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Ring-Opening 1,3-Dichlorination of Donor–Acceptor Cyclopropanes by Iodobenzene Dichloride

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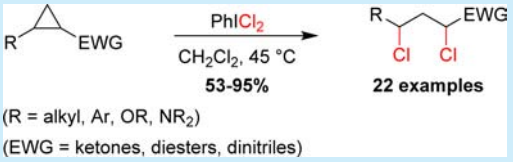
Supporting Information

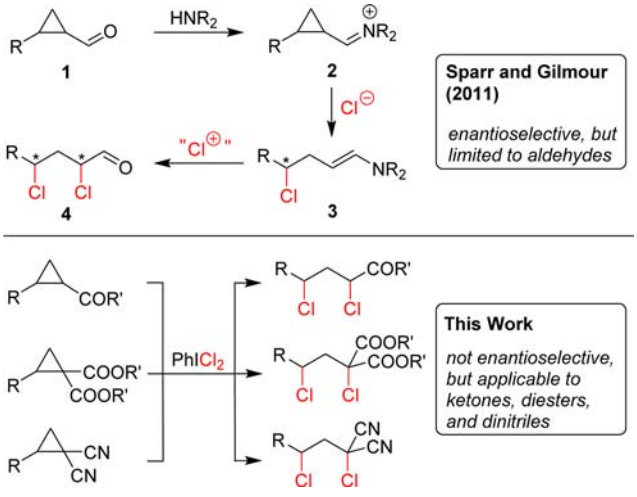
ABSTRACT: Donor–acceptor cyclopropanes are reacted with iodobenzene dichloride to afford ring-opened products bearing chlorine atoms in the 1- and 3-positions, adjacent to the donor and acceptor groups. A variety of different donors (e.g., alkyl, aryl, N, and O) and acceptor moieties (e.g., ketones, diesters, and dinitriles) are used.



The use of donor–acceptor (D–A) cyclopropanes as easily available building blocks in organic synthesis has flourished in the recent past.[1] Even though the groundwork was performed by Wenkert and Reissig[2] in the 1970s and 1980s, the field has been enjoying a marked renaissance for the past decade.[3,4] The capability of these highly polarized strained systems to undergo cycloadditions,[5] rearrangements,[6,7] and ring-opening reactions makes them attractive for heterocyclic chemistry, natural product syntheses,[8] and even medicinal chemistry.[9] Whereas cycloadditions and rearrangements of D–A cyclopropanes commonly increase the complexity of the compounds being utilized, ring-opening reactions transform the cyclic moiety into an open-chain system. Formally, a 1,3-addition of the reagent to the three-membered ring occurs. Promoted by Lewis acids which coordinate to the acceptor, nucleophiles commonly attack the emerging positive charge next to the donor while ring-opening takes place.[1] The resulting negative charge associated with the acceptor substituent is typically captured by a proton. A variety of heteroatoms as well as carbon nucleophiles (e.g., phenols, amines, azides, and indoles) have been successfully used for this purpose.[10−13] Only rare examples are known in which two non-hydrogen substituents were attached to the 1- and 3-positions next to the donor and acceptor.[1]

Of course, it has been known for more than 40 years that elemental chlorine and bromine react with cyclopropanes in an unselective reaction, leading to 1,3-disubstituted acyclic products together with 1,2-substituted isomers obtained by rearrangement.[14] Recently, Sparr and Gilmour have cleverly designed an enantioselective 1,3-dichlorination with cyclopropanes **1** bearing formyl groups (Scheme 1).[15] The key to this was a formal umpolung making use of a secondary amine in order to use nucleophilic chloride for γ-functionalization to afford intermediate **3** and electrophilic chlorine for α-attack. After hydrolysis, the 1,3-dichlorinated aldehyde **4** was obtained. Because of the obligatory enamine formation, this approach was restricted to reactive formyl groups as substituents. Accordingly, we have chosen to investigate a simple 1,3-dichlorination process[16] that might be compatible with a wider range of accepting moieties that are unable to generate enamine

