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α-Fluorotropinone Immobilized on Silica: A New Stereoselective Heterogeneous Catalyst for Epoxidation of Alkenes with Oxone

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The dioxirane-mediated epoxidation of alkenes in the presence of supported α-fluorotropinones **5** and **9** has been evaluated. The catalysts anchored onto silica supports **5** have shown comparable activity with respect to the homogeneous counterpart **10** and good stability on recycling. In the second part of this paper the enantiomerically enriched α-fluorotropinone **4*** was anchored onto both mesoporous MCM-41 and amorphous KG-60 silicas. The chiral-supported catalysts promoted the stereoselective epoxidation of several trans-substituted and trisubstituted alkenes with ee values up to 80% and were perfectly reusable with the same performance for at least three catalytic cycles.

Introduction

Preparation of fine chemicals by catalytic oxidation[1] with particular interest in nonracemic epoxides has been extensively studied in recent years since these compounds represent useful building blocks in stereoselective synthesis,[2] and the epoxide functionality constitutes the essential framework of various naturally occurring and biologically active compounds.[3] Among the impressive number of papers published on this topic, some general methods appear as fundamental routes for the synthesis of enantiomerically enriched epoxides. These include metal-catalyzed synthesis such as the Sharpless-[4] and the Jacobsen-type[5] approaches and the use of chiral oxidizing nonmetal reagents such as dioxiranes.[6] These compounds represent classes of versatile and powerful oxidants showing a widespread applicability. Dioxiranes can be utilized as isolated pure reagents or, more conveniently, generated in situ by oxidation of ketones with Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$).[7] The entire oxidative process consists of a ketone-mediated oxygen transfer from Oxone to the selected substrate affording the oxidation product and restoring the starting ketone, which is consequently required in catalytic amount.

Some of the most efficient ketones useful in this reaction are expensive and/or undergo unwanted side reactions with the oxidant, i.e. Baeyer−Villiger oxidation, dimerization, etc.[6]

The heterogenization of the ketone by supporting it on an insoluble material increases its stability, allows its easy recovery and reuse, and makes easier the reaction workup and product purification.[8]

In view of the increasing interest in this field[9] and in continuation of our involvement in this area,[10] we report here the preparation and use of an α-fluorotropinone derivative supported on silica materials, providing efficient and reusable solid catalysts for the epoxidation

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[†] Parma University.

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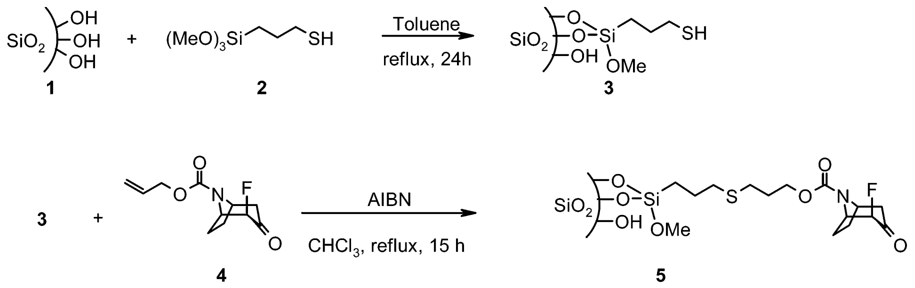
SCHEME 1. Preparation of Silica-Bound α-Fluorotropinones KG-60-FT and MCM-41-FT



of alkenes with Oxone. This particular ketone was selected since one of us recently reported[11] the epoxidation of alkenes with Oxone promoted by α-fluoro-*N*-carbethoxytropinone via the corresponding dioxirane under homogeneous conditions. Good stereoselective control could be achieved by using an enantiomerically pure α-fluorotropinone. Tropinone derivatives of this type are conformationally well defined, efficient catalysts which do not undergo Baeyer−Villiger decomposition under the reaction conditions.

In the first part of the present study we tested three heterogeneous catalysts prepared by anchoring α-fluorotropinone to the surface of the commercially available amorphous silica KG-60, the mesoporous silica MCM-41, prepared in our laboratory by the method reported in the literature,[12] and a Merrifield resin. The activity of the heterogeneous catalysts was compared with that of the homogeneous counterpart.

