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Modular Synthesis of Arylacetic Acid Esters, Thioesters, and Amides from Aryl Ethers via Rh(II)-Catalyzed Diazo Arylation

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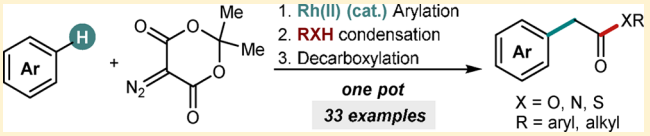
Supporting Information

ABSTRACT: One-pot formation of arylacetic acid esters, thioesters, and amides via Rh(II)-catalyzed arylation of a Meldrum's acid-derived diazo reagent with electron-rich arenes is described. The methodology was used to efficiently synthesize an anticancer compound.



INTRODUCTION

Diaryl ethers are privileged structures in medicinal chemistry,[1] and there are many examples of biologically active aryloxyphenylacetic acid derivatives that contain this motif (e.g., Figure 1).[2]

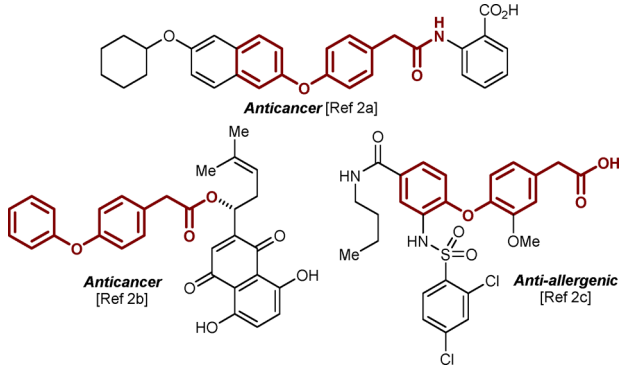
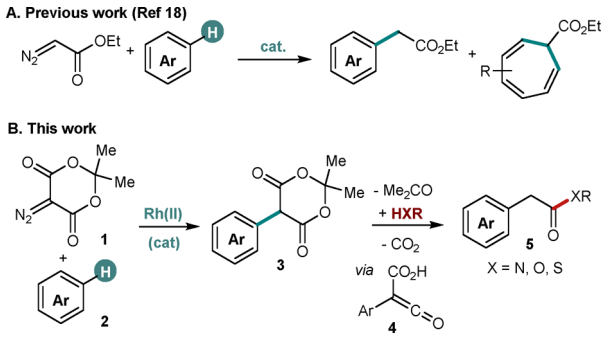


Figure 1. Biologically active aryloxyphenylacetic acid derivatives.

Several methods have been established for the synthesis of diaryl ethers,[3−7] but only S_NAr reactions, which are limited to electron-poor arenes, have shown general efficiency in delivering aryloxyphenylacetic acid derivatives directly;[2c,8] phenylacetic acid derivatives generally perform poorly in Cu-catalyzed phenolic O-arylation reactions[9,10] unless aryliodonium reagents are used.[7c,11] α-Arylation of acetic acid derivatives is well-developed[12] but requires reactive handles[13,14] or ortho-directors[15,16] on the arene and is thus rarely applied to diaryl ether systems.[17] Direct functionalization of commercially or readily available diaryl ethers would provide a convenient alternative route to medicinally relevant aryloxyphenylacetic acid derivatives. A few methods for direct formation of ethyl arylacetates via arylation of ethyl diazoacetate are known,[18] but these methods usually also form cycloheptatriene (Büchner addition) side products (Scheme 1A). A strategy that avoids this complication and provides a wider range of arylacetic acid derivatives would be advantageous for library synthesis and drug discovery. Para-selective functionalization of arenes with diazo compounds is well-developed for α-aryldiazo esters[19] but relatively uncommon for diazo-1,3-dicarbonyls.[20] Rh(II)-catalyzed functionalization of arenes (including diaryl ethers) was recently demonstrated with diazobarbiturates.[21] A similar insertion reaction of the bench-stable, crystalline diazo reagent **1** with arenes **2** would give products **3**, which are highly susceptible to hydrolysis/alcoholysis through ketene formation via cyclorevertive extrusion of acetone (Scheme 1B).[22] We postulated that products **3** could serve as latent ketenes[23] for the decarboxylative construction of arylacetic acid derivatives **5**.[16,24] Herein we describe a one-pot procedure for the modular construction of arylacetic esters, thioesters, and amides via $Rh_2(esp)_2$-catalyzed (0.1−0.25 mol %) arylation of diazo **1** with electron-rich arenes **2** and its application to the concise synthesis of an anticancer compound.

Scheme 1. Synthesis of Arylacetic Acid Derivatives via Rh(II) Catalysis



RESULTS AND DISCUSSION

In a preliminary experiment, **1** was stirred with $Rh_2(esp)_2$ in toluene at rt overnight, resulting in >95% conversion and formation of intermediate **3a** in 65% NMR yield (Scheme 2).[25] No other byproducts were detected by ^1H or $^{13}C\{^1H\}$ NMR,

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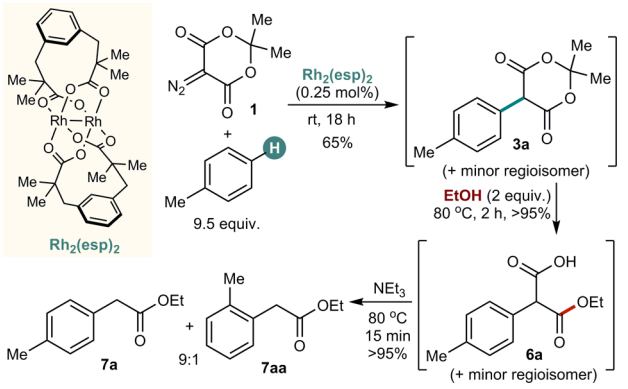
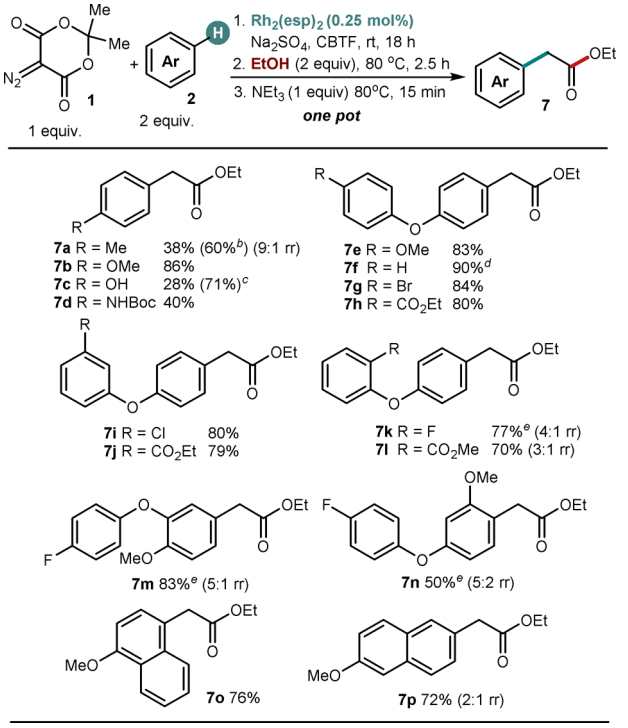
Scheme 2. Functionalization of Toluene Monitored by ^{1}H NMR[25]



suggesting competitive decomposition of diazo **1** into volatile products, which has been documented under photolytic conditions.[26] More nucleophilic anisole underwent a similar reaction in >95% NMR yield. Heating **3a** with EtOH resulted in quantitative conversion to half-ester **6a**, which rapidly and quantitatively decarboxylated on addition of NEt_3[27] to provide inseparable esters **7a** and **7aa** in a 9:1 ratio (Scheme 2), isolated in 60% yield in a repeat experiment (Table 1).

4-Chlorobenzotrifluoride (CBTF) was identified as an affordable solvent that did not react with in situ-generated Rh-carbenoids, allowing engagement of solid or expensive arenes in this transformation.[28] Inclusion of Na_2SO_4 and a dry atmosphere suppressed hydrolysis of **3**, which was occasionally observed if atmospheric humidity was high or when undried reagents were used. Reaction of **1** with anisole (2 equiv) in CBTF followed by ethanolysis and decarboxylation provided **7b** in 86% yield as a single isomer (Table 1). In the case of toluene, reducing the molar excess of the arene from 9.5 to 2 equiv reduced the yield of **7a** and **7aa** from 60% to 38% (9:1 rr), and less-electron-rich fluorobenzene and bromobenzene were not synthetically useful (<10%). While reaction of phenol produced a complex mixture from which **7c** was isolated in only 28% yield, similar treatment of (trimethylsilyl)oxybenzene gave the free phenol product **7c** in good yield (71%). As observed previously,[21] catalyst poisoning resulted in no conversion of *N*,*N*-dimethylaniline or decomposition of **1** in the arylation step. Introduction of a Boc group to the aniline system nullified this poisoning effect and led to the formation of **7d** in low yield (40%). The observation of similar yields of **7a** from toluene and **7d** from *N*-Boc-aniline correlates with the similar Hammett σ_p constants of alkyl and carbamate substituents.[29] Diaryl ethers reacted well; various electron-donating and -withdrawing groups were tolerated at the 4-position of the nonreacting benzene ring (products **7e**–**h**), and regioselectivity was >19:1 in all cases. In the case of **7f**, 5.0 equiv of diphenyl ether was used to avoid reaction at both phenyl rings. Electron-withdrawing substituents were similarly tolerated at the 3-position of the nonreacting ring (**7i**–**j**), but substitution at the 2-position led to moderate regioselectivity, with the minor isomer arising from reaction at the more substituted ring (**7k**–**l**).[30] Note that transesterification of the methyl ester in **7l** was not observed. 2- And 3-phenoxyanisole both produced inseparable mixtures of three regioisomers in moderate yield with poor selectivity,[31] indicating substantial reactivity of electron-rich disubstituted benzene rings. When 2-(4-fluorophenoxy)anisole was engaged in the reaction sequence, **7m** was formed in 83% yield (5:1 rr) with preferential reaction para to the methoxy group. 3-(4-Fluorophenoxy)anisole led primarily to **7n** (5:2 rr) via reaction at the least-hindered electron-rich center. Electron-rich naphthalenes were also competent reaction partners; 1-methoxynaphthalene reacted exclusively at the 4-position (**7o**), whereas 2-methoxynaphthalene gave **7p** in good yield but with low regioselectivity.[30]

Table 1. Synthesis of Ethyl Arylacetates 7[a]



[a]Reactions were conducted on 1.0 mmol scale (ca. 1 M with respect to **1**), and DCE cosolvent was sometimes added in step 2; see the Experimental Section. Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures and were >19:1 unless otherwise specified in parentheses; rr remained unchanged after purification. [b]Reaction conducted in neat toluene (9.5 equiv). [c]From TMSOPh. [d]Reaction conducted using 5.0 equiv of diphenyl ether. [e]Reaction conducted on 0.50 mmol scale.

Next, we examined the scope of the alcoholysis step using various aryl ethers (some of which differ from those used in Table 1). Benzyl and allyl alcohols led to esters **8a,b** in high yields (note the preservation of the ethyl ester in **8a**) (Table 2). *tert*-Amyl alcohol (**8c**) and cholesterol (**8e**) both reacted efficiently, despite their steric bulk, which may be explained by the formation and interception of unhindered ketene intermediates **4**. Nucleophilic trapping with phenol led to phenyl ester **8d** in good yield. The scope of the reaction was further extended by replacing the alcohol with anilines or thiols under otherwise similar conditions. Primary, secondary, and sterically hindered acetanilides **8f**–**h** formed efficiently; the third stage of the one-pot sequence was carried out at 100 °C to compensate for the slower rate of decarboxylation in these cases. Thioesters from an aliphatic thiol (**8i**) and thiophenol (**8j**) could also be accessed, which is of synthetic interest given the straightforward conversion of thioesters to aryl ketones (Liebeskind–Srogl coupling)[32] or aldehydes (Fukuyama reduction).[33] It should also be noted that allyl esters, aryl esters, thioesters, and secondary amides have limited compatibility with existing phenol O-arylation and carbonyl α-arylation methods.

