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Soluble Polymer-Supported Ruthenium Porphyrin Catalysts for Epoxidation, Cyclopropanation, and Aziridination of Alkenes

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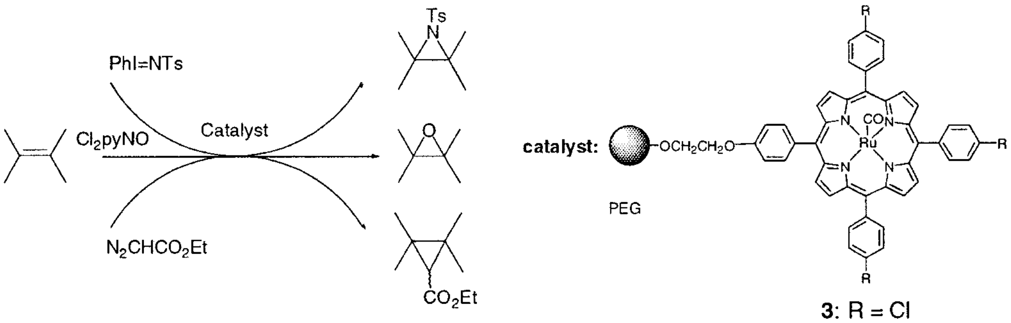
ABSTRACT



3: R = Cl
4: R = Cl
5: R = Me

Attachment of poly(ethylene glycol) (PEG) to ruthenium porphyrin via a covalent etheric bond gives soluble polymer-supported ruthenium catalysts 3–5. These catalysts exhibit high reactivity and selectivity toward alkene epoxidation with 2,6-dichloropyridine *N*-oxide and alkene cyclopropanation with diazo compounds. The application of these catalysts in the synthesis of unstable organic compounds has been demonstrated.

There is a growing interest in developing ruthenium porphyrin catalysts for carbon−oxygen,[1a−g] carbon−nitrogen,[1h−j] and carbon−carbon[1k−n] bond formation reactions. Extensive studies have demonstrated that ruthenium porphyrins exhibit high stability and remarkable selectivity in catalyzing organic oxidations by 2,6-dichloropyridine *N*-oxide and cyclopropanation of alkenes by diazo compounds. However, the reported catalytic reactions usually proceed in homogeneous media; this renders recycling of the ruthenium porphyrin catalyst difficult. In this regard, there are reports on attachment of an insoluble polymer support,[2] including surface-modified mesoporous molecular sieve (MCM-41),[2a,b] Merifield's peptide resin (MPR),[2c] and highly cross-linked

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(1) Selected examples: (a) Groves, J. T.; Quinn, R. *J. Am. Chem. Soc.* **1985**, *107*, 5790. (b) Higuchi, T.; Ohtake, H.; Hirobe, M. *Tetrahedron Lett.* **1989**, *30*, 6545. (c) Ho, C.; Leung, W.-H.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1991**, 2933. (d) Zhang, R.; Yu, W.-Y.; Lai, T.-S.; Che, C.-M. *Chem. Commun.* **1999**, 409. (e) Gross, Z.; Ini, S. *Org. Lett.* **1999**, *1*, 2077. (f) Liu, C.-J.; Yu, W.-Y.; Che, C.-M.; Yeung, C.-H. *J. Org. Chem.* **1999**, *64*, 7365. (g) Zhang, R.; Yu, W.-Y.; Wong, K.-Y.; Che, C.-M. *J. Org. Chem.* **2001**, *66*, 8145. (h) Au, S.-M.; Huang, J.-S.; Yu, W.-Y.; Fung, W.-H.; Che, C.-M. *J. Am. Chem. Soc.* **1999**, *121*, 9120. (i) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che. C.-M. *Org. Lett.* **2000**, *2*, 2233. (j) Liang, J.-L.; Huang, J.-S.; Zhu, L.-Y.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563. (k) Galardon, E.; Le Maux, P.; Simonneaux, G. *Chem. Commun.* **1997**, 927. (l) Lo, W.-C.; Che, C.-M.; Cheng, K.-F.; Mak, T. C. W. *Chem. Commun.* **1997**, 1205. (m) Che, C.-M.; Huang, J.-S.; Lee, F.-W.; Li, Y.; Lai, T.-S.; Kwong, H.-L.; Teng, P.-F.; Lee, W.-S.; Lo, W.-C.; Peng, S.-M.; Zhou, Z.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 4119. (n) Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2001**, *123*, 4843.

