Aerobic Ru-Catalyzed Epoxidations in Fluorous Biphasic System Using New Fluorous Benzimidazolic Ligands

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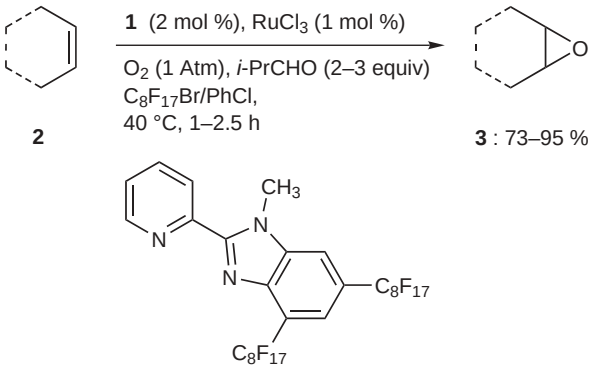
Abstract: An efficient ruthenium catalyzed fluorous biphasic epoxidation of alkenes with oxygen in the presence of a pyridine-benzimidazole ligand bearing perfluorinated ponytails is described. Excellent yields and reaction rates were obtained and the fluorous phase could be recycled up to ten times without any loss of activity.

Key words: aerobic epoxidations, catalysis, ruthenium, fluorous biphasic system, benzimidazoles

The epoxidation of olefins is an important reaction in organic chemistry since epoxides are key building blocks for the preparation of complex organic molecules and resins.[1] Common laboratory-scale methods require usually stoichiometric amounts of reactive oxidants like peracids, which are leading to safety hazards in large-scale industrial reactions. Development of environmentally benign procedures, which employ molecular oxygen, aqueous hydrogen peroxide or *tert*-butyl hydroperoxide is highly desirable. Advances have been made by using these oxidants in the presence of catalytic amounts of transition metal such as Ru, Mn or Ni.[2] Ruthenium complexes are versatile catalysts for a number of organic oxidations and reductions, and a large variety of ligands has been prepared and tested,[3] including porphyrines, macrocyclic tertiary amines or Schiff bases. In many cases, high yields and turnovers have been obtained, but major drawbacks are still related to leaching or deactivation, leading to a gradual loss in catalyst activity. The catalyst synthesis can often be tedious as in the case of porphyrine derivatives.[3b] Therefore, development of efficient oxidation protocols, which allow efficient catalyst recycling and use of cheap and environmentally friendly oxidants as molecular oxygen is of interest. The Fluorous Biphase Catalysis,[4–6] (FBC) which was introduced by Horváth and Rábai is, in this respect, particularly attractive.

Herein, we wish to report a novel fluorous pyridine-benzimidazole ligand Rf_2Bimpy (**1**), whose complex with $RuCl_3$ has been further used for aerobic epoxidations of alkenes of type **2** in FBC, leading to epoxides of type **3** (Scheme 1).

A metal/ligand ratio of 1:2 was used, in analogy to the structure of Ru-porphyrines which have already been used in ruthenium catalyzed epoxidations.[7a] After in situ formation of the Ru complex, no free ligand was detected in both organic and fluorous phases. For this reaction, the classical Mukaiyama[7b,c] protocol, which involves oxidation with molecular oxygen in the presence of two equivalents of isobutyraldehyde was used. Optimized conditions for the epoxidation of *cis*-cyclooctene required the use of 1 mol% of ruthenium salt at 40 °C. Complete conversion is achieved after only 1 hour reaction time. Experiments of catalyst recyclability in cyclooctene epoxidation were carried out. The fluorous phase was reused up to 10 times without any apparent loss of activity, resulting always in full conversion of the substrate. No leaching of ruthenium or ligand in the organic phase has been detected (Table 1).



Scheme 1

Various alkenes have been involved in this reaction in order to evaluate compatibility with functional groups and reactivity at the double bond (Table 2).

