Rhodium Acetate Dimer Immobilized in 1-Butyl-3-methylimidazolium Hexafluorophosphate Ionic Liquid: a Novel and Recyclable Catalytic System for the Cyclopropanation of Alkenes

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Abstract: Alkenes undergo smooth cyclopropanation with ethyl diazoacetate using a catalytic amount of rhodium acetate dimer, $Rh_2(OAc)_4$, immobilized in the air- and moisture-stable 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid, $[bmim]PF_6$, to afford cyclopropanecarboxylates in excellent yields with high *trans*-selectivity. The recovery of the catalyst is facilitated by the hydrophobic nature of $[bmim]PF_6$. The recovered ionic liquid containing $Rh_2(OAc)_4$ can be reused for three to five subsequent runs with only a gradual decrease in activity.

Keywords: alkenes; carbene insertion; cyclopropanation; cyclopropanecarboxylic esters; diazo compounds; ionic liquids (ILs)

Metal-catalyzed cyclopropanation remains of great interest because of its versatile applications in synthetic organic chemistry.[1] The cyclopropane ring is a core structure in a number of biologically active compounds.[2] Consequently, numerous methods have been developed for the construction of the cyclopropanes.[3] In particular, metal-catalyzed cyclopropanation of alkenes with ethyl diazoacetate is one of the most simple and straightforward approaches for the preparation of cyclopropanes.[4] Initially, copper complexes were widely used as catalysts for the cyclopropanation of alkenes with diazo compounds.[5] Subsequently, rhodium carboxylates have been reported to be highly effective catalysts for cyclopropanation.[6] Most of these copper-, cobalt-, rhodium- and ruthenium-catalyzed carbene insertion reactions show moderate to high *trans*-selectivity.[7,8] In recent reports, iron Lewis acids have been found to give *cis*-cyclopropanes predominantly.[9]

Recently, ionic liquids have gained recognition as environmentally benign alternatives to more volatile organic solvents.[10] They possess many interesting properties such as wide liquid range, negligible vapor pressure, high thermal stability and good solvating ability for a wide range of substrates and catalysts. They are particularly promising as solvents for the immobilization of transition metal catalysts, Lewis acids and enzymes.[11] The hallmark of such ionic liquids is the ability to alter their properties as desired by manipulating their structure with respect to the choice of organic cation, anion or side-chain attached to organic cation (Figure 1).

Their non-volatile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction solvents. Owing to the high polarity and ability to solubilize both organic and inorganic compounds, ionic liquids can enhance reaction rates and selectivities compared to conventional solvents. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[12]

In view of the emerging importance of ionic liquids as green solvents, we herein report the use of ionic liquids as recyclable reaction medium for the cyclopropanation of alkenes with ethyl diazoacetate using a catalytic amount of $Rh_2(OAc)_4$ under mild conditions (Scheme 1).

Treatment of styrene with ethyl diazoacetate in the presence of 1 mol % of $Rh(OAc)_4$ in 3 mL of $[bmim]PF_6$ ionic liquid resulted in the formation of ethyl 2-phenyl-1-cyclopropanecarboxylate in 88% yield (entry **3a**,

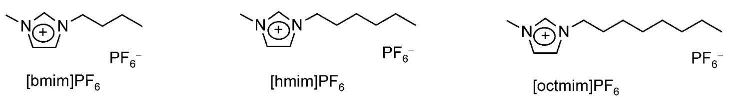

Figure 1.

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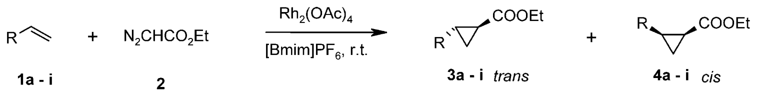
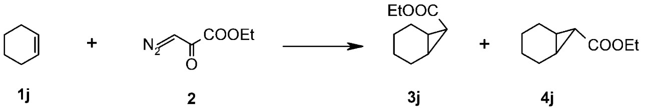


Scheme 1.



Scheme 2.