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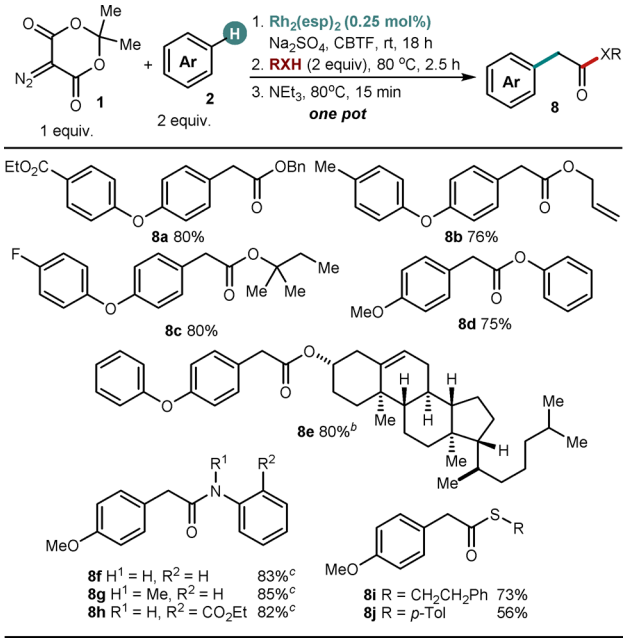
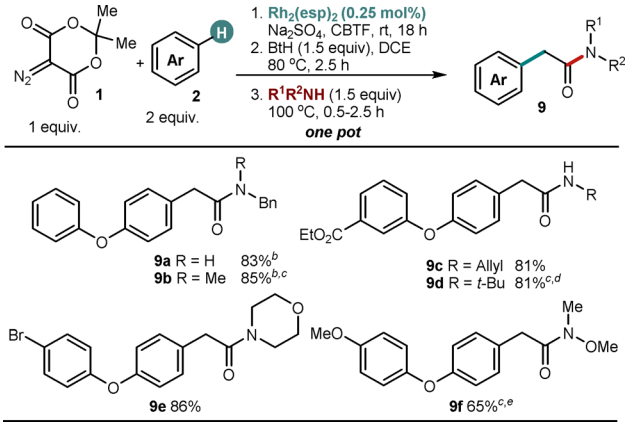
Table 2. Synthesis of Esters, Acetanilides, and Thioesters 8[a]



[a]Reactions were conducted on 0.50 mmol scale (*ca* 1 M with respect to **1**), and DCE cosolvent was sometimes added in step 2; see the Experimental Section. Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction mixtures and were >19:1 in all cases. [b]Reaction conducted using 5 equiv of diphenyl ether and 1.5 equiv of cholesterol. [c]The decarboxylation (step 3) was performed at 100 °C for 30 min.

Deprotonation of **3** interfered with its direct aminolysis by aliphatic amines, but we addressed this problem by using 1*H*-benzotriazole (BtH) as a synthetic auxiliary.[34] Following arylation of **1**, introduction of BtH followed by the amine coupling partner of choice led cleanly to the corresponding amide (Table 3). Secondary (**9a**, **9c**–**d**), tertiary (**9b**, **9e**), and bulky (**9d**) amides were readily synthesized; Morpholine amide **9e** and Weinreb amide **9f** have well-established synthetic utility as aldehyde or ketone precursors. Note that aminolysis of the ethyl ester in **9c**–**d** was not observed.

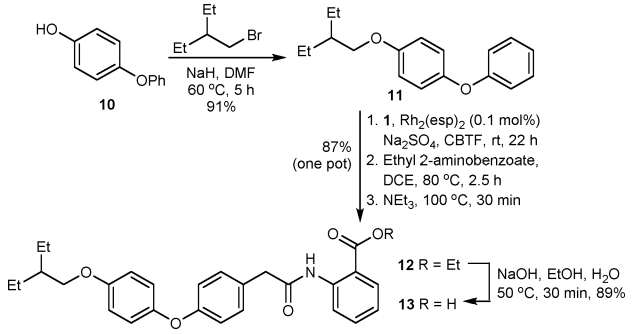
Table 3. Synthesis of Arylacetamides 9[a]



[a]Reactions were conducted on 0.50 mmol scale (ca. 1 M with respect to **1**). Regioisomeric ratios (rr) were >19:1 in all cases. [b]Reaction conducted using 5 equiv of diphenyl ether. [c]NEt_3 was also added in step 3. [d]DMF was used as a cosolvent in step 3. [e]*N*,*O*-Dimethylhydroxylamine hydrochloride was used in step 3.

Finally, we applied our methodology to the synthesis of known cytotoxic anticancer agent **13**[35] (LC_{50} = 48 nM vs L929 murine fibrosarcoma cells)[2a] via diaryl ether **11** (prepared by alkylation of 4-phenoxyphenol **10**, Scheme 3). Diazo **1** was arylated with

Scheme 3. Synthesis of Cytotoxic Anticancer Agent 13



ether **11** (2 mmol scale) in the presence of 0.1 mol % $Rh_2(esp_2)$, followed by aminolysis with ethyl 2-aminobenzoate and decarboxylation in the same pot to give product **12** in 87% yield. Alkaline hydrolysis of ethyl ester **12** provided cytotoxic agent **13** in an overall yield of 70% from **10**. Compound **13** was previously prepared from 4-(benzyloxy)phenol via Ullman coupling in 5% yield over six steps.[2a]

In conclusion, we have developed a one-pot, modular synthesis of arylacetic acid derivatives involving Rh(II)-catalyzed arylation of diazo reagent **1** with non-prefunctionalized aryl ethers, followed by nucleophilic lysis and decarboxylation. The procedure utilizes a low loading of a commercially available catalyst (down to 0.1 mol %) and exhibits high functional group tolerance with respect to the lysing nucleophile. Esters, thioesters, and amides (several of which have limited compatibility with existing arylation methods) are easily prepared. This method is particularly well-suited to the functionalization of simple diaryl ethers and can streamline access to products of pharmaceutical value that are otherwise laborious to prepare.

EXPERIMENTAL SECTION

General Information. Commercially available reagents and solvents were used as received. All reactions were performed under an Ar or N_2 atmosphere. Pet. ether refers to petroleum ether with bp 40–60 °C. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F_{254} aluminum plates. Compounds were visualized by exposure to UV light or by dipping the plates into potassium permanganate or phosphomolybdic acid solution followed by heating. Flash column chromatography was carried out using silica gel (particle size 40–63 μm) with step gradient elution as indicated. Melting points were recorded on a Kofler bench. Infrared (IR) spectra were recorded on the neat compound using an instrument with a UATR single reflection diamond, and only the characteristic peaks are reported. NMR spectra were acquired on 300 or 500 MHz spectrometers and were referenced to the residual protonated solvent (^{1}H NMR, 7.26 ppm for $CDCl_3$, 7.16 ppm for C_6D_6), the solvent itself ($^{13}C\{^1H\}$ NMR, 77.00 ppm for $CDCl_3$, 128.06 for C_6D_6), or $CFCl_3$ as an external standard at 0.00 ppm ($^{19}F\{^1H\}$ NMR). All chemical shifts are reported in parts per million (ppm). Abbreviations used in the description of resonances are s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), a (apparent), br (broad), and m (multiplet). Coupling constants (J) are quoted to the nearest 0.1 Hz. Assignments in $^{13}C\{^1H\}$ NMR were made on the basis of JMOD and HSQC spectra. High-resolution mass (HRMS) spectra were

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recorded on Q-TOF or TOF-Q instruments using electrospray ionization (ESI) techniques. Optical rotation (10^{-1}·deg·cm^2·g^{-1}) was measured on a polarimeter with a path length of 10 cm, and concentration (c) is quoted in 10^{-2}·g·cm^{-3}.

NMR-Monitored Synthesis of 7a and 7aa. A mixture of diazo **1** (85 mg, 0.50 mmol) and $Rh_2(esp)_2$ (1.0 mg, 1.3 μmol) was stirred in toluene (0.50 mL, 4.7 mmol) at rt for 18 h. The volatiles were removed in vacuo at <30 °C and 1,3,5-trimethoxybenzene (16.0 mg, 0.0952 mmol) was added. The mixture was completely dissolved in $CDCl_3$, and an aliquot was withdrawn for NMR analysis. The remaining bulk solution was concentrated in vacuo and resuspended in toluene (0.50 mL). EtOH (60 μL, 1.0 mmol) was added and the reaction mixture was heated to 80 °C for 2 h and cooled to rt. An aliquot of the homogeneous reaction mixture was withdrawn, concentrated, and analyzed by ^{1}H NMR. To the remaining bulk solution was added NEt_3 (70 μL, 0.50 mmol), and the reaction was heated at 80 °C for 15 min, concentrated, and analyzed by ^{1}H NMR. The crude ^{1}H NMR spectra (see the Supporting Information) indicated that the arylation step proceeded in 65% yield, and the subsequent alcoholysis and decarboxylation steps were quantitative.

Synthesis of Starting Materials 1 and 2. *5-Diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (**1**).*[36] To a solution of Meldrum's acid (7.20 g, 50.0 mmol) and *p*-acetamidobenzenesulfonyl azide (12.0 g, 50.0 mmol) in anhydrous MeCN (200 mL) at 0 °C was added NEt_3 (7.0 mL, 50 mmol). The reaction mixture was stirred at rt for 2 h, diluted with Et_2O (200 mL), filtered, and concentrated in vacuo. The residue was resuspended in 1:1 CH_2Cl_2/pet. ether (100 mL), stirred for 10 min at rt, filtered, and concentrated in vacuo. Purification by flash column chromatography (5 → 40% EtOAc/pet. ether) provided the diazo **1** as a white crystalline solid (6.95 g, 82%). NMR data were in accordance with the literature.[36] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (6H, s); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, C=N_2 not resolved) δ 158.2 (2 × C), 106.9 (C), 26.6 (2 × CH_3).

General Procedure A.[37] A mixture of CuI, *N*,*N*-dimethylglycine, phenol (7.5 mmol), aryl halide (5.0 mmol), and Cs_2CO_3 (3.26 g, 10.0 mmol) in anhydrous 1,4-dioxane (10 mL) was stirred at 90 °C under Ar for 18 h. The reaction mixture was cooled to rt, poured into 1 M NaOH (aq) (50 mL) and stirred with pet. ether (50 mL) for 5 min. The aqueous layer was discarded, and the organic was washed with water (50 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (Et_2O/pet. ether) provided the pure diaryl ether.

*4-Phenoxyanisole (**2a**).*[38] The title compound was prepared according to general procedure A using 4-methoxyphenol (930 mg, 7.50 mmol), iodobenzene (0.56 mL, 5.0 mmol), CuI (50 mg, 0.26 mmol), and *N*,*N*-dimethylglycine (80 mg, 0.78 mmol). Chromatographic purification (2 → 8% Et_2O/pet. ether) provided the title ether (827 mg, 83%) as a colorless oil. NMR data were in accordance with the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (2H, m, Ar*H*), 7.09–7.02 (1H, m, Ar*H*), 7.02–6.93 (4H, m, Ar*H*), 6.93–6.86 (2H, m, Ar*H*), 3.82 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.5 (C), 155.9 (C), 150.1 (C), 129.6 (2 × CH), 122.4 (CH), 120.8 (2 × CH), 117.5 (2 × CH), 114.8 (2 × CH), 55.6 (CH_3).

*4-Phenoxytoluene (**2b**).*[38] The title compound was prepared according to general procedure A using phenol (705 mg, 7.50 mmol), 4-iodotoluene (1.09 g, 5.00 mmol), CuI (50 mg, 0.26 mmol), and *N*,*N*-dimethylglycine (80 mg, 0.78 mmol). Chromatographic purification (1 → 4% Et_2O/pet. ether) provided the title ether (385 mg, 42%) as a pale yellow oil. NMR data were in accordance with the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.30 (2H, m, Ar*H*), 7.20–7.13 (2H, m, Ar*H*), 7.12–7.06 (1H, m, Ar*H*), 7.04–6.98 (2H, m, Ar*H*), 6.98–6.92 (2H, m, Ar*H*), 2.37 (3H, s, ArCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.8 (C), 154.7 (C), 132.9 (C), 130.2 (2 × CH), 129.6 (2 × CH), 122.8 (CH), 119.1 (2 × CH), 118.3 (2 × CH), 20.7 (CH_3).

