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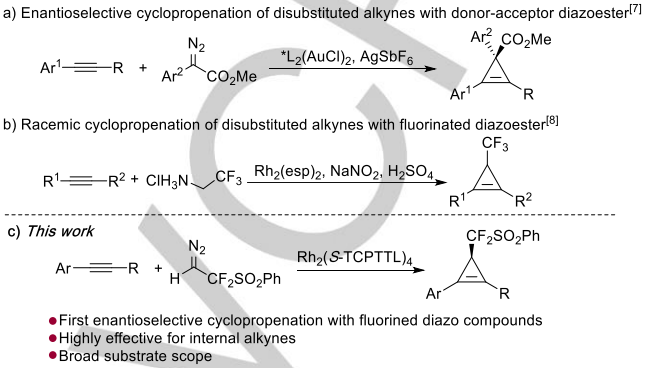
Catalytic Enantioselective Cyclopropenation of Internal Alkynes: Access to Difluoromethylated Three-Membered Carbocycles

Zhi-Qi Zhang,[a] Meng-Meng Zheng,[b] Xiao-Song Xue,[b] Ilan Marek,*[c] Fa-Guang Zhang,*[a] and Jun-An Ma*[a, b]

Abstract: Herein we described an expeditious Rh(II)-catalysed enantioselective cyclopropenation reaction of internal alkynes with a masked difluorodiazoethane reagent ($PhSO_2CF_2CHN_2$, Ps-DFA). This asymmetric transformation offers efficient access to a broad range of enantioenriched difluoromethylated cyclopropenes (40 examples, up to 99% yield, 97% ee). The synthetic utility of obtained strained carbocycles is demonstrated by subsequent stereo-defined processes including cross-couplings, hydrogenation, Diels-Alder reaction, and Pauson−Khand reaction.

Enantioenriched cyclopropenes have drawn increasingly considerable synthetic interest owing to their versatile reactivity.[1] In this context, catalytic enantioselective cyclopropenation reactions arguably represent one of the most straightforward and commonly-used transformations to access chiral cyclopropenes.[1] Pioneered by the elegant studies from Doyle,[2] Corey,[3] Davies,[4] among others,[5] this [2+1]-cycloaddition reaction with terminal alkyne has witnessed substantial advances in the past two decades. In sharp contrast, the extension of this chemistry for internal alkynes has proved extremely challenging, mainly due to the attenuated reactivity and difficult stereo-control associated with growing steric hindrance.[6] Until now, only the research group of Huw Davies has successfully used internal alkynes in a cooperative gold/silver-catalyzed enantioselective cyclopropenation reaction with donor/acceptor-substituted diazoesters (Scheme 1a).[7] In the same vein, Carreira and Morandi have reported a powerful racemic cyclopropenation reaction of internal alkynes by using trifluorodiazoethane as reaction partner (Scheme 1b).[8] As fluorinated diazo compounds have emerged as an attractive building block for the efficient construction of numerous fluoroalkylated carbocycles, heterocycles, and acyclic architectures,[9] the development of catalytic asymmetric [2+1]-cycloaddition of fluorodiazo derivatives with internal alkynes is still in its infancy.[10]

As part of our continuing interest in the realm of fluorinated carbene chemistry,[11] we hypothesized that the catalytic and enantioselective cyclopropenation of inert internal alkynes might



Scheme 1. Catalytic enantioselective cyclopropenation reactions of internal alkynes with diazo compounds.

be realized by taking advantage of our recently developed difluorodiazo reagent ($PhSO_2CF_2CHN_2$, Ps-DFA).[12] Herein we report our investigations toward this goal through a Rh(II)-catalyzed highly enantioselective cyclopropenation of Ps-DFA with a broad range of readily accessible unbiased internal alkynes (Scheme 1c). This reaction represents the first example of catalytic asymmetric addition of acceptor-(only) carbene precursor with internal alkynes.