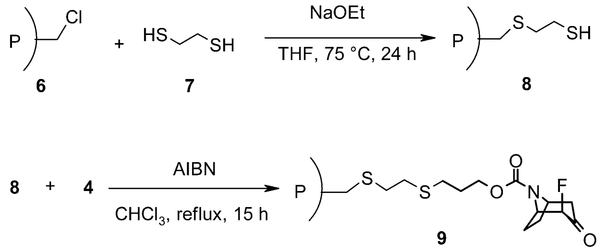
In the second part, we analyzed the efficiency of the enantiomerically enriched heterogeneous catalysts and we report the enantioselective epoxidation of alkenes with Oxone under heterogeneous catalysis.

Results and Discussion

Our plan to support α-fluorotropinone on different silica materials is shown in Scheme 1 and it was performed by slightly modifying a procedure reported in the literature for immobilization of cinchona alkaloids[13] and trifluoroketones.[8c]

The siliceous supports **1** (KG-60 or MCM-41) were first reacted with 3-mercaptopropyltrimethoxysilane (**2**) in refluxing toluene to give the corresponding 3-mercaptopropylsilicas **3** respectively called KG-60-SH (loading value 1.14 mmol/g) and MCM-41-SH (loading value 1.15 mmol/g). Further treatment of these modified materials with α-fluoro-*N*-carballyloxytropinone (**4**) in the presence of α,α′-azoisobutyronitrile (AIBN) as radical initiator in refluxing chloroform readily led to silica-supported α-fluorotropinones **5** through the formation of the sulfide linkage. The heterogeneous catalysts thus obtained were designated as KG-60-FT (loading value 0.58 mmol/g) and MCM-41-FT (loading value 0.78 mmol/g). The comparison of the loading values of the 3-mercaptopropylsilica intermediates **3** with those of the final catalysts **5** suggests that some unreacted thiol groups exist in the silica-bound α-fluorotropinones **5**, namely 0.56 mmol/g in KG-60-FT and 0.37 mmol/g in MCM-41-FT. As expected, the higher surface area and the ordered mesoporous structure of MCM-41 allow it to accommodate a larger amount of catalyst.

SCHEME 2. Preparation of Polystyrene-Bound α-Fluorotropinone POLY-FT



The Merrifield resin-bound α-fluorotropinone **9**, called POLY-FT, was prepared as shown in Scheme 2.

Chloromethylated styrene−divinylbenzene resin **6** (loading value 2.0−2.5 mmol/g) was reacted with 1,2-ethanedithiol (**7**) in dry THF in the presence of sodium ethoxide affording the modified resin **8** (loading value 0.60 mmol/g). This material was subjected to the previously described reaction with **4** in the presence of AIBN to afford the Merrifield resin-supported α-fluorotropinone **9** (loading value 0.56 mmol/g) with a lower amount of unreacted thiol groups (∼0.04 mmol/g).

Finally, the homogeneous counterpart **10** of the supported α-fluorotropinone was prepared by a similar AIBN-promoted coupling reaction between 1-propanethiol and compound **4** (Figure 1).

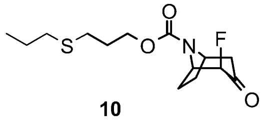


FIGURE 1. Homogeneous catalyst utilized in the model epoxidation reaction.

In addition to elemental analyses (giving the loading values), the anchoring of the α-fluorotropinone moiety to silica and Merrifield resin was confirmed via FT-IR spectroscopy. The presence in the supported α-fluorotropinone spectra of the same pattern of bands characteristic of the homogeneous counterpart **10** demonstrates that the anchored catalyst does not experience any further interaction with the support surface.

After modification, the starting siliceous materials showed a considerable lowering of the surface area (from

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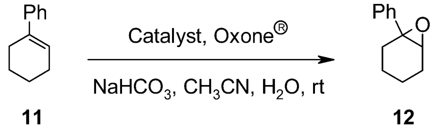
TABLE 1. Epoxidation of 1-Phenylcyclohexene



entry	catalyst	surface area (m^2/g)	loading (mmol/g)	oxone (equiv)	t (h)	conv.[a] of **11** (%)	yield[a] of **12** Sel.][b] (%)
a	**10**			2.5	0.5	100	98 [98]
b	KG-60-FT	200	0.58	5.0	1.0	62	58 [93]
c	MCM-41-FT	670	0.78	5.0	1.0	65	63 [98]
d	POLY-FT		0.56	5.0	1.0	60	18 [30]
e	KG-60-FT (A)	200	0.58	5.0	1.0	98	96 [98]
f	MCM-41-FT (A)	670	0.78	5.0	1.0	100	98 [98]
g	POLY-FT (A)		0.56	5.0	1.0	56	19 [34]

[a] Determined by ^{1}H NMR and GC. [b] (Yield/conv.) × 100.