Table 1 Epoxidation of Cyclooctene (**2a**) by Recycling the Ru-Complex of Ligand **1**

Run	Yield (%)	Time (h)	Run	Yield (%)	Time (h)
1	89	1 h 15 min	6	91	1
2	91	1	7	90	1
3	93	1	8	90	1
4	90	1	9	93	1
5	95	1	10	92	1

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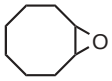
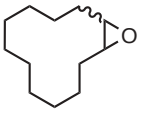
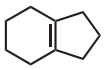
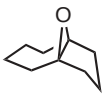
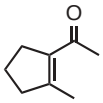
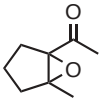
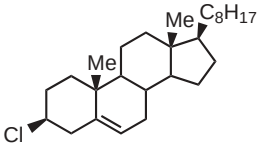
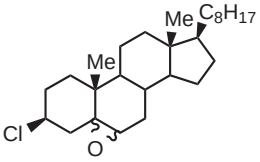
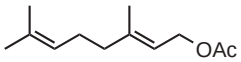
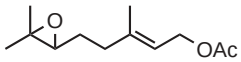
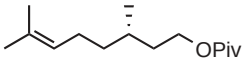
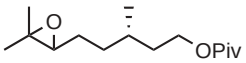
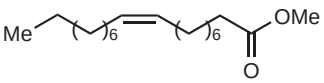
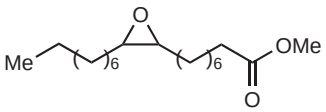
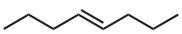
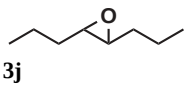
Table 2 Epoxides **3a–j** Obtained by the Aerobic Oxidation of the Alkenes **2a–j** in a Biphasic System of Chlorobenzene and Perfluorooctyl Bromide Using Isopropylaldehyde as co-Oxidant

Entry	Alkene	Product	Reaction time	Yield (%)[a]
1	 **2a**	 **3a**	1 h	89–95
2	 **2b**	 **3b**	50 min	92[b]
3	 **2c**	 **3c**	1 h 15 min	83
4	 **2d**	 **3d**	30 min	74
5	 **2e**	 **3e**	1 h	73
6	 **2f**	 **3f**	2.5 h	94[c]
7	 **2g**	 **3g**	1 h	81
8	 **2h**	 **3h**	40 min	92
9	 **2i**	 **3i**	1 h	95
10	 **2j**	 **3j**	1.5 h	78

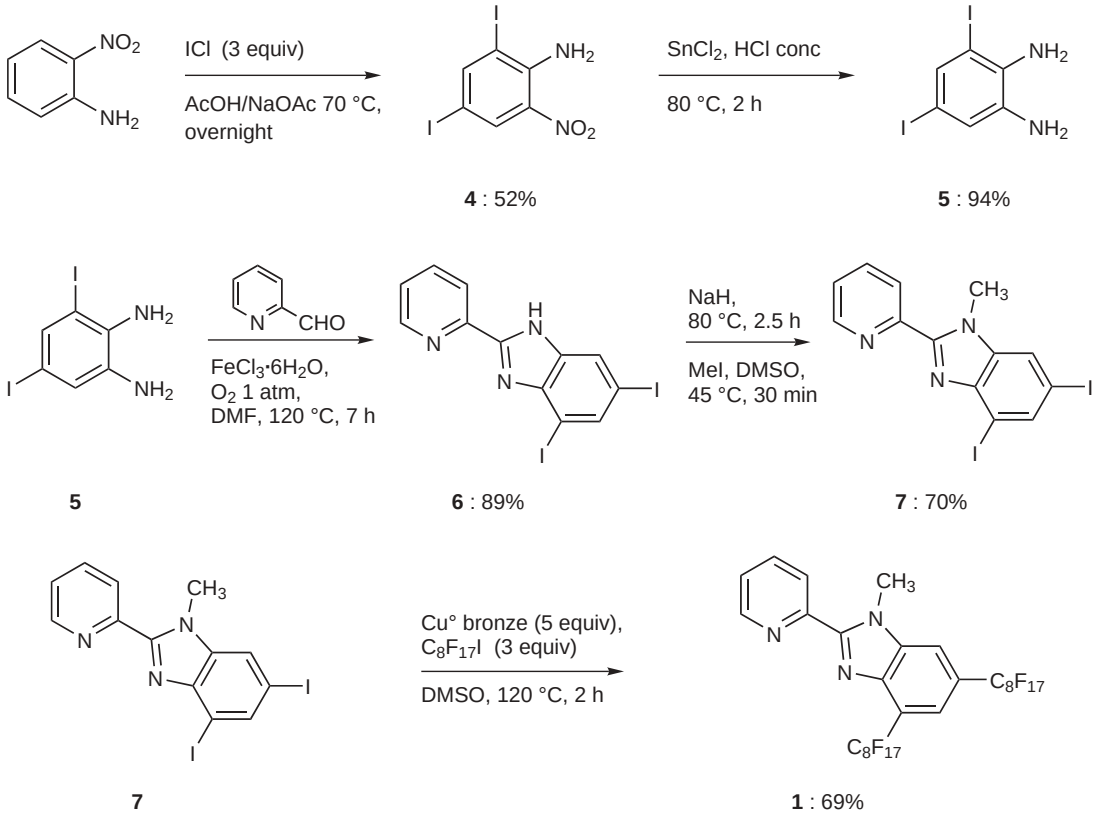
[a] Yield of analytically pure product.
[b] Mixture of *syn*- and *anti*-stereoisomers.
[c] Mixture of α- and β-stereoisomers (2:3).

