▌**Enantioselectivity**

Catalytic Synthesis of Trifluoromethyl Cyclopropenes and Oligo-Cyclopropenes**

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Abstract: The synthesis of trifluoromethylated cyclopropenes is often associated with important applications in drug discovery and functional materials. In this report, we describe the use of readily available chiral rhodium(II) catalysts for a highly efficient asymmetric cyclopropenation reaction of fluorinated donor–acceptor diazoalkanes with 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 alternative synthesis of bis-cyclopropenes.

Cyclopropenes are the smallest carbocycle 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 chal-

lenge in organic synthesis.[3] On the other hand, small molecules containing two or more 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 multistep 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 scarcely 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 a challenge 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 trifluoromethyl-cyclopropenes[3a] 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 diazocompounds. Such a 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).

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 the solvent.[9] The phthalimido rhodium series ([Rh₂((S)-NTTL)₄], [Rh₂((S)-

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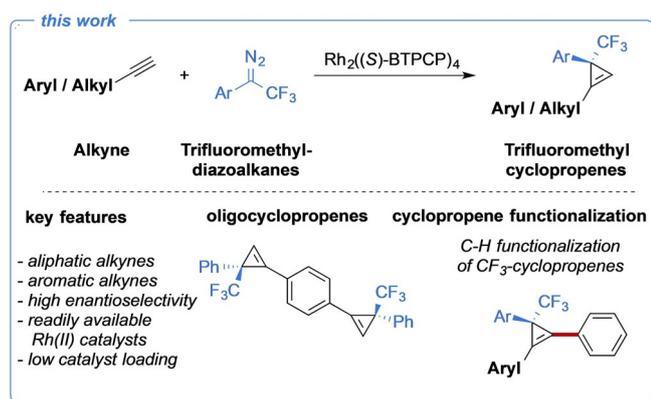E-mail: katharina.hock@rwth-aachen.de
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Scheme 1. Enantioselective synthesis of trifluoromethyl cyclopropenes.

Table 1. Reaction optimization.

Entry[a]	Catalyst	Solvent/T	Yield [%]	e.r.
1	[Rh₂((S)-NTTL)₄]	toluene/−78 °C	44	67:33
2	[Rh₂((S)-PTTL)₄]	toluene/−78 °C	58	64:36
3	[Rh₂((S)-PTAD)₄]	toluene/−78 °C	n.r.[c]	–
4	[Rh₂((S)-DOSP)₄]	toluene/−78 °C	n.r.[c]	–
5	**[Rh₂(S)-BTPCP)₄]**	**toluene/−78 °C**	**93**	**96:4**
6[b]	[Rh₂((S)-DOSP)₄]	toluene/−78 °C	97	94:6
7[b]	[Rh₂((S)-BTPCP)₄]	toluene/−78 °C	97	96:4
8	[Rh₂((S)-BTPCP)₄]	hexane/−78 °C	59	85:15
9	[Rh₂((S)-BTPCP)₄]	DCM/−78 °C	<5	n.d.
10	[Rh₂((S)-BTPCP)₄]	THF/−78 °C	<5	n.d.
11	[Rh₂((S)-BTPCP)₄]	toluene/−45 °C	59	94:6
12	[Rh₂((S)-BTPCP)₄]	toluene/RT	49	90:10

[a] Reaction conditions: **1a** (2.5 equiv.) and catalyst were dissolved in the appropriate solvent (1 mL) and a solution of **2** (1.0 equiv.) in 1 mL solvent was added over 3 h at the given temperature and stirred for 12 h. [b] Reaction with *p*-tolylacetylene instead of **1**. [c] n.r.: no reaction.

