A Fluorous Phase Approach to Rhodium-Catalyzed Carbenoid Reactions with Diazoacetates

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Abstract: The cyclopropanation of alkenes with methyl diazoacetate in dichloromethane was catalyzed by rhodium(II) carboxylates containing a perfluoralkyl chain (Rh_2L_4, L = $OOCC_7F_{15}$ and $OOC-C_6H_4-4-C_6F_{13}$). The catalysts could be extracted into perfluoro(methylcyclohexane) and were reused several times without significant loss of activity. The same catalysts were used to achieve carbene transfer to toluene in the solvent system toluene–perfluoro(methylcyclohexane) at 60 °C.
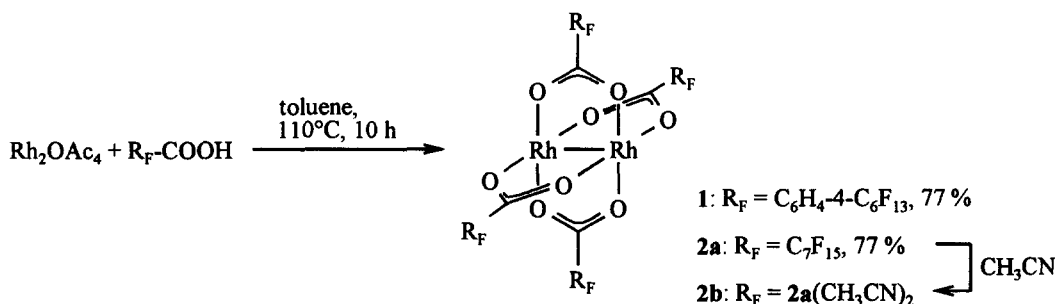
During the past twenty years, rhodium(II) carboxylates and amidates have emerged as the most versatile catalysts for carbene transfer from diazo compounds to appropriate substrates.[1,2] Since only small quantities of the catalyst are needed (typically 1-3 mol-%), efforts to recover and to reuse the catalyst have rarely been made. One notable exception is the report by Doyle and coworkers who developed a polyethylene-supported dirhodium(II) 2-pyrrolidone-5(S)-carboxylate, thereby switching from homogeneous to heterogeneous catalysis.[3]

Another strategy is suggested by the concept of "fluorous biphasic systems" which has been popularized by Horváth and Rábai.[4] In a major application of this approach, a two-phase system consisting of a common organic solvent and a perfluorinated solvent (e.g. n-C_6F_{14}, $C_8F_{17}Br$, CF_3-C_6F_{11}) containing a metal catalyst bearing perfluorinated ligands is used. Such a two-phase system often becomes homogeneous on warming, allowing a reaction under homogeneous catalysis to take place. Decreasing the temperature to rt at the end of the reaction reestablishes two phases, where the organic phase contains the product and the fluorous phase the catalyst which can be reused. The power of this new concept has been demonstrated recently by application to important chemical transformations such as Rh-catalyzed hydroformylation[4a] and hydroboration[5] as well as Pd-catalyzed cross-coupling[6] and alkene oxidation[7] reactions.

Another application of fluorous phase synthesis has been put forward by Curran.[8,9] A metal catalyst or any other substance bearing a sufficiently long perfluoroalkyl chain can be extracted into a perfluorinated solvent after a reaction which is performed in an organic solvent or an organic/fluorous hybride solvent.

Herein, we describe the first application of the latter strategy to rhodium-catalyzed cyclopropanation reactions with diazoacetates. To this end, we aimed at rhodium catalysts Rh_2L_4 where L is a carboxylate ligand featuring a long perfluoroalkyl chain. The dimeric rhodium(II) carboxylates **1** and **2a** were prepared according to an established method[10] from $Rh_2(OAc)_4$ by ligand exchange with 4-(perfluorohexyl)benzoic acid[11] and commercially available perfluorooctanoic acid, respectively (Scheme 1). Complex **1** was obtained as a light-

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Rh$_2$OAc$_4$ + R$_F$-COOH $\xrightarrow[\text{110°C, 10 h}]{\text{toluene,}}$

1: R$_F$ = C$_6$H$_4$-4-C$_6$F$_{13}$, 77 %

2a: R$_F$ = C$_7$F$_{15}$, 77 %

2b: R$_F$ = 2a(CH$_3$CN)$_2$ $\xleftarrow{\text{CH}_3\text{CN}}$

Scheme 1

green powder, and **2a**[12] as a dark-green, waxy material which formed a solid purple bis(acetonitrile) complex **2b** on exposure to CH$_3$CN.[13] The latter complex is an easy-to-handle and storable source of **2a**, and the acetonitrile ligands can be removed by heating at 80 °C/0.04 mbar for 5 h.

