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Highly Enantioselective Synthesis of Trifluoromethyl Cyclopropanes by Using Ru(II)–Pheox Catalyst

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An asymmetric synthesis of various trifluoromethyl cyclopropanes from olefins such as vinyl ferrocene, vinyl ethers, vinyl amines, vinyl carbamates and dienes was achieved by using Ru(II)–Pheox catalyst. This catalytic system can perform under low catalyst loading (3 mol%) compared with previous reports, and the desired cyclopropane products are obtained in high yields with excellent diastereoselectivity (up to >99:1) and enantioselectivity (up to 97% ee).

The derivatization of organic compounds with fluorinated units often affects their physicochemical and biological properties.[1,2] Consequently, approximately 20% of all pharmaceuticals and agrochemicals contain at least one fluorine atom.[3] In particular, trifluoromethyl cyclopropanes constitute attractive synthons in medicinal chemistry as they combine the conformational rigidity of three-membered rings with the unique and often highly beneficial feature of fluorinated substituent.[4] Indeed, several biological active compound substances with trifluoromethyl cyclopropane structure have been found such as analgesic **1**, Insecticide **2** and antibiotic **3** (Figure 1).[5]

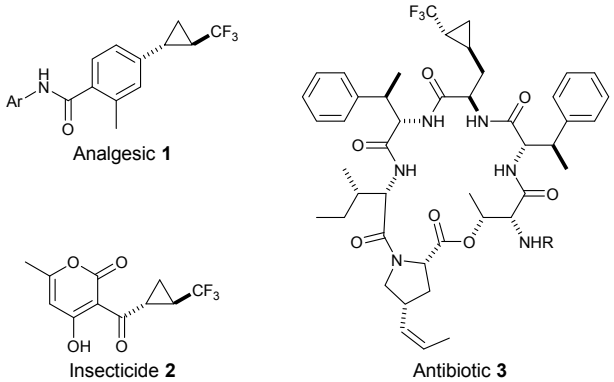
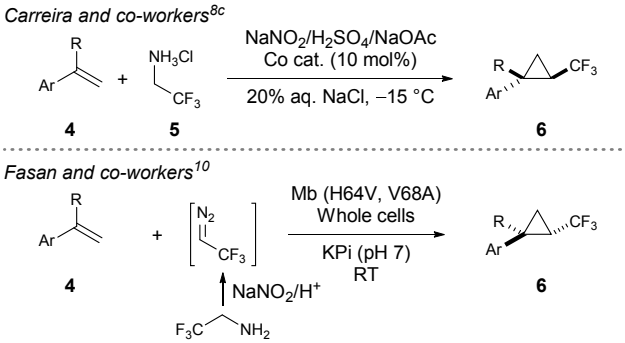


Figure 1 Examples of biologically relevant trifluoromethyl cyclopropane derivatives.

Among various methods to access cyclopropane-ring substructure, the efficient way is transition-metal catalyzed cyclopropanation of olefins with diazo compounds.[6] Recently, trifluorodiazoethane (CF_3CHN_2) is attracting attention as an carbene precursor for the construction of trifluoromethyl-containing chiral cyclopropanes. In 1943, CF_3CHN_2 was first synthesized from trifluoroethylamine and sodium nitrite.[7] However, CF_3CHN_2 did not find wide application in synthesis because of the potentially toxic and explosive gaseous compound for a long time. In 2010, The Carreira group developed convenient conditions to generate CF_3CHN_2 in situ in a solution.[8a] Since then, trifluoromethylcarbene has proven to be a versatile intermediate for the synthesis of trifluoromethyl-containg compounds,[8,9] which have found widespread application in medical and agricultural chemistry due to the unique properties of CF_3-functionality. To date, however, only a few studies have addressed the problem of developing highly enantioselective cyclopropanation reaction (Scheme 1). In 2011, the Carreira groups described the highly enantioselective Co(III)–salen-catalyzed synthesis of trifluoromethylated cyclopropanes under high catalyst loading (10 mol%).[8c] In 2017, the Fasan groups also developed a biocatalytic strategy for the asymmetric synthesis of



Scheme 1 Highly enantioselective synthesis of trifluoromethyl cyclopropanes.

