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Photoredox Catalysis | *Very Important Paper* |

VIP One-Pot Sequential Photoredox Chemistry and Asymmetric Transfer Hydrogenation with a Single Catalyst

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Abstract: A sequential process is reported, in which different photoredox reactions are placed in sequence with asymmetric transfer hydrogenations of aryl ketones to provide a diverse set of chiral alcohols with enantioselectivities of up to 99 % *ee*. The method relies on a single chiral-at-metal catalyst which is added at the beginning of the two step sequence and only a final purification of the reaction product is required.

Introduction

Structural and stereochemical complexity is often associated with superior biological properties regarding target affinity and binding selectivity,[1] and has therefore become an important concept for drug development.[2] Developing synthetic methodology to build such molecular complexity in a straightforward and economical fashion is therefore an important objective in organic synthesis.[3] This has been addressed with the concepts of multicomponent, cascade, domino, and tandem processes, including (concurrent) tandem and sequential catalysis.[4,5] We recently became interested in developing reaction schemes in which a single catalyst mediates two mechanistically distinct reactions in a sequential fashion and we reported a one-pot sequential asymmetric hydrogenation followed by a photoredox reaction (Figure 1a).[6,7] Herein, we complement our previous methodology with a one-pot sequential catalysis protocol in which a photoredox reaction[8–10] (one-electron-process) is executed first, followed by an asymmetric transfer hydrogenation[11] (two-electron-process) to provide diverse chiral alcohols with formation of a new C–C bond and establishing one or more chiral centers requiring only a single catalyst and a single final workup and purification step (Figure 1b).

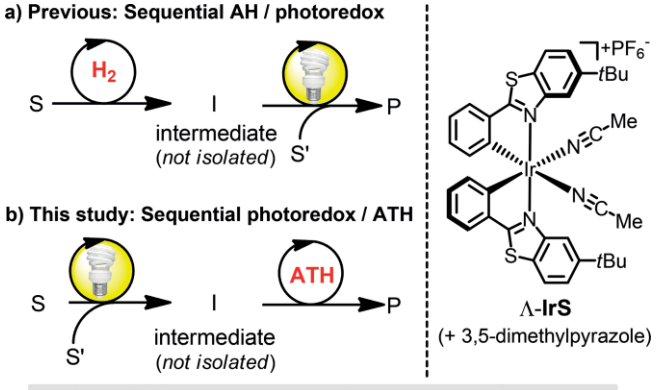

Figure 1. Previous work and this study regarding combining photoredox chemistry and asymmetric (transfer) hydrogenation in a sequential fashion with a single catalyst. AH = asymmetric hydrogenation, ATH = asymmetric transfer hydrogenation.

Results and Discussion

Initial Experiments

Previously, we introduced a novel class of asymmetric transition metal catalysts in which the chirality of the complexes originates solely from a stereogenic metal center.[12] Such chiral-at-metal complexes have demonstrated to be versatile catalysts for a large number of reaction types including visible-light-induced transformations.[13] For example, the bis-cyclometalated iridium(III) complex **IrS** (see Figure 1 for structure)[14] was demonstrated to catalyze enolate reactions, Michael additions, cycloadditions, asymmetric hydrogenations, asymmetric transfer hydrogenations, and a variety of different photoredox reactions. In previous work we demonstrated that **IrS** is capable of sequentially catalyzing asymmetric hydrogenations of ketones followed by photoredox reactions in a one-pot two-step reaction sequence by adding a single batch of the catalyst at the beginning of the process. We now wanted to investigate if it would be feasible to reverse the order of reactions, means executing the photoredox process first, followed by an asymmetric ketone reduction. This would provide additional flexibility in the design of synthetic procedures and provide access to other classes of products. Despite extensive experiments, we were not successful to use asymmetric hydrogenations in such a described Scheme most likely due to the sensitivity of the asymmetric hydrogenation to certain reagents. However, gratifyingly,

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we found that the previously reported Λ-**IrS**-catalyzed asymmetric transfer hydrogenation (ATH) of aryl ketones[15] is robust enough to be placed in sequence following an Λ-**IrS**-catalyzed/mediated photoredox reaction. In all discussed processes, the photoredox reaction introduces an aryl ketone functionality which is then enantioselectively reduced in the following ATH reaction. Note that the requirement for aryl ketones stems from an overall low asymmetric induction in the **IrS**-catalyzed ATH of alkyl ketones.[15] Since the **IrS**-catalyzed ATH reaction requires the presence of a pyrazole coligand,[15] 3,5-dimethylpyrazole (**dmp**) was added in most protocols right at the beginning of the two-step reaction protocol.