Table 1). The product was obtained as a mixture of **3** *trans*- and **4** *cis*-isomers, favoring *trans*-diastereomer **3**. The diastereomers **3** and **4** could be easily separated by column chromatography and were characterized by comparison of their NMR spectra with those of authentic samples.[6b] Both electron-rich and electron-deficient styrene derivatives afforded cyclopropanecarboxylates in high yields. In all cases, the reaction proceeds smoothly at room temperature with high *trans*-selectivity. α- and β-substituted styrene derivatives such as α-methylstyrene and β-methylstyrene also gave the corresponding cyclopropanecarboxylates in excellent yields with high *trans*-selectivity (entries **3k** and **3l**, Table 1). In general, the yield for an electron-rich olefin was higher than for electron-poor olefins. The treatment of cyclohexene with ethyl diazoacetate afforded ethyl bicyclo[4.1.0]heptane-7-carboxylate in 85% yield (Scheme 2).

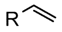
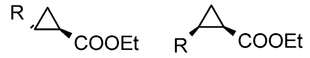
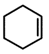
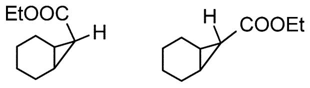
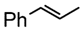
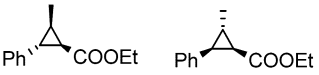
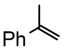
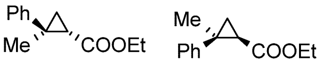
In case of cyclohexene, the product was obtained as a mixture of *endo*- and *exo*-isomers, favoring the *endo*-isomer. No allylic insertion product was observed in the reaction of cyclohexene with ethyl diazoacetate. Compared to conventional solvents, enhanced reaction rates, improved yields and higher *trans*-selectivity were observed in ionic solvents. For example, treatment of styrene with ethyl diazoacetate in the presence of 1 mol % of $Rh_2(OAc)_4$ in $[bmim]PF_6$ at room temperature for 6.0 h afforded the corresponding cyclopropane in 88% yield in a 9:1 *trans*:*cis* ratio whereas the same reaction in CH_2Cl_2 after 9.0 h gave the products in a 72% yield as a mixture of *trans*- and *cis*- isomers in a 4:1 ratio. In the absence of catalyst, no reaction was observed when a mixture of alkene and EDA was stirred in $[bmim]PF_6$ at room temperature for 8–12 h. The major advantage of the use of ionic liquids is that they can be easily recovered and recycled in subsequent reactions. Since the products were fairly soluble in ionic phase, they could be easily separated by simple extraction with diethyl ether. The remaining ionic liquid was further washed with ether and reused in three to five successive runs with only a gradual decrease in activity. For instance, styrene and ethyl diazoacetate in the presence of 1 mol % of $Rh_2(OAc)_4$ in $[bmim]PF_6$ afforded 88%, 85%, 81%, 75% and 72% yields over five cycles. To determine the quantity of the catalyst leaching out from ionic liquid, we have carried out ICP mass analysis. Only a trace amount of $Rh_2(OAc)_4$ (0.001%) was leached out of the ionic liquid, which did not appreciably effect the reaction rates. Furthermore, we have also performed the cyclopropanation reactions in the absence of ionic liquids. Low conversions and moderate selectivity (approximately 1:1 ratio of *cis*/*trans* isomers) were observed in the absence of ionic liquid and the comparative results are presented in Table 1. The recovery and reuse of the catalyst is especially simple in ionic liquids compared to organic solvents. The chemoselectivity for cyclopropane formation over carbene dimerization was achieved by the use of an excess of alkene and slow addition of the carbene source, e.g., ethyl diazoacetate (EDA) to the reaction mixture. No formation of side products such as diethyl fumarate or diethyl maleate was observed when the reaction was carried out using ionic liquid $[bmim]PF_6$. A wide range of alkenes including electron-rich, electron-deficient styrene derivatives and few acyclic and cyclic olefins underwent smooth cyclopropanation with ethyl diazoacetate under similar reaction conditions. In most cases, the products were obtained in high yields with higher *trans*-selectivity. The combination of 5 mol % of $Cu(OTf)_2$ with $[bmim]PF_6$ also gave similar results. The scope and generality of this process is illustrated with respect to various olefins and ethyl diazoacetate and the results are summarized in Table 1.

In summary, we describe a simple and efficient protocol for the cyclopropanation of olefins with ethyl diazoacetate using $Rh(OAc)_4$ immobilized in air- and moisture-stable $[bmim]PF_6$. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media are expected to contribute to the development of green strategy for the synthesis of cyclopropanes. In addition to its simplicity and milder reaction conditions, this method provides high yields of products with greater *trans*-selectivity which makes it a useful and attractive strategy for the preparation of *trans*-cyclopropanecarboxylates.

