Chiral Fluoro Ketones for Catalytic Asymmetric Epoxidation of Alkenes with Oxone

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Two structurally dissimilar, chiral fluoro ketones have been prepared and their potential as enantioselective catalysts for asymmetric epoxidation with Oxone has been evaluated. The tropinone-based ketone (−)-**5** was easily prepared and showed excellent reactivity but only modest enantioselectivity. The biphenyl-based ketone (−)-**6** was prepared in a somewhat lengthy synthesis (along with its monofluoro and geminal fluoro analogues). This ketone exhibited only modest reactivity; 30 mol % of (−)-**6** was needed to bring about complete conversion in a reasonable time. The enantioselectivity of this catalyst was generally much higher, but again very substrate dependent.

Introduction and Background

The epoxidation of alkenes is the most fundamental oxygen functionalization of carbon−carbon double bonds. The importance of this transformation is a direct consequence of the utility of the product epoxides as synthetic intermediates. Accordingly, the ability to carry out enantioselective oxygen atom transfer to alkenes has served as the vanguard for advances in asymmetric catalysis over the past two decades. The first practical asymmetric epoxidation reported by Sharpless et al. for allylic alcohols was a watershed event in the exploration for more selective and general methods of epoxidation.[1] In this reaction, the allylic hydroxyl group plays a fundamental role, in coordination of the substrate to the chiral titanium complex. As a result, a favorable asymmetric environment can be crafted between reactant and substrate by virtue of the strong coordination of the alcohol to the titanium metal center.

The next important advance in enantioselective oxygen atom transfer was the asymmetric epoxidation of unfunctionalized alkenes. In this case, the enantioselectivity must be controlled by nonbonding, which are much weaker and less directional than coordination bonds between reactant and substrate. The Jacobsen epoxidation system employing the now-familiar manganese−salen complexes is the archetypal example of this reaction and one that has been extensively developed and applied over the past 10 years.[2]

Despite the enormous success with Mn−salen complex mediated asymmetric epoxidation, the reaction of certain classes of alkenes still remained a challenging problem. Moreover, the interest in non-metal-based "organocatalysis" has achieved a heightened level of importance in recent years.[3] In this context, chiral dioxirane-mediated epoxidation represents an attractive alternative method.[4] The chemistry of dimethyldioxirane **1** has recently received much attention in both mechanistic and synthetic applications. Dioxiranes can be generated from ketones and Oxone (peroxymonosulfate) in situ, or in some instances they can be isolated[5] (Scheme 1). Because dioxiranes are powerful oxidants, they are quite useful in organic synthesis.[5]

The asymmetric epoxidation mediated by a chiral dioxirane is conceptually simple as shown in Scheme 2. A chiral ketone can be transformed to the corresponding dioxirane by the action of persulfate, and the chiral dioxirane may react selectively on one enantiotopic face of the substrate alkene. After oxygen atom transfer from dioxirane to alkene, the chiral ketone is regenerated, thus rendering the reaction system catalytic.

In 1984, Curci et al. reported first example of a chiral dioxirane mediated epoxidation. These workers employed the readily available ketone **2** (Chart 1) as the chiral ketone and observed a 12% ee for the reaction with 1-methyl-1-cyclohexene.[6] Significant progress has been made in the design and application of chiral ketones for asymmetric epoxidation in the intervening 17 years. The first critical advance was reported by Yang et al., who described a highly enantioselective epoxidation protocol using C_2-symmetric ketone **3**.[7] Subsequent reports de-

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (c) Johnson, R. A.; Sharpless, K. B. *Comprehensive Organic Synthesis, Vol. 7*; *Oxidation*; Ley, S. V., Ed.; Pergamon Press: Oxford, 1991; Chapter 3.2. (d) Katsuki, T. In *Comprehensive Asymmetric Catalysis, Vol. II*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Chapter 18.1.

(2) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296. (c) Jacobsen, E. N.; Wu, M. F. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. II, Chapter 18.2. See also: (d) Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* **1994**, *50*, 4311.

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(6) (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831.

(7) (a) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311.

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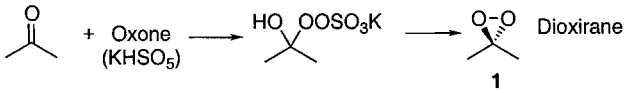
Scheme 1



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Scheme 2

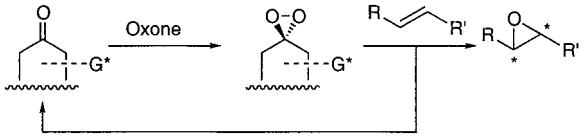
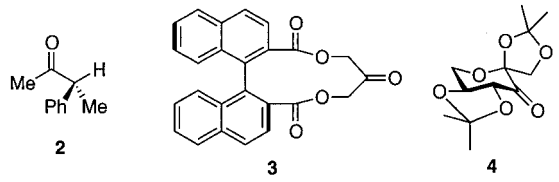


