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New chiral iodooxazoline catalysts for the I(III)-mediated α-tosyloxylation of ketones: refining the stereoinduction model

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ABSTRACT

A new family of iodooxazoline catalysts, derived from widely available chiral ketones (menthone and camphor), was developed to promote the iodine(III)-mediated α-tosyloxylation of ketone derivatives. The reaction conditions to achieve the direct formation of the oxazoline moieties from the corresponding aminoalcohols and an aldehyde were explored and optimized. These catalysts were tested for the α-tosyloxylation of propiophenone and led to new information on the stereoinduction process. The results demonstrate that modulation of the steric hindrance around the iodane center is critical to obtain good activity. Additionally, from the selectivities observed, a preliminary predictive model is proposed.

1. Introduction

Research to develop hypervalent iodine-mediated synthetic methodologies has shown a steady increase in recent years.[1] This is due in most part to the capacity of these reagents to replace transition metals in synthetically useful oxidative transformations.[2] In fact, hypervalent iodine reagents are considered the oxidation reagents of choice for numerous synthetic transformations. As a result, there have been numerous efforts put toward the development of stereoselective methods involving these reagents, either stoichiometrically or in a catalytic fashion.[3] Chiral iodoarene compounds, used either as reagents or catalysts, have found their way into such methodologies. Examples of successful enantioselective transformations have been reported for hydroxylative phenol dearomatization, using catalysts **1** and **2**,[4] and dearomatizing naphthol spirolactonization, using reagent **3**[5] and catalyst **4** (Fig. 1).[6]

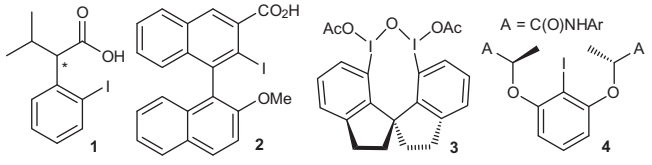
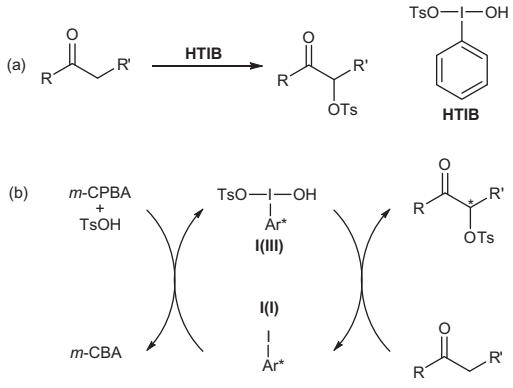


Figure 1. Representative iodoarene compounds used in hypervalent iodine mediated enantioselective reactions.

One synthetic transformation that has been particularly challenging to achieve in a stereoselective manner is the α-tosyloxylation of ketone compounds. This reaction (Scheme 1), initially popularized by Koser et al. using hydroxy(tosyloxy)iodobenzene **HTIB**,[7] enables easy access to very useful synthons, the alpha-tosyloxy ketones. In one simple step, these non-lacrymogenic[8] electrophiles can be obtained in good yield. Moreover, it was recently demonstrated by Togo et al. that this reaction could be rendered catalytic in the hypervalent iodine reagent.[9]



Scheme 1. (a) General α-tosyloxylation of ketones using **HTIB**. (b) Simplified cycle of catalytic iodine(III)-mediated α-tosyloxylation.

Despite more than 15 years of research on this particular reaction,[10–12] the enantioselectivities obtained with either chiral reagents or catalysts have never exceeded 58% ee. Currently the best enantioselectivities for the catalytic enantioselective α-tosyloxylation of propiophenone is 27% ee (78% yield) with catalyst **5**,[10b] 39% ee (42% yield) with **6** (R* = menthyl),[10b] and 53% ee (53% yield) with **7** (Fig. 2).[11] We recently reported on a new family of catalysts based on the iodoaryloxazoline scaffold

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and were able to obtain, with catalyst **8b**, up to 54% ee (48% ee and 80% yield under optimized conditions) for the α-tosyloxylation of propiophenone,[13] placing it among the best catalysts for this transformation.