In general, satisfactory yields and reaction rates were obtained. For the epoxidation of cyclic olefins, the ring size does not affect the reactivity, as shown for cyclooctene and cyclododecene (entries 1 and 2). Halogens (entry 6) and ester functionalities (entries 7, 8, 9) are well tolerated and no degradation was observed. Protection of hydroxyl groups is required, as for citronellol pivalate (entry 8). Attempts of epoxidation of citronellol lead to partial leaching of ruthenium (lower rates in further reaction runs). Polysubstituted olefins react well, as shown for hexa-

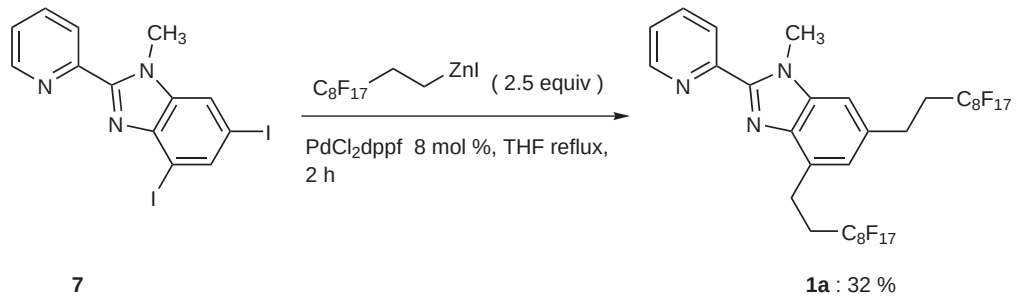
hydroindene **2d** (entry 4), which was completely converted within only 30 minutes. Electron-withdrawing substituents decreased the double bond reactivity as shown for geranyl acetate (entry 7): in this case 100% regioselectivity at the double bond in position 6 was obtained. Ketone **2e** (entry 5) shows an excellent reactivity. This is particularly surprising when compared with 2-methylcyclohexenone, which is completely unreactive under these conditions. A difference in reactivity was also observed between *cis*- and *trans*-4-octene. While the latter (entry 10) is completely converted to the desired epoxide, the *cis*-isomer undergoes decomposition in the same reaction conditions. Terminal olefins like 1-decane give only partial reaction and mixtures of products.

The ligand **1** is readily prepared in five steps starting from cheap, commercially available 2-nitroaniline. Selective diiodination with ICl in positions 3 and 5, followed by reduction of the nitro group by $SnCl_2/HCl$[8] leads to diiododiamine **5**, which condenses with an equivalent of pyridine-2-carboxaldehyde in the presence of oxygen and a catalytic amount of $FeCl_3$,[9] providing the diiodo-heterocycle **6**. Its treatment with methyl iodide, selectively providing the heterocycle **7** as the main isomer,[10] which is easily obtained pure by simple recrystallization from CH_2Cl_2 (mp 134 °C). Rf_2Bimpy (**1**) is obtained in 69% yield by classical Ullman-type reaction with perfluorooctyl iodide in the presence of a large excess of Cu bronze (Scheme 2).

Interestingly, the spacer-containing ligand Rf_2C_2Bimpy **1a** could be synthesized in moderate yields by Negishi cross-coupling between the diiodo-heterocycle **7** and the perfluorinated zinc reagent 1,1,2,2-tetrahydroperfluorodecylzinc iodide in the presence of $PdCl_2$(dppf) as a catalyst[11] (Scheme 3).



Scheme 2



Scheme 3

The complex of **1a** with $RuCl_3$ was also tested in the aerobic epoxidation of cyclooctene **2a**, under the same conditions as the ligand **1**. Complete conversion to cyclooctene oxide within 1 hour was achieved and no leaching of catalyst in the organic phase was observed. This shows that the presence of a spacer between the benzimidazole ring and the fluorous ponytail does not affect the reactivity of this catalyst.[12]

In summary, we have described an efficient ruthenium catalyzed epoxidation of alkenes in a fluorous biphasic system by using the novel fluorous ligand pyridine-benzimidazole Rf_2Bimpy. Excellent conversions and reaction rates could be achieved and the catalyst could be reused for further reaction runs without loss of activity.