Chart 1

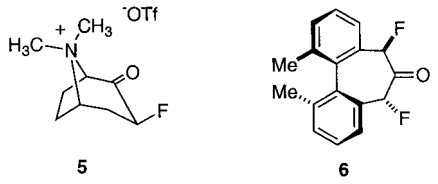


2 3 4

scribing the use of derivatives of **3** also showed promise, but mostly with a limited set of aromatic substrates. The second advance, due to Shi, was the successful catalytic epoxidation using fructose-derived ketone **4** as the catalyst.[8] Ketone **4** has a pseudo-C_2-symmetric structure, and it was found that a wide variety of (*E*)-alkenes can be oxidized with high enantioselectivity with substoichiometric amounts of **4** and Oxone in the presence of potassium carbonate.[8b] A detailed account of the evolution and the state of the art in catalytic enantioselective epoxidations with dioxiranes can be found in recent reviews.[2c,9]

Catalyst Design. The most important criteria for chiral, dioxirane-mediated catalytic asymmetric epoxidation are as follows: (1) high catalytic activity of the ketone, (2) high level of stereodifferentiation, (3) broad generality of substrate, and (4) ease of synthesis of the ketone. How to structurally engineer these characteristics is a not-insignificant challenge. At the outset, we recognized that the reactivity of the ketone was the most important and critical issue. Indeed, dioxirane-mediated epoxidation had been carried out with stoichiometric or excess amounts of ketone in many cases, and there are only a few example of *catalytic* epoxidation. In 1995, we published the first examples of catalytic, dioxirane-mediated epoxidation, which were accomplished with a 1-oxo-4-piperidinium triflate.[10] The success of this ketone was based on the ability of nearby electron-withdrawing substituents to increase the reactivity of a carbonyl group toward nucleophiles. In this case, the ammonium moiety plays a key role as an electron withdrawing function and as a phase-transfer mediator. In addition, we have also reported that α-fluorine substituents tremendously increase the reactivity of the carbonyl group in dioxirane-mediated epoxidation and that these effects are strongly stereoelectronically controlled. Thus, *cis*-4-*tert*-butyl-2-fluorocyclohexanone shows good catalytic activity for the epoxidation whereas the trans isomer does not.[11]

Chart 2



5 6

On the basis of these observations, the 3-fluorotropanone ammonium salt **5** (Chart 2) was designed as the first target.[12] To enhance reactivity, both the α-fluorine substituent and ammonium moiety should increase the electrophilicity of the carbonyl group to facilitate the formation of the dioxirane intermediate as well as oxygen atom transfer to alkene. Of course, another important issue is the chiral environment. In the case of **5**, it is necessary to control the facial selectivity of dioxirane intermediate due to the diastereotopic relationship of the two oxygen atoms in the dioxirane. We assumed that the top-face approach of an alkene to dioxiranes prepared from **5** would be shielded (and thus disfavored) by the methyl group of the ammonium bridge. Therefore, the alkene should approach more favorably from the bottom face. A different class of chiral ketones was inspired by our studies of epoxidation with fluorocyclohexanones.[11] To maintain an efficient asymmetric environment, we choose to incorporate the axial chirality of a biaryl by analogy to cyclic ketone **3**. However, **3** contains an 11-membered ketone, and the distance of the binaphthyl moiety seems to be far from the carbonyl group (and the corresponding dioxirane). Indeed, ketone **3** works well only for stilbene-type *trans*-diarylalkenes.[7] Accordingly, the seven-membered cyclic difluoro ketone **6** emerged as our second target. The expected dioxirane intermediate corresponding to **6** is also C_2 symmetric, so the oxygens of the dioxiranes are now homotopic. Although these candidates did not satisfy criterion 4 well, we were willing to make the synthetic investment to learn more about the success of the other elements of design. If the structural requirements for high catalytic activity, selectivity, and generality could be learned, then it was expected that a more synthetically accessible target could be envisioned.

Results and Discussion

Fluorotropanone Ammonium Salt 5. Preparation. The preparation of **5** has been carried out following Davies' 2-tropanone synthesis as shown in Scheme 3.[13] Thus, 2-ethoxycarbonylpyrrole **7** was converted to diester **9** by formylation and Horner−Emmons reaction in 63% and 92% yield, respectively. The aromatic diester **9** was then transformed to the saturated diester **10** by stepwise hydrogenation of the double bond with Raney Ni catalyst followed by reduction of the aromatic ring with $Rh-Al_2O_3$ in high yield. The *N*-methylpyrrolidine (obtained by reductive methylation of **10)** was cyclized under basic conditions to give bicyclic β-ketoester **11** in 79% yield. Finally, acidic saponification and decarboxylation of **11** afforded 2-tropanone **12** in 93% yield.

(8) (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099.

(9) (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979.

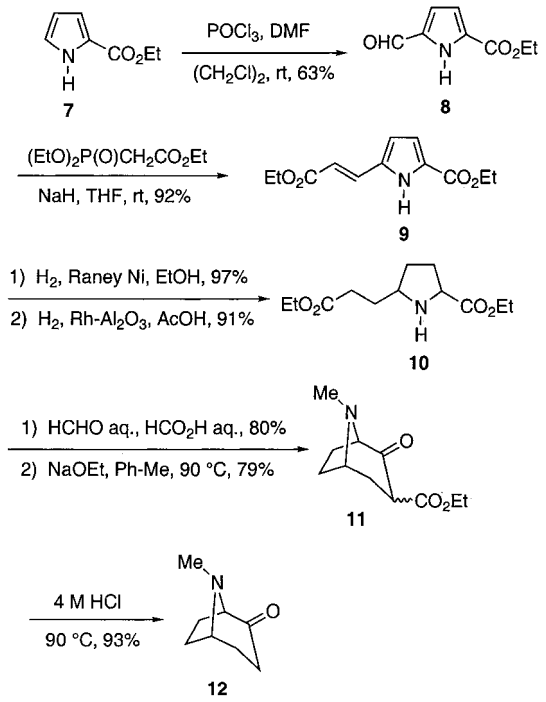
(10) Denmark, S. E.; Forbes, D. C.; Hay, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.