Iridium-Catalyzed Phenacyl Radical Addition to Electron-Rich Silyl Ketene Acetal and Sequential Asymmetric Transfer Hydrogenation

The first investigated strategy relies on the generation of phenacyl radicals via the photoredox-mediated reduction of phenacyl bromides, followed by a trapping of these electron-deficient radicals with electron-rich silyl ketene acetals and thereby providing the ketone intermediate **I** which is then enantioselectively reduced to the corresponding alcohol (Figure 2).[14a,16] Accordingly, we subjected phenacyl bromides **1** together with the silyl ketene acetal **2** in the presence of 2 mol-% Λ-**IrS** and **dmp** (40 mol-%) to irradiation with a compact fluorescence lamp (21 W) for 18 hours. Afterwards, the solvent was simply changed from MeCN to THF/H_2O (1:1), ammonium formate (9 equiv.) was added for the subsequent ATH reaction, and the reaction mixture was slightly warmed to 40 °C for 14 h. To our delight, the chiral alcohols **3a**–**c** were isolated in 73–85 % yields and with high enantioselectivities of 93–95 % *ee*. It is worth noting that a decreased enantioselectivity (86 % *ee*) was obtained for **3a** when blue LEDs were used instead, thereby revealing the importance of the light source (see SI, p. S3). Interestingly, the lactone (**3d**) was obtained in situ without any loss of enantioselectivity (95 % *ee*) by treating the product mixture with aqueous HCl.

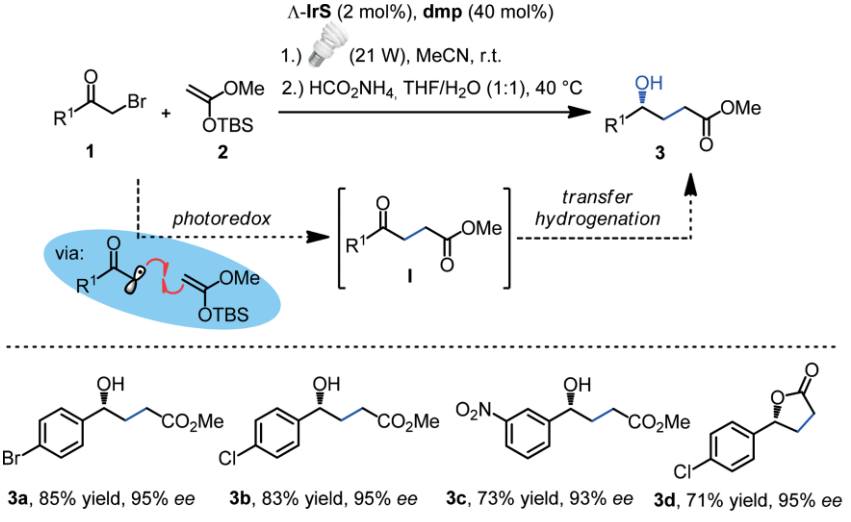

Figure 2. Iridium-catalyzed phenacyl radical addition to electron-rich silyl ketene acetal and sequential asymmetric transfer hydrogenation.

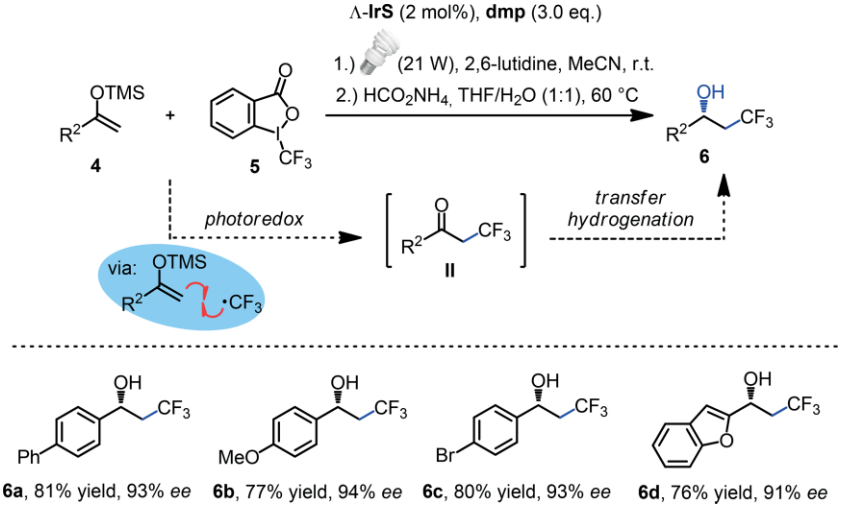

Figure 3. Iridium-catalyzed CF_3 radical addition to electron-rich silyl enol ether and sequential asymmetric transfer hydrogenation.

