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Intramolecular Oxyacylation of Alkenes Using a Hydroxyl Directing Group

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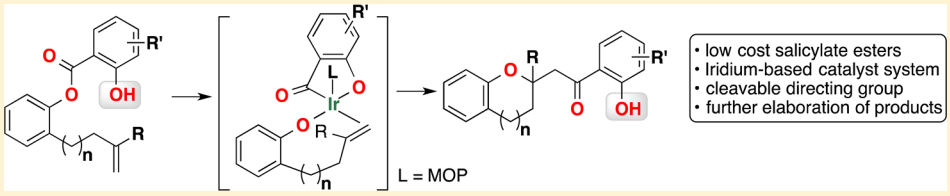
Supporting Information



ABSTRACT: Alkene oxyacylation is a new strategy for the preparation of β-oxygenated ketones. Now, with Ir catalysis and low-cost salicylate esters, alkene oxyacylation can be promoted by simple and versatile hydroxyl directing groups. This paper discusses catalyst optimization, substituent effects, mechanistic experiments, and the challenges associated with asymmetric catalysis. Crossover experiments point to several key steps of the mechanism being reversible, including the most likely enantiodetermining steps. The oxyacylation products are also prone to racemization without catalyst when heated alone; however, crossover is not observed without catalyst. These observations account for the low levels of enantioinduction in alkene oxyacylation. The versatility of the hydroxyl directing group is highlighted by demonstrating further transformations of the products.

INTRODUCTION

The ester is one of the most common functional groups in organic chemistry, yet most substitution reactions at the acyl C−O bond cause fragmentation. The transition-metal activation of the acyl C−O bond is an emerging concept for reaction discovery and method development.[1−7] Recently, we reported the union of rhodium-catalyzed activation of the acyl C−O bond of esters with the insertion of an alkene.[8] This process accomplished a catalytic alkene oxyacylation reaction via a complexity-building ester acyl substitution without fragmentation. This process enabled the synthesis of β-alkoxy ketones, which are typically thought of as products of aldol-type transformations (Figure 1, top). The transformation is a conceptually new entry into alkene addition reactions.[4,5] Our work also has served as precedent for new methods of metal-catalyzed acyl substitution reactions of esters.[7]

Our initial findings were limited, however, to the use of esters derived from quinoline-8-carboxylic acid (Figure 1, middle). This limitation stems from the requirement of a proximal heteroatom to direct the metal center toward the acyl C−O bond. Unfortunately, there are a limited number of strategies for further elaboration of 8-acylquinoline derivatives in complex molecule synthesis, limiting applications of alkene oxyacylation via quinoline-directed ester activation.

Directing groups have made a substantial impact in the area of C−H activation and functionalization, and there is now a staggering array of directing groups capable of mediating many transformations. Heteroatom directing groups for acyl C−O bond activation are much less developed, despite challenges of selecting C(acyl)−O over the activation of C(aryl)−O in ester C−O bond activation.[9,10] Expanding the types of directing

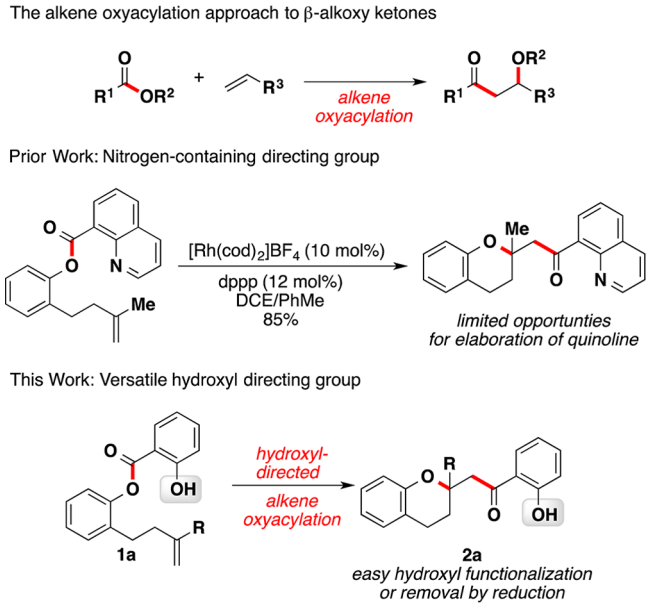


Figure 1. Oxyacylation of alkenes; salicylate hydroxyl as a potential directing group.

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groups capable of mediating and controlling acyl C−O bond activation would dramatically increase the applicability of this chemistry in synthesis.

Herein, we report that the versatile hydroxyl group of a phenol can facilitate alkene oxyacylation (Figure 1, bottom).[11] Nitrogen- and phosphorus-based directing groups have been demonstrated to facilitate stoichiometric acyl C−O bond activation by Rh(I).[12−14] The use of more weakly coordinating hydroxyl groups to direct acyl C−O bond activation has not, to our knowledge, been achieved. Related rhodium-catalyzed alkene and ketone hydroacylation chemistry using chelation in C−H activation of salicylaldehyde derivatives has been the subject of several recent reports, including examples of asymmetric catalysis.[15] This hydroacylation chemistry has also been highlighted in the synthesis of several natural products.[16] This work inspired us to pursue C−O activation in salicylate esters. We identified that the substructure directly prepared by salicylate ester alkene oxyacylation is found embedded in the core of several biologically relevant molecules, particularly orirubenones C and G and curvulone B (Figure 2).[17−19]

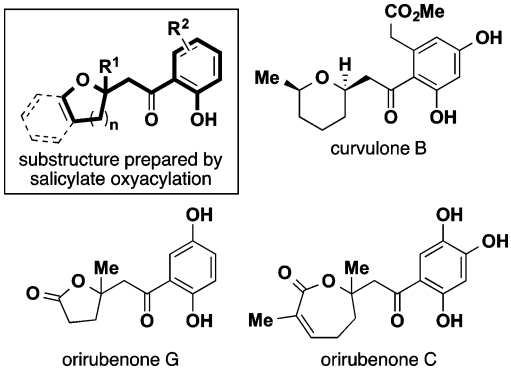


Figure 2. Natural products containing a substructure accessible by salicylate oxyacylation.

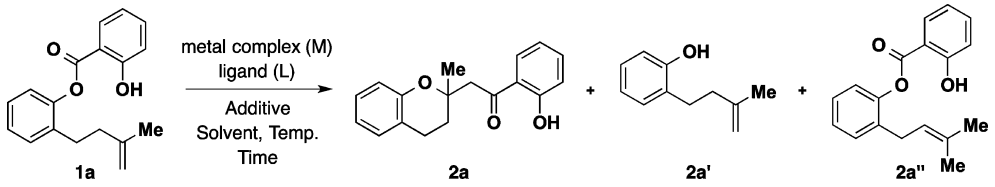
In this paper, we also report on the challenges we encountered in our attempts at catalytic asymmetric alkene oxyacylation. Our results from mechanistic study clearly show that chiral ligand-based approaches will be handicapped by the reversibility of the most likely enantiodetermining steps in alkene oxyacylation.

RESULTS AND DISCUSSION

Reaction Development. In our initial trial runs, reactions of **1a** with various potential transition-metal catalysts [Rh(I) or Ir(I)] did not afford any **2a** (Table 1, entries 1, 2, 5, and 6). In the presence of a mild base ($NaHCO_3$ or Na_2CO_3, 1 equiv), oxyacylation product **2a** was detected, albeit in <10% yield (Table 1, entries 3 and 4). In both cases, the main byproducts resulted from ester cleavage (**2a′**) or alkene isomerization (**2a″**). Alternate bases did not lead to improvement. We hypothesize that base facilitated the substrate coordination via deprotonation of the hydroxyl group, but this effect alone was insufficient to provide an effective catalytic system.

Considering how to facilitate effective binding between a Rh or Ir catalyst and the weak hydroxyl directing group in **1a**, we were inspired by the work of Oro and co-workers. According to their findings, phenol can rapidly replace the methoxide in $[Ir(cod)\mu\text{-}OMe]_2$ in the presence of a bulky, basic phosphine, PCy_3, to give $[Ir(cod)(PCy_3)OPh]$.[20] Applying Oro's findings to our system, reaction of **1a** with $[Ir(cod)\mu\text{-}OMe]_2/PCy_3$ afforded the oxyacylation product **2a** in 19% yield (Table 1, entry 7). The yield was low, but turnover was achieved. A control experiment (not shown) indicated that added $NaHCO_3$ no longer improved the yield of **2a**. The addition of the bidentate phosphine, diphenylphosphinopropane (dppp, Table 1, entry 6), which was effective in quinonline-directed oxyacylation reactions,[8] did not promote the formation of **2a**. Increasing the steric bulk of the phosphine ligand from PCy_3 to Me-Phos,[21] X-Phos,[22] or (*R*)-MOP[23] did, however, increase the yield of **2a** (Table 1, entries 7−10). Switching the solvent from

Table 1. Optimization of Oxyacylation with Salicylate Ester 1a



entry	[M] (mol %)	L (mol %)	solvent	*T* (°C)	additive	time (h)	yield of **2a** (%)
1	$[Rh(C_2H_4)_2Cl]_2$ (5 mol %)		*m*-xylene	170	$NaHCO_3$ (1 equiv)	24	ND
2	$Rh(cod)_2BF_4$ (10 mol %)		*m*-xylene	170	$NaHCO_3$ (1 equiv)	24	ND
3	$[Rh(cod)OH]_2$ (5 mol %)		*m*-xylene	170	$NaHCO_3$ (1 equiv)	24	3[a,b]
4	$[Ir(cod)OMe]_2$ (5 mol %)		*m*-xylene	170	$NaHCO_3$ (1 equiv)	24	6[a,b]
5	$[Ir(cod)OMe]_2$ (5 mol %)		*m*-xylene	170		24	ND
6	$[Ir(cod)OMe]_2$ (5 mol %)	dppp (6 mol %)	*m*-xylene	170		24	ND
7	$[Ir(cod)OMe]_2$ (5 mol %)	PCy_3 (12 mol %)	*m*-xylene	170		24	19[a]
8	$[Ir(cod)OMe]_2$ (5 mol %)	Me-Phos (12 mol %)	*m*-xylene	170		24	32[a]
9	$[Ir(cod)OMe]_2$ (5 mol %)	X-Phos (12 mol %)	*m*-xylene	170		24	47[a]
10	$[Ir(cod)OMe]_2$ (5 mol %)	MOP (12 mol %)	*m*-xylene	170		24	61[a]
11	$[Ir(cod)OMe]_2$ (5 mol %)	MOP (12 mol %)	*m*-xylene	150		24	49[a]
12	**$[Ir(cod)OMe]_2$ (4 mol %)**	**MOP (12 mol %)**	**mesitylene**	**170**		48	**78**[c]
13	**Ir(cod)(acac) (8 mol %)**	**MOP (12 mol %)**	**mesitylene**	**170**		48	**64**[c]

[a]Determined by NMR spectroscopy. [b]**2a′** and **2a″** also observed by NMR spectroscopy. [c]Isolated yield after column chromatography. cod = 1,5-cyclooctadiene, acac = acetoacetate, dppp = 1,3-diphenylphosphinopropane, Me-Phos = 2-methyl-2′-dicyclohexylphosphinobiphenyl, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, MOP = 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl.

