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Iron Catalysis

Iron-Catalyzed Cyclopropanation with Trifluoroethylamine Hydrochloride and Olefins in Aqueous Media: In Situ Generation of Trifluoromethyl Diazomethane**

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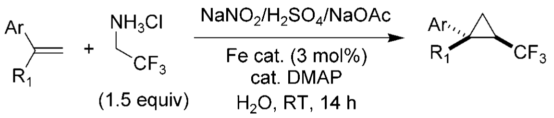
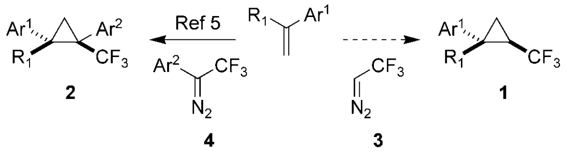
Our research group has been interested in the development of novel small-ring modules because of their potential ability to influence the pharmacokinetic properties of candidates in beneficial ways for the drug discovery process.[1] Despite the increasing importance of organofluorine compounds, there are relatively few practical methods available for their ready synthesis in the medicinal chemistry laboratory. Among the various fluorinated groups, the trifluoromethyl group has become increasingly important;[2] indeed, there have been recent advances in the development of chemical methods for the introduction of trifluoromethyl moieties that are noteworthy.[3] It is striking, however, that the use and preparation of trifluoromethyl-substituted cyclopropanes is rare, which is likely correlated to the absence of practical, general methods for their synthesis. Herein, we describe a process that furnishes trifluoromethyl-substituted cyclopropanes from styrenes by a diazotization/carbene generation/cyclopropanation sequence [Eq. (1)]. The active agent is generated in situ from $F_3CCH_2NH_2\cdot HCl$ and $H^+/NaNO_2$ in aqueous media under reaction conditions that are compatible with a simple iron–porphyrin catalyst. Thus, the method allows the diastereoselective preparation of substituted cyclopropanes without prior formation, isolation, or handling of trifluoromethyl diazomethane.



As reactive intermediates, carbenes provide access to valuable cyclopropanes upon their reaction with olefins.[4] The most general and widely used method for the generation of carbenes or carbenoids employs diazoalkanes. As shown in Scheme 1, there are two complementary approaches to the synthesis of trifluoromethyl-substituted cyclopropanes from olefins that give two distinct product classes **1** and **2**. In one of these methods, excess olefin reacts with carbenes that are doubly stabilized with donor/acceptor substituents to give adducts **2**.[5] The implementation of this method in the synthesis of a wide range of cyclopropanes requires the preparation of a collection of different diazoalkanes. The second method gives access to adducts with a different substitution pattern and only requires access to F_3CCHN_2. We have focused on the second approach because there is considerably less synthetic work of this class of cyclopropane compounds and it involves working with a single diazoalkane.



Scheme 1. Preparation of trifluoromethyl cyclopropanes.

Trifluoromethyl diazomethane is handled only with great difficulty because of its untoward physical properties (gas at room temperature) as well as the well-known toxicity and safety risks associated with this class of reagent.[6] It is generally appreciated that the diazoalkane precursors of reactive carbenes are often considerably safer to handle in aqueous media. Consequently, in addition to the many beneficial aspects of water as a reaction solvent,[7] conducting transformations that involve unwieldy reagents or intermediates under operationally safer, aqueous regimes would be advantageous. The broad realization of such transformations necessitates the development of reagents and catalysts compatible with water and suitable reaction conditions for the generation of the reactive intermediate (alkaline/acidic or reductive/oxidative). Accordingly, we embarked on the study of an approach relying on the generation of F_3CCH carbene in situ from $F_3CCH_2NH_2\cdot HCl$ (1 g $\approx$ 6€) in water to furnish trifluoromethyl-substituted cyclopropanes.

The few examples in the literature that describe the synthesis of trifluoromethyl-substituted cyclopropanes **1** rely on the use of F_3CCHN_2.[8] One of these prescribes the use of a fivefold excess of olefin and preformed diazoalkane that had been distilled twice into cold traps at −80° and −196 °C (32 % yield). The second procedure describes the synthesis of gaseous F_3CCHN_2 that is bubbled into a neat mixture of

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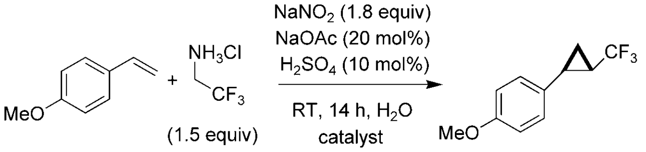
alkene and catalyst. In it the olefin is the limiting reagent, albeit with a large excess of the diazoalkane (5–10 equiv). The research groups of Charette and Braddock have reported the generation of ethyldiazoacetate in situ from the corresponding amine and its use in the rhodium-catalyzed cyclopropanation of styrene to give moderate yields (45–62 %) and no diastereoselectivity (1.5–1:1).[9] Inspired by this work, we decided to explore the generation of F_3CCHN_2 in situ in the presence of olefins with catalysts in aqueous media. With respect to the latter, we were particularly interested in investigating simple complexes of iron. The recent interest in this metal stems from the obvious advantages, namely its ready availability along with its relatively low price and toxicity. Of additional interest is that its use in the synthesis of fine chemicals is still relatively unexplored when compared to late-transition metals.[10]