*1-Fluoro-4-phenoxybenzene (**2c**).*[38] The title compound was prepared according to general procedure A using 4-fluorophenol (840 mg, 7.50 mmol), iodobenzene (0.56 mL, 5.0 mmol), CuI (50 mg, 0.26 mmol), and *N*,*N*-dimethylglycine (80 mg, 0.78 mmol). Chromatographic purification (1 → 4% Et_2O/pet. ether) provided the title ether (777 mg, 83%) as a colorless oil. NMR data were in accordance with the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (2H, m, Ar*H*), 7.15–7.07 (1H, m, Ar*H*), 7.09–6.96 (6H, m, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.8 (d, J = 241.6 Hz, C), 157.7 (C), 152.8 (d, J = 2.5 Hz, C), 129.8 (2 × CH), 123.1 (CH), 120.5 (d, J = 8.3 Hz, 2 × CH), 118.2 (2 × CH), 116.3 (d, J = 23.3 Hz, 2 × CH).

*1-Chloro-3-phenoxybenzene (**2d**).*[38] The title compound was prepared according to general procedure A using phenol (705 mg, 7.50 mmol), 1-bromo-2-fluorobenzene (0.55 mL, 5.0 mmol), CuI (200 mg, 1.05 mmol), and *N*,*N*-dimethylglycine (320 mg, 3.11 mmol). Chromatographic purification (1 → 4% Et_2O/pet. ether) provided the title ether (654 mg, 64%) as a colorless oil. NMR data were in accordance with the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.33 (2H, m, Ar*H*), 7.25 (1H, t, J = 8.1 Hz, Ar*H*), 7.20–7.12 (1H, m, Ar*H*), 7.10–6.98 (4H, m, Ar*H*), 6.93–6.87 (1H, m, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.3 (C), 156.3 (C), 135.0 (C), 130.5 (CH), 129.9 (2 × CH), 124.0 (CH), 123.2 (CH), 119.4 (2 × CH), 118.8 (CH), 116.7 (CH).

*1-Fluoro-2-phenoxybenzene (**2e**).*[39] The title compound was prepared according to general procedure A using 4-methoxyphenol (930 mg, 7.50 mmol), iodobenzene (0.56 mL, 5.0 mmol), CuI (50 mg, 0.26 mmol), and *N*,*N*-dimethylglycine (80 mg, 0.78 mmol). Chromatographic purification (2 → 8% Et_2O/pet. ether) provided the title ether (199 mg, 21%) as a colorless oil. NMR data were in accordance with the literature.[39] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.29 (2H, m, Ar*H*), 7.25–7.04 (5H, m, Ar*H*), 7.04–6.96 (2H, m, Ar*H*); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.4 (C), 154.4 (d, J = 248.7 Hz, C), 143.8 (d, J = 11.4 Hz, C), 129.7 (2 × CH), 124.74 (d, J = 6.9 Hz, CH), 124.64 (d, J = 3.9 Hz, CH), 123.1 (CH), 121.9 (d, J = 1.2 Hz, CH), 117.3 (2 × CH), 117.1 (d, J = 18.2 Hz, CH).

*2-(4-Fluorophenoxy)anisole (**2f**).* The title compound was prepared according to general procedure A using 2-methoxyphenol (930 mg, 7.50 mmol), 1-fluoro-4-iodobenzene (0.58 mL, 5.0 mmol), CuI (200 mg, 1.05 mmol), and *N*,*N*-dimethylglycine (320 mg, 3.11 mmol). Chromatographic purification (2 → 8% Et_2O/pet. ether) provided the title ether (395 mg, 36%) as a pale yellow oil. R_f = 0.55 (10% Et_2O/pet. ether; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (1H, ddd, J = 8.2, 5.9, 3.1 Hz, Ar*H*), 7.04–6.87 (7H, m, Ar*H*), 3.85 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.3 (d, J = 240.4 Hz, C), 153.7 (d, J = 2.4 Hz, C), 151.2 (C), 145.5 (C), 124.7 (CH), 121.1 (CH), 120.4 (CH), 118.66 (d, J = 8.2 Hz, 2 × CH), 116.0 (d, J = 23.3 Hz, 2 × CH); 112.8 (CH), 55.9 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −121.54; HRMS (ESI + ve) exact mass calculated for $C_{13}H_{11}O_2FNa^+$ [M + Na]$^+$ 241.0635, found 241.0635.

*3-(4-Fluorophenoxy)anisole (**2g**).*[40] The title compound was prepared according to general procedure A using 3-methoxyphenol (930 mg, 7.50 mmol), 1-fluoro-4-iodobenzene (0.58 mL, 5.0 mmol), CuI (200 mg, 1.05 mmol), and *N*,*N*-dimethylglycine (320 mg, 3.11 mmol). Chromatographic purification (1 → 4% Et_2O/pet. ether) provided the title ether (496 mg, 46%) as a pale yellow oil. NMR data were in accordance with the literature.[40] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.18 (1H, m, Ar*H*), 7.08–6.95 (4H, m, Ar*H*), 6.64 (1H, ddd, J = 8.3, 2.3, 1.0 Hz, Ar*H*), 6.57–6.51 (2H, m, Ar*H*), 3.78 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.0 (C), 158.93 (C), 158.89 (d, J = 241.8 Hz, C), 152.6 (d, J = 2.6 Hz, C), 130.2 (CH), 120.7 (d, J = 8.3 Hz, 2 × CH), 116.26 (d, J = 23.3 Hz, 2 × CH), 110.3 (CH), 108.7 (CH), 104.3 (CH), 55.3 (CH_3).

General Procedure B. Phenoxybenzoic acid (1.07 g, 5.0 mmol) was dissolved in EtOH/AcCl (9:1, 10 mL) and heated at reflux. The reaction mixture was cooled to rt, diluted with pet. ether (50 mL), and washed with $NaHCO_3$ (aq) (3 × 50 mL) and brine (25 mL). The organic fraction was dried over $MgSO_4$, concentrated in vacuo, and used without further purification.

*Ethyl 3-Phenoxybenzoate (**2h**).*[41] Ester **2h** was obtained from 3-phenoxybenzoic acid as a colorless oil (1.19 g, 98%) according to general procedure B; the reaction time was 2 h. NMR data were in accordance with the literature.[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, ddd, J = 7.7, 1.5, 1.1 Hz, Ar*H*), 7.68 (1H, dd, J = 2.3, 1.7 Hz, Ar*H*), 7.40 (1H, t, J = 7.9 Hz, Ar*H*), 7.39–7.31 (2H, m, Ar*H*), 7.20 (1H, ddd, J = 8.2, 2.6, 1.1 Hz, Ar*H*), 7.17–7.10 (1H, m, Ar*H*), 7.05–6.98 (2H, m, Ar*H*), 4.36 (2H, q, J = 7.1 Hz, OCH_2CH$_3$), 1.38 (3H, t, J = 7.1 Hz, OCH$_2$CH_3); ^{13}C{^{1}H}

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NMR (75 MHz, $CDCl_3$) δ 166.0 (C), 157.3 (C), 156.8 (C), 132.3 (C), 129.9 (2 × CH), 129.7 (CH), 124.3 (CH), 123.6 (CH), 123.2 (CH), 119.7 (CH), 119.0 (2 × CH), 61.1 (CH_2), 14.3 (CH_3).

*Ethyl 4-Phenoxybenzoate (**2i**).*[38] Ester **2i** was obtained from 4-phenoxybenzoic acid as a colorless oil (1.16 g, 96%) according to general procedure B; the reaction time was 3 h. NMR data were in accordance with the literature.[38] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−7.95 (2H, m, Ar*H*), 7.44−7.34 (2H, m, Ar*H*), 7.23−7.14 (1H, m, Ar*H*), 7.10−7.03 (2H, m, Ar*H*), 7.03−6.95 (2H, m, Ar*H*), 4.36 (2H, q, J = 7.1 Hz, OCH_2CH_3), 1.39 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 161.7 (C), 155.7 (C), 131.6 (2 × CH), 130.0 (2 × CH), 124.8 (C), 124.4 (CH), 120.0 (2 × CH), 117.3 (2 × CH), 60.8 (CH_2), 14.3 (CH_3).

Synthesis of 7 and 8. *General Procedure C.* A mixture of diazo **1** (170 mg, 1.00 mmol), arene **2** (2.0 mmol), $Rh_2(esp)_2$ (1.9 mg, 2.5 μmol), and Na_2SO_4 (200 mg) in 4-chlorobenzotrifluoride (CBTF) was stirred at rt for 18 h. Ethanol (0.12 mL, 2.0 mmol) and DCE (if indicated) were added, and the reaction mixture was stirred at 80 °C for 2.5 h and then cooled to rt. NEt_3 (0.15 mL, 1.1 mmol) was added and the reaction mixture was stirred at 80 °C for 15 min (evolution of CO_2 ceased). The reaction mixture was loaded directly onto a silica column and purified by flash chromatography using the eluent specified.

General Procedure D. A mixture of diazo **1** (85 mg, 0.50 mmol), arene **2** (1.0 mmol), $Rh_2(esp)_2$ (1.0 mg, 1.3 μmol), and Na_2SO_4 (100 mg) in 4-chlorobenzotrifluoride (CBTF) was stirred at rt for 18 h. Alcohol, aniline, or thiol (1.0 mmol) and DCE (if indicated) were added, and the reaction mixture was stirred at 80 °C for 2.5 h and then cooled to rt. NEt_3 (0.07 mL, 0.5 mmol) was added and the reaction mixture was stirred at 80 °C for 15 min (evolution of CO_2 ceased). The reaction mixture was loaded directly onto a silica column and purified by flash chromatography using the eluent specified.

*Ethyl 2-(4-Methylphenyl)acetate (**7a**)*[14d] *and Ethyl 2-(2-Methylphenyl)acetate (**7aa**).*[14d] *Method A.* A mixture of diazo **1** (170 mg, 1.00 mmol), $Rh_2(esp)_2$ (1.9 mg, 2.5 μmol), and Na_2SO_4 (200 mg) in toluene (1.0 mL, 9.5 mmol) was stirred at rt for 18 h. Ethanol (0.12 mL, 2.0 mmol) was added, and the reaction mixture was stirred at 80 °C for 2.5 h and then cooled to rt. NEt_3 (0.15 mL, 1.1 mmol) was added and the reaction mixture was stirred at 80 °C for 15 min (evolution of CO_2 ceased). ^{1}H NMR analysis of an aliquot of the crude mixture indicated a 9:1 mixture of regioisomers. The reaction mixture was loaded directly onto a silica column and purified by flash chromatography (2 → 10% Et_2O/pet. ether) to provide the title compounds **7a** and **7aa** in a 9:1 ratio (106 mg, 60%) as a colorless oil. NMR data were in accordance with the literature (for both isomers).[14d]

Method B. The title ester was prepared according to general procedure C using toluene (0.21 mL, 2.0 mmol) and CBTF (0.80 mL). ^{1}H NMR analysis of the crude reaction mixture indicated a 9:1 mixture of regioisomers. Chromatographic purification (2 → 10% Et_2O/pet. ether) provided a mixture of the title esters **7a** and **7aa** in a 9:1 ratio (67 mg, 38%) as a colorless oil. NMR data were in accordance with the literature (for both isomers).[14d] ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7a**) δ 7.23−7.08 (4H, m, Ar*H*), 4.15 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.58 (2H, s, CH_2CO_2), 2.34 (3H, s, ArCH_3), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7a**) δ 171.8 (C), 136.6 (C), 131.1 (C), 129.2 (2 × CH), 129.1 (2 × CH), 60.8 (CH_2), 41.0 (CH_2), 21.1 (CH_3), 14.2 (CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7aa**) δ 7.23−7.08 (4H, m, Ar*H*), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.63 (2H, s,), 2.33 (3H, s, ArCH_3), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7aa**) δ 171.5 (C), 136.8 (C), 132.9 (C), 130.3 (CH), 130.1 (CH), 127.3 (CH), 126.1 (CH), 60.8* (CH_2), 39.3 (CH_2), 19.6 (CH_3), 14.2* (CH_3) (*coincident with the major isomer).

