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Catalytic Enantioselective α-Tosyloxylation of Ketones Using Iodoaryloxazoline Catalysts: Insights on the Stereoinduction Process

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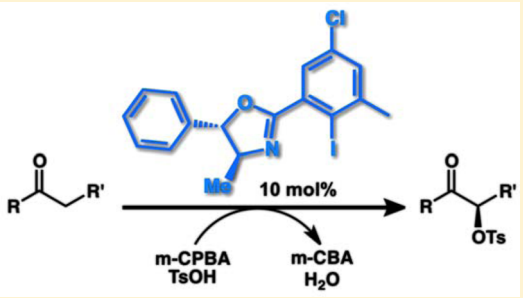
Supporting Information

ABSTRACT: A family of iodooxazoline catalysts was developed to promote the iodine(III)-mediated α-tosyloxylation of ketone derivatives. The α-tosyloxy ketones produced are polyvalent chiral synthons. Through this study, we have unearthed a unique mode of stereoinduction from the chiral oxazoline moiety, where the stereogenic center alpha to the oxazoline oxygen atom is significant. Computational chemistry was used to rationalize the stereoinduction process. The catalysts presented promote currently among the best levels of activity and selectivity for this transformation. Evaluation of the scope of the reaction is presented.



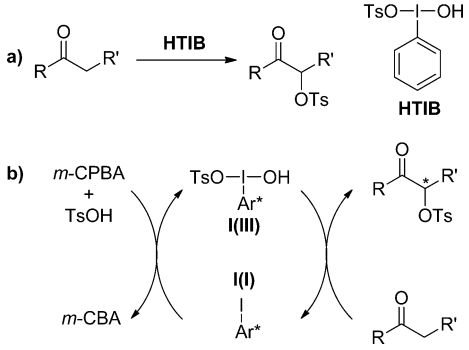
INTRODUCTION

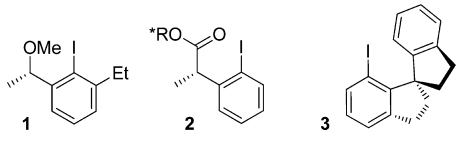
With the goal to provide environmentally friendly solutions to the field of oxidation reactions, hypervalent iodine compounds have received increasing attention in recent years.[1] They are polyvalent electrophiles and mild oxidants. In particular, efforts toward the development of chiral variants of these reagents have been made.[2] This has led to pioneering results in numerous useful synthetic oxidative transformations, such as the α-tosyloxylation of ketones,[3] hydroxylative phenol dearomatizations,[4] and dearomatizing naphthol spirolactonizations.[5]

Our group is interested in the α-oxidation of ketones compounds that leads to functionalized derivatives with versatile synthetic applications.[2a] In particular, the α-tosyloxylation of ketones enables the introduction of a potent leaving group alpha to a carbonyl. Additionally, and in contrast to α-halo ketones, these electrophiles are not lacrymators.[6] A method to access such compounds relies on the use of toxic thallium(III) reagents.[7] An iodine(III)-mediated variant has been popularized by Koser et al.[8] and uses hydroxy(tosyloxy)-iodobenzene[9] (Scheme 1a, HTIB). The process is an environmentally more moderate alternative to the Thallium-mediated process. Togo et al.[10] demonstrated a variant that requires only catalytic amounts of an iodoaryl catalyst and the presence of a co-oxidant (*m*-CPBA) in the reaction medium (Scheme 1b).

With these factors in mind, it is particularly interesting to consider a catalytic enantioselective variant of the transformation that can yield chiral α-tosyloxy ketones, polyvalent chiral synthons. The latter allow for a rapid and divergent synthesis of numerous α-chiral substituted ketones. Pioneering work in this field has been done by Wirth et al., in terms of both chiral stoichiometric reagents[3e,f] and chiral iodoaryl catalysts.[3b−d] Currently the best enantioselectivities for the catalytic enantioselective α-tosyloxylation of propiophenone is 78% (27% ee) with catalysts **1**, 42% (39% ee) with **2** (R* = menthyl),[3c] and 53% (53% ee) with **3**.[11] Achieving high enantioselectivities remains a formidable challenge with such catalytic systems. Here, we report progress in the use of iodoaryloxazoline derivatives as chiral catalysts to promote the α-tosyloxylation of ketones compounds and our insights on the process of stereoinduction.

Scheme 1. (a) Concept of α-Tosyloxylation of Ketones Using HTI; (b) Concept of Catalytic Iodine(III)-Mediated α-Tosyloxylation





We envision utilizing catalysts with the general structure **A** (Scheme 2), harboring a chiral oxazoline moiety ortho to the iodine. Inspiration for this type of scaffold was drawn from the family of PHOX (phosphinooxazoline) ligands **C** (Scheme 2)

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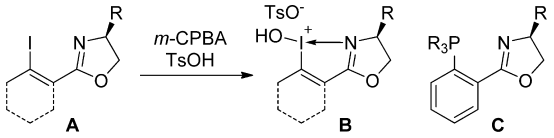
Scheme 2. Concept of Chiral Iodoaryloxazoline Catalysts

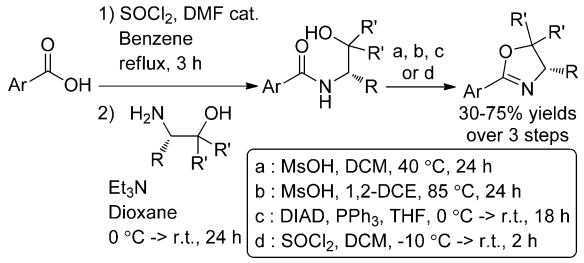


used in organometallic catalysis.[12] Upon oxidation, the iodane center can be coordinated by the oxazoline (Scheme 2, **B**). Birman et al. recently used similar chiral iodine(V) reagents for the oxidation of *o*-alkylphenols.[13] Birman's work and ours demonstrate that the oxazoline moiety is compatible with hypervalent iodine species of various oxidation states.

RESULTS AND DISCUSSION

A first family of catalysts was readily prepared using standard synthetic methods (Scheme 3).[14] The corresponding carboxylic

Scheme 3. Synthesis of the Iodoaryloxazoline Catalysts



acids were initially converted to their analogue acyl chlorides, followed by amide formation. Depending on the nature of the resulting amide, different cyclization conditions were used. Using these synthetic routes, catalysts **4**–**13** were obtained with yields between 30% and 75% over three steps (Scheme 4).

Catalyst activities and selectivities were evaluated using a model reaction for the α-tosyloxylation of propiophenone (**14**), and the results are summarized in Table 1. Catalysts **4**–**6**, derived from the 1,8-naphthyl scaffold, were initially tested but

Scheme 4. Iodoaryloxazoline Catalysts Synthesized

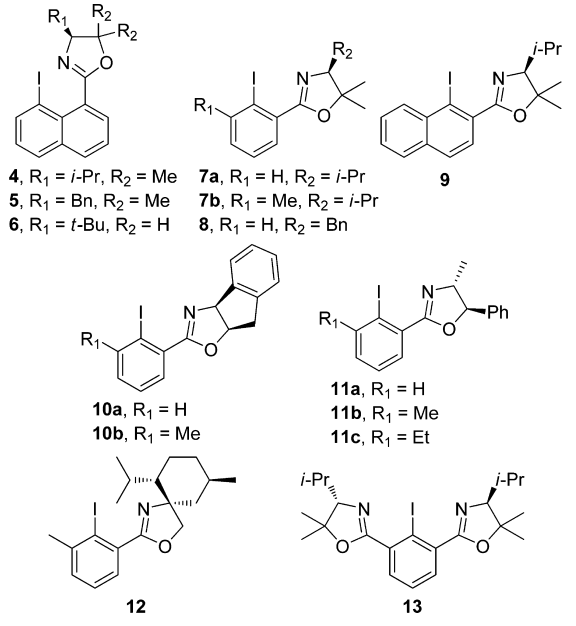
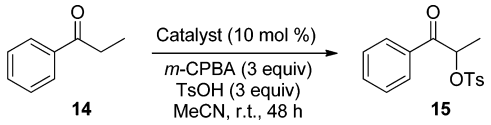


Table 1. Evaluation of the Chiral Iodoaryloxazoline Catalysts



entry	catalyst	yield [%][a]	ee [%][b]
1	**4**	7	5 (*S*)
2	**5**	2	4 (*S*)
3	**6**	34	<1 (*S*)
4	**7a**	2	2 (*S*)
5	**8**	2	1 (*R*)
6	**10a**	8	13 (*S*)
7	**11a**	9	24 (*S*)
8	**7b**	66	6 (*S*)
9	**10b**	80	12 (*S*)
10	**11b**	60	33 (*S*)
11	**11c**	59	30 (*S*)
12	**12**	55	4 (*R*)
13	**9**	43	6 (*S*)
14	**13**	12	7 (*S*)

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC.

did not offer any noticeable activity or selectivity (entries 1–3, Table 1). The 1,2-phenyl scaffold was then explored, offering broader potential for aromatic substitution. Catalysts **7a**, **8**, **10a**, and **11a**, derived from 2-iodobenzoic acid, did not show any noticeable activity (entries 4–6, Table 1).

Introduction of an alkyl group ortho to the iodine center in catalysts **7b**, **10b**, **11b**, **11c**, and **12**, however, led to a drastic improvement in activity (entries 8–12, Table 1). We have recently explained this drastic acceleration effect on iodoamide-derived catalysts.[15] Most chiral catalysts rely on a chiral Lewis base ortho to the iodine to coordinate the electrophilic iodane center following oxidation. For the α-tosyloxylation reaction to proceed, the Lewis base must uncoordinate from the iodane to free an electrophilic site for the nucleophile (i.e., enol). With stronger Lewis bases, such as amide or oxazoline groups, the energy required to dissociate the base can become rate-limiting and even prevent reaction. It is then necessary to destabilize the iodane intermediate, i.e., through introduction of a substituent ortho to the iodine atom, so that dissociation can occur at an acceptable rate. A naphthyl scaffold was used for catalyst **9**, in order to achieve similar destabilization without the use of an alkyl group. This catalyst shows lower activity (entry 13, Table 1). Attempts to replace the methyl group by a second chiral oxazoline, i.e., in catalyst **13**, showed lower activity (entry 14, Table 1). In all cases 5% to 20% of Baeyer–Villiger reaction products from **14** and **15** were found. The quantities were inversely proportional to the catalyst activity.

Most catalysts offered almost no enantioselectivities, even in the presence of bulky oxazolines (entry 12, Table 1). Surprisingly, the best enantioselectivities were obtained from catalysts bearing a stereogenic center alpha to the oxazoline-oxygen (entries 9–11, Table 1). To gain insights about the stereoinduction process, catalysts **16**–**18** (Scheme 5) were synthesized, and their performance was evaluated with regards to the model reaction (Table 1); the results are summarized in Table 2.

Complete removal of the stereogenic center alpha to the oxazoline-nitrogen did not result in a noticeable loss of enantioselectivity (entry 2, Table 2). Replacement of the

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Scheme 5. Iodoaryloxazoline Catalysts 16−18

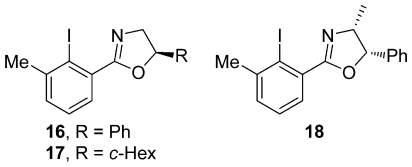


Table 2. Evaluation of Chiral Catalysts 16−18

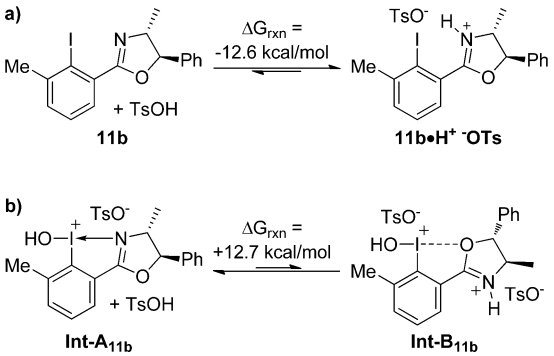
entry	catalyst	yield [%][a]	ee [%][b]
1	**11b**	60	33 (*S*)
2	**16**	56	30 (*S*)
3	**17**	60	31 (*S*)
4	**18**	54	25 (*R*)

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC.

phenyl group of catalyst **16** for a bulky aliphatic moiety (i.e., *c*-hexyl) in catalyst **17** did not result in a loss in enantioselectivity (entry 3, Table 2), indicating that the role of the phenyl group is mainly for steric hindrance. Additionally, the sense of stereoinduction is almost exclusively controlled by the stereogenic center alpha to oxazoline oxygen, as the epimer (**18**) of catalyst **11b** led to an inversion of the sense of induction with similar enantioselectivity. This unique mode of stereoinduction from an oxazoline group is quite surprising. To the best of our knowledge, this is the first example of a chiral oxazoline in which the stereoinduction is controlled by the stereogenic center alpha to the oxygen atom.

