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Concise Synthesis of a Potential 5-Lipoxygenase Activating Protein (FLAP) Inhibitor and Its Analogs through Late-Stage Alkene Dicarbofunctionalization

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Supporting Information

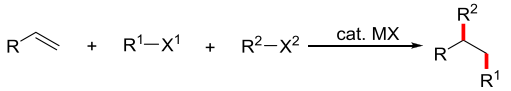
ABSTRACT: We report a five-step synthesis of the biologically important 1,1-diarylalkane **1**, a potential 5-lipoxygenase activating protein (FLAP) inhibitor that was synthesized previously in 12 steps. In this synthesis, we apply a three-component alkene dicarbofunctionalization reaction as a key final step to assemble the potential FLAP inhibitor **1** from commercially available starting materials. In addition, we also report the synthesis of a variety of new analogs of the inhibitor **1** and its regioisomer.

KEYWORDS: *alkenes, alkylarylation, 1,1-diarylalkanes, dicarbofunctionalization, FLAP inhibitor, three-component*

INTRODUCTION

Difunctionalization of alkenes with two carbon-based coupling partners, termed dicarbofunctionalization (Scheme 1),[1] offers an expeditious route for the synthesis of complex molecules from readily available starting materials.[2] A number of such reactions have been developed over the years, which have enabled the synthesis of complex carbo- and heterocycles through cyclization/coupling.[3] Recently, a number of reports have appeared to demonstrate the difunctionalization of alkenes in a three-component process through cross-coupling,[4] reductive coupling,[5] and C−H bond functionalization.[6] Despite growing interest in recent years in developing such reactions, their application as a new retrosynthetic disconnection to construct natural products and biologically active molecules is scarce. The known but limited examples have utilized the cyclization/coupling approach in which tethered alkenes are dicarbofunctionalized to synthesize a select number of lignan natural products[3l,m] and sesquiterpenes.[7] In contrast, the application of three-component alkene dicarbofunctionalization reactions in the synthesis of biologically important target molecules largely remains unknown.[4i] In this article, we report the application of a Ni-catalyzed alkylarylation of alkenes, a reaction that we recently developed,[4h] as a new retrosynthetic disconnection to synthesize concisely a potential 5-lipoxygenase activating protein (FLAP) inhibitor (**1**), its analogs, and regioisomers.

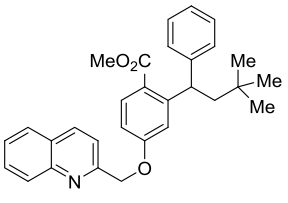
Scheme 1. Alkene Dicarbofunctionalization



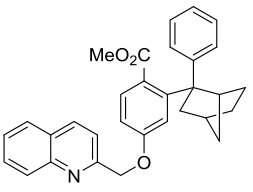
M = Ni, Pd, Cu, Co, Fe; X = halides
X^1, X^2 = organic halides and organometallic reagents

Molecules based on 1,1-diarylalkane scaffolds, such as compounds **1** and **2**, have been reported to show strong bioactivity against membrane protein FLAP (Scheme 2).[8] For example, Chu and co-workers from the Merck Research Laboratory reported that the compound **1** showed FLAP binding activity with IC_{50} at 3.0 nM.[8] Similar structural frameworks (**3** and **4**) have also been shown to be active against breast cancer (MCF-7), lung cancer (H-460), and brain cancer (SF-268).[9] In 2012, Chu and co-workers reported the synthesis of the potential FLAP inhibitor **1** in 12 steps.[8] The synthesis relied upon a four-step construction of the key intermediate **6** from 1,5-dimethoxybenzaldehyde (**5**), which involved a sequence of the Grignard reaction with PhMgBr, the

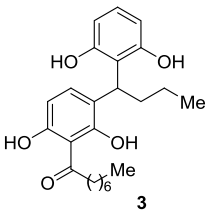
Scheme 2. 1,1-Diarylalkanes as Potential 5-Lipoxygenase Activating Protein (FLAP) Inhibitors and Anti-Breast, -Lung, and -Brain Cancer Agents



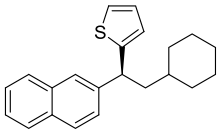
1
FLAP inhibitor
FLAP binding IC_{50} = 3.0 nM