*Ethyl 2-(4-Methoxyphenyl)acetate (**7b**).*[14d] The title ester was prepared according to general procedure C using anisole (0.22 mL, 2.0 mmol) and CBTF (0.80 mL). ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 10% Et_2O/pet. ether) provided the title ester **7b** (163 mg, 86%) as a colorless oil. NMR data were in accordance with the literature.[14d] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.16 (2H, m, Ar*H*), 6.90−6.83 (2H, m, Ar*H*), 4.14 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.79 (3H, s, OCH_3), 3.55 (2H, s, CH_2CO_2), 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 158.6 (C), 130.2 (2 × CH), 126.2 (C), 113.9 (2 × CH), 60.7 (CH_2), 55.2 (CH_3), 40.5 (CH_2), 14.2 (CH_3).

*Ethyl 2-(4-Hydroxyphenyl)acetate (**7c**).*[42] *Method A.* The title ester was prepared according to a modification of general procedure C (4 equiv of EtOH was added and an aqueous workup was performed) using phenol (188 mg, 2.0 mmol) and CBTF (0.80 mL). Following addition of ethanol (0.25 mL, 4.3 mmol), DCE (1.50 mL) was added for solubility. ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. The reaction mixture was diluted with EtOAc (10 mL), washed with 1 M HCl (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification (4 → 24% acetone/pet. ether) provided title ester **7c** (50 mg, 28%) as a colorless oil. NMR data were in accordance with the literature.[42]

Method B. The title ester was prepared according to a modification of general procedure C (4 equiv of EtOH was added and an aqueous workup was performed) using (trimethylsilyloxy)benzene (332 mg, 2.0 mmol) and CBTF (0.60 mL). Following addition of ethanol (0.25 mL, 4.3 mmol), DCE (0.50 mL) was added for solubility. ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. The reaction mixture was diluted with EtOAc (10 mL), washed with 1 M HCl (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Chromatographic purification (4 → 24% acetone/pet. ether) provided title ester **7c** (128 mg, 71%) as a colorless oil. NMR data were in accordance with the literature.[42] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.06 (2H, m, Ar*H*), 6.76−6.69 (2H, m, Ar*H*), 5.93 (1H, s, ArO*H*), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.54 (2H, s, CH_2CO_2), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.8 (C), 154.9 (C), 130.4 (2 × CH), 125.7 (C), 115.5 (2 × CH), 61.1 (CH_2), 40.5 (CH_2), 14.1 (CH_3).

*Ethyl 2-((4-(tert-Butoxycarbonyl)amino)phenyl)acetate (**7d**).*[43] The title ester was prepared according to a modification of general procedure C (DMF was also added in the second step) using *N*-Boc-aniline (286 mg, 2.0 mmol) and CBTF (2.0 mL). Following addition of ethanol (0.12 mL, 2.0 mmol), DCE (2.0 mL) and DMF (0.20 mL) were added for solubility. ^{1}H NMR analysis of the crude reaction indicated a single regioisomer. Chromatographic purification (6 → 30% Et_2O/pet. ether) provided title ester **7d** (112 mg, 40%) as a white crystalline solid. NMR data were in accordance with the literature.[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (2H, d, J = 8.5 Hz, Ar*H*), 7.19 (2H, d, J = 8.6 Hz, Ar*H*), 6.53 (1H, br-s, N*H*), 4.13 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.54 (2H, s, CH_2CO_2), 1.51 (9H, s, $C(CH_3)_3$), 1.23 (2H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 152.7 (C), 137.3 (C), 129.7 (2 × CH), 128.6 (C), 118.6 (2 × CH), 80.4 (C), 60.8 (CH_2), 40.7 (CH_2), 28.3 (3 × CH_3), 14.1 (CH_3).

*Ethyl 2-(4-(4-Methoxyphenoxy)phenyl)acetate (**7e**).* The title compound was prepared according to general procedure C using 1-methoxy-4-phenoxybenzene (**2a**) (400 mg, 2.00 mmol) and CBTF (0.60 mL). Following addition of ethanol, DCE (0.50 mL) was added for solubility. ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 14% EtOAc/pet. ether) provided the title ester **7e** (237 mg, 83%) as a colorless oil. R_f = 0.30 (10% EtOAc/pet. ether); IR 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25−7.19 (2H, m, Ar*H*), 7.02−6.96 (2H, m, Ar*H*), 6.94−6.86 (4H, m, Ar*H*), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.58 (2H, s, CH_2CO_2), 1.27 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 157.6 (C), 155.9 (C), 150.0 (C), 130.4 (2 × CH), 128.1 (C), 120.8 (2 × CH), 117.6 (2 × CH), 114.8 (2 × CH), 60.8 (CH_2), 55.6 (CH_3), 40.5 (CH_2), 14.2 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{17}H_{18}O_4Na^+$ [M + Na]$^+$ 309.1097, found 309.1099.

*Ethyl 2-(4-Phenoxyphenyl)acetate (**7f**).* The title compound was prepared according to a modification of general procedure C (5 equiv of arene was used) using diphenyl ether (850 mg, 5.00 mmol) and CBTF (0.20 mL). ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 10% Et_2O/pet. ether) provided the title ester **7f** (231 mg, 90%) as a colorless oil. R_f = 0.45 (10% EtOAc/pet. ether); IR 1731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (2H, m, Ar*H*), 7.28−7.22 (2H, m, Ar*H*), 7.13−

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7.06 (1H, m, Ar*H*), 7.04−6.99 (2H, m, Ar*H*), 6.99−6.93 (2H, m, Ar*H*), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.59 (2H, s, CH_2CO_2), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 157.1 (C), 156.3 (C), 130.6 (2 × CH), 129.7 (2 × CH), 128.9 (C), 123.2 (CH), 118.9 (4 × CH), 60.9 (CH_2), 40.6 (CH_2), 14.9 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{16}H_{16}O_3Na^+$ $[M + Na]^+$ 279.0992, found 279.0995.

*Ethyl 2-(4-(4-Bromophenoxy)phenyl)acetate (**7g**).* The title compound was prepared according to general procedure C using 1-bromo-4-phenoxybenzene (0.35 mL, 2.0 mmol) and CBTF (0.65 mL). Following addition of ethanol, DCE (2.0 mL) was added for solubility. ^1H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 10% Et_2O/pet. ether) provided the title ester **7g** (283 mg, 84%) as a colorless oil. R_f = 0.40 (10% EtOAc/pet. ether); IR 1731 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.46−7.38 (2H, m, Ar*H*), 7.29−7.22 (2H, m, Ar*H*), 6.99−6.92 (2H, m, Ar*H*), 6.92−6.84 (2H, m, Ar*H*), 4.16 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), (2H, s, CH_2CO_2), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 156.5 (C), 155.7 (C), 132.6 (2 × CH), 130.7 (2 × CH), 129.5 (C), 120.4 (2 × CH), 119.0 (2 × CH), 115.6 (C), 60.9 (CH_2), 40.6 (CH_2), 14.8 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{16}H_{15}O_3{}^{79}BrNa^+$ $[M + Na]^+$ 357.0097, found 357.0097.

*Ethyl 4-(4-(2-Ethoxy-2-oxoethyl)phenoxy)benzoate (**7h**).* The title compound was prepared according to general procedure C using ethyl 4-phenoxybenzoate (**2h**) (484 mg, 2.0 mmol) and CBTF (0.50 mL). Following addition of ethanol, DCE (0.25 mL) was added for solubility. ^1H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 14% EtOAc/pet. ether) provided the title ester **7h** (263 mg, 80%) as a colorless oil. R_f = 0.30 (10% EtOAc/pet. ether); IR 1730, 1712 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 8.07−7.88 (2H, m, Ar*H*), 7.33−7.26 (2H, m, Ar*H*), 7.04−6.95 (4H, m, Ar*H*), 4.35 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.61 (2H, s, CH_2CO_2), 1.38 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 166.0 (C), 161.5 (C), 154.7 (C), 131.6 (2 × CH), 130.8 (2 × CH), 130.2 (C), 124.8 (C), 120.0 (2 × CH), 117.3 (2 × CH), 60.9 (CH_2), 60.8 (CH_2), 40.6 (CH_2), 14.3 (CH_3), 14.1 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{19}H_{20}O_5Na^+$ $[M + Na]^+$ 351.1203, found 351.1206.

*Ethyl 2-(4-(3-Chlorophenoxy)phenyl)acetate (**7i**).* The title compound was prepared according to general procedure C using 1-chloro-3-phenoxybenzene (**2d**) (409 mg, 2.00 mmol) and CBTF (0.60 mL). ^1H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 10% EtOAc/pet. ether) provided the title ester **7i** (232 mg, 80%) as a colorless oil. R_f = 0.45 (10% EtOAc/pet. ether); IR 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.19 (3H, m, Ar*H*), 7.06 (1H, ddd, *J* = 8.0, 1.9, 0.9 Hz, Ar*H*), 7.01−6.95 (3H, m, Ar*H*), 6.88 (1H, ddd, *J* = 8.2, 2.4, 0.9 Hz, Ar*H*), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.60 (2H, s, CH_2CO_2), 1.27 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 158.2 (C), 155.3 (C), 135.0 (C), 130.7 (2 × CH), 130.4 (CH), 129.7 (C), 123.2 (CH), 119.4 (2 × CH), 118.7 (CH), 116.6 (CH), 60.9 (CH_2), 40.6 (CH_2), 14.1 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{16}H_{15}O_3{}^{35}ClNa^+$ $[M + Na]^+$ 313.0602, found 313.0605.

*Ethyl 3-(4-(2-Ethoxy-2-oxoethyl)phenoxy)benzoate (**7j**).* The title compound was prepared according to general procedure C using ethyl 3-phenoxybenzoate (**2i**) (484 mg, 2.0 mmol) and CBTF (0.50 mL). Following addition of ethanol, DCE (1.0 mL) was added for solubility. ^1H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (4 → 20% EtOAc/pet. ether) provided the title ester **7j** (259 mg, 79%) as a colorless oil. R_f = 0.30 (10% EtOAc/pet. ether); IR 1718 (br) cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.78 (1H, ddd, *J* = 7.7, 1.6, 1.1 Hz, Ar*H*), 7.68 (1H, dd, *J* = 2.2, 1.6 Hz, Ar*H*), 7.39 (1H, t, *J* = 7.9 Hz, Ar*H*), 7.30−7.23 (2H, m, Ar*H*), 7.19 (1H, ddd, *J* = 8.2, 2.2, 1.1 Hz, Ar*H*), 7.00−6.92 (2H, m, Ar*H*), 4.36 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.16 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.60 (2H, s, CH_2CO_2), 1.37 (3H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.26 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 166.0 (C), 157.2 (C), 155.9 (C), 132.3 (C), 130.7 (2 × CH), 129.7 (CH), 129.4 (C), 124.3 (CH), 123.2 (CH), 119.7 (CH), 118.9 (2 × CH), 61.1 (CH_2), 60.9 (CH_2), 40.6 (CH_2), 14.3 (CH_3), 14.2 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{19}H_{20}O_5Na^+$ $[M + Na]^+$ 351.1203, found 351.1205.

*Ethyl 2-(4-(2-Fluorophenoxy)phenyl)acetate (**7k**) and Ethyl 2-(3-Fluoro-4-phenoxyphenyl)acetate (**7ka**).* The title compounds were prepared according to general procedure D using 1-fluoro-2-phenoxybenzene (**2e**) (188 mg, 1.00 mmol), CBTF (0.30 mL), and ethanol (60 μL, 1.0 mmol). ^1H NMR analysis of the crude reaction mixture indicated a 3:1 mixture of regioisomers. Chromatographic purification (2 → 10% EtOAc/pet. ether) provided a mixture of the title esters **7k** and **7ka** in a 3:1 ratio (105 mg, 77%) as a colorless oil. R_f = 0.40 (10% EtOAc/pet. ether); IR 1731 cm^{-1}; ^1H (300 MHz, $CDCl_3$, isomer **7k**) δ 7.27−7.22 (2H, m, Ar*H*), 7.22−6.97 (4H, m, Ar*H*), 6.97−6.91 (2H, m, Ar*H*), 4.16 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.59 (2H, s, CH_2CO_2), 1.26 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, isomer **7k**) δ 171.6 (C), 156.4 (C), 154.3 (d, *J* = 248.7 Hz, C), 143.7 (d, *J* = 11.4 Hz, C), 130.5 (2 × CH), 128.8 (C), 124.8 (d, *J* = 6.9 Hz, CH), 124.61 (d, *J* = 3.9 Hz, CH), 121.9 (d, *J* = 1.1 Hz, CH), 117.3 (2 × CH), 117.0 (d, *J* = 18.2 Hz, CH), 60.8 (CH_2), 40.5 (CH_2), 14.1 (CH_3); $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$, isomer **7k**) δ −131.0; ^1H (300 MHz, $CDCl_3$, isomer **7ka**) δ 7.36−7.28 (2H, m, Ar*H*), 7.22−6.97 (6H, m, Ar*H*), 4.19 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.60 (2H, s, CH_2CO_2), 1.28 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, isomer **7ka**) δ 171.0 (C), 157.2 (C), 154.0 (d, *J* = 249.0 Hz, C), 142.7 (d, *J* = 11.6 Hz, C), 131.0 (d, *J* = 6.7 Hz, C), 129.6 (2 × CH), 125.4 (d, *J* = 3.6 Hz, CH), 123.1 (CH), 121.7 (d, *J* = 1.5 Hz, CH), 117.9 (d, *J* = 18.9 Hz, CH), 117.3 (2 × CH), 61.0 (CH_2), 40.4 (d, *J* = 1.3 Hz, CH_2), 14.1* (CH_3) (*coincident with the major isomer); $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$, isomer **7ka**) δ −130.6; HRMS (ESI + ve) exact mass calculated for $C_{16}H_{15}O_3FNa^+$ $[M + Na]^+$ 297.0897, found 297.0894.