We studied the reaction intermediates computationally to find a rationale for this surprising behavior.[16] Due to the excess of toluenesulfonic acid (TsOH) with respect to the catalyst, the oxazoline is driven to its protonated state. Calculations show that protonation of catalyst **11b** is exergonic, with a ΔG_{rxn} value of −12.6 kcal/mol (Scheme 6a). This value is in agreement

Scheme 6. Calculated Free Energies (kcal/mol) of Protonation of Catalyst 11b (a) and Corresponding Iodane Int-A_{11b} (b)



with the approximate expected value (−9.8 kcal/mol) calculated from the experimental pK_a(water) values of a protonated oxazoline (4.4)[17] and TsOH (−2.8).[18] In its reduced state, the catalyst is thus found almost exclusively in its protonated form.

A very different behavior is observed with the iodane intermediates (Scheme 6b). Following oxidation, protonation of the oxazoline in iodane intermediate **Int-A** is endergonic. While **Int-A** is the most stable iodane intermediate (resting state), it is not the most electrophilic intermediate, due to the strong nitrogen coordination on the iodane center. Protonation thus furnishes necessary activation to lead to **Int-B**, a much more electrophilic bis-cationic intermediate.

In intermediate **Int-B**, the oxazoline rotates to position its oxygen toward the iodine atom to maximize attractive Coulombic interactions (Figure 1b). In such an intermediate,

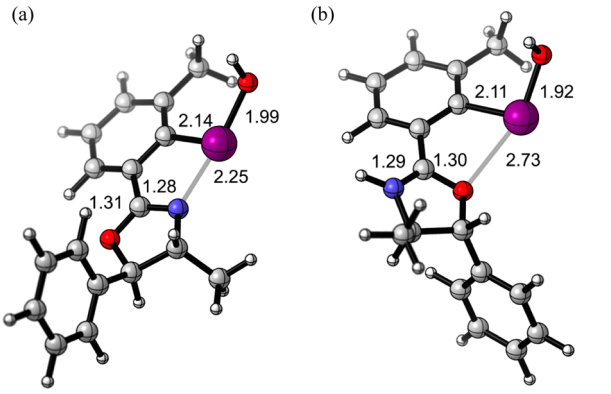
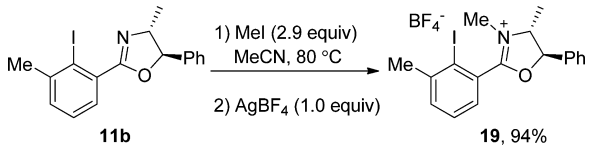


Figure 1. Optimized structures of **Int-A_{11b}** (a) and **Int-B_{11b}** (b).[16]

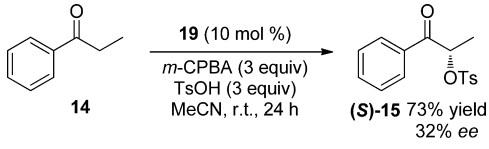
the stereogenic center adjacent to the oxygen atom is near the reactive iodine center and influences the approach of the substrate. Additionally, the O−I interaction in **Int-B** is much weaker than the N−I interaction of **Int-A**, which is evident from the iodine−heteroatom distance (Figure 1). This effectively introduces torsion strain in **Int-B**. The presence of the methyl group ortho to the iodine thus favor the protonation of **Int-A**. Calculations have shown that protonation of **Int-A** derived from catalyst **11a** is more endergonic (+14.9 kcal/mol), in accord with this rationale, and explain the positive effect of the methyl group on catalyst activity. To demonstrate the viability of **Int-B** in the reaction conditions, we elected to methylate catalyst **11b** to its corresponding *N*-methyl oxazolinium tetrafluoroborate salt. Methylation using methyl iodide, followed by counterion exchange, yielded the desired salt **19** in 94% yield (Scheme 7).

Scheme 7. Synthesis of the *N*-Methylated salt of 11b



Salt **19** is stable under the α-tosyloxylation conditions with no noticeable degradation over extended (>48 h) periods. It was then used as a catalyst for the α-tosyloxylation of propiophenone (Scheme 8). The enantioselectivity and sense of chiral induction with **19** was close to what was obtained with

Scheme 8. α-Tosyloxylation of 14 Using Catalyst 19



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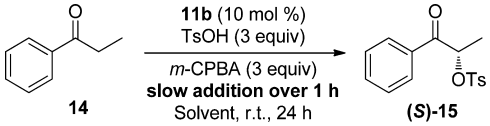
catalyst **11b**, although a slight increase in activity and higher yield were observed.

We elected to pursue the study with catalyst **11b**, as it is a neutral non-hygroscopic solid. We were able to enhance yield and selectivity by first premixing catalyst, substrate, and TsOH, followed by slow addition of *m*-CPBA over 1 h. With this approach, we were able to surpass **19** in terms of yield and selectivity. Conversely, slow addition of TsOH over a premixed solution of the substrate, catalyst, and *m*-CPBA led to yields equivalent to those with **19**, although at the expense of enantioselectivity. While no definitive catalyst degradation products could be isolated, *N*-oxidation of the neutral oxazoline nitrogen with *m*-CPBA is most probable. Premixing of the catalyst and TsOH thus greatly minimized *N*-oxidation through strongly favorable protonation. Using these optimized conditions, the effect of solvent on yields and selectivities was evaluated. The results are summarized in Table 3.

Table 3. Solvent Effect on the α-Tosyloxylation of Propiophenone under Optimized Model Reaction Conditions



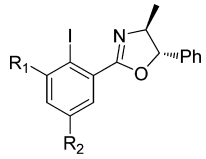
entry	solvent	yield [%][a]	ee [%][b]
1	MeCN	77	36
2	MeCN[c]	<5	
3	MeCN/DCM (2:1)	73	43
4	MeCN/DCM (1:1)	72	44
5	MeCN/DCM (1:2)	67	48
6	DCM	43	54
7	MeCN/PhMe (1:1)	67	45
8	PhMe	17	50
9	MeCN/$CHCl_3$ (1:1)	69	46
10	$CHCl_3$	45	54
11	MeCN/1,2-DCE (1:1)	49	45
12	1,2-DCE	51	50
13	Et_2O	41	47
14	THF	27	32
15	EtOAc	64	38
16	H_2O	<5	

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC. [c]4 Å molecular sieve was added to the reaction.

The use of less polar solvents was found to give enhanced enantioselectivities (entries 6, 8, 10, 12, 13, 15, Table 3). The observation was expected, as less polar solvents are known to allow for stronger electrostatic interactions and, in this context, for shorter O−I distances in **Int-B**. In most cases, this was also accompanied by a drastic loss of yields. The best alternative solvent was found to be dichloromethane (DCM), allowing for enantioselectivities of up to 54% ee (entry 6, Table 3) as well as an increased solubility of substrate and reagent. To circumvent the loss of yield, mixtures of MeCN and DCM were tested (entries 3−5, Table 3) and a 1:1 solution was found to be ideal (entry 4, Table 3). Water was not tolerated as a reaction solvent (entry 16, Table 3). Yet, no product formation was observed upon addition of a molecular sieve to the reaction flask (entry 2, Table 3). We conclude that the water that is bound to TsOH is necessary for the reaction to proceed.

The effect of various substituents on the catalyst aromatic ring was studied to enhance activity and selectivity. The results are summarized in Table 4. Replacement of the methyl group

Table 4. Optimization of Electronic Properties of the Catalyst for the Model Reaction



entry	R_1	R_2	catalyst	yield [%][a]	ee [%][b]
1	Me	H	***ent*-11b**	72	44 (*R*)
2	CF_3	H	**11d**	15	<1
3	OMe	H	**11e**	71	22 (*R*)
4	Me	OMe	**11f**	54	28 (*R*)
5	Me	Cl	**11g**	80	48 (*R*)
6	Me	F	**11h**	80	45 (*R*)

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC.

ortho to the iodine by a strong electron-withdrawing inductive group (CF_3), resulted in an almost inactive catalyst (entry 2, Table 4). Accordingly, replacement of the methyl with an electron-donating group (MeO) resulted in a catalyst with similar activity but decreased selectivity. A 4-methoxy-6-methyl variant was evaluated to assess whether the detrimental effect of the methoxy group is of mostly electronic nature or whether it interferes sterically with the approach of the nucleophile. Both activity and selectivity decreased noticeably (entry 4, Table 4). Consequently, electron-withdrawing inductive groups para to the iodine were introduced (entries 5 and 6, Table 4), and a chloro substitution was found to yield the optimal catalyst (**11g**).

We explored the reaction scope with catalyst **11g** and treated a variety of ketones under the described conditions (Table 5). Variation of the alkyl chain of propiophenone does not result in significant differences in terms of yields or enantioselectivities (entries 1−3, Table 5). Use of a cyclic ketone such as indanone gave a decrease in selectivity (entry 4, Table 5). Surprisingly, tetralone is unreactive under the reaction conditions (entry 5, Table 5). The method tolerates well electron-withdrawing groups on the aryl ring of propiophenone (entries 8−11, Table 5), but electron-donating groups result in a drastic decrease in reactivity (entries 6 and 7, Table 5), with the *p*-methoxy derivative being almost unreactive (entry 6, table 5). Introduction of ortho substitution on the aryl ring of propiophenone also has a detrimental effect on yield and selectivity (entry 12, Table 5). Finally, aliphatic ketones were tested and found to be unreactive under the reaction conditions (entries 13−15, Table 5). Rate-limiting enolization could explain the differences in terms of reactivity.

In order to further reduce the environmental impact of the method, we last explored the nature of the sulfonic acid used as well as the effect of the stoichiometry of the acid and co-oxidant. Toluenesulfonic acid can readily be replaced by methanesulfonic acid[19] with a decrease in enantioselectivity, but with no cost on yield (Scheme 9). Reduction of the number of equivalents of *m*-CPBA and TsOH is also readily possible, at the cost of longer reaction times (Table 6). Hence, by lowering the stoichiometry of *m*-CPBA and TsOH to 1.5 equiv, it is

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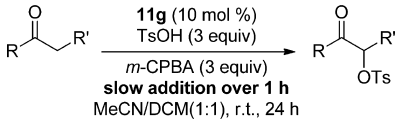
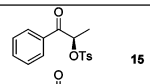
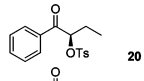
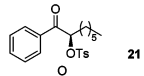
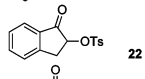
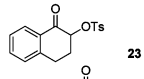
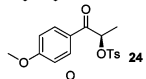
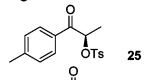
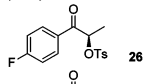
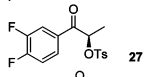
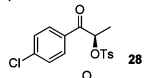
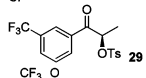
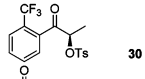
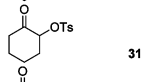
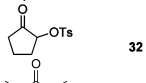
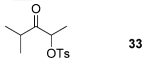
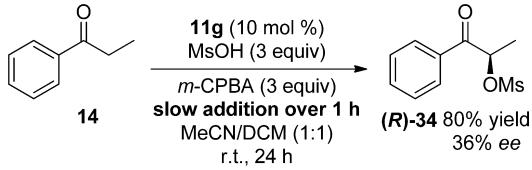
Table 5. Study of Reaction Scope of the α-Tosyloxylation of Ketones



Entry	Product	Yield [%][a]	ee [%][b]
1	 15	80	48 (*R*)
2	 20	70	48 (*R*)
3	 21	73	49 (*R*)
4	 22	60	33
5	 23	<5	-
6	 24	5	-
7	 25	48	45 (*R*)
8	 26	77	46 (*R*)
9	 27	67	40 (*R*)
10	 28	83	41 (*R*)
11	 29	65	47 (*R*)
12	 30	53	20 (*R*)
13	 31	<5	-
14	 32	<5	-
15	 33	<5	-

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC.