Iridium-Catalyzed CF_3 Radical Addition to Electron-Rich Silyl Enol Ethers and Sequential Asymmetric Transfer Hydrogenation

In order to construct more CF_3-containing chiral alcohols that might be attractive building blocks for the synthesis of bioactive compounds,[17] we chose silyl enol ethers as suitable precursors to introduce carbonyl motifs given their well-established capacity to accept electron-deficient radicals.[18–20] We were delighted to find that different silyl enol ethers **4** reacted with Togni's reagent (**5**) under photoredox conditions to provide the intermediate ketones **II**, which were then subjected to ATH conditions providing chiral trifluoromethyl alcohols **6a**–**d** in 76–81 % yields and with 91–94 % *ee* (Figure 3). It is worth mentioning that increasing the amount of **dmp** and the utilization of a compact fluorescence lamp are crucial for achieving high *ee* values (see SI, p. S5).

Iridium-Catalyzed Radical Conjugate Addition and Sequential Asymmetric Transfer Hydrogenation

In all photoredox reactions presented so far, **Λ-IrS**/**dmp** served as a photoredox mediator/catalyst for a reductive substrate activation in otherwise redox neutral reactions. In order to demonstrate that **Λ-IrS**/**dmp** is also capable of catalyzing or mediating oxidatively initiated photoredox processes in sequence with an ATH reaction, we chose the reaction sequence shown in Figure 4. Accordingly, aryl vinyl ketones **7** were treated with *N*-methyl-9,10-dihydroacridine (**8**) under photoredox conditions and in the presence of trifluoroacetic acid (TFA)[21] followed by ATH to provide the chiral alcohols **9**, including a newly formed C–C bond in the β-position to the chiral alcohol, in 71–79 % yields and with 98–99 % *ee* (3 examples).[22] Herein, the acridine is apparently converted into the corresponding γ-amino alkyl radical via a sequence of single electron oxidation by the photoexcited iridium catalyst and subsequent deprotonation, followed by trapping of this electron-rich radical with the vinyl ketone substrate and thereby forming the ketone intermediate **III**, which is subsequently reduced highly enantioselectively to the corresponding alcohol.

Two Catalytic Asymmetric Reactions in Sequence with Λ-IrS

As a proof-of-principle demonstration, our final efforts were dedicated to investigate the possibility to link two catalytic asymmetric reactions catalyzed both by **Λ-IrS** (Figure 5). This would demonstrate the merit of our modular, sequential strategy applied to products bearing two stereocenters. As shown

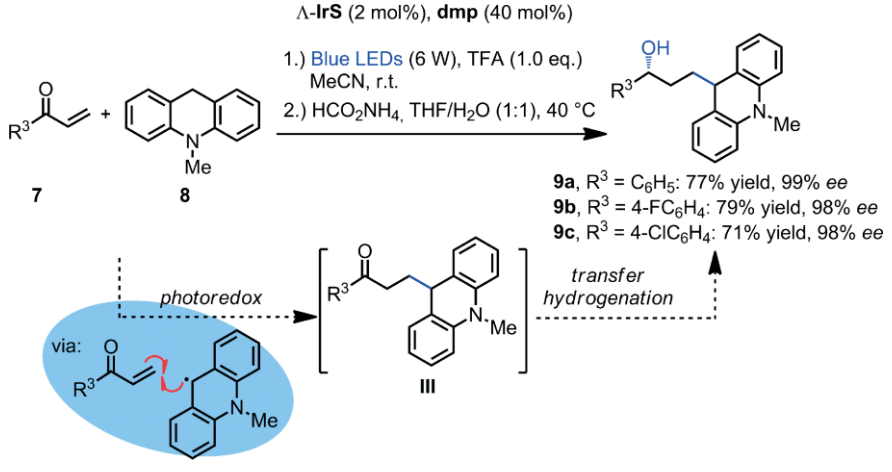

Figure 4. Iridium-catalyzed radical conjugate addition and sequential asymmetric transfer hydrogenation.