We commenced our investigations using the commercially available iron–porphyrin complex [Fe(TPP)Cl] (TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine), which is known to be a robust catalyst in carbene-transfer processes.[11] In the experimental set-up, a mixture of test substrate (4-methoxystyrene), $F_3CCH_2NH_2\cdot HCl$ (1.5 equiv), H_2SO_4 (10 mol %), and NaOAc (20 mol %) at ambient temperature was treated with an aqueous solution of $NaNO_2$ (0.8 M, 1.8 equiv) that was delivered by a syringe pump. The trial run that employed [Fe(TPP)Cl] and catalytic DMAP[12] afforded the trifluoromethyl-substituted cyclopropane as a single *trans* diastereomer in 89 % yield (Table 1, entry 1). Importantly, as little as 1.5 equivalents of trifluoroethyl amine hydrochloride was needed for full consumption of the olefin, which bodes well for the use of valuable substrates. Notably, the same reaction performed in a water/toluene (5:1) mixture afforded product in only 50 % yield. Thus, the reaction worked better in the absence of an organic solvent; it is possible that it proceeds "on" water[13] and that this leads to preferential reaction of the metal–carbene with the organic substrate.[14] Lowering the catalyst loading to 1 mol % led to a diminished 70 % yield of the isolated product (Table 1, entry 2). We subsequently turned to examining a cobalt–porphyrin catalysts [Co(TPP)], because they have been shown by Chen and Zhang to be more active than iron–porphyrins in the cyclopropanation reaction of olefins with ethyl diazoacetate.[15] Under otherwise identical reaction conditions, only partial conversion was observed, and the product was formed as a single diastereomer (Table 1, entry 3). As shown in Table 1, the corresponding [Ru(TPP)CO] catalyst was less efficient than [Fe(TPP)Cl] and furnished the product with a lower d.r. (86:14; Table 1, entry 4).

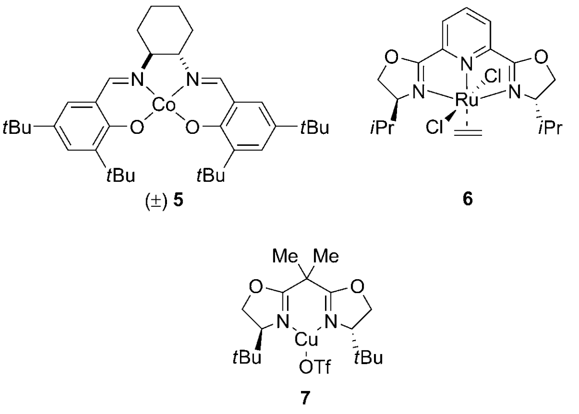
Table 1: Scope with diverse catalysts.[a]



Entry	Catalyst	Loading [mol %]	d.r.[b]	Yield [%][c]
1	[Fe(TPP)Cl][d]	3	> 95:5	89
2	[Fe(TPP)Cl][d]	1	> 95:5	70
3	[Co(TPP)][d]	3	> 95:5	50
4	[Ru(TPP)CO]	3	86:14	56
5	**5**[e]	5	> 95:5	51
6	**6**	5	–	n.r.
7	[$Rh_2(esp)_2$]	1.5	1:1	74
8	**7**	5	–	n.r.

[a] General procedure: alkene (0.22 mmol, 1 equiv), H_2O (1.3 mL). [b] Determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product. [d] DMAP (3 equiv relative to catalyst). [e] *N*-methylimidazole (10 mol %). DMAP = 4-dimethylaminopyridine, n.r. = no reaction.

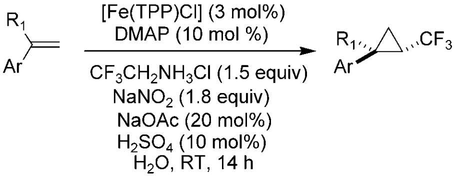
Nonporphyrin-based complexes were then examined (Scheme 2). (±)-Salen–cobalt complex **5**[16] afforded the product in 51 % yield and > 95:5 d.r (Table 1, entry 5). Complex **6** developed by Nishiyama and co-workers is a well-known catalyst for cyclopropanation and has been shown to be catalytically active in water.[17] Unfortunately, under the reaction conditions necessary for the formation of the diazoalkane in situ, none of the desired product was formed (Table 1, entry 6). Two of the most extensively used metals for olefin cyclopropanation were examined, namely, rhodium and copper. Du Bois's [$Rh_2(esp)_2$][18] furnished product in 74 % yield, albeit with 1:1 d.r (Table 1, entry 7). Interestingly, the Cu–BOX[19] complex **7** failed to give any traces of adduct (Table 1, entry 8). On the basis of these screening results, we decided to focus on the iron catalyst.