Scheme 9. α-Mesyloxylation of 14 Using Catalyst 11g

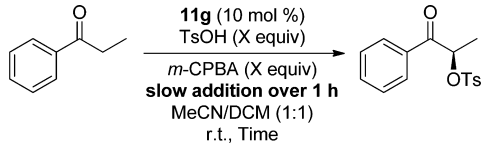


possible to achieve very similar yields and enantioselectivities over 48 h reaction time (entry 5, Table 6).

CONCLUSION

The iodine(III)-mediated catalytic enantioselective α-tosyloxylation of ketone compounds remains a highly valuable yet challenging reaction to master. With this family of iodoaryloxazoline-based catalysts, we were able to further improve on previously achieved enantioselectivities, while maintaining useful activity. We further report an unprecedented mode of stereoinduction from chiral oxazolines that provides a better understanding of the reaction mechanism. Further work toward the development of novel chiral catalysts based on this scaffold is under way as well as deeper mechanistic studies to better understand the process.

Table 6. Effet of *m*-CPBA and TsOH Equivalents



entry	X [equiv]	time [h]	yield [%][a]	ee [%][b]
1	3.0	48	79	48
2	3.0	24	80	48
3	3.0	12	69	45
4	3.0	6	61	45
5	1.5	48	74	46
6	1.5	24	62	46
7	1.5	12	41	43

[a]Isolated yields after flash chromatography. [b]Determined ia chiral HPLC.

COMPUTATIONAL DETAILS

All calculations were performed with the Gaussian 09 package.[20] All structures reported were fully optimized including PCM equilibrium solvation model for acetonitrile and BONDI cavity model,[21] with the MPW1K hybrid density functional[22] in combination with the 6-31+G(d,p) basis set for all atoms except iodine and LANL2DZdp + LANL2DZ ECP for iodine.[23] Unless otherwise stated, a fine grid density was used for numerical integration in the calculations. Harmonic vibrational frequencies were computed for all optimized structures to verify that they were minima, possessing zero imaginary frequencies. Energies reported incorporate unscaled energy corrections based on the vibrational analyses and temperature of 298 K.

EXPERIMENT SECTION

General Remarks. All nonaqueous 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.[24] 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) or over calcium hydride (CH_2Cl_2, Et_3N, $ClCH_2CH_2Cl$). 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 standard technique.[25] 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, HMQC) were recorded either on a 300 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

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DEPT experiments. High resolution mass spectra were obtgained using either a ZAB (EI) or UPLC-Q-TOF (ESI) mass spectrometer. 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)).

(*S*)-2-(8-Iodonaphthalen-1-yl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (4). General amide formation procedure 1: To a solution of 8-iodo-1-naphthoic acid[26] (5.00 g, 16.8 mmol) in 125 mL of $SOCl_2$ was added 25 drops of DMF. The reaction mixture was stirred for 3 h at 80 °C. The excess of thionyl chloride was removed under reduced pressure using coldfinger trap. To a solution of (*S*)-3-amino-2,4-dimethylpentan-2-ol[27] (2.0 g, 15.2 mmol) and triethylamine (6.39 mL, 45.51 mmol) in 43.0 mL of 1,4-dioxane was added dropwise a solution of the crude naphthoyl chloride (4.79 g, 15.2 mmol) in 43.0 mL of 1,4-dioxane was at 0 °C.[28] The reaction mixture was stirred 18 h at room temperature. The solution was diluted in DCM and water, and the layers were separated. The aqueous layer was back-extracted with DCM. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide 5.76 g (92%) of (*S*)-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)-8-iodo-1-naphthamide. General cyclization procedure (a): To a solution of this amide (96 mg, 0.233 mmol) in DCM (2.6 mL) was added MsOH (94 μL, 1.38 mmol) at 0 °C, and the reaction mixture was stirred for 18 h at 40 °C. The solution was diluted in DCM and $NaHCO_3$ (aq), and the layers were separated. The aqueous layer was back-extracted with DCM. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 56 mg (62%) of **4** as a beige solid; T_{fus} 126−128 °C; R_f 0.35 (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (dd, J = 7.4, 1.1 Hz, 1H), 7.86 (t, J = 7.6 Hz, 2H), 7.71 (dd, J = 7.1, 1.4 Hz, 1H), 7.47 (dd, J = 8.0, 7.3 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 3.60 (d, J = 10.4 Hz, 1H), 2.10−1.95 (m, 1H), 1.73 (s, 3H), 1.42 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 141.8, 135.3, 131.5, 130.7, 129.6, 126.9, 125.1, 91.9, 87.7, 81.9, 28.4, 22.1, 21.9, 20.8 ppm; IR (neat) 3770, 3706, 3051, 2970, 2872, 2827, 1659, 1467, 1370, 1285, 1195, 1117, 1026, 990, 916 cm^{-1}; HRMS EI (m/z): $[M]^+$ calcd for $C_{18}H_{20}INO$ 393.0590, found 393.0574. $[\alpha]^{25}_D$ +0.65 (c 1.23, $CHCl_3$).

(*S*)-4-Benzyl-2-(8-iodonaphthalen-1-yl)-5,5-dimethyl-4,5-dihydrooxazole (5). To a solution of 8-iodo-1-naphthoic acid[26] (5.00 g, 16.78 mmol) in 125 mL of thionyl chloride was added 25 drops of DMF. The reaction mixture was stirred at 80 °C for 3 h. The excess of thionyl chloride was removed under reduced pressure using a coldfinger trap. To a solution of (*S*)-3-amino-2-methyl-4-phenylbutan-2-ol[27] (283 mg, 1.58 mmol) and triethylamine (0.67 mL, 4.75 mmol) in 5.0 mL of 1,4-dioxane was added dropwise a solution of the crude naphthoyl chloride (500 mg, 1.58 mmol) in 5.0 mL of 1,4-dioxane at 0 °C.[28] The reaction mixture was stirred for 18 h at room temperature. The solution was diluted in DCM and water, and the layers were separated. The aqueous layer was back-extracted with DCM. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide 607 mg (84%) of (*S*)-*N*-(3-hydroxy-3-methyl-1-phenylbutan-2-yl)-8-iodo-1-naphthamide. General cyclization procedure (b): To a solution of this amide (549 mg, 1.20 mmol) in 1,2-DCE (14.2 mL) was added MsOH (490 μL, 7.17 mmol) at 0 °C. The reaction mixture was stirred for 18 h at 85 °C. The solution was diluted in DCM and $NaHCO_3$ (aq), and the layers were separated. The aqueous layer was back-extracted with DCM two times. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 350 mg (66%) of **5** as a yellow oil; R_f 0.25 (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (dd, J = 7.4, 1.1 Hz, 1H), 7.87 (ddd, J = 7.7, 6.6, 1.1 Hz, 2H), 7.75 (dd, J = 7.1, 1.4 Hz, 1H), 7.49 (dd, J = 8.0, 7.3 Hz, 1H), 7.41−7.28 (m, 5H), 7.15 (t, J = 7.7 Hz, 1H), 4.41 (t, J = 7.7 Hz, 1H), 3.37 (dd, J = 14.3, 7.4 Hz, 1H), 2.92 (dd, J = 14.3, 8.0 Hz, 1H), 1.49 (s, 3H), 1.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 142.1, 139.3, 135.6, 132.2, 131.9, 131.0, 129.8, 129.3, 128.7, 127.2, 126.5, 125.4, 92.3, 87.8, 76.1, 36.5, 22.6 ppm; IR (neat) 3060, 3027, 2969, 2917, 2850, 1659, 1496, 1444, 1372, 1291, 1195, 1128, 1076, 990 cm^{-1}; HRMS EI (m/z): $[M]^+$ calcd for $C_{22}H_{20}INO$ 441.0590, found 441.0594. $[\alpha]^{25}_D$ +3.72 (c 0.43, $CHCl_3$).

(*S*)-4-*tert*-Butyl-2-(8-iodonaphthalen-1-yl)-4,5-dihydrooxazole (6). To a solution of 8-iodo-1-naphthoic acid[26] (1.00 g, 3.36 mmol) in 25.0 mL of $SOCl_2$ was added 5 drops of DMF. The reaction mixture was stirred for 2 h at 80 °C. The excess of thionyl chloride was removed under reduced pressure using a coldfinger trap. To a solution of (*S*)-*tert*-leucinol (500 mg, 4.24 mmol) and triethylamine (1.18 mL, 8.48 mmol) in 15.0 mL of DCM was added dropwise a solution of the crude naphthoyl chloride (1.33 g, 4.24 mmol) in 15.0 mL of DCM at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The solution was diluted in DCM and HCl 1 N, and the layers were separated. The aqueous layer was back-extracted twice with DCM. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide 1.52 g (90%) of (*S*)-*N*-(2-hydroxy-2,4,4-trimethylpentan-3-yl)-8-iodo-1-naphthamide. General cyclization procedure (d): To thionyl chloride (23.1 mL, 317 mmol) was added a solution of this amide (1.08 g, 2.73 mmol) in DCM (25.0 mL) at −10 °C. The reaction mixture was stirred for 2.5 h at room temperature. The thionyl chloride excess was removed under reduced pressure using a coldfinger trap. The reaction mixture was diluted in DCM and NaOH 1 N, and the layers were separated. The aqueous layer was back-extracted with DCM. The combined organic extracts were washed with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 638 mg (62%) of **6** as a brown solid; T_{fus} 88−90 °C; R_f 0.39 (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 7.3 Hz, 1H), 7.82−7.70 (m,3H), 7.39 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 4.52 (dd, J = 10.1, 8.9 Hz, 1H), 4.28 (t, J = 8.5 Hz, 1H), 4.12 (dd, J = 10.1, 8.8 Hz, 1H), 1.02 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 141.7, 135.1, 132.0, 131.3, 130.9, 129.7, 129.2, 129.0, 128.0, 126.0, 125.1, 92.0, 76.6, 34.2, 26.4 ppm; IR (neat) 3060, 2959, 2902, 2869, 1726, 1662, 1477, 1346, 1257, 1184, 1138, 1003, 953, 911 cm^{-1}; HRMS EI (m/z): $[M]^+$ calcd for $C_{17}H_{18}INO$ 379.0433, found 379.0421. $[\alpha]^{25}_D$ +83.3 (c 1.39, $CHCl_3$).

(*S*)-2-(2-Iodophenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (7a). General amide formation procedure 1 was followed: 2-iodobenzoic acid (202 mg, 0.814 mmol), $SOCl_2$ (5.0 mL, 68.5 mmol), (*S*)-3-amino-2,4-dimethylpentan-2-ol[27] (107 mg, 0.811 mmol), triethylamine (0.34 mL, 2.43 mmol); 277 mg (95%) of (*S*)-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)-2-iodobenzamide. General cyclization procedure (a) was followed: To a solution of the amide was added MsOH (0.31 mL, 4.56 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 160 mg (61%) of **7a** as a yellow oil; R_f 0.74 (EtOAc/hexanes, 30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 8.1, 0.8 Hz, 1H), 7.60 (dd, J = 7.7, 1.8 Hz, 1H), 7.35 (dt, J = 7.6, 1.1 Hz, 1H), 7.07 (dt, J = 7.7, 1.7 Hz, 1H), 3.52 (d, J = 8.2 Hz, 1H), 2.00−1.87 (m, 1H), 1.56 (s, 3H), 1.45 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.05 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 140.4, 134.1, 131.3, 130.6, 127.7, 94.6, 87.4, 80.8, 29.4, 29.1, 21.5, 21.2, 20.6 ppm; IR (neat) 3068, 2969, 2867, 1658, 1641, 1584, 1467, 1426, 1376, 1331, 1246, 1081, 1037, 1016, 914 cm^{-1}; HRMS EI (m/z): $[M]^+$ calcd for $C_{14}H_{18}INO$ 343.0433, found 343.0444. $[\alpha]^{25}_D$ −39.8 (c 1.26, $CHCl_3$).