(11) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi H. *J. Org. Chem.* **1997**, *62*, 8288.

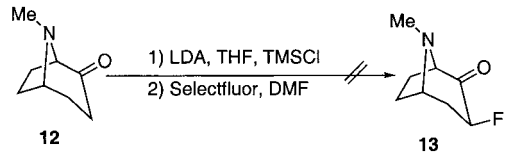
(12) For a structurally similar fluorotropanone catalyst, see: Armstrong, A.; Hayter, B. *Chem. Commun.* **1998**, 621.

(13) Davies, W. A. M.; Pinder, A. R.; Morris, I. G. *Tetrahedron* **1962**, *18*, 405.

Scheme 3



Scheme 4

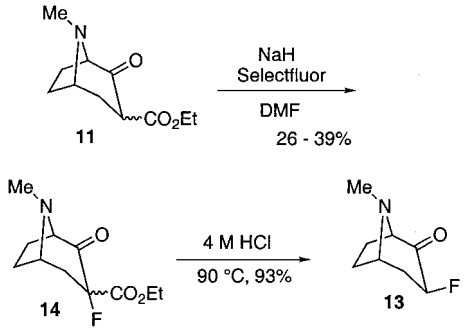


The introduction of a fluorine atom was first attempted with electrophilic fluorination of **12** via its TMS enol ether using the Selectfluor reagent,[14] Scheme 4. The TMS enol ether was prepared quantitatively by the usual procedure, however, no fluorinated product was obtained after treatment with Selectfluor. In addition, the starting material seemed to decompose under the reaction conditions. This result may arise from the low reactivity of the TMS enol ether and competitive oxidation of nitrogen atom.

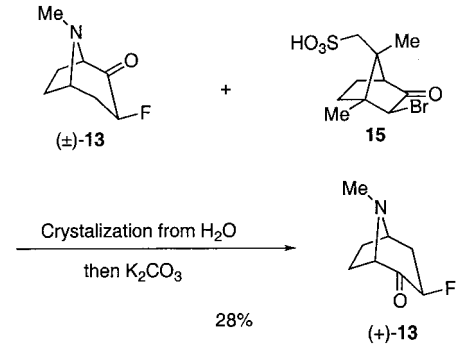
A simple solution was found by introducing the fluorine substituent on the more nucleophilic β-ketoester anion.[13] The previous substrate **11** was deprotonated to generate the stabilized anion, which was then treated with the Selectfluor to give α-fluoro-β-ketoester **14** as a mixture of diastereomers in low yield. After a survey of reaction conditions, we found that the reaction of the sodium enolate, generated from **11** with sodium hydride, and Selectfluor took place in DMF to provide **14** in 26−39% yield after distillation, Scheme 5. Saponification and decarboxylation of **14** took place readily under acidic conditions to afford the target 3-fluoro-2-tropanone in high yield. The equatorial orientation of the fluorine atom was easily established by the ^{1}H NMR coupling pattern and was later confirmed by X-ray crystallography.

Enantiomer resolution was performed by conversion of racemic **13** to its diastereomeric salt with (−)-bromocamphorsulfonic acid (**15**), as was reported for the resolution of 2-tropanone, Scheme 6. Equimolar amounts of racemate **13** and (−)-**15** (generated from its ammonium

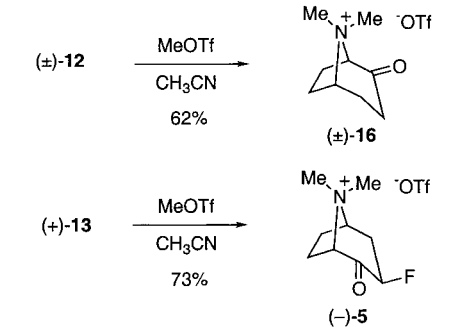
Scheme 5



Scheme 6



Scheme 7



salt with $Ba(OH)_2$) were dissolved in boiling water, and then the salt was recrystallized three times to provide (+)-**13**, which was >98% ee by CSP−GC analysis. The absolute configuration of the tropanone was determined by single-crystal X-ray analysis of the salt, thus allowing correlation to the configuration of (−)-**15**.[15a] After the salt was neutralized with K_2CO_3, (+)-**13** was obtained in 28% yield.

Treatment of 2-tropanones **12** and (+)-**13** with methyl triflate in acetonitrile provided the target ammonium salts (±)-**16** and (−)-**5** in 62% and 73% yields, respectively (Scheme 7).

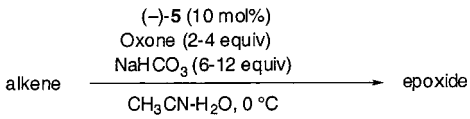
Epoxidation. With the tropanone ammonium triflates (−)-**5** and (±)-**16** in hand, their potential as catalysts for the epoxidation was evaluated. For the initial survey of conditions, we selected a convenient monophasic protocol for alkene epoxidation that was described by Yang et al.[16] The outlined general procedure involves the following steps: (1) the substrate and ammonium salt are dissolved

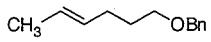
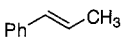
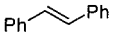
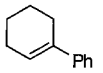
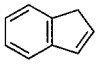
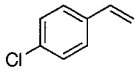
(14) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791.