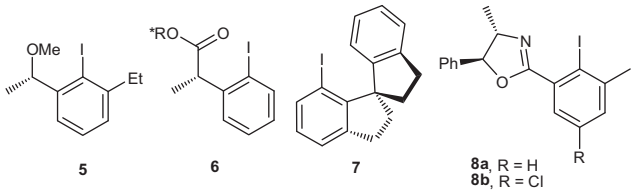


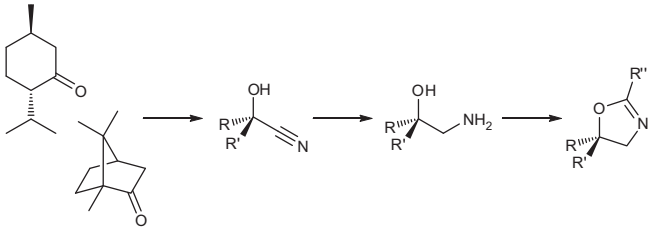
Figure 2. The best catalysts reported for the enantioselective α-tosyloxylation of ketone compounds.

We have found through an investigation of the stereoinduction process that it was the stereogenic center alpha to the oxygen atom that was responsible for the stereoselectivities. To the best of our knowledge, this is the first case of this type of unusual stereoinduction from a chiral oxazoline moiety. This also brings an important challenge. While access to chiral oxazolines bearing chirality alpha to the nitrogen atom is well known and mostly relies on chiral alpha-amino acids as starting materials,[14] access to oxazolines bearing a stereogenic center alpha to the oxygen atom is more challenging and rare (Scheme 2). Herein we report the synthesis of new iodoaryloxazoline catalysts bearing a sterically hindered stereogenic center alpha to the oxazoline oxygen. Their potential to promote the enantioselective α-tosyloxylation of ketones will be discussed (Scheme 1).

Scheme 2. Challenge of accessing chiral oxazolines bearing a stereogenic center alpha to the oxygen atom.

2. Results and discussion

With the challenge to access novel chiral oxazolines in mind, we envisioned exploiting the inherent chirality of widely available chiral ketones. The general synthetic approach is described in Scheme 3. The formation of a cyanohydrin followed by its reduction would lead rapidly to the corresponding aminoalcohol. We elected to use menthone and camphor as starting ketones because of their low cost and wide availability.



Scheme 3. General synthetic strategy to access oxazolines bearing a sterically hindered stereogenic center alpha to the oxygen.

Following the procedures reported by Dimitrov et al.,[15] involving the formation of a cyanohydrin using TMSCN with a catalytic quantity of $BF_3{\cdot}OEt_2$, followed by reduction using $LiAlH_4$, aminoalcohols **9**–**12** were rapidly obtained (Fig. 3). For aminoalcohol **9b**, the necessary corresponding ketone was obtained using a literature procedure.[16] This aminoalcohol was made in order to directly evaluate the effect of the increased steric hindrance on the α-tosyloxylation reaction.

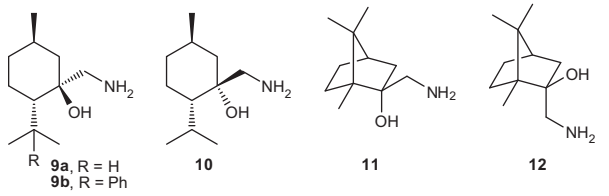
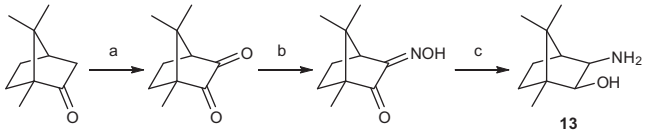


