Catalytic synthesis of trifluoromethyl cyclopropenes and *oligo*-cyclopropenes

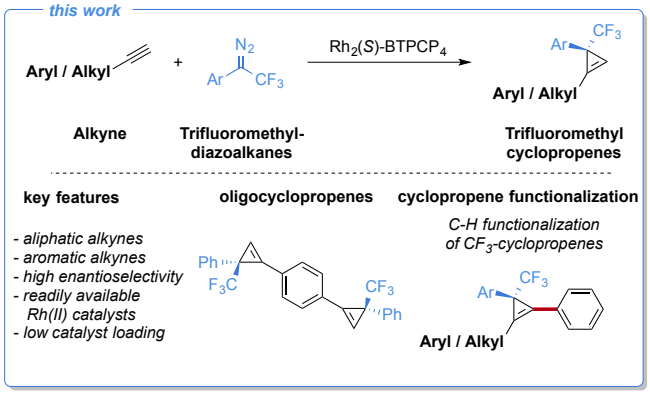
Uyen P. N. Tran,[a,b] Renè Hommelsheim,[a],+ Zhen Yang,[a],+ Claire Empel,[a] Katharina J. Hock,*[a] Thanh V. Nguyen*[b] and René M. Koenigs*[a]

Abstract: *The synthesis of trifluoromethylated cyclopropenes is very important for applications in drug discovery and functional materials. In this report, we describe the application of readily available, chiral rhodium(II) catalysts in a highly efficient asymmetric cyclopropenation reaction of fluorinated donor-acceptor diazoalkanes using a broad variety of aliphatic and aromatic alkynes. Further studies highlight the unique reactivity of fluorinated donor-acceptor diazoalkanes in the synthesis of oligo-cyclopropenes. Subsequent C-H functionalization of trifluoromethyl cyclopropenes furnishes densely substituted cyclopropene frameworks and also allows the synthesis of bis-cyclopropenes.*

Cyclopropenes are the smallest carbocycles containing at least one C-C double bond and are a fascinating class of highly strained small molecules with applications in the fields of drug discovery, catalysis and materials chemistry.[1] Existing methods to construct these compounds typically rely on catalytic carbene transfer reactions of ester-substituted diazoalkanes and alkynes using chiral Cu(I), Rh(II), Ir(III) or Au(III) catalysts.[2,3] More recently, light-mediated processes were demonstrated as powerful alternatives to access these important strained carbocycles.[4] Despite tremendous research efforts, the synthesis of the trifluoromethylated cyclopropene subclass remains a challenge in organic synthesis.[3] On the other hand, small molecules containing at least two cyclopropene units, or *oligo*-cyclopropenes, have been rarely reported, although their *oligo*-cyclopropane counterparts have been well explored in literature.[5] In 1986, Okamoto and co-workers described a synthetic protocol for *bis*-cyclopropenes by cycloaddition reactions of free carbenes and diaryl-substituted alkynes.[6a] Lin and co-workers subsequently demonstrated that *bis*-alkynes could be transformed into *bis*-cyclopropenes with a multi-step synthesis using ruthenium catalysts.[6b] To the best of our knowledge, there has been no report of a catalytic method for efficient synthesis of *oligo*-cyclopropenes.

From the perspective of the carbene-transfer reagent, while the majority of research was performed on ester-substituted diazoalkanes, limited examples report on cyclopropenation reactions of diazoalkanes with other electron-withdrawing substitutions such as nitrile, sulfonyl or fluorinated alkyl groups.[2,3] In particular, the asymmetric carbene-transfer reaction of trifluomethylated diazoalkanes for the enantioselective synthesis of their cyclopropene derivatives is even less investigated. In 2011, Katsuki *et al.* reported the application of a chiral Ir(III) complex in cyclopropenation reactions of trifluoromethyl-substituted diazoalkanes, though high catalyst loading was required to facilitate the reactions on a small substrate scope of only four aromatic alkynes.[2g] A general and broadly applicable catalytic approach for the enantioselective synthesis of fluorinated cyclopropenes has not been described until now and still remains one of the major challenges in asymmetric synthesis.