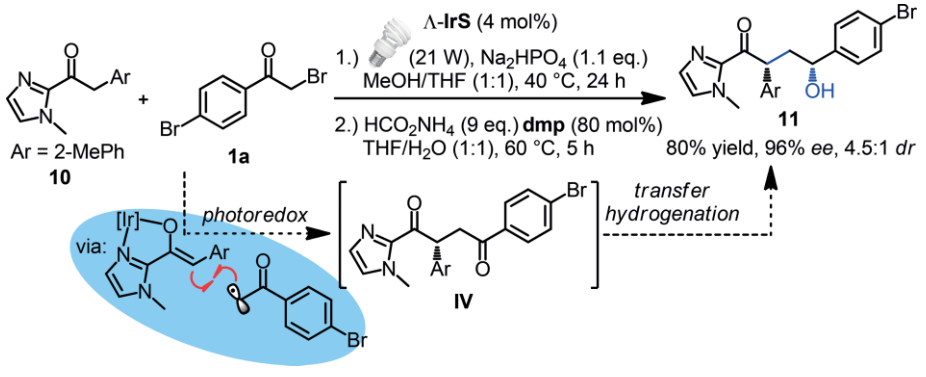

Figure 5. Iridium-catalyzed asymmetric photoredox chemistry and asymmetric transfer hydrogenation.

in Figure 5, 2-acyl imidazole **10** was first reacted with phenacyl bromide **1a** in the presence of Λ-**IrS** (4 mol-%) and a weak base under the activation by visible light to generate the intermediate product **IV** as reported recently,[14a] which was not isolated, but upon solvent exchange and the addition of ammonium formate and the ligand **dmp**, subjected to asymmetric transfer hydrogenation to provide compound **11** in 80 % yield, 96 % *ee*, and 4.5:1 *dr*. It is worth noting that the second carbonyl group is not affected in this chemoselective reduction which might be due to the higher steric crowding around the 2-acyl imidazole moiety. Intriguingly, in this process, a single charge of Λ-**IrS** was added at the beginning of the reaction, which catalyzed two mechanistically distinct asymmetric processes in a sequential fashion, and thereby implementing one new C–C bond and two new stereocenters.

Conclusions

We have introduced a sequential protocol, in which a single chiral-at-metal complex mediates a photoredox reaction in sequence with the catalysis of a subsequent asymmetric transfer hydrogenation to provide chiral alcohol building blocks with enantiomeric excess reaching up to 99 % *ee*. A single batch of catalyst is added at the beginning of the sequence and only a single purification step is required. Although this new protocol has clear limitations in scope, it nicely complements our previous work on sequential asymmetric hydrogenation/photoredox processes.

Experimental Section

General: All reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Catalytic reactions were performed in a Schlenk tube (10 mL). A 21 W compact fluorescent lamp (CFL), 6 W and 24 W Blue LEDs served as light sources. The catalyst Λ-**IrS**[14] was synthesized according to our published procedures. HPLC grade of solvents and deionized water were used without further purification. Reagents that were purchased from commercial suppliers were used without further purification. Flash column chromatography was performed with silica gel 60 M from Macherey–Nagel (irregular shaped, 230–400 mesh, pH 6.8, pore volume: 0.81 mL g^{-1}, mean pore size: 66 Å, specific surface: 492 m^2 g^{-1}, particle size distribution: 0.5 % < 25 μm and 1.7 % > 71 μm, water content: 1.6 %). ^{1}H NMR, ^{19}F NMR and proton decoupled ^{13}C NMR spectra were recorded on Bruker Avance 300 (300 MHz), or Bruker AM (500 MHz) spectrometers at ambient temperature. NMR standards were used as follows: ^{1}H NMR spectroscopy: δ = 7.26 ppm ($CDCl_3$). ^{19}F NMR spectroscopy: δ = 0 ppm ($CFCl_3$). ^{13}C NMR spectroscopy: δ = 77.0 ppm ($CDCl_3$). IR spectra were recorded on a Bruker Alpha FT-IR spectrophotometer. High-resolution mass spectra were recorded on a Bruker En Apex Ultra 7.0 TFT-MS instrument using ESI/EI/APCI/FD technique. Chiral HPLC chromatography was performed with an Agilent 1200, Agilent 1260 HPLC system or Shimadzu Lc-2030c HPLC system. Optical rotations were measured on a Krüss P8000-T polarimeter with $[\alpha]_D^{22}$ values reported in degrees with concentrations reported in g/100 mL.

General Procedure for Iridium-Catalyzed Phenacyl Radical Addition to Electron-rich Silyl Ketene Acetal and Sequential Asymmetric Transfer Hydrogenation: A dried 10 mL Schlenk tube was charged with phenacyl bromides **1** (0.20 mmol), Λ-**IrS** (3.8 mg, 2 mol-%), and 3,5-dimethyl pyrazole (7.7 mg, 40 mol-%). The tube was purged with nitrogen, then CH_3CN (0.5 mL, 0.4 M) was added via syringe, followed by silyl ketene acetal **2** (112.8 mg, 3.0 equiv.). The reaction mixture was degassed via freeze-pump-thaw for three cycles. After the mixture was thoroughly degassed, the vial was sealed and positioned approximately 5 cm from a compact fluorescent lamp (21 W). The reaction was stirred at room temperature for the indicated time (monitored by TLC) under nitrogen atmosphere. Afterwards, the solvent was removed, and HCO_2NH_4 (113.4 mg, 1.80 mmol, 9.0 equiv.) and THF/H_2O (0.1 mL/0.1 mL, 1.0 M) were added to the residual crude material. The reaction solution was stirred at 40 °C until complete disappearance of the starting material (detected by TLC), then cooled down to room temperature, concentrated under reduced pressure, and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) to afford the product **3**.