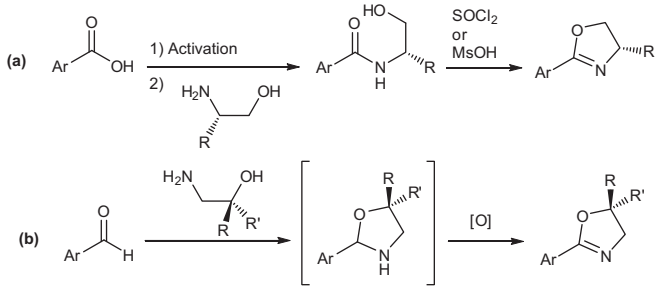
Figure 3. Aminoalcohols obtained following Dimitrov et al. procedures.

Additionally, the aminoalcohol **13** was obtained using an alternative procedure described in the literature and illustrated in Scheme 4.[17]



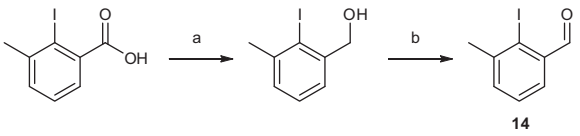
Scheme 4. Synthesis of aminoalcohol **13**. Reagents and conditions: (a) Se_2O, Ac_2O, reflux, 14 h, 80%; (b) $H_2NOH{\cdot}HCl$, pyridine, EtOH, 20 min, rt, 29%; (c) $LiAlH_4$, Et_2O, 1.5 h, rt, 80%.

Different synthetic approaches were evaluated for the synthesis of iodooxazolines. While oxazoline synthesis from aminoalcohols with no stereogenic center alpha to the oxygen usually rely on the simple activation (e.g., $SOCl_2$, MsOH) of the alcohol of the corresponding amide (Scheme 5a), it was envisioned that the steric hindrance of aminoalcohols and possible epimerization of the corresponding amide could lead to problems in such methods. In order to avoid the need to activate the alcohol and to simplify the synthesis, we elected to carry out a direct oxidative condensation of the aminoalcohols on an aldehyde substrate (Scheme 5b). This method, developed by Glorius et al., is reported to work well for a variety of aminoalcohols.[18]



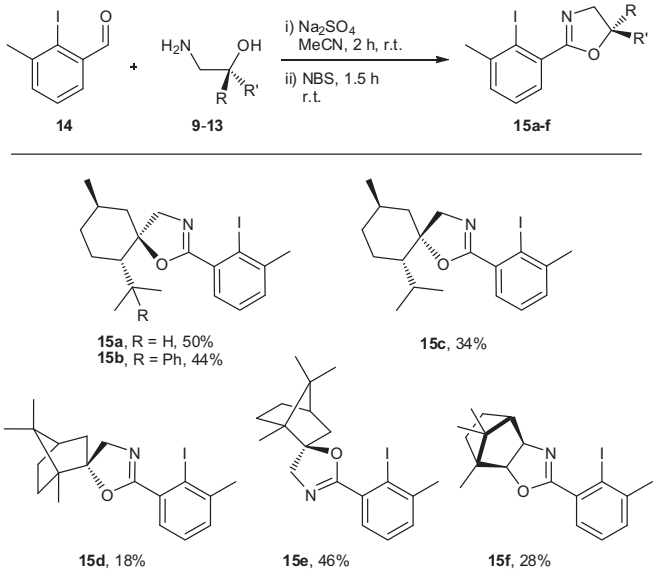
Scheme 5. Different approaches to access the chiral oxazolines.

In order to evaluate the feasibility of this synthetic route, the iodoaryl aldehyde **14** was synthesized from commercially available 2-iodo-3-methylbenzoic acid using the procedure illustrated in Scheme 6. The necessity for a methyl group *ortho* to the iodine atom is to achieve high catalytic activity, as was demonstrated by our group previously.[19]



Scheme 6. Synthesis of aldehyde **14**. Reagents and conditions: (a) $NaBH_4$, I_2, THF, rt, 85%; (b) PCC, CH_2Cl_2, 16 h, rt, 90%.

