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Rhodium(III)-Catalyzed Redox-Neutral Synthesis of Isoquinolinium Salts via C−H Activation of Imines

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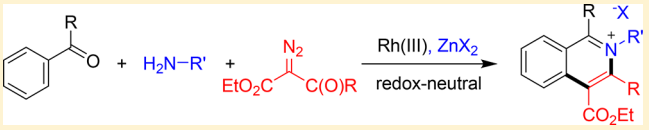
Supporting Information

ABSTRACT: Redox-neutral synthesis of isoquinolinium salts via C−H activation of presynthesized or in situ formed imines and coupling with α-diazo ketoesters has been realized, where a zinc salt promotes cyclization as well as provides a counteranion. Under three-component conditions, both ketone and aldehydes are viable arene sources. The coupling of imines with diazo malonates under similar conditions afforded isoquinolin-3-ones as the coupling product.



INTRODUCTION

The last few decades have witnessed significant progress of transition metal-catalyzed C−H bond activation of arenes as an increasingly important strategy for the construction of value-added aromatics with high step- and -atom economy. This strategy has been extensively employed in the synthesis of complex functional materials and natural products.[1] Among most C−H functionalization reactions, directing groups (DGs) have been commonly employed to enhance the effective concentration of the catalyst, leading to active metallacyclic intermediates for subsequent functionalization. However, the presence of a pendant directing group in the product is often undesirable for product applications.[2] Thus, bifunctional directing groups have been developed.[2,3]

As a common bifunctional DG, imine bears both electrophilic carbon and nucleophilic nitrogen sites and has been widely used in C−H activation. Cheng,[4] Miura,[5] Zhao,[6] and our group[7] have reported [3 + 2] coupling of imines with alkynes by taking advantage of the electrophilicity of imines. On the other hand, while the nucleophilicity of protic NH DGs in postcoupling C−H annulation is well-known,[8] *N*-substituted imines only occasionally participated in annulative N−C coupling, which led to ammonium salt formation.[1b] Thus, Cheng elegantly reported synthesis of isoquinolinium salts via Rh(III)- and Ru(II)-catalyzed oxidative coupling of imines and alkynes.[9] Following these reports, many quaternary ammonium salts have been accessed by this oxidative annulation approach.[10] The Glorius[11] group also reported that oximes could react as a special imine in redox-neutral coupling with diazo compounds to give isoquinoline *N*-oxides, where the nucleophilicity of the nitrogen allows for cyclization. Despite the progress, the scope of synthesis of isoquinoliniums and other quaternary ammoniums, which widely exist in natural products and functional materials,[9,10,12] remains rather limited, and the coupling partners are typically limited to alkynes under oxidative conditions. We reasoned that the postcoupling cyclization may be mediated by other Lewis acids such as Zn(II) salts,[13] which may also provide a counteranion for isoquinolinium salt. We now report one-pot synthesis of *N*-alkyl or *N*-aryl isoquinolinium by three-component reaction of aryl aldehyde or ketone, primary amine, and diazo compound via C−H activation under redox-neutral conditions. Of note, these three-component reactions proceed efficiently under operationally simple conditions.[14]

RESULTS AND DISCUSSION

Optimization studies have been performed on the three-component coupling of benzaldehyde (**1a**, 0.3 mmol), 4-methoxyaniline (**2a**, 0.2 mmol), and ethyl 2-diazo-3-oxobutanoate (**3a**, 0.24 mmol) with $[(Cp^*RhCl_2)_2]$ as a catalyst and $Zn(OTf)_2$ as an additive in CF_3CH_2OH, from which product **4aaa** was isolated in 45% yield (Table 1, entry 1). Increasing the temperature to 110 °C improved the yield to 56% (entry 2). The yield was further boosted when a stoichiometric amount of $Zn(OTf)_2$ was used (entry 3), and further introduction of NaOTf improved the yield to 91% (entry 4). Coupling in DCE or MeOH afforded lower yields, and TFE proved to be the optimal solvent (entries 4−6). A comparable yield was also reached when the triflate anion in the additives was switched to NTf_2 (entry 8).

With the optimized conditions in hand, we next investigated the scope of this one-pot system (Scheme 1). Benzaldehydes bearing various EDGs at the para, meta, and ortho positions were all applicable, and the desired products were isolated in high yields (**4baa**−**4faa**, 82−93%). 1-Naphthaldehyde and thiophene-2-carbaldehyde also coupled smoothly to afford the corresponding products **4gaa** and **4haa** in good yield. The reaction was not restricted to employment of 4-methoxyaniline; other anilines, benzylamine, and alkylamines also reacted efficiently to give various *N*-substituted isoquinolinium salts **4aba**−**4ada** in excellent yield. The scope of diazo substrate was

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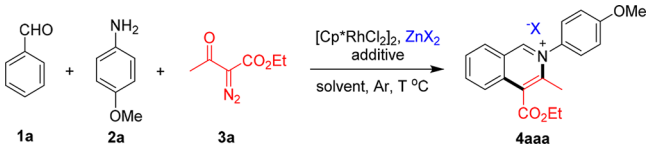
Table 1. Optimization on Isoquinolinium Synthesis[a]



1a 2a 3a 4aaa

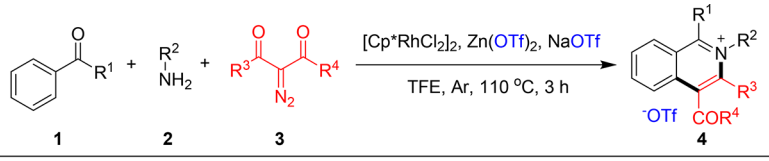
entry	ZnX_2 (equiv)	additive (equiv)	solvent	T (°C)	yield[b] (%)
1	$Zn(OTf)_2$ (0.5)		TFE	80	45
2	$Zn(OTf)_2$ (0.5)		TFE	110	56
3	$Zn(OTf)_2$ (1.0)		TFE	110	78
4	**$Zn(OTf)_2$ (1.0)**	**NaOTf (1.0)**	**TFE**	**110**	**91**
5	$Zn(OTf)_2$ (1.0)	NaOTf (1.0)	DCE	110	68
6	$Zn(OTf)_2$ (1.0)	NaOTf (1.0)	MeOH	110	57
7	$Zn(NTf_2)_2$ (0.5)		TFE	80	75
8	$Zn(NTf_2)_2$ (0.5)	$NaNTf_2$ (0.5)	TFE	110	88

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), TFE (2 mL), 80–110 °C, 3 h. [b]Isolated yield.

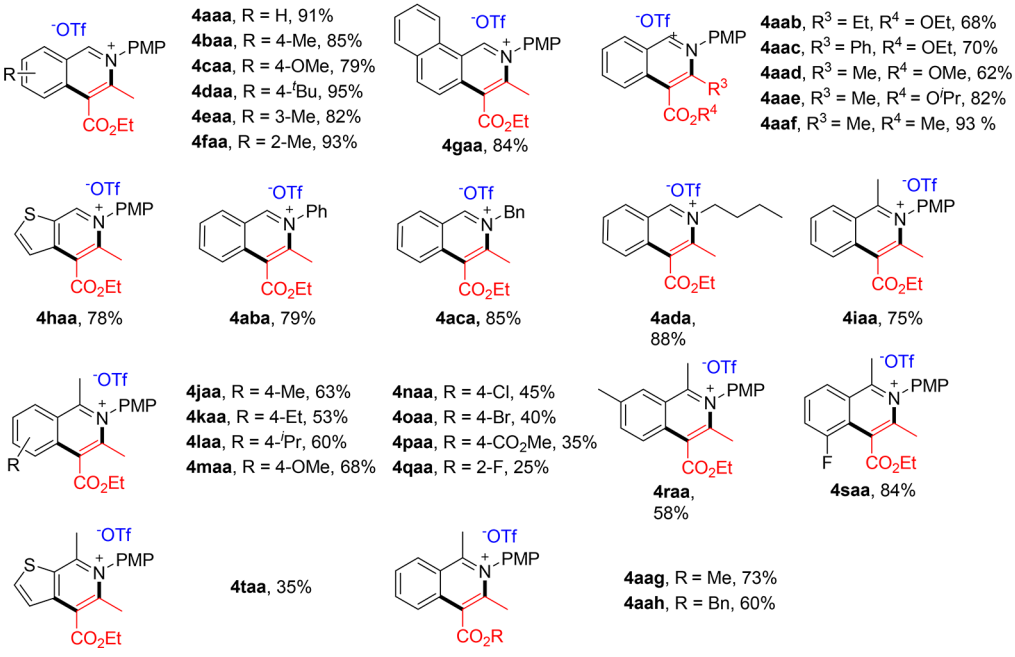
then briefly explored. It was found that α-diazo ketoesters with different ketone and ester groups as well as α-diazo acetylacetone participated in this reaction in good to excellent yield (**4aab**–**4aaf**, 62–93%). To better define the scope, the aldehyde substrate was extended to acetophenones, which had not been applied in one-pot synthesis of isoquinoliniums due to their lower reactivity in the initial stage imine formation. We reasoned that the high polarity of TFE should conduce to favorable imine condensation. Indeed, while acetophenones generally exhibited lower reactivity, the desired isoquinolinium salts were still isolated in moderate to good yields. The reaction was sensitive to steric effect as in the isolation of **4qaa** in low yield. However, electronic effects of the para substituent had only marginal influence (**4iaa**–**4paa**). Introduction of a meta substituent is also tolerated, and 3-methylacetophenone coupled in high regioselectivity at the less hindered ortho position to give **4raa** in 58% yield. The site-selectivity of 3-fluoroacetophenone was switched to the more hindered position likely due to secondary coordination effect of the F group.[15] In line with the reaction of benzaldehyde, 1-(thiophen-2-yl)ethan-1-one took part in this three-component system to give **4taa** in 35% yield.