Methyl (*R*)-4-(4-Bromophenyl)-4-hydroxybutanoate (3a):[23] According to the general procedure, the reaction between 2-bromo-1-(4-bromophenyl)ethan-1-one **1a** (55.6 mg, 0.20 mmol) and silyl ketene acetal **2** (112.8 mg, 3.0 equiv.) gave 46.2 mg (85 %) of **3a** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 95 % [HPLC: OD-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 9.87 min, t_r (major) = 11.62 min]. $[\alpha]_D^{22}$ = +20.4 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 8.1 Hz, 2 H), 4.68–4.63 (m, 1 H), 3.60 (s, 3 H), 2.38–2.33 (m, 3 H), 1.99–1.92 (m, 2 H) ppm.

Methyl (*R*)-4-(4-Chlorophenyl)-4-hydroxybutanoate (3b):[24] According to the general procedure, the reaction between 2-bromo-1-(4-chlorophenyl)ethan-1-one **1b** (46.6 mg, 0.20 mmol) and silyl ketene acetal **2** (112.8 mg, 3.0 equiv.) gave 38.0 mg (83 %) of **3b** as a yellow solid. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 95 % [HPLC: OD-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 9.13 min, t_r (major) = 10.81 min]. $[\alpha]_D^{22}$ = +28.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 4 H), 4.672–4.665 (m, 1 H), 3.60 (s, 3 H), 2.38–2.33 (m, 3 H), 1.99–1.93 (m, 2 H) ppm.

Methyl (*R*)-4-Hydroxy-4-(3-nitrophenyl)butanoate (3c): According to the general procedure, the reaction between 2-bromo-1-(3-nitrophenyl)ethan-1-one **1c** (48.8 mg, 0.20 mmol) and silyl ketene acetal **2** (112.8 mg, 3.0 equiv.) gave 35.0 mg (73 %) of **3c** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 93 % [HPLC: OD-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 13.77 min, t_r (major) = 15.32 min]. $[\alpha]_D^{22}$ = +24.3 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.52 (t, *J* = 7.8 Hz, 1 H), 4.93–4.89 (m, 1 H), 3.69 (s, 3 H), 2.80 (s, 1 H), 2.58–2.40 (m, 2 H), 2.18–2.01 (m, 2 H) ppm.

Lactone 3d:[25] Followed the general procedure for the reaction between 2-bromo-1-(4-chlorophenyl)ethan-1-one **1b** (46.6 mg, 0.20 mmol) and silyl ketene acetal **2** (112.8 mg, 3.0 equiv.), 10 mL of saturated HCl aqueous solution was added to quench the reaction. The mixture was extracted with EtOAc and concentrated to afford the crude residue, which was further dissolved in MeOH (0.2 mL). To the corresponding solution, a solution of HCl (1 M) was added. The mixture was stirred at 40 °C for 24 h, then the solvent was carefully evaporated under reduced pressure, water was added, and the solution was extracted with EtOAc. The organic layers were combined, dried with Na_2SO_4, and purified by flash chromatography on silica gel (*n*-hexane/dichloromethane/ethyl acetate = 8:2:1)

to afford 27.8 mg (71 %) of **3d** as a white solid. Enantiomeric excess was established by HPLC analysis using a Chiralpak AS-H column, *ee* = 95 % [HPLC: AS-H, 210 nm, *n*-hexane/2-propanol = 75:25, flow rate 1 mL/min, 35 °C, t_r (major) = 11.99 min, t_r (minor) = 14.36 min]. $[\alpha]_D^{22}$ = +27.4 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.22–7.19 (m, 2 H), 5.43–5.39 (m, 1 H), 2.65–2.54 (m, 3 H), 2.16–2.00 (m, 1 H) ppm.

