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Transition metal-catalyzed cyclopropanation of alkenes in fluorinated alcohols

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ABSTRACT

The system hexafluoroisopropanol/ethyl diazoacetate/$Cu(OTf)_2$ is efficient for the cyclopropanation reaction. The process is experimentally simple, and efficient with various olefins in particular terminal, disubstituted double bonds.

1. Introduction

Metal-catalyzed cyclopropanation remains of great interest because of its versatile applications in synthetic organic chemistry and in biological field [1]. Consequently, numerous methods have been developed for this synthetic transformation [1]. In particular, metal catalyzed cyclopropanation of alkenes with ethyldiazoacetate (EDA) is one of the most simple and straightforward approaches [2]. Generally these reactions are performed under anhydrous conditions due to the competiting O–H insertion reaction. However, some recent reactions have been reported in water, and in alcohol solvents [3]. These latter conditions require the use of specific hydrophobic modified catalysts and reagents. An alternative would be to perform the reaction in non nucleophilic alcohols. Under these conditions, the use of classical metal catalyst should be possible.

We and others showed that fluorinated alcohols, trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP), presenting some unique properties (in particular low nucleophilicity and also high hydrogen bonding donor ability, high ionizing power) were very efficient solvents in significant reactions and did not interfere into most reactions [4]. An asymmetric cyclopropanation reaction of styrene derivatives with EDA has been reported in trifluoroethanol at 80 °C with vitamin B_{12} derivatives as catalysts [5]. Furthermore recently we reported that diazo compounds are stable in fluoroalkyl alcohols (TFE and HFIP) and exhibit a great reactivity in insertion reaction of acids in the absence of catalyst [6]. In this paper, we now report our results concerning the cyclopropanation reaction with EDA in these fluoroalkyl alcohols.

2. Results and discussion

First, we explored the cyclopropanation reaction in fluoro alcohols between EDA **2** and styrene **1** without catalyst. No reaction occurred at room temperature, not even in refluxing solvent. Starting materials were completely recovered. Next we investigated the efficacy and the reactivity of the fluorinated alcohols in cyclopropanation at room temperature, in the presence of a wide range of usual metal catalysts (Table 1).

An equimolar amount of olefin and EDA **2** with $Cu(OTf)_2$ 1 mol%, led to cyclopropanes **3** in 85% of conversion in HFIP as solvent (entry 1). The reaction was successful with complete conversion in the presence of 1.5 equivalent of **2** to afford a mixture of *trans*/*cis* cyclopropanes (entry 2) [7]. The diastereomers **3**-*trans* and **3**-*cis* could be easily separated by column chromatography and were characterized by comparison of their NMR spectra with those of authentic samples [8]. The *Trans*/*Cis* ratio obtained in HFIP (42/58) is similar to that obtained in other solvents such as CH_2Cl_2, Et_2O, and toluene [2]. The advantages of HFIP in this reaction is the lack of specific experimental requirements: there is no need of slow addition, neither of excess of EDA, and/or using excess of the nucleophilic substrate which are drawbacks of cyclopropanation reactions. In HFIP, the formation of the side product which is the dimerisation of the EDA is limited (<10%), and no product of insertion of the OH group of HFIP was observed in despite of the presence of metal catalyst. The very low nucleophilicity of HFIP in comparison with TFE is spectacular. While in TFE no cyclopropanes were observed (entries 3, 5), a side product, corresponding to the insertion of the trifluoroethanol on EDA, was formed after 1 h

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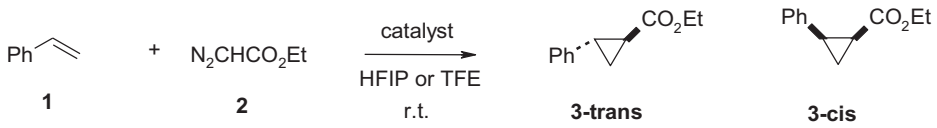
Table 1
Cyclopropanation in fluorinated alcohols.