The coupling of poorly reactive ketones (such as benzophenone) failed under the above standard conditions. Alternatively, presynthesized imines were employed. A mixture of imine **5a** and diazo **3a** was treated with $Cp^*Rh(OAc)_2$ in the presence of $Zn(NTf_2)_2$ in DCE at 40 °C. Thus, **6aa** was obtained in 35% yield, and the structure of **6aa** was characterized by X-ray crystallography (CCDC 1822604). To further improve the efficiency of this catalytic system, a series of solvents, additives, and the amounts of **5a** and **3a** were screened. Finally, we found that **6aa** could be achieved with 82% yield by treatment of **5a** (0.3 mmol) and **3a** (0.2 mmol) with $Cp^*Rh(OAc)_2$ in the presence of $Zn(NTf_2)_2/NaNTf_2$ and HOAc in TFE. In contrast, lower yield was isolated when different triflate salts were chosen as additives. Despite the acidity of the *N*-CH_2 methylene protons, deprotonation to give an isoquinolinium ylide was not observed. We then briefly

Scheme 1. Scope of Three-Component Coupling for Synthesis of Isoquinoliniums[a]



1 2 3 4



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), **3** (0.24 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $Zn(OTf)_2$ (100 mol %), NaOTf (100 mol %), TFE (2 mL), 110 °C, isolated yield.

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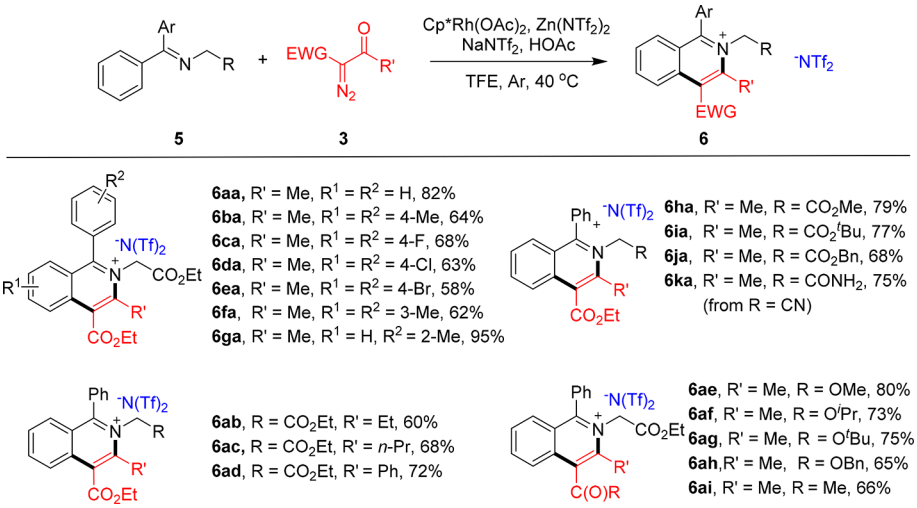
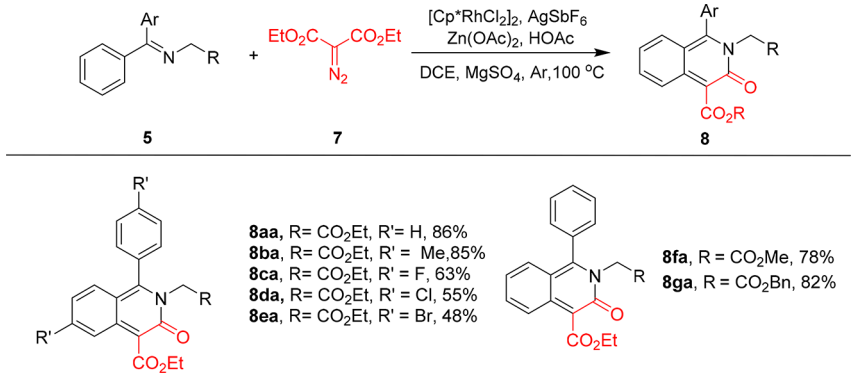
Scheme 2. Scope of Presynthesized Imine and Diazo Esters for Isoquinolinium Synthesis[a]



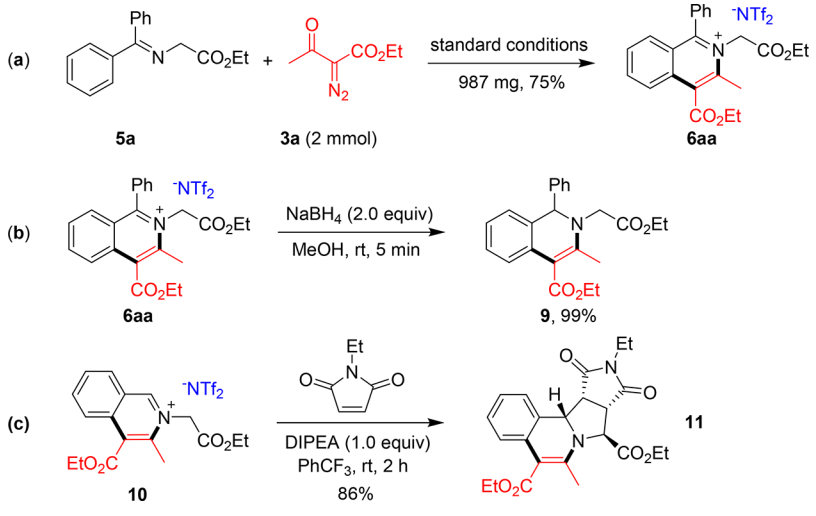
[a]Reaction conditions: $Cp^*Rh(OAc)_2$ (8 mol %), $Zn(NTf)_2$ (50 mol %), $NaNTf_2$ (1 equiv), HOAc (1 equiv), **5** (0.3 mmol), **3** (0.2 mmol), TFE (2 mL), 40 °C for 12 h, isolated yield.

Scheme 3. Synthesis of Isoquinolin-3-ones[a]



[a]Reaction conditions: **5** (0.3 mmol), diazo ester **7** (0.2 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Zn(OAc)_2$ (50 mol %), $MgSO_4$ (2 equiv), HOAc (2 equiv), DCE (2 mL), 100 °C, isolated yield.

Scheme 4. Gram-Scale Synthesis and Derivatization Reactions



examined the scope of this system, and the results are shown in Scheme 2. Introduction of alkyl and halogen groups is well tolerated (**6ba**–**6ga**). The reaction was sensitive to steric perturbation at the benzene rings, and the reaction proceeded selectively at the less hindered ring (**6ga**). Variation of the methylene-bound EWG group to other esters or a CN group

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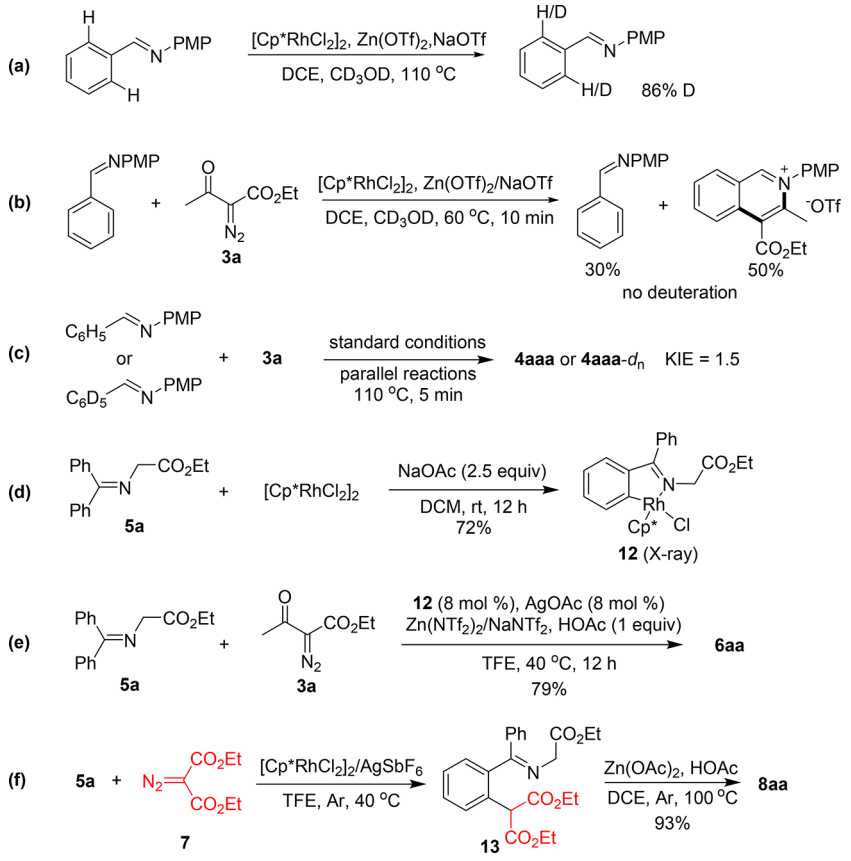
Scheme 5. Mechanistic Studies



had minimal influence (**6ha**–**6ka**, 68–79%). In the case of the CN group, complete hydrolysis to an amide group was observed although the annulation was also accommodated (**6ka**). In line with above observations, several different diazo esters were fully compatible, and the corresponding products were isolated in 60–80% yield (**6ab**–**6ai**).

α-Diazo diazomalonates, another class of diazo compounds, also coupled with benzophenone imines under different Rh(III)-catalyzed conditions to give isoquinolin-3-ones (Scheme 3), which had been only accessed under Co(III) catalysis.[8,16] The reaction of diethyl 2-diazomalonate **7** and imine **5a** in the presence of $[(Cp^*RhCl_2)_2]$, $Zn(OAc)_2$, and HOAc in DCE at 100 °C afforded product **8aa** in 86% yield. Introduction of methyl or halogen substituents into the para positions of the phenyl rings also afforded the corresponding products **8ba**–**8ea** in good yields. Changing the methylene-bound EWG group to other esters did not affect the efficiency of this reaction (**8fa**–**8ga**).

To showcase the utility of this method, we managed to prepare **6aa** on a 2.0 mmol scale. As a result, **6aa** was obtained in a total yield of 75% (Scheme 4a). Treatment of product **6aa** with $NaBH_4$ led to rapid formation of amine **9** in excellent yield (Scheme 4b).[17] Isoquinolinium salts synthesized from aromatic aldehyde may react with dipolarophiles leading to 1,3-dipolar cycloaddition products. Thus, we synthesized isoqinolinium salt **10** in 78% yield according to the conditions in Scheme 3. Subsequently, compound **10** was treated with *N*-ethyl-maleimide in the presence of DIPEA, and the [3 + 2] cycloaddition took place smoothly to give a polycycle **11** in 86% yield as a single diastereomer (Scheme 4c).