As part of our ongoing interest in small fluorinated molecules, we became intrigued by cyclopropenation reactions of fluoroalkyl-substituted donor-acceptor diazo compounds[7] with alkynes and *oligo*-alkynes. This approach would result in a concise synthesis of valuable unsaturated trifluoromethyl-cyclopropenes that can be readily functionalized for further synthetic values. Based on our previous study in this field,[8] we envisioned that commercially available chiral Rh(II) complexes would be suitable catalysts to promote cyclopropenation reactions of fluoroalkyl-substituted diazo compounds. Such method would not only provide a simple and convenient access to chiral trifluoromethyl-substituted cyclopropenes, but also be a significant improvement over existing methods in terms of efficiency and selectivity.



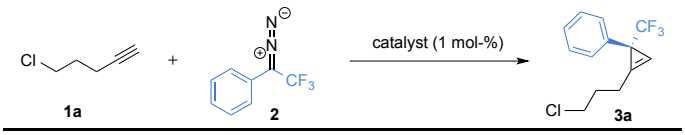
Scheme 1. Enantioselective synthesis of trifluoromethyl cyclopropenes.

We set out our investigations by examining different Rh(II) catalysts in the reaction of 5-chloro-pent-1-yne (**1a**) and (1-diazo-2,2,2-trifluoroethyl)benzene (**2**) using toluene as solvent.[9] The phthalimido rhodium series (Rh_2NTTL_4, Rh_2PTAD_4, Rh_2PTTL_4, see entries 1-3 in Table 1) only gave reasonable cyclopropene product yields with a moderate level of enantio-induction. Contrarily, Rh_2BTPCP_4 proved to be highly efficient and excellent stereoselectivity was observed (entry 5). Although Rh_2DOSP_4 has been reported to be an excellent catalyst for cyclopropenation reactions of ester-substituted diazoalkanes, as demonstrated by Davies and co-workers,[2c] this catalyst proved to be inefficient in our cyclopropenation reaction of the aliphatic alkyne **1a** with fluorinated diazoalkane **2** (entry 5). To further understand this marked difference in reactivity, we investigated the reactivity of aromatic alkynes with Rh_2DOSP_4 and Rh_2BTPCP_4. In the reaction of diazoalkane **2** with *p*-tolylacetylene, both catalysts proved to be highly efficient and the desired aryl-substituted cyclopropene was obtained with

[a] Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen, Germany
E-mail: rene.koenigs@rwth-aachen.de
E-mail: katharina.hock@rwth-aachen.de
[b] School of Chemistry, University of New South Wales
Sydney, NSW 2052, Australia
E-mail: t.v.nguyen@unsw.edu.au
[+] These authors contributed equally.

excellent stereoselectivity (entries 6-7), clearly indicating that Rh_2BTPCP_4 is more suitable for wider alkyne substrate scope. No better results were obtained using ethers or halogenated solvents; higher reaction temperatures resulted in significantly reduced product yields (entries 8-12, Table 1).

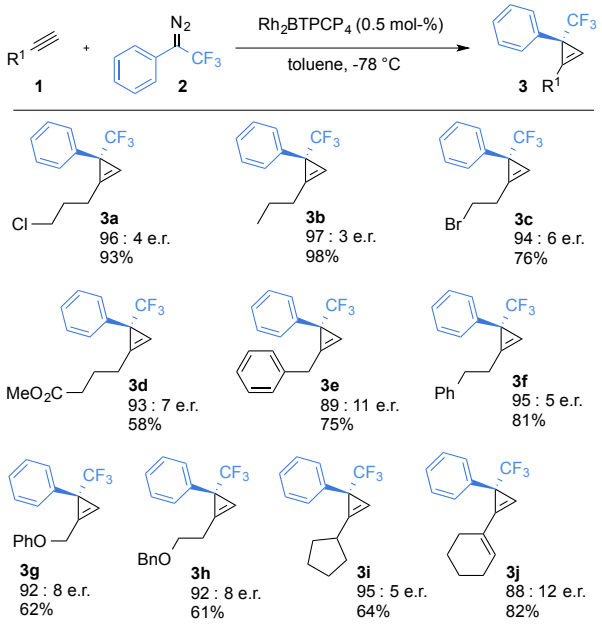
Table 1. Reaction Optimization.