*Methyl 2-(4-(2-Ethoxy-2-oxoethyl)phenoxy)benzoate (**7l**) and Methyl 5-(2-Ethoxy-2-oxoethyl)-2-phenoxybenzoate (**7la**).* The title compounds were prepared according to general procedure C using methyl 2-phenoxybenzoate (456 mg, 2.00 mmol) and CBTF (0.55 mL). ^1H NMR analysis of the crude reaction mixture indicated a 4:1 mixture of regioisomers. Chromatographic purification (4 → 28% Et_2O/pet. ether) provided a mixture of the title esters **7l** and **7la** in a 4:1 ratio (219 mg, 70%) as a colorless oil. R_f = 0.20 (10% EtOAc/pet. ether); IR 1727 (br) cm^{-1}; ^1H (300 MHz, $CDCl_3$, isomer **7l**) δ 7.91 (1H, dd, *J* = 7.8, 1.8 Hz, Ar*H*), 7.45 (1H, ddd, *J* = 8.2, 7.4, 1.8 Hz, Ar*H*), 7.26−7.21 (2H, m, Ar*H*), 7.17 (1H, ddd, *J* = 7.8, 7.4, 1.0 Hz, Ar*H*), 6.98 (1H, dd, *J* = 8.2, 1.0 Hz, Ar*H*), 6.94−6.89 (2H, m, Ar*H*), 4.15 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.57 (2H, s, CH_2CO_2), 1.25 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, isomer **7l**) δ 171.6 (C), 166.1 (C), 156.6 (C), 156.1 (C), 133.5 (CH), 131.8 (CH), 130.5 (2 × CH), 128.8 (C), 123.5 (CH), 120.8 (CH), 118.2 (2 × CH), 60.8 (CH_2), 52.1 (CH_3), 40.6 (CH_2), 14.2 (CH_3); ^1H (300 MHz, $CDCl_3$, isomer **7la**) δ 7.83 (1H, d, *J* = 2.1 Hz, Ar*H*), 7.39 (1H, dd, *J* = 8.5, 2.4 Hz, Ar*H*), 7.35−7.27 (2H, m, Ar*H*), 7.11−7.04 (1H, m, Ar*H*), 6.98−6.93 (3H, m, Ar*H*), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.62 (2H, s, CH_2CO_2), 1.27 (12 H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, isomer **7la**) δ 171.1 (C), 165.9 (C), 157.5 (C), 155.3 (C), 134.4 (CH), 132.6 (CH), 129.7 (2 × CH), 129.3 (C), 123.1 (CH), 121.0 (CH), 118.2* (2 × CH), 61.0 (CH_2), 52.1* (CH_3), 40.3 (CH_2), 14.2* (CH_3) (*coincident with the major isomer); HRMS (ESI + ve) exact mass calculated for $C_{18}H_{18}O_5Na^+$ $[M + Na]^+$ 337.1046, found 337.1046.

*Ethyl 2-(3-(4-Fluorophenoxy)-4-methoxyphenyl)acetate (**7m**) and Ethyl 2-(4-(4-Fluorophenoxy)-3-methoxyphenyl)acetate (**7ma**).* The title compounds were prepared according to general procedure D using 2-(4-fluorophenoxy)anisole (**2f**) (218 mg, 1.0 mmol), CBTF (0.3 mL), and ethanol (60 μL, 1.0 mmol). ^1H NMR analysis of the crude reaction mixture indicated a 5:1 mixture of regioisomers. Chromatographic purification (2 → 14% EtOAc/pet. ether) provided a mixture of the title esters **7m** and **7ma** in a 5:1 ratio (126 mg, 83%) as a colorless oil. R_f = 0.35 (10% EtOAc/pet. ether); IR 1731 cm^{-1}; ^1H NMR (300 MHz, C_6D_6, isomer **7m**) δ 6.97 (1H, d, *J* = 2.1 Hz, Ar*H*), 6.93 (1H, dd, *J* = 8.3, 2.2 Hz, Ar*H*), 6.77−6.61 (4H, m, Ar*H*), 6.55 (1H, d, *J* = 8.3 Hz, Ar*H*),

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3.90 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.28 (2H, s, CH_2CO_2), 3.22 (3H, s, OCH_3), 0.90 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7m**) δ 7.05−6.78 (4H, m, ArH), 4.13 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 3.50 (2H, s, CH_2CO_2), 1.22 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7ma**) δ 7.05−6.78 (4H, m, ArH), 4.18 (2H, q, J = 7.2 Hz, OCH_2CH_3), 3.84 (3H, s, OCH_3), 3.59 (2H, s, CH_2CO_2), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7m**) δ 171.46 (C), 158.4 (d, J = 240.5 Hz, C), 156.78 (C), 153.5 (d, J = 2.3 Hz, C), 150.2 (C), 145.4 (C), 127.0 (C), 125.27 (CH), 121.3 (CH), 118.8 (d, J = 8.2 Hz, 2 × CH), 115.98 (d, J = 23.3 Hz, 2 × CH), 112.8 (CH), 60.8 (CH_2), 56.0 (CH_3), 40.4 (CH_2), 14.1 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, isomer **7m**) δ −121.37; ^{1}H NMR (300 MHz, C_6D_6, isomer **7ma**) δ 6.84 (1H, d, J = 8.1 Hz, ArH), 6.80 (1H, d, J = 2.0 Hz, ArH), 6.78−6.60 (5H, m, ArH), 3.94 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.37 (2H, s, CH_2CO_2), 3.25 (3H, s, OCH_3), 0.94 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7ma**) δ 7.05−6.78 (4H, m, ArH), 4.18 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.84 (3H, s, OCH_3), 3.59 (2H, s, CH_2CO_2), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7ma**) δ 171.48 (C), 158.3 (d, J = 240.5 Hz, C), 156.75 (C), 153.6 (d, J = 2.3 Hz, C), 151.0 (C), 144.6 (C), 130.7 (C), 121.8 (CH), 120.2 (CH), 118.7 (d, J = 7.7 Hz, 2 × CH), 115.94 (d, J = 23.3 Hz, 2 × CH), 113.8 (CH), 60.9 (CH_2), 55.9 (CH_3), 41.1 (CH_2), 14.2 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, isomer **7ma**) δ −121.46; HRMS (ESI + ve) exact mass calculated for $C_{17}H_{17}O_4FNa^+$ $[M + Na]^+$ 327.1003, found 327.1003.

*Ethyl 2-(4-(4-Fluorophenoxy)-2-methoxyphenyl)acetate (**7n**) and Ethyl 2-(2-(4-Fluorophenoxy)-4-methoxyphenyl)acetate (**7na**).* The title compounds were prepared according to general procedure D using 3-(4-fluorophenoxy)anisole (**2g**) (218 mg, 1.0 mmol), CBTF (0.3 mL), and ethanol (60 μL, 1.0 mmol). ^{1}H NMR analysis of the crude reaction mixture indicated a 5:2 mixture of regioisomers. Chromatographic purification (2 → 12% EtOAc/pet. ether) provided a mixture of the title esters **7n** and **7na** in a 5:2 ratio (76 mg, 50%) as a colorless oil. R_f = 0.40 (10% EtOAc/pet. ether); IR 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7n**) δ 7.10 (1H, d, J = 8.2 Hz, ArH), 7.07−6.91 (4H, m, ArH), 6.55 (1H, d, J = 2.3 Hz, ArH), 6.46 (1H, dd, J = 8.2, 2.3 Hz, ArH), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.76 (3H, s, OCH_3), 3.57 (2H, s, CH_2CO_2), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7n**) δ 171.8, 158.8 (d, J = 241.7 Hz, C), 158.6 (C), 158.0 (C), 152.75 (d, J = 2.6 Hz, C), 131.3 (CH), 120.5 (d, J = 8.3 Hz, 2 × CH), 116.20 (d, J = 23.3 Hz, 2 × CH), 118.0 (CH), 109.4 (CH), 101.8 (CH), 60.6 (CH_2), 55.5 (CH_3), 35.3 (CH_2), 14.2 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, isomer **7n**) δ −120.09; ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7na**) δ 7.20 (1H, d, J = 8.4 Hz, ArH), 7.07−6.90 (4H, m, ArH), 6.64 (1H, dd, J = 8.4, 2.5 Hz, ArH), 6.35 (1H, d, J = 2.5 Hz, ArH), 4.09 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.72 (3H, s, OCH_3), 3.61 (2H, s, CH_2CO_2), 1.19 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7na**) δ 171.6 (C), 160.0 (C), 158.7 (d, J = 241.5 Hz, C), 156.3 (C), 152.80 (d, J = 2.6 Hz, C), 131.9 (CH), 120.1 (d, J = 8.2 Hz, 2 × CH), 116.16 (d, J = 23.3 Hz, 2 × CH), 117.7 (CH), 108.6 (CH), 104.5 (CH), 60.7 (CH_2), 55.3 (CH_3), 35.2 (CH_2), 14.1 (CH_3); ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, isomer **7na**) δ −120.34; HRMS (ESI + ve) exact mass calculated for $C_{17}H_{17}O_4FNa^+$ $[M + Na]^+$ 327.1003, found 327.1004.

*Ethyl 2-(4-Methoxynaphthalen-1-yl)acetate (**7o**).* The title compound was prepared according to general procedure C using 1-methoxynaphthalene (316 mg, 2.0 mmol) and CBTF (0.70 mL). ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 10% EtOAc/pet. ether) provided the title ester (186 mg, 76%) as a colorless oil. R_f = 0.35 (10% EtOAc/pet. ether); IR 1728 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 8.35−8.30 (1H, m, ArH), 7.97−7.92 (1H, m, ArH), 7.56 (1H, ddd, J = 8.4, 6.9, 1.6 Hz, ArH), 7.50 (1H, ddd, J = 8.1, 6.9, 1.4 Hz, ArH), 7.33 (1H, d, J = 7.8 Hz, ArH), 6.78 (1H, d, J = 7.8 Hz, ArH), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.00 (3H, s, OCH_3), 3.99 (2H, s, CH_2CO_2), 1.23 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.0 (C), 155.1 (C), 132.8 (C), 127.8 (CH), 126.7 (CH), 125.9 (C), 125.0 (CH), 123.6 (CH), 122.7 (C), 122.5 (CH), 103.3 (CH), 60.8 (CH_2), 55.4 (CH_3), 38.8 (CH_2), 14.2 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{15}H_{16}O_3Na^+$ $[M + Na]^+$ 267.0992, found 267.0991.

