Cyclopropanes

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# One Pot, Two Phases: Iron-Catalyzed Cyclopropanation with In Situ Generated Diazomethane**

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biphasic reaction · cyclopropanation · diazomethane · iron · porphyrins

Cyclopropyl units have proven to be important structural elements in organic chemistry. They occur in numerous natural products and active substances including terpenes, fatty acids, and unusual nonproteinogenic amino acids.[1] Cyclopropyl residues are frequently used in medicinal chemistry to fix the stereochemistry of substituents or to provide the middle ground between the space requirement of a methyl and an isopropyl moiety. Being flexible in their reactivity, cyclopropanes serve as versatile building blocks for the synthesis of a variety of heterocyclic frameworks.[2] Both the ring strain and the distinct "double-bond character" of the three-membered ring play a crucial role in the reactivity of cyclopropane rings.[3]

Methylene carbene, which can be generated in situ from highly toxic and explosive diazomethane, is the smallest and, therefore, a very important $C_1$ building block. For decades, the preparation of diazomethane has been achieved by the use of nitrosoamides. Under basic conditions diazald (**1**), *N*-nitroso-*N*-methylurea (**2**), and methylnitronitrosoguanidine (**3**) tend to release diazomethane (**4**; Figure 1). However, compounds **2** and **3** are carcinogenic and, therefore, strict safety precautions have to be taken when carrying out the indispensable work-up procedures, for example, distillations. Joints and small scratches on the glass apparatus also have to be avoided to reduce the danger of explosion.[4]

Recently, Morandi and Carreira established a new procedure, which minimized the risk as well as the time and effort for cyclopropanation with diazomethane.[5] They employed a water-soluble diazald derivative **5**, which released diazomethane on treatment with aqueous 6 molar potassium hydroxide solution. The liberated diazomethane subsequently transfers into the organic layer of the two-phase system, where a suitable catalyst mediates the [2+1] cycloaddition with alkenes **6** (Scheme 1).

The best catalytic effect under these strongly alkaline conditions was observed using an air-stable iron(III)-porphyrin complex (FeTPPCl; **7**); the corresponding rhodium, ruthenium, cobalt, palladium, and copper complexes showed lower activity. In 1995, Woo and co-workers had already demonstrated that iron can be used in cyclopropanation reactions and, hence, can serve as an alternative for the expensive and often toxic precious metals.[6] However, it should be remembered that, on the other hand, the required porphyrin ligand is also a cost factor.

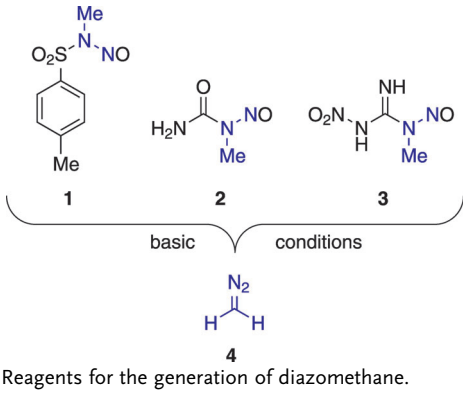
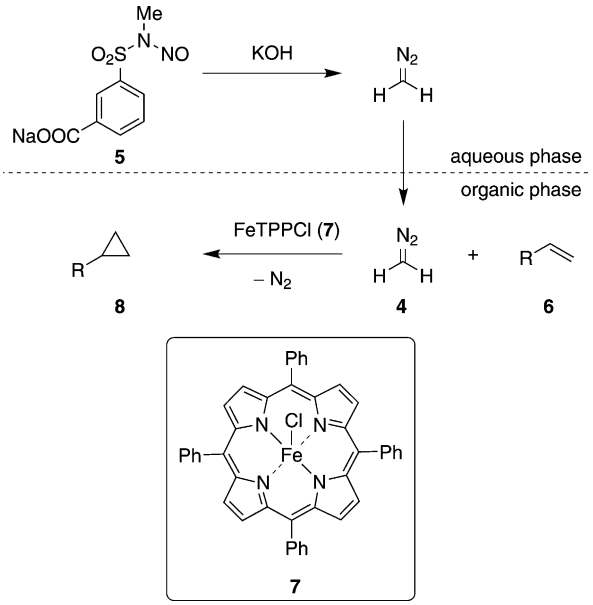