General Procedure for Iridium-Catalyzed CF_3 Radical Addition to Electron-rich Silyl Enol Ethers and Sequential Asymmetric Transfer Hydrogenation: A dried 10 mL Schlenk tube was charged with Togni's reagent **5** (63.2 mg, 0.20 mmol), Λ-**IrS** (3.8 mg, 2 mol-%) and 3,5-dimethyl pyrazole (57.6 mg, 3.0 equiv.). The tube was purged with nitrogen, then CH_3CN (0.5 mL, 0.4 M) was added via syringe, followed by silyl enol ethers **4** (0.30 mmol) and 2,6-lutidine (42.8 mg, 0.40 mmol). The reaction mixture was degassed via freeze-pump-thaw for three cycles. After the mixture was thoroughly degassed, the vial was sealed and positioned approximately 5 cm from a 21 W compact fluorescent lamp. The reaction was stirred at room temperature for the indicated time (monitored by TLC) under nitrogen atmosphere. Afterwards, the solvent was removed, HCO_2NH_4 (113.4 mg, 1.80 mmol, 9.0 equiv.) and THF/H_2O (0.1 mL/0.1 mL, 1.0 M) were added to the residual crude material. The reaction solution was stirred at 60 °C until complete disappearance of the starting material (detected by TLC), then cooled down to room temperature, concentrated under reduced pressure, and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 12:1) to afford the products **6**.

(*R*)-1-([1,1′-Biphenyl]-4-yl)-3,3,3-trifluoropropan-1-ol (6a):[26] According to the general procedure, the reaction between ({1-[(1,1′-biphenyl)-4-yl]vinyl}oxy)trimethylsilane **4a** (80.4 mg, 0.30 mmol) and Togni's reagent **5** (63.2 mg, 0.20 mmol) gave 43.0 mg (81 %) of **6a** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralpak AD-H column, *ee* = 93 % [HPLC: AD-H, 254 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 7.49 min, t_r (major) = 8.30 min]. $[\alpha]_D^{22}$ = +31.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.23 (m, 9 H), 5.02–4.97 (m, 1 H), 2.64–2.29 (m, 2 H), 2.18 (s, 1 H) ppm.

(*R*)-3,3,3-Trifluoro-1-(4-methoxyphenyl)propan-1-ol (6b): According to the general procedure, the reaction between {[1-(4-methoxyphenyl)vinyl]oxy}trimethylsilane **4b** (66.6 mg, 0.30 mmol) and Togni's reagent **5** (63.2 mg, 0.20 mmol) gave 34.0 mg (77 %) of **6b** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralcel OJ-H column, *ee* = 94 % [HPLC: OJ-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 11.42 min, t_r (major) = 12.13 min]. $[\alpha]_D^{22}$ = +19.4 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2 H), 6.86–6.81 (m, 2 H), 4.97–4.95 (m, 1 H), 3.74 (s, 3 H), 2.66–2.47 (m, 1 H), 2.45–2.27 (m, 1 H), 1.98 (s, 1 H) ppm.

(*R*)-1-(4-Bromophenyl)-3,3,3-trifluoropropan-1-ol (6c): According to the general procedure, the reaction between {[1-(4-bromophenyl)vinyl]oxy}trimethylsilane **4c** (81.0 mg, 0.30 mmol) and Togni's reagent **5** (63.2 mg, 0.20 mmol) gave 43.0 mg (80 %) of **6c** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralcel OJ-H column, *ee* = 93 % [HPLC: OJ-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (minor) = 8.34 min, t_r (major) = 9.13 min]. $[\alpha]_D^{22}$ = +32.8 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.1 Hz, 2 H), 5.00–4.97 (m, 1 H), 2.62–2.44 (m, 1 H), 2.42–2.30 (m, 1 H), 2.13 (d, *J* = 2.1 Hz, 1 H) ppm.

(*R*)-1-(Benzofuran-2-yl)-3,3,3-trifluoropropan-1-ol (6d): According to the general procedure, the reaction between {[1-(benzofuran-2-yl)vinyl]oxy}trimethylsilane **4d** (69.6 mg, 0.30 mmol) and Togni's reagent **5** (63.2 mg, 0.20 mmol) gave 35.0 mg (76 %) of **6d** as a yellow oil. Enantiomeric excess was established by HPLC analysis using a Chiralpak AS-H column, *ee* = 91 % [HPLC: AS-H, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (major) = 6.46 min, t_r (minor) = 7.46 min]. $[\alpha]_D^{22}$ = +25.6 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 7.5 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.25–7.14 (m, 2 H), 6.63 (s, 1 H), 5.16 (br. s, 1 H), 2.77–2.64 (m, 2 H), 2.28 (br. s, 1 H) ppm.