Several experiments have been conducted to probe the reaction mechanism (Scheme 5). H/D exchange has been carried out between *N*-PMP benzaldimine and CD_3OD (Scheme 5a). ^1H NMR analysis revealed significant exchange (86% D) at both ortho positions in the absence of a coupling reagent. In contrast, no deuteration was detected for the recovered imine when the diazo ester **3a** was present (Scheme 5b), indicating irreversibility of the C–H activation in the catalytic system. Kinetic isotope effect of this coupling was then measured from two parallel experiments (Scheme 5c), and a value of k_H/k_D = 1.5 suggests that the C–H cleavage is not involved in the turnover-limiting step. To further explore intermediates of this system, imine **5a** was treated with a stoichiometric amount of $[Cp^*RhCl_2]_2$ in the presence of NaOAc (Scheme 5d),[18] from which rhodacycle **12** was isolated in good yield and was characterized by X-ray crystallography (CCDC 1822360). Application of **12** as a catalyst precursor to the coupling of **5a** and **3a** afforded the product **6aa** in comparably good yield (Scheme 5e), further confirming relevancy of C–H activation. To examine the role of Zn(II) in a cyclization process, an ortho alkylated intermediate (**13**) was prepared. Treatment of **13** with $Zn(OAc)_2$/AcOH led to clean formation of product **8aa** (Scheme 5f), suggesting that the cyclization is Zn-mediated and this rhodium-catalyzed system follows an analogous mechanism proposed by Glorious.[8b] Accordingly, it is quite possible that the related cyclization to isoquinolinium salts is also Zn(II)-mediated.

On the basis of our preliminary results and related C–H activation systems,[8b,11] a tentative mechanism to account for the present catalytic system is proposed (Scheme 6). Starting from an active $[Cp^*RhX_2]$ (X = Cl or OTf) catalyst,

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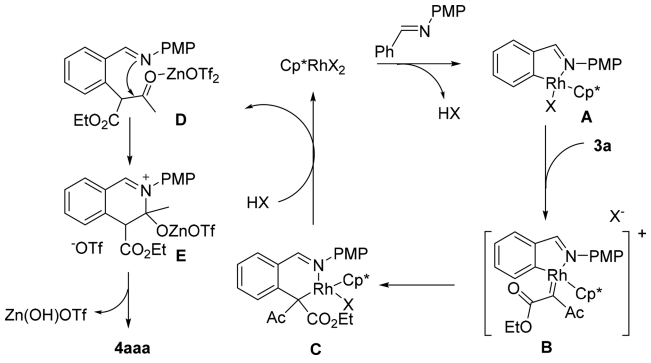
Scheme 6. Proposed Catalytic Cycle



cyclometalation of an imine generated a rhodacyclic intermediate **A**. Then coordination and denitrogenation of the diazo compound is followed to give a rhodium carbenoid intermediate **B**. Migratory insertion of the Rh-aryl bond to the carbene delivers a Rh(III) alkyl intermediate **C**, which is protonolyzed to give an alkylated intermediate. Subsequent Zn(II)-mediated activation of the carbonyl (**D**) and cyclization (via **E**) furnished the salt **4aaa**.

CONCLUSIONS

In summary, we have developed an effective method for synthesis of diverse isoquinolinium salts via rhodium(III)-catalyzed (three-component) coupling. The redox-neutral coupling of preformed or in situ generated imines with α-diazo ketoesters provided a new method for isoquinolinium synthesis, where the zinc salts promoted cyclization as well as provided a counteranion. This method of annulative coupling is complementary to existing systems in terms of redox-economy and entity of coupling partner and may find applications in synthesis of complex fused heterocycles.

EXPERIMENTAL SECTION

General Information. All chemicals were obtained from commercial sources and were used as received unless otherwise noted. All of the reactions were carried out under argon atmosphere using standard Schlenk technique. The ^{1}H NMR spectra were recorded on a 400 or 600 MHz NMR spectrometer. The ^{13}C NMR spectra were recorded at 100 or 150 MHz. The ^{19}F NMR spectra were recorded at 565 MHz. Chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), brs (broad singlet), etc. The residual solvent signals were used as references and the chemical shifts were converted to the TMS scale. High resolution mass spectra were obtained on an Agilent Q-TOF 6540 spectrometer. Column chromatography was performed on silica gel (300–400 mesh) using petroleum ether (PE)/dichloromathane (DCM). Thin layer chromatography was performed on precoated TLC plates and was visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel. The substrates **3**,[19] **5**,[20] **7**,[19] and *N*-PMP benzaldimine-d_5[21] were prepared according to the literature reports.

General Procedure for the Synthesis of Compound ***4***. A mixture of aldehyde **1** (0.3 mmol), amine **2** (0.2 mmol), diazo **3** (0.24 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol, 4.0 mol %), $Zn(OTf)_2$ (0.2 mmol, 1.0 equiv), NaOTf (0.2 mmol, 1.0 equiv), and TFE (2 mL) was charged into a pressure tube. The reaction mixture was stirred under Ar at 110 °C for 3 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using DCM/methanol (100:1 to 40:1) to afford the isoquinolinium triflate **4**.

General Procedure for the Synthesis of Compound ***6***. A mixture of **5** (0.3 mmol), **3** (0.2 mmol), $Cp^*Rh(OAc)_2$ (0.016 mmol, 8.0 mol %), $Zn(NTf_2)_2$ (0.1 mmol, 0.5 equiv), $NaNTf_2$ (0.2 mmol, 1 equiv), HOAc (0.2 mmol, 1.0 equiv), and TFE (2 mL) was charged into a pressure tube. The reaction mixture was stirred under Ar at 40 °C for 12 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using DCM/methanol (100:1) to afford the product **6**. Isoquinolinium salt **10** was also synthesized by this method.

General Procedure for the Synthesis of Compound ***8***. A mixture of **5** (0.3 mmol), **7** (0.2 mmol), $[Cp^*Rh(Cl)_2]_2$ (0.008 mmol, 4.0 mol %), $AgSbF_6$ (0.032 mmol, 0.016 mol%), $Zn(OAc)_2$ (0.1 mmol, 0.5 equiv), HOAc (0.4 mmol, 2.0 equiv), and DCE (2 mL) was charged into a pressure tube. The reaction mixture was stirred under Ar at 100 °C for 12 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using PE/EA 2:1) to afford the product **8**.

General Procedures for Synthesis of Compound ***12***. A mixture of **5a** (0.4 mmol, 2.0 equiv), $[Cp^*RhCl_2]_2$ (0.2 mmol, 1 equiv), NaOAc (0.5 mmol, 2.5 equiv), and DCM (20 mL) was added to a Schlenk tube equipped with a stir bar under argon atmosphere. The mixture was stirred at room temperature for 48 h. The reaction was filtrated and concentrated under vacuum. The residue was carefully washed with dried hexane (2 × 10 mL) to remove unreacted materials to give the red Rh complex **12** (72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 1H), 7.48–7.39 (m, 3H), 7.41–7.45 (m, 1H), 7.33–7.36 (m, 1 H), 7.22 (td, J = 7.2, 1.2 Hz, 1H), 7.13–7.15 (m, 1H), 6.87–6.91 (m, 1H), 6.78 (dd, J = 7.6, 1.2 Hz, 1H), 4.75 (d, J = 17.6 Hz, 1H), 4.54 (d, J = 17.6 Hz, 1H), 4.08–4.20 (m, 2H), 1.69 (s, 15H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 184.8 (d, J_{Rh-C} = 32.2 Hz), 169.9, 148.2, 136.2, 134.4, 131.1, 130.6, 129.4, 128.6, 128.4, 128.4, 128.0, 122.3, 96.7 (J_{Rh-C} = 9 Hz), 61.4, 59.3, 14.3, 9.5.

*Diethyl (E)-2-(2-(((2-Ethoxy-2-oxoethyl)imino)(phenyl)methyl) phenyl)malonate (****13****).* A mixture of **5a** (0.3 mmol, 1.5 equlv), **7a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol, 4.0 mol %), $AgSbF_6$ (0.032 mmol, 16 mol %), and TFE (2 mL) was charged into a pressure tube. The reaction mixture was stirred under Ar at 40 °C for 12 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using PE/EA (10:1) to afford the product **13** (59 mg, 70%) as a yellow semisolid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 1H), 7.62 (m, d, J = 7.2 Hz, 2H), 7.50 (t, J = 7.8 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.13 (d, J = 7.8 Hz, 1H), 4.44 (s, 1H), 4.13–4.22 (m, 5H), 4.05 (d, J = 17.6 Hz, 1H), 3.87–4.00 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.2 Hz, 2H), 0.99 (t, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.6, 168.1, 167.6, 138.4, 136.7, 131.0, 130.7, 130.2, 129.4, 128.8, 128.6, 128.3, 127.6, 62.1, 61.8, 61.0, 55.9, 54.3, 14.3, 14.0, 13.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{27}NO_6Na$ 448.1731, found: 448.1730.

Conversion of Intermediate ***13*** *to Product* ***8aa***. A mixture of **13** (0.1 mmol), $Zn(OAc)_2$ (0.05 mmol, 0.5 equiv), HOAc (0.2 mmol, 2.0 equiv), and DCE (2 mL) was charged into a pressure tube. The reaction mixture was stirred under Ar at 100 °C for 6 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using PE/EA (2:1) to afford the product **8aa**.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (****4aaa****).* A brown semisolid (86 mg, 91%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.29 (s, 1H), 8.75 (d, J = 8.4 Hz, 1H), 8.41 (t, J = 7.6 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.15 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 9.2 Hz, 2H), 7.31 (d, J = 9.2 Hz, 2H), 4.69 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 2.64 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.5, 162.6, 154.8, 144.1, 139.9, 136.3, 135.1, 132.1, 132.1, 130.9, 128.6, 127.4, 125.1, 122.3 (q, J_{C-F} = 320.2 Hz), 116.1, 64.2, 56.4, 19.2, 14.4. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{20}NO_3^+$ 322.1438, found: 322.1438. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9515.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3,6-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (****4baa****).* A brown semisolid (82 mg, 85%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.84 (s, 1H), 8.48 (d, J =