PTAD)₄], [Rh₂((S)-PTTL)₄], see entries 1–3 in Table 1) only gave reasonable cyclopropene product yields with a moderate level of enantioinduction. Contrarily, [Rh₂((S)-BTPCP)₄] proved to be highly efficient and excellent stereoselectivity was observed (Table 1, entry 5). Although [Rh₂((S)-DOSP)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 4). To further understand this marked difference in reactivity, we investigated the reactivity of aromatic alkynes with [Rh₂((S)-DOSP)₄] nd [Rh₂((S)-BTPCP)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 excellent stereoselectivity (entries 6–7), clearly indicating that [Rh₂((S)-BTPCP)₄] is more suitable for broader alkyne substrate scope. No better results were obtained using ethers or halogenated solvents; higher reaction
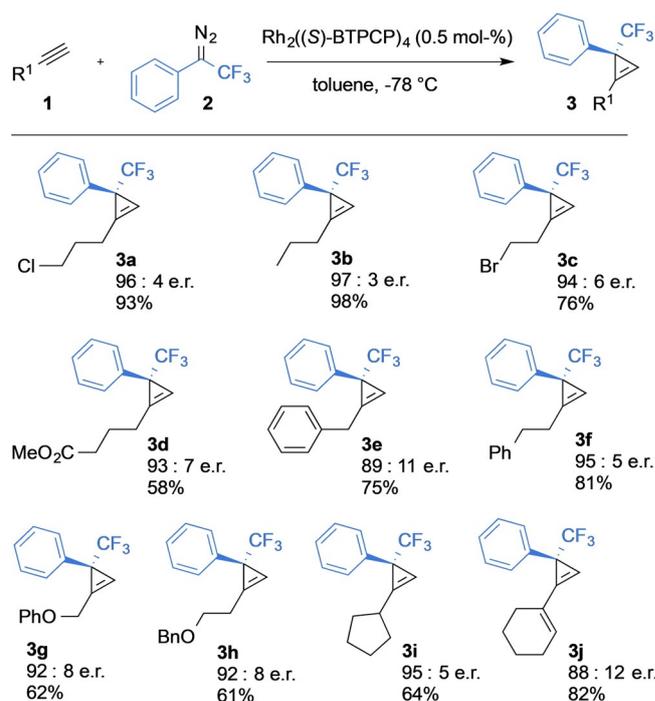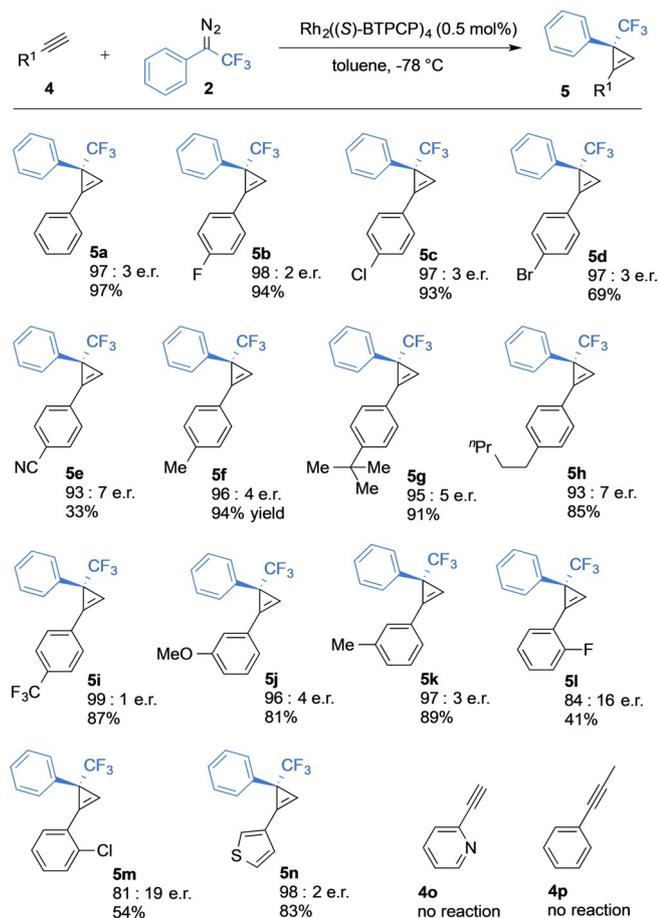

Scheme 2. Substrate scope of aliphatic alkynes.

temperatures resulted in significantly reduced product yields (entries 8–12).

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. To our surprise, benzylic and olefinic substituents (entries **3e** and **3j**) had a detrimental effect on the induction of stereochemistry. Nevertheless, a good level of enantioselectivity was obtained and exclusive cyclopropenation was observed for these two substrates. After 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 the *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 a reduced yield though at a high level of enantioinduction (**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 nonterminal alkynes, in contrast to an earlier study by the Carreira group,[3a] proved to be unreactive in this transformation (**4o,p**), presumably due to nucleophilicity mismatch or steric clash with our donor–acceptor carbene.

We subsequently decided to explore the challenging synthesis of oligo-cyclopropenes from substrates bearing multiple

Scheme 3. Substrate scope of aromatic alkynes.