General Procedure for Iridium-Catalyzed Radical Conjugate Addition and Sequential Asymmetric Transfer Hydrogenation: A dried 10 mL Schlenk tube was charged with 10-methyl-9,10-dihydroacridine **8** (39.0 mg, 0.20 mmol), Λ-**IrS** (3.8 mg, 2 mol-%) and 3,5-dimethyl pyrazole (7.7 mg, 40 mol-%). The tube was purged with nitrogen, then CH_3CN (0.8 mL, 0.25 M) was added via syringe, followed by enones **7** (0.40 mmol), and trifluoroacetic acid (22.8 mg, 0.20 mmol). The reaction mixture was degassed via freeze-pump-thaw for three cycles. After the mixture was thoroughly degassed, the vial was sealed and positioned approximately 3 cm from blue LEDs (6 W). The reaction was stirred at room temperature for the indicated time (monitored by TLC) under nitrogen atmosphere. Afterwards, the solvent was removed, HCO_2NH_4 (113.4 mg, 1.80 mmol, 9.0 equiv.) and THF/H_2O (0.1 mL/0.1 mL, 1.0 M) were added to the residual crude material. The reaction solution was stirred at 40 °C until complete disappearance of the starting material (detected by TLC), then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 12:1) to afford the products **9**.

(*R*)-3-(10-Methyl-9,10-dihydroacridin-9-yl)-1-phenylpropan-1-ol (9a): According to the general procedure, the reaction between 1-phenylprop-2-en-1-one **7a** (52.8 mg, 0.40 mmol) and 10-methyl-9,10-dihydroacridine **8** (39.0 mg, 0.20 mmol) gave 50.7 mg (77 %) of **9a** as a white solid. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 99 % [HPLC: OD-H, 254 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (major) = 14.03 min, t_r (minor) = 29.75 min]. $[\alpha]_D^{22}$ = +7.0 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.02 (m, 9 H), 6.87–6.80 (m, 4 H), 4.40 (t, *J* = 6.0 Hz, 1 H), 3.73 (t, *J* = 6.6 Hz, 1 H), 3.27 (s, 3 H), 1.71–1.56 (m, 4 H), 1.47–1.39 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.6, 142.4, 128.4, 128.2, 128.1, 127.6, 127.5, 127.4, 126.85, 126.81, 125.9, 120.5, 112.1, 112.0, 74.6, 44.0, 36.0, 33.6, 32.9 ppm. IR (film): $\tilde{\nu}$ = 3336, 3029, 2945, 2904, 2869, 2812, 1591, 1465, 1336, 1267, 1200, 1127, 1061, 1035, 928, 878, 841, 732, 697, 640, 574, 534, 500, 416 cm^{-1}. HRMS (APCI, *m/z*) calcd. for $C_{23}H_{22}N$ $[M + H - H_2O]^+$: 312.1747, found 312.1739.

(*R*)-1-(4-Fluorophenyl)-3-(10-methyl-9,10-dihydroacridin-9-yl)-propan-1-ol (9b): According to the general procedure, the reaction between 1-(4-fluorophenyl)prop-2-en-1-one **7b** (60.0 mg, 0.40 mmol) and 10-methyl-9,10-dihydroacridine **8** (39.0 mg, 0.20 mmol) gave 55.0 mg (79 %) of **9b** as a white solid. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 98 % [HPLC: OD-H, 254 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (major) = 14.26 min, t_r (minor) = 29.11 min]. $[\alpha]_D^{22}$ = +33.8 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14–7.01 (m, 6 H), 6.88–6.79 (m, 6 H), 4.35 (t, *J* = 6.0 Hz, 1 H), 3.72 (t, *J* = 6.6 Hz, 1 H), 3.25 (s, 3 H), 1.67–1.53 (m, 4 H), 1.42–1.34 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 161.1, 142.3, 140.22, 140.20, 128.12, 128.10, 127.6, 127.49, 127.46, 127.39, 126.89, 126.86, 120.5, 115.2, 115.1, 112.08, 112.05, 73.9, 44.0, 36.1, 33.4, 32.9 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –115.32 ppm. IR (film): $\tilde{\nu}$ = 3334, 3286, 3068, 3037, 2952, 2915, 2880, 1594, 1505, 1470, 1341,

1274, 1217, 1153, 1130, 1068, 1041, 929, 882, 828, 746, 649, 537, 499, 411 cm^{-1}. HRMS (APCI, *m/z*) calcd. for $C_{23}H_{21}FN$ $[M + H - H_2O]^+$: 330.1653, found 330.1653.

