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Enantioselective Synthesis of Trifluoromethyl-Substituted Cyclopropanes

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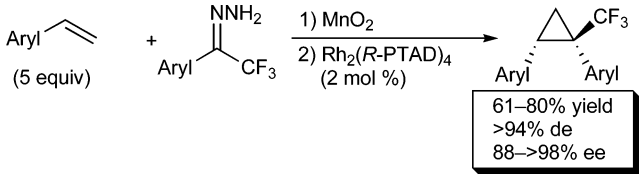
ABSTRACT



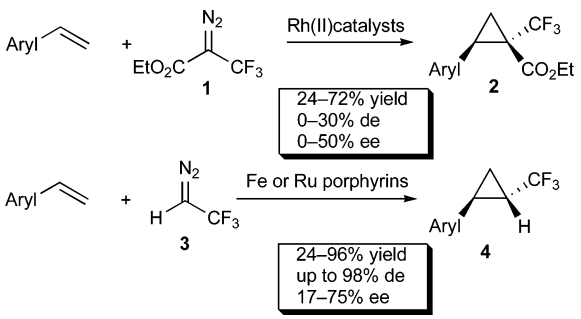
The reaction of 1-aryl-2,2,2-trifluorodiazoethanes with alkenes, catalyzed by the adamantylglycine-derived dirhodium complex Rh_2(*R*-PTAD)$_4$, generates trifluoromethyl-substituted cyclopropanes with high diastereoselectivity (>94%) and enantioselectivity (88–>98%).

The presence of fluorine functionality in organic compounds can have profound effects on their physical and chemical properties.[1] Fluorinated derivatives of pharmaceutical agents can modulate pharmacokinetic, electronic,[2] lipophilic,[3] and steric properties.[4] These effects can ultimately lead to improved efficacy of the therapeutic agent.[5] Consequently, there is considerable interest in developing new methods for the selective introduction of fluorinated groups into organic compounds.

2,2,2-Trifluorodiazoethanes have recently been recognized as attractive reagents for introduction of a trifluoromethyl group. On metal-catalyzed extrusion of nitrogen, the resulting metal carbenoid has been shown to be effective at cyclopropanation,[6] ylide generation,[7] and X−H insertion.[8]

The development of enantioselective transformations with these trifluoromethyl reagents is an attractive challenge. So far, enantioselective reactions have been limited to two systems. The rhodium(II)-catalyzed cyclopropanations conducted with ethyl 3,3,3-trifluoro-2-diazopropionate (**1**) generated cyclopropanes **2** in moderate yields (24−72%), diastereoselectivity (0−30% de), and enantioselectivity (0−50% ee) (Scheme 1).[6a] The generally poor results were

Scheme 1



ascribed to the fact that the rhodium carbenoid would be highly electrophilic due to the presence of two electron-

(1) (a) Hiyama, T. *Organofluorine Compounds. Chemistry and Applications*; Springer: New York, 2000. (b) O'Hagan, D.; Harper, D. B. *J. Fluorine Chem.* **1999**, *100*, 127.

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(6) (a) Müller, P.; Grass, S.; Shahi, S. P.; Bernardinelli, G. *Tetrahedron* **2004**, *60*, 4755. (b) Le Maux, P.; Juillard, S.; Simonneaux, G. *Synthesis* **2006**, *10*, 1701. (c) Wang, Y.; Zhu, S.; Zhu, G.; Huang, Q. *Tetrahedron* **2001**, *57*, 7337.

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withdrawing substituents. Somewhat better results were obtained with iron and ruthenium porphyrin catalyzed cyclopropanations of 2,2,2-trifluorodiazoethane (**3**). The cyclopropanes **4** were formed with high diastereoselectivity (up to 98% de) and moderate enantioselectivity (17−75% ee).[6b] The asymmetric induction is still inferior to the reactions of the more traditional carbenoid source, ethyl diazoacetate.[9]

In recent years, considerable attention has been directed toward the chemistry of donor/acceptor-substituted rhodium carbenoids (**5**) (Figure 1).[10] These carbenoids are more stable