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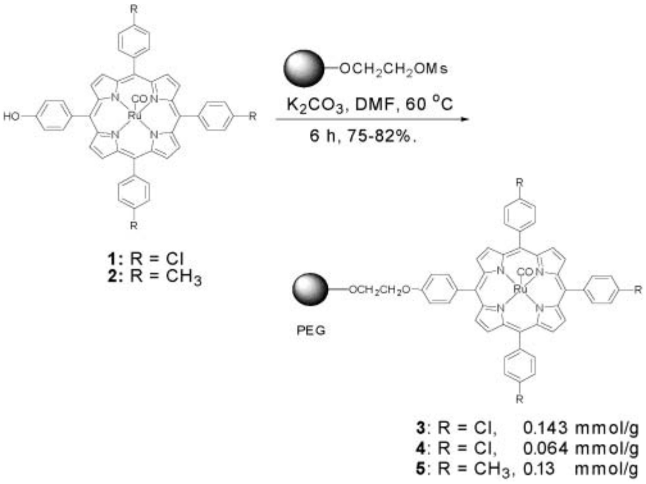
polymer,[2d] to ruthenium porphyrins to give heterogeneous catalysts. However, these ruthenium-modified heterogeneous catalysts suffer from limited mobility as a result of restriction of the polymer matrix and accessibility of active sites to organic substrates. To circumvent the problems encountered in previous homogeneous and heterogeneous ruthenium porphyrin catalysts, we set forth to develop dendritic ruthenium porphyrin and investigate its catalytic reactivity toward epoxidation and cyclopropanation of alkenes.[3] We were also attracted to the recent works by Janda and co-workers that metal catalysts containing poly(ethylene glycol) (PEG) have broad solubility profiles and are easily characterized and separated from organic products after reactions.[4] Anchoring ruthenium porphyrin to the commercially available PEG via covalent bond linkage provides a unique opportunity to combine the best features of both homogeneous and heterogeneous ruthenium catalysts. Herein we describe the applications of soluble polymer-supported ruthenium porphyrins in catalytic epoxidation, aziridination, and cyclopropanation of alkenes.

The unsymmetrically substituted *meso*-tetraaryl-porphyrins, 5,10,15-tris(4-R-phenyl)-20-(4-hydroxyphenyl) porphyrins (R = Cl, Me) were readily prepared via “one-pot” reactions of the corresponding aldehydes and pyrrole; subsequent reactions with $Ru_3(CO)_{12}$ in refluxing decalin afforded ruthenium(II) porphyrins **1** and **2** in high yields.[2c] Attachment of ruthenium porphyrins to methoxypoly(ethylene glycol) was realized in high yields (R = Cl, 75%; R = Me, 82%) by treating **1** or **2** and the polymer mesylate derivative in DMF in the presence of anhydrous potassium carbonate at 60 °C for 6 h. Three catalysts **3** (R = Cl), **4** (R = Cl), and **5** (R = Me) with different ruthenium porphyrin loadings were prepared (Scheme 1). UV−vis and IR spectroscopic measurements revealed that ruthenium porphyrins were covalently bonded to PEG. ^1H NMR spectra showed the disappearance of the Me signals of $MeSO_2-$PEG at 3.07 ppm and appearance of a new peak at 4.06 ppm attributed to $PEGCH_2\underline{CH_2}O-$Por. The loading was determined by ^1H NMR spectroscopy using the $PEGCH_2O\underline{Me}$ signal at ca. $\delta = 3.30$ as the internal reference.

To evaluate catalytic properties, we first investigated the catalytic activities of catalysts **3** and **5** toward oxidation of styrene in CH_2Cl_2. The terminal oxidants PhIO, TBHP, H_2O_2, and 2,6-Cl_2pyNO were used. The best conversion (96%) and selectivity (epoxide yield, 98%) were obtained with 2,6-Cl_2pyNO. For the epoxidation of styrene by 2,6-Cl_2pyNO, catalyst **3**, which bears electron-withdrawing Cl group, is superior to **5** and is more reactive than **4**, which has a lower ruthenium porphyrin loading. Thus, catalyst **3** was chosen for subsequent study.