Scheme 1. Enantioselective 1,3-Dichlorination Method of Sparr and Gilmour for Aldehydes and Our Approach for a Wider Range of Acceptor-Substituted Cyclopropanes



intermediates (Scheme 1). We anticipated that a hypervalent iodine reagent[17] such as $PhICl_2$ might be the reagent of choice for this purpose, since it formally bears both Cl^+ and Cl^- and in addition displays Lewis acidic character. Radical pathways are also often discussed for this compound.[17]

At the outset of our studies, we employed D–A cyclopropane **5a** to explore suitable conditions for the anticipated ring-opening 1,3-dichlorination to yield **6a**. We employed an aliphatic ketone with a donor of minimal electron-donating ability in order to test the desired reaction. Whereas DMF and toluene only afforded traces of the product (Table 1, entries 1–3), dichloromethane proved to be the solvent of choice for this process. The best results were obtained using a slight excess of the hypervalent iodine(III) reagent (1.2 equiv) at 45 °C with a reaction time of 16 h (entry 5). Shorter reaction times at 45 °C

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Table 1. Optimization of the $PhICl_2$-Mediated 1,3-Dichlorination[a]

entry	solvent	temp (°C)	time (h)	yield (%)
1	toluene	60	16	0
2	toluene	120	16	traces
3	DMF	100	16	0
4	CH_2Cl_2	45	16	89[b]
5	CH_2Cl_2	45	16	93
6	CH_2Cl_2	45	4	43
7	CH_2Cl_2	rt	48	11

[a]Reaction conditions: **5a** (0.2 mmol), $PhICl_2$ (0.24 mmol), solvent (3 mL); yields represent isolated 1,3-dichlorinated products; diastereomeric ratio 1:1. [b]$PhICl_2$ (0.4 mmol).

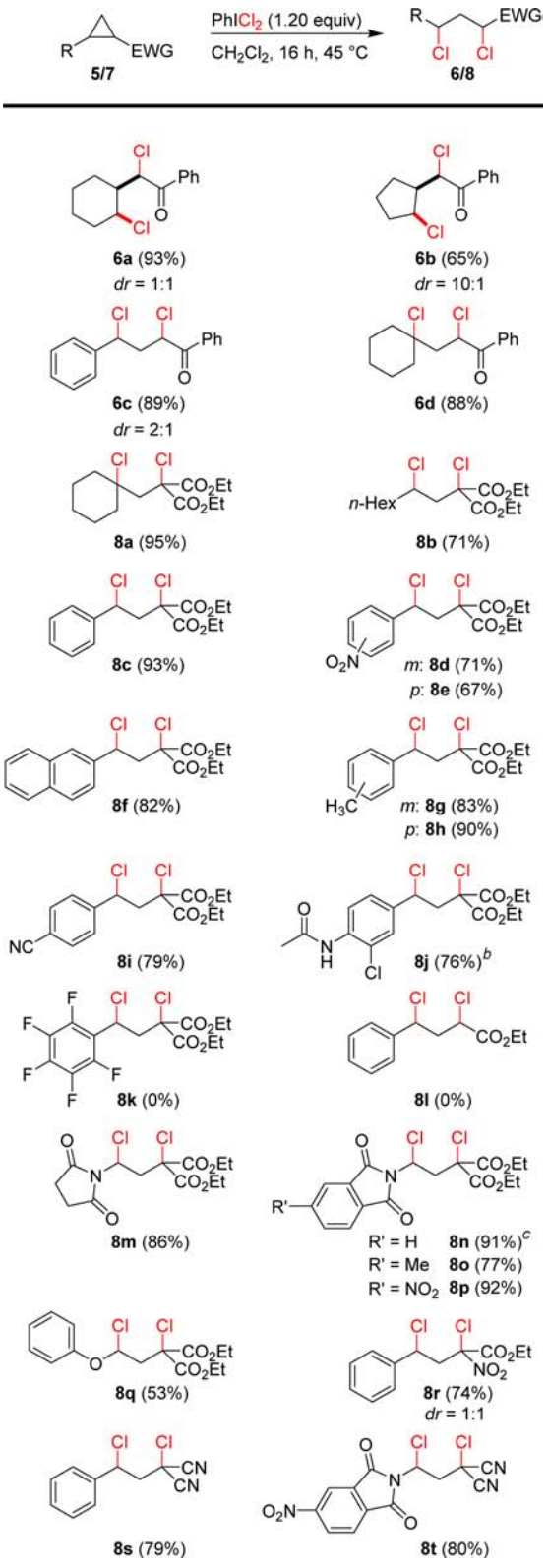
or reaction at room temperature (even with prolonged reaction times) gave only poor yields (entries 6 and 7).