entry[a]	catalyst	Solvent/T	Yield	e.r.
1	Rh_2NTTL_4	toluene / –78 °C	44%	67 : 33
2	Rh_2PTTL_4	toluene / –78 °C	58%	64 : 36
3	Rh_2PTAD_4	toluene / –78 °C	*no rct.*	-
4	Rh_2DOSP_4	toluene / –78 °C	*no rct.*	-
5	**Rh_2BTPCP_4**	**toluene / –78 °C**	**93%**	**96 : 4**
6[b]	Rh_2DOSP_4	toluene / –78 °C	97%	94 : 6
7[b]	Rh_2BTPCP_4	toluene / –78 °C	97%	96 : 4
8	Rh_2BTPCP_4	hexane / –78 °C	59%	85: 15
9	Rh_2BTPCP_4	DCM / –78 °C	<5%	n.d.
10	Rh_2BTPCP_4	THF / –78 °C	<5%	n.d.
11	Rh_2BTPCP_4	toluene / –45 °C	59%	94 : 6
12	Rh_2BTPCP_4	toluene / RT	49%	90:10

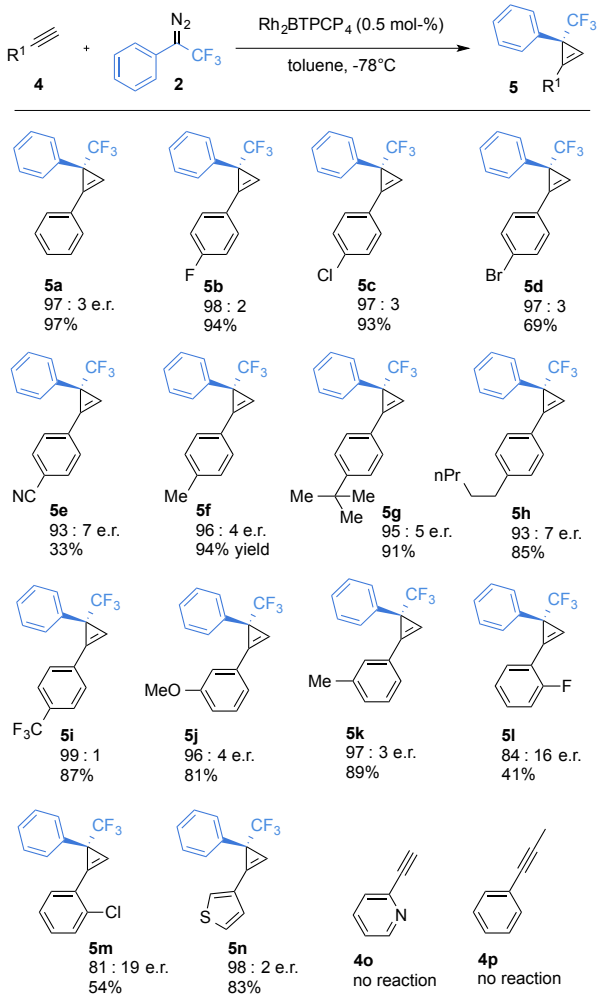
[a]*Reaction conditions:* **1a** (2.5 eq.) and catalyst were dissolved in the appropriate solvent (1 mL) and a solution of **2** (1.0 eq.) in 1 mL solvent was added over 3 hours at the given temperature and stirred for 12 h; [b]Reaction with *p*-tolylacetylene instead of **1**.