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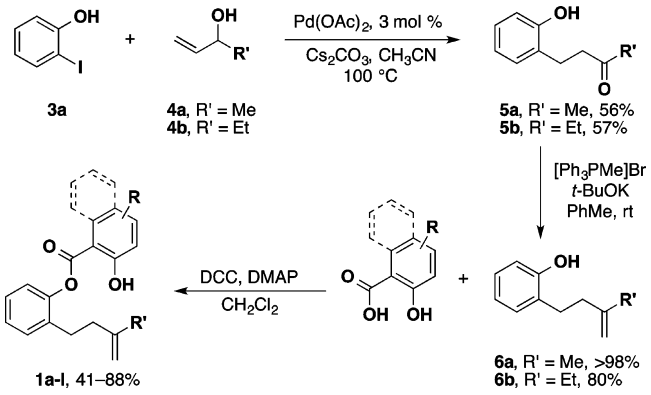
m-xylene to mesitylene (bp 163−166 °C) proved effective in minimizing byproduct formation (entry 12). Under the optimized conditions, reaction of **1a** with 4% $[Ir(cod)OMe]_2$ and 12% (*R*)-MOP in mesitylene at 170 °C afforded the oxyacylation product **2a** in 78% isolated yield. The product was formed as a racemate, as determined by HPLC for enantiomer separation.[24] The ^1H NMR spectra of crude products from entries 10 and 12 revealed a minor amount of methyl salicylate formed as a byproduct. This result is consistent with the notion that methoxide in the precatalyst is released upon reaction with the directing group and ligand. The ultimate fate of the released methoxide is transesterification with **1a**. Ir(cod)(acac) could be used as an alternate precatalyst (entry 13), and the formation of the methyl salicylate was not observed. Presumably, the iridium acetoacetate complex is sufficiently basic in mesitylene to undergo proton-coupled ligand exchange with the salicylate ester **1a** or the product **2a**.[25,26]

Substrate Scope Studies. With suitable conditions for salicylate-directed oxyacylation, we developed a concise synthesis of the salicylate ester precursors in order to study the substrate scope. Ester **1a** was prepared in just three steps from salicylic acid, 2-iodophenol, and (±)-3-buten-2-ol (Scheme 1).

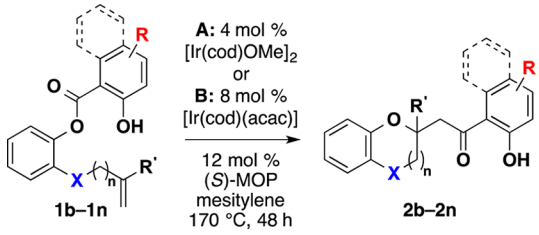
Scheme 1. Synthesis of Salicylate Esters 1a−l

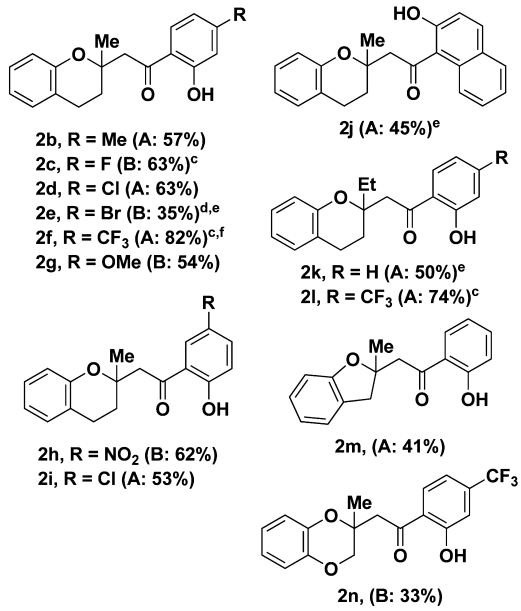


The substrate synthesis for esters **1a−l** was initiated with a Mizoroki−Heck reaction between 2-iodophenol (**3a**) and commercially available (±)-3-buten-2-ol (**4a**) or (±)-1-penten-3-ol (**4b**).[27,28] The resulting ketones **5a** and **5b** were obtained in 56% and 57% yield, respectively, as mixtures with their corresponding hemiketal forms (see the Supporting Information for NMR spectra). Wittig olefination provided the alkenes **6a** and **6b**. Esterification of **6a** and **6b** with the appropriate salicylic acid by the action of DCC and DMAP provided esters **1a−l**. Esters **1m** and **1n** were prepared via esterification of known phenols with the appropriate salicylic acids under similar conditions (see the Experimental Details).

With our two acceptable oxyacylation reaction conditions, substrates **1b−n** were examined (Table 2). Condition B was particularly useful when the oxyacylation product and the methyl ester byproduct formed under condition A coeluted during chromatography. Electron-donating groups (R = Me, OMe; **2b**, **2g**), electron-withdrawing groups (R = CF_3; **2f**), and halogens (R = F, Cl; **2c**, **2d**) are well-tolerated *para* to the carbonyl group. A substrate containing aryl bromide *para* to the carbonyl group afforded oxyacylation product (**2e**, 35% isolated yield, 60% brsm, unoptimized). Electron-withdrawing groups are also well-tolerated *para* to the directing hydroxyl group (R = NO_2, Cl; **2h**, **2i**). A 2-hydroxy-1-naphthoic ester was also a

Table 2. Substrate Scope for Oxyacylation of Alkenes with Salicylate Esters[a,b]





[a]Conditions A: $[Ir(cod)OMe]_2$ (4 mol %), (*S*)-MOP (12 mol %), mesitylene, 170 °C, 48 h. Conditions B: Ir(cod)(acac) (8 mol %), (*S*)-MOP (12 mol %), mesitylene, 170 °C, 48 h. [b]Isolated yield after chromatography. [c]Reaction performed at 150 °C. [d]42% recovered **1e**, 60% yield of **2e** based on recovered starting material. [e]Minor impurities remained after chromatography; see the Supporting Information for spectra. [f]Reaction conducted on a 1.35 mmol scale (473 mg **1f**) gave **2f** in 72% yield (341 mg, 0.97 mmol).

functional directing group, showing that additional steric bulk near the carbonyl did not preclude oxyacylation (Table 2, **2j**). Additional substitution on the alkene was tolerated (Table 2, **2k**, **2l**), and dihydrobenzofuran could also be prepared via oxyacylation of an alkene on a shorter tether (Table 2, **1m** → **2m**). Reactions of substrates containing electron-withdrawing groups *para* to the carbonyl on the salicylate fragment can be performed at a lower temperature (150 °C) and, in general, gave higher yields in comparison with runs at 170 °C (compounds **2c**, **2f**, **2l**). We suspect higher reaction temperatures may lead to decarbonylation and catalyst deactivation. Unfortunately, our attempts to isolate and characterize catalyst decomposition products were unsuccessful. Reactions for substrates without an electron-withdrawing group tend to be slower; a temperature of 170 °C was required for complete conversion.

Transformations of Oxyacylation Products. To demonstrate the versatility of the directing group, **2a** was subjected to various chemical transformations (Scheme 2). The phenol group was converted into ester **2p** in 87% yield upon standard acylation conditions. Base-mediated etherification of **2a** with methyl iodide and potassium carbonate provided methyl ether

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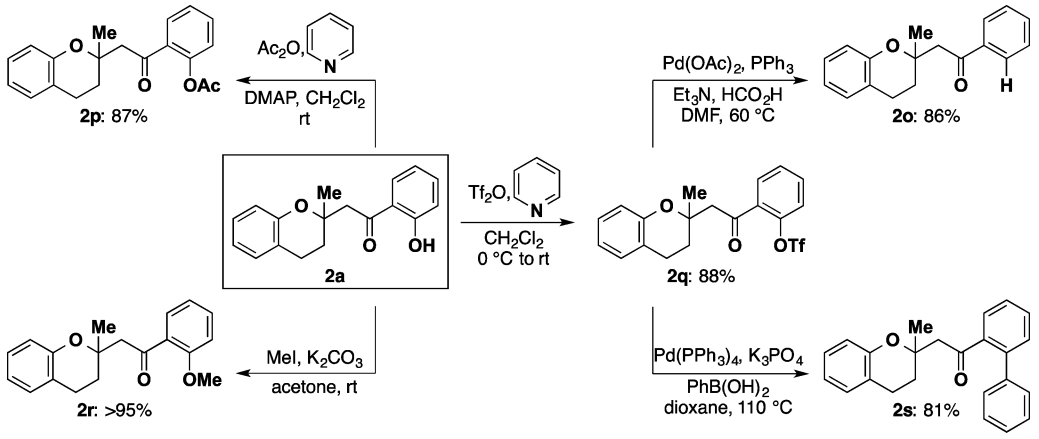
Scheme 2. Transformations of 2a



2r in >95% yield with no detectable rupture of the chromane ring by β-elimination. In addition, **2a** was treated with triflic anhydride and pyridine to yield aryl triflate **2q** in 88% yield. The triflate **2q** provided biaryl **2s** in 81% yield after Suzuki–Miyura reaction. The directing heteroatom could also be removed[29] entirely by palladium-catalyzed reduction of **2q** with formate to give **2o** in 86% yield. These results highlight the versatility of the oxyacylation products we have developed in this work.

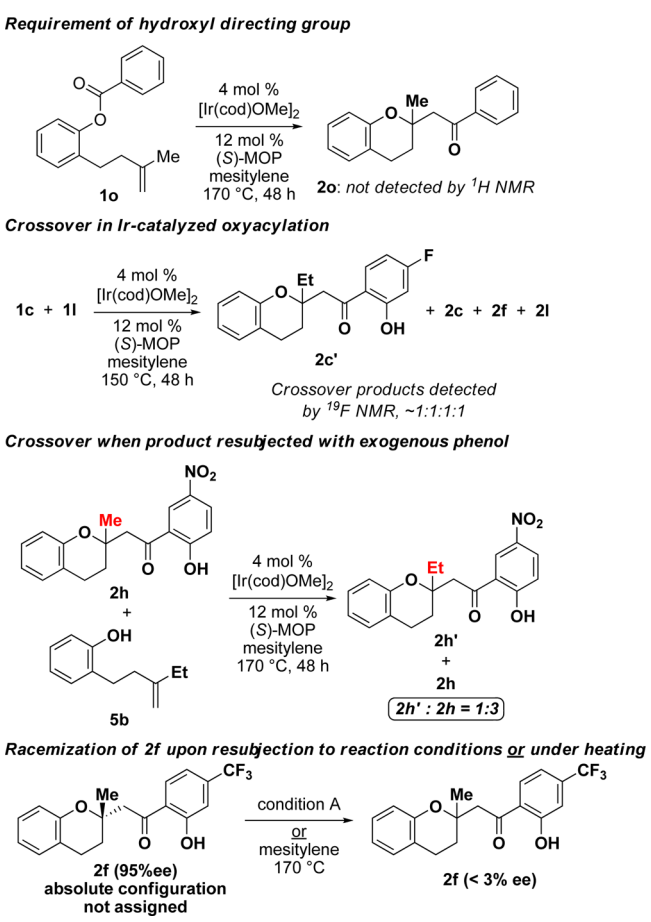
Mechanistic Studies. A control experiment with ester **1o** lacking the *o*-hydroxyl group did not produce any detectable amount of the corresponding product **2o** (Scheme 3, top). In addition, early attempts at alkene oxyacyltion using *ortho* SMe, PPh_2, and NH_2 groups were not successful, providing only products from ester hydrolysis and alkene isomerization along with unreacted starting material (not shown). These results clearly demonstrated that the hydroxyl group is required for oxyacylation.