(*S*)-2-(2-Iodo-3-methylphenyl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (7b). General amide formation procedure 1 was followed: 2-iodo-3-methylbenzoic acid (204 mg, 0.778 mmol), $SOCl_2$ (5.0 mL, 68.5 mmol), (*S*)-3-amino-2,4-dimethylpentan-2-ol[27] (103 mg, 0.780 mmol), triethylamine (0.32 mL, 2.28 mmol); 285 mg (100%) of (*S*)-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)-2-iodo-3-methylbenzamide. General cyclization procedure (a) was followed: To a solution of this amide was added MsOH (0.31 mL, 4.56 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 131 mg (48%) of **7b** as a

beige solid; T_{fus} 74−78 °C; R_f 0.62 (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.19 (m, 3H), 3.50 (d, J = 8.2 Hz, 1H), 2.46 (s, 3H), 1.93 (dq, J = 13.2, 6.6 Hz, 1H), 1.55 (s, 3H), 1.45 (s, 3H), 1.16 (d, J = 6.5 Hz, 2H), 1.03 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 142.8, 136.1, 130.8, 127.7(2), 101.8, 87.4, 80.9, 29.5, 29.1, 21.6, 21.3, 20.8 ppm; IR (neat) 3060, 2979, 2867, 1689, 1658, 1640, 1585, 1548, 1465, 1442, 1242, 1176, 1119, 1076, 1022, 910 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{15}H_{20}INO$ 357.0590, found 357.0594. $[\alpha]^{25}_D$ −1.13 (c 1.06, $CHCl_3$).

(*S*)-4-Benzyl-2-(2-iodophenyl)-5,5-dimethyl-4,5-dihydrooxazole (8). General amide formation procedure 1 was followed: 2-iodobenzoic acid (5.00 g, 20.2 mmol), $SOCl_2$ (100 mL, 1.37 mol), crude benzoic acyl (913 mg, 3.43 mmol), (*S*)-3-amino-2-methyl-4-phenylbutan-2-ol[27] (610 mg, 3.43 mmol), triethylamine (1.44 mL, 10.3 mmol); 1.40 g (100%) of (*S*)-*N*-(3-hydroxy-3-methyl-1-phenylbutan-2-yl)-2-iodobenzamide. General cyclization procedure (b) was followed: To a solution of this amide (1.32 g, 3.23 mmol) was added MsOH (1.31 mL, 19. mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 943 mg (75%) of **8** as a yellow oil; R_f 0.57 (EtOAc/hexanes, 30:70); ^{1}H NMR (300 MHz, $CDCl_3$) 7.91 (d, J = 7.1 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.40−7.18 (m, 6H), 7.09 (t, J = 7.7 Hz, 1H), 4.21 (dd, J = 8.3, 6.8 Hz, 1H), 3.10 (dd, J = 14.1, 8.3 Hz, 1H), 2.85 (dd, J = 14.1, 6.7 Hz, 1H), 1.45 (d, J = 2.3 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 140.3, 139.2, 1341, 131.5 130.7, 129.1, 128.4, 127.8, 126.2, 94.7, 87.3, 75.7, 37.5, 28.7, 22.1 ppm; IR ($CHCl_3$) 3084, 3065, 3027, 2969, 2926, 2864, 1946, 1659, 1635, 1583, 1492, 1468, 1434, 1367, 1329, 1291, 1248, 1166, 1080, 10032, 1009, 918 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{18}H_{18}INO$ 391.0433, found 391.0437. $[\alpha]^{25}_D$ −71.4 (c 1.18, $CHCl_3$).

1-Iodo-2-naphthoic acid. To a solution of (1-iodonaphthalen-2-yl)methanol[29] (500 mg, 1.76 mmol) in 18.0 mL of CH_3CN and 3.5 mL of water was added $KMnO_4$ (556 mg, 3.52 mmol). The reaction mixture was stirred for 18 h at room temperature. To the reaction mixture was added an aqueous solution of $NaHSO_3$, and the mixture was stirred for 15 min. The solution was diluted in EtOAc, and the layers were separeted. The aqueous layer was back-extracted three times with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was diluted in benzene. The solvent was removed under reduced pressure to provide 517 mg (98%) of the title compound as a yellow solid; T_{fus} 198−202 °C; R_f 0.15 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, CD_3OD) δ 8.30 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.65−7.50 (m, 3H) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 134.8, 134.4, 133.5, 129.0, 128.5, 128.4, 127.8, 125.0, 98.4 ppm; IR (KBr) 3041, 2686, 2362, 2005, 1965, 1925, 1682, 1456, 1402, 1269, 956, 760 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{11}H_7IO_2$ 297.9491, found 297.9493.

(*S*)-2-(1-Iodonaphthalen-2-yl)-4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole (9). General amide formation procedure 2: To a solution of 1-iodo-2-naphthoic acid[14] (50 mg, 0.167 mmol) and triethylamine (26 μL, 0.185 mmol) in 1.0 mL of DCM was added a solution of TFAA (23 μL, 0.167 mmol) in 0.7 mL of DCM at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. To this solution at 0 °C was added pyridine (14 μL, 0.167 mmol), and the reaction mixture was stirred for 40 min. To this solution was added a solution of triethylamine (26 μL, 0.185 mmol) and (*S*)-3-amino-2,4-dimethylpentan-2-ol[27] (24 mg, 0.185 mmol) in 0.5 mL of DCM at 0 °C. The reaction mixture was stirred for 18 h at room temperature. The reaction mixture was diluted in DCM and washed with 10% citric acid (aq). The organic layer was washed with brine and saturated $NaHCO_3$ (aq). The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to provide 36 mg (52%) of (*S*)-*N*-(2-hydroxy-2,4-dimethylpentan-3-yl)-1-iodo-2-naphthamide. General cyclization procedure (a) was followed: To a solution of the amide (36 mg, 0.088 mmol) in DCM (0.8 mL) was added MsOH (34 μL, 0.528 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (5:95 to 30:70) to provide 24 mg (69%) of **9** as a yellow oil; R_f 0.51 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.61−7.50 (m, 3H), 3.60 (d, J = 8.2 Hz, 1H), 2.06−1.94 (m, 1H), 1.63 (s, 3H), 1.51 (s, 3H), 1.22 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 134.8, 134.5, 134.1, 133.6, 128.8, 128.3, 128.2, 127.5, 126.6, 101.8, 87.7, 81.0, 29.5, 29.1, 21.6, 21.3, 20.8 ppm; IR (neat) 3065, 2969, 2931, 2874, 1668, 1463, 1367, 1329, 1243, 1085, 1023, 961, 927 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{18}H_{20}INO$ 393.0590, found 393.0593. $[\alpha]^{25}_D$ −12.9 (c 0.55, $CHCl_3$).

(3a*S*,8a*R*)-2-(2-Iodophenyl)-8,8a-dihydro-3a*H*-indeno[1,2-d]-oxazole (10a). General amide formation procedure 1 was followed: 2-iodobenzoic acid (5.00 g, 20.2 mmol), $SOCl_2$ (100 mL, 1.37 mol), crude benzoic acyl (806 mg, 3.03 mmol), (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (454 mg, 3.03 mmol), triethylamine (1.27 mL, 9.08 mmol); 1.15 g (100%) of *N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-2-iodobenzamide. General cyclization procedure (b) was followed: To a solution of this amide (926 mg, 2.44 mmol) was added MsOH (0.99 mL, 14.7 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (30:70) to provide 267 mg (35% bsmr) of **10a** as a brown oil; R_f 0.57 (EtOAc/hexanes, 30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.7 Hz, 2H), 7.36−7.27 (m, 4H), 7.07 (t, J = 7.7 Hz, 1H), 5.79 (d, J = 7.9 Hz, 1H), 5.53 (ddd, J = 8.2, 5.6, 2.9 Hz, 1H), 3.57−3.41 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 140.3, 139.7, 133.5, 131.5, 130.8, 128.5, 127.7, 127.4, 125.7, 125.2, 94.6, 83.7, 77.1, 39.6 ppm; IR ($CHCl_3$) 3060, 3031, 2960, 2922, 2835, 1951, 1721, 1659, 1640, 1625, 1578, 1477, 1463, 1425, 1348, 1291, 1229, 1171, 1090, 1018, 980, 851 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{16}H_{12}INO$, 360.9963, found 360.9969. $[\alpha]^{25}_D$ −135.5 (c 1.42, $CHCl_3$).

(3a*S*,8a*R*)-2-(2-Iodo-3-methylphenyl)-8,8a-dihydro-3a*H*-indeno[1,2-*d*]oxazole (10b). To a solution of 2-iodo-3-methylbenzoic acid (500 mg, 1.91 mmol) in 19.0 mL of benzene and a drop of DMF was added $SOCl_2$ (2.12 mL, 29.1 mmol) at 0 °C.[30] After the mixture was refluxed for 3 h, excess $SOCl_2$ was removed under reduced pressure using a coldfinger trap, which gave 535 mg (100%) of the acyl chloride. To a solution of (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (285 mg, 1.91 mmol) and triethylamine (0.80 mL, 5.72 mmol) in 4.8 mL of 1,4-dioxane was slowly added a solution of the crude benzoic acyle (535 mg, 1.91 mmol) in 4.8 mL of 1,4-dioxane at 0 °C.[28] The mixture was stirred for 18 h at room temperature. The solvent was removed under reduced pressure, the reaction mixture was diluted in DCM and water, and the layers were separated. The aqueous layer was back-extracted three times with DCM. The combined organic extracts were washed three times with water and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide 751 mg (100%) of the crude amide. To a solution of the amide (513 mg, 1.31 mmol) in 13.0 mL of 1,2-DCE was added MsOH (0.53 mL, 7.83 mmol) at 0 °C. The solution was stirred for 7 h at 85 °C. The reaction mixture was diluted in DCM and $NaHCO_3$ (aq), and the layers were separated. The aqueous layer was back-extracted three times with DCM. The combined organic extracts were washed three times with water and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with hexane/EtOAc (80:20 to 50:50) to provide 286 mg (58%) of **10b** as a beige solid; T_{fus} 104−106 °C; R_f 0.25 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.53 (m, 1H), 7.30−7.20 (m, 6H), 5,78 (d, J = 7.9 Hz, 1H), 5.56−5.51 (m, 1H), 3.51−3.48 (m, 2H), 2.45 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 142.8, 141.6, 139.8, 135.3, 131.0, 128.4, 127.7, 127.6, 127.3, 125.6, 125.1, 101.7, 83.8, 77.2, 39.5, 29.3 ppm; IR (neat) 3063, 3039, 2972, 1657, 1569, 1457, 1351, 1298, 1233, 1168, 1121, 1079, 1003, 849, 787 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{17}H_{14}INO$ 375.0120, found 375.0121. $[\alpha]^{25}_D$ −147.9 (c 1.16, $CHCl_3$).