With the optimal conditions in hand, we next investigated a range of aliphatic alkynes with different chain length, halogen- and ester substituents as well as branched aliphatic alkynes in this asymmetric cyclopropenation reaction (Scheme 2). In all cases we obtained the desired trifluoromethylated cyclopropenes with a high level of enantioselectivity and good to excellent isolated yields. Surprisingly, benzylic and olefinic substituents (entries **3e** and **3j**) had a slightly detrimental effect on the enantio-induction. Nevertheless a good level of enantioselectivity was obtained and exclusive cyclopropenation was observed for these two substrates. Having established a protocol for the asymmetric synthesis of trifluoromethylated cyclopropenes from aliphatic alkynes, we then explored the applicability with aromatic alkynes (Scheme 3). We were pleased to observe that different halogen, aliphatic and electron-donating substituents in *para*- and *meta*- position were well tolerated and the respective cyclopropenes were isolated in excellent yields and enantiomeric ratios. Electron-withdrawing groups, such as nitriles, resulted in reduced yield though at a high level of enantio-induction (**5e**). Substituents in the *ortho*-position gave significantly reduced yields and the cyclopropenes could be isolated with only moderate enantioselectivity, which can be attributed to the steric hindrance imposed by *ortho*-substituents (**5l,m**). Pyridinyl and non-terminal alkynes proved to be unreactive in this transformation (**4o,p**).



Scheme 2. Substrate scope of aliphatic alkynes.

We subsequently decided to apply our newly developed method to investigate the challenging synthesis of *oligo*-cyclopropenes from substrates bearing multiple alkyne moieties. These studies would a) reveal insights into the chemoselectivity and the reactivity of *oligo*-alkynes in this transformation and b) provide convenient access to the structural class of rare *oligo*-cyclopropenes. We commenced these studies by investigating the reaction of 1,4-bis(ethynyl)benzene (**6**, Table 2) with (1-diazo-2,2,2-trifluoroethyl) benzene (**2**). In principal three different reaction products can be obtained from this transformation, namely the *mono*-cyclopropene **7**, and two different diastereoisomers of *bis*-cyclopropene **8**. We therefore embarked to study the effect of different rhodium(II) catalysts and the stoichiometry of reactants on the outcomes this transformation. Much to our surprise, the latter had only little influence on the product distribution. The uses of one or two equivalents of 1,4-*bis*(ethynyl)benzene **6** both resulted in the *bis*-cyclopropene **8** as the only product with excellent yields (50% or 49% w.r.t. **6** respectively, see entries 1 and 2, Table 2), which is almost quantitative conversion of the diazoalkane **2** to the *bis*-cyclopropene **8**. The addition of two equivalents of diazo **2** resulted in excellent isolated yield of the *bis*-cyclopropene **8** (84% w.r.t to **6**, entry 3).[9]

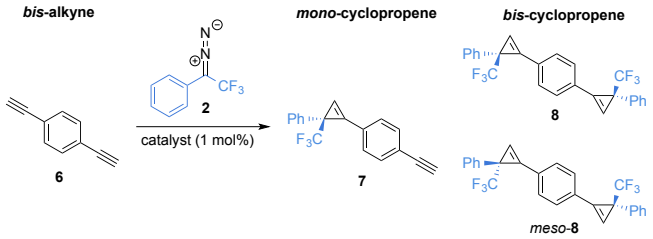


Scheme 3. Substrate scope of aromatic alkynes.

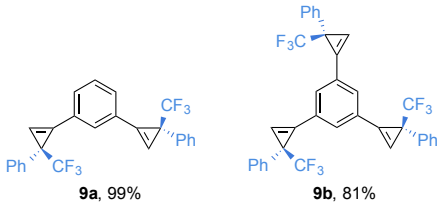
Careful analysis of the crude reaction mixtures by NMR spectroscopy and mass spectrometry revealed only trace amounts of *mono*-cyclopropene (**7**) and no formation of the *meso*-bis-cyclopropene (*meso*-**8**). Further experiments employing different achiral and chiral rhodium(II) catalysts and solvents did not improve the yield of the desired double-cyclopropenation product.[SI] The above data provided intriguing insights into the reaction mechanism of the double-cyclopropenation reaction. We hypothesized that the initial, first cyclopropenation reaction provides a highly reactive ethynyl-benzene substituted cyclopropene (**7**), which reacts rapidly with a second rhodium carbene species, hence resulting only in small quantities of the *mono*-cyclopropene 'intermediate' **7** in the reaction mixture. The high efficiency can presumably be attributed to a possible coordination of the rhodium catalyst, after the first cyclopropenation, to the newly formed cyclopropene ring itself. Such coordination have been observed in rhodium-activation chemistry of cyclopropene, which in this case renders the second alkyne moiety very reactive and thus favours the exclusive formation of the *bis*(cyclopropene) product over its mono-cyclized intermediate.[10]