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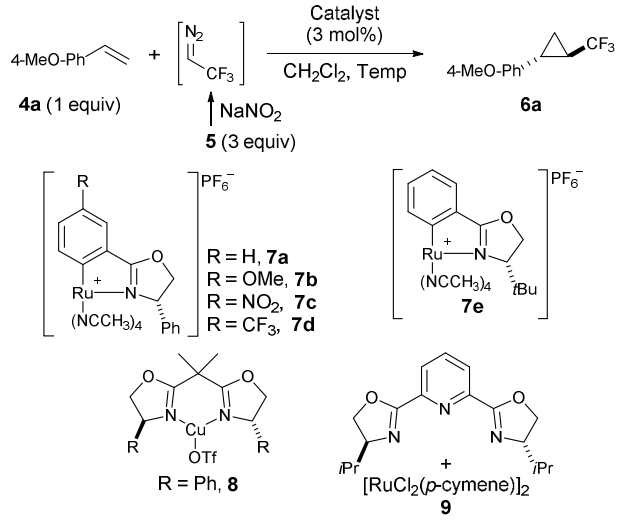
trifluoromethyl cyclopropanes via myoglobin catalyzed addition of trifluoromethylcarbene to olefins.[10] However, the bulkiness of the CF_3CHN_2 moiety was found to be an important factor in providing high enantiocontrol, and the cyclopropanation of CF_3CHN_2 with olefins such as vinyl ferrocene, vinyl ethers, vinyl amines, vinyl carbamates and dienes has not been reported yet. Herein, we report a highly stereoselective asymmetric cyclopropanation of various olefins with CF_3CHN_2 catalyzed by Ru(II)–Pheox complexes.[11]

To implement approach, we initially tested the possibly to carry out the Ru(II)–Pheox catalyzed cyclopropanation of *p*-MeO-styrene. We first examined the reaction of CF_3CHN_2 with MeO-styrene **4a** in the presence of 3 mol% of Ru(II)–Pheox **7a** at room temperature (Table 1, entry 1). To our delight, the desired trifluoromethyl cyclopropane product **6a** was obtained in 94% yield with high *trans*-selectivity (95:5 dr) and high enantioselectivity (96% *trans* ee). Chiral Ru(II)–Pheox catalysts bearing electron-donating or electron-withdrawing substituents (R = OMe, NO_2, CF_3) provided no improvement in yield or enantioselectivity (Table 1, entries 4-6). Moreover, performing the reaction at lower temperatures afforded higher enantioselectivities (Table 1, entry 3). Next, we tested the reaction with chiral Cu(I)–Box **8** and Pybox **9**[12] complexes, which have been reported to be efficient catalysts for asymmetric cyclopropanation reactions; however, under these conditions, the desired product was obtained in low yield with moderate enantioselectivity (Table 1, entries 8-9).

With the optimized conditions in hand, we next explored the scope and generality of the catalytic system (Table 2). First, a variety of vinyl arenes were reacted with CF_3CHN_2. Styrene derivatives bearing electron-donating groups, such as 4-MeO, and 2-MeO groups, were transformed into the corresponding trifluoromethyl cyclopropanes in high yields with excellent diastereo- and enantioselectivities (Table 2, entries 1-2). However, 4-Me_2N-styrene showed reduced yield because of side reactions. The reaction of styrene derivatives bearing electron-withdrawing groups at the 4-position also proceeded with high stereoselectivity and moderate yields (Table 2, entries 5-6). Moreover, vinyl ferrocene could also be cyclopropanated to afford the corresponding product **6g** in high yield and with high diastereo- and enantioselectivity (Table 2, entries 7). Since ferrocene derivatives have found widespread applications in catalytic and pharmaceutical chemistry, and the incorporation of CF_3-cyclopropyl motif into this scaffold may find new applications[13].

Encouraged by these results, we turned our attention to the cyclopropanation of electron-rich olefins such as vinyl

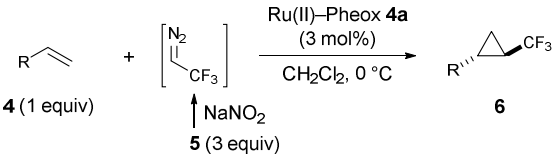
Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Temp (°C)	Yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*	*cis*
1	**7a**	rt	94	95/5	96	84
2[e]	**7a**	rt	80	95/5	94	77
3	**7a**	0	93	95/5	96	88
4	**7b**	rt	88	95/5	95	87
5	**7c**	rt	89	93/7	96	85
6	**7d**	rt	88	94/6	93	82
7	**7e**	rt	86	93/7	92	80
8	**8**	rt	20	69/31	56	50
9	**9**	rt	0	-	-	-

[a]Reaction conditions : to a solution of catalyst and styrene (1.0 mmol) in CH_2Cl_2 was added a solution of in situ generated CF_3CHN_2. [b]Isolated yield. [c]Determined by NMR. [d]Determined by chiral HPLC analysis. [e]1 mol% of catalyst was used.

Table 2 Cyclopropanation of vinyl arenes



Entry	Ar	Yield[a] (%)	*trans*/*cis*[b]	ee[c] (%)
1	MeO	96 **6a**	98/2	96
2	OMe	99 **6b**	95/5	96
3	Me_2N	56 **6c**	90/10	96
4		80 **6d**	98/2	97
5[d]	Cl	77 **6e**	97/3	96
6[d]	O_2N	48 **6f**	>99/1	97
7	Fe	85 **6g**	93/7	92

[a]Isolated yield. [b]Determined by NMR. [c]Determined by chiral HPLC analysis. [d] 6 mol% of Ru–Pheox was used at rt.