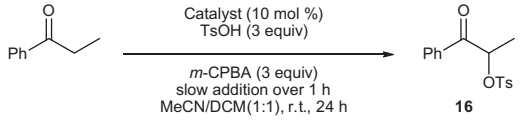
Initial tests to generate the desired oxazolines from the literature conditions resulted in low yields. We hypothesized that the steric hindrance of both reactants resulted in a slow reaction, which prompted us to modify the reported conditions. Optimization of the reaction time and solvent led to the conditions described in Scheme 7. Using these optimized conditions, catalysts **15a–f** could be obtained in modest to fair yields.



Scheme 7. Synthesis of the iodoaryloxazoline catalysts.

With catalysts **15a–f** in hand, we evaluated them in the model α-tosyloxylation reaction of propiophenone. The optimized conditions used for iodooxazoline catalysts were previously found by our group.[13] The results are summarized in Table 1.

Table 1
Evaluation of the activity and selectivity of the new iodoaryloxazoline catalysts

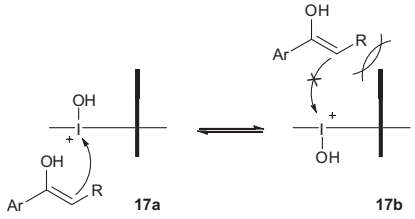


Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	**8a**	72	44 (*R*)
2	**15a**	64	17 (*S*)
3	**15b**	19	8 (*S*)
4	**15c**	79	8 (*S*)
5	**15d**	14	3 (*S*)
6	**15e**	26	3 (*S*)
7	**15f**	71	34 (*R*)

[a] Isolated yield.
[b] Determined by chiral HPLC.

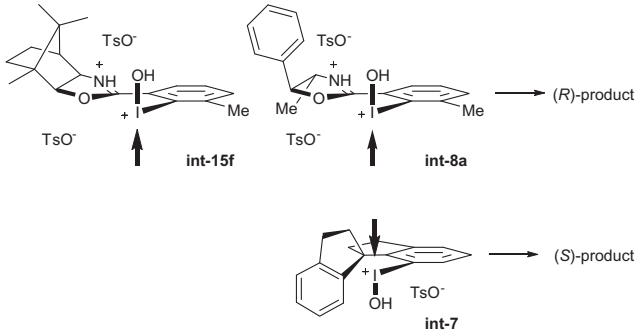
For the sake of comparison, our best iodooxazoline catalyst previously developed,[13] **8a** was also tested. Despite the presence of a bulky stereogenic center alpha to the oxazoline-oxygen atom, none of the new catalysts afforded a level of enantioselectivity comparable to **8a**, derived from norephedrine. Additionally, comparison of catalysts **15a** and **15b** (entries 2 vs 3) showed a drastic decrease in catalytic activity. Presumably, replacing the *i*-Pr group of **15a** by a bulkier dimethylphenyl group prevents efficient access to the iodane reactive center.

From these results and recent advances from our group and Zhang et al.,[11] a predictive stereoinduction model can be proposed. First of all, computational evidence points to a dissociative pathway, in which the enol form of the ketone substrate reacts with a highly electrophilic iodonium intermediate.[13] Enol will approach *trans* to the OH group, the most electronegative group on the iodonium. The reactive intermediate can adopt two conformations. For example, in the case of Zhang's catalyst **7**, two rotamers **17a** and **17b** are possible (Scheme 8). The approach of enol will be favored on **17a** due to the minimized steric interactions with the catalyst perpendicular phenyl group.



Scheme 8. Simplified representation of the rational for the facial selectivity of Zhang's catalyst **7**.