(15) (a) The crystallographic coordinates of **13**·**15** salt have been deposited with the Cambridge Crystallographic Data Centre, deposition no. 176803. (b) The crystallographic coordinates of (−)-**6** salt have been deposited with the Cambridge Crystallographic Data Centre, deposition no. 176802.

(16) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887.

Table 1. Epoxidation with Fluorotropinium Salt (−)-5



entry	substrate	time, h	isolated yield %	ee, %
1		9	97	6
2[a]		5	85	35 (*R,R*)[17a]
3		72	79 (91)[c]	58 (*R,R*)[17b]
4[a]		5	93	7 (*S,S*)
5[b]		4	78	14
6		30	90	29 (*S*)[d]

[a] Oxone (2.5 equiv) and $NaHCO_3$ (7.5 equiv) were added. [b] Oxone (2 equiv) and $NaHCO_3$ (6 equiv) were added. [c] Yield based on reacted starting material. [d] (+)-**5** was employed as catalyst.

in acetonitrile/aqueous Na_2EDTA (0.09%) (3/2) mixed solvent system; (2) Oxone (1 equiv) and $NaHCO_3$ (2.6 equiv) are added portionwise every 2 h. Under these conditions using 10 mol % of the parent salt **16**, only 21% conversion of β-methylstyrene to the epoxide was observed after 5 h.

Fortunately, α-fluorinated ketone (−)-**5** showed excellent catalytic activity. The epoxidation of various kinds of alkenes with 10 mol % catalyst are summarized in Table 1. The reactions were complete within 12 h in most cases, and there were no undesired side reactions, e.g., epoxide ring opening. Reactive alkenes such as β-methylstyrene, 1-phenyl-1-cyclohexene, and indene readily oxidized under the reaction conditions to give the corresponding epoxides in high yields (Table 1, entries 2, 4, and 5). The reaction took place even with relatively unreactive alkenes with high conversion after 9−30 h (Table 1, entries 1 and 6). In the case of (*E*)-stilbene, however, the reaction was not complete even after 72 h, and a significant amount of starting material was recovered (Table 1, entry 3). This may be due to the limited solubility of the substrate in the reaction medium. Indeed, before addition of Oxone and $NaHCO_3$, the substrate did not visibly dissolve at all.

Although (−)-**5** showed good general reactivity, its enantioselectivity depended upon the substrate structure. For *E*-alkenes, at least one aromatic substituent was necessary for modest selectivity; (*E*)-stilbene provided the highest ee (58%), and β-methylstyrene gave the epoxide product in 35% ee. On the other hand, this catalyst could not effectively differentiate the faces of a simple alkene such as 1-benzyloxy-4-hexene. With other alkenes, the product selectivity varied with each substrate with no obvious trend. The absolute stereochemical pathway for

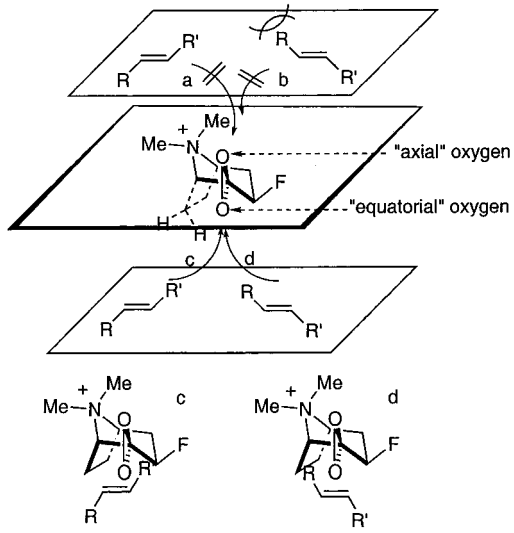


Figure 1. Hypothetical transition structures for approach of alkenes to dioxirane from (−)-**5**.

the two most selective cases ((*E*)-stilbene and β-methylstyrene) was established by comparison of the optical rotation to literature values.[17]

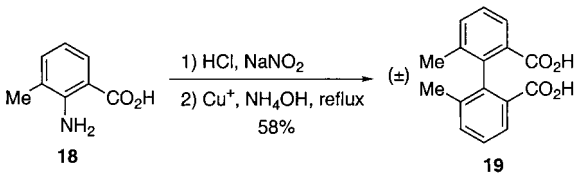
These results showed the significant catalytic potential for fluoro ammonium ketones such as **5**, but clearly the enantiotopic discrimination was not sufficient. To formulate a transition-structure model requires a detailed picture of the preferred approach of alkenes to dioxiranes in the oxygen atom transfer step. At present, there is no strong experimental evidence for either of the limiting transition structures proposed (spiro or butterfly), although most authors tend to rationalize the stereochemical course of epoxidation with chiral catalysts in terms of the spiro model.[7,8,18] Moreover, computational analyses have also led to the prediction of a preferred spiro transition structure.[19] Indeed, a recent computational study, specifically addressing the preferred approach of alkenes to fluorocyclohexanones, concluded that for the equatorial fluoro ketone, the preferred approach is toward the equatorially oriented oxygen of the dioxirane.[19b] Thus, incorporating these features into a model for reaction with (−)-**5** produces the hypothetical arrangements for the dioxirane intermediate shown in Figure 1. On the basis of both steric shielding by the *N*-methyl groups and the stereoelectronic factors noted above, we conclude that approaches **c** and **d** are more favorable than approaches **a** and **b**. From approach **c**, the (*S,S*)-epoxide is formed, whereas the (*R,R*) epoxide is produced from approach **d**. Inspection of molecular models reveals that the most distinguishing feature that differentiates these arrangements is the interaction of the alkene substituents with the two-carbon bridge and fluorine atom in **c**, which are absent in **d**. Although this analysis does rationalize the major enantiomer formed, the difference is not very dramatic, and it is thus not surprising that the enantioselectivities were only modest and highly substrate dependent.