2
FLAP inhibitor
FLAP binding IC_{50} = 2.1 nM



3
Anti-breast, lung and brain cancers



4
anti-breast-cancer
EC_{50} = 5.3 ± 1.1 μM

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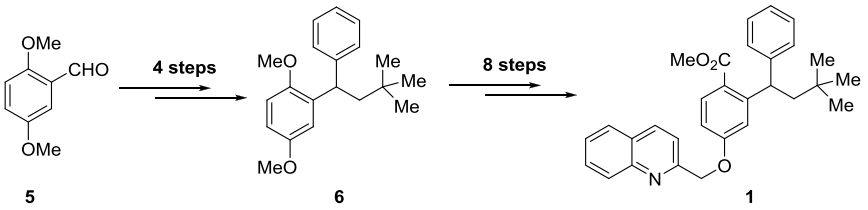
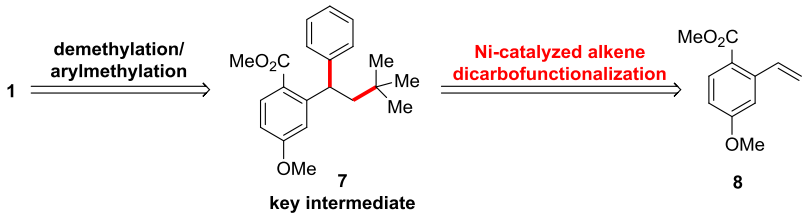
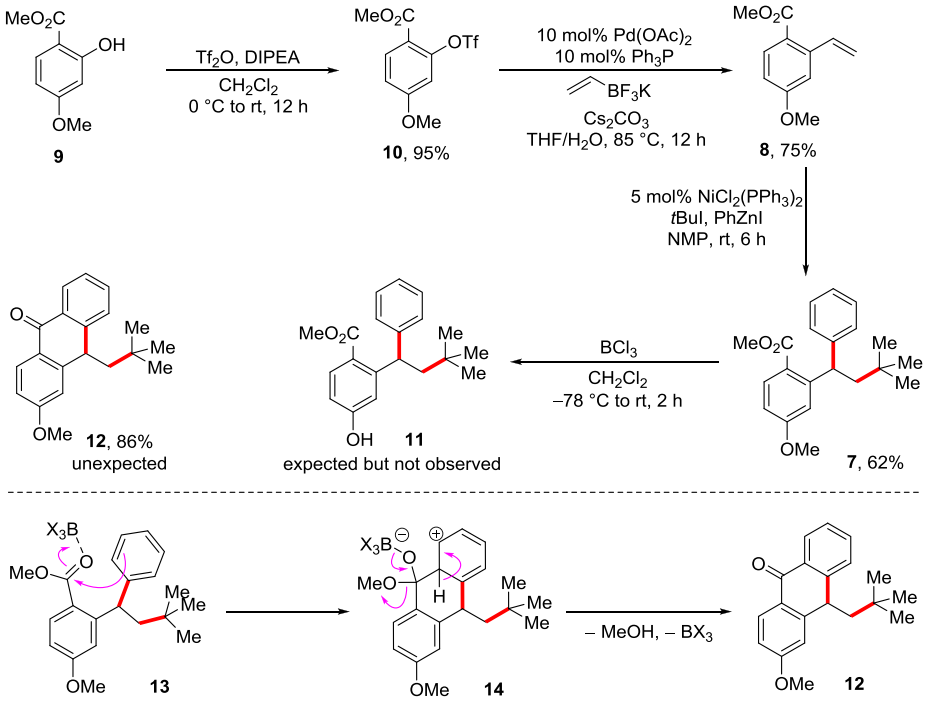
Scheme 3. Merck Synthesis of the Potential FLAP Inhibitor 1



Scheme 4. Retrosynthesis of Compound 1 with Alkene Dicarbofunctionalization as a Key Step



Scheme 5. Attempted Synthesis of Intermediate 11 and the Formation of the Anthracenone Derivative 12



Swern oxidation, the Grignard reaction with *t*BuCH$_2$MgBr, and the reduction of the resultant alcohol with Et$_3$SiH/trifluoroacetic acid (TFA) (Scheme 3). Herein, we apply a Ni-catalyzed alkene dicarbofunctionalization reaction on a vinylarene derivative to install both the *t*Bu and the Ph groups in one step and construct the *α*-phenyl-*β*-*tert*-butylethylaryl core of the potential FLAP inhibitor **1**.