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8.4 Hz, 1H), 7.73−7.77 (m, 2H), 7.41 (dd, J = 6.8 Hz, 2.4 Hz, 2H), 7.07 (dd, J = 6.8 Hz, 2.4 Hz, 2H), 4.55 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.63 (s, 3H), 2.45 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.6, 162.7, 153.7, 152.9, 144.2, 136.7, 135.2, 134.5, 132.2, 130.2, 128.7, 125.9, 124.0, 122.5 (q, J_{C-F} = 320.4 Hz), 116.24, 64.20, 56.46, 23.21, 19.24, 14.45. ^{19}F NMR (565 MHz, acetone) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(Ethoxycarbonyl)-6-methoxy-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4caa**).* A brown semisolid (79 mg, 79%). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.67 (s, 1H), 8.51 (d, J = 9.6 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.23 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 4.07 (s, 3H), 3.89 (s, 3H), 2.50 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 168.8, 165.6, 162.4, 152.1, 144.6, 139.3, 134.9, 134.7, 128.6, 124.8, 122.8, 122.3 (q, J_{C-F} = 320.1 Hz), 116.1, 103.7, 63.9, 57.4, 56.3, 19.2, 14.4. ^{19}F NMR (565 MHz, acetone) δ −78.81. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_4^+$ 352.1543, found: 352.1543. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(tert-Butyl)-4-(ethoxycarbonyl)-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate. (**4daa**).* A brown semisolid (97 mg, 95%). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.11 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.07 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.71 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 2.63 (s, 3H), 1.50−1.53 (m, 12H). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.5, 164.2, 162.4, 153.4, 144.1, 136.5, 134.9, 132.2, 131.1, 130.4, 128.4, 125.7, 122.1 (q, J_{C-F} = 320.1 Hz), 119.7, 116.0, 63.9, 56.2, 37.2, 30.6, 19.10, 14.4. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.91. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{28}NO_3^+$ 378.2064, found: 378.2064. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9516.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3,7-dimethylisoquinolin-2-ium Trifluoromethanesulfonate. (**4eaa**).* A brown semisolid (80 mg, 82%). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.07 (s, 1H), 8.48 (s, 1H), 8.26 (dd, J = 9.0, 1.2 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 4.68 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 2.68 (s, 3H), 2.62 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.4, 162.4, 153.4, 143.2, 142.9, 142.0, 135.0, 134.6, 130.6, 130.6, 128.4, 127.5, 124.8, 122.1 (q, J_{C-F} = 320.1 Hz), 116.0, 64.0, 56.2, 21.5, 19.0, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.78. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1593. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9516.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3,8-dimethylisoquinolin-2-ium Trifluoromethanesulfonate. (**4faa**).* A brown semisolid (90 mg, 93%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.58 (s, 1H), 8.01−5.05 (m, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 7.49 (dd, J = 7.2 Hz, 2.0 Hz, 2H), 7.09 (dd, J = 6.8 Hz, 2.0 Hz, 2H), 4.53 (q, J = 7.2 Hz, 2H), 3.82 (s, 3H), 2.79 (s, 3H), 2.45 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.6, 162.6, 151.8, 143.7, 141.9, 139.9, 137.1, 135.2, 132.8, 131.4, 128.7, 127.0, 123.16, 122.4 (q, J_{C-F} = 320.3 Hz), 116.1, 64.2, 56.4, 19.14, 18.68, 14.37. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9515.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3-methylbenzo[h]-isoquinolin-2-ium Trifluoromethanesulfonate. (**4gaa**).* A brown semisolid (88 mg, 84%). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.69 (s, 1H), 9.15−9.16 (m, 1H), 8.69 (d, J = 9.0 Hz, 1H), 8.29−8.30 (m, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.97−7.98 (m, 2H), 7.94 (dd, J = 6.6, 1.8 Hz, 2H), 7.35 (dd, J = 6.6, 1.8 Hz, 2H), 4.73 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 2.71 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.6, 162.6, 147.7, 146.9, 141.9, 138.4, 135.4, 133.2, 131.5, 131.4, 131.0, 129.4, 128.8, 125.9, 124.53, 122.4 (J_{C-F} = 320.1 Hz), 121.6, 116.2, 64.4, 56.4, 19.5 14.4. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.73. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{22}NO_3^+$ 372.1594, found: 372.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9516.

*4-(Ethoxycarbonyl)-6-(4-methoxyphenyl)-5-methylthieno[2,3-c]-pyridin-6-ium Trifluoromethanesulfonate (**4haa**).* A brown semisolid (75 mg, 78%). ^{1}H NMR (400 MHz, acetone-d_6) δ 9.98 (s, 1H), 9.03 (d, J = 5.2 Hz, 1H), 8.03 (d, J = 5.6 Hz, 1H), 7.84 (d, J = 9.2 Hz, 2H), 7.30 (d, J = 8.8 Hz, 2H), 4.63 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 2.70 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.7, 162.2, 149.0, 148.8, 147.9, 145.6, 136.6, 135.3, 128.3, 126.2, 122.0 (q, J_{C-F} = 320.0 Hz), 120.4, 115.9, 63.8, 56.1, 19.3, 14.1. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.76. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{18}H_{18}NO_3S^+$ 328.1002, found: 328.1001. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-(Ethoxycarbonyl)-3-ethyl-2-(4-methoxyphenyl)isoquinolin-2-ium Trifluoromethanesulfonate (**4aab**).* A brown semisolid (66 mg, 68%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.19 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.41−8.45 (m, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.18 (t, J = 7.6 Hz, 1H), 7.97 (dd, J = 7.2, 2.0 Hz, 2H), 7.34 (dd, J = 6.8, 2.0 Hz, 2H), 4.71 (q, J = 7.2 Hz, 2H), 3.99 (s, 3H), 3.06 (q, J = 7.6 Hz, 2H), 1.49 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.5, 162.7, 155.3, 148.5, 140.0, 136.6, 134.7, 132.5, 132.3, 131.1, 128.9, 127.4, 125.2, 122.4 (q, J_{C-F} = 320.0 Hz), 116.0, 64.3, 56.4, 25.5, 14.4, 14.1. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9519.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-3-phenylisoquinolin-2-ium Trifluoromethanesulfonate (**4aac**).* A brown semisolid (75 mg, 70%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.37 (s, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.50 (t, J = 7.6 Hz, 1H), 8.33 (d, J = 8.4 Hz, 1H), 8.28 (t, J = 7.6 Hz, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 6.4 Hz, 2H), 7.41−7.45 (m, 3H), 7.03 (d, J = 8.8 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 164.8, 162.0, 154.7, 145.6, 140.2, 136.0, 135.8, 133.0, 132.8, 132.4, 131.7, 131.6, 131.3, 129.3, 129.3, 128.2, 125.8, 122.4 (q, J_{C-F} = 320.1 Hz), 115.3, 63.7, 56.2, 13.9. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{22}NO_3^+$ 384.1594, found: 384.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(Methoxycarbonyl)-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4aad**).* A brown solid (60 mg, 62%, Mp 161−163 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.22 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.41 (t, J = 7.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 4.20 (s, 3H), 3.98 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.9, 162.6, 154.7, 144.3, 139.9, 136.4, 135.0, 132.5, 132.1, 130.8, 128.5, 127.3, 125.2, 122.4 (q, J_{C-F} = 320.0 Hz), 116.1, 56.4, 54.4, 19.25. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{18}NO_3^+$ 308.1281, found: 308.1281. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(Isopropoxycarbonyl)-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4aae**).* A brown semisolid (80 mg, 82%). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.22 (s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.42−8.44 (m, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.16 (t, J = 7.2 Hz, 1H), 7.89 (d, J = 9.0 Hz, 2H), 7.32 (d, J = 9.0 Hz, 2H), 5.56 (dt, J = 12.6, 6.0 Hz, 1H), 3.97 (s, 3H), 2.65 (s, 3H), 1.50 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.9, 162.5, 154.4, 143.8, 139.9, 136.2, 134.9, 132.5, 132.0, 131.0, 128.4, 127.3, 124.8, 122.2 (q, J_{C-F} = 320.0 Hz), 116.0, 72.6, 56.3, 22.1, 21.8, 19.0. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.76. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-Acetyl-2-(4-methoxyphenyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4aaf**).* A brown solid (97 mg, 93%. Mp 161−163 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.12 (s, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.37 (t, J = 7.2 Hz, 1H), 8.14 (t, J = 7.8 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.30 (d, J = 9.0 Hz, 2H), 3.97 (s, 3H), 2.84 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 202.4, 162.5, 153.6, 141.6, 139.5, 138.4, 135.7, 134.9, 132.5, 131.9, 128.5, 127.5, 124.7, 122.2 (q, J_{C-F} = 320.1 Hz), 116.1, 56.3, 32.8, 18.7. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.98. HRMS

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(ESI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{18}NO_2^+$ 292.1332, found: 292.1333. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-(Ethoxycarbonyl)-3-methyl-2-phenylisoquinolin-2-ium Trifluoromethanesulfonate (**4aba**).* A brown semisolid (70 mg, 79%). ^{1}H NMR (600 MHz, acetone-d_6) δ 10.26 (s, 1H), 8.73 (d, J = 8.4 Hz, 1H), 8.44 (t, J = 7.2 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.19 (t, J = 7.2 Hz, 1H), 7.98−7.80 (m, 2H), 7.83−7.98 (m, 3H), 4.70 (q, J = 7.2 Hz, 2H), 2.65 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.4, 154.3, 143.8, 142.4, 140.2, 136.5, 132.6, 132.6, 132.3, 131.4, 131.1, 127.4, 127.2, 125.3, 122.3 (q, J_{C-F} = 319.8 Hz), 64.3, 19.2, 14.4. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{18}NO_2^+$ 292.1332, found: 292.1332. HRMS (ESI-TOF) m/z: $[M]^-$: calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*2-Benzyl-4-(ethoxycarbonyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4aca**).* A brown semisolid (77 mg, 85%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.50 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.33−8.37 (m, 1H), 8.15 (d, J = 8.4 Hz, 1H), 8.10 (t, J = 8.0 Hz, 1H), 7.43−7.51 (m, 5H), 6.33 (s, 2H), 4.65 (q, J = 7.2 Hz, 2H), 2.89 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.4, 154.2, 143.2, 139.6, 135.8, 133.6, 132.4, 132.0, 131.9, 130.2, 130.0, 128.9, 127.6, 124.9, 122.2 (q, J_{C-F} = 319.7 Hz), 64.1, 63.0, 17.9, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.79. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{20}NO_2^+$ 306.1489, found: 306.1489. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9519.