In the case of catalysts **8a** and **15f**, similar discrimination is possible due to the rotational restriction of the protonated oxazoline moieties, favoring orientation of the oxazoline-oxygen toward the iodonium center.[13] From the low selectivities observed for catalysts **15a**–**15e**, introduction of a bulky stereogenic center alpha to the oxazoline-oxygen seems highly detrimental to the facial selectivity on the iodonium center. Conversely, facial selectivity on the iodonium species from catalysts **8a** and **15f**, bearing secondary chiral centers alpha to the oxygen-oxazoline correlates with the absolute stereochemistry of the final product. A simple predictive model, based on the facial selectivity on the iodonium intermediates **int-7**, **int-8a,** and **int-15f**, is represented in Scheme 9. The low enantioselectivities could therefore be due to a lack of facial discrimination on the enol substrate.



Scheme 9. Simple model to correlate the facial selectivity on the iodonium intermediate with the final product configuration.

3. Conclusion

We have developed a new family of iodooxazoline catalysts based on sterically hindered aminoalcohols derived from chiral ketones. From the results obtained, it now seems clear that there is a

limit in terms of the bulkiness of the chiral group that can be present next to the iodine center on these catalysts. Additionally, we can conclude that quaternary stereogenic centers alpha to the oxazoline oxygen atom might prevent efficient facial discrimination on the iodonium intermediate. In contrast, secondary stereogenic centers are predisposed to result in better facial selectivity on the iodonium intermediate. With the additional information obtained from our group and others, we are currently working on a computational model to better explain the stereoselectivities observed, as well as propose solutions to finally achieve high selectivites in what remains a great challenge of hypervalent iodine chemistry. Work on other families of chiral catalysts will be reported in due course.

4. Experimental

4.1. General remarks

Compounds **9**–**12**,[15] **13**,[17] and **14**[13] were all prepared according to reported procedures. All non-aqueous reactions involving air or moisture sensitive compounds were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques. All glassware was stored in the oven and/or was flame dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by distillation over sodium (THF, ether, benzene, toluene), over calcium hydride (CH_2Cl_2, Et_3N, and $ClCH_2CH_2Cl$). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash column chromatography was performed using 230–400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to the standard technique. Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were taken on a FTIR instrument and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^1H, ^{13}C, DEPT, COSY, and HMQC) were recorded either on a 300 MHz or 400 MHz spectrometers. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm, acetonitrile, δ 1.94 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextuplet, m = multiplet and br = broad), coupling constant in Hz, integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.23 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using COSY, NOESY, HMQC, and DEPT experiments. High resolution mass spectra were performed using UPLC-Q-TOF (ESI) mass spectrometers. Analytical High Performance Liquid Chromatography was performed on an HPLC system equipped with diode array UV detector. Data are reported as follows: (column type, eluent, flow rate: retention time (t_r)).

4.2. Preparation of the iodoaryloxazoline catalysts

4.2.1. (5*R*,6*R*,9*R*)-2-(2-Iodo-3-methylphenyl)-6-isopropyl-9-methyl-1-oxa-3-azaspiro[4.5]dec-2-ene 15a

General procedure: To a solution of (1*R*,2*S*,5*R*)-1-(aminomethyl)-2-isopropyl-5-methylcyclohexanol (161 mg, 0.869 mmol) in 4.35 mL of CH_3CN was added 2-iodo-3-methylbenzaldehyde (214 mg, 0.869 mmol). After the mixture was stirred for 2 h at room temperature, NBS (155 mg, 0.869 mmol) was added and the solution was stirred for 1.5 h. The solvents were removed under reduced pressure. The mixture was diluted in CH_2Cl_2 and washed twice with a saturated aqueous $NaHCO_3$ solution then once with brine. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography with hexanes:EtOAc (85:15) to provide 178 mg (50%) of (5*R*,6*R*,9*R*)-2-(2-iodo-3-methylphenyl)-6-isopropyl-9-methyl-1-oxa-3-azaspiro[4.5]dec-2-ene as a yellow oil; R_f 0.31 (hexanes:EtOAc, 85:15); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.28 (m, 3H), 4.04 (d, J = 14.8 Hz, 1H), 3.71 (d, J = 14.8 Hz, 1H), 2.48 (s, 3H), 1.69–2.23 (m, 4H), 1.39–1.63 (m, 3H), 1.17–1.29 (m, 1H), 0.89–1.10 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 142.9, 135.9, 130.9, 127.7, 127.4, 101.7, 90.6, 59.9, 49.5, 47.7, 34.5, 29.9, 29.6, 26.3, 25.0, 24.4, 22.1, 19.3 ppm; IR (neat) 3042, 2951, 2920, 2869, 1659, 1571, 1455, 1342, 1174, 1128, 1088, 1012, 972, 920, 789, 771, 722 cm^{-1}; HRMS EI (m/z): $[MH]^+$ calcd for $C_{19}H_{27}INO$, 412.1132; found 412.1135. $[\alpha]_D^{25} = -18.5$ (c 0.97, $CHCl_3$).