RESULTS AND DISCUSSION

We envisioned that the potential FLAP inhibitor **1** could be derived from the intermediate **7**, which can be readily accessed in one step by alkylarylation of the alkene moiety in 4-methoxy-2-vinylbenzoic acid methyl ester (**8**) (Scheme 4). Therefore, we first synthesized the intermediate **8** from the commercially available 2-hydroxy-4-methoxybenzoic acid methyl ester **9** in two steps by converting **9** to its triflate **10**[10] followed by the Pd-catalyzed Suzuki–Miyaura vinylation of the triflate **10** with the Molander reagent (Scheme 5).[11] The vinylarene **8** was then subjected to dicarbofunctionalization with *t*BuI and PhZnI in the presence of 5 mol % NiCl$_2$(PPh$_3$)$_2$ as a catalyst in NMP at room temperature.[4h] The reaction furnished the intermediate **7** in 62% yield. The intermediate **7** was then reacted with BCl$_3$ for selective demethylation of the ether MeO group in the presence of the ester group.[12] However, the reaction did not furnish the expected product **11**. Instead, BCl$_3$ promoted the intramolecular Friedel–Crafts acylation of the phenyl group with the *ortho*-ester and generated the anthracenone derivative **12** in 86% yield. Further attempts to selectively demethylate the ether MeO group under other reaction conditions, such as with PhSH/K$_2$CO$_3$,[13] MgI$_2$/ionic liquid,[14] Cu$_2$O/NaOMe,[15] and AlCl$_3$,[16] also failed to furnish the desired product.

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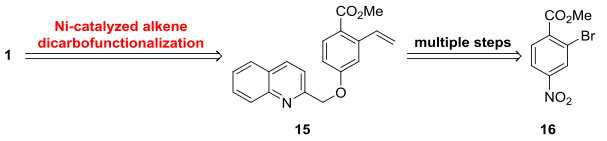
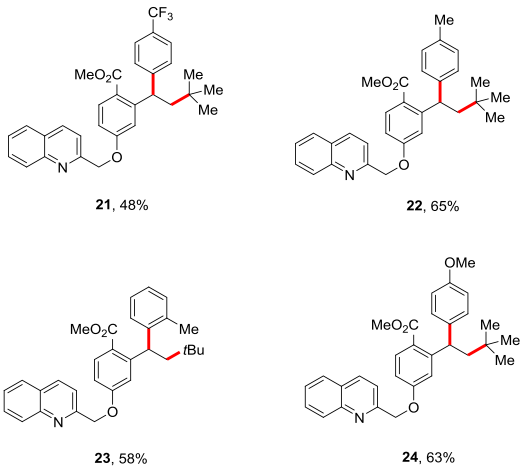
It became evident from the formation of the anthracenone derivative **12** that the Lewis acidic reaction condition for selective demethylation was incompatible with the 1,1-diaryl backbone bearing an *ortho*-ester group. Therefore, we revised our synthetic route in which the alkylarylation of a vinylarene would be conducted in the last step only after the quinolinylmethyl group was installed on the vinylarene (**15**) (Scheme 6). The vinylarene **15** could be expected to be

Scheme 6. Revised Retrosynthesis of Compound 1 with Alkene Dicarbofunctionalization as the Last Step



derived from the commercially available 2-bromo-4-nitrobenzoic acid methyl ester (**16**). We first converted the nitro compound **16** to the hydroxyl compound **18** in two steps involving the reduction of the NO_2 group to NH_2 by $SnCl_2$[17] followed by diazotization with $NaNO_2$/conc. H_2SO_4 and hydrolysis (Scheme 7).[18] The hydroxyl compound **18** was then vinylated by a Pd-catalyzed Suzuki−Miyaura coupling with the Molander reagent to form the hydroxyvinylarene compound **19**.[11] The hydroxyvinylarene **19** was then arylmethylated with 2-(chloromethyl)quinoline hydrochloride[19] to generate the vinylarene intermediate **15**. The vinylarene **15** was then subjected to Ni-catalyzed alkylarylation with *t*BuI and PhZnI. Despite the presence of the *ortho*-ester group and the acidic benzylic methylene group activated by both the oxygen and quinoline, the alkylarylation reaction proceeded smoothly to furnish the potential FLAP inhibitor **1** in 63% yield. The reaction can also be conducted in a gram-scale quantity (5.0 mmol, 1.474 g) without compromising the product yield (65%) (Scheme 7).[20] In order to demonstrate the versatility of the late-stage alkene alkylarylation reaction, we also synthesized four additional analogs (**21**−**24**) of the potential FLAP inhibitor **1** containing CF_3, *p*-Me, *o*-Me, and *p*-OMe substituents on the aryl ring (Scheme 8). These new analogs are formed in good yields (48−65%).[21]

