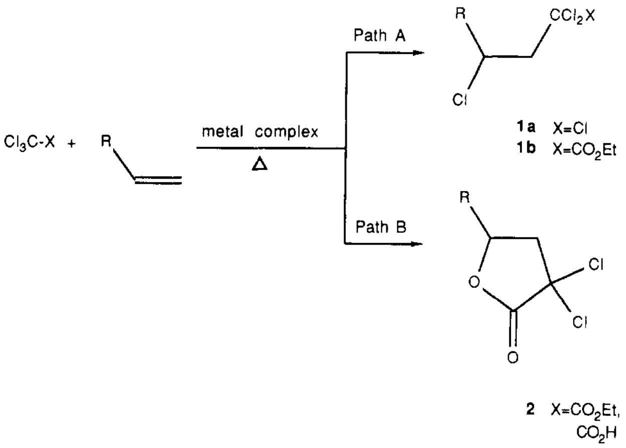
Transition Metal Promoted Intramolecular Cyclizations of α,α-Dichloro Esters and Acids

Summary: Carbocyclic α,γ-dichloro esters or annulated α-chloro γ-lactones can be selectively synthesized via a radical process starting from olefinic α,α-dichloro esters and acids by appropriate choice of transition-metal catalyst and substrate.

Scheme I



Sir: The addition of halocarbons to alkenes catalyzed by various transition-metal compounds has been known for many years.[1] This process, which has been shown to occur through metal-complexed radicals,[2] regioselectively affords adducts such as **1a** (path A, Scheme I). More recently, trichloroacetates were found to undergo analogous radical additions to give α,α,γ-trichloro esters **1b** and/or α,α-dichloro γ-lactones **2**.[3] Interestingly, with some metal catalysts (Cu^{1+}, $Co_2(CO)_8$, Ru^{2+}, etc.) the products of path A predominated, whereas with other catalysts ($[CpMo(CO)_3]_2$, $[CpFe(CO)_2]_2$) path B lactonic products were preferentially formed. Allylic trichloroacetates[4] and trichloroacetamides[5] can also be cyclized intramolecularly via a path A process to afford chlorinated lactones and lactams, respectively. These cyclizations show the regiochemical specificities expected for a free radical reaction.[6] We now report a novel, efficient intramolecular version of this methodology for the synthesis of highly functionalized carbocyclic systems. As discussed below, we have found that the appropriate choice of metal catalyst, or of substrate (i.e. chlorinated ester or carboxylic acid), allows one to efficiently control the nature of the cyclization product (i.e. path A vs. path B).

Initial experiments were carried out with α,α-dichloro ester **3a** and acid **3b**, which were readily prepared by alkylation of 5-bromo-1-pentene with lithio ethyl dichloroacetate[7] and dilithio ethyl dichloroacetic acid,[8] respectively. Cyclizations were conducted in benzene (0.5–1.5 M in substrate) at 160–165 °C in a sealed tube for several hours. Scheme II shows some typical results obtained with this system. α,α-Dichloro ester **3a** cyclized in the expected exo 5-hexenyl radical mode[6] with $RuCl_2(PPh_3)_3$[3c] and $FeCl_2$-

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[1] (a) Elzinga, J.; Hogeveen, H. *J. Org. Chem.* **1980**, *45*, 3957. (b) Bellus, D. *Pure Appl. Chem.* **1985**, *57*, 1827 and references cited therein.

[2] For recent mechanistic studies, see: Davis, R.; Groves, I. F. *J. Chem. Soc., Dalton Trans* **1982**, 2281. Bland, W. J.; Davis, R.; Durrant, J. L. A. *J. Organomet. Chem.* **1984**, *260*, C75. Bland, W. J.; Davis, R.; Durrant, J. L. A. *Ibid.* **1984**, *267*, C45.