300 to 200 m^2/g for KG-60 and from 1050 to 670 m^2/g for MCM-41). Moreover, since the X-ray diffraction patterns of the MCM-41 functionalized materials resemble that of the original MCM-41 silica, we argue that during the immobilization treatments the mesoporous structure of the support remains undisrupted and the molecules of α-fluorotropinone should be dispersed on the surface of the support and easily accessible to reagents.

Our catalytic studies begun by comparing the efficiency of all catalysts in the epoxidation of 1-phenylcyclohexene with Oxone. All reactions were carried out in acetonitrile containing aqueous Na$_2$EDTA by adding, under vigorous stirring, portions of a Oxone (2.5 equiv)/NaHCO$_3$ (3.9 equiv) mixture each 30 min for the selected time. The amount of both homogeneous and heterogeneous catalysts was chosen in order to utilize a 0.4 molar ratio between the α-fluorotropinone and the reagent **11**. The results are summarized in Table 1.

Reference experiments performed without any catalyst and in the presence of KG-60 and KG-60-SH silicas showed a low conversion with poor yield and selectivity (10−15% of **12** was obtained with 5 equiv of Oxone in all experiments). Moreover, as expected, the homogeneous catalyst **10**, bearing at the nitrogen atom of the α-fluorotropinone the same chain of the spacer present in the heterogeneous catalyst, afforded the product **12** in quantitative yield and excellent selectivity (entry a). It was noted that quite similar satisfactory results were achieved with both silica-supported catalysts independent from whether the amorphous or the mesoporous silica was utilized as the solid support (entries b and c). Surprisingly a very poor efficiency was observed by using α-fluorotropinone supported on the Merrifield resin (entry d). This result can partly be attributed to a low degree of swelling of the styrene−divinylbenzene polymeric support in the acetonitrile/water polar and hydrophilic reaction medium.[14]

While the silica-supported catalysts show good efficiency in the model reaction, we suspected that in the strongly oxidizing reaction medium the sulfide groups of the spacer arm could be converted to sulfoxide or sulfone[15] and the free mercaptopropyl groups still present on the surface of the silica (0.56 mmol/g in KG-60-FT and 0.37 mmol/g in MCM-41-FT) could undergo oxidation to sulfonic acid.[16] Thus we preoxidized the supported catalysts with Oxone [the preoxidized materials were named KG-60-FT(A), MCM-41-FT(A), and POLY-FT(A)] and the activity of the so-obtained catalysts was compared with that of the parent ones. Results from Table 1 (compare entries b−d with entries e−g) allow us to conclude that the oxidative pretreatment of the catalysts provided a remarkable increase in product **12** yield. For example, in the presence of KG-60-FT(A) the original conversion of 62% was improved to 98%. Similar enhancement was observed with MCM-41-FT(A); on the contrary the Merrifield resin supported catalyst showed unchanged low activity.

The relationship between the oxidation state of the linker and the catalyst activity is not easily rationalizable; however, the beneficial effect of the catalyst preoxidation on both stability and efficiency of similar catalysts has been previously observed.[17] We tentatively ascribe this enhancement to, at least, two facts: (i) part of the Oxone is consumed in the oxidation of the linker and (ii) the $-SH \rightarrow -SO_3H$ and $-S- \rightarrow -SO_2-$oxidation were shown to be ketone-catalyzed via oxirane,[18] which consequently represents a further competitive reaction affecting the desired epoxidation process.

To support this hypothesis we analyzed the progress of the yield of product **12** versus time in the model reaction performed in the presence of freshly prepared KG-60-FT (◆, Figure 2) and preoxidized KG-60-FT(A) (■, Figure 2) catalysts. Experiments were carried out by adding a single portion of Oxone (2.5 equiv)/NaHCO$_3$ (3.9 equiv) mixture to substrate **11** (Figure 2).