In our preliminary experiments, $[Rh_2(OAc)_4]$ was first evaluated as potential catalyst with 1-phenyl-1-propyne **1a**, as model substrate. However, in this condition, only a trace amount of the desired product **2a** was detected (Table 1, entries 1–3). To our delight, when the Du Bois catalyst [($[Rh_2(esp)_2]$)] was added to the same two substrates, cycloproprene **2a** was smoothly produced at –30 °C in decent yield (Table 1, entry 4).[13] Encouraged by these results, we have subsequently investigated the asymmetric variant of this carbene transfer reaction by screening an array of chiral Rh(II) complexes (entries 5–11). Although the Davies's $[Rh_2(S\text{-DOSP})_4]$[14] and Corey's $[Rh_2(OAc)(DPTI)_3]$[3] catalysts gave low enantiodiscrimination in this transformation (Table 1, entries 5 and 6, respectively), the Hashimoto's catalyst ($[Rh_2(S\text{-TCPTTL})_4]$)[15] delivered **2a** in good yield with high asymmetric induction (Table 1, entry 9, 80% yield, 96% ee). Further optimizations allowed to decrease the catalyst loading to only 1.5 mol% with 1.5 equivalent of Ps-DFA to provide the expected cyclopropene in only 40 min at –30 °C (Table 1, entry 16, 88% yield, 96% ee). At the outset, a scale-up experiment established our confidence in the robustness of the current method as **2a** could be prepared on a gram scale in 91% yield and 96% enantiomeric excess. Remarkably, constant high enantioselectivities were observed even when the reaction was performed in a short period of time (i.e. 5 minutes) albeit at the expense of slightly decreased yields (Table 1, entries 17–18). Alternatively, cyclopropene **2a** could also be obtained with 96% enantiomeric excess in practical yield while Ps-DFA was employed as the limiting starting material, thus providing a

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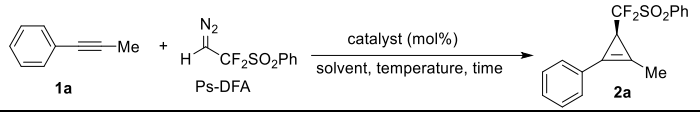
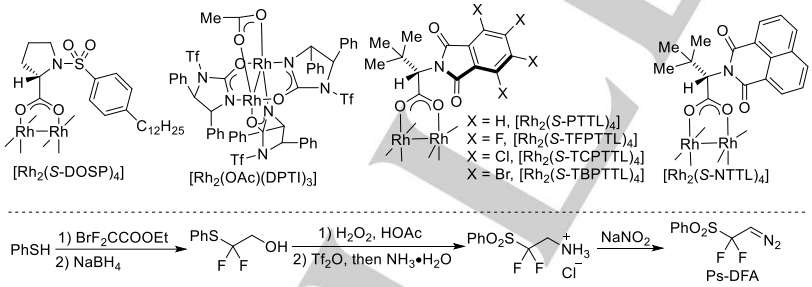
Table 1. Optimization of the reaction conditions. [a]