[3] (a) Murai, S.; Sonoda, N.; Tsutsami, S. *J. Org. Chem.* **1964**, *29*, 2104. (b) Mori, Y.; Tsuji, J. *Tetrahedron* **1972**, *28*, 29. (c) Matsumoto, H.; Nikaido, T.; Nagai, Y. *J. Org. Chem.* **1976**, *41*, 396. (d) Matsumoto, H.; Nakano, T.; Ohkawa, K.; Nagai, Y. *Chem. Lett.* **1978**, 363. (e) Matsumoto, H.; Ohkawa, K.; Ikemori, S.; Nakano, T.; Nagai, Y. *Ibid.* **1979**, 1011. See also: Kraus, G. A.; Landgrebe, K. *Tetrahedron* Lett. **1984**, *25*, 3939.

[4] Nagashima, H.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2395. Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Heterocycles* **1984**, *22*, 1779.

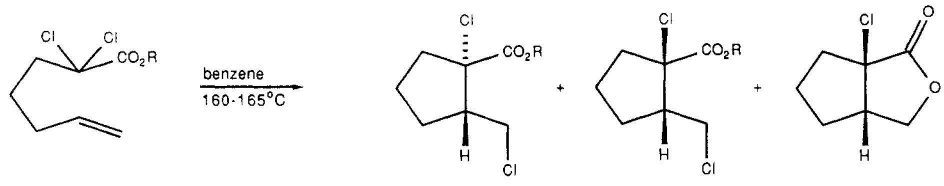
[5] Nagashima, H.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1984**, 652. Nagashima, H.; Ara, K.; Wakamatsu, H.; Itoh, K. *Ibid.* **1985**, 518.

[6] Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.

[7] Villieras, J.; Disnar, J. R.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, 524.

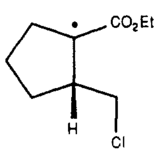
[8] Coutrot, P.; El Gadi, A. *Synthesis* **1984**, 115.

Scheme II



4 5 6

	catalyst	mol%	time (h)	% yield[15]		
				4	5	6
3a R=Et	$RuCl_2(PPh_3)_3$	3.1	7	41	36	–
		3.0	16	55	14	–
	$FeCl_2[P(OEt)_3]_3$	5.7	8	51	24	–
		8.7	20	32	51	–
		5.3	8	34	33	–
	$[CpMo(CO)_3]_2$	5.5	8	10	2	50
		3.4	7	31	5	49
		3.8	25	25	18	17
3b R=H	$RuCl_2(PPh_3)_3$	1.9	7	–	–	94
	$FeCl_2[P(OEt)_3]_3$	4.0	24	–	–	66
	$[CpMo(CO)_3]_2$	1.8	6	2	2	34



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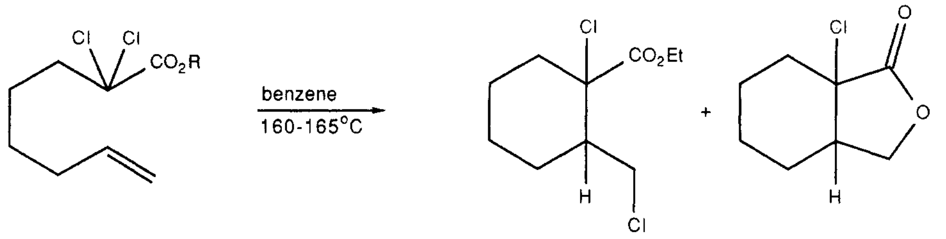
Scheme III



9 10

	catalyst	mol%	time (h)	% yield[15](isomer ratio)	
				9	10
8a R=Et	$RuCl_2(PPh_3)_3$	1.8	24	55 (1:1.3)	–
	$FeCl_2[P(OEt)_3]_3$	4.2	40	75 (1:1.7)	14 (1:6)
	$[CpMo(CO)_3]_2$	3.3	18	30 (1:1.3)	35 (1:1.5)
8b R=H	$RuCl_2(PPh_3)_3$	3.2	24	–	89 (1:2.1)
	$FeCl_2[P(OEt)_3]_3$	8.2	24	–	85 (1:1.7)
	$[CpMo(CO)_3]_2$	3.4	40	–	35 (1:1)

