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A Fluorous Chiral Dirhodium(II) Complex as a Recyclable Asymmetric Catalyst

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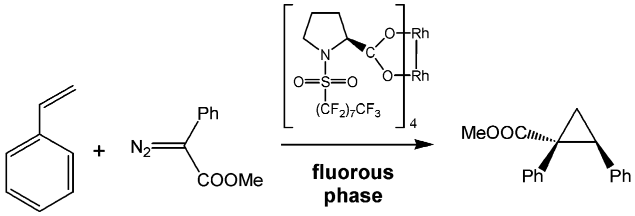
ABSTRACT



The chiral fluorous complex tetrakis-dirhodium(II)−(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate has been prepared and used as a catalyst in homogeneous or fluorous biphasic fashion. The catalyst displays good chemo- and enantioselectivity in intermolecular cyclopropanation and C−H bond activation reactions. The catalyst can be simply and thoroughly separated from the reaction mixture and is recyclable.

The synthetic potential of dimeric rhodium(II) complexes as catalysts for organic syntheses, most notably those involving diazocompounds, has been widely recognized in the course of the last 15 years.[1] There is an impressive variety of chemical transformations that can be mediated by such compounds through the formation of highly reactive metal carbene intermediates, including cyclopropanations, insertions into C−H, C−C, and heteroatom−H bonds, ylide formations, and dipolar cycloaddition reactions; efficient asymmetric variants of many of these reactions have been developed as well.[1,2] Among the complexes that have emerged as most useful for asymmetric transformation, the dirhodium(II) carboxylates of amino acid derivatives of type **1** introduced by Hashimoto and Ikegami,[3] the dirhodium(II) carboxyamidates of type **2** developed by Doyle,[4] and finally the dirhodium(II) prolinates of type **3** first reported by McKervey[5] and later extensively studied by Davies[6−8] need special mention (Figure 1). In particular, the latter type of catalyst exhibits some outstanding properties such as a high enantio- and diastereoselectivity in cyclopropanations involving aryl- or vinyl diazoacetates[7] as well as a high chemo- and stereoselectivity in intermolecular C−H insertion reactions.[8] Despite the potential of these catalysts, one of the

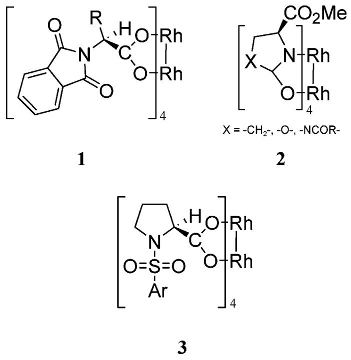


Figure 1.

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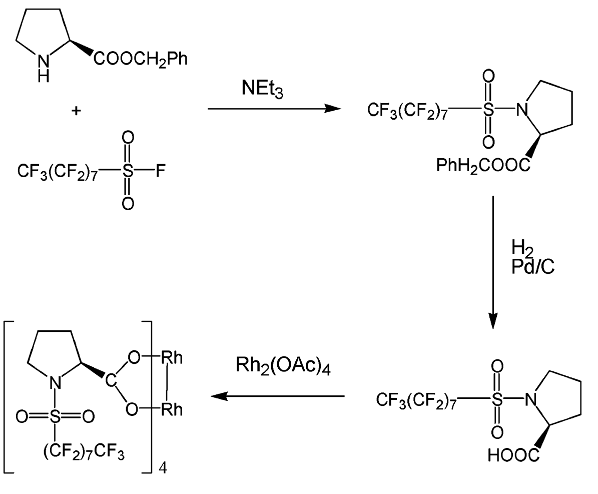
fundamental problems for their industrial application is the need for efficient catalyst recovery and recycling, which arises from the relatively large quantity of catalyst (1 mol %) usually needed for these reactions. In this connection, there have already been some successful attempts to heterogenize chiral dirhodium(II) catalysts on solid supports through covalent linkages[9] or monocoordination to one apical position of the catalyst.[10] We report in this paper on a novel dirhodium(II) prolinate catalyst bearing perfluoroalkyl chains. Such functionalization allows an easy recovery of the catalyst from the reaction mixture by confining it into a separated, perfluorinated liquid phase (Fluorous Biphasic Catalysis, FBS)[11] or solid phase (Bonded Fluorous Phase Catalysis, BFPC)[12,13] or by extracting it into a perfluorinated phase at the end of the reaction.