(17) (a) Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 197. (b) Chang, H.-T.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 6456.

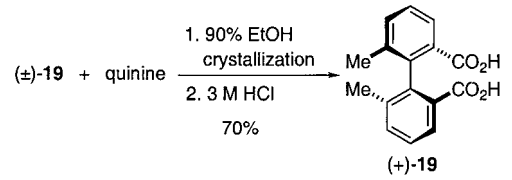
(18) Baumstark, A. L.; McCloskey, C. J. *Tetrahedron Lett.* **1987**, *28*, 3311.

(19) (a) Bach, R. D.; Andres, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W. *J. Am. Chem. Soc.* **1992**, *114*, 7207. (b) Armstrong, A.; Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 6297.

Scheme 8



Scheme 9



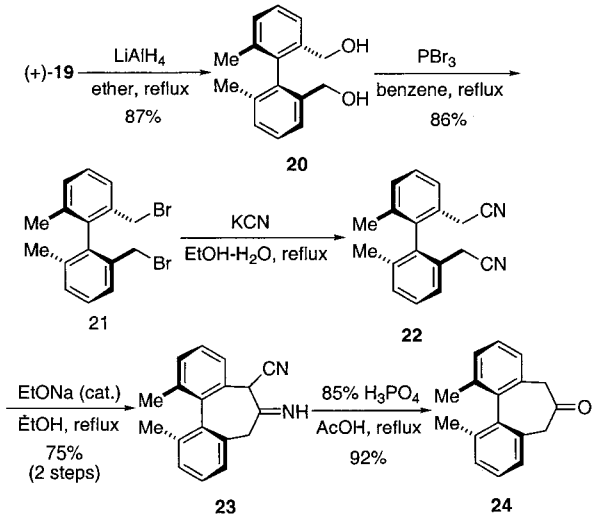
Difluorodibenzocycloheptanone ((−)-6). Preparation. The cyclic difluoro ketone (−)-**6** was prepared following the literature procedures.[20] The synthesis began with a copper(I)-mediated oxidative homocoupling of the diazonium salt generated from commercially available 2-amino-3-methylbenzoic acid **18** to afford biphenic dicarboxylic acid **19**,[20a] Scheme 8.

The optical resolution of **19** has been described using morphine.[20b] In view of the poor availability of this reagent, we examined other chiral bases for this resolution. After a brief survey, we found that quinine also worked well for this purpose. Thus, equimolar amounts of (±)-**19** and quinine were dissolved in 90% aqueous EtOH, and the resulting salt was recrystallized twice to give diastereomerically pure salt. After decomposition of the salt under acidic conditions, (+)-**19** ($[\alpha]^{25}_D$ +19.2 (*c* = 1.00, MeOH)) was obtained in 70% yield, Scheme 9. The enantiomeric purity of **19** was determined by HPLC analysis of the corresponding dimethyl ester, prepared by treatment of **19** with excess diazomethane. The absolute configuration of (+)-**19** was determined to be *S* by comparison with reported rotation value (lit.[20c] (*R*)-**19** $[\alpha]_D$ −20 (dioxane)).

With chiral acid (+)-**19** in hand, the remaining steps in the synthesis of ketone could be undertaken as outlined in Scheme 10. Dicarboxylic acid **19** was transformed to dibromide **21** by the two-step sequence of reduction with lithium aluminum hydride and bromidation of the corresponding alcohol in 87% and 86% yields, respectively.[20d] Treatment of **21** with potassium cyanide in aqueous EtOH under reflux gave the dinitrile.[20e] ^{1}H NMR analysis of the crude product showed that it contained small amount (ca. 5−10%) of the cyclized product **23**. Therefore, the crude material was treated with base directly to afford cyclic imine **23** in 75% yield over two steps. Finally, hydrolysis of the cyano group and imine, followed by decarboxylation under acidic conditions, provided target ketone **24** in 92% yield.[20c]

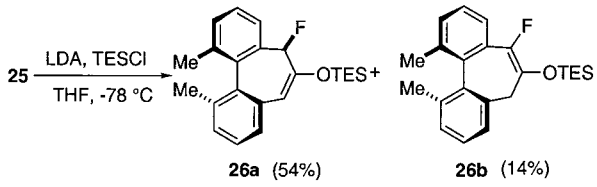
Fluorination of ketone **24** followed the previous sequence, Scheme 11. Thus, ketone **24** was converted to its TMS enol ether under the usual conditions, and the crude enol silane was treated with Selectfluor in DMF

Scheme 10



Scheme 11

Scheme 12



to give monofluoro ketone **25** as a mixture of diastereomers in a 1/1 to 2/1 ratio. Treatment of the mixture of diastereomers with triethylamine at room temperature resulted in the epimerization of the fluorine-bearing center to produce a single diastereomer **25**, where the fluorine atom is in an equatorial position. In this way, the desired compound **25** was obtained as a single diastereomer in 65% yield over three steps.