*Ethyl 2-(6-Methoxynaphthalen-2-yl)acetate (**7p**)[44] and Ethyl 2-(7-Methoxynaphthalen-1-yl)acetate (**7pa**).*[45] The title compounds were prepared according to general procedure C using 2-methoxynaphthalene (316 mg, 2.0 mmol) and CBTF (0.70 mL). Following addition of ethanol, DCE (0.50 mL) was added for solubility. ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of regioisomers. Chromatographic purification (2 → 10% EtOAc/pet. ether) provided a mixture of the title esters **7p** and **7pa** in a 2:1 ratio (176 mg, 72%) as a colorless oil. NMR data were in accordance with the literature (for both isomers).[44,45] ^{1}H NMR (300 MHz, $CDCl_3$, isomer **7p**) δ 7.75−7.65 (3H, m, ArH), 7.44−7.37 (1H, m, ArH), 7.21−7.11 (2H, m, ArH), 4.18 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.91 (3H, s, OCH_3), 3.76 (2H, s, CH_2CO_2), 1.27 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7p**) δ 171.7 (C), 157.5 (C), 133.5 (C), 129.2 (C), 129.1 (CH), 128.9 (C), 127.8 (CH), 127.7 (CH), 127.0 (CH), 118.9 (CH), 105.5 (CH), 60.8 (CH_2), 55.2 (CH_3), 41.3 (CH_2), 14.1 (CH_3); ^{1}H (300 MHz, $CDCl_3$, isomer **7pa**) δ 7.77 (1H, d, J = 8.9 Hz, ArH), 7.75−7.65 (1H, m, ArH), 7.44−7.37 (1H, m, ArH), 7.34−7.28 (2H, m, ArH), 7.21−7.11 (1H, m, ArH), 4.17 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.03 (2H, s, CH_2CO_2), 3.95 (3H, s, OCH_3), 1.24 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, isomer **7pa**) δ 171.5 (C), 157.9 (C), 133.2 (C), 130.1 (CH), 129.4 (C), 129.2 (C), 128.5 (CH), 127.6 (CH), 123.1 (CH), 118.2 (CH), 102.4 (CH), 60.9 (CH_2), 55.2 (CH_3), 39.7 (CH_2), 14.2 (CH_3).

*Ethyl 4-(4-(2-(Benzyloxy)-2-oxoethyl)phenoxy)benzoate **8a**.* The title compound was prepared according to general procedure D using ethyl 4-phenoxybenzoate (**2h**) (242 mg, 1.00 mmol), CBTF (0.25 mL), and benzyl alcohol (0.11 mL, 1.0 mmol). ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 12% EtOAc/pet. ether) provided the title ester **8a** (156 mg, 80%) as a colorless oil. R_f = 0.25 (10% EtOAc/pet. ether); IR 1734, 1714 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 8.06−7.98 (2H, m, ArH), 7.42−7.25 (7H, m, ArH), 7.05−6.95 (4H, m, ArH), 5.16 (2H, s, OCH_2Ph), 4.37 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.68 (2H, s, CH_2CO_2), 1.39 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 166.1 (C), 161.5 (C), 154.8 (C), 135.7 (C), 131.6 (2 × CH), 130.9 (2 × CH), 130.0 (C), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 124.9 (C), 120.1 (2 × CH), 117.3 (2 × CH), 66.7 (CH_2), 60.8 (CH_2), 40.5 (CH_2), 14.3 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{24}H_{22}O_5Na^+$ $[M + Na]^+$ 413.1359, found 413.1358.

*Allyl 2-(4-(4-Methylphenoxy)phenyl)acetate (**8b**).* The title compound was prepared according to general procedure D using 4-phenoxytoluene (**2b**) (182 mg, 1.00 mmol), CBTF (0.30 mL), and allyl alcohol (70 μL, 1.0 mmol). ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 8% EtOAc/pet. ether) provided the title ester **8b** (156 mg, 80%) as a colorless oil. R_f = 0.45 (10% EtOAc/pet. ether); IR 1734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.21 (2H, m, ArH), 7.15 (2H, d, J = 8.2 Hz, ArH), 6.98−6.90 (4H, m, ArH), 5.93 (1H, ddt, J = 17.1, 10.5, 5.7 Hz, $OCH_2CH{=}CH_2$), 5.30 (1H, dq, J = 17.1, 1.5 Hz, $OCH_2CH{=}CH_2$), 5.24 (1H, dq, J = 10.5, 1.2 Hz, $OCH_2CH{=}CH_2$), 4.62 (2H, dt, J = 5.7, 1.3 Hz, $OCH_2CH{=}CH_2$), 3.63 (2H, s, CH_2CO_2), 2.35 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 156.9 (C), 154.6 (C), 132.9 (C), 132.0 (CH), 130.5 (2 × CH), 130.2 (2 × CH), 128.2 (C), 119.1 (2 × CH), 118.3 (2 × CH), 118.2 (CH_2), 65.4 (CH_2), 40.4 (CH_2), 20.7 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{18}H_{18}O_3Na^+$ $[M + Na]^+$ 305.1148, found 305.1146.

*tert-Amyl 2-(4-(4-Fluorophenoxy)phenyl)acetate (**8c**).* The title compound was prepared according to general procedure D using 1-fluoro-4-phenoxybenzene (**2c**) (188 mg, 1.00 mmol), CBTF (0.30 mL), and *tert*-amyl alcohol (0.11 mL, 1.0 mmol). Following addition of *tert*-amyl alcohol, DCE (0.25 mL) was added for solubility. ^{1}H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 8% EtOAc/pet. ether) provided the title ester **8c** (156 mg, 80%) as a colorless oil. R_f = 0.55 (10% EtOAc/pet. ether); IR 1727 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 7.28−7.21 (2H, m, ArH), 7.08−6.96 (4H, m, ArH), 6.96−6.91 (2H, m, ArH), 3.53 (2H, s, CH_2CO_2), 1.78 (2H, q, J = 7.5 Hz, CH_2CH_3), 1.44 (6H, s, $C(CH_3)_2$),

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0.85 (3H, t, J = 7.5 Hz, CH_2CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 158.7 (d, J = 241.5 Hz, C), 156.5 (C), 152.9 (d, J = 2.5 Hz, C), 130.6 (2 × CH), 129.5 (C), 120.4 (d, J = 8.2 Hz, 2 × CH), 118.3 (2 × CH), 116.2 (d, J = 23.3 Hz, 2 × CH), 83.3 (C), 41.8 (CH_2), 33.4 (CH_2), 25.5 (2 × CH_3), 8.1 (CH_3); $^{19}F\{^1H\}$ NMR (471 MHz, $CDCl_3$) δ −120.2; HRMS (ESI + ve) exact mass calculated for $C_{19}H_{21}O_3FNa^+$ $[M + Na]^+$ 339.1367, found 339.1368.

*Phenyl 2-(4-(Methoxy)phenyl)acetate (**8d**).*[46] The title compound was prepared according to general procedure D using anisole (0.11 mL, 1.00 mmol), CBTF (0.40 mL), and phenol (94 mg, 1.0 mmol). ^1H NMR analysis of the crude reaction mixture indicated a single regioisomer. Chromatographic purification (2 → 12% EtOAc/pet. ether) provided the title ester **8d** (156 mg, 80%) as a colorless oil. NMR data were in accordance with the literature.[46] ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−7.29 (4H, m, ArH), 7.27−7.18 (1H, m, ArH), 7.11−7.04 (2H, m, ArH), 6.96−6.88 (2H, m, ArH), 3.82 (3H, s, OCH_3), 3.82 (2H, s, CH_2CO_2); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.3 (C), 158.8 (C), 150.7 (C), 130.3 (2 × CH), 129.3 (2 × CH), 125.8 (CH), 125.5 (C), 121.4 (2 × CH), 114.1 (2 × CH), 55.2 (CH_3), 40.5 (CH_2).

*(3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-(4-Phenoxyphenyl)acetate (**8e**).* The title compound was prepared according to a modification of general procedure D (5 equiv of arene and 1.5 equiv of alcohol were used) using diphenyl ether (425 mg, 2.50 mmol), CBTF (0.1 mL), and cholesterol (290 mg, 0.75 mmol). Following addition of cholesterol, additional CBTF (0.50 mL) was added for solubility. Chromatographic purification (2 → 10% Et_2O/pet. ether) provided the title ester **8e** (239 mg, 80%) as a colorless oil and a single isomer, which slowly crystallized on standing. R_f = 0.60 (10% EtOAc/pet. ether); mp 92−94 °C; $[\alpha]_D^{20}$ −23.7 (c = 1.12, $CHCl_3$); IR 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.29 (2H, m, ArH), 7.29−7.22 (2H, m, ArH), 7.14−7.07 (1H, m, ArH), 7.05−7.00 (2H, m, ArH), 7.00−6.95 (2H, m, ArH), 5.38 (1H, d, J = 4.0 Hz, C=CH), 4.73−4.58 (1H, m, CHO), 3.58 (2H, s, CH_2CO), 2.34 (2H, d, J = 7.8 Hz, OCHCH_2C=C), 2.08−1.93 (2H, m), 1.93−1.78 (3H, m), 1.70−0.83 (21H, m), 1.04 (3H, s, C=CCCH_3), 0.94 (3H, d, J = 6.5 Hz, CH_3CH), 0.89 (3H, d, J = 6.6 Hz CH(CH_3)$_2$), 0.88 (3H, d, J = 6.6 Hz CH(CH_3)$_2$), 0.70 (3H, s, CCH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 157.1 (C), 156.2 (C), 139.5 (C), 130.5 (2 × CH), 129.7 (2 × CH), 129.0 (C), 123.2 (CH), 122.7 (CH), 118.83 (2 × CH), 118.82 (2 × CH), 74.4 (CH), 56.6 (CH), 56.1 (CH), 50.0 (CH), 42.3 (C), 40.8 (CH_2), 39.7 (CH_2), 39.5 (CH_2), 38.0 (CH_2), 36.9 (CH_2), 36.5 (C), 36.2 (CH_2), 35.8 (CH), 31.9 (CH_2), 31.8 (CH), 28.2 (CH_2), 28.0 (CH), 27.7 (CH_2), 24.3 (CH_2), 23.8 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 21.0 (CH_2), 19.3 (CH_3), 18.7 (CH_3), 11.8 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{41}H_{56}O_3Na^+$ $[M + Na]^+$ 619.4122, found 619.4122.

*2-(4-Methoxyphenyl)-N-phenylacetamide (**8f**).*[47] The title compound was prepared according to a modification of general procedure D (temperature and reaction time for decarboxylation were altered) using anisole (0.11 mL, 1.0 mmol), CBTF (0.40 mL), and aniline (90 μL, 1.0 mmol). Following addition of aniline, DCE (0.50 mL) was added for solubility. Following addition of triethylamine, the reaction mixture was heated at 100 °C for 30 min. Chromatographic purification (5 → 35% acetone/pet. ether) provided the title acetanilide **8f** (100 mg, 83%) as a white solid. NMR data were in accordance with the literature.[47] ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, J = 7.6 Hz, ArH), 7.33 (1H, br-s, NH), 7.31−7.19 (4H, m, ArH), 7.08 (1H, t, J = 7.4 Hz, ArH), 6.95−6.88 (2H, m, ArH), 3.82 (3H, s, OCH_3), 3.66 (2H, s, CH_2C=O); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 169.6 (C), 159.0 (C), 137.6 (C), 130.6 (2 × CH), 128.9 (2 × CH), 126.3 (C), 124.3 (CH), 119.8 (2 × CH), 114.5 (2 × CH), 55.3 (CH_3), 43.8 (CH_3).

*2-(4-Methoxyphenyl)-N-methyl-N-phenylacetamide (**8g**).*[48] The title compound was prepared according to a modification of general procedure D (temperature and reaction time for decarboxylation were altered) using anisole (0.11 mL, 1.0 mmol), CBTF (0.4 mL), and *N*-methylaniline (0.11 mL, 1.0 mmol). Following addition of aniline, DCE (0.5 mL) was added for solubility. Following addition of triethylamine, the reaction mixture was heated at 100 °C for 30 min. Chromatographic purification (5 → 35% acetone/pet. ether) provided the title acetanilide **8g** (108 mg, 85%) as a colorless oil. NMR data were in accordance with the literature.[48] ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.30 (3H, m, ArH), 7.17−7.08 (2H, m), 6.97 (2H, d, J = 8.4 Hz, ArH), 6.77 (2H, d, J = 8.6 Hz, ArH), 3.77 (3H, s, OCH_3), 3.39 (2H, s, CH_2C=O), 3.27 (3H, s, NCH_3); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3) δ 171.3 (C), 158.3 (C), 144.0 (C), 130.0 (2 × CH), 129.6 (2 × CH), 127.8 (CH), 127.6 (2 × CH), 127.4 (C), 113.7 (2 × CH), 55.2 (CH_3), 39.9 (CH_2), 37.5 (CH_3).