Interested in further investigations of this phenomenon, we subsequently investigated a range of different oligo-aromatic alkynes (Table 2). Intriguingly, even 1,3,5-*tris*(ethinyl)benzene also gave excellent conversion to the *tris*-cyclopropene product **9b**.

Table 2. Investigations towards the synthesis of *bis*-cyclopropenes.



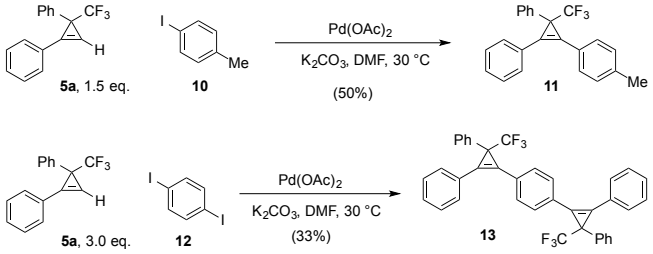
#[a]	catalyst	conditions	ratio of **6**:**2**	yield (**8**)
1	Rh_2esp_2 (1 mol%)	PhMe, 0 °C	1 : 1	>99%[b]
2	Rh_2esp_2 (1 mol%)	PhMe, 0 °C	2 : 1	98%[b]
3	**Rh_2esp_2 (1 mol%)**	**PhMe, 0 °C**	**1 : 2**	**84%**



9a, 99% **9b**, 81%

[a]*Reaction conditions:* **6** (0.2 mmol) and catalyst were dissolved in toluene (1 mL) and a solution of **2** (2 eq.) in 1 mL toluene was added over 3 hours at the given temperature and stirred for 12 h. Yields are based on **6**. [b]yield based on diazoalkanes.

Following this intriguing observation for the synthesis of *oligo*-cyclopropenes, we became interested in the C-H functionalization reaction of the cyclopropene ring of trifluoromethyl-substituted cyclopropene **5a**. We were delighted to observe that C-H functionalization of **5a** with iodobenzene **10** readily proceeds using cheap $Pd(OAc)_2$[11] without the need of any ligands or directing group and could obtain the tetra-substituted cyclopropene **11** with good isolated yield. Similarly, double C-H functionalization readily proceeds using 1,4-diiodobenzene **12** and the fully substituted *bis*-cyclopropene **13** can be isolated in moderate yield.



Scheme 4. C-H functionalization of CF_3-cyclopropenes.

In summary, we herein report on the synthesis of valuable trifluoromethyl cyclopropenes. Trifluoromethyl-substituted donor-acceptor diazoalkanes were shown to readily undergo highly enantioselective cyclopropenation reactions (up to 98% yield, up to 99 : 1 e.r.) with aliphatic and aromatic terminal alkynes using simple and commercially available Rh(II) catalysts. The reactivity of trifluoromethyl-substituted diazoalkanes was further investigated in cyclopropenation reactions of oligo-alkynes, which smoothly reacted to the rare subclass of *oligo*-cyclopropenes with up to four cyclopropene units. CF_3-cyclopropenes can be readily modified by C-H functionalization using a simple Pd(II) catalysts, which provides an access to fully-substituted CF_3-cyclopropenes and oligo-cyclopropenes. This Rh(II) catalyzed cyclopropenation reaction of trifluoromethyl-substituted diazoalkanes now opens up an efficient pathway towards chiral CF_3-cyclopropenes and gives access to rare *oligo*-cyclopropenes with applications in drug discovery and functional materials.

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Keywords: cyclopropene • rhodium • diazo • cycloaddition • enantioselective

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