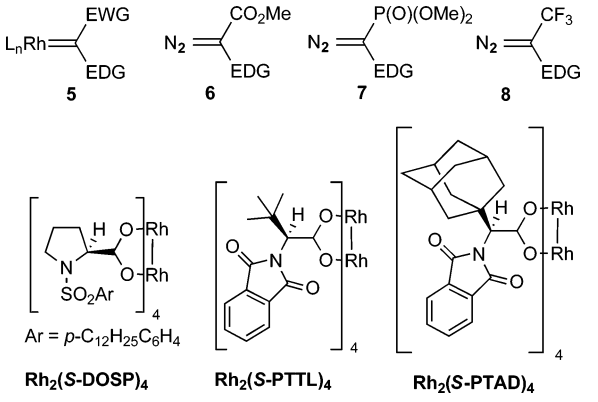
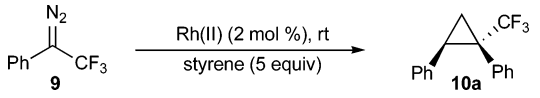


Figure 1. Carbenoid and catalyst structures.

than the conventional carbenoids, lacking a donor group, and are capable of a range of highly selective reactions. Rh$_2$(*S*-DOSP)$_4$ is ideally suited for the reactions of diazo esters **6**, and high enantioselectivity is routinely achieved in substrates with a range of aryl and vinyl functionality as the electron-donating group.[11] In contrast, the nature of the electron-withdrawing group dramatically influences the effectiveness of the chiral catalyst. With the diazophosphonates **7**, Rh$_2$(*S*-PTAD)$_4$ is the most effective catalyst.[12] In this paper, we describe exploratory studies on the cyclopropanation chemistry of the trifluoromethyl derivatives **8**.

The initial screen of the influence of the trifluoromethyl group on the reactions of donor/acceptor carbenoids was conducted on 1-phenyl-2,2,2-trifluorodiazoethane (**9**).[13] This compound was prepared from the corresponding tosylhydrazone in about 40% yield, but due to its high volatility, it was difficult to remove all traces of solvent from **9**. The effect of different catalysts (2 mol %) was explored in a standard reaction between **9** and styrene (5 equiv) to generate the trifluoromethyl-substituted cyclopropane **10a** (Table 1).

Table 1. Catalyst Optimization Studies

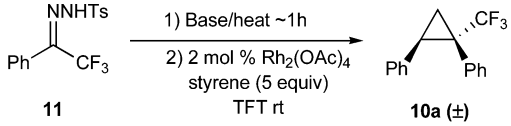


Rh(II) catalyst	solvent	de (%)[a]	ee (%)[b]	yield (%)[c]
Rh$_2$(*S*-DOSP)$_4$	hexanes	94	40[d]	80
Rh$_2$(*S*-DOSP)$_4$	TFT	90	37[d]	60
Rh$_2$(*S*-PTTL)$_4$	TFT	>94	97	95
Rh$_2$(*S*-PTTL)$_4$	DCM	>94	86	96
Rh$_2$(*S*-PTAD)$_4$	TFT	>94	>98	94

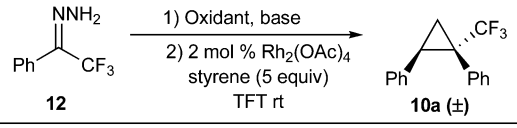
[a] de determined by ^{1}H NMR of crude material. [b] ee determined by a chiral HPLC OJ column. [c] Estimated isolated yields of **10a** after purification by column chromatography because **9** was contaminated with traces of pentane (<5% by ^{1}H NMR). [d] Opposite enantiomer preferentially formed. TFT = α,α,α-trifluorotoluene.

Rh$_2$(*S*-DOSP)$_4$ was not especially effective in this reaction (60% yield, 90% de, 37% ee), but much better results were achieved with Hashimoto's catalyst Rh$_2$(*S*-PTTL)$_4$[14] (95% yield, >94% de, 97% ee). The adamantyl derivative Rh$_2$(*S*-PTAD)$_4$ gave even better results (94% yield, >94% de, >98% ee). As previously noted,[12] Rh$_2$(*S*-DOSP)$_4$ and Rh$_2$(*S*-PTAD)$_4$ result in opposite asymmetric induction. Lowering the rhodium(II) catalyst loading to 1 mol % had a negative effect on the yield and enantioselectivity (39% yield, 74% ee).

Table 2. Optimization of a Two-Step Sequence



solvent	base	de (%)[a]	yield (%)[b]
MeOH	MeONa	>94	40
THF	NaH	>94	45-50



oxidant	base	solvent	de (%)[a]	yield (%)[b]
Pb(OAc)$_4$	TMG[c]	DMF	>94	40
MnO_2	none	TFT	>94	73

[a] de determined by ^{1}H NMR of crude material. [b] Isolated yields after column chromatography purification. [c] *N*′*N*′*N*′*N*′-Tetramethylguanidine.