Our working hypothesis for the catalytic cycle begins in analogy to Oro's Ir phenoxide synthesis. Salicylate **1a** and $[Ir(cod)OMe]_2$ in the presence of MOP may form **I-1** and release MeOH (Scheme 4).[20] The Ir phenoxide places the metal in close proximity to the ester, facilitating acyl C–O activation and forming **I-2**. Without an effective ligand, alkene isomerization occurred.[30] Migratory insertion of the alkene into the Ir–O bond of **I-2** produces **I-3**,[31] which undergoes reductive elimination to form **I-4**. Proton-exchange of **I-4** with **1a** affords product **2a** and regenerates **I-1**.

To further understand the mechanism of the reaction, we carried out crossover experiments. Subjecting a mixture of esters **1c** and **1l** to oxyacylation reaction conditions led to a mixture of the four possible crossover products (**2c**, **2c′**, **2l**, and **2f**). To probe reversibility, a crossover experiment was designed using **2h** and an exogenous phenol. Subjecting this mixture to our optimized oxyacylation conditions led the observation of a crossover product, **2h′** (Scheme 3, bottom).[32] Other, unidentified, byproducts were also observed.

An explanation for detecting significant quantities of **2h′** is that both migratory insertion and reductive elimination steps are reversible. The exact mechanism by which crossover takes place in both experiments (Scheme 3, middle) is not clear. It seems plausible, however, that the crossover event occurs at intermediate **I-2** by proton-coupled ligand exchange of the phenoxide (Scheme 4). In principle, crossover may also occur at intermediate **I-3** via metal–carbon bond homolysis and

Scheme 3. Mechanistic Experiments



recombination. A crossover reaction has been reported for rhodium(III) alkyls analogous to **I-3**, but only in cases where the resulting carbon-centered radical has significant stabilization.[33] In our related carboacylation reactions via C–C bond activation with 8-acyl quinoline directing groups, Johnson has shown these do not proceed with crossover, likely due to the fact that these would result in poorly stabilized primary carbon radical intermediates.[34−37] Given the general trend that third-row transition metals form stronger metal–carbon bonds, it seems unlikely that the crossover is due to iridium–carbon homolysis in **I-3**. Reversibility of the likely steps involved in the formation of the stereogenic center (**I-2** → **I-3**), however,

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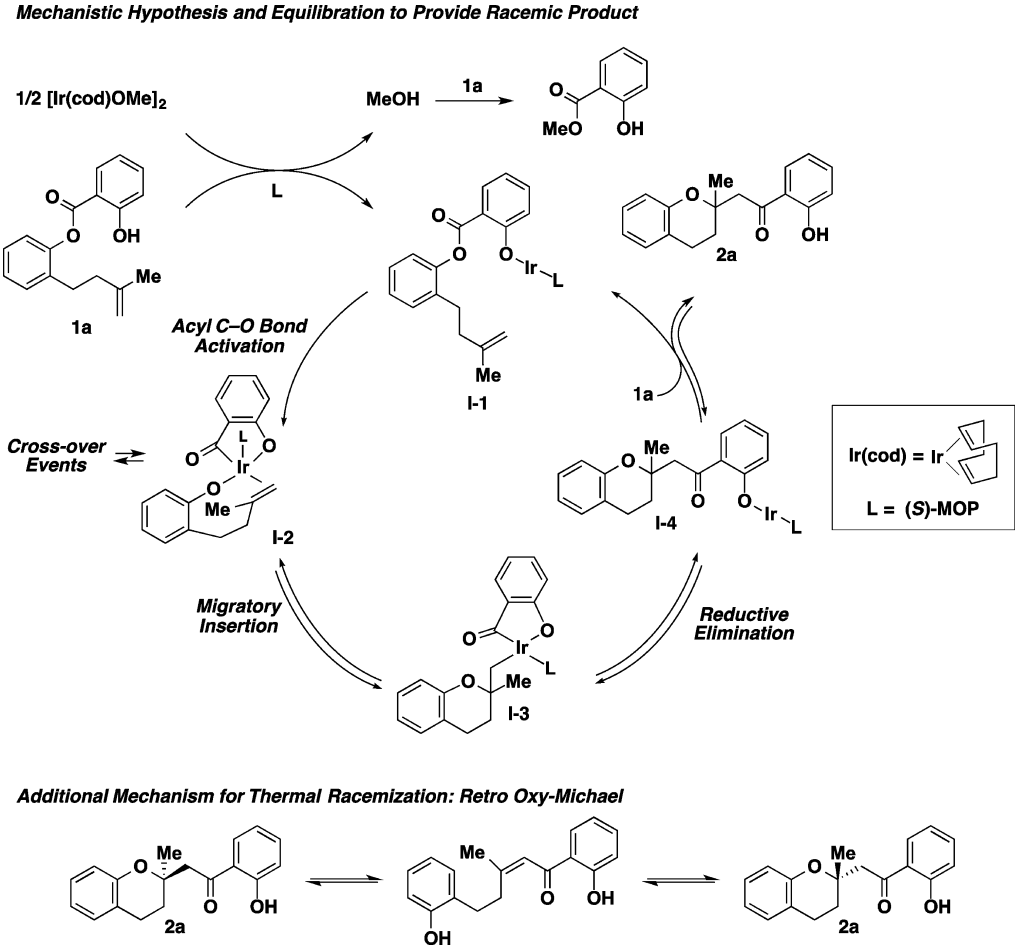
Scheme 4. Mechanistic Hypotheses



would explain the lack of enantioinduction from the optically active MOP ligand. We confirmed that racemization of the MOP ligand does not take place at the temperatures at which oxyacylation takes place (150−170 °C). We generated a scalemic mixture of MOP by mixing enantiomeric ligand samples and developed an HPLC method for their separation. Heating (*R*)-MOP in mesitylene at 170 °C for 24 or 48 h did not lead to detectible loss of enantiomeric purity.[38] We also resolved a sample of **2f** via HPLC. Upon resubjection to condition A (150 °C), enantioenriched **2f** was converted to a racemic sample (Scheme 3, bottom). We also observed racemization of **2f** upon simply heating the sample to 150 °C in mesitylene, indicating an alternate mechanism for racemization can operate. It seems plausible that this could occur via a retro-oxy-Michael/oxy-Michael pathway (Scheme 4, bottom). We also did not observe crossover when **2f** and **2c** were heated in the absence of iridium, implicating iridium in the crossover event. See the Supporting Information for copies of the HPLC chromatograms. This suggests that reversibility of key mechanistic steps, rather than ligand racemization, is the origin of racemic **2a** as the product of oxyacylation. These findings significantly increase the challenge of asymmetric induction in oxyacylation reactions.

■ CONCLUSIONS

We have disclosed the development of a simple and versatile hydroxyl directing group for intramolecular alkene oxyacylation. This is a significant expansion in the scope of alkene oxyacylation using ester acyl C−O bond activation as a key mechanistic step. Identifying precatalysts bearing basic x-type ligands were effective at binding to the directing group and forming active species capable of turnover was a key observation during reaction optimization, likely due to proton-coupled ligand exchange. Mechanistic experiments demonstrate that the reaction involves reversible steps, and a crossover experiment demonstrates that the acyl and alkoxy portions of the ester undergo exchange during the reaction. The reversibility of the reaction, in combination with the relatively high reaction temperatures promoting racemization, combined to thwart asymmetric induction in oxyacylation reactions. We will continue to develop new directing groups for alkene oxyacylation to expand the scope of this chemistry.

■ EXPERIMENTAL DETAILS

Acetonitrile, toluene, dichloromethane, 1,4-dioxane, and *N*,*N*-dimethylformamide were distilled prior to use. Solvents for oxyacylation reactions (anhydrous *m*-xylene or mesitylene) were degassed by bubbling a stream of argon through the liquid in a Strauss flask and then stored in a nitrogen-filled glovebox. Rhodium and iridium complexes and phosphine ligands were purchased from commercial vendors with few exceptions. $[Ir(cod)OMe]_2$ was synthesized from $IrCl_3$ in two steps, according to a known procedure.[39,40] We noticed that commercial samples of $[Ir(cod)OMe]_2$ generally provided lower yields in the oxyacylation reaction, though oxyacylation products were still observed. We tentatively attributed this to water or methanol in the commercial sample since oxyacylation yields were improved after desiccation of the commercial samples of $[Ir(cod)OMe]_2$ under active

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vacuum. We note that the final purification of this complex involved vacuum-drying over P_2O_5. (*S*)-MOP was synthesized from (*S*)-BINOL as previously described.[41,42] All other chemicals were purchased from commercial sources and used as received.

All rhodium- or iridium-catalyzed reactions were carried out in a nitrogen-filled glovebox in 1 dram vials with PTFE lined caps, and heating was applied by aluminum block heaters. Infrared (IR) spectra were obtained as films from CH_2Cl_2. High-resolution mass spectrometry (HRMS) measurements using electrospray ionization (ESI) were performed with a time-of-flight (TOF) mass analyzer, either in positive- or negative-ion detecting mode.

4-(2-Hydroxyphenyl)butan-2-one (5a). To a 20 mL reaction vial with a PTFE-lined cap were added 2-iodophenol (1.10 g, 5.0 mmol), palladium acetate (34 mg, 0.15 mmol), cesium carbonate (0.651 g, 2.0 mmol), and freshly distilled acetonitrile (7.2 mL). 3-Buten-2-ol **4a** (0.7 mL, 8.0 mmol) was added, and the reaction vessel was purged with argon gas for 3−5 min. The cap was replaced tightly, and the reaction mixture was maintained at 100 °C for 24 h using an aluminum heating block. The reaction mixture was transferred to a 250 mL beaker, and saturated aqueous NH_4Cl solution (20 mL), water (50 mL), and ethyl acetate (20 mL) were added (occasionally insoluble particles remained then the mixture was filtered through Celite). The organic layer was separated, washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford **5a** as a colorless oil (0.4578 g, 2.78 mmol, 56%): R_f = 0.23 (1:4 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.13−7.09 (m, 1H), 7.05 (dd, J = 8.0, 2.0 Hz, 1H), 6.90−6.88 (m, 1H), 6.85 (dt, J = 7.5, 1.5 Hz, 1H), 2.92−2.89 (m, 2H), 2.85−2.82 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 154.3, 130.4, 128.0, 127.3, 120.6, 117.4, 45.3, 29.7, 23.1; IR (thin film) 3404, 2933, 1702, 1490, 1233; HRMS (ESI) calcd for $[C_{10}H_{12}O_2 + Na]^+$ 187.0730, found 187.0731. Note: The ^{1}H and ^{13}C NMR of **5a** show an inseparable compound that was no longer observed after the Wittig step. We tentatively assign it to the hemiketal form of ketone **5a**; see the Supporting Information for copies of the spectra.