4.2.2. (5*R*,6*S*,9*R*)-2-(2-Iodo-3-methylphenyl)-9-methyl-6-(2-phenylpropan-2-yl)-1-oxa-3-azaspiro[4.5]dec-2-ene 15b

The general procedure was followed: (1*R*,2*S*,5*R*)-1-(aminomethyl)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexanol (111 mg, 0.42 mmol), 2.1 mL CH_3CN, 2-iodo-3-methylbenzaldehyde (104 mg, 0.42 mmol), NBS (138 mg, 0.777 mmol). The crude product was purified by flash chromatography with hexanes:EtOAc (85:15) to provide 90 mg (44%) of (5*R*,6*S*,9*R*)-2-(2-iodo-3-methylphenyl)-9-methyl-6-(2-phenylpropan-2-yl)-1-oxa-3-azaspiro[4.5]dec-2-ene as a yellow oil; R_f 0.33 (hexanes:EtOAc, 85:15); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.20 (m, 7H), 7.09 (t, J = 6.8 Hz, 1H), 4.13 (d, J = 15.1 Hz, 1H), 3.74 (d, J = 14.9 Hz,1H), 2.51 (s, 3H), 2.19 (d, J = 12.6 Hz, 1H), 2.06 (d, J = 11.5 Hz,1H), 1.64–1.37 (m, 10H), 1.14–0.82 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 150.8, 143.0, 135.2, 131.0, 127.8 (2), 127.6, 125.9, 125.4, 101.9, 91.2, 60.0, 53.8, 50.1, 41.5, 34.9, 30.1, 29.9, 29.7, 26.4, 25.6, 21.8 ppm; IR (neat) 3059, 2952, 2924, 2869, 2219, 1657, 1575, 1498, 1456, 1370, 1345, 1292, 1262, 1178, 1134, 1089, 1013, 972, 911, 840, 790, 776, 727, 701 cm^{-1}; HRMS EI (m/z): $[MH]^+$ calcd for $C_{25}H_{31}INO$, 488.1445; found 488.1447. $[\alpha]_D^{25} = -18.2$ (c 0.91, $CHCl_3$).

4.2.3. (5S,6S,9R)-2-(2-Iodo-3-methylphenyl)-6-isopropyl-9-methyl-1-oxa-3-azaspiro[4.5]dec-2-ene 15c

