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Poly(ethylene glycol)-supported α,α,α-trifluoroacetophenone in dioxirane mediated alkene epoxidation reactions

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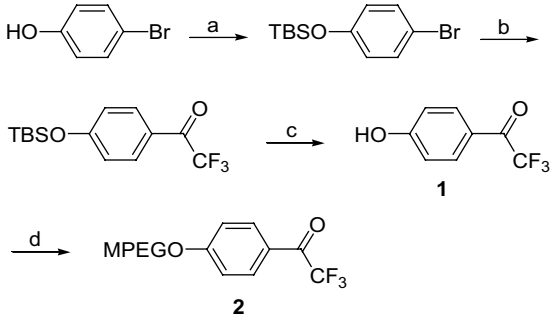
Abstract—Poly(ethylene glycol) (PEG) was used for the immobilization of α,α,α-trifluoroacetophenone and the utility of this supported ketone has been examined in dioxirane mediated epoxidation of alkenes. The PEG-ketone reagent was found to be an effective homogeneous catalyst for the epoxidation of a variety of alkenes in the presence of Oxone® and was readily recovered from the reaction mixtures and reused.

The use of small organic molecules to catalyze reactions in what is known as organocatalysis is a rapidly expanding field of research.[1] Some of the most useful such compounds for this type of catalysis are amines, such as amino acids and their derivatives[2,3] and naturally occurring alkaloids.[4] These catalysts have been found to be effective in Baylis–Hillman,[5] Strecker,[6] and anhydride desymmetrization[7] reactions. Another class of useful organic catalysts are dioxirane compounds, derived from the oxidation of ketones with Oxone® ($2KHSO_5$–$KHSO_4$–K_2SO_7), that are effective oxidants in alkene epoxidation reactions.[8,9]

Our long-standing interest in the development of new polymer supports[10,11] and the attachment of amine,[12] phosphine,[13] sulfide[14] and sulfoxide[15] reagents to these polymers led us to investigate the attachment of such a ketone organic catalyst to a polymer support in order to simplify its recovery and reuse.[16] There have been several previous reports regarding attachment of ketones to various polymeric supports and their use in dioxirane-mediated alkene epoxidation reactions, including attachment of a methyl ketone to polystyrene,[17] a trifluoromethyl ketone attached to both polystyrene and Tentagel®,[18] and both an achiral trifluoromethyl ketone[19,20] and a chiral fluoro ketone[21] immobilized on silica.

These prior reports used insoluble supports that rendered the reagents attached to them heterogeneous. Due to this, incomplete coupling of the ketone to the support was observed in some cases and in all cases, prolonged reaction times were required for reactions to be completed, as compared to reactions using small molecule ketone catalysts. As a result these reagents have not yet found wide use in organic synthesis. In order to overcome these issues and to prepare what might be a more broadly useful reagent, we chose to use poly(ethylene glycol) (PEG),[22,23] a polymer that is soluble in both water and organic solvents such as 1,4-dioxane and THF, as the support for α,α,α-trifluoroacetophenone.

For attachment of the ketone to PEG via an ether linkage, phenol **1** was prepared from 4-bromophenol in three steps (Scheme 1). Initial protection of the phenol



Scheme 1. Reactions and conditions: (a) TBDMSCl, Imidazole, DMF, 0 °C to rt, 100%; (b) Mg, THF, *N*-trifluoroacetylpiperidine, rt, 56%; (c) TBAF, THF, rt, 90%; (d) $CsCO_3$, Bu_4NI, MPEG-OMs, DMF, 65 °C, 90%.

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group as a silyl ether was followed by reaction with magnesium to form the corresponding Grignard reagent. This reagent was reacted with *N*-trifluoroacetylpiperidine[24] to introduce the trifluoromethyl ketone group. Finally, removal of the silyl ether group afforded phenol **1**.[25] Reaction of **1** with MPEG-OMs[26] (MPEG = poly(ethylene glycol) monomethyl ether, average MW = 5000) in the presence of $CsCO_3$ and Bu_4NI afforded supported catalyst **2**.[27]

The epoxidation of a variety of alkenes using catalyst **2** was examined (Table 1). In these reactions, ketone **2** was converted in situ to the corresponding dioxirane by Oxone® in water/dioxane at room temperature. It should be noted that these reactions were all quite efficient and the complete disappearance of the alkene required less than 5 min, according to TLC analysis, when only 0.1 equiv of **2** was used.[28,29] The yields listed in Table 1 represent purified isolated products.[30] In most cases, the epoxide was the sole product formed (according to TLC analysis) and the less than quantitative yields are a result of product loss during the workup and purification processes. Both styrene derivatives (Table 1, entries 1–10) and alkyl substituted alkenes (Table 1, entries 11 and 12) were good substrates.