2-(3-Methylbut-3-en-1-yl)phenol (6a). In a dry round-bottom flask, methyltriphenylphosphonium bromide (4.28 g, 12 mmol) was suspended in freshly distilled toluene (10 mL). The mixture was cooled in an ice bath, and potassium *tert*-butoxide (1.34 g, 12 mmol) was added slowly. The reaction mixture was stirred at room temperature for 2 h under nitrogen atmosphere. The mixture was cooled to 0 °C, and a solution of **5a** (0.458 g, 2.78 mmol) in 5 mL of toluene was added. The reaction was stirred at room temperature overnight. Upon completion of the reaction (confirmed by TLC), saturated aqueous NH_4Cl solution (10 mL) was added. The mixture was filtered through a pad of Celite with excess EtOAc. The layers were separated, and the aqueous phase was washed with EtOAc (2 × 20 mL). The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to afford phenol **6a** as a yellow oil (0.450 g, 0.278 mmol, quantitative yield): R_f = 0.5 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (dd, J = 7.3, 1.5 Hz, 1H), 7.17 (td, J = 7.8, 1.5 Hz, 1H), 6.98 (td, J = 7.3, 1.0 Hz, 1H), 6.83 (dd, J = 7.8, 1.0 Hz, 1H), 5.38 (br s, 1H), 4.88−4.86 (m, 2H), 2.89−2.86 (m, 2H), 2.44−2.41 (m, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 145.8, 130.0, 128.2, 127.1, 120.8, 115.2, 110.1, 37.6, 28.4, 22.6; IR (thin film) 3424, 3072, 1648, 1236; HRMS (ESI) calcd for $[C_{11}H_{14}O - H]^-$ 161.0972, found 161.0968.

1-(2-Hydroxyphenyl)pentan-3-one (5b). Prepared in analogy to the preparation of **5a**. Starting with 2-iodophenol (1.10 g, 5.0 mmol), palladium acetate (34 mg, 0.15 mmol), cesium carbonate (0.651 g, 2.0 mmol), alcohol **4b** (0.68 mL, 6.5 mmol), and freshly distilled acetonitrile (7.2 mL), the reaction afforded **5b** as a colorless oil (0.5064 g, 2.84 mmol, 57%) after flash chromatography: R_f = 0.22 (1:9 EtOAc/Hex); **5b** (ketone form); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.14−7.09 (m, 1H), 7.04 (dd, J = 7.5, 1.7 Hz, 1H), 6.90 (dd, J = 8.1, 1.2 Hz, 1H), 6.84 (td, J = 7.4, 1.2 Hz, 1H), 2.92−2.81 (m, 4H), 2.44 (q, J = 7.3 Hz, 2H), 1.04 (t, J = 7.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 154.1, 130.2, 127.6, 127.5, 120.4, 116.7, 43.3, 35.5, 23.5, 7.5; **5b** (hemiketal form) ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 128.9, 127.0, 121.8, 120.3, 116.8, 97.9, 34.0, 28.6, 21.1, 7.5; IR (thin film) 3438, 2974, 1702, 1455, 1265; HRMS (ESI) calcd for $[C_{11}H_{14}O_2 + Na]^+$ 201.0886, found 201.0880. Note: The ^{1}H and ^{13}C NMR of **5b** show an inseparable compound that was no longer observed after the Wittig step. We tentatively assign it to the hemiketal form of ketone **5b**; see the Supporting Information for copies of the spectra.

4-(2-Hydroxyphenyl)butan-2-one (6b). Prepared in analogy to the preparation of **6a**. Starting with ketone **5b** (0.534 g, 3.0 mmol), methyltriphenylphosphonium bromide (4.28 g, 12 mmol), and potassium *tert*-butoxide (1.34 g, 12 mmol), the reaction afford **6b** as a colorless oil (0.423 g, 2.4 mmol, 80%) after flash column chromatography: R_f = 0.6 (1:4 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.02 (m, 2H), 6.88 (t, J = 7.4 Hz, 1H), 6.76 (d, J = 7.9 Hz, 1H), 4.84−4.81 (m, 3H), 2.76 (m, 2H), 2.40−2.26 (m, 2H), 2.09 (q, J = 7.5 Hz, 2H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 151.4, 130.1, 128.2, 127.1, 120.8, 115.2, 108.0, 36.2, 29.0, 28.8, 12.3; IR (thin film) 3065, 2961, 2927, 1643, 1609, 1590, 1327, 1233. HRMS (ESI) calcd for $[C_{12}H_{16}O - H]^-$ 175.1128, found 175.1133.

General Procedure for Ester Synthesis. In an oven-dried 25 mL round-bottom flask, carboxylic acid (1.2 mmol, 1.2 equiv), *N*,*N*′-dicyclohexylcarbodiimine (1.8 mmol, 1.8 equiv), 4-(dimethylamino)-pyridine (0.2 mmol, 0.2 equiv), phenol (1.0 mmol, 1 equiv), and 4 mL of dichloromethane were added. The mixture was maintained at reflux overnight (oil bath) or stirred at room temperature for 48−72 h as noted below. The mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (50 mL). Insoluble materials were removed by vacuum filtration with the aid of Celite. The filtrate was washed with saturated aqueous NH_4Cl (2 × 30 mL) followed by saturated aqueous $NaHCO_3$ (30 mL). The organic portion was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by flash chromatography (gradient, CH_2Cl_2:Hex or EtOAc/Hex) to provide the ester.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxybenzoate (1a). Prepared under reflux conditions. Starting with salicylic acid (0.49 g, 3.5 mmol), phenol **6a** (0.38 g, 2.3 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.86 g, 4.2 mmol) and 4-(dimethylamino)pyridine (0.14 g, 1.2 mmol), the reaction afforded **1a** as a colorless oil (0.441 g, 1.56 mmol, 68%) after flash column chromatography. R_f = 0.53 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.10 (dd, J = 8.0, 1.7 Hz, 1H), 7.56 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.35−7.29 (m, 1H), 7.29−7.23 (m, 2H), 7.15 (dd, J = 7.8, 1.4 Hz, 1H), 7.06 (dd, J = 8.4, 1.0 Hz, 1H), 7.01−6.96 (m, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 2.74−2.69 (m, 2H), 2.33−2.28 (m, 2H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 162.2, 148.3, 144.8, 136.5, 134.0, 130.4, 130.2, 127.2, 126.6, 122.2, 119.5, 117.9, 111.7, 110.7, 38.2, 28.8, 22.2; IR (thin film) 3227, 3074, 2932, 1683, 1651, 1616, 1583, 1247; HRMS (ESI) calcd for $[C_{18}H_{18}O_3 + Na]^+$ 305.1146, found 305.1162.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-4-methylbenzoate (1b). Prepared under reflux conditions. Starting with 4-methyl salicylic acid (0.365 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.049 g, 0.4 mmol), the reaction afforded **1b** as a colorless oil (0.320 g, 1.08 mmol, 54%) after flash column chromatography. R_f = 0.45 (1:1 CH_2Cl_2:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.35−7.32 (m, 1H), 7.31−7.25 (m, 2H), 7.18 (dd, J = 8.0, 1.5 Hz, 1H), 6.89 (s, 1H), 6.82 (dd, J = 8.0, 1.0 Hz, 1H), 4.72 (app s, 1H), 4.67 app s, 1H) 2.75−2.72 (m, 2H), 2.41 (s, 3H), 2.34−2.31 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 162.2, 148.3, 148.0, 144.8, 134.1, 130.3, 129.9, 127.1, 126.5, 122.3, 120.8, 118.0, 110.7, 109.1, 38.2, 28.9, 22.3, 21.9; IR (thin film) 3431, 3075, 2934, 1684, 1625, 1249, 1208; HRMS (ESI) calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, found 319.1309.

2-(3-methylbut-3-en-1-yl)phenyl 4-fluoro-2-hydroxybenzoate (1c). Prepared under reflux conditions. Starting with 4-fluoro salicylic acid (0.375 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.049 g, 0.4 mmol), the reaction afforded **1c** as a colorless oil (0.529 g, 1.76 mmol, 88%) after flash column

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chromatography. R_f = 0.80 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.54 (d, J = 1 Hz, 1H), 8.13 (dd, J = 8.5, 6.5 Hz, 1H), 7.35−7.27 (m, 3H), 7.16 (dd, J = 8.0, 1.5 Hz, 1H), 6.77 (dd, J = 10.0, 2.0 Hz, 1H), 6.72 (td, J = 8.3, 2.5 Hz, 1H), 4.72 (s, 1H), 4.66 (s, 1H), 2.74−2.71 (m, 2H), 2.34−2.30 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 167.7 (d, $^1J_{F-C}$ = 255.3 Hz), 164.4 (d, $^3J_{F-C}$ = 14.0 Hz), 148.1, 144.7, 134.0, 132.3 (d, $^3J_{F-C}$ = 12.0 Hz), 130.4, 127.2, 126.7, 122.1, 110.7, 108.4, 107.8 (d, $^2J_{F-C}$ = 23.1 Hz), 104.7 (d, $^2J_{F-C}$ = 24.0 Hz), 38.2, 28.8, 22.3; IR (thin film) 3427, 3080, 2937, 1688, 1622, 1258, 1209; HRMS (ESI) calcd for $[C_{18}H_{17}FO_3 + Na]^+$ 323.1054, found 323.1064.

2-(3-methylbut-3-en-1-yl)phenyl 4-chloro-2-hydroxybenzoate (1d). Prepared under reflux conditions. Starting with 4-chloro salicylic acid (0.414 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.049 g, 0.4 mmol), the reaction afforded **1d** as a colorless oil (0.544 g, 1.72 mmol, 86%) after flash column chromatography. R_f = 0.65 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.36−7.33 (m, 1H), 7.32−7.27 (m, 2H), 7.17 (dd, J = 8.0, 1.5 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 8.5, 3 Hz, 1H), 4.74 (s, 1H), 4.67 (s, 1H), 2.75−2.72 (m, 2H), 2.34−2.31 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 162.7, 148.1, 144.6, 142.3, 133.9, 131.0, 130.4, 127.2, 126.7, 122.1, 120.2, 118.0, 110.7, 110.3, 38.1, 28.8, 22.3; IR (thin film) 3425, 3076, 2935, 1693, 1614, 1281, 1201; HRMS (ESI) calcd for $[C_{18}H_{17}ClO_3 - H]^-$ 315.0793, found 315.0794.

