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Screening chiral fluorinated binaphthyl ketone catalysts for asymmetric epoxidation

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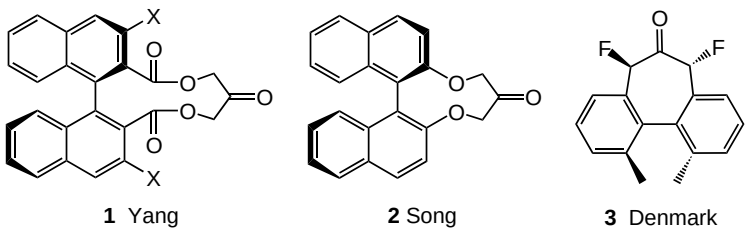
Abstract—A series of five chiral binaphthyl ketone catalysts **4**–**8** with variable distributions of fluorine atoms alpha to the carbonyl have been synthesized. These catalysts were screened in the asymmetric epoxidation of *trans*-β-methylstyrene. The best catalyst was α,α′-difluoroketone **6** which catalyzed the epoxidation to *trans*-β-methylstyrene oxide with 100% conversion and 86% e.e. at 10 mol% catalyst loading. © 2002 Elsevier Science Ltd. All rights reserved.

The asymmetric epoxidation of unfunctionalized alkenes by dioxiranes derived from chiral ketones remains an active area of research.[1] As part of initial screens for promising new catalysts we were interested in pursuing structures containing the binaphthyl scaffold for three reasons. First the binaphthyl system has a proven record in asymmetric synthesis as a strong agent of chirality induction.[2] Secondly, the binaphthyl skeleton is easily modified to change the shape and depth of a chiral pocket by the introduction of vaulting substituents at the 3 and 3′ positions.[2b,3] Finally, and most importantly, functionalization at the 6 and/or 6′ positions has been utilized to anchor the binaphthyl nucleus to various solid supports to facilitate catalyst recovery.[4]

Chiral ketone catalyst systems based on the binaphthyl skeleton have been developed by Yang[3,5] and Song[6] (Fig. 1) for asymmetric epoxidation albeit with limited success. The Yang catalyst **1** is effective in the epoxidation of 4,4′-substituted *trans*-stilbenes, a rather limited class of substrates and Shi[1b] suggested that the distance between the ketone group and the binaphthyl chiral element is too large for effective epoxidation of smaller substrates. The Song catalyst **2** moves the carbonyl closer to the chirality axis, but only modest enantiomeric excesses are reported. This has been attributed to the relatively unactivated carbonyl, which lacks alpha electron-withdrawing groups critical to good catalytic turnover.[1b]

Finally, during the course of our work, Denmark reported in a review[1a] unpublished results on the epoxidation of *trans*-disubstituted alkenes in good yields and modest to high enantioselectivities with 10–30 mol% of a closely related chiral biphenyl catalyst **3** (Fig. 1). The carbonyl is not only in closer proximity to the biaryl axis, but it also incorporates the necessary electron withdrawing groups to ensure good catalytic turnover. We felt a binaphthyl moiety should provide a more prominent chiral element and the absence of inductively electron-donating methyl groups as found in catalyst **3**, would further improve the performance of a biaryl-



1 Yang **2** Song **3** Denmark

Figure 1. Related biaryl ketone catalysts.

Keywords: asymmetric synthesis; epoxidation; dioxirane.

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based ketone epoxidation catalyst. Examination of the literature led us to consider chiral ketone **4** (Fig. 2), which had been synthesized in optically pure form by Mislow and co-workers.[7] We report herein an improved preparation of ketone **4** and novel fluorinated derivatives **5**–**8** (Fig. 2) and their reactivity in the asymmetric epoxidation of *trans*-β-methylstyrene.

Synthesis of the parent catalyst **4** (Scheme 1) commenced with known diester **9**, prepared by the method of Takaya.[8] Reduction of the ester groups with DibalH proceeded in 85% yield to provide diol **10**. Conversion

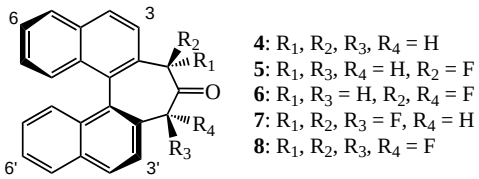
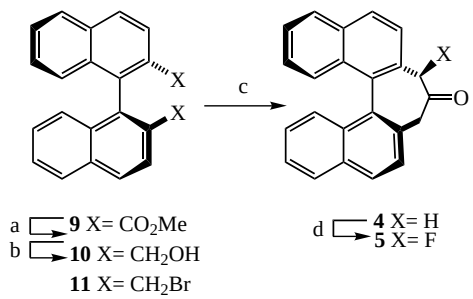


Figure 2. Novel ketone catalysts for asymmetric epoxidation.



Scheme 1. Synthesis of parent ketone **4** and α-fluoroketone **5**. (a) DibalH (4.4 equiv., 1.0 M toluene), CH_2Cl_2, −67°C–rt, (85%); (b) HBr/AcOH (10 equiv., 30% soln), AcOH, rt, (81%); (c) TosMIC (1.1 equiv.), NaOH (5 equiv.), TBAI (5 mol%), CH_2Cl_2–H_2O, rt (82%); (d) i. KH, rt, ii. NFSI, −78°C to rt (77%).