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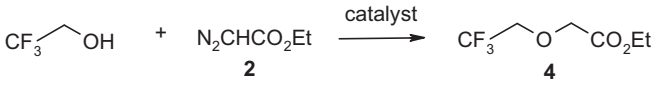
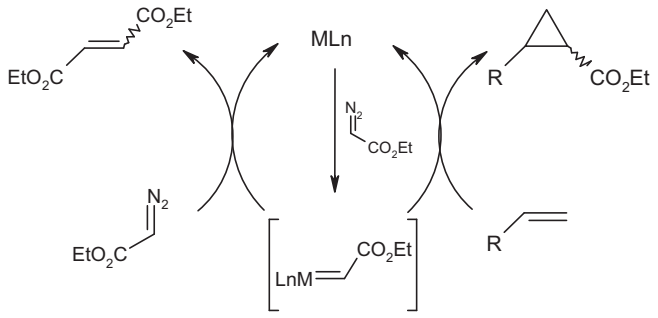
Entry	Catalyst (mol%)	EDA (equiv.)	Solvent	Time (h)	Conversion of 1 (%)	3-*Trans*/*Cis*[b]
1	$Cu(OTf)_2$ (1)	1.0	HFIP	4	85	42/58
2	$Cu(OTf)_2$ (1)	1.5	HFIP	4	100	42/58
3	$Cu(OTf)_2$ (1)	1.5	TFE	2	0[a]	–
4	$Rh_2(OAc)_4$ (1)	1.5	HFIP	8	55	48/52
5	$Rh_2(OAc)_4$ (1)	1.5	TFE	1	0[a]	–
6	$Pd(OAc)_2$ (1)	4	HFIP	14	80	40/60
7	CuI (5)	4	HFIP	24	75	40/60
8	Co_2O_3 (2)	2	HFIP	12	65	43/57

[a] Insertion of TFE on EDA.
[b] The ratio is based on GC analysis of crude mixture.



Scheme 1.



Scheme 2.

(Scheme 1). This clearly demonstrates the great advantage of HFIP which is not prone to undergo an insertion on EDA.

The use of other catalysts did not improve the course or the stereoselectivity of the reaction. With $Rh_2(OAc)_4$, the reaction was less efficient in HFIP, and afforded the cyclopropanated product with 55% of conversion (entry 4). With $Pd(OAc)_2$, CuI, and cobalt oxide the reaction proceeded with moderate conversions (80, 75 and 65% respectively, entries 6–8). For these different metals, an excess of **2** was required to obtain a complete conversion due to the competition with dimerisation of EDA.

The catalytic cyclopropanation is assumed to proceed via a carbene transfer mechanism similar to that proposed for metal mediated cyclopropanation systems (Scheme 2) [9,2b,2c]. In addition it is reported in the literature that the active catalyst for cyclopropanation, is copper(I) which is obtained *in situ* by reduction of Copper(II)triflate with the diazo compound [10].

Having in hand new conditions of cyclopropanation reaction (HFIP, 1% $Cu(OTf)_2$, 1.5 EDA, 1 alkene), various alkenes were used as substrates. Results are summarized in Table 2.

Table 2
Cyclopropanation in HFIP with various alkenes.[a]

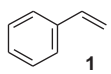
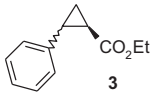
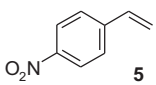
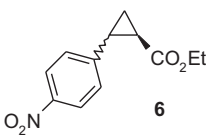
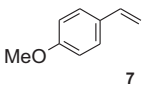
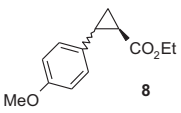
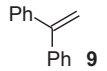
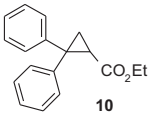
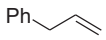
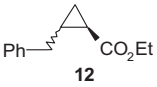
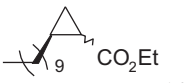
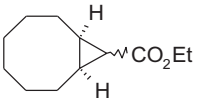
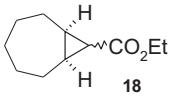
Entry	Alkene	Product	Time (h)	Yields (%)[b]	*Trans*/*Cis*[c]
1	 1	 3	4	86	42/58
2	 5	 6	12	10	58/42
3	 7	 8	5	Traces	–