Entry	Catalyst (mol%)	Solvent	Temperature (℃) / Time (h)	Yield (%)[b]	ee (%)[c]
1	$Rh_2(OAc)_4$ (2.5)	CH_2Cl_2	0 / 3	trace	-
2	$Rh_2(esp)_2$ (2.5)	CH_2Cl_2	0 / 3	5	-
3[e]	$Rh_2(OAc)_4$ (2.5)	CH_2Cl_2	–20 / 3	6	-
4	$Rh_2(esp)_2$ (2.5)	CH_2Cl_2	–30 / 2	63	-
5	Rh_2(*S*-DOSP)$_4$ (2.5)	CH_2Cl_2	–30 / 2	50	50
6	$Rh_2(OAc)(DPTI)_3$ (2.5)	CH_2Cl_2	–30 / 2	30	14
7	Rh_2(*S*-PTTL)$_4$ (2.5)	CH_2Cl_2	–30 / 2	85	64
8	Rh_2(*S*-TFPTTL)$_4$ (2.5)	CH_2Cl_2	–30 / 2	85	93
9	Rh_2(*S*-TCPTTL)$_4$ (2.5)	CH_2Cl_2	–30 / 2	80	96
10	Rh_2(*S*-TBPTTL)$_4$ (2.5)	CH_2Cl_2	–30 / 2	59	93
11	Rh_2(*S*-NTTL)$_4$ (2.5)	CH_2Cl_2	–30 / 2	53	57
12	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 2	80	96
13	Rh_2(*S*-TCPTTL)$_4$ (1.0)	CH_2Cl_2	–30 / 2	72	95
14	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–40 / 2	69	96
15[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 1	82	96
16[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 40 min	88	96
17[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 20 min	79	96
18[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 5 min	74	96
19[e]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	CH_2Cl_2	–30 / 40 min	69	96
20[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	$ClCH_2CH_2Cl$	–30 / 40 min	85	94
21[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	$CHCl_3$	–30 / 40 min	63	96
22[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	THF	–30 / 40 min	65	98
23[d]	Rh_2(*S*-TCPTTL)$_4$ (1.5)	Et_2O	–30 / 40 min	50	98

[a] Reaction was conducted as following unless otherwise noted: To a stirred solution of Rh(II) catalyst and internal alkyne **1a** (0.3 mmol, 1 equiv) in solvent (1 mL) was added diazo compound Ps-DFA (0.6 mmol, 2 equiv) in 1 mL of corresponding solvent dropwise at indicated temperature. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase using a Daicel Chiralpak column. [d] 1.5 equiv of Ps-DFA was employed. [e] Ps-DFA (0.3 mmol, 1 equiv) with alkyne **1a** (0.6 mmol, 2 equiv) was employed.



cyclopropenes (**2ai** could only be formed in 5% yield), we were interested to develop an alternative substrate that would be able to provide subsequently the desired diaryl cyclopropenes. In this context, we were pleased to observe that the treatment of halogenated internal alkynes **1af**–**1ah** in our experimental condition led to the corresponding halogeno-cyclopropenes **2af**–**2ah** in 86–93% ee (Scheme 3a). Having now access to cyclopropenyl bromide **2af**, smooth cross-coupling reactions have been performed to lead to the expected dissymmetric 1,2-disubstituted cyclopropenes **2ai**–**2ap**.[18] For instance, enantioenriched diaryl cyclopropenes **2ai**–**2ak** were obtained from **2af** via a Suzuki cross-coupling reaction with different aryl boronic acids (Scheme 3b), whereas an array of previously inaccessible chiral vinyl cyclopropenes (Scheme 3c, products **2al**–**2ap**) could also be readily prepared under mild conditions by a Heck reaction on **2af** with easily available styrenyl or acrylate derivatives. In all cases, the products are obtained with the same enantiomeric excess than that the initial starting material **2af**.

The developed cyclopropenation reaction provides a viable route to access densely functionalized cyclopropenes containing enantioenriched fluoroalkyl carbon stereogenic centers, which should find a range of applications as useful chiral building blocks for stereoselective organic syntheses. Therefore, the phenyl sulfone moiety was smoothly cleaved by using magnesium under complementary protocol for future applications (Table 1, entry 19). In addition, this reaction is also well compatible with other solvents, such as chloroform, tetrahydrofuran, and diethyl ether (entries 20–23).