(*R*)-1-(4-Chlorophenyl)-3-(10-methyl-9,10-dihydroacridin-9-yl)-propan-1-ol (9c): According to the general procedure, the reaction between 1-(4-chlorophenyl)prop-2-en-1-one **7c** (66.4 mg, 0.40 mmol) and 10-methyl-9,10-dihydroacridine **8** (39.0 mg, 0.20 mmol) gave 51.6 mg (71 %) of **9c** as a white solid. Enantiomeric excess was established by HPLC analysis using a Chiralcel OD-H column, *ee* = 98 % [HPLC: OD-H, 254 nm, *n*-hexane/2-propanol = 90:10, flow rate 1 mL/min, 25 °C, t_r (major) = 14.21 min, t_r (minor) = 27.66 min]. $[\alpha]_D^{22}$ = +4.2 (*c* = 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.10 (m, 4 H), 7.05–7.02 (m, 4 H), 6.87–6.81 (m, 4 H), 4.38 (t, *J* = 5.7 Hz, 1 H), 3.73 (t, *J* = 6.0 Hz, 1 H), 3.27 (s, 3 H), 1.65–1.56 (m, 4 H), 1.45–1.36 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 142.4, 133.0, 128.5, 128.1, 127.45, 127.40, 127.3, 126.93, 126.90, 120.5, 112.11, 112.09, 73.8, 44.0, 36.0, 33.4, 32.9 ppm. IR (film): $\tilde{\nu}$ = 3417, 3370, 3058, 3030, 2907, 2837, 2012, 1590, 1469, 1338, 1269, 1209, 1133, 1085, 1061, 1008, 921, 882, 826, 746, 578, 541, 500, 463, 418 cm^{-1}. HRMS (APCI, *m/z*) calcd. for $C_{23}H_{21}ClN$ $[M + H - H_2O]^+$: 346.1357, found 346.1356.

Iridium-Catalyzed Asymmetric Photoredox Chemistry and Asymmetric Transfer Hydrogenation: A dried 10 mL Schlenk tube was charged with 2-bromo-1-(4-bromophenyl)ethan-1-one **1a** (27.8 mg, 0.10 mmol), 2-acyl imidazole **10** (34.6 mg, 0.20 mmol), Na_2HPO_4 (15.6 mg, 0.11 mmol) and Λ-**IrS** (3.8 mg, 4 mol-%). The tube was purged with nitrogen, then MeOH/THF (0.4 mL/0.1 mL, 0.2 M) was added via syringe. The reaction mixture was degassed via freeze-pump-thaw for three cycles. After the mixture was thoroughly degassed, the vial was sealed and positioned approximately 5 cm from a 21 W compact fluorescent lamp. The reaction mixture was stirred at 40 °C for the indicated time (monitored by TLC) under nitrogen atmosphere. Afterwards, the solvent was removed, 3,5-dimethyl pyrazole (7.7 mg, 80 mol-%), HCO_2NH_4 (56.8 mg, 0.9 mmol, 9.0 equiv.) and THF/H_2O (0.10 mL/0.10 mL, 0.5 M) were added to the residual crude material. The reaction mixture was stirred at 60 °C until complete disappearance of the starting material (detected by TLC), then cooled down to room temperature, concentrated under reduced pressure and purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 2:1) to afford 33.0 mg of **11** (80 % yield, 4.5:1 *dr*) as a yellow oil. The enantioselectivity for the major product was 96 % *ee*. Enantiomeric excess was established by HPLC analysis using a Chiralpak IG column, 96 % *ee* [HPLC: IG, 220 nm, *n*-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, 25 °C, t_r (minor) = 19.39 min, t_r (major) = 22.21 min]. $[\alpha]_D^{22}$ = +30.9 (*c* = 1.0, CH_2Cl_2). The product was present as a 4.5:1 mixture of diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 8.4 Hz, 3 H), 7.17–6.97 (m, 6 H), 6.94–6.86 (m, 1 H), 5.66–5.54 (m, 1 H), 4.51–4.47 (m, 1 H), 3.86 and 3.81 (s, 3 H), 2.57–2.31 (m, 4 H), 1.97–1.88 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 193.5, 143.7, 143.4, 137.6, 136.3, 131.2, 130.4, 129.2, 127.6, 127.53, 127.46, 127.40, 126.9, 126.1, 120.8, 70.6, 44.9, 44.2, 36.1, 20.1 ppm. IR (film): $\tilde{\nu}$ = 3390, 3109, 3055, 3020, 2954, 2921, 2866, 1669, 1593, 1482, 1401, 1289, 1265, 1232, 1156, 1067, 1006, 962, 908, 868, 825, 770, 735, 694, 662, 625, 597, 559, 520, 456 cm^{-1}. HRMS (APCI, *m/z*) calcd. for $C_{21}H_{21}BrN_2O_2H$ $[M + H]^+$: 413.0859, found 413.0852.

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