Cyclopropenation

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Rhodium-Catalyzed Cyclopropenation of Alkynes: Synthesis of Trifluoromethyl-Substituted Cyclopropenes**

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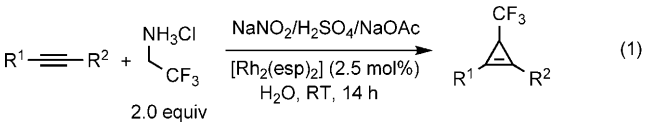
The trifluoromethyl group is a structural subunit that is extensively relied upon in the drug discovery process in medicinal chemistry. However, its introduction during the course of a synthesis remains a challenge for the organic chemist.[1] Trifluoromethyl-substituted cyclopropenes are potentially highly useful subunits whose synthesis and use have been only sparsely described in the literature.[2] We recently documented an iron-catalyzed domino diazotization/cyclopropanation of alkenes that utilizes $F_3CCH_2NH_2$·HCl as a precursor for the in situ generation of F_3CCHN_2 in water.[3] Herein, we report a rhodium-catalyzed cyclopropenation reaction of alkynes that proceeds with remarkable efficiency in aqueous media, to enable the synthesis of a previously unknown class of trifluoromethyl-substituted cyclopropenes [Eq. (1)]. Furthermore, we describe a range of possible transformations for these trifluoromethylcyclopropene building blocks.

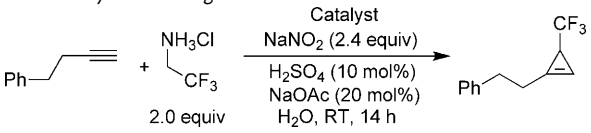


(1)

The in situ conversion of trifluoroethylamine hydrochloride into trifluoromethyldiazomethane in aqueous media permits safer handling of this reactive species in the laboratory.[4] To extend the uses of F_3CCHN_2, we have been interested in examining a number of other carbene-transfer reactions, as this could lead to the preparation of novel building blocks that contain the trifluoromethane unit. It is important to note that the development of these reactions require the identification of robust catalysts that are compatible with the strongly oxidizing and acidic conditions that are required for the generation of the reactive intermediate. Our interest in the chemistry of alkynes led us to prioritize the cyclopropenation of this class of starting materials. Furthermore, the cyclopropenation of alkynes in general is considerably less well-developed than the alkene reaction because of their attenuated reactivity.[5]

Preliminary experiments using our previously described conditions for the iron-catalyzed cyclopropanation of alkenes (cat. FeTPPCl, DMAP, H_2SO_4, NaOAc, 1.5 equiv $CF_3CH_2NH_3Cl$, 1.8 equiv $NaNO_2$) and 4-phenyl-1-butyne as test substrate failed to afford any cyclopropene product. Attempts with a [Co(salen)] catalyst led to complete recovery of the starting material. We then screened several rhodium complexes, and the results are shown in Table 1. The lipophilicity of the ligand that is associated with the metal complex plays a crucial role in the reaction, as the conversion increases inversely proportional to the polarity, from the most polar complex, $[Rh_2(OAc)_4]$, to the least polar, $[Rh_2(O_2CC_7H_{15})_4]$. We speculate this happens because the more lipophilic ligands enhance the hydrophobicity of the metal–carbene complex, ensuring that the reaction proceeds heterogeneously, and thus avoiding a quenching of the putative reactive metal–carbenoid intermediate by water. Further screening led us to identify the $[Rh_2(esp)_2]$ catalyst reported by Du Bois and co-workers[6] as the best catalyst under the harsh conditions ($NaNO_2$, H_2SO_4) required for the production of the diazoalkane, affording almost full conversion of the starting material. The combined lipophilicity of the ligand along with its chelating nature likely ensures high stability under the reaction conditions.