Scheme 1



As depicted in Table 1, **3** is an efficient catalyst for epoxidation of a wide variety of alkenes by Cl_2pyNO. In the cases of styrene, *cis*-stilbene, norbornene, cyclohexene, cyclooctene, 1,2-dihydronaphthalene, and 1-octene, the yields and selectivity of the epoxides were comparable to those obtained with heterogeneous ruthenium porphyrin catalysts.[1a−g] For reactions with *trans*-stilbene and *trans*-β-methylstyrene, the *trans*-epoxides were obtained in high overall yields (88% and 93%, respectively). Chalcone, an electron-deficient alkene, was also oxidized to the corresponding epoxide in moderate yield. To our knowledge, epoxidation of electron-deficient alkenes using metalloporphyrin catalysts has seldom been reported.[5] The applicability of **3** in the synthesis of organic building blocks has been examined. Using 1-phenethynyl cyclohexene as substrate, the reaction afforded the corresponding epoxide, a valuable intermediate in the synthesis for bioactive enedyne antitumor agents, in high overall yield (90%).[6] 3,4,6-Tri-*O*-acetyl-D-glycal was converted to the epoxide derivative, which is a useful intermediate for carbohydrate synthesis,[7] in 67% isolated yield with the α:β ratio being 10:1. This α/β diastereoselectivity is significantly higher than that with ruthenium porphyrin immobilized on MCM-41[2a,b] and comparable to that with $[Ru^{II}(2,6\text{-}Cl_2\text{-TPP})(CO)]$[2b], dendritic ruthenium porphyrin, and ruthenium porphyrin immobilized on Merrifield’s peptide resin[2c]. Last, cholesteryl acetate was epoxidized in high overall yield (90%) and with complete β- selectivity; similar findings were previously reported using the “$[Ru^{VI}(TMP)(O)_2]$ + air”[8f,g] and “dendritic ruthenium porphyrin + 2,6-Cl_2pyNO”[3] protocols.[8]

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(2) (a) Liu, C.-J.; Li, S.-G.; Pang, W.-Q.; Che, C.-M. *Chem. Commun.* **1997**, 65. (b) Liu, C.-J.; Yu, W.-Y.; Li, S.-G.; Che, C.-M. *J. Org. Chem.* **1998**, *63*, 7364. (c) Yu, X.-Q.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc*. **2000**, *122*, 5337. (d) Nestler, O.; Severin, K. *Org. Lett*. **2001**, *3*, 3907.

(3) Zhang, J.-L.; Zhou, H.-B.; Huang, J.-S.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1554.

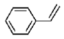
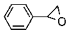
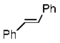
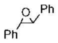
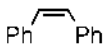
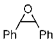
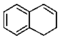
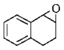
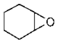
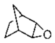
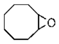
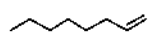
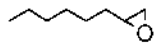
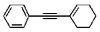
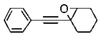
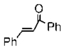
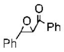
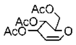
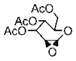
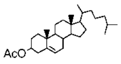
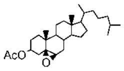
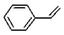
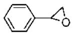
(4) For recent reviews, see: (a) Wentworth, P.; Janda, K. D. *Chem. Commun.* **1999**, 1917. (b) Clapham, B.; Reger, T. S.; Janda, K. D. *Tertrahedron.* **2001**, *57*, 4637. (c) Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546. (d) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489.

(5) (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc*. **1983**, *105*, 5786. (b) Selke, M.; Sisemore, M. F.; Valentine, J. S. *J. Am. Chem. Soc*. **1996**, *118*, 2008. (c) Higuchi, T.; Ohtake, H.; Hirobe, M. *Tetrahedron Lett.* **1989**, *30*, 6545.

(6) Myers, A. G.; Proteau, P. J. *J. Am. Chem. Soc*. **1989**, *111*, 1146.

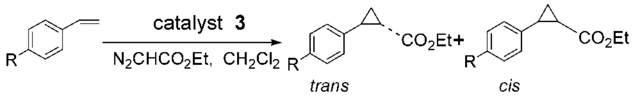
(7) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc*. **1989**, *111*, 6661.

Table 1. Epoxidation of Alkenes with Cl_2pyNO Catalyzed by **3**[a]

entry	substrates	products	conv.%[b]	yield%[c]	TON[d]
1			96	98	940
2			88	99	870
3			94	99	930
4			90	99	890
5			88	99	870
6			76	48[e]	360
7		 (exo)	96	99	950
8			99	99	980
9			88	99	870
10			90	99[f]	890
11			70	99[f]	690
12			90	67[g]	670
13			99	90[h]	900
14			68	90	9180[i]

[a] All reactions were carried out in CH_2Cl_2 at 40 °C for 24 h with a catalyst/Cl_2pyNO/alkene molar ratio of 1:1100:1000, unless otherwise noted. [b] Conversion was determined by GLC analysis of the reaction mixture using the internal standard method (1,4-dichlorobenzene or 1,3,5-tribromobenzene); error, ±2% of the stated values. [c] Based on the amount of olefin consumed. [d] TON = turnover numbers. [e] Other products: cyclo-2-en-1-one (41%) and cyclo-2-en-1-ol (11%). [f] Conversion and yield were determined by ^1H NMR (400 MHz). [g] Isolated yield after epoxidation and methanolysis. [h] Isolated yield. The ratio of β/α was determined by ^1H NMR according to the previous literature. [i] The reaction was performed in CH_2Cl_2 at 40 °C for 48 h with a catalyst/oxidant/substrate molar ratio of 1:17000:15000.