The general procedure was followed: (1*S*,2*S*,5*R*)-1-(aminomethyl)-2-isopropyl-5-methylcyclohexanol (144 mg, 0.777 mmol), 4.9 mL CH_3CN, 2-iodo-3-methylbenzaldehyde (191 mg, 0.777 mmol), NBS (138 mg, 0.777 mmol). The crude product was purified by flash chromatography with hexanes:EtOAc (85:15) to provide 108 mg (34%) of (5*S*,6*S*,9*R*)-2-(2-iodo-3-methylphenyl)-6-isopropyl-9-methyl-1-oxa-3-azaspiro[4.5]dec-2-ene as a yellow oil; R_f 0.31 (hexanes:EtOAc, 85:15); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23–7.26 (m, 3H), 4.04 (d, J = 14.8 Hz, 1H), 3.72 (d, J = 14.8 Hz, 1H), 2.49 (s, 3H), 1.94–2.23 (m, 2H), 1.95–2.03 (m, 1H), 1.70–1.81 (m, 2H), 1.39–1.59 (m, 3H), 1.01–1.11 (m, 1H), 1.96–1.97 (m, 6H), 0,92 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 142.9, 135.9, 130.8, 127.7, 127.4, 101.7, 90.6, 64.8, 59.8, 49.4, 47.6, 34.4, 29.8, 26.3, 24.9, 24.4, 22.1, 19.3 ppm; IR (neat) 3045, 2951, 2923, 2869, 1661, 1571, 1454, 1345, 1265, 1177, 1128, 1085, 1009, 969, 923, 789, 771, 722 cm^{-1}; HRMS EI (m/z): $[MNa]^+$ calcd for $C_{19}H_{26}INONa$, 434.0951; found 434.0950. $[\alpha]_D^{25} = -12.7$ (c 1.32, $CHCl_3$).

4.2.4. (1*R*,2*S*,4*R*)-2′-(2-Iodo-3-methylphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-2,5′-oxazole] 15d

The general procedure was followed: (1*S*,2*S*,4*R*)-2-(aminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (43 mg, 0.235 mmol),

1.18 mL CH_3CN, 2-iodo-3-methylbenzaldehyde (58 mg, 0.235 mmol), NBS (42 mg, 0.235 mmol). The crude product was purified by flash chromatography with hexanes:EtOAc (80:20) to provide 17 mg (18%) of (1*R*,2*S*,4*R*)-2′-(2-iodo-3-methylphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1] heptane-2,5′-oxazole] as a colorless oil; R_f 0.30 (hexanes:EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.32 (m, 3H), 4.29 (d, J = 15.0 Hz, 1H), 3.65 (d, J = 15.1 Hz, 1H), 2,50 (s, 3H), 2.19–2.28 (m, 1H), 1.91–2.07 (m, 2H), 1.72–1.83 (m, 2H), 1.24–1.45 (m, 2H), 0.96 (s, 3H), 0.88 (d, J = 9.0 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 142.9, 136.2, 130.9, 127.8, 127.7, 101.7, 95.0, 67.0, 52.4, 48.5, 47.5, 45.6, 29.9, 29.7, 29.6, 27.5, 20.3, 20.0, 11.3 ppm; IR (neat) 3045, 2951, 2872, 2358, 1662, 1571, 1455, 1388, 1345, 1272, 1177, 1131, 1091, 1012, 969, 893, 777, 719 cm^{-1}; HRMS EI (m/z): [MH]$^+$ calcd for $C_{19}H_{25}INO$, 410.0975; found 410.0982. $[\alpha]_D^{25} = -11.8$ (c 0.54, $CHCl_3$).

4.2.5. (1*R*,2*R*)-2′-(2-Iodo-3-methylphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-2,5′-oxazole] 15e

The general procedure was followed: (1*S*,2*R*,4*R*)-2-(aminomethyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (20 mg, 0.109 mmol), 0.55 mL CH_3CN, 2-iodo-3-methylbenzaldehyde (27 mg, 0.109 mmol), NBS (20 mg, 0.109 mmol). The crude product was purified by flash chromatography with hexanes:EtOAc (80:20) to provide 16 mg (36%) of (1*R*,2*R*)-2′-(2-iodo-3-methylphenyl)-1,7,7-trimethyl-4′*H*-spiro[bicyclo[2.2.1]heptane-2,5′-oxazole] as a colorless oil; R_f 0.32 (hexanes:EtOAc, 80:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.28 (m, 3H), 4.16 (d, J = 14.8 Hz, 1H), 3.85 (d, J = 14.7 Hz, 1H), 2.56 (ddt, J = 13.9, 3.6, 0.8 Hz, 1H), 2.50 (s, 3H), 1.25–1.84 (m, 5H), 1.08–1.17 (m, 4H), 0.90 (d, J = 2.7 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 142.8, 136.0, 130.9, 127.8, 127.7, 101.7, 95.7, 63.9, 52.1, 49.3, 48.2, 45.7, 30.2, 29.6, 27.1, 20.6, 20.3, 10.3 ppm; IR (neat) 2951, 2872, 1662, 1571, 1452, 1391, 1345, 1284, 1174, 1128, 1055, 1015, 963, 890, 777, 722 cm^{-1}; HRMS EI (m/z): [MNa]$^+$ calcd for $C_{19}H_{24}INONa$, 432.0795; found 432.0795. $[\alpha]_D^{25} = -31.9$ (c 1.15, $CHCl_3$).

