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CuCl-catalyzed isomerization of *gem*-chlorofluorocyclopropanes into chlorofluoroalkenes

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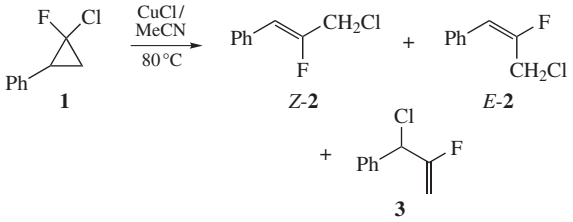
CuCl-catalyzed isomerization of *gem*-chlorofluorocyclopropanes into chlorofluoroalkenes occurs as a result of the ring opening accompanied by the migration of chlorine atom. In the case of vinyl- or cyclopropyl-containing substrates, chlorofluoroalkadienes are formed.

A common feature of *gem*-dihalogenocyclopropanes is their ability to undergo solvolytic and thermal cyclopropyl-allylic type ring-opening of the three-membered cycle.[1–3] Such reactions are induced by stoichiometric amounts of silver salts[1–3,4] or some other electrophilic reagents[3] or by heating[1–3,5] and lead to 2-haloallylic derivatives or 2-halo-1,3-dienes. *gem*-Dihalogenocyclopropanes can also thermally isomerize into 2,3-dihaloalkenes[1–3,6] *via* the cleavage of a C–C bond opposite to the dihalomethylene group and the migration of a halogen atom to the adjacent carbon atom. At the same time, reported examples of similar reactions for *gem*-chlorofluoro analogues are limited to the thermal rearrangements of strained bicyclic *gem*-chorofluorocyclopropanes[7–9] in high-boiling solvents and the isomerizations of *gem*-chlorofluoro(vinyl)cyclopropanes under gas-phase pyrolysis.[10] To the best of our knowledge no catalytic version of such processes has been published to date. Herein, we report the general procedure for CuCl-catalyzed transformation of *gem*-chlorofluorocyclopropanes† in aprotic solvents leading to corresponding chlorofluoroalkenes in 60–98% overall yields.



Scheme 1

In fact, heating of 1-chloro-1-fluoro-2-phenylcyclopropane **1** (*syn*:*anti* = 58:42) in acetonitrile in the presence of 0.1–1.0 equiv. CuCl at 80 °C leads mainly to stereoisomeric (*Z*)- and (*E*)-3-chloro-2-fluoro-1-phenylpropenes **2** and small amounts of 3-chloro-2-fluoro-3-phenylpropene **3** (Scheme 1, Table 1).‡ Note that in the absence of CuCl no isomerization of **1** was observed even after prolonged heating.

The conversion of **1** and the ratio between the resulting isomeric products depend on reaction time and the amount of CuCl used (see Table 1). In this case, the *syn* and *anti*-isomers of **1** exhibited noticeably different reactivity. For example, with the use of 0.2–0.5 equiv. of CuCl the conversion of *syn*-**1** after

† *General procedure for the synthesis of* gem-*chlorofluorocyclopropanes.* The starting *gem*-chlorofluorocyclopropanes were synthesized as reported[10] by the addition of chlorofluorocarbene, which was generated from dichlorofluoromethane under the action of KOH under the conditions of phase-transfer catalysis, to corresponding alkenes. Typically, 130 g of a 50% aqueous solution of KOH (1.2 mol) were added to a solution of 0.5 mol of an alkene, 0.7 mol of $CHCl_2F$ and 1.0 g of $BnEt_3NCl$ in 100 ml of CH_2Cl_2 cooled to –5 °C with intense stirring for 1 h keeping the temperature of the reaction mixture in a range of 0–5 °C. Thereafter, the reaction mixture was additionally stirred for 8 h and diluted with water. The organic layer was washed with water and dried with $CaCl_2$, and *gem*-chlorofluorocyclopropanes were separated by distillation.

‡ *General procedure for the isomerization of* gem-*chlorofluorocyclopropanes.* *Method A*. A mixture of 2–4 mmol of *gem*-chlorofluorocyclopropane and 0.1–2 mmol of CuCl in 2 ml of MeCN was stirred under argon at 80 °C for 7–90 h depending on the experiment (GLC control). After completion of the reaction, the mixture was diluted with 20 ml of CH_2Cl_2, washed with water (3×50 ml) and dried with Na_2SO_4. The solvent was distilled off, and the residue was analyzed by GLC, NMR spectroscopy, and GS/MS.

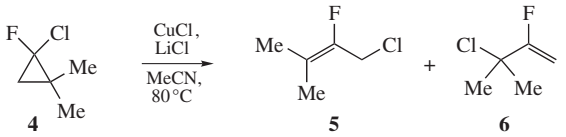
Table 1 Isomerization of **1** (*syn*:*anti* = 58:42) in the presence of CuCl or CuCl/LiCl depending on reaction time, catalyst amount, and solvent.