With our optimized conditions in hand, we probed the scope of this 1,3-difunctionalization by changing both donor and acceptor moieties. Besides ketones, we also employed carboxylic esters and diesters as well as a nitroester and some dinitriles as electron-withdrawing groups (Scheme 2). Not only the weakly donating aliphatic groups were tested as donors, but also various arene units differing strongly in electron-donating ability, and also nitrogen and oxygen donors. In total, we subjected 24 D−A cyclopropane derivatives to the reaction conditions. The transformation proceeded smoothly, with ketones furnishing the desired products in yields of 65−93%. Since cyclopropyl ketones with strongly electron-donating arene units or heteroatoms such as oxygen or nitrogen as donors tend to rearrange easily to the five-membered ring systems, we abstained from investigating the dichlorination reaction with these systems.[18] As a further type of electron-withdrawing substituent, we employed carboxylic esters. Whereas two ester groups as acceptors are commonly sufficient to trigger the ring-opening process in concert with aromatic and aliphatic groups, a perfluoroarene as a strongly electron-withdrawing group completely prevents the scission of the three-membered ring. This result can be rationalized in terms of the donor/acceptor strength of the various residues. In contrast, electron-withdrawing nitro and cyano groups attached in the *p*-position are unable to completely counter the donating ability of the arene moiety and do not significantly decrease the yield. In contrast, the electron-withdrawing power of only one ester group is not sufficient to polarize a cyclopropane to an adequate extent for ring cleavage to take place. Oxygen and nitrogen donors protected as imide moieties also act as perfectly suitable residues to initiate the desired 1,3-dichlorination, as examples **8m**−**8q** demonstrate.

The last examples in Scheme 2 reveal that one of the two ester groups can also be exchanged for a nitro functionality, affording compound **8r** in 74% yield. Since cyano functionalities display the same oxidation state as carboxylic acids or esters, we were keen to test also two examples of corresponding dinitriles. Indeed, the reaction proceeded smoothly and yielded the respective ring-opened chlorinated dinitriles **8s** and **8t**.

To prove the 1,3-dichlorination unambiguously, we obtained single crystals of **8n**. The X-ray crystallographic analysis[19,20]

Scheme 2. 1,3-Dichlorination of Donor−Acceptor Cyclopropanes by Iodobenzene Dichloride[a]



[a]All yields represent isolated 1,3-dichlorinated products. [b]Monochlorination of the aromatic ring could not be suppressed. [c]Methylester was used.

confirmed the anticipated structure involving a quaternary carbon atom and another carbon bearing the nitrogen and the

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second chlorine. The molecular structure of this compound is depicted in Figure 1.

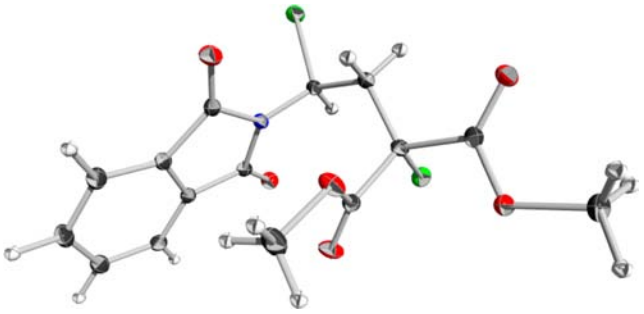
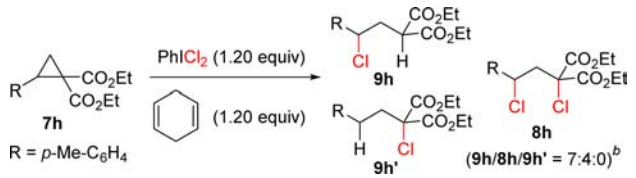