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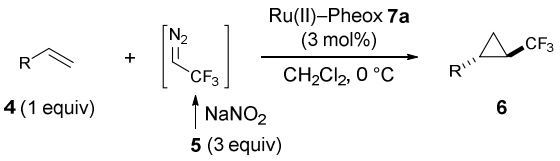
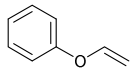
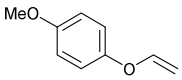
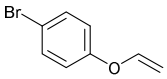
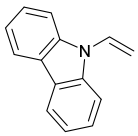
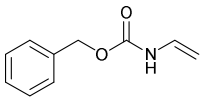
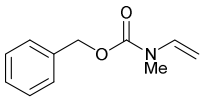
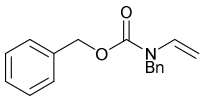
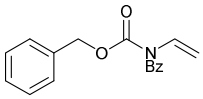
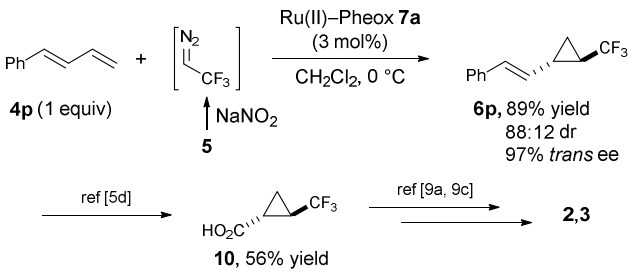
ethers, vinyl amines, and vinyl carbamates (Table 3). Under the optimized conditions, all reactions was proceeded in high yield with high enantioselectivity. However, 4-Br phenyl vinyl ether **6j** showed reduced reactivity because of the electron withdrawing properties. Unfortunately, the diastereoselectivity slightly decreased in the cyclopropanation of vinyl carbamate (Table 3, entry 5). This is probably due to hydrogen bonding between the *N*-hydrogen of the vinyl carbamate and the fluorine of the carbenoid intermediate, which leads to a *cis*-selective approach of the reactants as described in our previous report.[11d] Benzyl benzyl(vinyl)carbamate **6n** also decreased diastereoselectivity because of steric hindrance. Moreover, the cyclopropanation of benzyl benzoyl(vinyl)carbamate **6o** was also investigated (Table 3, entry 8). Interestingly, the diastereoselectivity could be increased to 92:8 dr, while the reactivity decreased.

Table 3 Cyclopropanation of vinyl ethers and vinyl amines



Entry	Ar	Yield[a] (%)	*trans*/*cis*[b]	ee[c] (%)
1		74 **6h**	90/10	93
2		88 **6i**	91/9	92
3[d]		81 **6j**	88/12	92
4		96 **6k**	96/4	97
5		93 **6l**	80/20	92
6		94 **6m**	85/15	97
7		92 **6n**	75/25	95
8[d]		90 **6o**	92/8	91

[a] Isolated yield. [b] Determined by NMR. [c] Determined by chiral HPLC analysis. [d] 6 mol% of Ru–Pheox was used at rt.



Scheme 2 Preparation of trifluoromethylated vinyl cyclopropane

Finally, to demonstrate the utility of our direct enantioselective cyclopropanation, we prepared vinyl cyclopropane **6p** with high enantiopurity. This compound can easily transform to trifluoromethylcyclopropane carboxylic acid **10** by oxidative cleavage which was known to be a key intermediate in the formation of insecticide **2**[5a] and antibiotic **3**[5c].

In summary, we have developed a highly stereoselective Ru(II)–Pheox-catalyzed asymmetric cyclopropanation of various olefins with CF_3CHN_2. Variously functionalized trifluoromethyl cyclopropanes were synthesized in high yields (up to 99%) with excellent enantioselectivity (up to 97% ee). CF_3CHN_2 proved to be efficient carbene precursors for asymmetric olefin cyclopropanation reactions catalyzed by Ru(II)–Pheox complexes. Further investigations on the application of functionalized chiral trifluoromethyl cyclopropanes in organic synthesis are currently underway in our laboratory.

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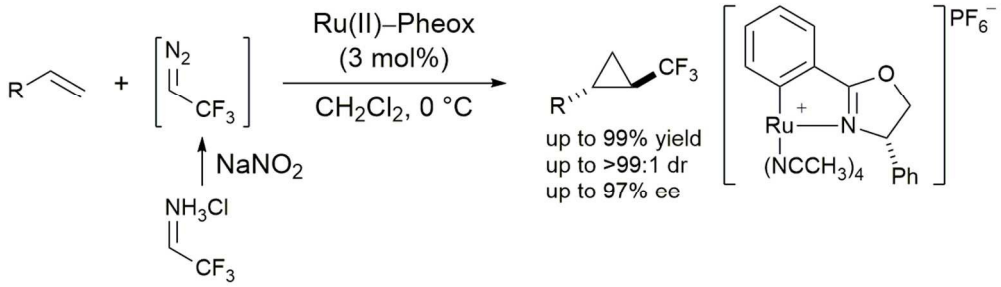

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