The catalyst tetrakis-dirhodium(II)−(*S*)-*N*-(*n*-perfluorooctylsulfonyl)prolinate **4** has been prepared from L-proline benzyl ester hydrochloride in three steps following the reaction pathway outlined in Scheme 1. We have extensively tried to avoid protection of the carboxylate function, without success: simple proline does not react with the sulfonyl fluoride under any of the conditions we have employed.

Complex **4** has a weight percentage of fluorine of 50%. Although as a rule of thumb suitable catalysts for fluorous biphasic catalysis should contain a weight percentage of fluorine of at least 60%,[11b−d] several metal complexes have already been reported that exhibit good performance at lower fluorine content (see Chapter 6 in ref 11a). Indeed, **4** shows high affinity for a fluorous phase, both solid and liquid (vide infra). For example, it can be conveniently heterogenized on a solid support functionalized with perfluoroalkyl chains by simple addition of the support to a toluene or dichloromethane solution of the complex. Quantitative adsorption of **4** from the organic solution occurs using as support a fluorous reversed-phase silica prepared by surface functionalization with 1*H*,1*H*,2*H*,2*H*-pefluorodecyldimethylchlorosilane,[14] which we have already successfully employed for the heterogenization of dirhodium(II) perfluorocarboxylate complexes;[12] such bonded fluorous phase (BFP)-supported catalyst will be hereafter termed as BFP-**4**.

Scheme 1



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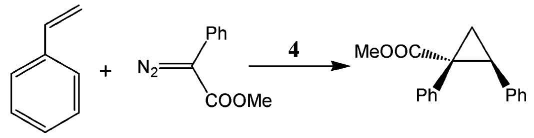
Catalytic tests have been performed on a standard asymmetric cyclopropanation reaction with styrene and methyl phenyldiazoacetate as the reagents. Reaction conditions derived from the work of Davies[15] (10 equiv of styrene, 1 equiv of diazocompound, 0.01 equiv of catalyst, room temperature, controlled diazocompound addition over 30 min) have been employed (see also Supporting Information). The results are reported in Table 1.

Initial tests were run under homogeneous conditions in dichloromethane solution (entries 1−4). As expected from

Table 1. Asymmetric Cyclopropanation Reactions with Homogeneous and Supported **4**[a]



entry	catalyst	solvent[b]	yield[c] (%)	ee (%)
1	**4**	CH_2Cl_2	82	48
2[d]	**4**	CH_2Cl_2	87	49
3[e]	**4**	CH_2Cl_2	80	51
4[f]	**4**	CH_2Cl_2	86	56
5	**4**	CH_2Cl_2/PFD	39	47
6	BFP-**4**	CH_2Cl_2	53	47
7[d]	BFP-**4**	CH_2Cl_2	47	54
8	BFP-**4**	*n*-pentane	66	60
9	**4**	PFMC	79	62
10[g]	**4**	PFMC	81	72
11[h]	**4**	PFMC	65	74
12[i]	$Rh_2(S\text{-TBSP})_4$	CH_2Cl_2	77	61
13[i]	$Rh_2(S\text{-TBSP})_4$	*n*-pentane	73	85

[a] Reaction conditions: see text. [b] PFD = perfluorodecalin; PFMC = perfluoro(methylcyclohexane). [c] Isolated yield of the *E* product. [d] Diazocompound addition in 5 h. [e] Recycle of entry 1. [f] Recycle of entry 3. [g] Recycle of entry 9. [h] Recycle of entry 10. [i] Literature data[16] for the reference catalyst tetrakis-dirhodium(II)−(*S*)-*N*-(*tert*-butylbenzensulfonyl)-prolinate [$Rh_2(S\text{-TBSP})_4$].