*2-Butyl-4-(ethoxycarbonyl)-3-methylisoquinolin-2-ium Trifluoromethanesulfonate (**4ada**).* A brown semisolid (72 mg, 88%). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.41 (s, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.30−8.34 (m, 1H), 8.07−8.14 (m, 2H), 5.01 (t, J = 8.0 Hz, 2H), 4.68 (q, J = 7.2 Hz, 2H), 3.02 (s, 3H), 2.14−2.22 (m, 2H), 1.46−1.66 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.6, 153.5, 143.0, 139.2, 135.6, 131.9, 131.9, 131.8, 127.7, 125.0, 122.3 (q, J_{C-F} = 319.7 Hz), 64.2, 59.8, 33.1, 20.28, 17.49, 14.37, 13.83. ^{19}F NMR (565 MHz, acetone-d_6) δ −78.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{22}NO_2^+$ 272.1645, found: 272.1645. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9515.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4iaa**).* A brown semisolid (73 mg, 75%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.61 (d, J = 9.2 Hz, 1H), 8.23 (t, J = 7.6 Hz, 1H), 8.03−8.07 (m, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 9.2 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 3.02 (s, 3H), 2.42 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.3, 164.5, 162.2, 143.0, 138.8, 135.0, 132.2, 132.0, 130.1, 129.70, 127.5, 127.0, 125.5, 121.3 (q, J_{C-F} = 319.2 Hz), 117.0, 64.1, 56.5, 20.9, 20.6, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.01. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{22}NO_3^+$ 336.1594, found: 336.1594. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-1,3,6-trimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4jaa**).* A brown semisolid (63 mg, 63%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.48 (d, J = 8.8 Hz, 1H), 7.87 (dd, J = 8.8, 0.8 Hz, 1H), 7.78 (s, 1H), 7.36 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 2.96 (s, 3H), 2.72 (s, 3H), 2.40 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.5, 163.4, 162.2, 151.7, 142.9, 135.2, 134.2, 132.1, 129.8, 128.9, 127.5, 125.3, 124.5, 121.3 (q, J_{C-F} = 319.2 Hz), 116.9, 64.0, 56.5, 23.3, 20.6, 20.3, 14.4. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.02. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{24}NO_3^+$ 350.1751, found: 350.1751. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*4-(Ethoxycarbonyl)-6-ethyl-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4kaa**).* A brown semisolid (54 mg, 53%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.51 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.00−2.04 (m, 5H), 2.40 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H), 1.39 (t, J = 7.6 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.5, 163.3, 162.2, 157.3, 142.9, 135.4, 133.2, 132.1, 129.9, 129.1, 127.5, 125.5, 123.2, 121.3 (q, J_{C-F} = 319.7 Hz), 117.0, 64.0, 56.5, 30.4, 20.6, 20.5, 14.7, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.02. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{26}NO_3^+$ 364.1907, found: 364.1914. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9519.

*4-(Ethoxycarbonyl)-6-isopropyl-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4laa**).* A brown semisolid (63 mg, 60%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.44 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.71 (s, 1H), 7.28 (d, J = 9.2 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 4.54 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 3.14−3.21 (m, 1H), 2.88 (s, 3H), 2.32 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.5, 163.3, 162.2, 161.6, 142.9, 135.4, 132.1, 131.9, 130.1, 129.2, 127.5, 125.6, 121.9, 121.3 (q, J_{C-F} = 319.2 Hz), 116.9, 64.0, 56.5, 35.7, 23.3, 20.6, 20.54, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.01. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{28}NO_3^+$ 378.2064, found: 378.2063. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-(Ethoxycarbonyl)-6-methoxy-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4maa**).* A brown semisolid (70 mg, 68%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.50 (d, J = 9.6 Hz, 1H), 7.61 (dd, J = 9.6, 2.4 Hz, 1H), 7.35 (d, J = 9.2 Hz, 2H), 7.22−7.24 (m, 3H), 4.61 (q, J = 7.2 Hz, 2H), 4.09 (s, 3H), 3.94 (s, 3H), 2.91 (s, 3H), 2.38 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 167.8, 165.6, 162.1, 161.7, 143.6, 138.1, 132.4, 132.0, 127.7, 127.6, 124.4, 122.2, 121.4 (q, J_{C-F} = 319.2 Hz), 116.9, 104.1, 63.9, 57.2, 56.5, 20.7, 20.5, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.01. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{24}NO_4^+$ 366.1700, found: 366.1700. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9519.

*6-Chloro-4-(ethoxycarbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4naa**).* A brown semisolid (47 mg, 45%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.59 (d, J = 9.2 Hz, 1H), 8.02 (d, J = 1.6 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.42 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 4.62 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.01 (s, 3H), 2.42 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.0, 164.9, 162.3, 146.0, 144.6, 135.8, 132.8, 132.2, 132.1, 128.4, 127.5, 125.6, 124.6, 121.2 (q, J_{C-F} = 319.2 Hz), 116.9, 64.3, 56.5, 21.1, 20.8, 14.4. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.08. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{21}ClNO_3^+$ 370.1204, found: 370.1205. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9517.

*6-Bromo-4-(ethoxycarbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4oaa**).* A brown semi solid (45 mg, 40%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.42 (d, J = 9.2 Hz, 1H), 8.11 (s, 1H), 8.01(dd, J = 8.4, 1H), 7.36(d, J = 9.2 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 4.65 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 2.93 (s, 3H), 2.34 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H).^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.0, 164.9, 162.3, 144.7, 135.7, 135.5, 135.4, 132.2, 131.5, 128.4, 128.1, 127.4, 125.8, 121.3 (q, J_{C-F} = 318.9 Hz), 117.0, 64.3, 56.5, 21.0, 20.8, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.08. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{21}BrNO_3^+$ 416.0681, found: 416.0681. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-(Ethoxycarbonyl)-6-(methoxycarbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoro-methanesulfonate (**4paa**).* A brown semi solid (38 mg, 35%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.65−8.68 (m, 2H), 8.50 (d, J = 9.2 Hz, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.66 (q, J = 7.2 Hz, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.05 (s, 3H), 2.45 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.3, 165.2, 165.0, 162.3, 144.3, 138.5, 134.8, 132.3, 130.7, 130.7, 130.4, 128.8, 127.4, 127.3, 121.2 (q, J_{C-F} = 319.2 Hz), 117.0, 64.3, 56.5, 53.8, 21.25, 20.75, 14.48. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.09. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{24}NO_5^+$ 394.1649, found: 394.1648. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9519.

*4-(Ethoxycarbonyl)-8-fluoro-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4qaa**).* A brown semisolid (25 mg, 25%). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 8.18 (td, J = 7.8, 4.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.66−7.69 (m, 1H), 7.42

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(d, J = 9.0 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.61 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.09 (d, J = 5.4 Hz, 3H), 2.40 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.2, 163.7 (d, J_{C-F} = 7.5 Hz), 162.3, 161.9 (d, J_{C-F} = 265.5 Hz), 144.1, 139.8 (d, J_{C-F} = 10.8 Hz), 136.1, 131.8, 129.5, 127.6, 121.9 (d, J_{C-F} = 4.6 Hz), 121.2 (q, J_{C-F} = 319.4 Hz), 118.9 (d, J_{C-F} = 10.2 Hz), 117.5 (d, J_{C-F} = 23.2 Hz), 117.0, 64.3, 56.5, 24.3 (d, J_{C-F} = 16.8 Hz), 20.9, 14.4. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.11, −98.85. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{21}FNO_3^+$ 354.1500, found: 354.1501. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9521.

*4-(Ethoxycarbonyl)-2-(4-methoxyphenyl)-1,3,7-trimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4raa**).* A brown semisolid (58 mg, 58%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.35 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.61 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 2.98 (s, 3H), 2.70 (s, 3H), 2.40 (s, 3H), 1.47 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.4, 163.3, 162.2, 143.3, 142.1, 141.1, 133.3, 132.3, 129.5, 128.6, 127.4, 127.2, 125.3, 121.4 (q, J_{C-F} = 319.3 Hz), 117.0, 64.1, 56.5, 22.4, 20.7, 20.5, 14.4. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.03. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{24}NO_3^+$ 350.1751, found: 350.1751. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9520.

*4-(Ethoxycarbonyl)-5-fluoro-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4saa**).* A brown semisolid (85 mg, 84%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.46 (d, J = 8.8 Hz, 1H), 7.99−8.04 (m, 1H), 7.88−7.92 (m, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.8 Hz, 2H), 4.55 (q, J = 7.2 Hz, 2H), 3.94 (s, 3H), 3.04 (s, 3H), 2.39 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.6, 164.9, 162.3, 156.8 (d, J_{C-F} = 255.9 Hz), 143.4, 132.5 (d, J_{C-F} = 8.4 Hz), 132.2, 128.4 (d, J_{C-F} = 2.2 Hz), 127.4, 126.7 (d, J_{C-F} = 4.5 Hz), 125.7, 125.0 (d, J_{C-F} = 14.1 Hz), 123.1 (d, J_{C-F} = 20.4 Hz), 121.2 (q, J_{C-F} = 319.1 Hz), 117.0, 64.2, 56.5, 21.5, 20.1, 14.2. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.08, −112.51. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{21}FNO_3^+$ 354.1500, found: 354.1500. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9515.

*4-(Ethoxycarbonyl)-6-(4-methoxyphenyl)-5,7-dimethylthieno-[2,3-c]pyridin-6-ium Trifluoromethanesulfonate (**4taa**).* A brown semisolid (34 mg, 35%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.58 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.40 (d, J = 9.2 Hz, 2H), 7.23 (d, J = 9.2 Hz, 2H), 4.59 (d, J = 7.2 Hz, 2H), 3.94 (s, 3H), 2.81 (s, 3H), 2.56 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H).^{13}C NMR (150 MHz, CD_2Cl_2) δ 164.7, 162.3, 155.4, 149.0, 147.7, 145.7, 138.2, 131.6, 127.7, 125.6, 124.9, 121.3 (q, J_{C-F} = 319.0 Hz), 117.0, 64.1, 56.5, 23.1, 20.8, 14.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.04. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{19}H_{20}SNO_3^+$ 342.1158, found: 342.1158. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9518.

*4-(Methoxycarbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium Trifluoromethanesulfonate (**4aag**).* A brown semisolid (66 mg, 73%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.59 (d, J = 8.8 Hz, 1H), 8.23 (t, J = 7.2 Hz, 1H), 8.05 (t, J = 8.8 Hz, 2H), 7.39 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 9.2 Hz, 2H), 4.14 (s, 3H), 3.95 (s, 3H), 3.02 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.9, 164.6, 162.3, 143.3, 138.8, 135.0, 132.2, 132.0, 130.0, 129.5, 127.4, 127.0, 125.6, 121.3 (q, J_{C-F} = 319.0 Hz), 117.0, 56.5, 54.4, 20.8, 20.7. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.07. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{20}H_{20}NO_3^+$ 322.1438, found: 322.1438. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9515.