2-(3-methylbut-3-en-1-yl)phenyl 4-bromo-2-hydroxybenzoate (1e). Prepared under reflux conditions. Starting with 4-bromo salicylic acid (0.521 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1e** as a colorless oil (0.592 g, 1.64 mmol, 82%) after flash column chromatography. R_f = 0.54 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.35−7.26 (m, 4H), 7.17−7.14 (m, 2H), 4.72 (s, 1H), 4.66 (s, 1H), 2.74−2.70 (m, 2H), 2.33−2.30 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 162.5, 148.0, 144.6, 133.9, 131.0, 130.9, 130.4, 127.2, 126.7, 123.1, 122.1, 121.1, 110.7, 110.7, 38.2, 28.8, 22.4 ; IR (thin film) 3424, 2935, 1690, 1607, 1280, 1201; HRMS (ESI) calcd for $[C_{18}H_{17}BrO_3 + Na]^+$ 383.0253, found 383.0248.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-4-(trifluoromethyl)benzoate (1f). Prepared under reflux conditions. Starting with trifluoromethyl salicylic acid (0.445 g, 2.16 mmol), phenol **6a** (0.288 g, 1.78 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.668 g, 3.24 mmol) and 4-(dimethylamino)pyridine (0.048 g, 0.4 mmol), the reaction afforded **1f** as an colorless amorphous solid (0.4752 g, 1.35 mmol, 76%) after flash column chromatography. R_f = 0.57 (4:6 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.21−8.20 (m, 1H), 7.34 (dt, J = 11.4, 3.1 Hz, 2H), 7.30 (m, 2H), 7.25−7.21 (m, 1H), 7.16 (dd, J = 7.7, 1.5 Hz, 1H), 4.70 (s, 1H), 4.64 (s, 1H), 2.74−2.68 (m, 2H), 2.34−2.28 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.1, 148.0, 144.6, 137.6 (q, $^2J_{F-C}$ = 33.0 Hz), 133.9, 131.0, 130.5, 127.3, 126.9, 123.0 (q, $^1J_{C-F}$ = 273 Hz), 122.0, 115.8 (q, $^3J_{C-F}$ = 3.5 Hz), 115.37 (q, $^3J_{C-F}$ = 3.9 Hz), 114.4, 110.8, 38.2, 28.7, 22.4; IR (thin film) 3082, 2941, 1645, 1573, 1322; HRMS (ESI) calcd for $[C_{19}H_{17}F_3O_3 + Na]^+$ 373.1022, found 373.1023.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-4-(methoxy)-benzoate (1g). Prepared under reflux conditions. Starting with 4-methoxy salicylic acid (0.404 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1g** as a colorless oil (0.472 g, 1.52 mmol, 76%) after flash column chromatography. R_f = 0.65 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.33 (dd, J = 7.5, 1.5 Hz, 1H), 7.32−7.28 (m, 1H), 7.26 (dd, J = 7.5, 1.5 Hz, 1H), 7.16 (dd, J = 8.0, 1.5 Hz, 1H), 6.56 (dd, J = 8.5, 2.5 Hz, 1H), 6.54 (d, J = 2.5 Hz, 1H), 4.72 (s, 1H), 4.67 (s, 1H), 3.87 (s, 1H), 2.75−2.71 (m, 2H), 2.34−2.30 (m, 2H), 1.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 166.2, 164.5, 148.3, 144.8, 134.1, 131.5, 130.3, 127.1, 126.4, 122.3, 110.6, 108.1, 104.6, 100.8, 55.5, 38.2, 28.9, 22.3; IR (thin film) 3431, 3078, 2936, 1679, 1625, 1254, 1216; HRMS (ESI) calcd for $[C_{19}H_{20}O_4 + Na]^+$ 335.1254, found 335.1250.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-5-nitrobenzoate (1h). Prepared by stirring at room temperature for 48 h. Starting with 5-nitro salicylic acid (0.543 g, 3.0 mmol), phenol **6a** (0.243 g, 1,5 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.620 g, 3.0 mmol) and 4-(dimethylamino)pyridine (0.100 g, 0.8 mmol). The reaction mixture was allowed to stir for 72 h at room temperature to afford **1h** as a yellow amorphous solid (0.380 g, 1.16 mmol, 77%) after flash column chromatography. R_f = 0.50 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 11.20 (s, 1H), 9.05 (d, J = 3.0 Hz, 1H), 8.43 (dd, J = 9.5, 3.0 Hz, 1H), 7.36 (dd, J = 6.5, 2.5 Hz, 1H), 7.34−7.29 (m, 2H), 7.18 (d, J = 9.5 Hz, 1H), 7.17 (dd, J = 7.5, 2.0 Hz, 1H), 4.72 (s, 1H), 4.67 (s, 1H), 2.74−2.71 (m, 2H), 2.34−2.31 (m, 2H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 166.7, 147.8, 144.5, 140.2, 133.9, 131.2, 130.6, 127.4, 127.1, 126.8, 121.9, 119.0, 111.5, 110.9, 38.2, 28.7, 22.4; IR (thin film) 3424, 2936, 1697, 1627, 1252, 1204; HRMS (ESI) calcd for $[C_{18}H_{17}NO_5 - H]^-$, 326.1034 found 326.1027.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-5-chlorobenzoate (1i). Prepared under reflux conditions. Starting with 5-chloro salicylic acid (0.414 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1i** as a colorless oil (0.540 g, 1.62 mmol, 81%) after flash column chromatography. R_f = 0.80 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.07 (d, J = 2.5 Hz, 1H), 7.50 (dd, J = 9, 2.5 Hz, 1H), 7.34 (dd, J = 7.0, 2.0 Hz, 1H), 7.32−7.26 (m, 2H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 4.74 (s, 1H), 4.68 (s, 1H), 2.74−2.71 (m, 2H), 2.34−2.31 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 160.7, 148.0, 144.6, 136.4, 133.9, 130.4, 129.3, 127.2, 126.8, 124.3, 122.0, 119.5, 112.6, 110.8, 38.2, 28.8, 22.4; IR (thin film) 3425, 3076, 2935, 1696, 1615, 1284, 1196; HRMS (ESI) calcd for $[C_{18}H_{17}ClO_3 - H]^-$ 315.0793, found 315.0784.

2-(3-methylbut-3-en-1-yl)phenyl 2-hydroxy-1-naphthoate (1j). Prepared by stirring at room temperature for 72 h. Starting with 2-hydroxy-1-naphthoic acid (0.452 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol). The reaction was allowed to stir for 48 h at room temperature to afford **1j** as an off-white amorphous solid (0.480 g, 1.44 mmol, 72%) after flash column chromatography. R_f = 0.60 (1:1 CH_2Cl_2:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.25 (br s, 1H), 9.03 (d, J = 9.0 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.65 (td, J = 7.5, 1.5 Hz, 1H), 7.46 (dt, J = 7.5, 1.0 Hz, 1H), 7.42 (dd, J = 7.5, 2.0 Hz, 1H), 7.40−7.37 (m, 1H), 7.36−7.33 (m, 1H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 7.27 (d, J = 9.0 Hz, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 2.82−2.79 (m, 2H), 2.39−2.36 (m, 2H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 165.6, 148.2, 144.6, 137.8, 134.1, 131.7, 130.4, 129.3, 128.8, 128.7, 127.3, 126.7, 125.3, 123.9, 122.4, 119.3, 110.7, 103.8, 38.2, 28.8, 22.2; IR (thin film) 3423, 3072, 2934, 1660, 1620, 1243, 1203; HRMS (ESI) calcd for $[C_{22}H_{20}O_3 + Na]^+$ 355.1305, found 355.1325.

2-(3-methylenepentyl)phenyl 2-hydroxybenzoate (1k). Prepared under reflux conditions. Starting with salicylic acid (0.166 g, 1.2 mmol), phenol **6b** (0.176 g, 1 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.371 g, 1.8 mmol) and 4-(dimethylamino)pyridine (0.024 g, 0.2 mmol), the reaction afforded **1k** as a colorless oil (0.122 g, 0.41 mmol, 41%) after flash column chromatography. R_f = 0.44 (1:2 CH_2Cl_2:Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.11 (dd, J = 8.0, 1.7 Hz, 1H), 7.63−7.50 (m, 1H), 7.38−7.21 (m, 3H), 7.16 (dd, J = 7.5, 1.6 Hz, 1H), 7.10−7.04 (m, 1H), 7.03−6.94 (m, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 2.72 (dd, J = 9.6, 6.7 Hz, 2H), 2.39−2.26 (m, 2H), 2.00 (q, J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 162.2, 150.4, 148.3, 136.5, 134.2, 130.4, 130.2, 127.2, 126.6, 122.2, 119.5, 117.9, 111.7, 108.4, 36.6, 29.1, 28.7, 12.2; IR (thin film) 3215, 3069, 2933, 1698, 1644, 1582, 1488, 1129; HRMS (ESI) calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, found 319.1306.

2-(3-methylenepentyl)phenyl 2-hydroxy-4-(trifluoromethyl)benzoate (1l). Prepared under reflux conditions.

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Starting with trifluoromethyl salicylic acid (0.495 g, 2.4 mmol), phenol **6b** (0.352 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1l** as a colorless amorphous solid (0.582 g, 1.6 mmol, 80%) after flash column chromatography. R_f = 0.58 (1:2 CH_2Cl_2:Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 7.40−7.20 (m, 5H), 7.17−7.12 (m, 1H), 4.73 (s, 1H), 4.68 (s, 1H), 2.72 (dd, J = 9.4, 6.7 Hz, 2H), 2.39−2.24 (m, 2H), 2.01 (q, J = 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 162.1, 150.2, 148.0, 137.6 (q, $^2J_{F-C}$ = 33.0 Hz), 134.0, 131.0, 130.5, 127.3, 126.9, 123.1 (q, $^1J_{F-C}$ = 273.2 Hz), 122.0, 115.8 (q, $^3J_{F-C}$ = 3.5 Hz), 115.30 (q, $^3J_{F-C}$ = 3.9 Hz), 114.4, 108.5, 36.6, 29.0, 28.7, 12.2; IR (thin film) 3194, 3078, 2964, 1698, 1650, 1508, 1325; HRMS (ESI) calcd for $[C_{20}H_{17}F_3O_3 - H]^-$ 363.1214, found 363.1218.

2-(2-methylallyl)phenyl 2-hydroxybenzoate (1m). Prepared under reflux conditions. Starting with salicylic acid (0.166 g, 1.2 mmol), phenol 2-(2-methylallyl)phenol[43] (0.148 g, 1 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.371 g, 1.8 mmol) and 4-(dimethylamino)pyridine (0.024 g, 0.2 mmol), the reaction afforded **1m** as a colorless oil (0.2035 g, 0.76 mmol, 76%) after flash column chromatography. R_f = 0.65 (1:9 EtOAc/Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.07 (dd, J = 8.0, 1.7 Hz, 1H), 7.55 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H), 7.39−7.22 (m, 3H), 7.19−7.12 (m, 1H), 7.05 (dd, J = 8.4, 0.9 Hz, 1H), 6.98 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H), 4.77 (app s, 1H), 4.62 (s, 1H), 3.31 (d, J = 5.4 Hz, 2H), 1.67 (d, J = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 162.1, 148.6, 143.2, 136.4, 131.8, 131.1, 130.2, 127.5, 126.5, 122.4, 119.4, 117.8, 112.5, 111.8, 38.8, 22.1; IR (thin film) 3234, 3076, 3293, 1694, 1650, 1615, 1448, 1249; HRMS (ESI) calcd for $[C_{17}H_{16}O_3 + Na]^+$ 291.0992, found 291.0981.

2-((2-methylallyl)oxy)phenyl 2-hydroxy-4-(trifluoromethyl)-benzoate (1n). Prepared under reflux conditions. Starting with 4-trifluoromethyl salicylic acid (0.495 g, 2.4 mmol), phenol 2-((2-methylallyl)oxy)phenol[44] (0.328 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1n** as a colorless amorphous solid (0.1080 g, 0.30 mmol, 15%) after flash column chromatography. R_f = 0.46 (2:3 CH_2Cl_2:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.32 (s, 1H), 7.28 (td, J = 7.5, 1.5 Hz, 1H), 7.23−7.19 (m, 2H), 7.05−7.02 (m, 2H), 4.99 (s, 1H), 4.91 (s, 1H), 4.47 (s, 2H), 1.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 161.9, 149.9, 140.0, 139.0, 137.3 (q, $^2J_{F-C}$ = 32.0 Hz), 131.4, 127.6, 123.1 (q, $^1J_{F-C}$ = 271.4 Hz), 122.5, 121.0, 115.8 (q, $^3J_{F-C}$ = 3.0 Hz), 115.1 (q, $^3J_{F-C}$ = 4.0 Hz), 114.5, 113.8, 112.7, 72.2, 19.1; IR (thin film) 3431, 2932, 1702, 1671, 1320, 1280, 1111; HRMS (ESI) calcd for $[C_{18}H_{15}F_3O_4 - H]^-$ 351.0850, found 351.0849.