Scheme 8. Synthesis of the Analogs of Compound 1

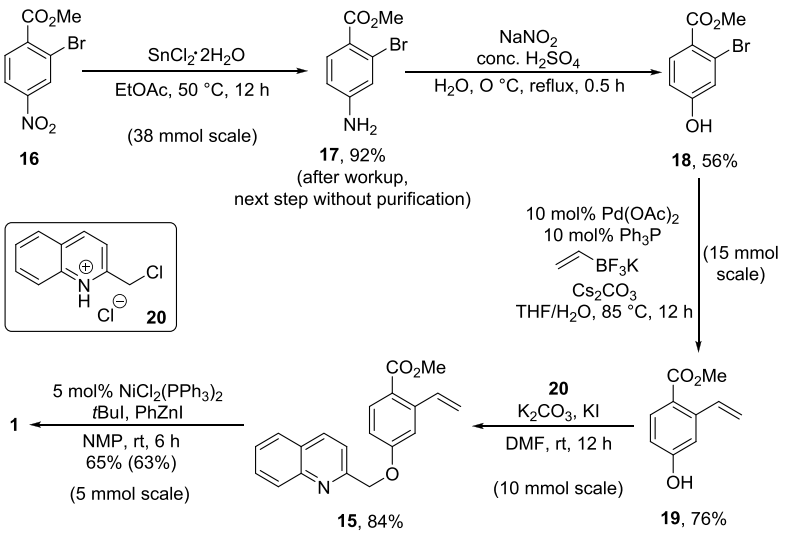


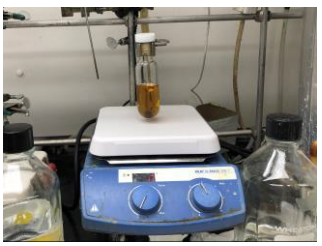
Encouraged by the result of the late-stage alkene alkylarylation, we also synthesized a 5-quinolinylmethoxy regioisomer **29** of the potential FLAP inhibitor **1** in four steps (Scheme 9) from the commercially available 2-bromo-5-methoxybenzoic acid methyl ester (**25**). The ether MeO group in **25** was selectively demethylated in the presence of the ester group with BCl_3 to obtain the hydroxy compound **26**.[12] The hydroxy compound **26** was then vinylated by the Pd-catalyzed Suzuki−Miyaura coupling with the Molander reagent followed by quinolinylmethylation of the hydroxyl group to generate the vinylarene intermediate **28**. The Ni-catalyzed alkylarylation of the vinylarene **28** with *t*BuI and PhZnI furnished the 5-quinolinylmethoxy regioisomer **29** in 56% yield.[21]

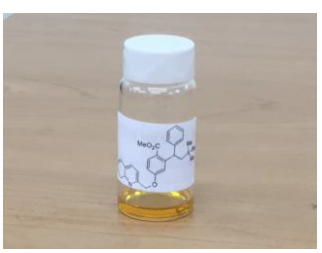
CONCLUSION

In summary, we have demonstrated an application of the three-component alkene dicarbofunctionalization reaction in the five-step synthesis of a potential FLAP inhibitor **1**, a bioactive

Scheme 7. Synthesis of Compound 1 Using Late-Stage Alkene Dicarbofunctionalization







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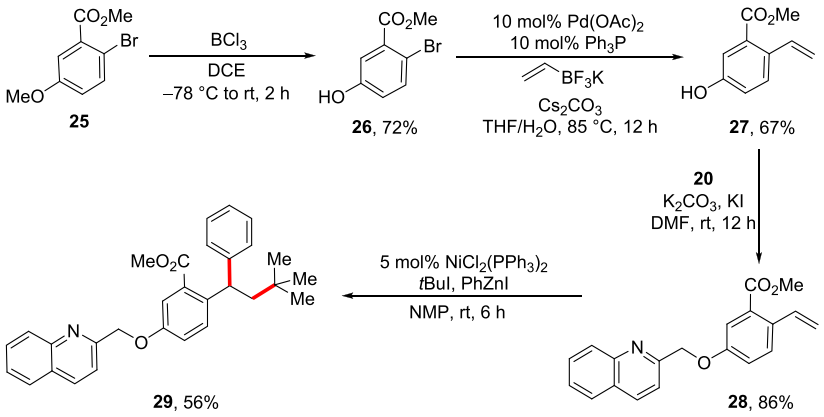
Scheme 9. Synthesis of 5-Quinolinylmethoxy Regioisomer 29 of the Potential FLAP Inhibitor 1