Introduction of the second fluorine atom by the same protocol was, expectedly, plagued by formation of regioisomeric silyl enol ethers from **25**. To facilitate separation of the isomers, the triethylsilyl (TES) enol ether was chosen. Monofluoro ketone **25** was transformed to its TES enol ether by deprotonation with LDA in the presence of TESCl at low temperature. Separation of the mixture of enol ethers by silica gel chromatography afforded the desired isomer **26a** (54%) and more substituted isomer **26b** (14%), Scheme 12.

The fluorination of **26a** with Selectfluor took place under the usual conditions to afford target difluoroketone (−)-**6** in moderate yield, Scheme 13. The configuration of (−)-**6** was determined by single-crystal X-ray analysis.[15b] *gem*-Difluoro ketone **27** was also prepared from the regioisomer **26b** to test the effect of geminal fluorine substitution in the epoxidation reaction.

Optimization of Epoxidation. Orienting experiments with difluoro ketone (−)-**6** under monophasic reaction conditions were initially disappointing. For example, the epoxidation of β-methylstyrene with 18 mol

(20) (a) Atkinson, E. R.; Lawler, H. J. In *Organic Syntheses*; Wiley: New York, 1941; Collect. Vol. I, p 222. (b) Bell, F. *J. Chem. Soc.* **1934**, 835. (c) Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455. (d) Bergmann, E. D.; Pelchowicz, Z. *J. Am. Chem. Soc.* **1953**, *75*, 2663. (e) Newman, P.; Rutkin, P.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 465.

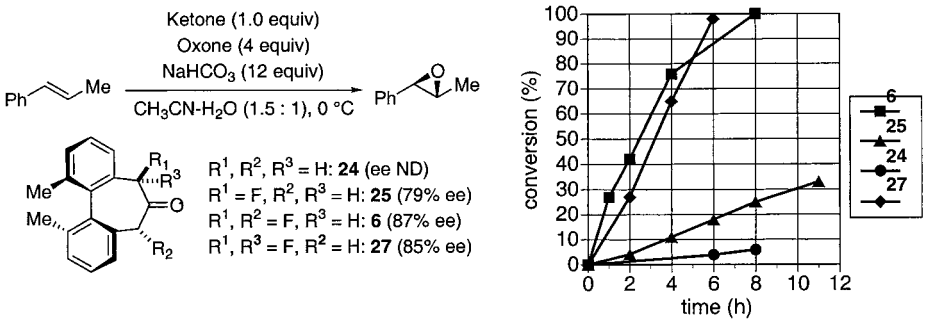
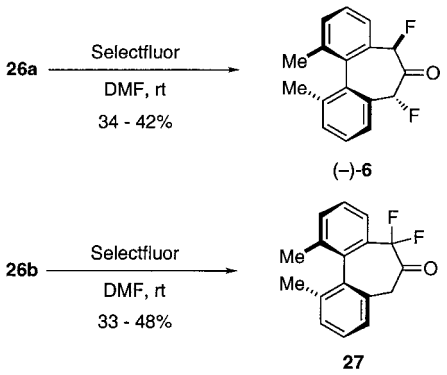
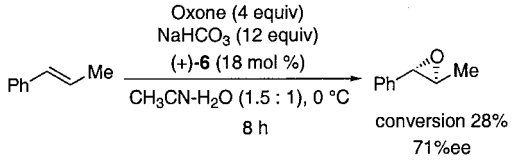


Figure 2. Epoxidation rates at (*E*)-2-methylstyrene with ketones.

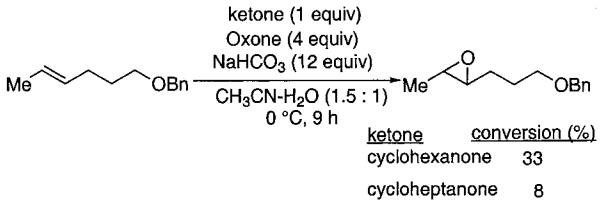
Scheme 13



Scheme 14



Scheme 15



% of (+)-**6** proceeded quite slowly, and only 28% of the alkene was converted to the epoxide after 8 h, Scheme 14. This result suggested that two α-fluorine substituents may not provide sufficient activation for the carbonyl group of **6**. Alternatively, the low reactivity may be partially caused by the conformation of the cyclic ketone moiety. It is known that the reaction of cyclohexanone is more favorable than of cycloheptanone with nucleophiles.[21] Indeed, there was a significant difference in rate of epoxidation between cyclohexanone and cycloheptanone when the reactions were tested using 1-benzyloxy-4-hexene as a substrate with 1 equiv of the ketone, Scheme 15.