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the literature,[6,15,16] the *E* reaction product is formed in high yields (diastereomeric ratio = 98:2). Compared to the original catalyst reported by Davies (entry 12), the perfluorinated catalyst appears to be slightly more chemoselective but less enantioselective (about 50% ee vs 60% favoring the same (1*R*,2*S*)-product); we have tried to improve the reaction outcome by adding the diazocompound very slowly to the reaction mixture (entry 2) but observed no improvement in selectivity. Nevertheless, the catalyst was found to be readily recyclable upon extraction from the reaction mixture into a fluorous solvent followed by solvent evaporation and redissolution into a fresh styrene solution in dichloromethane.

We have conducted an accurate screening of different fluorous solvents in order to identify the best extractant for our catalyst. Tests were performed by dividing into different aliquots a sample of the reaction mixture after reaction and then extracting each sample with a different fluorous solvent; the concentration of Rh remaining in the reaction mixture was subsequently evaluated by ICP-AAS (for experimental details, see Supporting Information). The results reported in Table 2 show that, although all fluorous solvents perform quite well, it is perfluoro(methylcyclohexane) (PFMC) that gives the best results, enabling 95% catalyst recovery.

Table 2. Efficiency of the Extraction of **4** from Cyclopropanation Reaction Mixtures into Different Fluorous Solvents

fluorous solvent	% **4** extracted
perfluoro(methylcyclohexane)	95
perfluorodecalin	88
Fluorinert FC-77[a]	89
perfluoroheptane	88
Miteni RM101[b]	86

[a] Mixture of perfluoro(butyltetrahydrofurans). [b] Mixture of perfluoro(butyltetrahydrofurans) and perfluoro(propyltetrahydropyrans).

We have performed in this way two catalyst recycles (Table 1, entries 3 and 4), observing no decrease in the reaction yield and even a small improvement in the enantioselectivity of the reaction.

We continued our study by investigating alternative strategies for catalyst recovery and recycling. Running the reaction under fluorous biphasic conditions results in a dramatic drop of the chemoselectivity of the reaction, whereas the enantioselectivity remains almost constant (entry 5). A less dramatic but still significant decrease in chemoselectivity is also observed using the catalyst in BFP form (entry 6), and no improvement is seen on very slow addition of the diazocompound (entry 7); the enantioselectivity is also in this case fully comparable to that of the homogeneous reaction. Thus, catalyst confinement in a separated fluorous phase appears to have a detrimental effect on the chemoselectivity but not on the enantioselectivity under the employed reaction conditions. Apparently, such confinement promotes side reactions of the transient carbenoid such as dimerization to the corresponding alkene or reaction with the diazocompound to the corresponding azine.

We have subsequently determined the effect of the reaction solvent on the selectivity of the reaction. In fact, it is known that use of hydrocarbon solvents such as *n*-pentane has a positive effect on the enantioselectivity of chiral *N*-arylsulfonylprolinate catalysts (compare entries 12 and 13 in Table 1).[6,15,16] Unfortunately, **4** is insoluble in *n*-pentane alone and only slightly soluble in an *n*-pentane solution of styrene. Therefore, we have tested two alternative protocols for running the reaction in solvents of low polarity. First, we tried to run the reaction in *n*-pentane using the catalyst in BFP form (entry 8). We were pleased to see that the enantioselectivity of the reaction indeed increased, although to a lower extent than with the reference catalyst. The reaction yield was also significantly higher than in the reaction run with the BFP catalyst in dichloromethane; however, it was still lower than in the homogeneous reaction. Finally, we chose to try to run the reaction with the catalyst dissolved in PFMC and no other organic solvent. Under these conditions, the reaction product dissolves in the excess styrene reagent, which builds up a separate phase and is conveniently and quantitatively removed from the fluorous phase containing the catalyst by simple decantation, without the need for extraction with organic solvents. The catalyst itself remains confined in the fluorous phase throughout the reaction; only 2 ppm of rhodium, corresponding to 0.1% metal leaching, is found in the product phase at the end of the reaction. As it is reported in Table 1, entries 9−11, the reaction yield under these conditions equals that of the experiments in the homogeneous phase (entry 1), and the enantioselectivity rises to 62% ee. The catalyst is fully recyclable, with a slight decrease of the reaction yield occurring only in the third reaction cycle; moreover, also observed in this case is a significant increase in the enantioselectivity upon recycling (up to 74% ee).