molecule containing a 1,1-diarylalkane scaffold that was previously synthesized in 12 steps. Furthermore, we also applied the alkene dicarbofunctionalization reaction in generating four different analogs and a 5-quinolinylmethoxy regioisomer of the potential FLAP inhibitor **1**. In these examples, the alkene dicarbofunctionalization reaction was performed in the last step of the synthesis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all the reactions and chemicals were handled under a nitrogen atmosphere. All glassware were properly dried in an oven before use. Solvents and reagents were purchased from commercial sources. Organozinc reagents were prepared according to a literature procedure.[22] ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker instrument (300 and 500, 75 and 126, and 282 and 470 MHz, respectively) at the Department of Chemistry and Chemical Biology, the University of New Mexico (UNM) and internally referenced to the residual solvent signals of $CDCl_3$ for ^{1}H and ^{13}C NMR at 7.26 and 77.16 ppm, and externally referenced to C_6F_6 for ^{19}F NMR at −164.9 ppm. The chemical shifts of NMR and the coupling constants (J) for ^{1}H, ^{13}C, and ^{19}F NMR are reported in δ parts per millions (ppm) and in hertz, respectively. The following conventions are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublet; br, broad. High resolution mass spectra for new compounds were recorded at the Mass Spectrometry facilities at the Department of Chemistry and Chemical Biology, UNM.

General Procedure for Alkylarylation. In a glovebox, a solution of phenylzinc iodide (0.60 mmol, 720 μL of 0.833 M stock solution in THF) was taken in a 1-dram vial and the solvent was removed under vacuum. To the PhZnI residue were added $NiCl_2(PPh_3)_2$ (9.81 mg, 0.015 mmol), methyl 4-(quinolin-2-ylmethoxy)-2-vinylbenzoate (95.7 mg, 0.30 mmol), and tertiary butyl iodide (110.4 mg, 0.60 mmol). The mixture was then dissolved in 1.5 mL of NMP. The vial was tightly capped and removed from the glovebox, and the reaction mixture was vigorously stirred at room temperature. After 6 h, the reaction was diluted with EtOAc (10 mL) and washed several times with water. The organic layers were collected and dried. The products were purified by silica gel column chromatography.

General Procedure for Large Scale Alkylarylation. In a glovebox, a solution of phenylzinc iodide (10 mmol, 12.3 mL of 0.81 M stock solution in THF) was taken in a sealed tube and the solvent was removed under vacuum. To the PhZnI residue were added $NiCl_2(PPh_3)_2$ (163.5 mg, 0.25 mmol), methyl 4-(quinolin-2-ylmethoxy)-2-vinylbenzoate (**15**) (1595 mg, 5.0 mmol), and tertiary butyl iodide (1840 mg, 10 mmol). The mixture was then dissolved in 25 mL of NMP. The vial was tightly capped and removed from the glovebox, and the reaction mixture was vigorously stirred at room temperature. After 6 h, the reaction was diluted with EtOAc (50 mL) and washed several times with water. The organic layers were collected and dried. The compound **1** was purified by silica gel column chromatography using THF/hexanes (1:10).

*Methyl 4-Methoxy-2-(((trifluoromethyl)sulfonyl)oxy)-benzoate (**10**).* Compound **10** was prepared according to a literature procedure.[10] To a solution of methyl 2-hydroxy-4-methoxybenzoate (1.8 g, 10 mmol) in CH_2Cl_2 (30 mL) in a round-bottom flask, DIPEA (1.55 g, 12 mmol) was added and stirred at 0 °C for 10 min. Triflic anhydride (3.66g, 13 mmol) was added dropwise to the reaction mixture and stirred at room temperature. After 12 h, CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (5 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous fraction was further extracted with CH_2Cl_2 (15 mL). The organic layers were collected, and the solvent was removed in a rotary evaporator. The title compound **10** was obtained as a brown solid (2.9 g, 95% yield) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.93 (s, 3H), 6.77 (s, 1H), 6.95 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 6.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.4, 56.1, 109.0, 113.5, 116.4, 118.8 (q, J = 320.8 Hz), 134.2, 149.7, 164.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.2; IR (neat) cm^{-1}: 1731, 1614, 1420, 1128, 1068; HRMS (ESI): Calcd for $C_{10}H_{10}F_3O_6S$ $(M + H)^+$ 315.0150, found 315.0147.