*4-((Benzyloxy)carbonyl)-2-(4-methoxyphenyl)-1,3-dimethylisoquinolin-2-ium trifluoromethanesulfonate (**4aah**).* A brown semisolid (64 mg, 60%). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.59 (d, J = 8.8 Hz, 1H), 8.17 (t, J = 8.0 Hz, 1H), 8.03 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.50−7.52 (m, 2H), 7.40−7.45 (m, 3H), 7.37 (d, J = 9.2 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 5.58 (s, 2H), 3.94 (s, 3H), 3.01 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.2, 164.6, 162.3, 143.1, 138.8, 135.0, 134.9, 132.1, 132.0, 130.1, 129.7, 129.6, 129.4, 129.4, 127.4, 127.0, 125.4, 121.3 (q, J_{C-F} = 319.3 Hz), 117.0, 69.6, 56.5, 20.9, 20.5. ^{19}F NMR (565 MHz, CD_2Cl_2) δ −79.04. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{26}H_{24}NO_3^+$ 398.1751, found: 398.1751. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $CF_3O_3S^-$ 148.9526, found: 148.9516.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6aa**).* A pale-yellow solid (108 mg, 82%, Mp 90−92 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.39 (t, J = 7.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.90 (t, J = 7.8 Hz, 1H), 7.85 (t, J = 7.8 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 6.6 Hz, 2H), 5.63 (s, 2H), 4.74 (q, J = 7.2 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.01 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.7, 165.6, 164.2, 143.5, 139.9, 136.2, 133.1, 132.5, 131.9, 130.9, 130.8, 129.5, 128.5, 125.4, 121.1 (q, J_{C-F} = 319.4 Hz), 64.5, 64.1, 57.7, 19.06, 14.34, 14.22. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.83. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{24}NO_4^+$ 378.1700, found: 378.1701. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3,6-dimethyl-1-(p-tolyl)isoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ba**).* A pale-yellow semisolid (102 mg, 64%). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.00 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.63−7.68 (m, 3H), 7.51 (d, J = 7.6 Hz, 2H), 5.57 (s, 2H), 4.71 (q, J = 7.2 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.96 (s, 3H), 2.73 (s, 3H), 2.56 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.9, 165.7, 163.7, 152.7, 143.5, 143.4, 136.3, 134.6, 132.3, 131.3, 130.9, 129.4, 128.0, 126.9, 124.2, 121.0 (q, J_{C-F} = 319.5 Hz), 64.3, 64.0, 57.3, 22.83, 21.58, 19.02, 14.33, 14.22. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.83. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{28}NO_4^+$ 406.2013, found: 406.2014. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-6-fluoro-1-(4-fluorophenyl)-3-methylisoquinolin-2-ium Bis((trifluoromethyl) sulfonyl)-amide (**6ca**).* A pale-yellow solid (94 mg, 68%, Mp 65−67 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 7.94−7.99 (m, 2H), 7.86 (t, J = 8.4 Hz, 1H), 7.77 (m, 2H), 7.63 (t, J = 8.4 Hz, 2H), 5.63 (s, 2H), 4.74 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.01 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 168.9 (d, J_{C-F} = 263.5 Hz), 166.5, 165.4 (d, J_{C-F} = 250.2 Hz), 165.0, 163.0, 144.8, 138.6 (d, J_{C-F} = 12.9 Hz), 137.1 (d, J_{C-F} = 11.6 Hz), 133.2 (d, J_{C-F} = 9.3 Hz), 132.3 (d, J_{C-F} = 9.1 Hz), 131.2 (d, J_{C-F} = 5.7 Hz), 126.6 (d, J_{C-F} = 3.6 Hz), 126.1, 123.0 (d, J_{C-F} = 25.8 Hz), 120.8 (q, J_{C-F} = 319.4 Hz), 118.0 (d, J_{C-F} = 22.5 Hz), 109.8 (d, J_{C-F} = 24.0 Hz), 64.5, 64.0, 57.5, 19.1, 14.1, 14.0. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.86, −92.94, −108.22. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{22}F_2NO_4^+$ 414.1511, found: 414.1511. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*6-Chloro-1-(4-chlorophenyl)-2-(2-ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methylisoquinolin-2-ium Bis((trifluoromethyl) sulfonyl)-amide (**6da**).* A pale-yellow solid (91 mg, 63%, Mp 123−127 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.27 (s, 1H), 8.00 (d, J = 9.6 Hz, 1H), 7.87−7.89 (m, 3H), 7.72 (d, J = 7.8 Hz, 2H), 5.66 (s, 2H), 4.75 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.02 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H).^{13}C NMR (100 MHz, acetone-d_6) δ 166.5, 164.9, 163.1, 146.4, 145.2, 138.9, 136.8, 134.5, 133.3, 131.4, 131.0, 130.9, 129.0, 127.1, 124.3, 120.1 (q, J_{C-F} = 318.8 Hz), 64.7, 64.1, 57.8, 19.2, 14.2, 14.1. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.83. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{22}Cl_2NO_4^+$ 446.0920, found: 446.0919. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*6-Bromo-1-(4-bromophenyl)-2-(2-ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methylisoquinolin-2-ium Bis((trifluoromethyl) sulfonyl)-amide (**6ea**).* A pale-yellow solid (95 mg, 58%, Mp 138−140 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.45 (s, 1H), 8.14 (d, J = 9.0 Hz, 1H), 8.04 (d, J = 7.8 Hz, 2H), 7.78 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 5.67 (s, 2H), 4.75 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.2 Hz, 2H), 3.02 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.5, 165.0, 163.4, 145.3, 136.8, 136.1, 135.9, 134.2, 134.1, 131.6, 130.8, 129.5, 127.7, 127.4, 127.3, 120.1 (q, J_{C-F} = 319.6 Hz), 64.7, 64.1, 57.9, 19.2, 14.2, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.89. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{23}H_{22}Br_2NO_4^+$ 535.9894, found: 535.9894. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

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*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3,7-dimethyl-1-(m-tolyl)isoquinolin-2-ium Bis((trifluoromethyl)sulfonyl) amide (**6fa**).* A pale-yellow solid (85 mg, 62%, Mp 124−126 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.25 (d, J = 8.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.71−7.74 (m, 2H), 7.59 (s, 1H), 7.45 (m, 2H), 5.59 (s, 2H), 4.73 (q, J = 7.2 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 2.98 (s, 3H), 2.54 (s, 3H), 2.51 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H).^{13}C NMR (100 MHz, acetone) δ 166.8, 165.7, 163.4, 143.6, 142.7, 142.1, 141.0, 134.6, 133.6, 131.6, 130.9, 130.8, 130.7, 129.7, 128.7, 126.6, 125.2, 121.1 (q, J_{C-F} = 319.0 Hz), 64.4, 64.0, 57.6, 21.8, 21.5, 19.0, 14.4, 14.3.^{19}F NMR (565 MHz, acetone-d_6) δ −79.92. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{28}NO_4^+$ 406.2013, found: 406.2013. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1-(o-tolyl)-isoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ga**).* A pale-yellow solid (128 mg, 95%, Mp 87−89 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.39−8.43 (m, 1H), 8.27 (d, J = 8.4 Hz, 1H), 8.05 (t, J = 7.2 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 5.85 (d, J = 18.0 Hz, 1H), 5.44 (d, J = 18.0 Hz, 1H), 4.74 (q, J = 7.2 Hz, 2H), 4.22−4.31 (m, 2H), 3.02 (s, 3H), 2.09 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.5, 165.6, 164.1, 144.3, 140.1, 137.6, 136.2, 133.4, 133.1, 132.8, 132.1, 131.9, 130.4, 129.5, 128.2, 128.0, 125.8, 121.1 (q, J_{C-F} = 319.3 Hz), 64.6, 64.1, 57.4, 19.78, 19.18, 14.40, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.89. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{26}NO_4^+$ 392.1856, found: 392.1856. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9169.

*4-(Ethoxycarbonyl)-2-(2-methoxy-2-oxoethyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ha**).* A pale-yellow solid (102 mg, 79%, Mp 124−126 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.39 (t, J = 7.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 8.89 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 7.2 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 7.2 Hz, 2H), 5.64 (s, 2H), 4.74 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.01 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 167.1, 165.4, 164.1, 143.4, 139.8, 136.1, 133.0, 132.4, 132.4, 131.8, 130.7, 129.4, 128.4, 125.3, 120.9 (q, J_{C-F} = 319.3 Hz), 64.4, 57.4, 54.2, 18.9, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{22}NO_4^+$ 364.1543, found: 364.1543. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-(Tert-butoxy)-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ia**).* A semi solid (106 mg, 77%). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.39 (t, J = 7.2 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.91 (t, J = 7.8 Hz, 1H), 7.86 (t, J = 7.2 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 6.6 Hz, 2H), 5.73 (s, 1H), 5.35 (s, 1H), 4.74 (q, J = 7.2 Hz, 2H), 2.99 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, acetone-d_6) δ 165.6, 165.4, 163.8, 143.2, 139.6, 135.9, 132.9, 132.3, 132.3, 131.6, 130.7, 130.6, 129.3, 128.2, 125.2, 120.8 (q, J_{C-F} = 319.3 Hz), 85.7, 64.3, 58.1, 27.7, 18.9, 14.1. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.85. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{28}NO_4^+$ 406.2013, found: 406.2013. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9170.