With the optimized reaction conditions in hand (Table 1, entry 15), a wide variety of disubstituted alkynes were evaluated in the cyclopropenation reaction (Scheme 2). Alkyl substituents in *ortho*, *meta* or *para* position of the aromatic ring (Scheme 2, **2b**–**2d** respectively) were equally tolerated and in all cases, good to high yields and high enantioselectivities were consistently observed. The absolute configuration of compound **2d** was unambiguously determined by X-ray crystallography analysis,[16] and the absolute configuration of all other cyclopropenes were assigned by analogy. Similarly, various halogen substituents at different positions of the phenyl ring could be tolerated under identical conditions (Scheme 2, **2h**–**2m**). It was found that substrates bearing strong electron-withdrawing groups such as -CF_3, -CN, and -NO_2, are also compatible in this reaction, giving rise to the corresponding cyclopropenes **2n**–**2r** with 92–96% ee. This Rh(II)-catalyzed cycloaddition reaction could be extended to naphthyl-, thienyl-, and pyridinyl-substituted alkynes as demonstrated by the enantioselective formation of **2s**–**2u**. Notably, the current protocol also exhibits high level of tolerance toward a broad range of alkyl groups as regards to the second substituent of the internal alkyne (Scheme 2, products **2v**–**2ae**). It is interesting to note that this carbene transfer reaction is chemoselective as the C-H insertion at the benzylic as well as the methylene sites next to the alkoxy group was not observed (Scheme 2, **2z** and **2aa**).

As one of the limitations[17] of our proposed strategy concerned the catalytic and enantioselective cyclopropenation of diaryl acetylenes *en route* to the formation of diaryl

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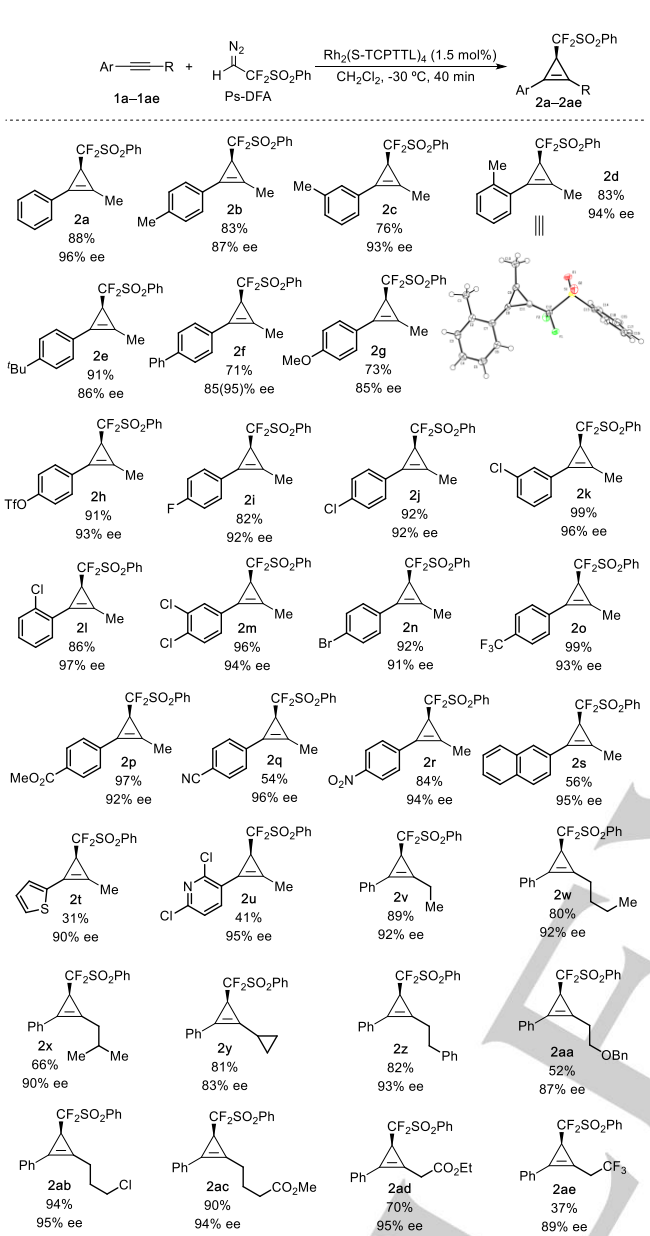
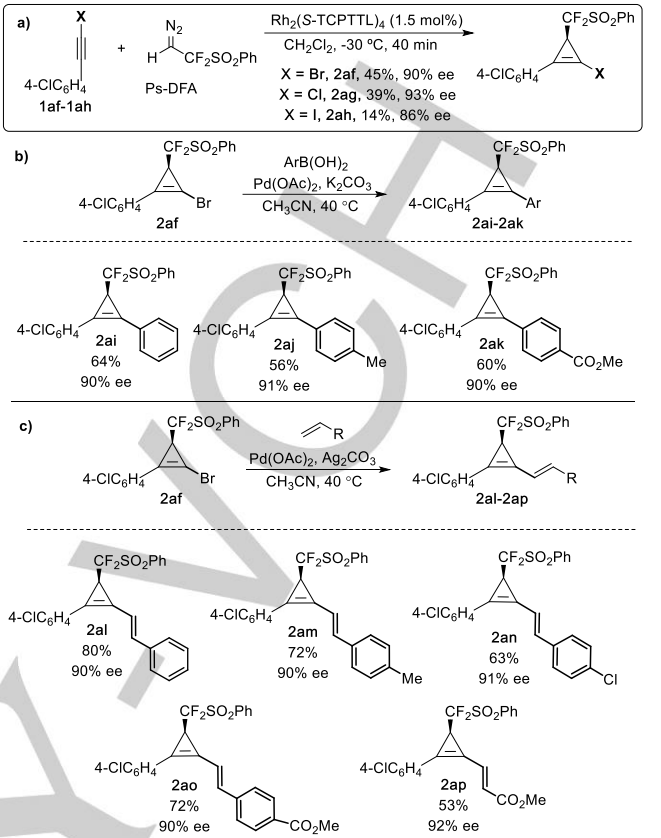
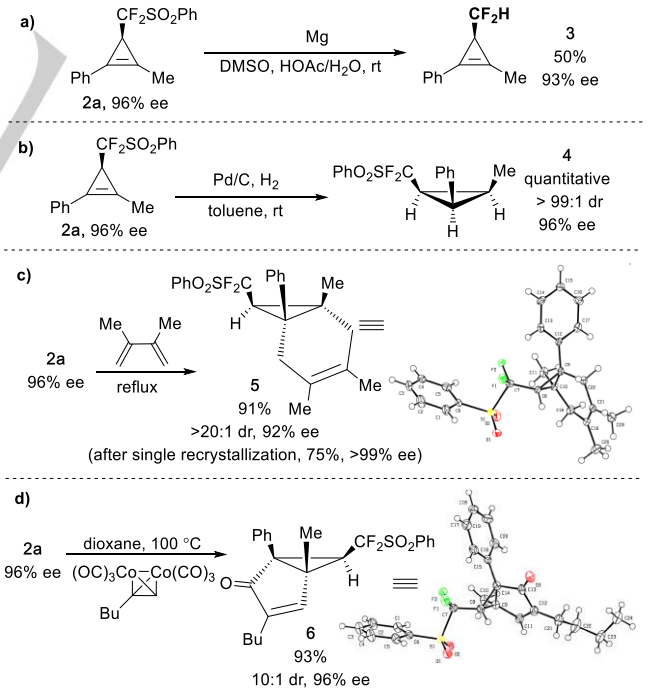