*Methyl 4-Methoxy-2-vinylbenzoate (**8**).* Compound **8** was prepared according to a literature procedure.[11] $Pd(OAc)_2$ (112 mg, 0.5 mmol), PPh_3 (132 mg, 0.5 mmol), Cs_2CO_3 (4.9 g, 15 mmol), potassiumvinyltrifluoroborate (0.8 g, 6.0 mmol), and methyl 2-bromo-4-hydroxybenzoate (1.57 g, 5.0 mmol) were weighed in a sealed tube. 15 mL of THF and 1.3 mL of H_2O were added to the reaction mixture and heated at 85 °C. After 12 h, diethyl ether (20 mL) and water (5 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous fraction was further extracted with diethyl ether (4 × 20 mL). The organic layers were collected, and the solvent was removed in a rotary evaporator. The title compound **8** was obtained as a white solid (2.1 g, 75% yield) after purification

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by silica gel column chromatography using ethyl acetate/hexanes (1:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (s, 6H), 5.35 (d, J = 10.0 Hz, 1H), 5.62 (d, J = 15.0 Hz, 1H), 6.82 (dd, J = 10.0 Hz, 3.0 Hz, 1H), 7.03 (d, J = 5.0 Hz, 1H), 7.55 (dd, J = 20.0 Hz, 10.0 Hz, 1H), 7.91 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 51.9, 55.4, 112.5, 112.9, 116.4, 120.8, 132.8, 136.5, 142.4, 162.6, 167.3; IR (neat) cm^{-1}: 1708, 1598, 1433, 1232, 1125; HRMS (ESI): Calcd for $C_{11}H_{13}O_3$ $(M + H)^+$ 193.0865, found 193.0866.

*Methyl 2-(3,3-Dimethyl-1-phenylbutyl)-4-methoxybenzoate (**7**).* The title compound **7** was obtained as a colorless liquid from a 3 mmol scale reaction (606 mg, 62% yield) after purification by silica gel column chromatography using ether/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 9H), 2.10 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H), 3.91 (s, 3H), 5.54 (t, J = 7.5 Hz, 1H), 6.69 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 7.08 (d, J = 3.0 Hz, 1H), 7.14−7.17 (m, 1H), 7.26 (t, J = 7.5 Hz, 2H), 7.42 (d, J = 9.0 Hz, 2H), 7.82 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3, 31.8, 41.0, 50.1, 51.9, 55.3, 110.1, 114.9, 121.8, 125.9, 128.0, 128.3, 132.9, 146.7, 150.8, 162.2, 168.2; IR (neat) cm^{-1}: 1711, 1601, 1432, 1232, 1124; HRMS (ESI): Calcd for $C_{21}H_{27}O_3$ $(M + H)^+$ 327.1960, found 327.1947.

*3-Methoxy-10-neopentylanthracen-9(10H)-one (**12**).* Compound **7** (326 mg, 0.5 mmol) was weighed in a round-bottom flask, dissolved in CH_2Cl_2 (10 mL), and the reaction mixture was cooled to −78 °C. BCl_3 (1 mL of 1 M solution in hexanes) was then added dropwise over 10 min, and the reaction mixture was stirred for additional 30 min at −78 °C before allowing it to warm up to room temperature. After 2 h, the reaction was quenched with water (5 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were collected, and the solvent was removed in a rotary evaporator. The title compound **12** was obtained as a white solid (126.4 mg, 86% yield) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.65 (s, 9H), 1.95−2.07 (m, 2H), 3.89 (s, 3H), 4.31 (t, J = 6.0 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 6.98 (s, 1H), 7.36−7.41 (m, 1H), 7.50 (d, J = 3.0 Hz, 2H), 8.22 (t, J = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.7, 32.5, 41.6, 55.2, 55.5, 112.8, 113.1, 126.1, 126.8, 127.5, 128.3, 130.1, 132.1, 132.6, 146.5, 149.3, 162.9, 184.1; IR (neat) cm^{-1}: 1651, 1598, 1456, 1274, 1241, 1091, 931; HRMS (ESI): Calcd for $C_{20}H_{23}O_2$ $(M + H)^+$ 295.1698, found 295.1702.