Figure 1. Molecular structure (50% ellipsoid probability) of **8n** in the solid state. Oxygen atoms are shown in red, nitrogen atoms in blue, and chlorine atoms in green.[20]

In order to obtain insights as to whether a radical or an ionic process takes place, we performed several experiments. Initial screening results revealed that the reaction is much slower in the dark. Thus, radical inhibitors such as TEMPO and BHT were added to the reaction mixture. Both additives completely inhibited the reaction, and starting material was reisolated. As a side product of the latter reaction we were able to detect a BHT dimer, implying that Cl radicals abstracted hydrogen, thus paving the way for dimerization. In a further experiment compound **7h** was subjected to the typical conditions of our 1,3-dichlorination, but 1,4-cyclohexadiene was added to the reaction mixture.[21]

Because of facile aromatization this homoconjugated compound is capable of delivering H radicals. Our notion was to intercept a monochlorinated radical intermediate and to elucidate which position is initially chlorinated. Indeed, besides the dichlorinated product **8h** a single monochlorinated species **9h** was unequivocally detected via GC-MS. Its fragmentation pattern clearly indicated that Cl was located next to the donor (Scheme 3). The regioisomer **9h′** was not found.

Scheme 3. Trapping Experiment with 1,4-Cyclohexadiene[a]

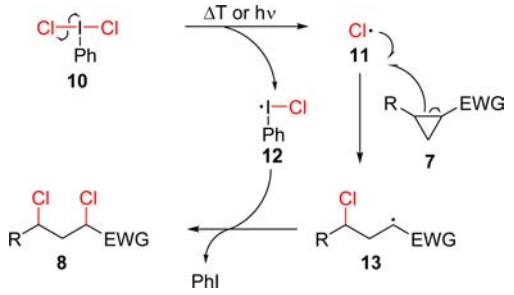


[a]Reaction conditions: **7h** (0.11 mmol), $PhICl_2$ (0.13 mmol), 1,4-cyclohexadiene (0.13 mmol), CH_2Cl_2 (3 mL), 45 °C, 16 h. [b]Ratio determined by GC-MS.

These observations led us to propose a simple mechanism as depicted in Scheme 4. Thermolysis or photolysis of $PhICl_2$ leads via homolytic cleavage of the I−Cl bond to the release of Cl atoms **11**. These highly reactive species attack the strained three-membered ring **7**. The weakest bond of the cyclopropane, the bond between the adjacent donor and acceptor moieties, breaks, and a delocalized radical is formed that either abstracts Cl from $PhICl_2$ or combines with a Cl atom **11** or with a PhICl radical **12** releasing PhI.

In conclusion, we have developed a novel and broadly applicable 1,3-dichlorination reaction. A variety of donor−acceptor cyclopropanes were converted with the readily

Scheme 4. Proposed Reaction Mechanism



available iodobenzene dichloride into the corresponding ring-opened 1,3-dichlorinated compounds. Besides aliphatic residues, oxygen and nitrogen and also aromatic systems can be successfully employed as donors, unless their electron-releasing ability is too poor. As acceptors, a wide range of carbonyl derivatives such as ketones, diesters, and dinitriles can be utilized to initiate the process, whereas a single ester moiety proved to be insufficient to trigger the process. It is expected that such a simple 1,3-dichlorination reaction will inspire the design of other ring-opening 1,3-difunctionalization reactions using hypervalent iodine reagents.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, analytical data for all new compounds, and crystal data (CIF) for **8n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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