*Ethyl 2-(2-(4-Methoxyphenyl)acetamido)benzoate (**8h**).* The title compound was prepared according to a modification of general procedure D (temperature and reaction time for decarboxylation were altered) using anisole (0.11 mL, 1.0 mmol), CBTF (0.40 mL), and ethyl 2-aminobenzoate (0.15 mL, 1.0 mmol). Following addition of 2-aminobenzoate, DCE (0.50 mL) was added for solubility. Following addition of triethylamine, the reaction mixture was heated at 100 °C for 30 min. Chromatographic purification (6 → 42% acetone/pet. ether) provided the title acetanilide **8h** (128 mg, 82%) as an off-white solid. R_f = 0.35 (20% acetone/pet. ether); mp 94−96 °C; IR 3252, 1703, 1679, 1605, 1590 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 8.71 (1H, dd, J = 8.5, 1.0 Hz, ArH), 8.00 (1H, dd, J = 8.1, 1.4 Hz, ArH), 7.50 (1 H, ddd, J = 8.5, 7.4, 1.4 Hz, ArH), 7.34−7.27 (2H, m, ArH), 7.05 (1H, ddd, J = 8.1, 7.4, 1.0 Hz, ArH), 6.94−6.87 (2H, m, ArH), 4.32 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.80 (3H, s, OCH_3), 3.70 (2H, s, CH_2C=O), 1.38 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 168.0 (C), 158.8 (C), 141.4 (C), 134.3 (CH), 130.6 (CH), 130.5 (2 × CH), 126.5 (C), 122.4 (CH), 120.2 (CH), 115.3 (C), 114.2 (2 × CH), 61.2 (CH_2), 55.2 (CH_3), 44.9 (CH_2), 14.1 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{18}H_{19}NO_4Na^+$ $[M + Na]^+$ 336.1206, found 336.1204.

*S-Phenyl 2-(4-Methoxyphenyl)ethanethioate (**8i**).* The title compound was prepared according to general procedure D using anisole (0.11 mL, 1.0 mmol), CBTF (0.40 mL), and 2-phenylethanethiol (0.13 mL, 1.0 mmol). Chromatographic purification (2 → 10% EtOAc/pet. ether) provided the title thioester **8j** (103 mg, 73%) as a colorless oil. R_f = 0.45 (10% EtOAc/pet. ether); IR 1680 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.35−7.26 (2H, m, ArH), 7.25−7.16 (5H, m, ArH), 6.93−6.85 (2H, m, ArH), 3.81 (3H, s, OCH_3), 3.77 (2H, s, CH_2C=O), 3.11 (2H, a-dd,* J = 8.9, 6.6 Hz, SCH_2CH_2Ph), 2.85 (2 H, a-dd,* J = 8.9, 6.6 Hz, SCH_2CH_2Ph); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 197.7 (C), 158.9 (C), 139.9 (C), 130.6 (2 × CH), 128.5 (2 × CH), 128.4 (2 × CH), 126.4 (CH), 125.6 (C), 114.0 (2 × CH), 55.2 (CH_3), 49.7 (CH_2), 35.7 (CH_2), 30.6 (CH_2) (*second-order coupling effects); HRMS (ESI + ve) exact mass calculated for $C_{17}H_{18}O_2SNa^+$ $[M + Na]^+$ 309.0920, found 309.0921.

*S-Phenethyl 2-(4-Methoxyphenyl)ethanethioate (**8j**).*[49] The title compound was prepared according to general procedure D using anisole (0.11 mL, 1.0 mmol), CBTF (0.4 mL) and 4-methylbenzenethiol (124 mg, 1.0 mmol). Chromatographic purification (2 → 10% EtOAc/pet. ether) provided the title thioester **8i** (76 mg, 56%) as a white crystalline solid. NMR data were in accordance with the literature.[49] ^1H NMR (300 MHz, $CDCl_3$) δ 7.29−7.22 (4H, m, ArH), 7.19 (2H, d, J = 8.1 Hz, ArH), 6.93−6.85 (2H, m, ArH), 3.84 (2H, s, CH_2C=O), 3.81 (3H, s, OCH_3), 2.36 (3H, s, ArCH_3); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 196.3 (C), 159.0 (C), 139.6 (C), 134.4 (2 × CH), 130.8 (2 × CH), 129.9 (2 × CH), 125.3 (C), 124.3 (C), 114.1 (2 × CH), 55.2 (CH_3), 49.2 (CH_2), 21.3 (CH_3).

Synthesis of Arylacetamides 9. *General Procedure E.* A mixture of diazo **1** (85 mg, 0.50 mmol), arene **2** (1.0 mmol), $Rh_2(esp)_2$ (1.0 mg, 1.3 μmol), and Na_2SO_4 (100 mg) in 4-chlorobenzotrifluoride (CBTF) was stirred at rt for 18 h. 1*H*-Benzotriazole (BtH) (90 mg, 0.75 mmol) in warm DCE (0.50 mL) was added and the reaction mixture was stirred at 80 °C for 2.5 h mand then cooled to rt. The amine (0.75 mmol) was added and the reaction mixture was stirred at 100 °C for the indicated time. The reaction mixture was loaded directly onto a silica column and purified by flash chromatography using the eluent specified.

*N-Benzyl-2-(4-phenoxyphenyl)acetamide (**9a**).*[50] The title compound was prepared according to a modification of general procedure E (5 equiv of arene was used) using diphenyl ether (425 mg, 2.5 mmol), CBTF (0.10 mL), and benzylamine (80 μL, 0.75 mmol). The reaction time for the final stage was 30 min. Chromatographic purification (2 → 10% EtOAc/CH_2Cl_2) provided the title amide **9a** (134 mg, 83%) as a white crystalline solid. NMR data were in accordance with the

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literature.[50] ^{1}H (300 MHz, $CDCl_3$) δ 7.38−7.17 (9H, m, Ar*H*), 7.16−7.08 (1H, m, Ar*H*), 7.05−6.92 (4H, m, Ar*H*), 5.79 (1H, br-s, N*H*), 4.43 (2H, d, J = 5.8 Hz, CH_2Ph), 3.59 (2H, s, CH_2C═O); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 156.9 (C), 156.6 (C), 138.1 (C), 130.7 (2 × CH), 129.7 (2 × CH), 129.5 (C), 128.6 (2 × CH), 127.5 (2 × CH), 127.4 (CH), 123.4 (CH), 119.1 (2 × CH), 118.9 (2 × CH), 43.6 (CH_2), 42.9 (CH_2).

*N-Benzyl-N-methyl-2-(4-phenoxyphenyl)acetamide (**9b**).* The title compound was prepared according to a modification of general procedure E (5 equiv of arene was used and NEt_3 was added in the decarboxylation stage) using diphenyl ether (425 mg, 2.5 mmol), CBTF (0.10 mL), and *N*-benzylmethylamine (0.10 mL, 0.75 mmol). For the final stage, NEt_3 (0.10 mL, 0.75 mmol) was added and the reaction time was 1.5 h. Chromatographic purification (2 → 6% Et_2O/CH_2Cl_2) provided a 6:1 mixture of **9b** and 1-(2-chloroethyl)-1*H*-1,2,3-benzotriazole, which was further purified by chromatography (30 → 90% Et_2O/pet. ether) to provide the pure title amide **9b** (141 mg, 85%) as a colorless oil. NMR analysis indicated a 4:3 mixture of rotamers. R_f = 0.70 (15% EtOAc/CH_2Cl_2); IR 1640 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$, major rotamer) δ 7.41−7.19 (8H, m, Ar*H*), 7.14−7.06 (2H, m, Ar*H*), 7.05−6.93 (4H, m, Ar*H*), 4.63 (2H, s, CH_2Ph), 3.76 (2H, s, CH_2C═O), 2.94 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, major rotamer) δ 171.1 (C), 156.0 (C), 137.2 (C), 130.2 (2 × CH), 129.8 (C), 129.7 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.3 (CH), 123.13 (CH), 119.05 (2 × CH), 118.71 (2 × CH), 50.9 (CH_2), 40.2 (CH_2), 35.2 (CH_3); ^{1}H (300 MHz, $CDCl_3$, minor rotamer) δ 7.41−7.19 (8H, m, Ar*H*), 7.14−7.06 (2H, m, Ar*H*), 7.05−6.93 (4H, m, Ar*H*), 4.57 (2H, s, CH_2Ph), 3.73 (2H, s, CH_2CO_2), 2.97 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 171.5 (C), 157.2 (C), 136.4 (C), 130.1 (2 × CH), 129.9 (C), 129.7 (2 × CH),* 128.9 (2 × CH), 127.6 (CH), 126.3 (2 × CH), 123.10 (CH), 119.10 (2 × CH), 118.67 (2 × CH), 53.6 (CH_2), 39.9 (CH_2), 34.1 (CH_3) (*coincident with major rotamer); HRMS (ESI + ve) exact mass calculated for $C_{22}H_{21}NO_2Na^+$ $[M + Na]^+$ 354.1465, found 354.1462.

*Ethyl 3-(4-(2-(Allylamino)-2-oxoethyl)phenoxy)benzoate (**9c**).* The title compound was prepared according to general procedure E using ethyl 3-phenoxybenzoate (**2i**) (242 mg, 1.00 mmol), CBTF (0.25 mL), and allylamine (60 μL, 0.75 mmol). The reaction time for the final stage was 45 min. Chromatographic purification (2 → 12% EtOAc/CH_2Cl_2) provided the title amide **9c** (137 mg, 81%) as a colorless oil. R_f = 0.45 (15% EtOAc/CH_2Cl_2); IR 3290, 1717, 1641 (br), 1584 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 7.79 (1H, ddd, J = 7.8, 1.0, 1.5 Hz, Ar*H*), 7.67 (1H, dd, J = 2.5, 1.5 Hz, Ar*H*), 7.40 (1H, t, J = 8.0 Hz, Ar*H*), 7.27−7.22 (2H, m, Ar*H*), 7.19 (1H, ddd, J = 8.2, 2.5, 1.0 Hz, Ar*H*), 7.01−6.95 (2H, m, Ar*H*), 5.79 (1H, ddt, J = 17.5, 10.0, 5.5 Hz, NCH_2CH═CH_2), 5.62 (1H, br-s, N*H*), 5.12−5.09 (1H, m, NCH_2CH═CH_2), 5.06 (1H, dq, J = 4.9, 1.5 Hz, NCH_2CH═CH_2), 4.35 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.86 (2H, tt, J = 5.7, 1.5 Hz, NCH_2CH═CH_2), 3.57 (2H, s, CH_2C═O), 1.37 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.7 (C), 165.9 (C), 156.9 (C), 156.2 (C), 134.0 (CH), 132.3 (C), 130.9 (2 × CH), 129.9 (C), 129.7 (CH), 124.5 (CH), 123.4 (CH), 119.8 (CH), 119.2 (2 × CH), 116.2 (CH_2), 61.2 (CH_2), 42.9 (CH_2), 41.9 (CH_2), 14.25 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{20}H_{21}NO_4Na^+$ $[M + Na]^+$ 362.1363, found 362.1366.

*Ethyl 3-(4-(2-(tert-Butylamino)-2-oxoethyl)phenoxy)benzoate (**9d**).* The title compound was prepared according to a modification of general procedure E (NEt_3 and DMF were added in the final stage) using ethyl 3-phenoxybenzoate (**2i**) (242 mg, 1.00 mmol), CBTF (0.25 mL), and *tert*-butylamine (80 μL, 0.75 mmol). For the final stage, NEt_3 (0.10 mL, 0.75 mmol) and DMF (0.20 mL) were added (a thick precipitate of *tert*-butylammonium benzotriazolide is otherwise obtained), and the reaction time was 2.5 h. Chromatographic purification (2 → 8% EtOAc/CH_2Cl_2) provided the title amide **9d** (146 mg, 81%) as a colorless oil, which crystallized on standing. R_f = 0.70 (15% EtOAc/CH_2Cl_2); mp 88−90 °C; IR 3323, 1713, 1667, 1637, 1588 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 7.79 (1H, d, J = 7.7, 1.5, 1.1 Hz, Ar*H*), 7.67 (1H, dd, J = 2.5, 1.5 Hz, Ar*H*), 7.39 (1H, t, J = 7.9 Hz, Ar*H*), 7.25−7.19 (2H, m, Ar*H*), 7.19 (1H, ddd, J = 8.1, 2.5, 1.0 Hz, Ar*H*), 7.00−6.93 (2H, m, Ar*H*), 5.27 (1H, br-s, N*H*), 4.35 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.45 (2H, s, CH_2C═O), 1.37 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.31 (9H, s, $C(CH_3)_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.1 (C), 166.0 (C), 157.1 (C), 155.9 (C), 132.3 (C), 130.71 (2 × CH), 130.66 (C), 129.7 (CH), 124.4 (CH), 123.3 (CH), 119.7 (CH), 119.2 (2 × CH), 61.2 (CH_2), 51.3 (C), 43.9 (CH_2), 28.7 (3 × CH_3), 14.3 (CH_3); HRMS (ESI + ve) exact mass calculated for $C_{21}H_{25}NO_4Na^+$ $[M + Na]^+$ 378.1676, found 378.1675.