*Methyl 4-Amino-2-bromobenzoate (**17**).* Compound **17** was prepared according to a literature procedure.[17] Methyl 2-bromo-4-nitrobenzoate (10 g, 38.0 mmol) and $SnCl_2{\cdot}2H_2O$ (35.9 g, 190 mmol) were weighed in a round-bottom flask and dissolved in EtOAc (190 mL). After the reaction was stirred for 12 h at 50 °C, EtOAc (150 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added to the reaction mixture. The organic layer was separated, and the remaining aqueous fraction was extracted with EtOAc (3 × 100 mL). The organic layer was collected, and the solvent was removed in a rotary evaporator. The title compound **17** was obtained as an analytically pure light-yellow solid (7.97 g, 92% yield), which was used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 3H), 4.13 (br.s, 2H), 6.54 (dd, J = 10.0 Hz, 2.5 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 7.73 (d, J = 2.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 51.9, 112.9, 119.5, 119.8, 124.1, 133.7, 150.7, 166.1; IR (neat) cm^{-1}: 3324, 1704, 1586, 1428, 1240, 1032; HRMS (ESI): Calcd for $C_8H_9BrNO_2$ $(M + H)^+$ 229.2817, found 229.9809.

*Methyl 2-Bromo-4-hydroxybenzoate (**18**).* Compound **18** was prepared according to a literature procedure.[18] In a round-bottom flask, methyl 4-amino-2-bromobenzoate (7.786 g, 30 mmol) was weighed, the flask was cooled to 0 °C and H_2SO_4 (13.6 mL in 92 mL H_2O) was added dropwise. After the resulting solution was stirred at 0 °C for 20 min, $NaNO_2$ (3.5 g, 51 mmol) in 35 mL water was added dropwise and the reaction mixture was allowed to stir for an additional 30 min at 0 °C before refluxing at 100 °C for 45 min. The reaction mixture was brought to room temperature, $CHCl_3$ (100 mL) was added. The organic layer was separated, and the remaining aqueous fraction was extracted with $CHCl_3$ (4 × 100 mL). The organic layer was collected, and the solvent was removed in a rotary evaporator. The title compound **18** was obtained as a white solid (56% yield, 3.847 g) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.94 (br.s, 1H), 6.82 (d, J = 9.0 Hz, 1H), 7.13 (s, 1H), 7.77 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4, 115.3, 122.2, 123.0, 124.1, 134.4, 162.5, 167.6; IR (neat) cm^{-1}: 3333, 1684, 1261, 1031; HRMS (ESI): Calcd for $C_8H_8BrO_3$ $(M + H)^+$ 230.9657, found 230.9663.

*Methyl 4-Hydroxy-2-vinylbenzoate (**19**).* Compound **19** was prepared according to a literature procedure.[11] $Pd(OAc)_2$ (336 mg, 1.5 mmol), PPh_3 (393 mg, 1.5 mmol), Cs_2CO_3 (14.625 g, 45 mmol), potassiumvinyltrifluoroborate (2.41 g, 18 mmol), and methyl 2-bromo-4-hydroxybenzoate (3.435 g, 15 mmol) were weighed in a sealed tube. 45 mL of THF (45 mL) and H_2O (4 mL) were added to the reaction mixture and heated at 85 °C. After 12 h, diethyl ether (50 mL) and water (25 mL) were added to the reaction mixture. The organic layer was separated, and the remaining aqueous fraction was extracted with diethyl ether (4 × 50 mL). The organic layer was collected, and the solvent was removed in a rotary evaporator. The title compound **19** was obtained as a white solid (76% yield, 2.03 g) after purification by silica gel column chromatography in ether/hexanes (1:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 5.32 (d, J = 9.0 Hz, 1H), 5.57 (d, J = 15.0 Hz, 1H), 5.89 (s, 1H), 6.78 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 7.00 (d, J = 3.0 Hz, 1H), 7.50 (dd, J = 18.0 Hz, 12.0 Hz, 1H), 7.86 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.2, 114.2, 114.7, 116.8, 120.4, 133.2, 136.0, 142.8, 159.6, 168.2; IR (neat) cm^{-1}: 3291, 1677, 1560, 1438, 1138; HRMS (ESI): Calcd for $C_{10}H_{11}O_3$ $(M + H)^+$ 179.0708, found 179.0713.