Entry	Amount of **1**/mmol	Amount of CuCl/mmol	Solvent	*T*/°C	Amount of LiCl/mmol	Time/h	Composition (mol%, GLC)				
							syn-**1**	*anti*-**1**	*Z*-**2**	*E*-**2**	**3**
1	2.0	0.0	MeCN	80	0.0	48	58	42	0	0	0
2	2.0	0.4	MeCN	80	0.0	7	28	3	51	18	1
3	4.0	0.8	MeCN	80	0.0	24	1	0	68	30	1
4	2.0	1.0	MeCN	80	0.0	7	18	0	56	25	1
						50	0	0	65	33	1
5	2.0	2.0	MeCN	80	0.0	7	0	0	64	33	3
						80	0	0	89	8	3
6	2.0	1.0	MeCN	80	2.0	7	4	0	64	31	1
						50	0	0	79	19	1
7	4.0	0.4	MeCN	80	0.4	20	0	0	84	15	1
8	2.0	1.0	diglyme	120	2.0	4	0	0	86	9	2
9	2.0	1.0	dioxane	110	2.0	6	0	0	66	29	4

7 h was 52–69% at the almost complete conversion of *anti*-**1**, whereas prolongation of the processing to 20–50 h or the use of 1.0 equiv. of CuCl for 7 h resulted in the quantitative conversion of both of the isomers. Entry 5 (Table 1) demonstrates that further prolongation after achievement of the complete conversion of **1** leads to the rise of the fraction of the more thermodynamically stable (*Z*)-isomer **2**, whose concentration grew from 64 to 89% with a drop of (*E*)-isomer **2** from 33 to 8%. In all cases, the relative concentration of isomer **3** did not exceed 1–4%. It is likely that the reversible isomerization of chlorofluorophenylpropenes *Z*-**2**, *E*-**2** and **3** occurs in the course of reaction through the 1,3-chlorine shift.

With the use of diglyme or dioxane as a solvent in the presence of 0.5 equiv. of CuCl, no noticeable transformations of **1** were observed even at 110–120 °C for 24 h; this was likely due to the insolubility of CuCl in these solvents. However, the addition of lithium chloride to CuCl caused its dissolution and consequently, full isomerization of **1** within 4–6 h (entries 8, 9). Note that, for analogous reactions in acetonitrile, which dissolves CuCl relatively well, the addition of LiCl also accelerated the reaction, although the effect of LiCl in this case was not so pronounced (*cf.* entries 4 and 6).

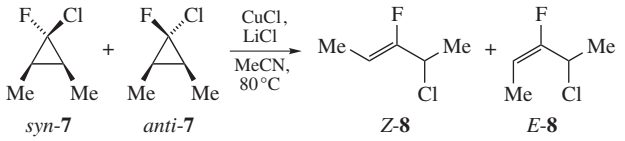
The developed catalytic isomerization turned to be a general method, which can be used for analogous transformations of methyl-, vinyl- and cyclopropyl-substituted *gem*-chlorofluorocyclopropanes. Thus, heating of 1-chloro-1-fluoro-2,2-dimethylcyclopropane **4** in acetonitrile in the presence of 0.05 equiv. of CuCl and 0.05 equiv. of LiCl at 80 °C for 30 h yielded almost quantitatively a mixture of 1-chloro-2-fluoro-3-methylbut-2-ene **5** and 3-chloro-2-fluoro-3-methylbut-1-ene **6** in a ratio of 3 : 1 (Scheme 2).



4 **5** **6**

Scheme 2

Under analogous conditions, 1-chloro-1-fluoro-*cis*-2,3-dimethylcyclopropane **7** (*syn* : *anti* = 68 : 32) underwent isomerization with the formation of (*Z*)- and (*E*)-4-chloro-3-fluoropent-2-enes **8** (Scheme 3, Table 2).



syn-**7** *anti*-**7** *Z*-**8** *E*-**8**

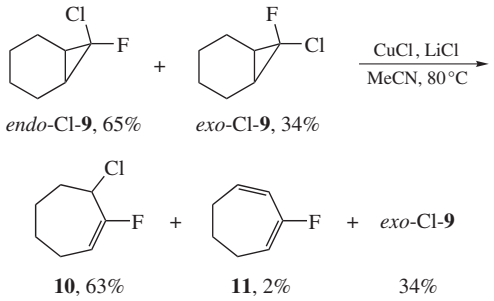
Scheme 3

In this case, as can be seen in Table 2, the rate of conversion of *anti*-**7** was much higher than that of *syn*-**7**. Thus, the complete conversion of *anti*-**7** at 80 °C was achieved within 20 h, whereas the complete conversion of *syn*-**7** required 90 h.