In the presence of KG-60-FT(A) the yield reaches 60% after 30 min; the data were better described by a first-order irreversible kinetic with $k = 4.2 \times 10^{-1} (3 \times 10^{-2})$ min^{-1}. On the contrary, with the catalyst KG-60-FT the yield reaches only 25% after 30 min; in this case data were fitted by assuming that the apparent kinetic constant is proportional to the catalyst amount (i.e. $k = k'C_{cat}$). A first-order kinetic for the catalyst oxidation

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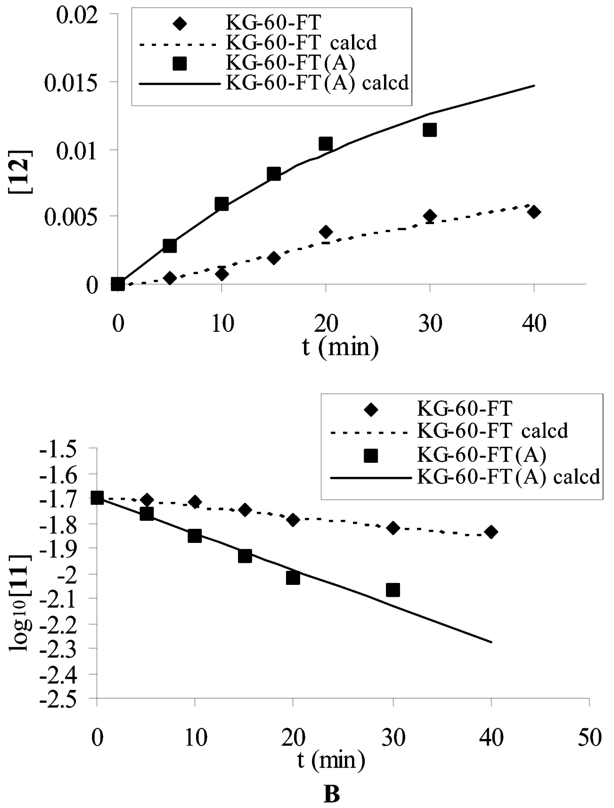

FIGURE 2. (A) [**12**] = $f(t)$. The continuous line refers to the previously oxidized catalyst KG-60-FT(A) and plots the function [**12**] = $0.02[1 - \exp((-4.2 \times 10^{-2})t)]$, whereas the dotted line refers to the catalyst KG-60-FT and plots the function [**12**] = $0.02(1 - \exp[(-4.4 \times 10^{-2})0.02[1 - \exp(-0.14t)]t])$. (B) log10-[**11**] = $f(t)$.

reaction was supposed and consequently a $k = 4.4 \times 10^{-1}(4 \times 10^{-2})$ min^{-1} was calculated, in very good agreement with that obtained for the reaction carried out with the preoxidized catalyst. In addition, in a comparative experiment the model compound **10** was treated with the Oxone (2.5 equiv)/$NaHCO_3$ (3.9 equiv) mixture under the same reaction conditions. The reaction after a few minutes showed complete conversion of **10** into the corresponding sulfone **13**. All these results are in satisfactory agreement with the hypothesis that Oxone is initially involved in the fast oxidation of $-S-$ and $-SH$ groups.

Recycling studies were successively carried out with the catalyst KG-60-FT in the model reaction performed under the above-reported experimental conditions. To this end, after the first cycle the catalyst was filtered, washed with CH_3CN, dried, and immediately reused. On the basis of the results shown in Table 1 and Figure 2, the reused catalyst showed higher activity affording product **12** in almost quantitative yield and selectivity for at least five successive cycles (see Table 2). Elemental analysis of the recovered catalyst confirmed its good stability.

Our next objective was to support the nonracemic α-fluorotropinone to both KG-60 and MCM-41 silicas and to examine the chemical behavior of the nonracemic heterogeneous catalysts prepared. We utilized enantiomerically enriched α-fluoro-*N*-carballyloxytropinone **4*** (ee 78%), which was prepared by desymmetrization of the parent ketone with (*R*,*S*,*S*,*R*)-1,2-diphenyl-*N*,*N*′-bis(1-phenylethyl)ethane-1,2-diamine.[19] It was anchored to amorphous silica KG-60 and to mesoporous silica MCM-41 by using the same strategy described in Scheme 1. Both KG-60-FT* and MCM-41-FT* materials were activated by reaction with Oxone before use in the first cycle giving the heterogeneous catalysts called KG-60-FT(A)* and MCM-41-FT(A)*. Results of their efficiency in the model reaction of 1-phenylcyclohexene (0.4 molar ratio between supported tropinone and alkene) with Oxone, including ee values, are reported in Table 3. The ee_{max} value is the expected epoxide ee if enantiomerically pure catalysts were used, based on a linear relationship between catalyst ee and product ee, which has been shown for the homogeneous catalytic system.[11b]