Despite the low reactivity of **6**, it still exhibited good asymmetric induction as shown in Scheme 14. Accordingly, it was deemed profitable to survey the various fluoro ketones for their rate and enantioselectivity in the asymmetric epoxidation using a stoichiometric amount of chiral ketone. These initial studies employed β-methylstyrene as a substrate, and the results are graphically depicted in Figure 2. Difluoro ketone (−)-**6** promoted the reaction much more efficiently than the corresponding monofluoro ketone **25** and parent ketone **24**. The reaction promoted by (−)-**6** was complete within 8 h, whereas the reaction promoted with **25** was quite slow and only 33% conversion was observed after 11 h. In the case of **24**, it did not promote the reaction at all, as the reaction conversion was almost the same as the background reaction (8 h, 6% conversion). Interestingly, *gem*-difluoro ketone **27** was the most effective promoter of the reaction affording complete consumption of the alkene in 6 h. This intriguing result contrasts our previous observation of lower epoxidation rates with a *gem*-difluorocyclohexanone skeleton.[11]

Although the reactivity of (−)-**6** was lower than expected, it should be noted that α-fluorine substitution still strongly activated the carbonyl group. In previous studies, we have employed the rate and degree of hemiketal formation as a measure of the propensity to form the intermediate dioxirane. Whereas this does not necessarily correlate with epoxidation efficiency, it does reflect the electrophilicity of the ketone.[11,22] The graph in Figure 3 illustrates significant enhancement of hemiketal formation for **6** compared to **25**.

Catalytic Epoxidation. Encouraged by the high asymmetric induction observed with (−)-**6**, we next investigated the optimal reaction conditions for catalytic epoxidation. The standard system chosen for evaluation was β-methylstyrene together with 4 equiv of Oxone and 10 mol % of (−)-**6**. The first variable tested was the reaction medium.[7] Of the many aqueous solvent blends tested (propionitrile, DME, DMF, DMAC, dioxane, DMPU) only CH_3CN/H_2O (3/2) gave appreciable conversion (28%) to the epoxide. Increasing the proportion of acetonitrile to 5/1 decreased the conversion to 10%. The reason for this solvent effect is not apparent. One possibility is that the cyano group of CH_3CN may contribute to the reaction in some way.[23] In the case of propionitrile, the reaction did not take place because of phase separation.

The next variable we tested that is known to influence the reaction rate was pH. Shi had already pointed out

(21) Forbes, D. C. Ph.D. Thesis, University of Illinois, Urbana−Champaign, 1996.

(22) (a) Stewart, R.; Van Dyke, J. D. *Can. J. Chem.* **1970**, *48*, 3962. (b) Yang has reported that for a series of α,α′-diacyloxy ketones, there is no correlation between hydration equilibrium and oxidation rate: Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, *63*, 9888. Although we have clearly stated that there needs to be a balance of effects to produce a good catalyst, we are skeptical of conclusions based on time to complete reaction under heterogeneous conditions.

(23) Bose, D. S.; Baquer, S. M. *Synth. Commun.* **1997**, *27*, 3119.

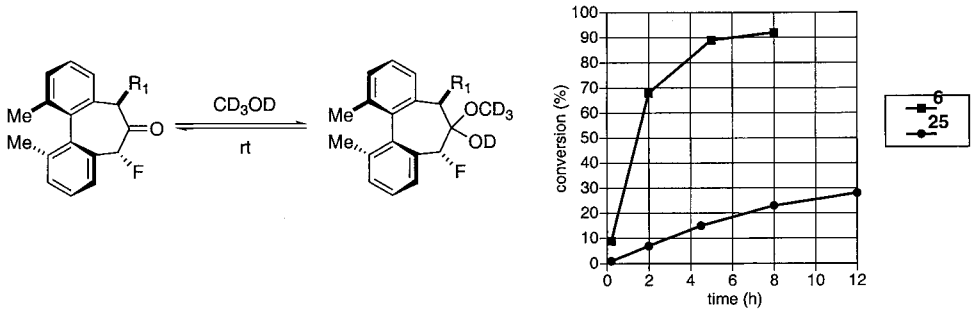
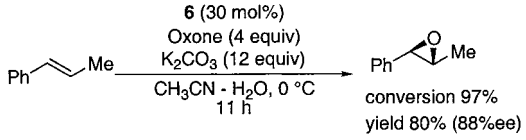
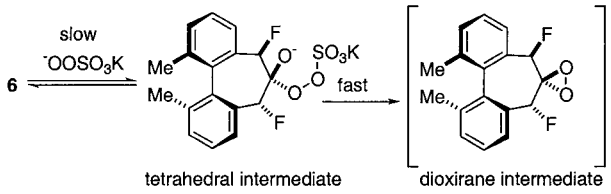


Figure 3. Hemiketalization of ketones **6** and **25**.

Scheme 16



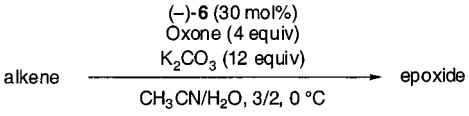
Scheme 17

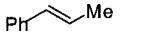
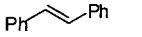
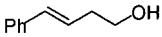
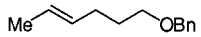
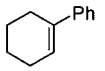
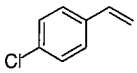


that simply changing the buffer solution to potassium carbonate increases the reaction rate.[8d] In our system, the reaction conversion was 55% after 8 h with 10 mol % of **6**. We also compared the reactivity of *gem*-difluoro ketone **27** under the same conditions and were pleased to find that again **27** showed slightly higher reactivity than **6**. This result reflects the behavior observed with stoichiometric amounts of catalysts. To consume all of the test alkene required the use of 30 mol % of (−)-**6**; under these conditions, the reaction was complete after 11 h, Scheme 16. The improved reactivity at higher pH can be understood in terms of the increased rate of formation of the dioxirane. As mentioned above, the low reactivity of **6** may have its origin in the slow formation of the tetrahedral intermediate from nucleophilic attack of peroxymonosulfate to the carbonyl group. At higher pH (∼10) the concentration of the peroxymonosulfate dianion ($KOOS(O)_2OK$) is higher and the concentration of the conjugate base of the adduct will also be higher, thus facilitating the formation of the dioxirane, Scheme 17.