Scheme 2. Rh-catalysed enantioselective cyclopropenation reaction of internal alkynes with Ps-DFA.



Scheme 3. Preparation and reactivity of halogeno-cyclopropenes.

acidic conditions, leading to the formation of CF_2H-cyclopropene **3** with very minor epimerization of the stereogenic center (Scheme 4a). Furthermore, we showed that **2a** could easily be reduced to cyclopropane **4** as a single diastereoisomer in almost quantitative yield upon simple treatment with Pd/C/H_2 at room temperature without again any loss of the enantiopurity (Scheme 4b). Next, a Diels–Alder reaction of **2a** with 2,3-dimethylbutadiene was found to proceed smoothly to produce the fused-bicycle **5** in high yield and selectivities (>20:1, Scheme 4c). The absolute configuration of **5** was determined by X-ray crystallography analysis.[16] Finally, cyclopropene **2a** was also subjected to an intermolecular Pauson−Khand reaction,[19] furnishing the bicyclic cyclopentenone **6** in high yield without any erosion of its enantiopurity (Scheme 4d).[16]



Scheme 4. Synthetic transformations with cyclopropene **2a**.

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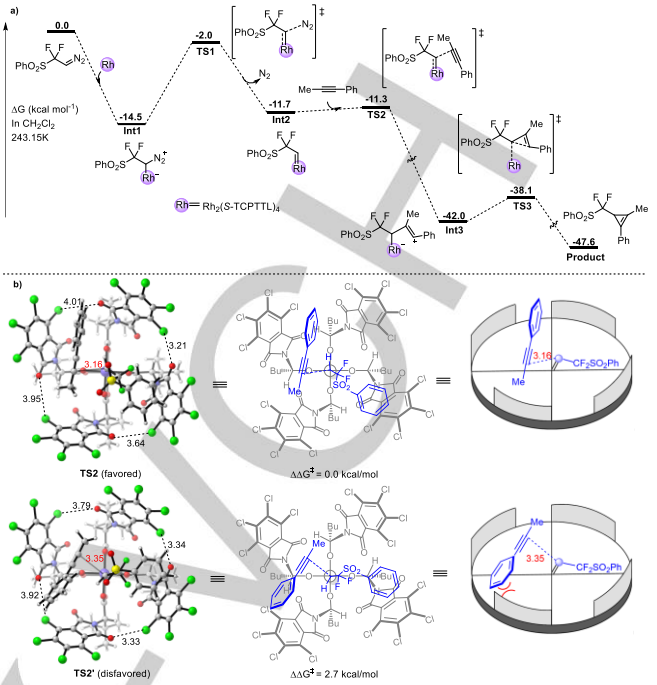
To better understand the origin of the selectivity for the cyclopropenation on disubstituted alkynes,[20] the reaction mechanism was investigated by density functional theory calculation[21] for the cycloaddition of Ps-DFA with **1a** using [Rh_2(*S*-TCPTTL)$_4$] as the catalyst (Scheme 5).[22] The theoretical calculations indicate that the reaction is highly exergonic by 47.6 kcal/mol, and the rate-determining step among the whole catalytic process could be the extrusion of nitrogen (**Int1** to **TS1**, 12.5 kcal/mol). The difluoroalkyl-substituted rhodium carbenoid **Int2** is stabilized relative to the starting reactants by 11.7 kcal/mol. This *in-situ*-formed organometallic intermediate is very electrophilic and tends to cyclopropenate with internal alkyne **1a** in a step-wise process involving a zwitterionic intermediate **Int3**. Based on these results and the previously reported C4-symmetry-like chiral crown conformation of [Rh_2(*S*-TCPTTL)$_4$],[20] the origin of enantioselectivity was proposed in Scheme 5b. In the located two transition states, the alkyne approaches the Rh-carbenoid with a tilted side-on trajectory preferentially from the hydrogen side. The calculated lengths of the forming C−C bonds are 3.16 Å in **TS2** and 3.35 Å in **TS2'**, implying that this step has a relatively early transition state ($\Delta_{\text{bond length}}$(TS-product) = 1.65 and 1.84 Å, respectively). The Gibbs free energy of **TS2** (leading to product *S*-**2a**) is 2.7 kcal/mol lower than that of **TS2'** (leading to product *R*-**2a**), which is consistent with the observed sense of asymmetric induction. The preferential formation of **TS2** over **TS2'** presumably results from the considerable steric repulsion between the aryl group located on the alkyne and the tetrachlorophthalimido group in **TS2'**.[22]



Scheme 5. Free energy profile for the Rh-catalysed cyclopropenation reaction between Ps-DFA and alkyne **1a** calculated at the SMD-B3LYP-D3/6-311+G**(Rh: SDD)//B3LYP/6-31G*(Rh: lanl2dz) level of theory and plausible stereochemical mode for enantioselective cyclopropenation. The selected bond lengths are in Å.