2-(3-methylbut-3-en-1-yl)phenyl benzoate (1o). Prepared under reflux conditions. Starting with benzoic acid (0.293 g, 2.4 mmol), phenol **6a** (0.324 g, 2.0 mmol), *N*,*N*′-dicyclohexylcarbodiimine (0.743 g, 3.6 mmol) and 4-(dimethylamino)pyridine (0.122 g, 1.0 mmol), the reaction afforded **1o** as a colorless oil (0.490 g, 1.84 mmol, 92%) after flash column chromatography. R_f = 0.65 (4:6 CH_2Cl_2:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.5, 1.5 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 8.0 Hz, 2H), 7.36−7.33 (m, 1H), 7.31 (dd, J = 8.0, 1.5 Hz, 1H), 7.27−7.24 (m, 1H), 7.21 (dd, J = 8.0, 1.0 Hz, 1H), 4.73 (s, 1H), 4.69 (s, 1H), 2.79−2.76 (m, 2H), 2.37−2.34 (m, 2H), 1.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 149.1, 144.9, 134.0, 133.6, 130.1, 130.0, 129.4, 128.6, 127.1, 126.1, 122.3, 110.5, 38.2, 28.9, 22.3; IR (thin film) 3440, 3072, 2936, 1736, 1649, 1264; HRMS (ESI) calcd for $[C_{18}H_{18}O_2 + Na]^+$ 289.1199, found 289.1198

General procedure for intramolecular oxyacylation reaction. In a nitrogen-filled glovebox, a 1 dram vial containing salicylic ester substrate (0.1 mmol) was charged with a freshly prepared solution of $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol, condition A) or Ir(cod)(acac) (3.20 mg, 0.008 mmol, condition B) in 0.4 mL mesitylene. A solution of (*R*)- or (*S*)-MOP (5.62 mg, 0.012 mmol) in 0.4 mL mesitylene was added. Additional mesitylene (0.2 mL) was added, this additional volume could be used for rinsing purposes. The vial was sealed and the mixture was maintained at 170 or 150 °C (as noted) for 48 h. The reaction vial was then removed from the glovebox and solvent was removed under high vacuum. The crude mixture was purified by flash column chromatography (gradient, EtOAc/Hex or Et_2O/Hex) to afford the oxyacylation product.

Compounds **2a**, **2b**, **2d**, **2g**, **2i**, **2j**, **2k** and **2m** were prepared by the general procedure at 170 °C. Compounds **2c**, **2f**, **2h**, **2l**, and **2n** were prepared were prepared by the general procedure at 150 °C.

1-(2-hydroxyphenyl)-2-(2-methylchroman-2-yl)ethanone (2a). Prepared under condition A. Starting with **1a** (28.2 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*R*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2a** as a colorless oil (22.0 mg, 0.078 mmol, 78%) after flash column chromatography. R_f = 0.50 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.41 (s, 1H), 7.77 (dd, J = 8.1, 1.6 Hz, 1H), 7.47 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.13−7.04 (m, 2H), 6.97 (dd, J = 8.4, 1.0 Hz, 1H), 6.91−6.81 (m, 2H), 6.71 (d, J = 8.1 Hz, 1H), 3.40 (d, J = 14.9 Hz, 1H), 3.20 (d, J = 14.9 Hz, 1H), 2.89−2.72 (m, 2H), 2.13 (dt, J = 13.6, 6.7 Hz, 1H), 2.07−1.92 (m, 1H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 162.7, 153.0, 136.5, 131.3, 129.5, 127.4, 120.7, 120.2, 120.1, 118.7, 118.3, 117.3, 75.6, 46.7, 31.1, 25.0, 21.9; IR (thin film) 2916, 2848, 1632, 1581, 1487, 1350, 1244; HRMS (ESI) calcd for $[C_{18}H_{18}O_3 + Na]^+$ 305.1146, found 305.1161.

1-(2-hydroxy-4-methylphenyl)-2-(2-methylchroman-2-yl)-ethanone (2b). Prepared under condition A. Starting with **1b** (29.6 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2b** as a colorless oil (16.9 mg, 0.057 mmol, 57%) after flash column chromatography. R_f = 0.50 (1:9 Et_2O:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.47 (s, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.12−7.07 (m, 2H), 6.86 (td, J = 8.0, 1.5 Hz, 1H), 6.78 (app s, 1H), 6.73 (dd, J = 8.0, 1.5 Hz, 1H), 6.67 (dd, J = 8.5, 1.5 Hz, 1H), 3.37 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 14.5 Hz, 1H), 2.87−2.80 (m, 2H), 2.35 (s, 3H), 2.13−2.10 (m, 1H), 2.03−1.98 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 162.8, 153.1, 148.3, 131.2, 129.5, 127.4, 120.9, 120.2, 120.0, 118.4, 118.2, 117.4, 75.7, 46.6, 31.2, 25.0, 22.0, 21.9; IR (thin film) 3040, 2978, 2933, 1635, 1581, 1488, 1353, 1247; HRMS (ESI) calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, found 319.1295.

1-(4-fluoro-2-hydroxyphenyl)-2-(2-methylchroman-2-yl)-ethanone (2c). Prepared under condition B. Starting with **1c** (30.0 mg, 0.1 mmol), Ir(cod)(acac) (3.20 mg, 0.008 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 150 °C, after 48 h, the reaction afforded **2c** as a colorless oil (18.9 mg, 0.063 mmol, 63%) after flash column chromatography. R_f = 0.45 (1:9 Et_2O:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.77 (d, J = 1.5 Hz, 1H), 7.79 (dd, J = 8.5, 6.5 Hz, 1H), 7.12−7.08 (m, 2H), 6.87 (td, J = 8.0, 1.0 Hz, 1H), 6.70 (d, J = 8.5 Hz, 1H), 6.65 (dd, J = 10.0, 2.5 Hz, 1H), 6.57 (app td, J = 9.0, 2.5 Hz, 1H), 3.36 (d, J = 14.5 Hz, 1H), 3.13 (d, J = 14.5 Hz, 1H), 2.88−2.77 (m, 2H), 2.10−2.08 (m, 1H), 2.03−1.98 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.4, 167.4 (d, $^1J_{C-F}$ = 256.3 Hz), 165.3 (d, $^3J_{C-F}$ = 14.1 Hz), 152.9, 134.0 (d, $^3J_{C-F}$ = 14.1 Hz), 129.5, 127.5, 120.7, 120.3, 117.5, 117.3, 106.9 (d, $^2J_{C-F}$ = 22.1 Hz), 104.8 (d, $^2J_{C-F}$ = 24.0 Hz), 75.6, 47.2, 31.4, 24.9, 21.9; IR (thin film) 2978, 2933, 1637, 1582, 1488, 1356, 1251; HRMS (ESI) calcd for $[C_{18}H_{17}FO_3 + Na]^+$ 323.1054, found 323.1051.

1-(4-chloro-2-hydroxyphenyl)-2-(2-methylchroman-2-yl)-ethanone (2d). Prepared under condition A. Starting with **1d** (31.7 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2d** as a colorless oil (20.0 mg, 0.063 mmol, 63%) after flash column chromatography. R_f = 0.49 (1:9 Et_2O:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.56 (d, J = 1.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.12−7.08 (m, 2H), 6.99 (d, J = 2.0 Hz, 1H), 6.87 (t, J = 2.5 Hz, 1H), 6.84 (dd, J = 9.5, 1.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.37 (d, J = 14.5 Hz, 1H), 3.13 (d, J = 14.5 Hz, 1H), 2.88−2.76 (m, 2H), 2.13−2.07 (m, 1H), 2.03−1.98 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 163.4, 152.9, 142.3, 132.6, 129.5, 127.5, 120.7, 120.3, 119.3, 118.9, 118.3, 117.3, 75.6, 47.2, 31.3, 24.9, 21.9; IR (thin film) 3053, 2980, 2933, 1633, 1582, 1488, 1349, 1241; HRMS (ESI) calcd for $[C_{18}H_{17}ClO_3 + Na]^+$ 339.0758, found 339.0748.

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1-(4-bromo-2-hydroxyphenyl)-2-(2-methylchroman-2-yl)-ethanone (2e). Prepared under condition B. Starting with **1e** (36.1 mg, 0.1 mmol), Ir(cod)(acac) (3.20 mg, 0.008 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2e** as a colorless oil (12.6 mg, 0.035 mmol, 35%) after flash column chromatography. R_f = 0.50 (1:9 Et_2O:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.52 (s, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.12−7.08 (m, 2H), 6.99 (dd, J = 8.5, 2.0 Hz, 1H), 6.87 (app td, J = 7.5, 1.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 3.35 (d, J = 14.5 Hz, 1H), 3.13 (d, J = 14.5 Hz, 1H), 2.82−2.79 (m, 2H), 2.09−2.07 (m, 1H), 2.02−2.00 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 163.2, 152.9, 132.5, 131.0, 129.5, 127.5, 122.2, 121.5, 120.7, 120.3, 119.2, 117.3, 75.6, 47.2, 31.4, 24.9, 21.9; IR (thin film) 3417, 2978, 2933, 1631, 1582, 1487, 1349, 1240; HRMS (ESI) calcd for $[C_{18}H_{17}BrO_3 + Na]^+$ 383.0253, found 383.0261.

1-(4-trifluoromethyl-2-hydroxyphenyl)-2-(2-methylchroman-2-yl)ethanone (2f). Prepared under condition A. Starting with **1f** (35.0 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 150 °C, after 48 h, the reaction afforded **2f** as a colorless amorphous solid (28.7 mg, 0.082 mmol 82%) after flash column chromatography. R_f = 0.40 (1:9 EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.42 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 1.1 Hz, 1H), 7.11−7.07 (m, 3H), 6.87 (td, J = 7.5, 1.1 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.43 (d, J = 14.6 Hz, 1H), 3.20 (d, J = 14.6 Hz, 1H), 2.84−2.80 (m, 2H), 2.10 (ddd, J = 13.8, 7.6, 6.2 Hz, 1H), 2.01 (dt, J = 13.5, 6.6 Hz, 1H), 1.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 162.5, 152.8, 137.3 (app q, $^2J_{C-F}$ = 32.9 Hz),[45] 132.3, 129.6, 127.6, 123.0 (app q, $^1J_{C-F}$ = 271 Hz),38 122.2, 120.6, 120.4, 117.3, 115.8 (q, $^3J_{C-F}$ = 3.9 Hz), 114.9 (q, $^3J_{C-F}$ = 3.6 Hz), 75.6, 47.4, 31.4, 24.9, 21.9; IR (thin film) 3052, 2981, 2927, 1656, 1573, 1507, 1457, 1216; HRMS (ESI) calcd for $[C_{19}H_{17}F_3O_3 + Na]^+$ 373.1022, found 373.1028.

1-(4-methoxy-2-hydroxyphenyl)-2-(2-methylchroman-2-yl)-ethanone (2g). Prepared under condition B. Starting with **1g** (31.2 mg, 0.1 mmol), Ir(cod)(acac) (3.20 mg, 0.008 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2g** as a colorless oil (16.8 mg, 0.054 mmol, 54%) after flash column chromatography. R_f = 0.32 (1:9 Et_2O:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.97 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.11−7.07 (m, 2H), 6.85 (td, J = 7.0, 1.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.42−6.38 (m, 2H), 3.84 (s, 3H), 3.31 (d, J = 14.0 Hz, 1H), 3.09 (d, J = 14.0 Hz, 1H), 2.81 (app t, J = 7.0 Hz, 2H), 2.14−2.08 (m, 1H), 2.02−1.96 (m, 1H), 1.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 166.2, 165.8, 153.1, 133.2, 129.5, 127.4, 120.9, 120.2, 117.4, 114.6, 107.5, 100.7, 75.7, 55.6, 46.6, 31.3, 25.0, 22.0; IR (thin film) 3427, 2975, 2935, 1625, 1582, 1488, 1363, 1252, 1209; HRMS (ESI) calcd for $[C_{19}H_{20}O_4 + Na]^+$ 335.1254, found 335.1252.