(4*R*,5*R*)-2-(2-Iodophenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11a).[15] To a suspension of 2-iodobenzoic acid (195 mg, 0.79 mmol) in benzene (7.9 mL) was added $SOCl_2$ (0.88 mL, 12.0 mmol) and a drop of DMF at 0 °C. After the mixture was refluxed for 3 h, and excess $SOCl_2$ was removed under reduced pressure, affording the crude acyl chloride product. A solution of the crude acyl chloride (210 mg, 0.79 mmol) in DCM (0.7 mL) was slowly added to a solution of

(1*S*,2*R*)-(+)-norephedrine (119 mg, 0.79 mmol) and triethylamine (0.11 mL, 0.79 mmol) in DCM (0.7 mL) at 0 °C. The mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, the reaction mixture was diluted in DCM and water, and the layers were separated. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to provide 221 mg (74%) of *N*-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodobenzamide. General cyclization procedure (c): To a solution of this amide (221 mg, 0.58 mmol) in THF (3.9 mL) was added triphenylphosphine (189 mg, 0.72 mmol) followed by DIAD (0.14 mL, 0.72 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with hexanes/EtOAc (80:20) to provide 90 mg (43%) of **11a** as a white solid; T_{fus} 65−67 °C, R_f 0.38 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.0, 1.1 Hz, 1H), 7.71 (dd, J = 7.7, 1.7 Hz, 1H), 7.45−7.34 (m, 6H), 7.12 (dt, J = 7.7, 1.7 Hz, 1H), 5.14 (d, J = 8.1 Hz, 1H), 4.27 (dq, J = 8.1, 6.7 Hz, 1H), 1.53 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 140.4, 139.9, 133.5, 131.6, 130.6, 128.7, 128.3, 127.8, 125.8, 94.8, 88.61, 71.1, 21.3 ppm; IR (neat) 3057, 3028, 2963, 2921, 1658, 1581, 1463, 1316, 1292, 1233, 1109, 1079, 1009, 967, 755, 725, 696 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{16}H_{14}INO$ 363.0120, found 363.0114. $[\alpha]_D$ = −33.7° (c 1.32, $CHCl_3$).

(4*R*,5*R*)-2-(2-Iodo-3-methylphenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11b).[15] General amide formation procedure 1 was followed: 2-iodo-3-methylbenzoic acid (1.00 g, 3.82 mmol), $SOCl_2$ (4.2 mL, 58.2 mmol), (1*S*,2*R*)-(+)-norephedrine (578 mg, 3.82 mmol), triethylamine (0.54 mL, 3.82 mmol); 1.51 g (100%) of *N*-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-3-methylbenzamide. General cyclization procedure (c) was followed: To a solution of this amide (1.51 g, 3.82 mmol) were added triphenylphosphine (1.25 g, 4.78 mmol) and DIAD (0.94 mL, 4.78 mmol). Isolated 848 mg (59%) of **11b** as a white solid; T_{fus} 70−72 °C; R_f 0.68 (EtOAc/hexanes, 40:60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.26 (m, 8H), 5.16 (d, J = 8.3 Hz, 1H), 4.27 (dq, J = 8.3, 6.6 Hz, 1H), 2.51 (s, 3H), 1.55 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 142.9, 139.9, 135.4, 131.1, 128.7, 128.3, 127.8, 127.6, 125.9, 101.9, 88.7, 71.1, 29.5, 21.1 ppm; IR (neat) 3057, 3028, 2968, 2921, 1666, 1446, 1316, 1127, 1079, 1009, 967, 790, 749, 698 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{17}H_{16}INO$ 377.0277, found 377.0278. $[\alpha]^{25}_D$ −23.2 (c 1.10, $CHCl_3$).

(4*R*,5*R*)-2-(3-Ethyl-2-iodophenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11c). A solution of 3-ethylanthranilic acid (1.02 g, 6.16 mmol) and H_2SO_4 (2.00 mL, 38.2 mmol) in water (13.5 mL) was heated until the acid was completely dissolved. After cooling to 10 °C, a solution of $NaNO_2$ (425 mg, 6.16 mmol) in water (0.95 mL) was added. The resulting mixture was added to a solution of KI (3.07 g, 18.5 mmol) in water (14.5 mL), and the mixture was heated to 100 °C for 20 min. After cooling to room temperature, the mixture was cooled to −20 °C for 2 h. The resulting precipitate was collected and air-dried, and the solid was dissolved in Na_2CO_3 (aq). The solution was filtrated, reacidified with HCl conc, and cooled to −20 °C for 1 h. The resulting precipitate was collected and dried to provide 1.26 g (74%) of 2-iodo-3-ethylbenzoic acid. General amide formation procedure 1 was followed: 2-iodo-3-ethylbenzoic acid (205 mg, 0.743 mmol), $SOCl_2$ (0.83 mL, 11.3 mmol); 2-iodo-3-methylbenzoyl chloride (218 mg, 0.743 mmol), (1*S*,2*R*)-(−)-norephedrine (112 mg, 0.741 mmol), triethylamine (0.10 mL, 0.736 mmol); 291 mg (96%) of 3-ethyl-*N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodobenzamide as a yellow oil. General cyclization procedure (c) was followed: To a solution of this amide (291 mg, 0.711 mmol) was added triphenylphosphine (233 mg, 0.888 mmol) followed by DIAD (0.18 mL, 0.890 mmol). The crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (5:95 to 50:50) to provide 116 mg (42%) of **11c** as a colorless oil; R_f 0.34 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.24 (m, 8H), 5.16 (d, J = 8.3 Hz, 1H), 4.27 (dq, J = 8.2, 6.6. Hz, 1H), 2.84 (q, J = 7.5 Hz, 2H), 1.55 (d, J = 6.6 Hz, 3H), 1.22 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 147.9, 139.9, 135.8, 129.9, 128.7, 128.3, 128.1, 127.7, 125.9, 101.1, 88.8, 71.1, 35.0, 21.1, 14.6 ppm; IR (neat) 3062, 3032, 2967, 2928, 2870, 1667, 1573, 1495, 1455, 1414, 1372, 1331, 1319, 1301, 1173, 1130, 1086, 1010, 976, 903, 799, 756, 726, 699 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{18}H_{18}INO$ 391.0433, found 391.0441. $[\alpha]^{25}_D$ −21.2 (c 0.49, $CHCl_3$).

(5*S*,6*S*,9*R*)-2-(2-Iodo-3-methylphenyl)-6-isopropyl-9-methyl-3-oxa-1-azaspiro[4.5]dec-1-ene (12). General amide formation procedure 1 was followed: 2-iodo-3-methylbenzoic acid (283 mg, 1.08 mmol), $SOCl_2$ (1.20 mL, 16.5 mmol), ((1*S*,2*S*,5*R*)-1-amino-2-isopropyl-5-methylcyclohexyl)methanol[31] (200 mg, 1.08 mmol), triethylamine (0.46 mL, 3.24 mmol); 438 mg (94%) of *N*-((1*S*,2*S*,5*R*)-1-(hydroxymethyl)-2-isopropyl-5-methylcyclohexyl)-2-iodo-3-methylbenzamide. General cyclization procedure (b) was followed: To a solution of this amide (329 mg, 0.77 mmol) was added MsOH (0.31 mL, 4.60 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (20:80) to provide 227 mg (72%) of **12** as a white solid; T_{fus} 72−74 °C, R_f 0.83 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 3H), 4.37 (d, J = 8.3 Hz, 1H), 3.94 (d, J = 8.3 Hz, 1H), 2.47 (s, 3H), 2.10−1.97 (m, 2H), 1.93 (ddd, J = 13.0, 3.5, 2.3 Hz, 1H), 1.87−1.80 (m, 1H), 1.71 (ddd, J = 25.8, 13.0, 3.5 Hz, 1H), 1.58 (dq, J = 13.3, 3.5 Hz, 1H), 1.23 (ddd, J = 12.4, 3.7, 1.0 Hz, 1H), 1.15 (dd, J = 22.1, 9.5 Hz, 1H), 1.01−088 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 142.7, 136.4, 130.7, 127.8, 127.2, 102.0, 77.8, 75.4, 50.3, 49.7, 35.2, 29.3, 28.6, 26.3, 24.2, 22.5, 22.4, 18.6 ppm; IR (neat) 3051, 2950, 2906, 2866, 1658, 1575, 1451, 1357, 1316, 1286, 1127, 1079, 1009, 973, 932, 784, 719 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{19}H_{26}INO$ 411.1059, found 411.1061. $[\alpha]^{25}_D$ +16.2 (c 0.97, $CHCl_3$).

(4*S*,4′*S*)-2,2′-(2-Iodo-1,3-phenylene)bis(4-isopropyl-5,5-dimethyl-4,5-dihydrooxazole) (13). General amide formation procedure 2 was followed: 2-iodoisophthalic acid[32] (100 mg, 0.342 mmol), TFAA (96 μL, 0.684 mmol), DMAP instead of pyridine (92 mg, 0.754 mmol), triethylamine (106 μL, 0.754 mmol), (*S*)-3-amino-2,4-dimethylpentan-2-ol[27] (99 mg, 0.752 mmol). Isolated 102 mg, 0.197 mmol (58%) of the amide as a beige solid. General cyclization procedure (b) was followed: To a solution of this amide was added MsOH (77 μL, 1.18 mmol). Isolated 73 mg (77%) of **13** a yellow oil; R_f 0.15 (EtOAc/hexanes, 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 7.7 Hz, 2H), 7.35 (dd, J = 8.0, 7.2 Hz, 1H), 3.51 (d, J = 8.1 Hz, 2H), 2.00−1.88 (m, 2H), 1.55 (s, 6H), 1.45 (s, 6H), 1.15 (d, J = 6.5 Hz, 6H), 1.03 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 136.9, 131.5, 127.6, 95.7, 87.6, 80.9, 29.5, 29.1, 21.6, 21.3, 20.7 ppm; IR (neat) 2968, 2927, 2868, 1658, 1575, 1457, 1369, 1286, 1239, 1192, 1115, 1068, 1021, 938, 837, 784, 719 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{22}H_{31}IN_2O_2$ 482.1430, found 482.1432. $[\alpha]^{25}_D$ = −47.1 (c 0.48, $CHCl_3$).

General Procedure for Catalyst Evaluation on Substrate 14 (Table 1). To a solution of the catalyst **11b** (0.024 mmol) in 1.3 mL of CH_3CN was added *p*-TsOH·H_2O (138 mg, 0.73 mmol) and *m*-CPBA 77% (162 mg, 0.72 mmol). To this solution was added propiophenone (34 mg, 0.25 mmol). The resulting solution was stirred at room temperature for 48 h and then quenched with $Na_2S_2O_3$ (aq). The aqueous layer was extracted with AcOEt (3×). The combined organic layers were washed twice with $NaHCO_3$ (aq) and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (5:95 to 20:80) to provide 46 mg (60%) of **15** as a white solid of the *S* enantiomer (33% ee), R_f 0.42, (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, CD_3CN) 7.86 (d, J = 7.0 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.78 (q, J = 7.0 Hz, 1H), 2.39 (s, 3H), 1.58 (d, J = 7.0 Hz, 3H) ppm. The ee was determined by HPLC on the purified product: Chiracel AS-H column, 50:50 hexanes/i-PrOH, 0.7 mL/min, rt, t_R = 10.1 min (*S*), t_R = 11.6 min (*R*).[3c]

2-Iodo-3-methylbenzaldehyde. The title compound was obtained following a literature procedure[33] using (2-iodo-3-methylphenyl)methanol (4.02 g, 16.2 mmol) and PCC (4.19 g, 19.5 mmol). The crude product was purified by flash chromatography with EtOAc/hexanes (10:90) to provide 3.6 g (90%) of the title compound as a white solid; T_{fus} 46−48 °C, R_f 0.87 (EtOAc/hexanes, 20:80); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.66 (dd, J = 7.6, 1.7 Hz, 1H), 7.47 (dd, J = 7.3, 1.1 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 2.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0, 143.2, 135.9, 135.3, 128.2, 127.6, 108.0, 28.5 ppm; IR (neat) 3065, 2979, 2855, 2731, 1690, 1673, 1570, 1447, 1371, 1236, 1016, 907, 779, 694 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for C_8H_7IO 245.9542, found 245.9547.

(*R*)-*tert*-Butyl (2-Cyclohexyl-2-hydroxyethyl)carbamate. The title compound was obtained following a literature procedure[34] using 2-cyclohexyloxirane[35] (516 mg, 4.09 mmol), (*S*,*S*)-(salen)Co^{II} complex (49.5 mg, 0.08 mmol), *p*-nitrobenzoic acid (26.7 mg, 0.16 mmol), and *tert*-butylcarbamate (218 mg, 1.86 mmol). The crude product was purified by column chromatography on silica gel with EtOAc/hexanes (30:70) to provide 318 mg (70%) of the title compound (>99% ee) as a dark orange oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89 (s, 1H), 3.46−3.30(m, 2H), 3.11−2.98 (m, 1H), 1.90−1.60 (m, 6H), 1.45 (s, 9H), 1.29−0.94 (m, 5H) ppm.