***Figure 1.*** Reagents for the generation of diazomethane.




***Scheme 1.*** Two-phase model for the iron-porphyrin-catalyzed cyclopropanation.

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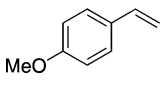
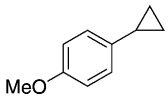
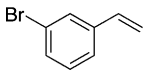
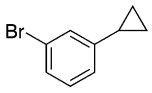
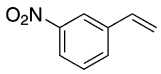
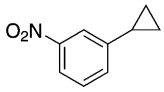
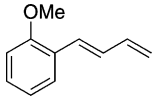
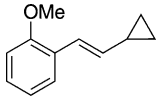
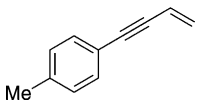
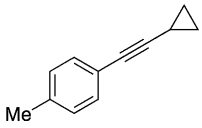
To test the scope of their reaction, Morandi and Carreira employed both electron-rich and electron-poor as well as halogenated styrene derivatives. Furthermore, phenyl-substituted dienes and the corresponding enyne-containing substrates could be used, which generally resulted in excellent yields (Table 1). Mechanistic studies have revealed that the

***Table 1:*** Selected examples for the iron-catalyzed cyclopropanation of in situ generated diazomethane.

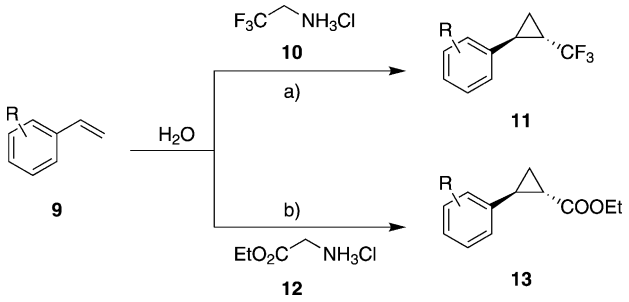
| Entry | Substrate **6** | Product **8** | Yield [%] |
|---|---|---|---|
| 1[a] |  |  | 89 |
| 2[a] |  |  | 81 |
| 3[b] |  |  | 64 |
| 4[b] |  |  | 78 |
| 5[b] |  |  | 74 |

[a] **7** (2 mol%), **5** (3.0 equiv), **6** (0.22 mmol), KOH (6 M, 2 mL). [b] **7** (3 mol%), **5** (5.0 equiv), **6** (0.22 mmol), KOH (6 M, 3 mL).

two-phase model depicted in Scheme 1 provides the optimal reaction conditions. The use of a hydrophilic substrate or a water-soluble catalyst results in a sharp deterioration of the yield. The addition of ethanol to form a homogeneous mixture leads to poor conversion under otherwise identical conditions.

Recently, a slightly different approach for the safe handling of diazomethane was reported by Kim and co-workers. They utilized a microreactor consisting of two reaction channels separated by a polydimethylsiloxane membrane. Diazomethane generated in situ from diazald (**1**) was able to pass through the membrane to enter the second channel of the microreactor. The use of such a continuous flow system thus prevented direct exposure to harmful diazomethane.[7] An increased expense would be anticipated for substituted diazo congeners (cf. Scheme 2) because of the need for a different membrane, which would have to be adjusted for the respective reagent.

In contrast, the method described by Morandi and Carreira also allows the conversion of alkenes with in situ generated trifluoromethyldiazomethane or ethyl diazoacetate to synthesize vicinally substituted cyclopropanes of type **11**[8] and **13**,[9] respectively. Carreira and co-workers again made use of the fact that the FeTPPCl catalyst tolerates the presence of water, which is necessary for the preparation of the respective diazo compounds (Scheme 2). The advantage of this reaction pathway is the direct reaction of the carbene precursor, generated by acid-catalyzed diazotization, with the available substrate. This diazotization/cyclopropanation se-




***Scheme 2.*** Further FeTPPCl-catalyzed cyclopropanations in water: a) **7** (3 mol%), 4-dimethylaminopyridine (10 mol%), **10** (1.5 equiv), $NaNO_2$ (1.8 equiv), NaOAc (20 mol%), $H_2SO_4$ (10 mol%), RT; b) **7** (1 mol%), **12** (2.0 equiv), $NaNO_2$ (2.4 equiv), HOAc (15 mol%), 40 °C.

quence is even more powerful in terms of the yield and diastereoselectivity compared to an older method developed by Barrett et al. based on rhodium-porphyrin catalysis.[10]

The described iron-catalyzed cyclopropanation, which makes use of in situ generated diazo compounds in aqueous media, offers important advantages over the methods already known. Safe protocols that require little expense and deliver excellent yields are in demand by organic chemists. Thus, the studies performed by Carreira and co-workers are not only important, but have trend-setting potential. However, it would be highly desirable to develop a method to generate diazomethane under less basic conditions, which would also allow more sensitive substrates to be used. It would be interesting whether this concept could be extended to other double-bond systems, for example, higher substituted olefins or enol ethers, and whether modified catalysts would lead to asymmetric cyclopropanation reactions.

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