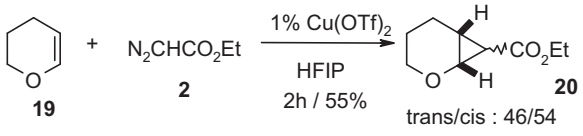
Table 2 (*Continued*)

Entry	Alkene	Product	Time (h)	Yields (%)[b]	*Trans*/*Cis*[c]
4	 **9**	 **10**	5	Traces	–
5	 **11**	 **12**	3	56	44/56
6	 **13**	 **14**	9	98	41/59
7	 **15**	 **16**	3	75	27/73
8	 **17**	 **18**	5	82	20/80

[a] 1 mol% of $Cu(OTf)_2$, 1.5 equiv. of EDA, 1 equiv. of alkene in HFIP.
[b] Isolated yield of *cis*/*trans* isomers.
[c] The ratio is based on GC analysis of crude mixture.

From *p*-nitro-styrene **5**, the corresponding cyclopropane **6** was obtained in very low yield (10%). Furthermore from *p*-methoxy styrene **7** and 1-phenyl styrene **9** (entries 3, 4), only traces of cyclopropanes were observed. Under these conditions (HFIP, copper catalyst) these styrene derivatives polymerised immediately. With the hope to disfavour polymerisation, the smoother catalysts (Pd, Rh) were checked but no reaction occurred. The dimerisation of EDA was only observed. The alkyl substituted olefins **11** and **13** afforded the corresponding cyclopropanes **12** and **14** in 56% and 98% yields respectively. With cyclic alkenes such as cyclooctene **15** and cycloheptene **17**, reaction was also efficient and furthermore stereoselective (entries 7, 8), similarly to what was previously described in the literature [11].

We previously reported that HFIP acts as self-promoter and reagent in the reaction of addition onto enol ether [12]. So an investigation on the competition between HFIP addition and cyclopropanation have been investigated. Indeed with dihydrofuran, ethyl and butyl enol ethers, from the addition of $Cu(OTf)_2$ the formation of hexafluoropropyloxy acetals is instantaneous. Conversely with the dihydropyran **19** the corresponding acetal was not formed. The reaction provided after 2 h cyclopropane **20** as 54/46 a mixture of *cis*/*trans* isomers (Scheme 3).



Scheme 3.

3. Conclusion

The system hexafluoroisopropanol/$Cu(OTf)_2$ is proved to be efficient for the cyclopropanation reaction. The great advantages of HFIP as solvent in these reactions are: – easy process (a slow addition is not required); – chemioselectivity (low amounts of side dimerisation products); – economy of reagent (only one 1% of catalyst, 1.5 of EDA). The process is compatible with various olefins in particular terminal, or cyclic double bonds.

4. Experimental

All commercially available reagents were used without further purification. THF and Et_2O were distilled over Na/benzophenone. Toluene was distilled over NaH. Distillations were run under argon atmosphere. ^1H NMR spectra were recorded at 200, 300 or 400 MHz, and ^{13}C NMR at 50, 75 or 100 MHz. Me_4Si was used as external standard. ^{19}F NMR spectra were recorded at 188 MHz using $CFCl_3$ as external standard. Chemical shifts (δ) are reported in ppm (s: singlet, d: doublet, t: triplet, q: quadruplet, m:multiplet) relative to TMS. Coupling constants are reported in hertz. Melting points were measured on a Büchi apparatus. Infra red were performed on a Brucker. Gas chromatography analysis were performed using a Hewlett Packard 4890A instrument with a capillary column SGE BP*5 (10 m, Ø 0.25 mm). Flash column chromatography was performed using 40–60 μm and 70–200 Merck silica gel.

4.1. Cyclopropanation reaction: general procedure

To a solution of olefin (1.0 mmol) and $Cu(OTf)_2$ (0.01 mmol) in HFIP (1.5 ml) was added ethyldiazoacetate (EDA, 1.5 mmol) at 0 °C. After stirring at room temperature until completion of reaction (monitored by GC analysis), the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (2 ml), and extracted with CH_2Cl_2 (2× 5 ml). The organic layers were washed with brine (10 ml), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel.