Table 2. Cyclopropanation of Styrenes with Ethyl Diazoacetate Catalyzed by **3**[a]



entry	R	conv. %[b]	yield %[c]	*trans*/*cis* ratio[d]	TON
1	H	65	88	9.7	572
2	CH_3	86	98	9.3	843
3	OCH_3	93	80	9.5	744
4	F	56	93	8.8	521
5	Cl	82	91	10	746
6	Br	66	88	11	581
7	CF_3	47	82	9.2	385

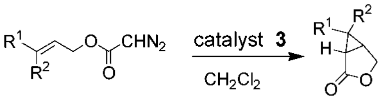
[a] All reactions were performed in dichloromethane at room temperature for 24 h with a **3**/EDA/alkene ratio of 1:1200:1000. [b] Conversion was determined by GC analysis of the reaction mixture using the internal standard method (1,4-dichlorobenzene or chlorobenzene); error, ±2% of the stated values. [c] Isolated yield based on the alkene consumed. [d] Determined by GC.

The soluble polymer catalyst **3** is oxidatively robust. Product turnovers up to 9.18 × 10^3 have been attained for styrene epoxidation in a 48 h reaction (entry 14, Table 1). After being reused five times, its activity decreased only slightly upon recycling of the catalyst by filtration.

Catalyst **3** is effective for intra- and intermolecular cyclopropanation of alkenes. The results for the reactions between styrenes and ethyl diazoacetate (EDA) catalyzed by **3** are listed in Table 2. The para-substituent of styrene has an effect on the conversion but minimally affects the *trans*/*cis* ratio (~10:1) of the cyclopropane products. These results are different from that obtained with dendritic and monomeric ruthenium porphyrin catalysts.[3,1k−n] Catalyst **3** displays high stability in the cyclopropanation reactions; recycling up to six times has been found not to affect its reactivity.

Intramolecular cyclopropanation is a useful reaction for the synthesis of natural products.[9] First, we used **3** to catalyze cyclopropanation of primary allylic diazoacetates in CH_2Cl_2 at room temperature. The results are listed in Table 3.

Table 3. Intramolecular Cyclopropanation of Primary Allylic Diazoacetates Catalyzed by **3**[a]



entry	R^1	R^2	isolated yield %[b]	TON[c]
1	H	H	83	720
2	Ph	H	85	620
3	*trans*-$CH_3CH{=}CH$	H	78	740

[a] All reactions were performed in CH_2Cl_2 at room temperature for 24 h with a catalyst/substrate ratio of 1:1000. [b] On the basis of consumed substrates. [c] TON = turnover numbers.

We found that the catalyst exhibited high reactivity and could be conveniently removed by adding diethyl ether to the reaction mixture. Upon concentrating the filtrate, the organic product could be obtained without purification by column chromatography.

In this work, we also investigated intramolecular cyclopropanation of secondary allylic diazoacetates. Using 2-cyclohexen-1-yl diazoacetate as substrate, the reaction afforded tricyclic cyclopropane as the main product in 85% yield (Scheme 2). The side product 2-cyclohexenone was obtained

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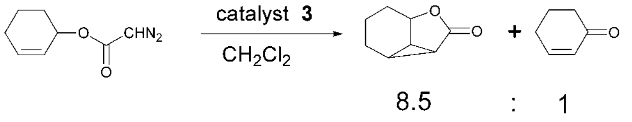
(8) Selected examples: (a) Parish, E. J.; Li, S. *J. Org. Chem.* **1996**, *61*, 5665. (b) Syamala, M. S.; Das, J.; Baskaran, S.; Chandrasekaran, S. *J. Org. Chem.* **1992**, *57*, 1928. (c) Salvador, J. A. R.; Sàe Melo, M. L.; Campos Nevers, A. S. *Tetrahedron Lett.* **1996**, *37*, 687. (d) Kesavan, V.; Chandrasekaran, S. *J. Org. Chem.* **1998**, *63*, 6999. (e) Yang, D.; Jiao, G.-S. *Chem. Eur. J.* **2000**, *6*, 3517. (f) Tavarès, M.; Ramasseul, R.; Marchon, J.-C.; Bachet, B.; Brassy, C.; Mornon, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1321. (g) Marchon, J.-C.; Ramasseul, R. *Synthesis* **1989**, 389.

