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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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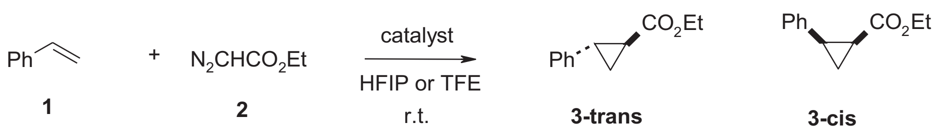
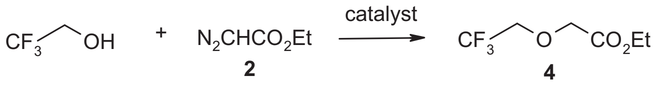
Table 1
Cyclopropanation in fluorinated alcohols.



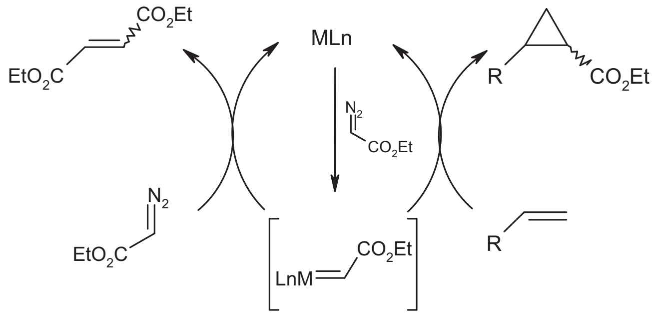
Entry	Catalyst (mol%)	EDA (equiv.)	Solvent	Time (h)	Conversion of 1 (%)	3-*Trans*/*Cis*[b]
1	$Cu(OTf)_2$ (1)	1.0	HFIP	4	85	42/58
2	$Cu(OTf)_2$ (1)	1.5	HFIP	4	100	42/58
3	$Cu(OTf)_2$ (1)	1.5	TFE	2	0[a]	–
4	$Rh_2(OAc)_4$ (1)	1.5	HFIP	8	55	48/52
5	$Rh_2(OAc)_4$ (1)	1.5	TFE	1	0[a]	–
6	$Pd(OAc)_2$ (1)	4	HFIP	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.

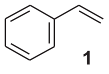
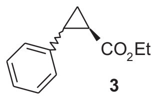
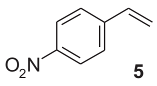
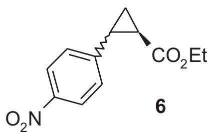
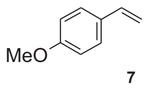
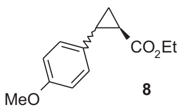
(Scheme 1). This clearly demonstrates the great advantage of HFIP which is not prone to undergo an insertion on EDA.

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			4	86	42/58
2			12	10	58/42
3			5	Traces	–