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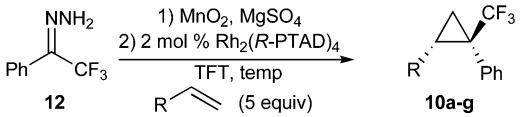
Further optimization studies were then conducted using a two-step sequence, to avoid isolation of the diazo compound **9**.[15] A summary of the key results is given in Table 2. Reaction of the tosylhydrazone **11**[13a] with NaH generated the diazo compound **9** *in situ*, which was then exposed to the cyclopropanation conditions to give **10a** in 45−50% combined yield and >94% de. Oxidation of the hydrazone **12** was an alternative process,[16] and when this was conducted with MnO_2[17] in trifluorotoluene (TFT) followed by a 3 h syringe pump addition of the resulting orange filtrate to $Rh_2(OAc)_4$ and styrene, **10a** was isolated in an overall 73% yield and >94% de.

The two-step process is effective with a range of styrene derivatives (Table 3). In the Rh_2(*R*-PTAD)$_4$-catalyzed reactions of **12**, the cyclopropanes **10a**−**f** were formed in 61−76% yield, >94% de, and 88−>98% ee. The reaction was far less effective with unactivated olefins as the $Rh_2(OAc)_4$-catalyzed cyclopropanation of 1-decene (5 equiv) went in only 20% yield, even under refluxing conditions.

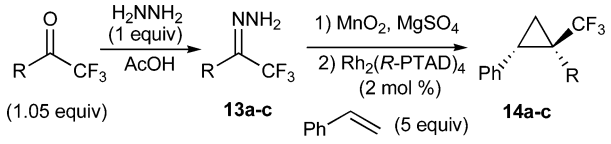
Table 3. Cyclopropanation of Various Styrenes with **12**



product	temp (°C)	R	de (%)[a]	ee (%)[b]	yield (%)[c]
10a	rt	C_6H_5	>94	>98	71
10b	rt	*p*-MeC_6H_4	>94	90	72
10c	rt	*p*-$MeOC_6H_4$	>94	88	76
10d	rt	*p*-ClC_6H_4	>94	90	64
10e	rt	*p*-$CF_3C_6H_4$	>94	>94[d]	61
10f	rt	2-naphthyl	>94	89	75
	0	2-naphthyl	>94	90	72
10g	reflux	*n*-octyl	–	–	20[e]

[a] de determined by ^{1}H NMR of crude material. [b] ee determined by a chiral HPLC OJ column. [c] Isolated yield after column chromatography purification. [d] Due to the broad nature of the peaks, the signal for the minor enantiomer was not observed. [e] Reaction was conducted with the achiral catalyst $Rh_2(OAc)_4$.

Table 4. Cyclopropanation of Styrene with **13a**−**c**



compd	R	**13** yield (%)[a]	**14** yield (%)[a]	de (%)[b]	ee (%)[c]
a	*p*-MeC_6H_4	91	75	>94	>98
b	*p*-FC_6H_4	90	78	>94	97
c	*p*-BrC_6H_4	91[d]	77	>94	98

[a] Isolated yields after column chromatography purification. [b] de determined by ^{1}H NMR of crude material. [c] ee determined by a chiral HPLC OJ column. [d] Slight impurities were seen in ^{1}H NMR of isolated material.

The reaction could be extended to a range of trifluoromethyl hydrazones (Table 4). The hydrazones **13a**−**c** were formed easily from the corresponding trifluoromethyl ketones by condensation of hydrazine in ethanol with a catalytic amount of acetic acid. The two-step process (oxidation/cyclopropanation) was then performed on **13a**−**c** to form the cyclopropanes **14a**−**c** in 71−78% yield, >94% de and 97−>98% ee. The data show that electron-withdrawing substituents on the phenyl ring increase the yield of the cyclopropane but slightly lower the enantioselectivity.