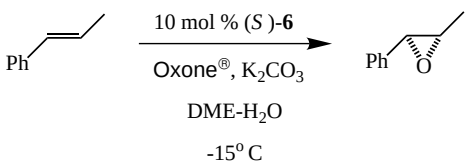
to bis-bromide **11** (81%) by treatment with HBr in acetic acid was followed by ring closure to ketone **4** with ketone synthon TosMIC[9] in 82% yield. Ketone **4** is thus readily available in gram quantities in both enantiomeric forms.

The next task was to determine a convenient way to introduce fluorine atoms sequentially about the ketone alpha positions. Ketone **4** was thus treated with 1 equiv. of potassium hydride and the resultant enolate quenched with *N*-fluorobenzosulfonimide (NFSI)[10] to give monofluorinated ketone **5**[11] in 77% yield as shown in Scheme 1. Assignment of the stereochemistry of the fluorination was made by literature comparison of proton–fluorine coupling constants.[12] Furthermore, AM1 calculations revealed the equatorial fluorinated product was 3.6 kcal/mol more stable than the axial fluorinated product.

Further fluorination could be effected by treatment of ketone **5** with various equivalents of LDA and quenching with NFSI.[13] Although it proved difficult to optimize the yield for installing each fluorine atom sequentially beyond the first, each of the fluorinated products were readily separable by conventional flash chromatography. This gave us the opportunity to screen all the catalysts without concern for optimization of the synthesis until the most efficient catalyst was identified.

Attention therefore turned to the catalyst screening process to determine the effects of fluorination on the efficiency of epoxidation. We chose as our standard of comparison the epoxidation of *trans*-β-methylstyrene. The results are summarized in Table 1 below. A direct comparison with the Song system **2** showed that even stoichiometric quantities of catalyst **2** gave only 29% e.e. of the *trans*-β-methylstyrene oxide product.[6] The Denmark catalyst **3** gave only 55% conversion to *trans*-

Table 1. Epoxidation of *trans*-β-methylstyrene with catalysts **2**–**8**



Catalyst	Mol%	Time (h)	Temp. (°C)	Yield (%)	e.e.
2	100	1	25	95[a]	29[b]
3	10	10	0	55	–[c]
3	30	10	0	80	88
4	10	4	−15	35[d]	46[e]
5	10	4	−15	57[d]	80[e]
6	10	3.5	−15	100[d]	86[e]
7	10	3.5	−15	100[d]	83[e]
8	10	3.5	−15	32[d]	40[e]

[a] Yield determined by GC.
[b] Determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$.
[c] Enantiomeric excess was not reported.
[d] Percent conversion was determined by ^{1}H NMR at 400 MHz.
[e] Enantioselectivity was determined by HPLC (Chiralcel OD).

β-methylstyrene oxide at 10 mol% catalyst loading. Unfortunately, no measure of the enantiomeric excess was reported. Increasing the catalyst loading to 30 mol% gave 80% conversion and 88% e.e.[1a] The reactions with catalysts **4**–**8** were all run under the same conditions with 10 mol% catalyst at pH 9.3 and −15°C. Parent ketone **4** epoxidized *trans*-β-methylstyrene to 35% conversion with 46% e.e. This was encouraging since the non-fluorinated version of Denmark's catalyst **3** only proceeded to about 5% conversion under similar conditions. This was the first indication that we had a more reactive catalyst.

Monofluorinated ketone **5** drove the reaction to 57% conversion, and further increased the enantiomeric excess to 80%. The trend continued with the α,α′-difluorinated catalyst **6** completely converting the substrate to epoxide with 86% e.e. The effect of additional fluorination leveled off and trifluoroketone catalyst **7** offered no improvement in the enantiomeric excess though the conversion to epoxide was still complete. Denmark had previously shown that fluorinated cyclohexanone derivatives that were conformationally constrained showed a dramatic stereoelectronic effect, with axial fluorination resulting in little activation of the ketone moiety.[11] This is consistent with the third fluorine atom in catalyst **7** presumably occupying a pseudoaxial position, thus offering no advantage compared to difluorinated catalyst **6**. Tetrafluorinated ketone **8**, which exists almost exclusively as the hydrate, gave results similar to parent ketone **4**. The strong preference for formation of the hydrate makes catalyst **8** less available for dioxirane formation and hence the drop in conversion and enantiomeric excess.

In the screening process we have identified α,α′-difluorinated ketone **6** to contain the optimal degree of fluorination for catalytic asymmetric epoxidation. The activity of this catalyst in the epoxidation of *trans*-β-methylstyrene is the highest to date for biaryl-based ketone epoxidation catalysts. The next goal is to define the scope of substrates accepted by this catalyst system. Additionally, attachment to a solid support to facilitate catalyst recycling is under active investigation.