Complexes **1** and **2a** (2 mol-%) were used to achieve the cyclopropanation of alkenes **3** with methyl diazoacetate (**4**) in CH$_2$Cl$_2$ (Scheme 2). A tenfold excess of the alkene was applied to minimize the formation of the formal carbene dimers, dimethyl fumarate and maleate. While the catalysts were not soluble in CH$_2$Cl$_2$ alone, a homogeneous deep-green solution was obtained in most cases after addition of the alkene. At the end of the reaction, both catalysts could be extracted from the mixture into perfluoro(methylcyclohexane) (CF$_3$-C$_6$F$_{11}$, PFMC) and were reused three or four times with no or little loss of catalytic activity.[14] As expected, the yields of cyclopropanes **5** (Table 1) are influenced by the catalyst. While the results obtained with **1** compare quite well with those of the widely used catalyst Rh$_2$(OAc)$_4$,[1] the decreased yields (entries 1-3) with **2a** as catalyst do not come as a surprise. Similar to rhodium(II) perfluorobutyrate [Rh$_2$(OOCC$_3$F$_7$)$_4$], **2a** is a highly electrophilic catalyst due to its strongly electron-withdrawing ligands. As compared to Rh$_2$(OAc)$_4$, these catalysts can be expected to display a modified chemoselectivity[2c,15] and to be deactivated more easily by donor molecules which are present in the reaction mixture.

The bis(acetonitrile) complex **2b** was only briefly examined. Cyclopropanation of α-methylstyrene was shown to proceed in good yield at 40 °C (entry 2 of Table). This result indicates that one or both acetonitrile ligands are readily displaced from the metal under the reaction conditions.

Scheme 2

3, 5	a	b	c	d
R^1	Ph	Ph	nBu	Me
R^2	H	Me	H	Me
R^3	H	H	H	Me
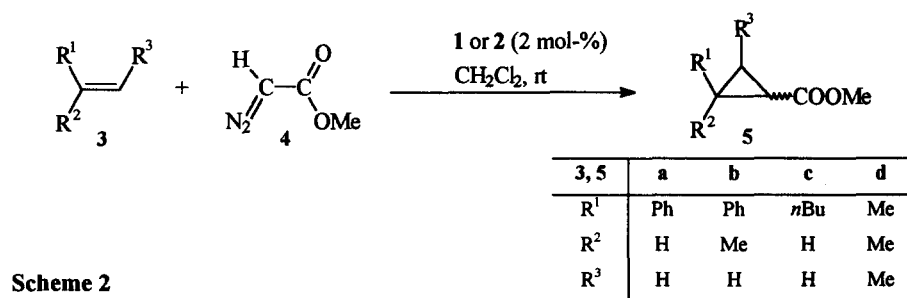
The concept of "fluorous biphasic catalysis"[4] was applied to the carbenoid reaction of diazoacetate **4** with toluene in which catalysts **1** and **2a** are not soluble (Scheme 3). Toluene and PFMC form a homogeneous phase containing the dissolved catalyst (1 mol-%) at 60 °C, and the carbenoid reaction affords a mixture of

isomeric methyl 1,3,5-cyloheptatriene-7-carboxylates **6** besides the carbene dimers as minor by-products [with **1**: 1-Me:2-Me:3-Me = 77:23:10, total yield 71 %, carbene dimers 5 %; with **2a**: 1-Me:2-Me:3-Me = 58:26:16,

Table 1. Cyclopropanation of alkenes **3** with diazoacetate **4** catalyzed by complexes **1** or **2a,b**