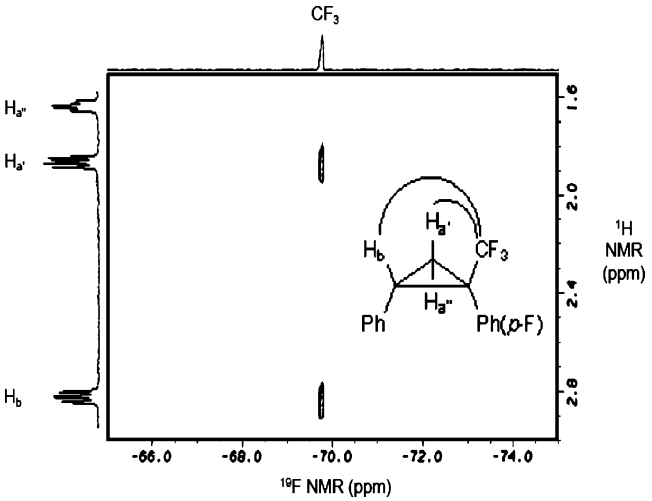
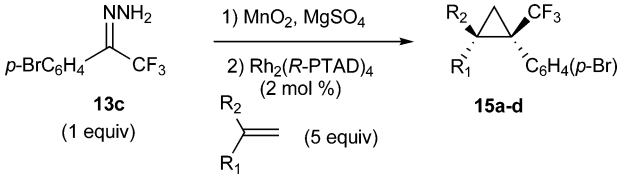


Figure 2. $^{19}F\{^1H\}$ HOESY spectra of **14b**.

Table 5. Rh_2(*R*-PTAD)$_4$-Catalyzed Cyclopropanation by **13c**



product	R_1	R_2	yield (%)[a]	de (%)[b]	ee (%)[c]
15a	*p*-BrC_6H_4	H	78	>94	>98
15b	*p*-$NO_2C_6H_4$	H	75	>94	>98
15c	2-naphthyl	H	80	>94	98
15d	Ph	Ph	75	–	>98

[a] Isolated yields after column chromatography purification. [b] de determined by ^{1}H NMR of crude material. [c] ee determined by a chiral HPLC OJ column.

A $^{19}F\{^1H\}$ HOESY NMR experiment[18] on cyclopropane **14b** was performed to determine its relative stereochemistry

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(15) Diazo compounds should always be handled with care. In this case, we did not observe any instability problems with **9**, but it was difficult to obtain in a pure form because it was relatively volatile.

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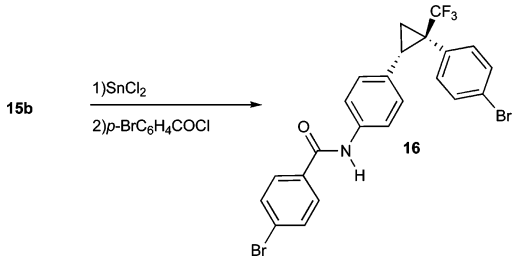
Scheme 2



(Figure 2). The spectrum shows direct correlations of the trifluoromethyl group at −69.8 ppm with two cyclopropane protons at 2.84 and 1.88 ppm. No correlation was observed for the cyclopropane proton at 1.65 ppm. It was concluded that the relative stereochemistry of **14b** was the expected (*Z*)-diarylcyclopropane. Thus, as is typical for donor/acceptor carbenoids, the major cyclopropane formed has the donor group cis to the alkene substituent.

To verify the absolute configuration of the cyclopropane, the bromophenyl hydrazone **13c** was reacted with a variety of alkenes with the goal of generating a crystalline product suitable for X-ray analysis (Table 5). None of the products gave suitable crystalline material, but these efforts further illustrate the potential of this chemistry as the cyclopropanes **15a**−**d** were obtained in 98% ee and above.

After considerable experimentation, a crystalline product was obtained by reduction of the enantiomerically pure nitrocyclopropane **15b** with $SnCl_2$ to the aniline, followed by *N*-acylation to form **16** (Scheme 2). X-ray crystallographic analysis of crystals of **16** revealed that the absolute configuration was (1*R*,2*S*). All other trifluoromethyl-substituted cyclopropanes were tentatively assigned the same relative and absolute configuration by analogy.

In conclusion, Rh_2(*R*-PTAD)$_4$ has shown to be an effective chiral catalyst in the decomposition of 1-phenyl-2,2,2-trifluorodiazoethane and its derivatives to form chiral trifluoromethyl-substituted cyclopropanes with very high enantioselectivity. These studies further broaden the range of donor/acceptor-substituted rhodium carbenoids that are capable of highly stereoselective transformations.

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Supporting Information Available: Experimental data for the reported reactions and a CIF file for the X-ray crystallographic data for **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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