General epoxidation procedure: To a 10 mL round-bottomed flask were added tetrabutylammonium hydrogen sulfate (1.0 mg, 0.002 mmol), *trans*-β-methylstyrene (0.250 mL, 0.05 mmol, 0.2 M in DME) and a solution of ketone (**4**–**8**) (0.250 mL, 0.005 mmol, 0.02 M in DME) followed by 0.4 mL buffer (prepared: 0.5 mL acetic acid added to 100 mL 0.1 M aqueous K_2CO_3). Using a well salted ice bath, the reaction mixture was cooled to −15°C. While vigorously stirring the above solution, solutions of K_2CO_3 (0.2 mL, 1.44 M in water) and Oxone (0.2 mL, 0.34 M in 1×10^{-4} M aq. Na_2EDTA) were delivered simultaneously via separate syringes over a 3.5 h period using a syringe pump. Immediately following the addition, the reaction was quenched by dilution with ether and water. The water layer was extracted with ether three times. The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo to afford *trans*-β-methylstyrene oxide as a colorless to slightly yellow liquid. Conversion of *trans*-β-methylstyrene to *trans*-β-methylstyrene oxide was measured by ^1H NMR at 400 MHz. Enantioselectivity was determined by HPLC (Chiralcel OD).

Acknowledgements

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11. **(*S*)-α Fluoro ketone 5**: To a suspension of KH (240 mg, 6 mmol) in THF (3 mL) was added a solution of (*S*)-ketone **4** (183 mg, 0.6 mmol) in THF (3 mL) via cannula. After 3 h the resulting orange potassium enolate was then transferred to a solution of NFSI in THF at −78°C via cannula. The solution was allowed to warm slowly to room temperature. After 12 h the reaction was quenched with aqueous NH_4Cl. The reaction was partitioned between water and CH_2Cl_2 and extracted three times with CH_2Cl_2. Organic layers were combined and concentrated in vacuo. Flash chromatography (EtOAc/hexanes, 1:3) afforded α-fluoro ketone **5** (135 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05–7.25 (m, 12H), 5.98 (d, CHF, $J=47$ Hz), 3.71 (s, 2H). ^{19}F NMR (470 MHz, $CDCl_3$): δ −208.05 (dm, $J=47$ Hz). IR (NaCl plate, thin film) 1741 cm^{-1}. HRMS (CI) calcd for (M+H$^+$): 327.11852, found: 327.11813.
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13. **Fluorinated derivatives 6–8**: To a solution of LDA (0.54 mL of a 0.93 M soln) in 2.3 mL THF at 0°C was added a solution of (*S*)-ketone **5** (150 mg, 0.46 mmol) in 2.3 mL THF via cannula. After 1 h the resulting lithium enolate was transferred to NFSI (160 mg, 0.506 mmol) in 2.3 mL THF at −78°C via cannula dropwise over a period of 15 min. The reaction was allowed to warm slowly to room temperature. After 12 h the reaction was quenched with aqueous NH_4Cl. The reaction was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 mL×2). Organic layers were combined and concentrated. Successive flash chromatography (EtOAc/benzene, 0.1:1.0 followed by EtOAc/hexanes 0.1:1.0) afforded **4** (18%), **5** (26%), **6** (3%), **7** (26%) and **8** (16%). Compound **6** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05–8.02 (d, 2H), 7.94–7.92 (d, 2H), 7.75–7.73 (d, 2H), 7.50–7.44 (m, 2H), 7.36–7.34 (d, 2H), 7.30–7.25 (m, 2H), 5.93 (dm, 2H, CHF, $J=45.7$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$): δ −208.41 (dm, $J=46$ Hz). IR (NaCl, thin film) 1764 cm^{-1}. HRMS (EI) calcd for (M$^+$): 344.10127, found: 344.10178. Compound **7** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15–7.25 (m, 12H), 6.23 (dd, CFH, doublet $J=46.3$ Hz, doublets $J=4.75$ Hz), hydrate 5.47 (d, CHF, $J=46.8$ Hz). ^{19}F NMR (470 MHz, $CDCl_3$) δ −83.7 (dd, $J_1=283.8$ Hz, $J_2=4.59$ Hz), −121.10 (ddd, $J_1=284$ Hz, $J_2=8.84$ Hz, $J_3=0.86$ Hz), −208.6 (ddd, $J_1=46.3$ Hz, $J_2=8.75$ Hz, $J_3=1.15$ Hz). IR (NaCl plate, thin film) 1769 cm^{-1}. HRMS (CI) calcd for (M+H$^+$): 363.09967, found: 363.09964. Compound **8** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37–7.23 (Ar, 12H), 4.1 (s (br), OH. ^{19}F NMR (470 MHz, $CDCl_3$): δ −82.89 (dd, $J_1=269$ Hz, $J_2=7$ Hz), −121.10 (ddd, $J_1=273$ Hz, $J_2=6$ Hz, $J_3=3$ Hz), hydrate −97.68 (d, $J=250$ Hz), −125.92 (dd, $J_1=241.5$ Hz, $J_2=9$ Hz). HRMS (CI) calcd for (M+H$^+$): 381.09025, found: 381.09037.