*2-(4-(4-Bromophenoxy)phenyl)-1-morpholinoethan-1-one (**9e**).* The title compound was prepared according to a modification of general procedure E (additional DCE was added) using 1-bromo-4-phenoxybenzene (249 mg, 1.0 mmol), CBTF (0.30 mL), and morpholine (70 μL, 0.75 mmol). A total of 1.0 mL of DCE was added in the second stage of the sequence. For the final stage, the reaction mixture was heated at reflux (bath temp. 90−100 °C) for 2 h. Chromatographic purification (2 → 10% acetone/CH_2Cl_2) provided the title amide **9e** (162 mg, 86%) as a white crystalline solid. R_f = 0.50 (10% acetone/CH_2Cl_2); mp 108−110 °C; IR 1646 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 7.45−7.37 (2H, m, Ar*H*), 7.24−7.16 (2H, m, Ar*H*), 6.98−6.91 (2H, m, Ar*H*), 6.90−6.83 (2H, m, Ar*H*), 3.69 (2H, s, CH_2C═O), 3.64 (4H, a-s, NCH_2CH_2O), 3.57−3.51 (2H, m, NCH_2CH_2O), 3.49−3.42 (2H, m, NCH_2CH_2O); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 156.3 (C), 155.5 (C), 132.6 (2 × CH), 130.1 (2 × CH), 130.0 (2 × CH), 120.3 (2 × CH), 119.2 (2 × CH), 115.6 (C), 66.7 (CH_2), 66.4 (CH_2), 46.4 (CH_2), 42.1 (CH_2), 39.7 (CH_2); HRMS (ESI + ve) exact mass calculated for $C_{18}H_{18}NO_3{}^{79}BrNa^+$ $[M + Na]^+$ 398.0362, found 398.0362.

*N-Methoxy-2-(4-(4-methoxyphenoxy)phenyl)-N-methylacetamide (**9f**).* The title compound was prepared according to a modification of general procedure E (a hydrochloride salt was used and NEt_3 was added) using 1-methoxy-4-phenoxybenzene (**2a**) (200 mg, 1.0 mmol), CBTF (0.30 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (75 mg, 0.75 mmol). For the final stage, NEt_3 (0.15 mL, 1.1 mmol) was also added, and the reaction time was 1 h. Chromatographic purification (2 → 8% EtOAc/CH_2Cl_2) provided the title amide **9f** (98 mg, 65%) as a colorless oil. R_f = 0.65 (15% EtOAc/CH_2Cl_2); IR 1659 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) δ 7.22 (2H, br-d, J = 8.6 Hz, Ar*H*), 7.00−6.93 (2H, m, Ar*H*), 6.92−6.83 (4H, m, Ar*H*), 3.81−3.78 (3H, m, $ArOCH_3$),* 3.73 (2H, br-s, CH_2C═O), 3.65−3.63 (3H, m, $NOCH_3$),* 3.20−3.18 (3H, m, NCH_3)* (*complexity due to rotameric forms); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 172.4 (br, C), 157.3 (C), 155.8 (C), 150.1 (C), 130.5 (2 × CH), 128.8 (C), 120.7 (2 × CH), 117.6 (2 × CH), 114.7 (2 × CH), 61.3 (CH_3), 55.6 (CH_3), 38.4 (br, CH_2), 32.2 (br, CH_2); HRMS (ESI + ve) exact mass calculated for $C_{17}H_{19}NO_4Na^+$ $[M + Na]^+$ 324.1206, found 324.1206.

Synthesis of Cytotoxic Agent 13. *1-(2-Ethylbutoxy)-4-phenoxybenzene (**11**).* To a solution of 4-phenoxyphenol (**10**) (930 mg, 5.00 mmol) in DMF (5.0 mL) at 0 °C was added NaH (60% mineral oil dispersion, 240 mg, 6.00 mmol). The reaction mixture was stirred at 0 °C for 10 min and then at rt for 10 min, followed by addition of 1-bromo-2-ethylbutane (1.00 mL, 7.15 mmol) and stirring at 60 °C for 4 h. The reaction mixture was cooled to rt, and additional 1-bromo-2-ethylbutane (0.20 mL, 1.4 mmol) and NaH (60% mineral oil dispersion, 60 mg, 1.5 mmol) were added. The mixture was stirred at 60 °C for a further 1 h, cooled to rt, diluted with pet. ether (50 mL), washed with 1:1 brine/water (2 × 50 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (1 → 4% Et_2O/pet. ether) provided the title ether **11** (1.23 g, 91%) as a colorless oil. R_f = 0.70 (5% Et_2O/pet. ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (2H, m, Ar*H*), 7.09−7.01 (1H, m, Ar*H*), 7.01−6.93 (4H, m, Ar*H*), 6.93−6.86 (2H, m, Ar*H*), 3.85 (2H, d, J = 5.7 Hz, CH_2O), 1.67 (1H, sept, J = 6.1 Hz, Et_2CH), 1.61−1.38 (4H, m, $(CH_3CH_2)_2CH$), 0.96 (6H, t, J = 7.4 Hz, $(CH_3CH_2)_2CH$); ^{13}C{^{1}H } NMR (75 MHz, $CDCl_3$) δ 158.6 (C), 155.7 (C), 149.8 (C), 129.6 (2 × CH), 122.3 (CH), 120.8 (2 × CH), 117.5 (2 × CH), 115.4 (2 × CH), 70.6 (CH_2), 40.9 (CH), 23.4 (2 × CH_2), 11.1 (2 × CH_3); HRMS (ESI + ve) exact mass calculated for $C_{18}H_{22}O_2Na^+$ $[M + Na]^+$ 293.1512, found 293.1512.

*Ethyl 2-(2-(4-(4-(2-Ethylbutoxy)phenoxy)phenyl)acetamido)-benzoate (**12**).* A mixture of diazo **1** (340 mg, 2.00 mmol), arene **11** (1.08 g, 4.00 mmol), Rh_2(esp)$_2$ (1.5 mg, 2.0 μmol), and Na_2SO_4 (400 mg) in 4-chlorobenzotrifluoride (CBTF, 1.0 mL) was stirred at rt for 22

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h. Ethyl 2-aminobenzoate (0.60 mL, 4.1 mmol) in DCE (2.0 mL) was added and the reaction mixture was stirred at 80 °C for 2.5 h and then cooled to rt. NEt_3 (0.30 mL, 2.2 mmol) was added and the reaction mixture was stirred at 100 °C for 30 min. The reaction mixture was cooled to rt, loaded directly onto a silica column, and purified by flash chromatography (5 → 35% Et_2O/pet. ether) to provide the title acetanilide **12** (824 mg, 87%) as a pale yellow oil. R_f = 0.35 (25% Et_2O/pet. ether); IR 3267, 1683 (br), 1605, 1588 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 11.13 (1H, s, N*H*), 8.73 (1H, dd, *J* = 8.5, 1.0 Hz, Ar*H*), 8.01 (1H, dd, *J* = 8.0, 1.5 Hz, Ar*H*), 7.52 (1H, ddd, *J* = 8.7, 7.4, 1.6 Hz, Ar*H*), 7.34−7.28 (2H, m, Ar*H*), 7.06 (1H, ddd, *J* = 8.1, 7.4, 1.2 Hz, Ar*H*), 7.02−6.92 (4H, m, Ar*H*), 6.92−6.83 (2H, m, Ar*H*), 4.34 (2H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 3.83 (2H, d, *J* = 5.7 Hz, CH_2O), 3.72 (2H, s, $CH_2C{=}O$), 1.65 (1H, sept, *J* = 6.0 Hz, Et_2CH), 1.58−1.42 (4H, m, $(CH_3CH_2)_2CH$), 1.40 (3H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 0.94 (6H, t, *J* = 7.4 Hz, $(CH_3CH_2)_2CH$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 168.0 (C), 157.8 (C), 155.6 (C), 149.9 (C), 141.4 (C), 134.4 (CH), 130.8 (2 × CH), 130.7 (CH), 128.3 (C), 122.4 (CH), 120.6 (2 × CH), 120.2 (CH), 118.0 (2 × CH), 115.4 (2 × CH), 115.3 (C), 70.5 (CH_2), 61.2 (CH_2), 45.0 (CH_2), 40.9 (CH), 23.3 (2 × CH_2), 14.1 (CH_3), 11.1 (2 × CH_3); HRMS (ESI + ve) exact mass calculated for $C_{29}H_{33}NO_5Na^+$ $[M + Na]^+$ 498.2251, found 498.2254.

2-(2-(4-(4-(2-Ethylbutoxy)phenoxy)phenyl)acetamido)benzoic Acid ***13***. To a solution of ester **12** (712 mg, 1.50 mmol) in EtOH (9 mL) at 50 °C was added 2 M NaOH (aq) (3 mL) dropwise. The mixture was stirred at 50 °C for 30 min, cooled to rt, acidified with 1 M HCl (7 mL), and diluted with EtOAc (50 mL). The organic fraction was washed with brine (3 × 30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting sticky foam was stirred in 1:20 EtOH/pet. ether (10.5 mL) for 15 min and the precipitate collected by filtration to provide the title acid **13** (596 mg, 89%) as a white crystalline solid. R_f = 0.45 (25% acetone/pet. ether; 1% AcOH on AcOH-doped SiO_2); mp 122−124 °C; IR 3277, 1672 (br), 1603, 1584 cm^{-1}; ^1H (300 MHz, $CDCl_3$, CO_2H not resolved) δ 10.82 (1H, s, N*H*), 8.77 (1H, d, *J* = 8.5 Hz, Ar*H*), 8.14 (1H, dd, *J* = 8.0, 1.3 Hz, Ar*H*), 7.59 (1H, ddd, *J* = 8.7, 7.4, 1.5 Hz, Ar*H*), 7.29 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.14−7.07 (1 H, m, Ar*H*), 7.01−6.95 (2H, m, Ar*H*), 6.95−6.89 (2H, m, Ar*H*), 6.85−6.78 (2H, m, Ar*H*), 3.78 (2H, s, $CH_2C{=}O$), 3.77 (2H, d, *J* = 5.7 Hz, CH_2O), 1.65 (1H, sept, *J* = 6.0 Hz, Et_2CH), 1.56−1.35 (4H, m, $(CH_3CH_2)_2CH$), 0.92 (6H, t, *J* = 7.4 Hz, $(CH_3CH_2)_2CH$); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 172.7 (br, C), 170.8 (C), 158.0 (C), 155.7 (C), 149.7 (C), 141.8 (C), 135.6 (CH), 132.0 (CH), 131.0 (2 × CH), 127.6 (C), 123.0 (CH), 120.6 (2 × CH), 120.5 (CH), 118.1 (2 × CH), 115.4 (2 × CH), 114.3 (br, C), 70.5 (CH_2), 45.0 (CH_2), 40.9 (CH), 23.3 (2 × CH_2), 11.1 (2 × CH_3); HRMS (ESI + ve) exact mass calculated for $C_{27}H_{29}NO_5Na^+$ $[M + Na]^+$ 470.1938, found 470.1935.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01426.

Solvent- and ligand-screening information, ^1H NMR spectra for the NMR-monitored synthesis of **7a** and **7aa**, and ^1H and $^{13}C\{^1H\}$ NMR spectra for compounds **1**, **2**, **7**−**13** (PDF)

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Notes

The authors declare no competing financial interest.

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