*2-(2-(Benzyloxy)-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ja**).* A pale-yellow solid (98 mg, 68%, Mp 86−88 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.3−8.42 (m, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 8.0 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.70−7.76 (m, 3H), 7.59 (d, J = 6.8 Hz, 2H), 7.41−7.42 (m, 3H), 7.33−7.36 (m, 2H), 5.69 (s, 2H), 5.29 (s, 2H), 4.74 (q, J = 7.2 Hz, 2H), 3.00 (s, 3H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.7, 165.6, 164.3, 143.6, 140.0, 136.3, 135.8, 133.1, 132.6, 132.0, 130.9, 129.8, 129.6, 129.5, 128.6, 125.5, 121.1 (q, J_{C-F} = 319.3 Hz), 69.5, 64.6, 57.8, 19.1, 14.4. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.89. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{28}H_{26}NO_4^+$ 440.1856, found: 440.1857. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Amino-2-oxoethyl)-4-(ethoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ka**).* A pale-yellow solid (94 mg, 75%, Mp 161−162 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.35 (t, J = 7.2 Hz, 1H), 8.22 (d, J = 8.8 Hz, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 2H), 7.72 (d, J = 8.8 Hz, 1H), 7.64 (m, 2H), 7.39 (s, 1H), 7.18 (s, 1H), 5.56 (s, 2H), 4.73 (q, J = 7.2 Hz, 2H), 2.96 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.4, 165.4, 163.6, 143.4, 139.1, 135.5, 132.5, 132.0, 132.0, 131.2, 130.8, 130.3, 129.2, 128.0, 125.0, 120.7 (q, J_{C-F} = 319.3 Hz), 64.1, 58.5, 18.7, 14.0. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.82. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{21}H_{21}N_2O_3^+$ 349.1547, found: 349.1546. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-ethyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ab**).* A pale-yellow semisolid (81 mg, 60%). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.37−8.42 (m, 1H), 8.24 (d, J = 8.8 Hz, 1H), 8.01−8.05 (m, 1H), 7.82−7.91 (m, 3H), 7.75 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 5.6 Hz, 2H), 5.65 (s, 2H), 4.76 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.36 (q, J = 7.6 Hz, 2H), 1.46−1.54 (m, 6H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.9, 165.5, 164.2, 147.6, 139.8, 136.4, 132.9, 132.6, 132.3, 132.0, 130.8, 130.7, 129.5, 128.7, 125.40, 121.0 (q, J_{C-F} = 319.4 Hz), 64.5, 64.0, 57.1, 26.0, 14.3, 14.2, 14.0.^{19}F NMR (565 MHz, acetone-d_6) δ −79.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{26}NO_4^+$ 392.1856, found: 392.1856. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-1-phenyl-3-propylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ac**).* A pale-yellow solid (93 mg, 68%, Mp 97−99 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.40 (t, J = 7.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.67 (m, 2H), 5.66 (s, 2H), 4.76 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.26−3.29 (m, 2H), 1.89−1.97 (m, 2H), 1.53 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 167.0, 165.7, 164.4, 146.7, 140.0, 136.5, 133.1, 132.7, 132.5, 132.4, 131.0, 130.8, 129.7, 128.8, 125.61, 121.1 (q, J_{C-F} = 319.6 Hz), 64.6, 64.1, 57.3, 34.5, 23.8, 14.5, 14.3, 14.3. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.89. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{28}NO_4^+$ 406.2013, found: 406.2013. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9169.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-1,3-diphenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ad**).* A pale-yellow semisolid (103 mg, 72%). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.48 (t, J = 7.8 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.15 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 9.0 Hz, 2H), 7.84 (t, J = 7.8 Hz, 2H), 7.75 (d, J = 7.2 Hz, 3H), 7.71 (t, J = 7.2 Hz, 2H), 7.62 (d, J = 7.2 Hz, 2H), 5.33 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 1.08 (t, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.8, 164.5, 164.2, 144.8, 140.3, 136.0, 133.4, 133.2, 133.1, 132.9, 132.7, 131.2, 130.8, 130.7, 130.6, 130.3, 129.8, 129.4, 126.2, 121.1 (q, J_{C-F} = 319.4 Hz), 64.0, 63.9, 58.8, 14.2, 13.9. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{28}H_{26}NO_4^+$ 440.1856, found: 440.1857. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Ethoxy-2-oxoethyl)-4-(methoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ae**).* A pale-yellow solid (103 mg, 80%, Mp 105−107 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.39 (t, J = 7.8 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.04 (t, J = 7.8 Hz, 1H), 7.90 (t, J = 7.8 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.66 (t, J = 6.6 Hz, 2H), 5.63 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.24 (s, 3H), 3.00 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.7, 166.0, 164.2, 143.7, 139.9, 136.2, 133.1, 132.5, 132.5, 131.7, 130.8, 130.9, 129.5, 128.4, 125.5, 121.0 (q, J_{C-F} = 319.3 Hz), 64.0, 57.7, 54.6, 19.1, 14.2. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.84. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{22}NO_4^+$ 364.1543, found: 364.1543. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*2-(2-Ethoxy-2-oxoethyl)-4-(isopropoxycarbonyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6af**).* A

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pale-yellow solid (98 mg, 73%, Mp 98−100 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.40 (t, J = 8.4 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 6.0 Hz, 2H), 5.60−5.63 (m, 3H), 4.28 (q, J = 7.2 Hz, 2H), 3.01 (s, 3H), 1.53 (d, J = 6.0 Hz, 6H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 166.6, 164.9, 164.0, 143.2, 139.8, 136.0, 133.0, 132.4, 132.4, 131.9, 130.8, 130.7, 129.4, 128.4, 125.1, 120.9 (q, J_{C-F} = 319.2 Hz), 72.9, 64.0, 57.6, 21.8, 18.8, 14.1. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{24}H_{26}NO_4^+$ 392.1856, found: 392.1856. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9170.

*4-(Tert-butoxycarbonyl)-2-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ag**).* A pale-yellow solid (103 mg, 75%, Mp 78−80 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.42 (t, J = 7.8 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 8.03 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.76 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 6.6 Hz, 2H), 5.61 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.01 (s, 3H), 1.78 (s, 9H), 1.22 (t, J = 7.2 Hz, 3H).^{13}C NMR (150 MHz, acetone-d_6) δ 166.6, 164.7, 163.7, 142.8, 139.8, 135.9, 132.9, 132.5, 132.4, 132.3, 130.8, 130.7, 129.4, 128.4, 125.0, 120.9 (q, J_{C-F} = 319.3 Hz), 86.9, 64.0, 57.6, 28.14, 18.73, 14.12. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.84. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{25}H_{28}NO_4^+$ 406.2013, found: 406.2015. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9167.

*4-((Benzyloxy)carbonyl)-2-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ah**).* A pale-yellow solid (94 mg, 65%, Mp 129−131 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.34 (t, J = 7.2 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.01 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 1H), 7.84 (t, J = 7.2 Hz, 2H), 7.76 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 6.6 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.43−7.49 (m, 3H), 5.74 (s, 2H), 5.60 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 2.95 (s, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.6, 165.3, 164.2, 143.5, 139.8, 136.1, 135.7, 133.0, 132.4, 131.5, 130.7, 130.1, 129.8, 129.6, 129.4, 128.4, 125.2, 120.9 (q, J_{C-F} = 319.5 Hz), 70.0, 64.0, 57.6, 18.9, 14.1.^{19}F NMR (565 MHz, acetone-d_6) δ −79.78. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{28}H_{26}NO_4^+$ 440.1856, found: 440.1857. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9168.

*4-Acetyl-2-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenylisoquinolin-2-ium Bis((trifluoromethyl)sulfonyl)amide (**6ai**).* A pale-yellow solid (83 mg, 66%, Mp 135−137 °C). ^{1}H NMR (600 MHz, acetone-d_6) δ 8.37 (t, J = 7.8 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.02 (t, J = 7.8 Hz, 1H), 7.89 (t, J = 7.8 Hz, 1H), 7.84 (t, J = 7.8 Hz, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.64 (d, J = 6.6 Hz, 2H), 5.59 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 2.94 (s, 3H), 2.90 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 202.2, 166.8, 163.5, 141.2, 139.7, 139.1, 135.7, 133.1, 132.7, 132.5, 131.0, 130.9, 129.6, 128.6, 125.1, 122.1 (q, J_{C-F} = 319.3 Hz), 64.1, 57.5, 33.1, 18.6, 14.3. ^{19}F NMR (565 MHz, acetone-d_6) δ −79.86. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{22}H_{22}NO_3^+$ 348.1594, found: 348.1595. HRMS (ESI-TOF) m/z: $[M]^-$: calcd for $C_2F_6NO_4S_2^-$ 279.9178, found: 279.9170.

*Ethyl 2-(2-ethoxy-2-oxoethyl)-3-oxo-1-phenyl-2,3-dihydroisoquinoline-4-carboxylate (**8aa**).* A yellow solid (65 mg, 86%, Mp 70−72 °C). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.66−7.69 (m, 3H), 7.49−7.53 (m, 3H), 7.39−7.43 (m, 1H), 6.85−6.92 (m, 2H), 4.73 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6) δ 168.3, 167.5, 157.6, 156.0, 140.9, 134.3, 133.2, 131.4, 130.2, 129.9, 129.9, 122.7, 116.8, 113.1, 62.2, 61.6, 50.1, 14.7, 14.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{21}NO_5Na$ 402.1312, found: 402.1312.

*Ethyl 2-(2-ethoxy-2-oxoethyl)-6-methyl-3-oxo-1-(p-tolyl)-2,3-dihydroisoquinoline-4-carboxylate (**8ba**).* A yellow solid (69 mg, 85%, Mp 132−134 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.8 Hz, 1H), 6.65 (dd, J = 8.8, 1.2 Hz, 1H), 4.70 (s, 2H), 4.50 (q, J = 7.2 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 2.47 (s, 3H), 2.35 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 167.4, 157.7, 155.0, 144.7, 141.2, 140.8, 130.0, 129.4, 129.1, 128.8, 125.1, 120.7, 115.8, 110.5, 61.9, 61.4, 49.5, 22.7, 21.6, 14.5, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{25}NO_5Na$ 430.1625, found: 430.1626.

*Ethyl 2-(2-ethoxy-2-oxoethyl)-6-fluoro-1-(4-fluorophenyl)-3-oxo-2,3-dihydroisoquinoline-4-carboxylate (**8ca**).* A yellow solid (52 mg, 63%, Mp 150−152 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 11.6, 2.3 Hz, 1H), 7.42−7.34 (m, 2H), 7.33−7.23 (m, 2H), 6.95 (dd, J = 9.6, 5.9 Hz, 1H), 6.64 (ddd, J = 9.8, 7.7, 2.4 Hz, 1H), 4.69 (s, 2H), 4.49 (q, J = 7.1 Hz, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.7, 165.6 (d, J_{C-F} = 257.0 Hz), 163.9 (d, J_{C-F} = 251.2 Hz), 157.2, 154.8, 142.7 (d, J_{C-F} = 12.7 Hz), 132.9 (d, J_{C-F} = 11.1 Hz), 131.0 (d, J_{C-F} = 8.4 Hz), 127.8 (d, J_{C-F} = 3.7 Hz), 116.9 (d, J_{C-F} = 21.9 Hz), 114.8, 114.7 (d, J_{C-F} = 28.0 Hz), 110.9 (d, J_{C-F} = 7.2 Hz), 105.4 (d, J_{C-F} = 23.9 Hz), 62.2, 61.6, 49.6, 14.5, 14.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{19}F_2NO_5Na$ 438.1124, found: 438.1124.