(*R*)-*tert*-Butyl (2-Hydroxy-2-phenylethyl)carbamate. Title compound was obtained following a literature procedure[34] using styrene oxide (2.1 mL, 18.2 mmol), (*S*, *S*)-(salen)Co^{II} complexe (200 mg, 0.331 mmol), *p*-nitrobenzoic acid (111 mg, 0.662 mmol), and *tert*-butylcarbamate (970 mg, 8.28 mmol). The crude product was purified by flash chromatography with toluene/Et_2O (30:70) to provide 541 mg (51%) of the title compound (>99% ee) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.23 (m, 5H), 5.02 (bs, 1H), 4.84−4.73 (m, 1H), 3.53−3.35 (m, 1H), 3.30−3.14 (m, 1H), 3.01 (bs, 1H), 1.44 (s, 9H) ppm.

(*R*)-2-(2-Iodo-3-methylphenyl)-5-phenyl-4,5-dihydrooxazole (16). To a suspension of (*R*)-*tert*-butyl (2-hydroxy-2-phenylethyl)-carbamate[14] (472 mg, 1.99 mmol) in dichloromethane (6.0 mL) was added TFA (4.0 mL, 51.7 mmol). The mixture was stirred at room temperature for 6 h, and the solvent was removed under reduced pressure to provide the corresponding amino alcohol as the TFA salt in quantitative yield. To a solution of amino alcohol TFA salt (30 mg, 0.122 mmol) in 1.1 mL of toluene was added an excess of K_2CO_3, and the mixture was stirred for 5 min. To the solution was added 180 mg of 4 Å MS and 2-iodo-3-methylbenzaldehyde (30 mg, 0.122 mmol). The reaction mixture was stirred for 16 h at room temperature. NBS (22 mg, 0.122 mmol) was then added, and the reaction was stirred 5 min with K_3PO_4 (78 mg, 0.366 mmol). The mixture was stirred for 5 h and filtered on Celite to remove the molecular sieve. The organic layer was washed with saturated solution of $NaHCO_3$ (aq) and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (5:95 to 40:60) to provide 10 mg (23%) of **16** as a colorless oil; R_f 0.53 (EtOAc/hexanes, 30:70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.25 (m, 8H), 5.70 (dd, J = 9.9, 9.2 Hz, 1H), 4.54 (dd, J = 14.7, 10.2 Hz, 1H), 4.05 (dd, J = 14.7, 8.8 Hz, 1H), 2.52 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 143.1, 140.3, 135.2, 131.2, 128.7, 128.3, 127.8, 127.7, 126.1, 101.9, 81.6, 63.3, 29.6 ppm; IR (neat) 3063, 3033, 2951, 2868, 1664, 1569, 1457, 1333, 1257, 1168, 1122, 1084, 1012, 938, 784, 759, 698 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{16}H_{14}INO$ 363.0120, found 363.0114. $[\alpha]^{25}_D$ −59.6 (c 1.10, $CHCl_3$).

(*R*)-5-Cyclohexyl-2-(2-iodo-3-methylphenyl)-4,5-dihydrooxazole (17). To a suspension of (*R*)-*tert*-butyl (2-cyclohexyl-2-hydroxyethyl)carbamate[14] (229 mg, 0.941 mmol) in 2.8 mL of DCM was added TFA (1.9 mL, 24.5 mmol). The mixture was stirred at room temperature for 3 h, and the solvent was removed under reduced pressure to provide the corresponding amino alcohol as the TFA salt in quantitative yield.[15] General amide formation procedure 1 was followed: 2-Iodo-3-methylbenzoic acid (267 mg, 1.02 mmol), $SOCl_2$ (1.13 mL, 15.6 mmol); the crude acyl chloride (286 mg, 1.02 mmol), amino alcohol TFA salt (262 mg, 1.02 mmol), triethylamine (0.29 mL, 2.04 mmol). The crude product was purified by flash chromatography with EtOAc/hexanes (30:70) to provide 112 mg (28%) of (*S*)-*N*-(2-cyclohexyl-2-hydroxyethyl)-2-iodo-3-methylbenzamide as a white solid. General cyclization procedure (c) was followed: To a solution of the amide (49 mg, 0.127 mmol) was added triphenylphosphine (42 mg, 0.160 mmol) followed by DIAD (32 μL, 0.158 mmol). The crude mixture was purified by column chromatography on silica gel with EtOAc/hexanes (15:85) to provide 11 mg (23%) of **17** as a colorless oil; R_f 0.71 (EtOAc/hexanes, 40:60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.22 (m, 3H), 4.46 (ddd, J = 9.7, 8.5, 7.1 Hz, 1H), 4.07 (dd, J = 14.5, 9.8 Hz, 1H), 3.79 (dd, J = 14.5, 8.5 Hz, 1H), 2.50 (s, 3H), 1.98 (d, J = 12.9 Hz, 1H), 1.83−1.60 (m, 5H), 1.35−1.00 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 142.9, 135.9, 131.0, 127.7, 127.6, 101.8, 84.8, 58.1, 42.3, 29.6, 28.7, 28.0, 26.4, 25.8, 25.6 ppm; IR (neat) 2927, 2852, 1729, 1662, 1574, 1463, 1449, 1405, 1340, 1263, 1238, 1175, 1125, 1088, 1012, 974, 927, 888, 839 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{16}H_{20}INO$ 369.0590, found 369.0587. $[\alpha]^{25}_D$ +8.53 (c 0.95, $CHCl_3$).

(4*R*,5*S*)-2-(2-Iodo-3-methylphenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (18). To a solution of (1*R*,2*S*)-(−)-norephedrine (122 mg, 0.807 mmol) in 4.8 mL of DCM was added 2-iodo-3-methylbenzaldehyde[14] (200 mg, 0.813 mmol). After the reaction mixture was stirred with 1.30 g of 4 Å MS for 16h at room temperature, NBS (144 mg, 0.809 mmol) was added. The reaction mixture was stirred for 45 min at room temperature. The solution was filtered on Celite and washed with $NaHCO_3$ (aq) and 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 EtOAc/hexanes/Et_3N (19:80:1) to provide 153 mg (50%) of **18** as a colorless oil; R_f 0.33 (EtOAc/hexanes, 30:70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.26 (m, 8H), 5.82 (d, J = 9.7 Hz, 1H), 4.67 (dq, J = 9.7, 7.0 Hz, 1H), 2.52 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 142.9, 136.5, 135.5, 131.1, 128.1, 127.7, 126.1, 101.8, 84.6, 65.7, 29.5, 17.5 ppm; IR (neat) 3063, 3032, 2974, 2928, 1664, 1574, 1495, 1450, 1402, 1376, 1342, 1316, 1301, 1248, 1170, 1125, 1091, 1012, 967, 907, 788, 731, 698 cm^{-1}; HRMS EI (m/z): [M]$^+$ calcd for $C_{17}H_{16}INO$ 377.0277, found 377.0271. $[\alpha]^{25}_D$ +157.9 (c 0.79, $CHCl_3$).

(4*R*,5*R*)-2-(2-Iodo-3-methylphenyl)-3,4-dimethyl-5-phenyl-4,5-dihydrooxazolium Tetrafluoroborate (19). The title compound was obtained as colorless oil (94% yield) according to the following procedure: **11b** (28 mg, 0.074 mmol) was dissolved in CH_3Cl (0.5 mL). MeI (31 mg, 0.215 mmol) was added then the reaction mixture was heated at 80 °C for 3 h. The solvent was removed under reduced pressure, and the resulting solid was washed with diethyl ether. The solid was dissolved in CH_2Cl_2 (1 mL), and $AgBF_4$ (14 mg, 0.074 mg) was added. The reaction mixture was stirred for 5 min, and the resulting precipitate was removed by filtration. The solvent was evaporated under reduced pressure to provide the salt **19** (94%) as a deliquescent solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 5.6 Hz, 1H), 7.67 (d, J = 3.7 Hz, 2H), 7.62−7.43 (m, 6H), 5.93 (s, 1H), 4.85 (s, 1H), 3.32 (s, 3H), 2.54 (s, 3H), 1.76 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 143.7, 134.6, 132.1, 131.4, 130.1, 129.8, 129.2, 128.4, 127.9, 99.1, 94.1, 66.6, 33.2, 28.6, 15.0 ppm; ^{19}F NMR (377 MHz, $CDCl_3$) δ −152.26 ppm; IR (neat) 1664, 1433, 1389, 1290, 1212, 1059, 917, 887, 799, 764, 700 cm^{-1}; HRMS ESI (m/z): calcd for $C_{18}H_{19}INO^+$ [M−BF_4]$^+$ 392.0506, found 392.0514; $[\alpha]^{25}_D$ +24.2° (c 0.9, $CHCl_3$).

(4*S*,5*S*)-2-(3-(Trifluoromethyl)-2-iodophenyl)-4,5-dihydro-4-methyl-5-phenyloxazole (11d). 2-Amino-3-trifluoromethylbenzoic acid (1 g, 4.87 mmol) was dissolved at 0 °C into concentrated HCl (3 mL). The solution was stirred at 0 °C for 15 min, and then ice (2 g) was added. After 10 min a solution of $NaNO_2$ (370 mg, 5.36 mmol) in water (2 mL) was added and stirred for 10 min. A solution of KI (3.56g, 21.4 mmol) in water (6 mL) was then added. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were washed with saturated $Na_2S_2O_3$ (aq) and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to provide 1.37g (93%) of 2-iodo-3-trifluoromethylbenzoic acid as a beige solid that was used without further purification. To a supsension of 2-iodo-3-trifluoromethylbenzoic acid (720.5 mg, 2.28 mmol) in benzene (22.6 mL) was added $SOCl_2$ (2.49 mL, 34.2 mmol) and a drop of DMF at 0 °C. The reaction mixture was refluxed for 3 h, and then the excess $SOCl_2$ was removed under reduced pressure, affording the crude acyl chloride product. A solution of the crude acyl chloride (762.6 mg, 2.28 mmol)

in DCM (4.4 mL) was slowly added to a solution of (1*R*,2*S*)-(−)-norephedrine (299.2 mg, 2.28 mmol) and triethylamine (0.32 mL, 2.28 mmol) in CH_2Cl_2 (4.4 mL) at 0 °C. The mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the reaction mixture was washed with a solution of citric acid (10% in water) and with saturated $Na_2S_2O_3$ and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to provide 1.02 g (100%) of 3-(trifluoromethyl)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodobenzamide. To a solution of this amide (1.02 g, 2.28 mmol) in THF (15 mL) was added triphenylphosphine (747.5 mg, 2.85 mmol), followed by DIAD (0.59 mL, 2.85 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with hexanes/EtOAc (80:20) and then toluene/acetonitrile to provide 393.3 mg (40%) of **11d** as a light yellow oil. R_f = 0.49 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.62 (m, 2H), 7.52 (t, J = 7.7 Hz, 1H), 7.47−7.30 (m, 5H), 5.20 (d, J = 8.4 Hz, 1H), 4.30 (dq, J = 8.3, 6.7 Hz, 1H), 1.56 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (s), 145.0 (s), 139.4 (s), 138.5 (s), 134.8 (s), 129.0 (d, J = 5.6 Hz), 128.9 (s), 128.6 (s), 128.1 (s), 125.9 (s), 122.7 (d, J = 274.6 Hz), 92.9 (s), 89.2 (s), 71.1 (s), 21.0 (s) ppm; IR (neat) 1669, 1418, 1298, 1195, 175, 1137, 1064, 971, 807, 699 cm^{-1}; HRMS ESI (m/z): calcd for $C_{17}H_{14}F_3INO^+$ $[MH]^+$ 432.0067, found 432.0074; $[\alpha]^{25}_D$ = +5.8° (c 0.5,$CHCl_3$).