4.1.1. Ethyl 2-phenylcyclopropane-1-carboxylate 3 [8]

Using the general procedure, to a solution of styrene (105 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) in 1 ml of HFIP was added EDA (0.21 ml, 1.5 mmol). After purification by silica gel chromatography (Et_2O/Hexane: 1/9), **3** was isolated as colorless oil product (174 mg, 86%).

^{1}H NMR: δ (*trans*-isomer) 7.09–7.31 (m, 5H), 4.17 (q, *J* = 7.2 Hz; 2H), 2.52 (ddd, *J* = 9.3; 6.6; 5.2 Hz, 1H), 1.90 (ddd, *J* = 8.7; 5.4; 4.5 Hz, 1H), 1.60 (ddd, *J* = 8.5; 6.5; 4.2 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.29–1.32 (m, 1H). ^{13}C NMR δ (*trans*-isomer) 173.4, 140.1, 128.4, 126.4, 126.1, 60.7, 26.2, 24.2, 17.1, 14.3. I.R. (neat): ν = 1720 cm^{-1}.

^{1}H NMR: δ (*cis*-isomer) 7.19–7.28 (m, 5H), 3.90 (q, *J* = 7.1 Hz, 2H), 2.59 (ddd, *J* = 7.4; 8.7; 9.3 Hz, 1H), 2.05 (ddd, *J* = 5.6; 7.8; 9.3 Hz, 1H), 1.70 (ddd, *J* = 5.1; 5.6; 7.4 Hz, 1H), 1.33 (ddd, *J* = 5.1; 7.8; 8.7 Hz, 1H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ (*cis*-isomer) 170.9, 136.5, 129.2, 127.8, 126.6, 60.1, 25.4, 21.7, 14.0, 11.1. I.R. (neat): ν = 1728 cm^{-1}.

Anal. calcd. for $C_{15}H_{14}O_2$ C, 75.76; H, 7.42 found C, 75.63; H, 7.58.

4.1.2. Ethyl 2-(3-nitro-phenyl)-cyclopropanecarboxylate 6

Product **6** was prepared from 3-nitrostyrene (150 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **6** was isolated after purification by silica gel chromatography (Ethyl acetate/Hexane: 1/9), as yellow oil (24 mg, 10%).

Yellow oil ^{1}H NMR δ 8.02–8.11 (m, 1H), 7.93 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.54–2.69 (m, 1H), 1.98 (ddd, *J* = 9.0; 8.0; 5.0 Hz, 1H), 1.92–2.21 (m, 1H), 1.35–1.51 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR δ 14.2; 172.5, 148.5, 142.4, 132.6, 129.3, 121.5, 120.9, 61.0, 25.3, 24.4, 17.1. I.R. (neat): ν = 1725 cm^{-1}.

4.1.3. Ethyl 2-Benzylcyclopropanecarboxylate 12 [8]

Product **12** was prepared from allyl-benzene (118 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **12** was isolated after purification by silica gel chromatography (Et_2O/Hexane: 1/9), as colorless oil (116 mg, 56%).

Trans-isomer: ^{1}H NMR δ 7.27 (m, 5H), 4.13 (q, *J* = 7.0 Hz, 2H), 2.79 (dd, *J* = 6.0 Hz, 15.0 Hz, 1H), 2.59 (dd, *J* = 7.0 Hz, 15 Hz, 1H), 1.67–1.74 (m, 1H), 1.51–1.56 (m, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.20–1.32 (m, 1H); 0.82–0.89 (m, 1H). ^{13}C NMR δ 173.5, 141.0, 128.0, 127.9, 125.8, 60.4, 38.4, 22.9, 20.2, 15.1, 14.2. HRMS (Cl, NH_3) calculated for $C_{13}H_{20}NO_2$: $(M+NH_4)^+$ 222.1494; found $(M+NH_4)^+$ 222.1491. I.R. (neat): ν = 1723 cm^{-1}.