1-(2-hydroxy-5-nitrophenyl)-2-(2-methylchroman-2-yl)-ethan-1-one (2h). Prepared under condition B. Starting with **1h** (32.7 mg, 0.1 mmol), Ir(cod)(acac) (3.20 mg, 0.008 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 150 °C, after 48 h, the reaction afforded **2h** as a yellow amorphous solid (20.3 mg, 0.062 mmol, 62%) after flash column chromatography. R_f = 0.35 (1:9 EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 13.03 (s, 1H), 8.86 (d, J = 1.5 Hz, 1H), 8.33 (dd, J = 9.0, 2.0 Hz, 1H), 7.08−7.04 (m, 3H), 6.85 (td, J = 7.0, 1.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 3.41 (d, J = 14.5 Hz, 1H), 3.32 (d, J = 14.5 Hz, 1H), 2.90−2.78 (m, 2H), 2.08−1.98 (m, 2H), 1.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6, 167.4, 152.6, 139.4, 131.1, 129.5, 128.5, 127.7, 120.6, 120.3, 119.3, 119.2, 117.3, 75.4, 48.2, 31.2, 24.7, 21.9; IR (thin film) 2926, 1639, 1582, 1525, 1487, 1342, 1294; HRMS (ESI) calcd for $[C_{18}H_{17}NO_5 - H]^-$ 326.1034, found 326.1034.

1-(2-hydroxy-5-chlorophenyl)-2-(2-methylchroman-2-yl)-ethan-1-one (2i). Prepared under condition A. Starting with **1i** (31.7 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2i** as a colorless oil (16.8 mg, 0.053 mmol, 53%) after flash column chromatography. R_f = 0.49 (1:9 Et_2O:Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.30 (s, 1H), 7.76 (d, J = 3.0 Hz, 1H), 7.40 (dd, J = 8.5, 2.5 Hz, 1H), 7.13−7.09 (m, 2H), 6.93 (d, J = 9.5 Hz, 1H), 6.87 (td, J = 7.5, 1.0 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 3.36 (d, J = 14.5 Hz, 1H), 3.14 (d, J = 14.5 Hz, 1H), 2.88−2.76 (m, 2H), 2.12−2.06 (m, 1H), 2.03−1.98 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.0, 161.2, 152.8, 136.4, 130.8, 129.5, 127.7, 123.4, 120.8, 120.6, 120.4, 119.9, 117.4, 75.5, 47.4, 31.4, 24.9, 21.9; IR (thin film) 2979, 2934, 1637, 1582, 1487, 1348, 1241; HRMS (ESI) calcd for $[C_{18}H_{17}ClO_3 + Na]^+$ 339.0758, found 339.0762.

1-(2-hydroxynaphthalen-1-yl)-2-(2-methylchroman-2-yl)-ethan-1-one (2j). Prepared under condition A. Starting with **1j** (33.2 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*S*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2j** as an off-white amorphous solid (14.9 mg, 0.045 mmol, 45%) after flash column chromatography. R_f = 0.32 (2:8 EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 9.43 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.73 (dd, J = 8.0, 1.0 Hz, 1H), 7.62 (td, J = 7.0, 1.5 Hz, 1H), 7.41 (td, J = 7.0, 1.0 Hz, 1H), 7.11−7.06 (m, 3H), 6.84 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (dd, J = 8.0, 1.0 Hz, 1H), 5.44 (br s, 1H), 3.02 (d, J = 16.0 Hz, 1H), 2.87−2.76 (m, 3H), 2.21−2.15 (m, 1H), 2.11−2.04 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 161.8, 153.6, 137.5, 131.2, 130.0, 129.5, 128.8, 128.3, 127.6, 127.4, 125.5, 124.6, 120.7, 119.3, 115.3, 111.6, 81.5, 48.4, 39.1, 24.4, 23.3; IR (thin film) 3147, 2975, 1649, 1596, 1458, 1437, 1376, 1240; HRMS (ESI) calcd for $[C_{22}H_{20}O_3 + Na]^+$ 355.1305, found 355.1304.

2-(2-ethylchroman-2-yl)-1-(2-hydroxyphenyl)ethan-1-one (2k). Prepared under condition A. Starting with **1k** (29.6 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*R*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2k** as a colorless oil (14.8 mg, 0.050 mmol, 50%) after flash column chromatography. R_f = 0.57 (1:4 Et_2O:Hex); ^1H NMR (300 MHz, $CDCl_3$) δ 12.42 (s, 1H), 7.79 (dd, J = 8.1, 1.5 Hz, 1H), 7.48−7.45 (m, 1H), 7.10−7.06 (m, 2H), 6.96 (dd, J = 8.4, 0.9 Hz, 1H), 6.90−6.83 (m, 2H), 6.72 (d, J = 8.1 Hz, 1H), 3.34 (d, J = 15.2 Hz, 1H), 3.25 (d, J = 15.2 Hz, 1H), 2.81−2.77 (m, 2H), 2.10−2.05 (m, 2H), 1.86 (q, J = 7.4 Hz, 2H), 1.02−0.99 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.8, 162.7, 153.1, 136.5, 131.3, 129.5, 127.4, 121.0, 120.4, 120.1, 118.7, 118.3, 117.4, 78.0, 43.7, 29.6, 28.5, 21.7, 7.8.; IR (thin film) 3053, 2930, 1629, 1574, 1487, 1456, 1305. HRMS (ESI) calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, found 319.1308.

2-(2-ethylchroman-2-yl)-1-(2-hydroxy-4-(trifluoromethyl)-phenyl)ethan-1-one (2l). Prepared under condition A. Starting with **1l** (38.0 mg, 0.104 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*R*)-MOP (5.62 mg, 0.012 mmol), at 150 °C, after 48 h, the reaction afforded **2l** as a colorless oil (28.0 mg, 0.077 mmol 74%) after flash column chromatography. R_f = 0.51 (1:9 EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.43 (s, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 1.2 Hz, 1H), 7.10−7.06 (m, 3H), 6.85 (td, J = 7.5, 1.1 Hz, 1H), 6.70−6.67 (m, 1H), 3.33 (d, J = 14.8 Hz, 1H), 3.28 (d, J = 14.8 Hz, 1H), 2.81−2.77 (m, 2H), 2.08−2.06 (m, 2H), 1.86−1.83 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.9, 162.5, 152.9, 137.2 (q, $^2J_{C-F}$ = 33.0 Hz), 132.3, 129.5, 127.5, 123.0 (q, $^1J_{C-F}$ = 271.3 Hz), 122.2, 120.8, 120.3, 117.3, 115.8 (q, $^3J_{C-F}$ = 4.0 Hz), 114.9 (q, $^3J_{C-F}$ = 3.0 Hz), 78.1, 44.4, 29.5, 28.5, 21.6, 7.8; IR (thin film) 2970, 1930, 1649, 1624, 1582, 1488, 1329, 1236; HRMS (ESI) calcd for $[C_{20}H_{19}F_3O_3 - H]^-$ 363.1214, found 363.1216.

1-(2-hydroxyphenyl)-2-(2-methyl-2,3-dihydrobenzofuran-2-yl)ethan-1-one (2m). Prepared under condition A. Starting with **1m** (26.8 mg, 0.1 mmol), $[Ir(cod)OMe]_2$ (2.65 mg, 0.004 mmol) and (*R*)-MOP (5.62 mg, 0.012 mmol), at 170 °C, after 48 h, the reaction afforded **2m** as a colorless oil (11.0 mg, 0.041 mmol 41%) after flash column chromatography. R_f = 0.37 (1:9 EtOAc/Hex); ^1H NMR (500 MHz, $CDCl_3$) δ 12.25 (s, 1H), 7.74 (dd, J = 8.3, 1.5 Hz, 1H), 7.49−7.45 (m, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.89−6.83 (m, 2H), 6.70 (d, J = 7.8 Hz, 1H), 3.53 (d, J = 16.1 Hz, 1H), 3.39 (d, J = 16.1 Hz, 1H), 3.34 (d, J = 16.1 Hz, 1H), 3.17 (d, J = 15.6 Hz, 1H), 1.64 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.8, 162.6, 158.0, 136.6, 130.6, 128.1, 126.7, 125.2, 120.5, 120.0, 118.9, 118.5, 109.6, 86.9, 48.0, 41.6, 26.6; IR (thin film) 3054, 1642, 1598, 1447, 1242; HRMS (ESI) calcd for $[C_{17}H_{16}O_3 + Na]^+$ 291.0992, found 291.0989.

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1-(2-hydroxy-4-(trifluoromethyl)phenyl)-2-(2-methyl-2,3-dihydrobenzo[b][1,4]dioxin-2-yl)ethan-1-one (2n). Prepared under condition B. Starting with **1n** (120.0 mg, 0.34 mmol), Ir(cod)(acac) (9.60 mg, 0.024 mmol) and (*S*)-MOP (16.90 mg, 0.036 mmol), at 150 °C, after 48 h, the reaction afforded **2n** as a colorless amorphous solid (39.5 mg, 0.112 mmol, 33%) after flash column chromatography. R_f = 0.55 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.27 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 7.04 (dd, J = 8.5, 1.0 Hz, 1H), 6.94−6.91 (m, 1H), 6.90−6.86 (m, 2H), 6.80−6.77 (m, 1H), 4.34 (d, J = 12.0 Hz, 1H), 3.99 (d, J = 11.0 Hz, 1H), 3.46 (d, J = 16.0 Hz, 1H), 3.27 (d, J = 15.5 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 162.4, 142.1, 141.7, 137.5 (q, $^2J_{C-F}$ = 33.0 Hz), 131.5, 122.9 (q, $^1J_{C-F}$ = 272.0 Hz), 122.3, 121.8, 121.5, 117.7, 117.2, 116.0 (q, $^3J_{C-F}$ = 4.0 Hz), 115.1 (q, $^3J_{C-F}$ = 4.0 Hz), 73.8, 70.2, 43.1, 21.8; IR (thin film) 3423, 2982, 2928, 1653, 1594, 1494, 1331, 1263; HRMS (ESI) calcd for $[C_{18}H_{15}F_3O_4 - H]^-$ 351.0850, found 351.0837.

2-(2-(2-methylchroman-2-yl)acetyl)phenyl acetate (2p):[46] To a solution of **2a** (0.036 g, 0.128 mmol), pyridine (21 μL, 0.26 mmol), 4-(dimethylamino)pyridine (0.0024 g, 0.02 mmol) in freshly distilled CH_2Cl_2 was added acetic anhydride (21 μL, 0.20 mmol). The reaction was stirred at room temperature until TLC indicated the complete consumption of starting material. The reaction mixture was diluted with EtOAc (20 mL), washed with 1 M HCl (10 mL), H_2O (10 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by flash column chromatography (5:95 EtOAc/Hex) to give **2p** as a colorless oil (0.0360 g, 87%). R_f = 0.32 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 9.8, 1.5 Hz, 1H), 7.52 (td, J = 7.3, 1.0 Hz, 1H), 7.29 (td, J = 7.8, 1.0 Hz, 1H), 7.11 (dd, J = 7.8, 1.0 Hz, 1H), 7.09−7.06 (m, 2H), 6.84 (td, J = 7.3, 1.0 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 3.28 (d, J = 15.6 Hz, 1H), 3.18 (d, J = 16.1 Hz, 1H), 2.81−2.75 (m, 2H), 2.28 (s, 3H), 2.18−2.13 (m, 1H), 2.01−1.97 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 169.4, 153.1, 148.6, 133.1, 131.7, 130.0, 129.5, 127.3, 125.9, 123.8, 120.9, 120.1, 117.3, 75.6, 49.4, 30.7, 24.9, 22.0, 21.0; IR (thin film) 3072, 2932, 1765, 1689, 1581, 1487, 1451, 1368, 1246, 1221, 1190; HRMS (ESI) calcd for $[C_{20}H_{20}O_4 + Na]^+$ 347.1254, found 347.1259.