$[P(OEt)_3]_3$[9] catalysts to give mixtures of epimeric α,γ-dichloro esters **4** and **5** in good overall yields. However, the ratio of **4**/**5** was observed to be quite variable and was highly dependent upon catalyst and substrate concentration and reaction time as can be seen from the data in Scheme II. We believe that partial stereochemical equilibration is occuring here via radical **7**, produced from **4** and **5** by the metal catalyst. With the molybdenum catalyst,[3b] the major cyclization product was annulated α-chloro γ-lactone **6**, which was a single stereoisomer, assumed to be the cis-fused compound.[10] Small amounts of **4** and **5** were also produced. It should be noted that Cu^{1+} complexes[1b,3a] and $Co_2(CO)_8$[3b] did not promote cyclization of **3a**, whereas $[CpFe(CO)_2]_2$[3b] gave results similar to the molybdenum catalyst.

On the other hand, cyclization of acid **3b** with $RuCl_2(PPh_3)_3$[3d] and $FeCl_2[P(OEt)_3]_3$ gave *exclusively* the annulated γ-lactone **6** in good yields. Although the molybdenum catalyst also gave lactone **6** predominantly, traces of **4** and **5** were also produced, and the overall yield of cyclization products in this case was poor.

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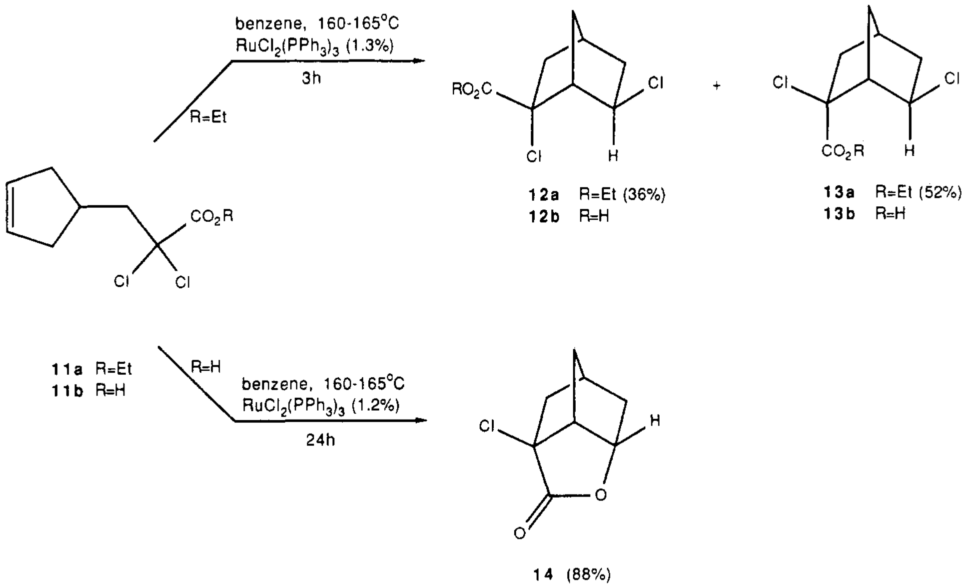
[9] Ittel, S. D.; English, A. D.; Tolman, C. A.; Jesson, J. P. *Inorg. Chim. Acta* **1979**, *33*, 101. We are grateful to Dr. W. A. Nugent (Du Pont) for suggesting this inexpensive catalyst.

[10] Compound **5** is believed to have the stereochemistry indicated since it could be converted to **6** with $AgNO_3$/dioxane/H_2O/Δ, whereas **4** was unreactive under these conditions. See: Carlson, R. M.; Oyler, A. R. *J. Org. Chem.* **1976**, *41*, 4065.