Differences in reactivity were even more pronounced in the case of the rearrangements of stereoisomeric 7-chloro-7-fluoro-bicyclo[4.1.0]heptanes **9**. Thus, *endo*-Cl isomer was completely converted into chlorofluorocycloheptene **10** and a small amount of fluorocycloheptadiene **11** (the product of its dehydrochlorination) upon the heating of a mixture of 65% *endo*-Cl-**9** and 34% *exo*-Cl-**9** in acetonitrile in the presence of 0.1 equiv. of CuCl and 0.1 equiv. of LiCl for 24 h (Scheme 4). Under these conditions, *exo*-Cl-**9** remained essentially intact.

Table 2 Isomerization of **7** (*syn* : *anti* = 68 : 32) in the presence of 0.05 equiv. of CuCl, 0.05 equiv. of LiCl in MeCN at 80 °C.

Time/h	Composition, mol% (GLC)			
	syn-**7**	*anti*-**7**	*Z*-**8**	*E*-**8**
20	26	0	61	11
46	13	0	73	10
70	5	0	85	8
90	1	0	86	7



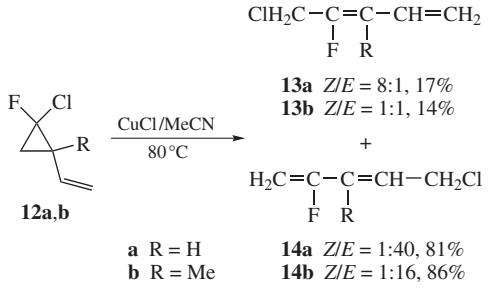
endo-Cl-**9**, 65% *exo*-Cl-**9**, 34%

10, 63% **11**, 2% 34%

Scheme 4

Note that the previously described[7] thermal transformations of *endo*-Cl-**9** in quinoline at 200 °C occurred with the formation of only cycloheptatriene, and the isomerization products that were formed in our catalytic reactions were not observed.

It is known[10] that the gas-phase thermal rearrangements of 2-chloro-2-fluoro-1-vinylcyclopropanes **12a**,**b** occur nonselectively because of the competitive processes of vinylcyclopropane-cyclopentene and cyclopropyl-allyl transformations.[10] On the contrary, we found that catalytic isomerization of **12a**,**b** in the presence of 0.1–0.4 equiv. CuCl proceeds with the formation of only acyclic chlorofluorodienes **13** and **14** (Scheme 5).



12a,**b**

a R = H **14a** *Z*/*E* = 1:40, 81%
b R = Me **14b** *Z*/*E* = 1:16, 86%

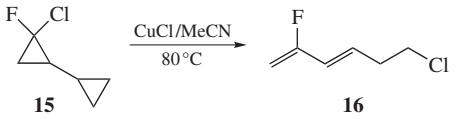
Scheme 5

In this case, the expected typical products of cyclopropyl-allyl isomerization, corresponding chlorofluorodienes **13a**,**b**, were obtained in small amounts (14–17%), and the main products were 5-chloro-2-fluoropenta-1,3-dienes **14a**,**b** (81–86%). The latter may be formed in the course of the isomerization of **12a**,**b** through cyclopropane ring opening with the migration of chlorine atom to the terminal carbon atom of the vinyl group or as a result of the isomerization of chlorofluorodienes **13a**,**b** through the 1,5-chlorine shift.

Interesting results were obtained in the case of 2-chloro-2-fluoro-1,1′-bi(cyclopropyl) **15** (*syn* : *anti* = 48 : 52, 0.5 equiv. of

Method B. A mixture of 40–80 mmol of cyclopropane, 4–8 mmol of CuCl, 4–8 mmol of LiCl and 20 ml of MeCN was heated under argon in a glass liner in a steel autoclave at 80 °C for 24–96 h (GLC control). After completion of the reaction, the mixture was diluted with 50 ml of CH_2Cl_2, washed with water (3×50 ml) and dried with Na_2SO_4. The solvent was distilled off using a rotary evaporator or by fraction distillation at atmospheric pressure, and the residue was distilled.

For full experimental details and characterization data for all compounds, see Online Supplementary Materials.



15 **16**

Scheme 6

CuCl, 80 °C, 6 h), affording (3*E*)-6-chloro-2-fluorohexa-1,3-diene **16** in 60% yield as the only product (Scheme 6).

In summary, the catalytic isomerization of phenyl-, alkyl-, vinyl- and cyclopropyl-substituted *gem*-chlorofluorocyclopropanes can be readily performed in the presence of CuCl. In this case, the resulting chlorofluoroalkenes or chlorofluoroalkadienes containing a reactive allylic chlorine atom along with fluorine-containing 1,3-diene fragments can be further used for the preparation of various fluorine-containing functional alkenes and also for the diene synthesis of carbocyclic organofluorine compounds.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.01.006.

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