Table 1. Alkene epoxidation catalyzed by ketone **2** in the presence of Oxone®

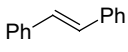
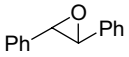
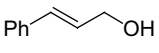
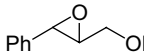
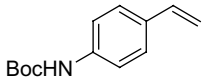
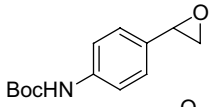
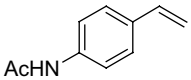
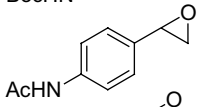
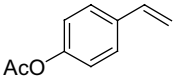
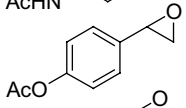
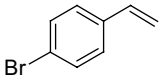
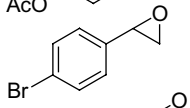
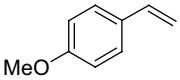
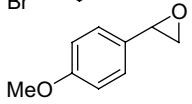
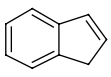
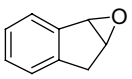
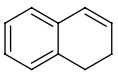
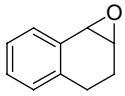
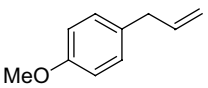
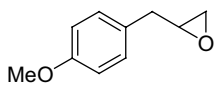
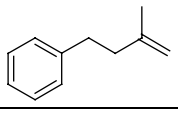
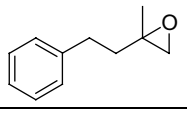
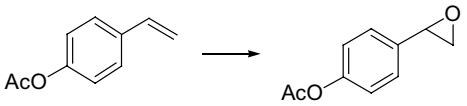
Entry	Alkene	Product	Yield (%)
1			85
2			74
3			77
4			90
5			79
6			84
7			87
8			78
9			84
10			82
11			72
12			76

Table 2. Alkene epoxidation catalyzed by recycled ketone **2**



Cycle	Yield (%)
1	84
2	82
3	84
4	81
5	85

Once the utility of **2** was established, the reaction represented by Table 1, entry 6 was used to determine if **2** recovered at the end of the reactions[31] could be reused. As can be seen in Table 2, a single sample of catalyst **2** can be effectively reused at least five times with essentially no decrease in isolated product yield.[32]

In summary, we have prepared for the first time, a soluble polymer-supported trifluoromethyl ketone that is an effective catalyst in dioxirane mediated alkene epoxidation reactions and that is approximately as efficient as is the analogous small molecule ketone, α,α,α-trifluoroacetophenone.[18,33,34] Due to its solubility, **2** functions as a homogeneous catalyst and, therefore, allows for much shorter reaction times and comparable yields compared to other previously reported insoluble polymer-supported fluorinated ketone catalysts and thus it should be a useful new tool in the synthetic chemistry toolbox. Along this line, it is interesting to note that in the synthesis of epothilones by Ley and coworkers in which all steps were carried out using polymer-supported reagents, the final conversion of epothilone C to epoxide containing epothilone A was not performed, presumably due to the lack of an available supported epoxidation catalyst.[35] Perhaps if a reagent such as **2** had been available at that time, the complete synthesis of epothilone A using polymer-supported reagents in every step would have been possible.

Acknowledgements

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25. Characterization data for phenol **1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (1H, s, br), 6.96 (2H, d, $J=10.1$ Hz), 8.02 (2H, d, $J=8.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.6–121.2 ($J_{CF}=289.4$ Hz), 116.1 (2C), 122.7, 133.2 (2C), 162.6, 179.4 ($J_{CF}=34.6$ Hz). IR (CH_2Cl_2, cm^{-1}) 3046, 2984, 1685, 1653, 1603, 1580, 1520, 1443, 1255. HRMS (*m*/*z*) calcd for $C_8H_5F_3O_2$ (M^+) 190.0242, found. 190.0241.
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27. Characterization data for ketone **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (–OC<u>H</u>$_3$, s), 3.46–3.81 (*n*–OC<u>H</u>$_2$, m), 6.91 (2 C–<u>H</u>, d, $J=8.2$ Hz), 8.09 (2 C–<u>H</u>, d, $J=8.6$ Hz). IR (CH_2Cl_2, cm^{-1}) 3052, 2853, 1684, 1653, 1603, 1574, 1521, 1452, 1352.
28. Sample epoxidation procedure: A mixture of alkene (0.4 mmol, 1.0 equiv), **2** (0.1 equiv), Oxone® (3.0 equiv) and $NaHCO_3$ (9.0 equiv) in 1,4-dioxane/aq 4×10^{-4} M EDTA (1.5/1.0 v/v, 5 mL) was stirred vigorously at rt for 5 min. At this time, the reaction was diluted with CH_2Cl_2 (20 mL) and H_2O (2 mL). The organic layer was separated and ether (20 mL) was added to it in order to precipitate **2**. This was filtered off and the filtrate was concentrated. The crude residue was purified by radial chromatography (EtOAc/hexanes) to afford the desired epoxide.
29. For Table 1, entries 1–4, 0.2 equiv of **2** were used.
30. All epoxide products were characterized by ^{1}H NMR and by HRMS analysis.
31. The ^{1}H NMR spectra of recovered **2** was identical to that of unused **2**.
32. Reactions involving recycled **2** were somewhat sluggish and required up to 30 min for the alkene to disappear.
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