Scheme IV



This cyclization methodology can also be used to produce six-membered carbocycles as shown in Scheme III. Results with α,α-dichloro ester **8a** and acid **8b** closely paralleled those for **3a** and **3b**. Thus, with the ruthenium and iron catalysts, ester **8a** gave primarily **9** as a mixture of epimers. The molybdenum catalyst afforded substantial amounts of lactone **10** (also as a mixture of epimers).[11] Similarly, acid **8b** yielded only the annulated γ-lactone **10** with all catalysts employed. As with the five-membered ring system, epimer ratios were reaction condition dependent.

Bridged carbocyclic compounds are also available by this procedure. Cyclization of dichloro ester **11a** (Scheme IV) with the ruthenium catalyst under the conditions used for **3a** and **8a** gave only two of four possible diastereomeric norbornyl α,γ-dichloro esters **12a** (36%) and **13a** (52%). Very similar results were obtained with $FeCl_2[P(OEt)_3]_3$ as catalyst. The stereochemistry of these products was established by ^1H NMR and by the fact that **13a** cyclizes to lactone 14 with $AgNO_3$, while **12a** can be recovered from similar treatment.

Likewise, acid **11b** cyclized to lactone **14** in high yield under the same reaction conditions. The structure of **14** was firmly established by X-ray crystallography.[12] We have monitored this reaction and found that acid **11b** cyclizes over 3 h to a mixture of exo acid **12b** and endo acid **13b**, which upon further heating (10–12 h) with the ruthenium catalyst is cleanly converted to the γ-lactone. Clearly, the exo α,γ-dichloro acid **12b** must epimerize during the transformation, and we suggest this occurs via reversible α-carboxylate radical formation (cf. **7**).

The methodology described here has several advantages over other free radical cyclizations.[6] Starting α,α-dichloro esters and acids are easily synthesized.[7,8] These cyclizations afford products which are more highly functionalized than those from radical processes terminated by hydrogen atom abstraction.[6,13] Also, only catalytic amounts of transition metal are required, unlike some metal-induced radical reactions requiring stoichiometric quantities of reagents.[14] We are currently investigating the scope of this reaction and its applications in natural product synthesis.

Acknowledgment. We are grateful to the National Institutes of Health (GM-32299) for financial support.

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[11] Stereochemistry of the epimers of **9** and **10** has not been unambiguously assigned.

[12] Details of the determination will be given in a full paper.

[13] For an interesting case, see: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489.

[14] Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron* **1986**, *42*, 3429 and references cited therein.

[15] Yields reported were determined by GLC. All compounds were isolated in pure form by preparative TLC in somewhat lower yields and were fully characterized spectroscopically.

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Total Synthesis of (+)-Dihydrocostunolide via Tandem Cope–Claisen Rearrangement[1]

Summary: The total synthesis of (+)-dihydrocostunolide via tandem Cope–Claisen rearrangement has been accomplished.

Sir: The total synthesis of germacrane sesquiterpenes[2] presents a formidable challenge.[3] The construction of a 10-membered ring with the control of stereochemistry is of paramount importance in this endeavor. We recently reported that the tandem Cope–Claisen rearrangement of **1a** provides a method for the construction of the cyclo-

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[1] Synthesis via Sigmatropic Rearrangements. 12. For previous paper in this series: Raucher, S.; Gustavson, L. M. *Tetrahedron Lett.* **1986**, *27*, 1557.

[2] Review: Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Fortschr. Chem. Org. Naturst.* **1979**, *38*, 47.

[3] Syntheses of dihydrocostunolide: (a) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736. (b) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *32*, 1717. (c) Fujimoto, Y.; Shimizu, T.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 2041. (d) Fujimoto, Y.; Shimizu, T.; Ohmori, M.; Tatsuno, T. *Chem. Pharm. Bull.* **1979**, *27*, 923. For a recent list of other syntheses of germacrane sesquiterpene, see: (e) Kitahara, T.; Mori, K. *J. Org. Chem.* **1984**, *49*, 3281, footnote 6. Recent synthesis of (±)-costunolide: (f) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.