We have also performed a preliminary evaluation of the catalytic performance of **4** in the asymmetric C−H bond activation of cyclohexane. The results are reported in Table 3.

Our idea was to employ the reaction conditions reported by Davies et al.[17] (excess cyclohexane, 1 equiv of diazocompound, 0.01 equiv of catalyst, room temperature, controlled diazocompound addition over 90 min), which imply using cyclohexane as the reaction solvent. However, **4** turned out to be only partially soluble in cyclohexane at room temperature. Nevertheless, the recorded yield of C−H insertion product is quite good, although the achieved ee is significantly lower than that of the reference catalyst (compare entries 1 and 6, Table 3). We have tried to improve the reaction ee by decreasing the reaction temperature;[17] however, this further decreases the solubility of the perflu-

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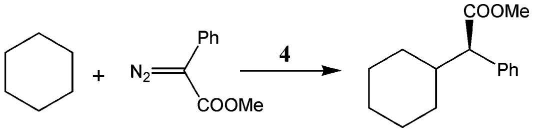
Table 3. Asymmetric C−H Bond Activation with Homogeneous and Supported **4**[a]



entry	catalyst	*T* (°C)	yield[b] (%)	ee (%)
1	**4**	25	71	61
2	**4**	10	22	61
3	**4**[c]	25	56	61
4	BFP-**4**	25	59	58
5[d]	BFP-**4**	25	33	53
6[e]	Rh_2(*S*-DOSP)$_4$	25	74	92

[a] Reaction conditions: see text. [b] Isolated yield. [c] Catalyst dissolved in PFMC. [d] Recycle of entry 4. [e] Literature data[17] for the reference catalyst tetrakis-dirhodium(II)−(*S*)-*N*-(*n*-dodecylbenzensulfonyl)-prolinate [Rh_2(*S*-DOSP)$_4$].

orinated catalyst to such an extent that the reaction yield drops considerably (entry 2). The catalyst can be also in this case quantitatively separated from the reaction mixture by extraction into PFMC. In fact, although many hydrocarbons are miscible with PFMC at room temperature,[11a,18] we have found that cyclohexane/PFMC mixtures remain biphasic up to 53 °C.

We have tried to get rid of the solubility problems by running the reaction with the catalyst in a separated fluorous phase. Use of a liquid−liquid biphasic system with the catalyst dissolved in PFMC allows, as in the previous case, an easy and quantitative separation of the catalyst from the reaction mixture. The enantioselectivity is fully comparable to that obtained in the homogeneous phase (entry 3); however, the chemoselectivity of the reaction is lower, since the carbenoid intermediate tends to react further before being able to give the C−H insertion product. Indeed, the main decomposition byproduct, which in this case has been identified as the azine, partly precipitates out of the liquid−liquid biphasic system in the course of the reaction. We have also evaluated the performance of the BFP-supported catalyst (entries 4 and 5). The reaction yield is again somewhat lower than in the homogeneous phase experiment, but the ee remains almost the same. The catalyst can be easily separated from the reaction mixture by simple filtration; leaching of Rh in the organic phase amounts to 3.5% of the total metal present. Catalyst recycling is possible; however, the reaction yield in the second cycle decreases considerably (entry 5), whereas only a small decrease in enantioselectivity is observed.

In conclusion, we have developed a fluorous chiral dirhodium(II) catalyst that displays excellent chemo- and regioselectivity and good enantioselectivity in cyclopropanation reactions. The catalyst can be simply and thoroughly separated from the reaction mixture and is recyclable. Furthermore, it enables the use of a reaction protocol without organic solvents besides the reagents and a tiny amount of fluorous solvent. Finally, the catalyst is also active and selective in C−H bond activation reactions, although in this case the solubility of the catalyst in the reaction environment and/or its recyclability need to be improved. We are currently working toward such improvements and also at further improving the enantioselectivity of the catalyst.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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