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

Entry[a]	Cat. ([mol%])	Conditions	Ratio of 6:2	Yield [%] (8)
1	[Rh$_2$(esp)$_2$] (1 mol%)	PhMe, 0 °C	1:1	> 99[b]
2	[Rh$_2$(esp)$_2$] (1 mol%)	PhMe, 0 °C	2:1	98[b]
3	**[Rh$_2$(esp)$_2$] (1 mol%)**	**PhMe, 0 °C**	**1:2**	**84**
4	[Rh$_2$((S)-BTPCP)$_4$] (1 mol%)	PhMe, 0 °C	1:2	49

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

alkyne moieties (Table 2). 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 principle, three different reaction products can be obtained from this transformation, namely the *mono*-cyclopropene **7**, and two different diastereoisomers of bis-cyclopropene **8**. Therefore, it would be interesting to study the effect of different rhodium(II) catalysts and the stoichiometry of reactants on the outcomes this transformation. Due to the more challenging nature of the double cyclopropenation process, the reaction conditions were slightly modified from the optimized settings in Table 1 in that the reaction temperature was raised to 0 °C to allow shorter reaction time. [Rh$_2$(esp)$_2$] proved to be the best catalyst for this particular transformation giving the same diastereoisomer compared to [Rh$_2$(BTPCP)$_4$] (see Table S1, page 4 in the Supporting Information for more details). Much to our surprise when we embarked on this investigation, reactant stoichiometry 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 a quantitative conversion of the diazoalkane **2** to the bis-cyclopropene **8**. The addition of two equivalents of diazo **2** resulted in an excellent isolated yield of the bis-cyclopropene **8** (84% w.r.t to **6**, entry 3), which was identified as *rac*-**8** by analysis of ^{19}F- and ^{13}C NMR spectra.[9]

Careful analysis of the crude reaction mixtures by NMR spectroscopy and mass spectrometry revealed only trace amounts of mono-cyclopropene (**7**). Further experiments employing different achiral and chiral rhodium(II) catalysts and solvents did not improve the yield of the desired double-cyclopropenation product (see Table S1, page 4 in the Supporting Information for more details). It is important to note that when using [Rh$_2$((S)-BTPCP)$_4$] the same double cyclopropenated product **8** was obtained as a single diastereoisomer albeit in moderate yield. The above data provided intriguing insights into the reaction mechanism of the double-cyclopropenation reaction that warrant a full investigation in future. It seemed that the initial, first cyclopropenation product (**7**) tends to react 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 has 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-cyclopropenated intermediate.[10]

Looking back to our newly developed cyclopropenation method, the substrate scope was indeed limited to terminal alkynes. However, the resulting products bear cyclopropenylic C–Hs, which offer an excellent motif for another interesting but under-investigated chemical transformation. Thus, we became interested in the C–H functionalization reaction of the cyclopropene ring of trifluoromethyl-substituted cyclopropenes **5**. In a preliminary study, we were delighted to observe that C–H functionalization of **5a** with iodobenzene **9** readily

proceeds by using a simple catalyst, namely Pd(OAc)$_2$,[11] without the need of any ligands or directing group. We could obtain the tetra-substituted cyclopropene **10** in good isolated yield. Furthermore, double C−H functionalization using 1,4-diiodobenzene **11** and **5a** proceeded with similar efficiency to afford the fully substituted bis-cyclopropene **12** in moderate yield (Scheme 4).
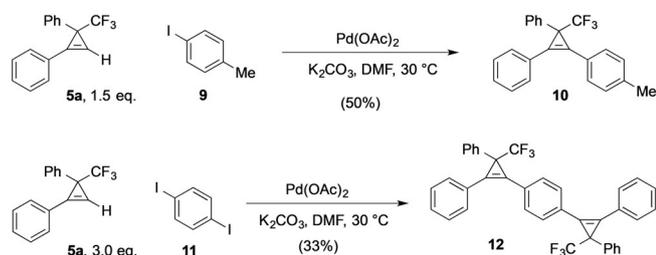
Scheme 4. C−H functionalization of CF$_3$-cyclopropenes.

In summary, we report a novel method for the asymmetric 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. Mono-cyclopropene products can also be readily modified by C−H functionalization using a simple Pd^{II} catalyst, which provides access to fully-substituted CF$_3$-cyclopropenes and oligo-cyclopropenes. Our Rh^{II}-catalyzed cyclopropenation reaction of trifluoromethyl-substituted diazoalkanes opens up an efficient pathway towards chiral CF$_3$-cyclopropenes and gives access to rare oligo-cyclopropenes with potential applications in drug discovery and functional materials.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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