TABLE 2. Recycling of the KG-60-FT in the Epoxidation of 1-Phenylcyclohexene by Oxone

entry	cycle	conv.[a] of **11** (%)	yield[a] of **12** [Sel.][b] (%)
a	1	62	58 [93]
b	2	98	96 [98]
c	3	95	94 [99]
d	4	96	95 [99]
e	5	98	96 [99]
f	6	96	93 [97]

[a] Determined by ^1H NMR and GC. [b] (Yield/conv.) × 100.

Results from Table 3 show good levels of enantioselectivity achieved in all cases with only a 10% difference between the homogeneous (0.1 molar ratio between supported tropinone and alkene) and heterogeneous catalysts.[11a] Moreover, the products isolated in all the homogeneous and heterogeneous experiments showed the same (*S*,*S*)-absolute configuration indicating that the ability of the catalyst to effectively differentiate the faces of reagent **11** is only slightly affected by the siliceous support.

Finally we faced the problem of the catalyst recycling and we found that both heterogeneous catalysts showed the same high level of activity and good stereochemical control on recycling.

Having found satisfactory catalytic conditions for the model reaction, a number of different alkenes were subjected to the standard reaction with use of KG-60-FT(A)* as the enantiomerically enriched heterogeneous catalyst, this being more easily available than MCM-41-FT(A)*. As previously shown,[11] each substrate requires specific reaction time and Oxone amount (Table 4). Usually, if the alkene is poorly soluble in the reaction mixture (i.e. *trans*-stilbene) or if it bears bulky groups (i.e. TBS-cinnamyl alcohol), a higher amount of oxidant and longer reaction times are required. It can be seen from the results in Table 4 that the catalyst promotes the reaction with high yield and excellent selectivity with a satisfactory to high level of stereocontrol for a variety of substrates showing the generality of this method for trans-substituted and trisubstituted olefins. For all examined alkenes the observed enantiomeric excesses are comparable to those previously obtained with the homogeneous α-fluoro-*N*-carbethoxytropinone,[11] evidencing

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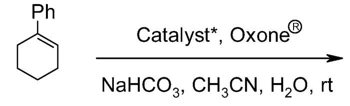
(19) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391.

TABLE 3. Enantioselective Epoxidation of 1-Phenylcyclohexene

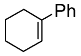
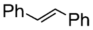
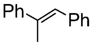
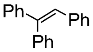
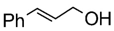
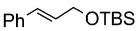


11 **12**

entry	catalyst	oxone (equiv)	*t* (h)	cycle	conv.[a] of **11** (%)	yield[a] of **12** [Sel][a] (%)	ee$_{max}$[c] [ee$_{obs}$] (%)
a	**10***	2.5	0.5	1	100	98 [98]	69 [54]
b	KG-60-FT(A)*	5.0	1.0	1	96	94 [98]	58 [45]
c		5.0	1.0	2	100	97 [97]	61 [48]
d		5.0	1.0	3	100	97 [97]	63 [49]
e	MCM-41-FT(A)*	5.0	1.0	1	100	98 [98]	62 [48]
f		5.0	1.0	2	100	99 [99]	63 [49]
G		5.0	1.0	3	100	98 [98]	62 [48]

[a] Determined by ^{1}H NMR and GC. [b] (Yield/conv.) × 100. [c] ee$_{max}$ = (ee$_{obs}$/ee$_{cat}$) × 100.

TABLE 4. Enantioselective Epoxidation of Various Alkenes over KG-60-FT(A)*

Entry	Substrate	Oxone® (eqs)	t (h)	Conversion[a] (%)	Yield[a] [Sel][b] (%)	ee$_{max}$ (ee$_{obs}$) [abs. conf] (%)
a		5.0	1.0	96	94 [98]	58[c] (45) [*S,S*]
b		10.0	2.0	98	97 [99]	66[d] (51) [*S,S*]
c		7.5	1.5	95	93 [98]	67[c] (52) [*S,S*]
d		10.0	2.0	93	91 [98]	80[c] (62) [*S*]
e		7.5	1.5	100	90 [90]	50[c] (39) [*S,S*]
F		12.5	2.5	100	95 [95]	48[d] (37) [*S,S*]

[a] Determined by ^{1}H NMR and GC. [b] (Yield/conv.) × 100. [c] Enantiomeric excess calculated by NMR with chiral Eu(hfc)$_3$. [d] Enantiomeric excess calculated by chiral HPLC (CHIRACEL OD).

that the heterogenization of the catalyst led only to a slight lowering of the ee values.