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(10) Main isomer **7**: 1–5% of the 5,7-diiodo isomer was also detected.

(11) Analytical data for $C_{29}H_9N_3F_{34}$ (**1**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 4 Hz, 1 H), 8.51 (d, *J* = 7.8 Hz, 1 H), 7.89 (td, *J* = 7.8 and 1.6 Hz, 1 H), 7.87 (s, 1 H), 7.73 (s, 1 H), 7.42 (m, 1 H), 4.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 147.7, 137.2, 136.1, 136.0, 122.0–113.0(bm), 32.3, 28.7 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –79.7 (s, 6 F), –107.4 (m, 4 F), –120.1 (s, 8 F), –120.7 (s, 8 F), –121.6 (s, 4 F), –125.0 (s, 4 F) ppm. IR (KBr, pellets): 3440 (m), 2922 (w), 2856 (w), 1635 (w), 1208 (s), 1150 (s), 666 (w) cm^{-1}. MS (EI, 70 eV): *m/e* (rel. int.) = 1045 (100), 1025 (19), 967 (1), 706 (6), 676 (23), 626 (6), 338 (2), 307 (3), 258 (7), 168 (1). HRMS: calcd 1045.0254; found: 1045.0230. Mp 134 °C.
Analytical data for $C_{33}H_{17}N_3F_{34}$ (**1a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 3.6 Hz, 1 H), 8.37 (d, *J* = 6.0 Hz, 1 H), 7.84 (td, *J* = 5.4 and 0.9 Hz, 1 H), 7.34 (m, 1 H), 7.15 (s, 1 H), 6.98 (s, 1 H), 4.25 (s, 3 H), 3.37 (m, 2 H), 3.06 (m, 2 H), 2.73 (m, 2 H), 2.45 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.7, 149.6, 147.5, 139.5, 136.7, 135.8, 133.7, 130.4, 123.9, 123.8, 122.6, 121.6, 122.0–108.0 (m), 107.0, 32.7 (t), 31.8, 30.5 (t), 28.7 ppm. ^{19}F NMR (400 MHz, $CDCl_3$): δ = –79.7 (s, 6 F), –113.4 (s, 4 F), –120.5 (s, 4 F), –120.6 (s, 8 F), –120.8 (s, 4 F), –121.6 (s, 4 F), –122.3 (s, 4 F), –125.0 (s, 4 F). IR (KBr, pellets): 2961 (w), 1591 (w), 1470 (w), 1204 (s), 1150 (s), 724 (w), 659 (w) cm^{-1}. MS (EI, 70 eV): *m/e* (rel. int.) = 1101 (100), 1082 (24), 732 (55), 682 (23), 668 (25), 355 (2), 334 (3), 281 (4), 207 (3). HRMS: calcd.1101.088; found: 1101.044. Mp 104 °C.

(12) **Typical Procedure:** Preparation of cyclooctene oxide (**3a**): A 50 mL Schlenk tube, equipped with a stirrer and a O_2-inlet was charged with the fluorous benzimidazole **1** (52.0 mg, 50 μmol, 2 mol%) dissolved in perfluorooctyl bromide (2.5 mL), and $RuCl_3 \cdot xH_2O$ (36% Ru, 7 mg, 25 μmol, 1 mol%) dissolved in a few drops of acetone leading to a red solution. After stirring for 0.5 h, a solution of *cis*-cyclooctene (220 mg, 2.0 mmol) and *i*-PrCHO (288 mg, 4.0 mmol, 2 equiv) in chlorobenzene (2 mL) was added. The biphasic reaction mixture was stirred at 40 °C while a gentle stream of oxygen from a balloon was passing. The color of the reaction mixture changes from red to deep blue within 15 min. At the end of the reaction, the mixture was cooled to 10 °C, the organic layer was decanted and the fluorous phase was washed with chlorobenzene (4 × 2 mL). The chlorobenzene is removed in vacuo and the residue diluted with CH_2Cl_2 (20 mL). The organic phase is treated with cold NaOH (0.1 M, 20 mL) and washed with brine. After drying ($MgSO_4$), filtration and evaporation of the solvent in vacuo the crude product was purified by flash chromatography (eluent: Et_2O–pentane), yielding 224 mg (89%) of analytically pure cyclooctene oxide. The blue fluorous phase containing the Ru-catalyst was used directly for further reaction runs without loss of activity.