Cis-isomer: ^{1}H NMR δ 7.28 (m, 5H), 4.14 (q, *J* = 7.0 Hz, 2H), 2.93 (dd, *J* = 7.0 Hz, 15.0 Hz, 1H), 2.83 (dd, *J* = 7.0 Hz, 15 Hz, 1H), 1.78 (m, 1H), 1.54 (m, 1H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.22–1.29 (m, 1H); 1.12 (m, 1H). ^{13}C NMR δ 172.3, 139.6, 128.0, 127.8, 125.6, 61.2, 32.3, 22.1, 18.0, 13.7, 13.0. HRMS (Cl, NH_3) calculated for $C_{13}H_{20}NO_2$: $(M+NH_4)^+$ 222.1494; found $(M+NH_4)^+$ 222.1454. I.R. (neat): ν = 1733 cm^{-1}.

4.1.4. Ethyl 2-decylcyclopropanecarboxylate 14

Product **14** was prepared from *n*-dodecene (168 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **14** was isolated after purification by silica gel chromatography (Ethyl acetate/Hexane: 1/9) as yellow oil (251 mg, 98%).

^{1}H NMR δ (mixture *cis*/*trans*) 4.06 (q, *J* = 8.2 Hz, 4H), 1.01–1.39 (m, 50H); 0.81 (t, *J* = 7.7 Hz, 6H). ^{13}C NMR δ 174.4, 172.9, 60.1, 60.0, 33.0, 31.8, 29.5, 29.0, 26.9, 22.8, 22.6, 21.8, 20.1, 18.1, 15.3, 14.3, 14.2, 14.0, 13.2. I.R. (neat): ν = 1727 cm^{-1}.

4.1.5. Ethyl bicyclo[6.1.0]nonane-9-carboxylate 16 [8]

Product **16** was prepared from cyclooctene (109 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **16** was isolated after purification by silica gel chromatography (Ethyl acetate/Hexane: 1/9) as yellow oil (148 mg, 75%).

^{1}H NMR δ (mixture of *cis*/*trans*): 4.05 (q, *J* = 7.2 Hz, 4H), 1.92–2.08 (m, 2H), 1.47–1.73 (m, 12H), 1.26–1.46 (m, 12H), 1.12–1.24 (m, 6H), 0.48–1.08 (m, 4H). ^{13}C NMR δ 174.3, 172.2, 60.0, 59.5, 29.3, 29.0, 27.2, 27.0, 26.3, 25.7, 24.5, 20.7, 14.2. I.R. (neat): ν = 1730 cm^{-1}.

4.1.6. Ethyl bicyclo[5.1.0]octane-8-carboxylate 18 [13]

Product **18** was prepared from cycloheptene (97 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **18** was isolated after purification by silica gel chromatography (Ethyl acetate/Hexane: 1/9) as yellow oil (167 mg, 82%).

^{1}H NMR δ *trans*-isomer: 4,08 (q, *J* = 7.0 Hz, 2H), 0.90–2.46 (m, 16H); ^{13}C NMR δ 175.3, 60.5, 59.5, 32.3, 29.8, 29.3, 29.1, 28.5, 25.7, 22.7, 14.12. I.R. (neat): ν = 1729 cm^{-1}.

4.1.7. Ethyl 2-oxa-bicyclo[4. 1. 0]heptane-7-carboxylate 20 [14]

Product **20** was prepared from dihydropyrane (84 mg, 1 mmol), $Cu(OTf)_2$ (2 mg, 0.01 mmol) and EDA (0.21 ml, 2 mmol). **20** was isolated after purification by silica gel chromatography (Ethyl acetate/*n*-Pentane: 1/9) as colorless oil (93 mg, 55%).

^{1}H NMR δ (*trans*-isomer): 4.06 (q, *J* = 7.1 Hz, 2H), 3.2–3.9 (m, 3H), 2.1–1.2 (m, 6H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{1}H NMR δ (*cis*-isomer): 4.13 (q, *J* = 7.1 Hz, 2H), 3.3–3.95 (m, 3H), 2.46 (d of d, *J* = 6.6; 7.8 Hz, 1H), 1–1.8 (m, 5H), 1.26 (t, *J* = 7.1 Hz, 3H).

Acknowledgements

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