(9) For reviews, see: (a) Doyle, M. P.; Forbs, D. C. *Chem. Rev.* **1998**, *98*, 911. (b) Doyle, M. P.; Mckervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998.

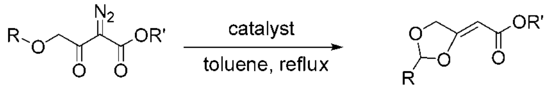
Scheme 2



in 10% yield. This is the first example of intramolecular cyclopropanation of secondary allylic diazoacetates using ruthenium porphyrin as catalyst, and the result is comparable to that previously reported by using rhodium or copper catalysts.[10]

We have extended the application of catalyst **3** for cyclization of γ-alkoxy-α-diazo-β-keto esters to (*Z*)-2-alkyl-4-(alkoxycarbonylmethylene)-1,3-dioxolanes.[11] The results are listed in Table 4. Catalyst **3** displayed remarkably high reactivity (conversions were up to 99%) and turnovers (up to 460) compared with the monomeric [Ru^{II}(TTP)CO] [H$_2$-TTP = *meso*-tetrakis(*p*-tolyl) porphyrin] catalyst. For the latter, the isolated product yields were lower (entries 2 and 4, Table 4); this was attributed to product decomposition upon chromatography on silica gel column. In this work, the products were obtained in higher yields (entries 1 and 3, Table 4) by adding diethyl ether to the reaction mixture followed by filtering of the polymer catalyst. No column chromatography was needed to remove the catalyst from the products.

Table 4. Unusual α-Diazocarbonyl Reaction of γ-Alkoxy-α-diazo-β-keto Esters Catalyzed by **3**[a] and [Ru^{II}((TTP)CO]

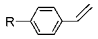
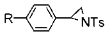
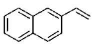
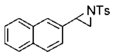


entry	R	R′	catalyst	yield %[b]	TON[c]
1	Ph	Me	**3**	92	460
2[d]	Ph	Me	[Ru^{II}(TTP)CO]	68	22
3	2-cyclohexenyl	(−)-menthyl	**3**	85	430
4[d]	2-cyclohexenyl	(−)-menthyl	[Ru^{II}(TTP)CO]	50	16

[a] All reactions were performed in refluxed toluene for 6 h with a catalyst/substrate ratio of 1:500. [b] On the basis of consumed substrates. [c] TON = turnover numbers. [d] According to ref 11.

Catalyst **3** was also tested for catalytic aziridination of alkenes by PhI═NTs. To our knowledge, there has been no report on metalloporphyrin catalysts immobilized on soluble or insoluble polymer support for alkene aziridination. The results are listed in Table 5; moderate reactivity toward aromatic alkenes was found.

Table 5. Aziridination of Alkenes with PhI═NTs Catalyzed by **3**[a]

entry	substrates	products	conv.%[b]	yield%[c]	TON[d]
1		 R = H	58	88	38
2		R = F	46	76	26
3		R = Cl	62	79	37
4		R = Br	53	80	32
5		R = Me	62	88	41
6			78	85	50

[a] All reactions were carried out at 40 °C for 8 h with a catalyst/PhINTs/alkene molar ratio of 1:150:75, unless otherwise noted. [b] Conversion was determined by GLC analysis of the reaction mixture using the internal standard method (1,4-dichlorobenzene or chlorobenzene). [c] Isolated yield based on the amount of olefin consumed. [d] TON = turnover numbers.

In summary, we prepared soluble polymer-supported ruthenium porphyrin catalysts by treatment of ruthenium porphyrins with methoxypoly(ethylene glycol). Catalyst **3** exhibits high reactivity, selectivity, and stability in epoxidation and cyclopropanation of alkenes. It is worthy to note that catalyst **3** is particularly useful for synthesis of unstable organic compounds such as (*Z*)-2-alkyl-4-(alkoxycarbonylmethylene)-1,3-dioxolanes that are easily decomposed upon chromatography on silica gel column.

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Supporting Information Available: Experimental details for the synthesis and characterization of **3**, **4**, and **5**; the effects of oxidants, solvents and catalysts on epoxidation of styrene in this protocol; and detailed procedures for the catalytic reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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