Conclusions

We have shown that α-fluorotropinone supported on silica materials represents the first example of efficient heterogenized chiral ketone for the stereoselective epoxidation of alkenes with Oxone. The activity of the supported catalyst is comparable to that of the homogeneous counterpart and of the reported α-fluoro-*N*-carbethoxytropinone even though a larger amount of oxidant and longer reaction times are required to obtain the same high level of yields and selectivities. Moreover the homogeneous and heterogeneous chiral catalysts promoted the reaction with similar values of enantiomeric excess, proving that the support does not significantly interfere with the chirality transfer. Finally from elemental analysis and recycling experiments we can conclude that all the silica-supported catalysts are stable in the strong oxidizing and aqueous reaction medium and that they can be easily recovered by filtration and reused with unchanged high activity and stereoselectivity.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Mass spectra were obtained in EI mode at 70 eV. Microanalyses were carried out by the Dipartimento di Chimica Generale ed Inorganica, Chimica Analitica, Chimica Fisica dell'Università di Parma, Italy. TLC analyses were performed on Merck 60 PF$_{254}$ silica gel plates with mixtures of hexanes−ethyl acetate (25−35%). All the reagents were of commercial quality from freshly opened containers and were used as received without further purification. Solvents were distilled under nitrogen and dried before use. The amorphous silica used was the commercial Kieselgel 60 (KG-60) purchased from Merck. MCM-41 mesoporous material was prepared, according to the procedure reported in the literature,[12] by mixing, at room temperature and under vigorous stirring, a 25% sodium silicate solution, tetramethylammonium hydroxide, a 25% cetyltrimethylammonium chloride solution, and water and aging at 110 °C for 4 days the resulting gel (composition: $SiO_2 \cdot 0.39Na_2O \cdot 0.25CTMACl \cdot 0.24TMAOH \cdot 50.7H_2O$). The XRD pattern and the high surface area of the material are characteristic of MCM-41 silica with a long-range order in the mesopore arrangement. The Merrifield's peptide resin 2% cross-linked used contains 2.0−2.5 mmol Cl$^-$/g and was purchased from Aldrich. The surface area was measured by the B.E.T. method,[20] using a PulseChemiSorb 2705 Micromeritics instrument. Pore dimensions were determined by N$_2$ adsorption on a C. Micromeritics ASAP 2010 instrument. Elemental analyses were Performed on a Carlo Erba CHNS-O EA1108 Elemental Analyser.

Reaction Procedure. All reactions were carried out in a Schlenk tube equipped with a magnetic stirrer. In a typical experiment, the selected alkene (0.1 mmol) was added to a suspension of KG-60-FT(A)* (4.0×10^{-2} mmol of supported catalyst, 69 mg) in acetonitrile (3 mL) and 4×10^{-4} M aqueous Na_2EDTA (2 mL). Then, under vigorous stirring, portions of Oxone (0.25 mmol, 0.154 g) and $NaHCO_3$ (0.39 mmol, 0.033 g) were added each 30 min for the selected time. Finally, water (10 mL) and methylene chloride (10 mL) were added, the catalyst was filtered off on a Büchner funnel, and the organic phase was dried with $MgSO_4$. The solvent was distilled off under reduced pressure and the product identified by GLC analysis.

(S,S)-1-Phenylcyclohexene oxide (12):[21] Colorless oil, yield 94%, ee_{max} 58%.

(S,S)-*trans*-Stilbene oxide (14):[21] White solid, yield 97%, ee_{max} 66%.

(S,S)-*trans*-Methylstilbene oxide (15):[21] White solid, yield 93%, ee_{max} 67%.

(S,S)-*trans*-Phenylstilbene oxide (16):[22] White solid, yield 91%, ee_{max} 80%.

(S,S)-3-Phenyloxiranemethanol (17):[21] Colorless oil, yield 90%, ee_{max} 50%.

(S,S)-2-[(*tert*-Butyldimethylsiloxy)methyl]-3-phenyloxirane (18):[21] Colorless oil, yield 95%, ee_{max} 48%.

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

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