Table 1: Catalyst screening.[a]



Entry	Catalyst	Loading [mol%]	Conversion [%][b]
1	[Fe(TPP)Cl][c]	3	n.r.
2	[Co(salen)][d]	5	n.r.
3	$[Rh_2(OAc)_2]$	2.5	20
4	$[Rh_2(CF_3COO^-)_4]$	2.5	32
5	$[Rh_2(C_7H_{15}COO^-)_4]$	2.5	60
6	$[Rh_2(esp)_2]$	2.5	92

[a] General procedure: alkyne (0.22 mmol, 1.0 equiv), $F_3CCH_2NH_3Cl$ (2.0 equiv), $NaNO_2$ (2.4 equiv), NaOAc (20 mol%), H_2SO_4 (10 mol%), H_2O (1.3 mL). [b] Conversion determined by NMR spectroscopy. [c] 10 mol% DMAP. [d] 10 mol% *N*-methylimidazole. n.r. = no reaction. [Co(salen)] = *rac-trans-N,N*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt(II). esp = espino, TPP = 5,10,15,29-tetraphenyl-21*H*,23*H*-porphine, DMAP = 4-(dimethylamino)pyridine.

In the optimized experimental procedure, a mixture of 4-phenyl-1-butyne, $[Rh_2(esp)_2]$ (2.5 mol%), $CF_3CH_2NH_3Cl$

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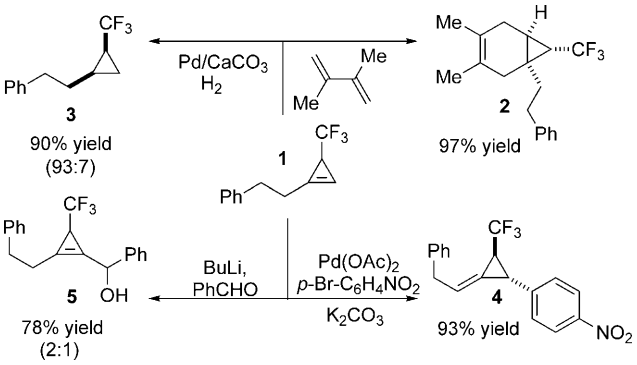
(2 equiv), H_2SO_4 (10 mol%), and NaOAc (20 mol%) at ambient temperature was treated with an aqueous solution of $NaNO_2$ (0.8 M, 2.4 equiv) by syringe pump addition. The reaction gave complete conversion, and (2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene was isolated in 78% yield. It is important to note that addition of toluene as a co-solvent led to reduced conversion (50%) of the alkyne into the cyclopropene product. We hypothesize that the reaction might proceed on water, because both catalyst and substrate are insoluble in the aqueous phase.[7] The diazotization reaction likely transpires in the aqueous phase whilst the cyclopropenation of the alkyne occurs in the organic alkyne phase. This hypothesis is supported by the strong coloration of the alkyne droplets owing to the dissolved violet rhodium complex.

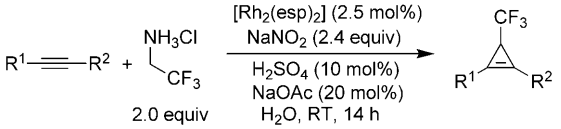
Next, the scope of the reaction was probed (Table 2). Interestingly, unactivated aliphatic alkynes were excellent substrates for this transformation, affording cyclopropene adducts in good yields. Furthermore, even the disubstituted aliphatic substrates reacted successfully. Phenylacetylene did not furnish the corresponding product under these conditions; rather, complete decomposition of the starting material into unidentified products was observed. However, gratifyingly, methylphenylacetylene afforded the cyclopropene product in good yield (Table 2, entry 5). Common alcohol protecting groups are tolerated in the reaction (OBn and OTBS; Table 2, entries 3, 6, and 7). This method shows a broad substrate scope and affords a facile and quick access to this new type of trifluoromethylated building blocks. It is well worth noting that although 1,1-trifluoromethyl-alkoxycarbonyl-substituted cyclopropenes have been previously reported,[2] the cyclopropene class described herein has not been previously documented.

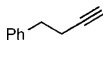
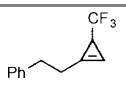
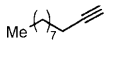
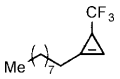
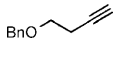
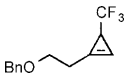
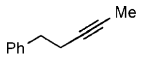
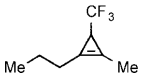
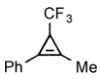
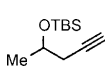
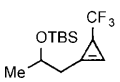
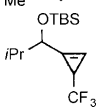
Next, a study of the reactivity[8] of these novel cyclopropenes in a variety of chemical transformations was conducted (Scheme 1). To examine the reactivity of the



Scheme 1. Transformations of cyclopropene **1**.