1-(2-methoxyphenyl)-2-(2-methylchroman-2-yl)ethan-1-one (2r):[47] To a 1 dram vial with PTFE lined cap, **2a** (0.0282 g, 0.1 mmol), potassium carbonate (0.041 g, 0.3 mmol) and acetone (0.5 mL, Technical grade) were added. Iodomethane (25 μL, 0.4 mmol) was added via a microsyringe. The reaction was stirred at room temperature until TLC indicated the complete consumption of starting material. The solvent was evaporated under vacuum and 5 mL water was added. The mixture was stirred for 1 h and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give **2r** as a colorless oil (0.0298 g, >95%) after flash column chromatography. R_f = 0.28 (1:9 Et_2O:Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 2.0 Hz, 1H), 7.43 (td, J = 7.5, 1.5 Hz, 1H), 7.06−7.03 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.82 (td, J = 7.0, 1.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 3.72 (s, 3H), 3.56 (d, J = 15.5 Hz, 1H), 3.20 (d, J = 15.5 Hz, 1H), 2.78−2.75 (m, 2H), 2.13−2.09 (m, 1H), 2.00−1.94 (m, 1H), 1.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 157.9, 153.3, 133.0, 129.9, 129.8, 129.3, 127.2, 121.1, 120.6, 119.8, 117.2, 111.4, 75.8, 55.2, 51.0, 31.0, 25.4, 22.1; IR (thin film) 3432 (br), 3037, 2972, 2934, 1675, 1597, 1581, 1487, 1454, 1350, 1246; HRMS (ESI) calcd for $[C_{19}H_{20}O_3 + Na]^+$ 319.1305, found 319.1308.

2-(2-(2-methylchroman-2-yl)acetyl)phenyl trifluoromethanesulfonate (2q):[48] To a solution of **2a** (0.0565 g, 0.2 mmol) and pyridine (32 μL, 0.4 mmol) in freshly distilled CH_2Cl_2 (2.0 mL) was added trifluoromethanesulfonic anhydride (40 μL, 0.24 mmol) via a microsyringe at 0 °C. The mixture was warmed to room temperature and stirred for 24 h. The mixture was then diluted with CH_2Cl_2 (30 mL) and washed with 1 M HCl, satd $NaHCO_3$ and brine. After drying over Na_2SO_4 and concentration in vacuo, the crude product was purified by flash column chromatography (1:99 EtOAc/Hex) to give compound **2q** as a light brown oil (0.0730 g, 88%): R_f = 0.35 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.0, 2.0 Hz, 1H), 7.58 (td, J = 7.8, 1.5 Hz, 1H), 7.43 (td, J = 8.0, 2.0 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.07−7.03 (m, 2H), 6.84 (td, J = 7.5, 1.0 Hz, 1H), 6.56 (dd, J = 7.5, 1.0 Hz, 1H), 3.39 (d, J = 15.5 Hz, 1H), 3.18 (d, J = 15.0 Hz, 1H), 2.82−2.77 (m, 2H), 2.16−2.12 (m, 1H), 2.03−1.98 (m, 1H), 1.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 152.8, 146.3, 133.2, 130.6, 129.5, 128.4, 127.3, 122.6, 120.8, 120.2, 118.5 (q, $^1J_{C-F}$ = 318 Hz), 117.1, 75.6, 50.0, 31.9, 24.7, 21.9 (one carbon signal is not resolved in the aromatic region); IR (thin film) 3425, 2979, 2934, 1697, 1582, 1487, 1425, 1248, 1213; HRMS (ESI) calcd for $[C_{19}H_{17}F_3O_5S + Na]^+$ 437.0641, found 437.0649.

1-([1,1′-Biphenyl]-2-yl)-2-(2-methylchroman-2-yl)ethan-1-one (2s).[49] To a 1 dram vial with a PTFE lined cap were added **2q** (0.0414 g, 0.1 mmol), tetrakis(triphenylphosphine)palladium (0.0058 g, 0.005 mmol), potassium phosphate (0.0255 g, 0.12 mmol), phenylboronic acid (0.0146 g, 0.12 mmol), and degassed 1,4-dioxane (0.5 mL) under N_2 atmosphere. The reaction was maintained at 110 °C for 14 h. After allowing to cool to room temperature, the mixture was diluted with EtOAc (20 mL) and filtrated to remove any insoluble materials. After concentration in vacuo, the crude mixture was purified by flash column chromatography (1:99 EtOAc/Hex) to give compound **2s** as a white amorphous solid (0.0276 g, 0.081 mmol, 81%): R_f = 0.52 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.48 (dd, J = 7.5, 1.0 Hz, 1H), 7.45−7.42 (m, 1H), 7.35−7.33 (m, 3H), 7.27 (d, J = 7.5 Hz, 1H), 7.08−7.06 (m, 2H), 6.98−6.95 (m, 2H), 6.81 (t, J = 7.0 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 2.64 (d, J = 14.5 Hz, 1H), 2.62−2.57 (m, 1H), 2.43−2.36 (m, 1H), 2.37 (d, J = 14.5 Hz, 1H), 1.83−1.74 (m, 2H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 152.9, 141.9, 140.4, 140.0, 130.3, 129.9, 129.2, 128.9, 128.5, 127.8, 127.7, 127.4, 127.1, 120.6, 120.0, 117.1, 75.3, 50.2, 31.4, 25.3, 21.7; IR (thin film) 3059, 2932, 1679, 1581, 1487, 1454, 1376, 1306, 1243; HRMS (ESI) calcd for $[C_{24}H_{22}O_2 + Na]^+$ 365.1512, found 365.1530.

2-(2-Methylchroman-2-yl)-1-phenylethan-1-one (2o).[50] To a 1 dram vial with PTFE lined cap were added **2q** (0.1242 g, 0.3 mmol), palladium acetate (0.0015 g, 0.006 mmol), triethylamine (125.5 μL, 0.9 mmol), triphenylphosphine (0.003 g, 0.012 mmol), and freshly distilled DMF (0.6 mL). Formic acid (88% aqueous solution, 26.0 μL, 0.6 mmol) was added. The reaction was stirred at 60 °C for 4 h under nitrogen. After allowing to cool to room temperature, the mixture was diluted with Et_2O (20 mL) and washed with 2 M LiCl (20 mL). The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (3:97 EtOAc/Hex) to give compound **2o** as a colorless oil (0.0690 g, 0.259 mmol, 86%): R_f = 0.56 (1:9 EtOAc/Hex); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.5, 1.0 Hz, 2H), 7.57 (tt, J = 7.0, 1.5 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.12−7.08 (m, 2H), 6.88 (td, J = 7.0, 1.0 Hz, 1H), 6.75 (dd, J = 8.5, 1.0 Hz, 1H), 3.41 (d, J = 15.5 Hz, 1H), 3.26 (d, J = 16.0 Hz, 1H), 2.82−2.79 (m, 2H), 2.22−2.16 (m, 1H), 2.07−2.02 (m, 1H), 1.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 153.1, 137.7, 133.0, 129.5, 128.4, 128.36, 127.3, 121.0, 120.0, 117.3, 75.7, 46.7, 30.8, 25.0, 22.0; IR (thin film) 3060, 2931, 1686, 1582, 1487, 1449, 1350, 1306, 1249; HRMS (ESI) calcd for $[C_{18}H_{18}O_2 + Na]^+$ 289.1199 found 289.1191.

Attempted Racemization of MOP. A scalemic mixture of MOP was generated by mixing solutions of (*R*)-MOP and (*S*)-MOP. HPLC analysis: Chiracel-OD-H column (diameter: 0.46 cm, length: 25 cm), isocratic mobile phase (0.5:99.5 IPA/hexanes) at a flow rate of 1.0 mL/min, UV detector (λ = 225 nm). (*S*)-MOP eluted at t_R = 7.4 min, and (*R*)-MOP eluted at t_R = 9.1 min. A sample of (*R*)-MOP (5 mg) in mesitylene (1.0 mL) was heated to 170 °C in a 1 dram vial with a PTFE-lined cap and maintained for 48 h. The solution was allowed to cool to room temperature, and a portion was diluted with hexanes and analyzed by HPLC using the conditions above, which indicated the sample was (*R*)-MOP (99% ee).

Resolution and Racemization of 2f. Enantioenriched samples of **2f** were obtained by HPLC separation using a Diacel Chemical Industries Chiracel-OD column (diameter: 0.46 cm, length: 25 cm), isocratic mobile phase (10:10:80 IPA/EtOH/hexanes) at a flow rate of 0.25 mL/min, UV detector (λ = 254 nm). Racemate was injected in 10

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μL injections at a concentration of ∼1 mg/5 μL. The fast eluting enantiomer eluted at 17.0 min, and the slow eluting enantiomer eluted at 27.6 min. After four injections, we obtained 3.6 mg of the fast eluting enantiomer and 4.0 mg of the slow eluting enantiomer.

A 1 dram vial containing enantioenriched **2f** (fast eluting enantiomer, 3.6 mg, 0.010 mmol) was brought into a nitrogen-filled glovebox. The vial was charged with mesitylene (0.1 mL), sealed with a PTFE-lined cap, heated at 150 °C, and stirred for 24 h. After cooling to room temperature, the solution was diluted with hexanes and analyzed by HPLC, Chiracel-OD column (diameter: 0.46 cm, length: 25 cm), isocratic mobile phase (10:10:80 IPA/EtOH/hexanes) at a flow rate of 0.25 mL/min, UV detector (λ = 254 nm), fast eluting enantiomer (t_R = 17.0 min, area percent 51.4), slow eluting enantiomer (t_R = 27.6, area percent 48.6), indicating an ee of <3%.

A 1 dram vial containing enantioenriched **2f** (slow eluting enantiomer, 4.0 mg, 0.011 mmol) was brought into a nitrogen-filled glovebox. $[Ir(cod)OMe]_2$ (0.3 mg, 0.00044 mmol) and (*R*)-MOP (0.4 mg, 0.00088 mmol) were added as a solution in mesitylene (0.01 and 0.02 M, respectively) via microsyringe. The vial was charged with mesitylene (0.1 mL), sealed with a PTFE-lined cap, heated at 150 °C, and stirred for 24 h. After cooling to room temperature, the solution was diluted with hexanes and analyzed by HPLC Chiracel-OD column (diameter: 0.46 cm, length: 25 cm), isocratic mobile phase (10:10:80 IPA/EtOH/hexanes) at a flow rate of 0.25 mL/min, UV detector (λ = 254 nm), fast eluting enantiomer (t_R = 17.0 min, area percent 51.7), slow eluting enantiomer (t_R = 27.6, area percent 48.3), indicating an ee of 3%.

■ ASSOCIATED CONTENT

Supporting Information

HPLC chromatograms for racemization studies, copies of NMR spectra for new compounds, and associated original NMR FID files. 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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