Experimental Section

Melting points were recorded on a Büchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Table 1. $Rh_2(OAc)_4$-catalyzed synthesis of cyclopropane caboxylates in $[bmim]PF_6$.

Entry	Alkene	Cyclopropane[a]	Time (h)	Yield (%)[b]	*trans:cis*[c]
					
a	R = Ph	R = Ph	6.0	88	90:10
b	R = 3-Cl-Ph	R = 3-Cl-Ph	7.0	82	85:15
c	R = 4-Cl-Ph	R = 4-Cl-Ph	6.5	86	87:13
d	R = 4-Br-Ph	R = 4-Br-Ph	7.5	85	83:17
e	R = 4-Me-Ph	R = 4-Me-Ph	6.0	89	89:11
f	R = 4-AcO-Ph	R = 4-AcO-Ph	8.0	78	84:16
g	R = 4-MeO-Ph	R = 4-MeO-Ph	6.5	87	87:13
h	R = 2-naphthyl	R = 2-naphthyl	7.5	84	90:10
i	R = *n*-hexyl	R = *n*-hexyl	8.5	79(60)[c]	60:40
j		 *endo* *exo*	9.0	85(54)[e]	79:21[d]
k		 *trans* *cis*	8.0	86(62)[e]	75:25
l		 *trans* *cis*	6.5	91(71)[e]	82:18

[a] All products were characterized by 1HNMR, IR and mass spectroscopy.
[b] Yield refers to pure products after column chromatography.
[c] The ratios were determined by ^{1}H-NMR.
[d] Ratio of *endo:exo.*
[e] Yield reported in parethesis refers to isolated prodcts in the absence of ionic liquid.

General Procedure

To a stirred solution of alkene (3 mmol) and 1 mol % of $Rh_2(OAc)_4$ or 5 mol % of $Cu(OTf)_2$ in $[bmim]PF_6$ (3 mL), ethyl diazoacetate (1 mmol) was added slowly in a dropwise manner. The resulting mixture was stirred at 27 °C for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum and purified by column chromatography on silica gel (Merck, 100–200 mesh ethyl acetate-hexane, 1:9) to afford pure the cyclopropanecarboxylate. The cyclopropanes thus obtained were identified by comparison of their NMR, IR, mass spectra and physical data with literature values. The spectral data of all the products were identical with those of authentic samples.[5–7]

***trans*-Ethyl 2-phenylcyclopropane-1-carboxylate (3a):** Liquid, IR (KBr): ν = 2985, 2931, 2865, 1720, 1605, 1458, 1369, 1257, 1153, 1070, 1045, 935, 780, 697 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.02 (t, 3H, *J* = 6.9 Hz), 1.25 (ddd, 1H, *J* = 4.4, 6.4, 8.4 Hz), 1.53 (ddd, 1H, *J* = 4.4, 5.2, 9.2 Hz), 1.85 (ddd, 1H, *J* = 4.2, 5.2, 8.4 Hz), 2.45 (ddd, 1H, *J* = 4.2, 6.4, 9.2 Hz), 3.99–4.05 (m, 2H), 7.05–7.32 (m, 5H); EIMS: *m/z* = 190 (M$^+$), 162, 141, 115, 91, 43.

***cis*-Ethyl 2-phenylcyclopropane-1-carboxylate (4a):** Liquid; IR (KBr): ν = 3059, 2982, 2933, 1728, 1607, 1454, 1381, 1265, 1086, 961, 795, 694 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.98 (t, 3H, *J* = 7.1 Hz), 1.33 (ddd, 1H, *J* = 5.1, 7.8, 8.7 Hz), 1.70 (ddd, 1H, *J* = 5.1, 5.6, 7.4 Hz), 2.05 (ddd, 1H, *J* = 5.6, 7.8, 9.3 Hz), 2.59 (ddd, 1H, *J* = 7.4, 8.7, 9.3 Hz), 3.90 (q, 2H, *J* = 7.1 Hz), 7.19–7.28 (m, 5H); EIMS: *m/z* = 190 (M$^+$), 163, 91, 55; anal. calcd. for $C_{15}H_{14}O_2$ (190.241): C 75.76, H 7.42; found: C 75.63, H 7.58.

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