In summary, we have developed the first highly enantioselective Rh(II)-catalyzed cyclopropenation reaction of unactivated internal alkynes with a fluorinated diazo reagent (Ps-DFA) providing a facile route for the construction of a broad range of enantioenriched densely functionalized unsaturated three-membered carbocycles. This study brings an easy and straightforward answer to the long-standing challenge of catalytic enantioselective cyclopropenation of internal alkynes with acceptor-(only) carbene precursors. Furthermore, the synthetic utility of the obtained novel strained molecules has been demonstrated through versatile stereocontrolled transformations. Future investigations including substrate scope expansion and synthetic applications are ongoing in our laboratory, and these results will be reported in due course.

Acknowledgements

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Keywords: cyclopropenes • difluoromethyl group• diazo compounds• metal carbenes • internal alkynes

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[12] The preparation of the diazo reagent PS-DFA was shown in the bottom of Table 1, including sulfidation of ethyl bromodifluoroacetatesulfidation, reduction of ester, oxidation of sulfide, amination, and diazotization, with a total yield of 62%. For experimental details and our previous studies, see: a) J.-L. Zeng, Z. Chen, F.-G. Zhang, J.-A. Ma, *Org. Lett.* **2018**, *20*, 4562-4565; b) J.-A. Ma, J.-L. Zeng, F.-G. Zhang, China Patent CN 108383761A, 2018; c) X. Peng, M.-Y. Xiao, J.-L. Zeng, F.-G. Zhang, J.-A. Ma, *Org. Lett.* **2019**, *21*, 4808−4811; d) J.-L. Zeng, Y. Zhang, M.-M. Zheng, Z.-Q. Zhang, X.-S. Xue, F.-G. Zhang, J.-A. Ma, *Org. Lett.* **2019**, *21*, DOI: 10.1021/acs.orglett.9b02989.

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[16] CCDC 1934783 (**2d**), 1934959 (**5**), and 1934966 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre. HF_2CCHN_2 was also employed to react with 1-phenyl-1-propyne **1a** under otherwise identical reaction conditions, but resulted in the formation of desired product **2a** in trace amount (<10% yield) with only 30% ee.

[17] Two terminal alkynes (phenyl acetylene and 4-phenyl-1-butyne) have been evaluated in this reaction under otherwise identical conditions. In the case of 4-phenyl-1-butyne, the desired cyclopropene **2aq** was obtained in 70% yield, but with no enantioselectivity. No desired cyclopropene was observed when phenyl acetylene was employed (unidentified complex mixtures).

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[22] See the supporting information (SI) for calculation details. Noncovalent interaction (NCI) analysis on **TS2** and **TS2'** has also been conducted. As shown in Scheme S2 in the SI, the NCIPLOT suggests a steric repulsion between the aryl group of the alkyne and the tetrachlorophthalimido group in transition state **TS2'**. Therefore, the enantioselectivity is assumed to be mainly controlled by the steric effect of the alkyne-insertion step, which is in line with the proposed stereo-control model in Scheme 5b.

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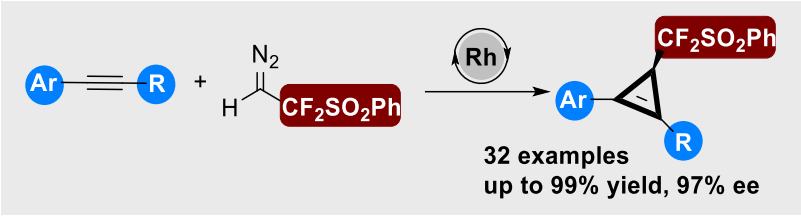

Overcoming Internal Alkynes: A Rh(II)-catalysed highly enantioselective cyclopropenation reaction of difluorodiazoethane ($PhSO_2CF_2CHN_2$) with challenging internal alkynes is disclosed (up to 99% yield, 97% ee). Versatile stereoselective transformations of these unique strained cyclopropenes is also demonstrated.

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Catalytic Enantioselective Cyclopropenation of Internal Alkynes: Access to Difluoromethylated Three-Membered Carbocycles