4.2.6. (3a*S*,4*R*,7*S*,7a*R*)-2-(2-Iodo-3-methylphenyl)-8,8-dimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[d]oxazole 15f

The general procedure was followed: (1*S*,2*S*,4*S*)-3-amino-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (215 mg, 1.27 mmol), 6.35 mL of CH_3CN, 2-iodo-3-methylbenzaldehyde (312 mg, 1.27 mmol), NBS (226 mg, 1.27 mmol). The crude product was purified by flash chromatography with hexanes:EtOAc (85:15) to provide 128 mg (26%) of (3a*S*,4*R*,7*S*,7a*R*)-2-(2-iodo-3-methylphenyl)-8,8-dimethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanobenzo[*d*]oxazole as a colorless oil; R_f 0.27 (hexanes:EtOAc, 85:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.23 (m, 3H), 4.41 (d, J = 8.7 Hz, 1H), 4.20 (d, J = 8.7 Hz, 1H), 2.43 (s, 3H), 2.13 (d, J = 4.5 Hz, 1H), 1.67–1.75 (m, 2H), 1.44–1.52 (m, 2H), 1.18 (s, 3H), 1.01 (d, J = 2.4 Hz, 3H), 0.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 143.1, 135.4, 131.2, 127.7, 127.4, 101.9, 91.9, 48.7, 48.6, 47.1, 32.1, 29.8, 29.7, 26.1, 23.4, 19.3, 11.4 ppm; IR (neat) 3045, 2954, 2885, 1653, 1574, 1459, 1391, 1357, 1327, 1121, 1084, 991, 970, 786, 725 cm^{-1}; HRMS EI (m/z): [MH]$^+$ calcd for $C_{18}H_{23}INO$, 396.0819; found 396.0830. $[\alpha]_D^{25} = +14.6$ (c 1.01, $CHCl_3$) (see Figs. 1–3).

4.2.7. General α-tosyloxylation procedure for the evaluation of catalysts (Table 1)

Catalyst **8a** (9.1 mg, 0.025 mmol) was dissolved in acetonitrile:CH_2Cl_2 (1:1) (0.6 mL). Propiophenone (134.0 mg, 0.25 mmol) and *p*-TsOH hydrate (138 mg, 0.73 mmol) was added. A solution of *m*-CPBA (162 mg, 77% pure, 0.72 mmol) in acetonitrile:CH_2Cl_2 (1:1) (0.8 mL) was added over 1 h. The reaction was stirred for 24 h. The reaction mixture was washed with a saturated solution of $Na_2S_2O_3$ (aq) and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with a saturated solution of $NaHCO_3$ (aq) and then brine. The organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced atmosphere. The crude mixture was purified by column chromatography on silica gel with EtOAc:hexanes (5:95 to 20:80) to provide 56 mg (73%) of **16** as a white solid of the (*R*)-enantiomer (44% ee).[13] The ee were determined by HPLC on the purified product: Chiracel AS-H column, 50:50 hexanes:*i*-PrOH, 0.7 mL/min, rt, t_S = 10.1 min (*S*), t_R = 11.6 min (*R*).

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