Table 2: Scope of the cyclopropenation.[a]



Entry	Alkyne	Product	Yield[b]
1			78
2			71
3			71
4			70
5			67
6			69[c]
7			73[c]

[a] General procedure: alkyne (0.22 mmol, 1 equiv), $F_3CCH_2NH_3Cl$ (2.0 equiv), $NaNO_2$ (2.4 equiv), NaOAc (20 mol%), H_2SO_4 (10 mol%), H_2O (1.3 mL). [b] Yield of isolated product. [c] 1:1 d.r. TBS = *tert*-butyldimethylsilyl.

trifluoromethylcyclopropenes, larger amounts of cyclopropene **1** were required; therefore, the quantities used in the cyclopropenation reaction were scaled up. Under optimized preparative conditions, the amount of trifluoroethylamine hydrochloride was successfully lowered to 1.5 equivalents; the reaction performed on a 4.4 mmol (572 mg) scale afforded the product in 75% yield.

The first transformation we examined was the Diels–Alder reaction of **1** with 2,3-dimethylbutadiene, which afforded **2** in 97% yield (Scheme 1).[9c] The efficiency with which the cycloaddition took place underscores the versatility of trifluoromethyl-substituted cyclopropenes as a point of divergence for the preparation of fused-ring systems. Cyclopropene **1** was also subjected to reduction with $Pd/CaCO_3/H_2$ to furnish cyclopropane **3** with excellent diastereoselectivity (93:7).[9c] That the product of the reduction is the *cis* diastereomer provides a complementary approach to our earlier report regarding the cyclopropanation of mono-substituted alkenes, which displays high *trans*-selectivity. Therefore, both families of *cis*- and *trans*-trifluoromethyl-substituted cyclopropanes may now be accessed with exceptional diastereocontrol. When **1** was subjected to Heck coupling with *para*-bromonitrobenzene, arylated product **4** was isolated in 93% yield,[10] wherein the double bond in the product had been incorporated *exo* to the cylopropane ring. The formation of the double bond is consistent with a β-hydride elimination reaction that can only occur in an *exo* fashion because of stereoelectronic constraints with regard to the β hydride. Methylenecyclopropanes have a rich chemistry, which makes our transformation a useful route to this class of compounds.[8] Finally, cyclopropenes may be subjected to lithiation and trapping.[11] We were pleased to observe that cyclopropene **1** was stable upon deprotonation with BuLi, and the lithiated cyclopropene did not suffer decomposition even upon warm-

ing to room temperature. This observation is in contrast to what has been reported for cyclopropenes that are stabilized by electron-withdrawing groups, which lead to formation of a ring-opened alkyne product.[11] The lithiated cyclopropene underwent reaction with benzaldehyde at −78 °C to afford product **5** in 78 % yield.

In summary, we have described the first cyclopropenation reaction of alkynes with trifluoromethyldiazomethane. The reaction proceeds in aqueous media under conditions in which the reactive diazoalkane is generated in situ from trifluoroethylamine hydrochloride in the presence of H_2SO_4 and $NaNO_2$. Key to enabling the transformation is the identification of the rhodium catalyst $[Rh_2(esp)_2]$ as being robust and compatible with the harsh reaction conditions. We have also showcased, in preliminary experiments, the versatility of these previously unknown products for further organic transformations. Therefore, the trifluoromethylcyclopropenes represent a promising class of compounds for the preparation of new building blocks in medicinal and materials chemistry. In a broader sense, this work highlights the opportunities for synthesis in the identification of new processes and catalysts under acidic, strongly oxidizing, and aqueous conditions that lead to the in situ generation of reactive intermediates. Development of other transformations and asymmetric cyclopropenation reactions are currently being investigated in our laboratory.

Experimental Section

General procedure for cyclopropenation: $[Rh_2(esp)_2]$ (4.3 mg, 0.0055 mmol) and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then, trifluoroethylamine hydrochloride (60 mg, 0.44 mmol) and H_2SO_4 (1.2 μL, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with argon. The alkyne (0.22 mmol) was added next, and $NaNO_2$ (36 mg, dissolved in 0.5 mL of water) was added by syringe pump over 10 hours. After 4 hours, CH_2Cl_2 and water were added, and the water phase was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$, and evaporated under reduced pressure. After analysis of the crude NMR spectrum, the mixture was purified by column chromatography on silica gel (pentane/diethyl ether) to afford the product.

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