Entry	Alkene **3**	Catalyst	Yield of cyclopropane **5** (%, upper line) and E/Z (*anti/syn*) ratio (lower line)			
			cycle 1	cycle 2[b]	cycle 3[b]	cycle 4[b]
1		**1**[c]	71	70	70	71
			1.43	1.44	1.44	1.46
		2a[d]	54	53		
			1.28	1.29		
2		**1**[c]	83	79	76	76
			1.04	1.00	1.11	1.11
		2a[c]	56	56	50	
			1.03	1.03	1.09	
		2b[c,e]	73			
			0.99			
3		**1**[d]	82	82	81	
			1.47	1.40	1.32	
		2a[d]	60	57		
			1.56	1.70		
4		**1**[d]	75	75	75	76
			0.83	1.08	0.95	0.96
		2a[d]	79	78	75	75
			1.02	0.87	0.88	1.00

[a] Reactions were carried out at 20 °C; the combined yield of dimethyl maleate and fumarate was 1-5 %. – [b] The catalyst recovered from the previous cycle was reused. – [c] Yields and E/Z-ratios were determined by GC. – [d] Yields and E/Z-ratios were determined by ¹H NMR spectroscopy. – [e] At 40 °C.

total yield 78 %, carbene dimers 9 %]. For comparison, the so far best catalyst for this type of transformation,[16] $Rh_2(OOCCF_3)_4$, provided **6** with a total yield of 95 % and an isomer distribution of 56:23:17.

Phase separation took place at -20 °C. In both cases, the color of the fluorous phase had changed from deep-green to dark-brown, indicating at least a partial destruction of the catalyst. In fact, only a fraction of the catalyst [ca. 76 % of **1** and 50 % of the bis(acetonitrile) complex of **2a**] could be recovered from this phase. Deactivation and/or destruction of rhodium catalysts has been observed before for the same carbenoid transformation.[15] Although the goal to recycle the catalyst completely cannot be reached in such a case, it is evident that the fluorous phase approach can serve as a convenient means in the purification procedure.
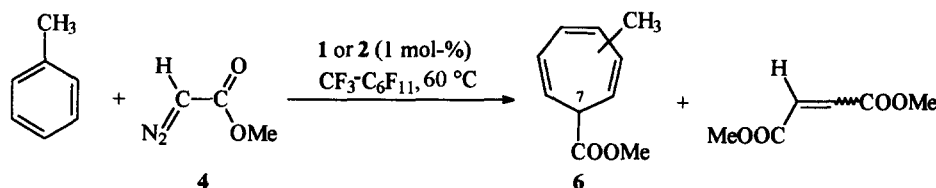
Scheme 3

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13. The ligand exchange was indicated by the observation of a carbonyl stretching vibration at a wavenumber different from that of the free carboxylic acid and of $Rh_2(OAc)_4$. Furthermore, the expected molecular ion peak could be found in the mass spectrum of **2a**, but not of **1** (matrix-free laser desorption time-of-flight spectra, Bruker Reflex III, negative ion mode). – $Rh_2(OOC-C_6H_4-4-C_6F_{13})_4$ (**1**): beginning decomposition at >210 °C; IR (KBr): v 1604(s), 1564(s), 1409(vs), 1286(s), 1242(vs), 1203(vs), 1146(vs), 1122(s), 1094(s) cm^{-1}. – $Rh_2(OOCC_7F_{15})_4$ (**2a**): IR (KBr): v 1663(s), 1424(m), 1365(m), 1244, 1207, 1148 (all vs) cm^{-1}; MS: *m/e* 1857.7 (calcd. for molecular ion: 1857.7). – $Rh_2(OOCC_7F_{15})_4(CH_3CN)_2$ (**2b**): dec.p. 71 °C (color change from purple to green, indicating loss of CH_3CN ligands and formation of **2a**).

14. **Typical procedure**; preparation of methyl-2-butylcyclopropane-1-carboxylate (**5c**; entry 3 of Table 1): A two-necked Schlenk flask (25 ml volume) was charged with CH_2Cl_2 (6 ml), 1-hexene (6.2 ml, 50 mmol), and catalyst **1** (0.20 g, 2 mol-%). To the resulting green suspension, a solution of **4** (0.50 g, 5 mmol) in CH_2Cl_2 (4 ml) was added during 8 h with a syringe pump. After an additional time of 4 h the solvent and most of the alkene were removed at 40 °C/500 mbar. The liquid residue was stirred for 15 min with perfluoro(methylcyclohexane) (0.6 ml). After phase separation the dark-green fluorous phase was removed and the liquid residue was distilled at 100°C/ 0.1 mbar to afford **5d**.

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