*Ethyl 6-chloro-1-(4-chlorophenyl)-2-(2-ethoxy-2-oxoethyl)-3-oxo-2,3-dihydro isoquinoline-4-carboxylate (**8da**).* A yellow solid (49 mg, 55%, Mp 158−160 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 1.2 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 9.6 Hz, 1H), 6.76 (dd, J = 9.2, 1.6 Hz, 1H), 4.68 (s, 2H), 4.50 (q, J = 7.2 Hz, 2H), 4.18 (q, J = 7.2 Hz, 3H), 1.44 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 166.5, 157.5, 154.3, 141.1, 140.9, 137.4, 130.5, 130.3, 130.1, 130.0, 124.1, 121.3, 115.1, 111.3, 62.3, 61.7, 49.7, 14.5, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{19}Cl_2NO_5Na$ 470.0532, found: 470.0533.

*Ethyl 6-bromo-1-(4-bromophenyl)-2-(2-ethoxy-2-oxoethyl)-3-oxo-2,3-dihydro isoquinoline-4-carboxylate (**8ea**).* A yellow solid (51 mg, 48%, Mp 164−166 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.89 (dd, J = 9.2, 1.6 Hz, 1H), 6.75 (d, J = 9.2 Hz, 1H), 4.67 (s, 2H), 4.50 (q, J = 7.2 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 166.4, 157.4, 154.4, 141.2, 132.9, 130.5, 130.5, 130.2, 130.1, 126.5, 125.7, 124.8, 115.1, 111.2, 62.3, 61.8, 49.7, 14.5, 14.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{19}Br_2NO_5Na$ 559.9503, found: 559.9517.

*Ethyl 2-(2-methoxy-2-oxoethyl)-3-oxo-1-phenyl-2,3-dihydroiso quinoline-4-carboxylate (**8fa**).* A yellow solid (57 mg, 78%, Mp 98−100 °C). ^{1}H NMR (400 MHz, acetone) δ 7.66−7.69 (m, 3H), 7.50−7.52 (m, 3H), 7.39−7.43 (m, 1H), 6.86−6.93 (m, 2H), 4.74 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 3.66 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, acetone) δ 168.8, 167.5, 157.6, 156.1, 140.9, 134.3, 133.2, 131.4, 130.2, 130.0, 129.9, 122.8, 116.9, 113.1, 61.6, 52.9, 50.0, 14.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{19}NO_5Na$ 388.1155, found: 388.1156.

*Ethyl 2-(2-(benzyloxy)-2-oxoethyl)-3-oxo-1-phenyl-2,3-dihydro isoquinoline-4-carboxylate (**8ga**).* A yellow semisolid (72 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 9.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.32−7.38 (m, 4H), 7.25−7.28 (m, 4H), 6.90 (d, J = 8.8 Hz, 1H), 6.797−6.83 (m, 1H), 5.15 (s, 2H), 4.79 (s, 2H), 4.52 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 167.0, 157.5, 155.0, 140.9, 135.2, 133.7, 132.1, 130.6, 129.4, 129.1, 128.8, 128.6, 128.6, 128.5, 122.6, 122.4, 116.8, 112.0, 67.6, 61.5, 49.6, 14.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{27}H_{23}NO_5Na$ 464.1468, found: 464.1469.

Derivatization Reaction. Ethyl 2-(2-ethoxy-2-oxoethyl)-3-methyl-1-phenyl-1,2-dihydroiso quinoline-4-carboxylate (**9**): A mixture of **6aa** (0.2 mmol) with $NaBH_4$ (0.4 mmol, 2 equiv) and MeOH (2 mL) was stirred at room temperature for 5 min, followed by quenched with water. The residue was extracted with EA. The organic phase was combined, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel chromatography using PE/EA (10:1) to afford the product **9** (75 mg, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.0 Hz, 1H), 7.15−7.23(m, 5H), 7.08 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.2 Hz, 1H), 5.38 (s, 1H), 4.19−4.28 (m, 2H), 4.10 (d, J = 18.0 Hz, 1H), 4.93−4.05 (m, 2H), 3.90 (d, J = 18.0 Hz, 1H), 2.24 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H).

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^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 168.9, 149.4, 142.1, 130.5, 12986, 128.7, 127.9, 127.3, 126.9, 126.0, 125.0, 123.5, 103.1, 67.5, 61.4, 59.9, 52.2, 17.9, 14.5, 14.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{25}NO_4Na$ 449.1683, found: 449.1682.

*2-(2-Ethoxy-2-oxoethyl)-4-(ethoxycarbonyl)-3-methylisoquinolin-2-ium bis((trifluoromethyl)sulfonyl)amide (**10**).* A yellow oil. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 9.72 (s, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.26 (t, J = 7.2 Hz, 1H), 8.00−8.06 (m, 2H), 5.62 (s, 2H), 4.64 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 2.77 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, CD_2Cl_2) δ 165.0, 164.2, 153.4, 141.9, 139.4, 135.7, 131.6, 131.4, 131.2, 126.6, 124.4, 119.8 (q, J_{C-F} = 319.2 Hz) 63.9, 63.9, 59.0, 17.3, 13.9, 13.6. ^{19}F NMR (376 MHz, CH_2Cl_2) δ −79.00. HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{17}H_{20}NO_4^+$ 302.1387, found: 302.1387. HRMS (ESI-TOF) m/z: $[M]^-$ calcd for $C_2F_6NO_4S_2$ 279.9178, found: 279.9168.

*Diethyl (±)-(8S,8aS,11aR,11bS)-10-ethyl-6-methyl-9,11-dioxo-8a,9,10,11,11a,11b-hexahydro-8H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-5,8-dicarboxylate Diethyl (**11**).* A mixture of **10** (0.1 mmol), *N*-ethylmaleimide (0.12 mmol), and DIPEA (0.1 mmol, 1.0 equiv) in $PhCF_3$ (2 mL) were charged into a round flask. The reaction mixture was stirred under air at room temperature for 2 h. After the solvent was removed under reduced pressure, the residue was purified by silica gel chromatography using PE/EA = 5:1 to afford the product **11** (37 mg, 86%) as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.19 (d, J = 7.2 Hz, 1H), 7.14 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.10 (dt, J = 8.0 Hz, 1.2 Hz, 1H), 7.04 (dt, J = 7.2 Hz, 1.6 Hz, 1H), 5.16 (d, J = 7.6 Hz, 1H), 4.96 (s, 1H), 4.13−4.21 (m, 4H), 3.62 (dd, J = 8.0, 1.2 Hz, 1H), 3.52 (t, J = 7.6 Hz, 1H), 3.30 (q, J = 7.2 Hz, 2H), 1.97 (s, 3H), 1.20−1.26 (m, 6H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.6, 174.0, 169.3, 168.6, 143.3, 129.6, 128.5, 127.5, 125.3, 124.0, 123.3, 104.1, 63.7, 62.7, 62.7, 60.5, 49.7, 46.1, 34.5, 17.4, 14.4, 14.3, 12.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{26}N_2NaO_6^+$ 449.1683, found: 449.1683.

*H/D Exchange. Procedures for the Reaction without **3a**.* A mixture of *N*-PMP benzaldimine (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol, 4.0 mol %), $Zn(OTf)_2$ (0.2 mmol), NaOTf (0.2 mmol), and CD_3OD (10 equiv) were weighted into a pressure tube equipped with a stir bar. DCE (2.0 mL) was added, and the mixture was stirred at 110 °C for 3 h under Ar atmosphere. Afterward, it was evaporated under reduced pressure, and the residue was absorbed to small amounts of silica. The recovered *N*-PMP benzaldimine was obtained by flash column chromatography on silica gel (eluent: PE/EA/Et_3N = 50:1:0.2). ^{1}H NMR analysis revealed H/D exchange at the ortho positions.

*Procedures for H/D Exchange Studies in the Presence of **3a**.* A mixture of *N*-PMP benzaldimine (0.2 mmol), **3a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (0.008 mmol, 4.0 mol %), $Zn(OTf)_2$ (0.2 mmol), NaOTf (0.2 mmol, 1.0 equlv), and CD_3OD (10 equiv) were added into a pressure tube equipped with a stir bar. DCE (2.0 mL) was added, and the mixture was stirred at 60 °C for 10 min under Ar atmosphere. Afterward, it was evaporated under reduced pressure and the residue was absorbed onto small amounts of silica. The product **4aaa** and the recovered *N*-PMP benzaldimine were obtained by flash column chromatography on silica gel (eluent: PE/EA = 50:1 to DCM/methanol = 40:1). ^{1}H NMR analysis revealed no deuteration of the product and the recovered imine.

KIE Experiments. Two pressure tubes each was charged with *N*-PMP benzaldimine (0.1 mmol, 0.5 equiv) or *N*-PMP benzaldimine-d_5 (0.1 mmol, 0.5 equiv) and a stir bar. To each tube was added **3a** (0.2 mmol, 1 equiv), $[Cp^*RhCl_2]_2$ (0.008 mmol, 4.0 mol %), $Zn(OTf)_2$ (0.2 mmol, 1.0 equiv), and NaOTf (0.2 mmol, 1.0 equlv). TFE (2.0 mL) was added to each tube, and the mixtures were stirred side-by-side in a preheated oil bath at 110 °C for 5 min. The reaction tubes were quenched in ice-water. The two mixtures were rapidly combined, and the solvent was rapidly evaporated under reduced pressure. The residue was adsorbed onto small amounts of silica. The purification was performed by flash column chromatography on silica gel (eluent:DCM/methanol = 40:1) to afford a mixture of **4aaa** and **4aaa-d_4**. The KIE value was determined to be k_H/k_D = 1.5 on the basis of ^{1}H NMR analysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00758.

Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds, deuterium-labeling experiments, and X-ray crystal structure and data of **6aa** and **12** (PDF)

CIF files for the corresponding compounds (CIF)

CIF files for the corresponding compounds (CIF)

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Notes

The authors declare no competing financial interest.

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