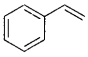
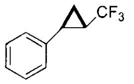
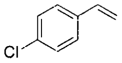
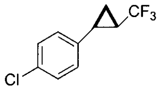
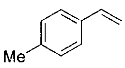
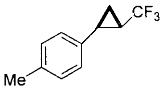
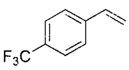
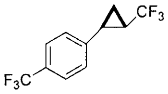
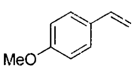
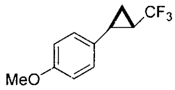
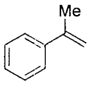
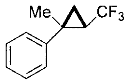
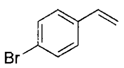
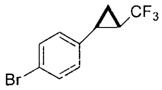
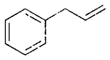
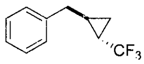


Scheme 2. Structures of nonporphyrin catalysts tested. Tf = trifluoromethanesulfonyl.

The styrene derivatives studied to date have proven to be excellent substrates for the transformation, leading to product in high yield as a single *trans* diastereomer, as assayed by analysis of the ^{1}H NMR spectra (Table 2). Even a disubstituted styrene derivative (Table 2, entry 6) afforded the product in good yield and diastereoselectivity. Extension of the method to alkyl-substituted olefins gave the product in 10 % yield (Table 2, entry 8). This poor yield might result from the lower reactivity of this class of olefin, thus making the decomposition of the metal–carbene faster than reaction with the olefin.[11] Although the process is currently limited to styrenes, it is important to note that most of the products in Table 2 are either unknown (Table 2, entries 2–4 and 6), have only been previously synthesized in low yields (24–50 %;

Table 2: Scope of the cyclopropanation.[a]



Entry	Alkene	Product	Yield [%][b]
1			86
2			85
3			99
4			77
5			89
6			86
7			95
8			10[c]

[a] General procedure: alkene (0.22 mmol, 1 equiv), H_2O (1.3 mL). [b] Yield of isolated product. [c] Yield based on ^{1}H NMR spectroscopy.

Table 2, entries 1,5,7), or with a poor d.r. (Table 2, entry 1).[8a,b] Thus the process described here is a clean and suitable way to access these new building blocks.

In summary, we have described a practical procedure for the diastereoselective preparation of trifluoromethyl-substituted cyclopropanes with the olefin partner as the limiting component (1 equiv). The reaction is made possible by the use of an iron catalyst that functions in aqueous media under reaction conditions required for in situ conversion of trifluoroethyl amine hydrochloride into the corresponding carbene species. The work thus merges a number of areas: water as a reaction medium, iron catalysis, access to reactive intermediates under operationally safer regimes, and synthesis of novel building blocks. Furthermore, the generation of trifluoromethyl diazomethane in situ and its demonstrated compatibility with diverse collection of catalysts could lead to the discovery and development of this versatile reagent in the preparation of trifluoromethyl-substituted building blocks by carbene-transfer reactions. Viewed in a broader context, the line of investigation described here highlights a wide range of opportunities in the study of reaction processes that involve access to reactive intermediates in water mediated by active catalysts from Group 8 and 9 metals (especially, Fe, Ru, Co, and Rh) under unusual conditions (acidic/alkaline/oxidative/reductive). Development of an asymmetric version and other carbene-transfer reactions are currently being pursued and will be reported as the results become available.

Experimental Section

General procedure for cyclopropanation: [Fe(TPP)Cl] (4.6 mg, 0.0066 mmol), DMAP (2.6 mg, 0.022 mmol), and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then trifluoroethylamine hydrochloride (45 mg, 0.33 mmol) and H_2SO_4 (1.2 μL, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with Ar. The alkene (0.22 mmol) was subsequently added, and $NaNO_2$ (27 mg, dissolved in 0.5 mL of water) was added by a syringe pump over 10 h. After 4 h, CH_2Cl_2 and water were added, and the water phase was extracted with CH_2Cl_2 (3 ×), dried with $MgSO_4$, and evaporated under reduced pressure. After analysis of ^{1}H NMR spectrum of the crude mixture (to determine the diastereoselectivity), the mixture was purified by column chromatography on silica gel (pentane/diethyl ether) to afford the product.

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Keywords: alkenes · cyclopropanation · homogeneous catalysis · iron · water

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