(4*S*,5*S*)-2-(2-Iodo-3-methoxyphenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11e). A solution of 2-amino-3-methoxybenzoic acid (2.00 g, 12.0 mmol) and H_2SO_4 (4.0 mL, 74.2 mmol) in water (26.0 mL) was heated until the acid dissolved. After cooling to room temperature, a solution of $NaNO_2$ (825 mg, 12.0 mmol) in water (1.84 mL) was added at 10 °C. The resulting solution was added to a solution of KI (5.95 g, 36.0 mmol) in water (27.0 mL), and the mixture was heated at 140 °C over 45 min. After cooling to room temperature, the mixture was cooled to −20 °C for 2 h. The resulting precipitate was filtered, and the solid was dissolved in Na_2CO_3 (aq). The solution was filtered, reacidified with HCl conc to pH < 2 and cooled to −20 °C for 1 h. The resulting precipitate was collected, air-dried for 10 min, and dried under reduced pressure 1 h to provide 2.80 g (84%) of 2-iodo-3-methoxybenzoic acid as a beige solid which was used without further purification. General amide formation procedure 1 was followed: 2-Iodo-3-methoxybenzoic acid (1.00 g, 3.60 mmol), $SOCl_2$ (4.0 mL, 54.9 mmol), 2-iodo-3-methoxybenzoyl chloride (1.07 g, 3.60 mmol), (1*R*,2*S*)-(−)-norephedrine (544 mg, 3.60 mmol), triethylamine (0.51 mL, 3.60 mmol); 228 mg (81%) of *N*-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-3-methoxybenzamide as a beige solid. General cyclization procedure (c) was followed: To a solution of this amide (1.42 g, 3.45 mmol) was added triphenylphosphine (1.13 g, 4.31 mmol) followed by DIAD (0.85 mL, 4.31 mmol). The crude mixture was purified by column chromatography on silica gel first with EtOAc/hexanes (10:90 to 30:70) and then with CH_2Cl_2 to provide 744 mg (55%) of **11e** as a white solid; T_{fus} 44−46 °C; R_f 0.23 (EtOAc/hexanes, 20:80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.30 (m, 6H), 7.23 (dd, J = 7.6, 1.2 Hz, 1H), 6.89 (dd, J = 8.2, 1.2 Hz, 1H), 5.15 (d, J = 8.2 Hz, 1H), 4.27 (dq, J = 13.3, 6.7 Hz, 1H) 3.90 (s, 3H), 1.54 (d, J = 6.7 Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 158.5, 139.9, 136.2, 129.3, 128.7, 128.3, 125.9, 122.8, 112.3, 88.8, 88.0, 71.1, 56.7, 21.2 ppm; IR (neat) 3067, 3030, 2965, 2925, 2854, 1667, 1585, 1565, 1494, 1465, 1422, 1373, 1324, 1264, 1179, 1134, 1093, 1041, 972, 911 cm^{-1}; HRMS EI (m/z): calcd for $C_{17}H_{16}INO_2$ $[M]^+$ 393.0226, found 393.0232. $[\alpha]^{25}_D$ +23.5 (c 0.80, $CHCl_3$).

(4*S*,5*S*)-2-(2-Iodo-5-methoxy-3-methylphenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11f). To a solution of (2-iodo-5-methoxy-3-methylphenyl)methanol[36] (622 mg, 2.24 mmol) in 7.2 mL of acetone was added dropwise Jones reagent (0.72 mL, 1.95 mmol of CrO_3) at 0−5 °C. The reaction mixture was stirred for 20 min at 0 °C and stirred for 18 h at room temperature. The reaction mixture was diluted in EtOAc, and $NaHSO_3$ (aq) was added. The solution was poured into HCl 1 N and extracted with EtOAc tree times. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude mixture was dissolved in 7.7 mL of $MeCN/H_2O$ (25:1), and $NaH_2PO_4{\cdot}H_2O$ (31 mg, 0.224 mmol), 50% H_2O_2 (0.13 mL, 2.24 mmol), and a solution of 80% $NaClO_2$ (253 mg, 2.24 mmol) in 0.29 mL of water were added at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, a saturated solution of $NaHSO_3$ (aq) and a solution of HCl (1 N) were added. The organic layer was extracted tree times with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to yield 561 mg (86%) of the crude benzoic acid as a white solid, which was used without further purification. General amide formation procedure 1 was followed: The crude benzoic acid (200 mg, 0.685 mmol), $SOCl_2$ (0.76 mL, 10.4 mmol); the crude benzoic acyl chloride (212 mg, 0.685 mmol), (1*R*,2*S*)-(−)-norephedrine (104 mg, 0.685 mmol), triethylamine (96 μL, 0.685 mmol); 263 mg (90%) of *N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-5-methoxy-3-methylbenzamide as a yellow oil. General cyclization procedure (c) was followed: To a solution of this amide (263 mg, 0.618 mmol) was added triphenylphosphine (205 mg, 0.782 mmol) followed by DIAD (0.15 mL, 0.762 mmol). The crude mixture was purified by column chromatography on silica gel first with EtOAc/hexanes (5:95 to 50:50) then with acetone/toluene (0:100 to 10:90) to provide 133 mg (53%) of **11f** as a colorless oil; R_f 0.44 (EtOAc/hexanes, 40:60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.31 (m, 5H), 6.97 (d, J = 3.0 Hz, 1H), 6.91 (dd, J = 3.0, 0.5 Hz, 1H), 5.15 (d, J = 8.4 Hz, 1H), 4.25 (dq, J = 8.4, 6.6 Hz, 1H), 3.80 (s, 3H), 2.48 (s, 3H), 1.54 (d, J = 6.7 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 159.2, 144.0, 139.8, 135.9, 128.7, 128.3, 125.9, 117.8, 113.0, 90.6, 88.9, 71.1, 55.5, 29.5, 21.1 ppm; IR (neat) 3065, 3031, 2965, 2926, 2840, 1667, 1588, 1494, 1461, 1339, 1260, 1206, 1172, 1129, 1057, 1012, 964, 911, 851, 797, 757, 734, 698 cm^{-1}; HRMS EI (m/z): $[MH]^+$ calcd for $C_{18}H_{19}INO_2$ 408.0461, found 408.0464. $[\alpha]^{25}_D$ +25.4 (c 0.56, $CHCl_3$).

(4*S*,5*S*)-2-(5-Chloro-2-iodo-3-methylphenyl)-4-methyl-5-phenyl-4,5-dihydrooxazole (11g). A solution of 2-amino-5-chloro-3-methylbenzoic acid (590 mg, 2.69 mmol) and H_2SO_4 (0.89 mL, 16.7 mmol) in water (5.8 mL) was heated until the acid was completely dissolved. After, cooling to 10 °C, a solution of $NaNO_2$ (186 mg, 2.69 mmol) in water (0.41 mL) was added. The resulting solution was added to a solution of KI (1.34 g, 8.07 mmol) in water (6.2 mL), and the mixture was heated to 130 °C over 30 min. After cooling to room temperature, the mixture was cooled to −20 °C for 2 h. The resulting precipitate was collected and air-dried, and the solid was dissolved in Na_2CO_3 (aq). The solution was filtered, reacidified with HCl conc, and cooled to −20 °C for 1 h. The resulting precipitate was collected and dried to provide 471 mg (59%) of 5-chloro-2-iodo-3-methylbenzoic acid. General amide formation procedure 1 was followed: The crude benzoic acid (471 mg, 1.59 mmol), $SOCl_2$ (1.8 mL, 24.7 mmol); crude benzoic acyl chloride (501 mg, 1.59 mmol), (1*R*,2*S*)-(−)-norephedrine (240 mg, 1.59 mmol), triethylamine (0.22 mL, 1.59 mmol); 617 mg (90%) of 5-chloro-*N*-((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-3-methylbenzamide as a yellow oil. To a solution of this amide (600 mg, 1.40 mmol) was added triphenylphosphine (458 mg, 1.75 mmol) followed by DIAD (0.35 mL, 1.75 mmol). The crude mixture was purified by column chromatography on silica gel first with EtOAc/hexanes (5:95 to 50:50), second with acetone/toluene (5:95), and then with EtOAc/hexanes (5:95 to 15:85) to provide 249 mg (43%) of **11g** as a colorless oil; R_f 0.43 (EtOAc/hexanes, 20:80); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.29 (m, 7H), 5.15 (d, J = 8.4 Hz, 1H), 4.27 (dq, J = 8.4, 6.5 Hz, 1H), 2.49 (s, 3H), 1.53 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 144.7, 139.6, 136.6, 134.0, 130.9, 128.8, 128.4, 127.6, 125.9, 99.3, 89.0, 71.1, 29.3, 21.1 ppm; IR (neat) 3031, 2965, 2924, 1667, 1565, 1495, 1453, 1406, 1375, 1317, 1301, 1140, 1012, 974, 955, 885, 867, 773, 755, 698 cm^{-1}; HRMS EI (m/z): $[MH]^+$ calcd for $C_{17}H_{16}ClINO$ 411.9965, found 411.9989. $[\alpha]^{25}_D$ +23.6 (c 0.75, $CHCl_3$).

(4*S*,5*S*)-2-(5-Fluoro-2-iodo-3-methylphenyl)-4,5-dihydro-4-methyl-5-phenyloxazole (11h). 3-Fluoro-5-methylbenzoic acid (1g, 6.49 mmol) and KNO_3 (721 mg, 7.13 mmol) were dissolved in concentrated H_2SO_4 (8 mL) at 0 °C. The mixture was stirred at room temperature for 1 h. Water (15 mL) was added, and the resulting

precipitate was filtered and dried to provide 879.5 mg (68%) of 5-fluoro-3-methyl-2-nitrobenzoic acid, which was used without further purification. 5-Fluoro-3-methyl-2-nitrobenzoic acid (770 mg, 3.87 mmol) and $SnCl_2$ (4.36g, 19.33 mmol) were dissolved in ethanol (7.7 mL). The mixture was heated at 70 °C for 30 min. After cooling at room temperature, the pH was adjusted to 7−8 with saturated $NaHCO_3$ (aq). The mixture was extracted with EtOAc, and the organic layer was washed with brine, filtered through Celite, and dried over $MgSO_4$ to provide 2-amino-5-fluoro-3-methylbenzoic acid (629.2 mg, 3.71 mmol), which was used without further purification. 2-Amino-5-fluoro-3-methylbenzoic acid (465.5 mg, 2.75 mmol) was dissolved at 0 °C into concentrated HCl (1.5 mL). After 15 min under stirring, ice (1 g) was added at 0 °C. After 10 min a solution of $NaNO_2$ (208.9 mg, 3.03 mmol) in water (1 mL) was added. After 10 min a solution of KI (1.83g, 11.0 mmol) in water (3 mL) was added. The mixture was stirred at room temperature for 16 h. The reaction mixture was extracted with EtOAc, and the combined organic layers were washed with saturated $Na_2S_2O_3$ (aq) and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to provide 287 mg (37%) of 2-iodo-5-fluoro-3-methylbenzoic acid as a beige solid. General amide formation procedure 1 was followed: The crude benzoic acid (287 mg, 1.10 mmol); $SOCl_2$ (1.2 mL, 16.5 mmol); crude benzoic acyl chloride (303.4 mg, 1.02 mmol), (1*R*,2*S*)-(−)- norephedrine (133.8 mg, 1.02 mmol) and triethylamine (0.144 mL, 1.02 mmol); 422 mg (100%) of 5-fluoro-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-2-iodo-3-methylbenzamide. To a solution of this amide (421.5 g, 1.02 mmol) in THF (6.8 mL) was added triphenylphosphine (334.4 g, 1.28 mmol) followed by DIAD (0.279 mL, 1.28 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography on silica gel with hexanes/EtOAc (80:20) then toluene/acetonitrile to provide 192.6 mg (43%) of **11h** as a light yellow oil; R_f = 0.45 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.29 (m, 5H), 7.17 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.15 (d, *J* = 8.4 Hz, 1H), 4.27 (dq, *J* = 13.3, 6.7 Hz, 1H), 2.51 (s, 3H), 1.54 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (s), 162.1 (d, *J* = 248.1 Hz), 145.3 (d, *J* = 7.5 Hz), 139.6 (s), 136.6 (d, *J* = 8.4 Hz), 128.8 (s), 128.5 (s), 125.9 (s), 118.2 (d, *J* = 21.4 Hz), 115.1 (d, *J* = 23.8 Hz), 95.1 (s), 89.0 (s), 71.1 (s), 29.6 (s), 21.1 (s) ppm; IR (neat) 2963, 2924, 1667, 1587, 1456, 1337, 1175, 1119, 1016, 981, 867, 756, 698 cm^{-1}; HRMS ESI (*m*/*z*): calcd for $C_{17}H_{15}FINO$ $[MH]^+$ 396.0255, found 396.0261; $[\alpha]^{25}_D$ +15.8° (*c* 0.5, $CHCl_3$).