Having established suitable conditions for catalytic epoxidation, we surveyed the generality of the asymmetric epoxidation with various alkenes using 30 mol % of (−)-**6**. The results are summarized in Table 2. The reactions were carried out at 0 °C with portionwise addition of Oxone (1 equiv every 2 h) and K_2CO_3 (3 equiv every 2 h) into CH_3CN/H_2O (3/2) mixed solvent. The reaction with trans alkenes proceeded in excellent ee (Table 2, entries 1−4), albeit with lesser selectivity for the aliphatic (*E*)-alkene. No undesired byproducts were observed due, in part, to the mild reaction conditions. Moderate selectivities were observed in case of trisubstituted and monosubstituted alkenes (Table 2, entries 5 and 6). The absolute configuration of the products was

Table 2. Asymmetric Epoxidations of Various Alkenes with (−)-6



entry	substrate	time, h	yield, %	ee, %
1		10	80	88 (*R,R*)[17a]
2[a]		72	46[b]	94 (*R,R*)[17b]
3		7	93	89
4[c]		11	72[d]	68
5		4	78	59 (*R,R*)[24a]
6		30	55	43 (*R*)[24b]
7		11	67	12

[a] The reaction was carried out in CH_3CN/H_2O (3/1). [b] Starting material (53%) was recovered. [c] The reaction was carried out with 50 mol % of **6**. [d] Starting material (23%) was recovered.

established by comparison of the optical rotations to literature values.[17,24]

Analysis of the stereochemical outcome of epoxidation with (−)-**6** (via the dioxirane intermediate) is simplified because of the overall C_2 symmetry of the molecule, which renders the two oxygens homotopic. Proceeding from the reasonable assumption that the reaction occurs via a spiro transition state, two limiting arrangements of the alkene with respect to the dioxirane can be formulated, Figure 4. These two approaches, **a** and **b**, differ only in the proximity of the alkene substituents to the biaryl skeleton and the methyl groups in particular. Clearly, approach **b** is disfavored compared to approach **a** because of this steric interaction. It is not clear if, in the case of aromatic substituted alkenes, there is an additional electronic interaction between substrate and catalyst, such as $\pi-\pi$ stacking of the aromatic rings, enforced by a hydrophobic effect of the aqueous medium. From this analysis, the absolute configuration of the major enantiomer formed from (−)-**6** can be correctly predicted. This

(24) (a) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378. (b) Pedragosa-Moreau, S.; Morisseau, C.; Zylber, J.; Archelas, A.; Baratti, J.; Furstoss, R. *J. Org. Chem.* **1996**, *61*, 7402.

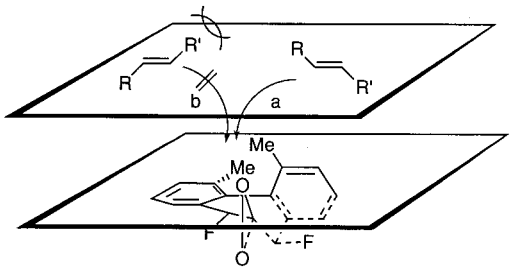


Figure 4. Hypothetical transition structures for approach of alkenes to dioxirane from (−)-**6**.

model also can explain the less than stellar selectivities observed with trisubstituted and monosubstituted alkenes.

If indeed the origin of enantioselectivity is as portrayed in Figure 4, then one possible improvement would be to increase the size of the substituents responsible for the stereodifferentiating effect, e.g., resorting to a structurally analgous binaphthyl ketone. Of course, the problems associated with catalyst synthesis and solubility are not addressed by this modification. Moreover, it is likely that the rather simplistic picture of the spiro transition state is much more maleable than is currently viewed. Small angular deviations from the spiro arrangement may not be very energetically costly and can thus provide low energy access to diastereomeric transition structures in sterically nondemanding substrates.

Conclusion

The two fluoro ketones prepared and examined herein provided useful lessons that can be applied to the design of newer more synthetically useful catalysts. The solubility and strong electronic activation provided by the ammonium group afforded excellent reactivity characteristics to (−)-**5**. For this class of catalyst to be useful, there needs to be a greater differentiation of the two competing equatorial approaches to the dioxirane. In biphenyl-derived ketone (−)-**6**, the need to for at least two fluorine atoms was clearly established to render it sufficiently electrophilic to promote oxygen atom transfer. Even so, the reaction rates were modest with as much as 30 mol % of ketone. The enantioselectivity was quite high in some cases, but structurally dependent in such a way as to suggest the need for a more sterically defined environment. Finally, the need to experimentally establish the preferred alignment of alkene and dioxirane is apparent to aid the design of more selective catalyst structures.

Acknowledgment. We are grateful to the Pharmacia Corp. for generous support of this research.

Supporting Information Available: Complete experimental details with full spectroscopic and analytical data for all new compounds and general procedures for epoxidation is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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