General Optimized α-Tosyloxylation Procedure (Table 6). Compound **11g** (11.1 mg, 0.027 mmol) was dissolved in acetonitrile/CH_2Cl_2 (1:1) (0.6 mL). Propiophenone (36.4 mg, 0.271 mmol) and *p*-TsOH hydrate (154.7 mg, 0.810 mmol) were added. A solution of *m*-CPBA (184.4 mg, 77% pure, 0.803 mmol) in acetonitrile/CH_2Cl_2 (1:1) (0.8 mL) was added over 1 h. The reaction mixture was stirred for 23 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) 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 61 mg (80%) of **15** as a white solid of the *R* enantiomer (48% ee).

1-Oxo-1-phenylbutan-2-yl 4-Methylbenzenesulfonate (20). The title compound was obtained as cololess solid (70% yield, 48% ee) according to the general α-tosyloxylation procedure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 2H), 5.55 (dd, *J* = 7.9, 5.0 Hz, 1H), 2.39 (s, 3H), 2.05−1.83 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H) ppm; HRMS ESI (*m*/*z*): calcd for $C_{17}H_{18}NaO_4S$ $[MNa]^+$ 341.0818, found 341.0810. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 83:17 hexanes/*i*-PrOH, 1.0 mL/min, rt, t_R = 12.5 min (*S*), t_R = 16.9 min (*R*).[3c]

1-Oxo-1-phenyloctan-2-yl 4-Methylbenzenesulfonate (21). The title compound was obtained as light brown solid (73% yield, 49% ee) according to the general α-tosyloxylation procedure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.78 (m, 2H), 7.77−7.68 (m, 2H), 7.62−7.52 (m, 1H), 7.44 (dd, *J* = 10.8, 4.8 Hz, 2H), 7.24 (t, *J* = 6.7 Hz, 2H), 5.58 (dd, *J* = 8.2, 4.9 Hz, 1H), 2.39 (s, 3H), 1.96−1.74 (m, 2H), 1.48−1.37 (m, 1H), 1.33 (ddd, *J* = 12.6, 9.2, 5.0 Hz, 1H), 1.27−1.11 (m, 6H), 0.83 (t, *J* = 6.9 Hz, 3H) ppm; HRMS ESI (*m*/*z*): calcd for $C_{21}H_{26}NaO_4S$ $[MNa]^+$ 397.1444, found 397.1444. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 83:17 hexanes/*i*-PrOH, 1.0 mL/min, rt, t_R = 8.9 min (*S*), t_R = 9.5 min (*R*).[3c]

2,3-Dihydro-1-oxo-1*H*-inden-2-yl 4-Methylbenzenesulfonate (22). The title compound was obtained as colorless solid (60% yield, 33% ee) according to the general α-tosyloxylation procedure: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.3 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 3H), 5.12 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.64 (dd, *J* = 17.2, 8.0 Hz, 1H), 3.26 (dd, *J* = 17.2, 4.7 Hz, 1H), 2.46 (s, 3H) ppm; HRMS ESI (*m*/*z*): calcd for $C_{16}H_{14}NaO_4S$ $[MNa]^+$ 325.0505, found 325.0508. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 50:50 hexanes/*i*-PrOH, 0.7 mL/min, rt, t_1 = 16.5 min, t_2 = 20.7 min.[3c]

1-Oxo-1-*p*-tolylpropan-2-yl 4-Methylbenzenesulfonate (25). The title compound was obtained as light brown solid (48% yield, 45% ee) according to the general α-tosyloxylation procedure: R_f = 0.48 (20% EtOAc/hexanes); T_{fus} = 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.66 (m, 4H), 7.34−7.18 (m, 4H), 5.82−5.69 (m, 1H), 2.40 (s, 3H), 2.39 (d, *J* = 5.9 Hz, 3H), 1.57 (dd, *J* = 6.9, 3.3 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 145.2, 145.1, 133.7, 131.3, 130.0, 129.7, 129.1, 128.2, 77.6, 22.0, 21.9, 19.1 ppm; IR (neat) 1705, 1364, 1177, 817, 776, 666 cm^{-1}; HRMS ESI (*m*/*z*): calcd for $C_{17}H_{18}NaO_4S$ $[MNa]^+$ 341.0818, found 341.0810. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 50:50 hexanes/*i*-PrOH, 0.7 mL/min, rt, t_R = 10.9 min (*S*), t_R = 12.8 min (*R*).

1-(4-Fluorophenyl)-1-oxopropan-2-yl 4-methylbenzenesulfonate (26). The title compound was obtained as light brown solid (77% yield, 46% ee) according to the general α-tosyloxylation procedure: R_f = 0.50 (20% EtOAc/hexanes); T_{fus} = 68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.86 (m, 2H), 7.78−7.68 (m, 2H), 7.32−7.23 (m, 2H), 7.11 (t, *J* = 8.6 Hz, 2H), 5.68 (q, *J* = 6.9 Hz, 1H), 2.40 (s, 3H), 1.56 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.7, 166.6, 164.1, 144.5, 132.6, 131.0, 130.9, 129.1, 127.2, 115.4, 115.2, 76.8, 21.0, 17.9 ppm; IR (neat) 1701, 1362, 1177, 818, 758, 666 cm^{-1}; HRMS ESI (*m*/*z*): calcd for $C_{16}H_{15}FNaO_4S$ $[MNa]^+$ 345.0567, found 345.0555. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 50:50 hexanes/*i*-PrOH, 0.7 mL/min, rt, t_R = 10.4 min (*S*), t_R = 12.4 min (*R*).

1-(3,4-Difluorophenyl)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (27). The title compound was obtained as white solid (66% yield, 42% ee) according to the general α-tosyloxylation procedure: R_f = 0.36 (20% EtOAc/hexanes); T_{fus} = 83 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.66 (m, 4H), 7.31−7.18 (m, 3H), 5.62 (q, *J* = 7.0 Hz, 1H), 2.42 (s, 2H), 1.57 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7 (s), 155.7 (d, *J* = 12.8 Hz), 152.1 (t, *J* = 13.3 Hz), 148.7 (d, *J* = 12.7 Hz), 145.4 (s), 133.1 (s), 130.6 (s), 129.8 (s), 127.9 (s), 126.1 (s), 118.0 (dd, *J* = 43.7, 17.7 Hz), 77.4 (s), 21.6 (s), 18.4 (s) ppm; ^{19}F NMR (377 MHz, $CDCl_3$) δ = −128.2, −135.6 ppm; IR (neat) 1704, 1363, 1177, 871, 816, 753, 666 cm^{-1}; HRMS ESI (*m*/*z*): calcd for $C_{16}H_{14}F_2NaO_4S$ $[MNa]^+$ 363.0473, found 363.0478. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 50:50 hexanes/*i*-PrOH, 0.7 mL/min, rt, t_R = 9.7 min (*S*), t_R = 11.8 min (*R*).

1-(4-Chlorophenyl)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (28). The title compound was obtained as colorless solid (82% yield, 42% ee) according to the general α-tosyloxylation procedure: R_f = 0.62 (20% EtOAc/hexanes); T_{fus} = 102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.79 (m, 2H), 7.77−7.70 (m, 2H), 7.47−7.38 (m, 2H), 7.26 (dd, *J* = 6.0, 4.4 Hz, 2H), 5.67 (q, *J* = 6.9 Hz, 1H), 2.41 (s, 3H), 1.61−1.54 (m, 3H) ppm; ^{13}C NMR (101 MHz,

$CDCl_3$) δ 194.1, 145.4, 140.6, 133.5, 132.2, 130.5, 130.1, 129.3, 128.2, 77.7, 21.9, 18.8 ppm; IR (neat) 1702, 1364, 1176, 816, 773, 666 cm^{-1}; HRMS ESI (m/z): calcd for $C_{16}H_{15}ClNaO_4S$ $[MNa]^+$, 361.0272, found 361.0262; The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 50:50 hexanes/*i*-PrOH, 0.7 mL/min, rt, t_R = 10.9 min (*S*), t_R = 12.8 min (*R*).

1-(3-(Trifluoromethyl)phenyl)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (29). The title compound was obtained as colorless oil (65% yield, 44% ee) according to the general α-tosyloxylation procedure: ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5, 2H), 7.83 (d, J = 7.8, 1H), 7.71 (d, J= 8.3 Hz 2H), 7.60 (t, J = 7.7, 1H), 7.29−7.21 (m, 2H), 5.70 (q, J = 7.0, 1H), 2.40 (s, 3H), 1.61 (d, J = 7.0, 3H) ppm; HRMS ESI (m/z): calcd for $C_{17}H_{15}F_3NaO_4S$ $[MNa]^+$ 395.0535, found 395.0532. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 83:17 hexanes/*i*-PrOH, 1.0 mL/min, rt, t_R = 7.9 min (*S*), t_R = 8.6 min (*R*).[3c]

1-(2-(Trifluoromethyl)phenyl)-1-oxopropan-2-yl 4-Methylbenzenesulfonate (30). The title compound was obtained as colorless oil (53% yield, 19% ee) according to the general α-tosyloxylation procedure: R_f = 0.63 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 10.4, 6.1 Hz, 3H), 7.61−7.51 (m, 2H), 7.44 (dd, J = 5.1, 3.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 5.50 (q, J = 6.9 Hz, 1H), 2.41 (s, 3H), 1.53 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.8, 145.1, 135.9, 133.2, 131.6, 130.7, 129.8, 127.7, 127.6 (q, J = 63.1 Hz), 127.5, 126.9 (q, J = 5.7 Hz), 123.1 (d, J = 274.0 Hz), 79.2, 21.6, 17.5 ppm; IR (neat) 1724, 1369, 1177, 817, 770, 664 cm^{-1}; HRMS ESI (m/z): calcd for $C_{17}H_{15}F_3NaO_4S$ $[MNa]^+$ 395.0535, found 395.0528. The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 87:17 hexanes/*i*-PrOH, 1.0 mL/min, rt, t_R = 11.4 min (*S*), t_R = 12.4 min (*R*).

1-Oxo-1-phenylpropan-2-yl Methanesulfonate (34). Catalyst **11g** (11.1 mg, 0.027 mmol) was dissolved in acetonitrile/CH_2Cl_2 (1:1) (0.6 mL). Propiophenone (36.4 mg, 0.271 mmol) and methanesulfonic acid (77.7 mg, 0.809 mmol) were added. A solution of *m*-chloroperoxybenzoic acid (184.4 mg, 0.803 mmol) in acetonitrile/CH_2Cl_2 (1:1) (0.8 mL) was added over 1 h. The reaction was stirred for 23 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 product was purified by silica gel chromatography with hexanes/EtOAc (80:20) to provide 49.2 mg (80%, 36% ee) of **34** as a colorless solid; R_f = 0.19 (20% EtOAc/hexanes); T_{fus} = 58 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02−7.85 (m; 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 6.05 (q, J = 6.99 Hz, 1H), 3.13 (s, 3H), 1.65 (d, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 134.2, 133.6, 129.0, 128.6, 77.1, 39.4, 18.7 ppm; IR (neat) 1696, 1357, 1173, 819, 767, 662 cm^{-1}; HRMS ESI (m/z): calcd for $C_{10}H_{12}NaO_4S$ $[MNa]^+$ 251.0349, found 251.0356; The ee was determined by HPLC analysis on the purified product: Chiracel AS-H column, 83:17 hexanes/*i*-PrOH, 1.0 mL/min, rt, t_R = 14.5 min (*S*), t_R = 15.5 min (*R*).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Characterization and NMR spectra for all new compounds. Full Gaussian reference (ref 20), Cartesian coordinates, and electronic and zero-point vibrational energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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