*Methyl 4-(Quinolin-2-ylmethoxy)-2-vinylbenzoate (**15**).* Compound **15** was prepared according to a literature procedure.[19] In a round-bottom flask, methyl 4-hydroxy-2-vinylbenzoate (1.78 g, 10 mmol) was weighed and dissolved in DMF (30 mL). K_2CO_3 (3.450 g, 25 mmol) and KI (2.49 g, 15 mmol) were added, and the reaction mixture was allowed to stir at room temperature. 2-(Chloromethyl)quinolin-1-ium chloride (2.556 g, 12 mmol) was added to the reaction suspension and stirred at room temperature. After 12 h, EtOAc (30 mL) and water (15 mL) were added to the reaction mixture. The aqueous fraction was removed, and the organic layer was further washed with water (3 × 10 mL). The organic layer was collected, and the solvent was removed in a rotary evaporator. The title compound **15** was obtained as a white solid (85% yield, 2.711 g) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:5). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (s, 3H), 5.34 (d, J = 12.0 Hz, 1H), 5.45 (s, 2H), 5.60 (d, J = 18.0 Hz, 1H), 6.95 (dd, J = 9.0 Hz, 3.0 Hz, 1H), 7.23 (d, J = 2.4 Hz, 1H), 7.48−7.59 (m, 2H),

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7.65 (d, J = 12.0 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.87 (dd, J = 18.0 Hz, 9.0 Hz, 2H), 8.08 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 51.9, 71.4, 113.6, 113.7, 116.7, 119.1, 121.4, 126.7, 127.7, 127.8, 129.0, 130.0, 132.9, 136.2, 137.2, 142.4, 147.6, 157.1, 161.3, 167.2; IR (neat) cm^{-1}: 1709, 1564, 1426, 1258, 1138, 1091; HRMS (ESI): Calcd for $C_{20}H_{18}NO_3$ (M + H)$^+$ 320.1287, found 320.1293.

*Methyl 2-(3,3-Dimethyl-1-phenylbutyl)-4-(quinolin-2-ylmethoxy)benzoate (**1**).* The title compound **1** was obtained as a light yellow liquid from a 5 mmol scale reaction (1.474 g, 65% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (s, 9H), 1.98 (dd, J = 6.0 Hz, 3.0 Hz, 2H), 3.88 (s, 3H), 5.42 (s, 2H), 5.45 (t, J = 4.5 Hz, 1H), 6.82 (dd, J = 3.0 Hz, 1.5 Hz, 1H), 7.05−7.11 (m, 3H), 7.18 (d, J = 3.0 Hz, 1H), 7.29 (d, J = 3.0 Hz, 2H), 7.57−7.61 (m, 2H), 7.76−7.78 (m, 2H), 7.83 (d, J = 6.0 Hz, 1H), 8.14 (dd, J = 12.0 Hz, 6.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.2, 31.7, 41.0, 50.0, 52.0, 71.4, 112.3, 114.9, 119.2, 122.2, 125.8, 126.8, 127.7, 127.8, 127.9, 128.3, 129.1, 130.0, 132.8, 137.2, 146.6, 147.7, 151.0, 157.4, 160.9, 168.2; IR (neat) cm^{-1}: 2949, 1711, 1598, 1430, 1234, 1124, 1041; HRMS (ESI): Calcd for $C_{30}H_{32}NO_3$ (M + H)$^+$ 454.2382, found 454.2397.

Methyl (E)-2-(3,3-Dimethylbut-1-en-1-yl)-4-(quinolin-2-ylmethoxy)benzoate. Along with the title compound **1**, this Heck product was obtained as a colorless liquid (50.6 mg, 27% yield) after purification by silica gel column chromatography using THF/hexanes (1:10) from a 0.5 mmol scale reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12 (s, 9H), 3.85 (s, 3H), 5.45 (s, 2H), 6.07 (d, J = 15.0 Hz, 1H), 6.88 (dd, J = 5.0 Hz, J = 10.0 Hz, 1H), 7.15−7.19 (m, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 10.0 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.84 (d, J = 10.0 Hz, 1H), 7.88 (d, J = 10.0 Hz, 1H), 8.09 (d, J = 15.0 Hz, 1H), 8.21 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 29.6, 33.8, 51.8, 71.4, 113.0, 113.3, 119.2, 121.1, 124.1, 126.8, 127.7, 127.8, 129.0, 130.0, 133.0, 137.3, 143.0, 144.9, 147.6, 157.3, 161.2, 167.5; HRMS (ESI): Calcd for $C_{24}H_{26}NO_3$ (M + H)$^+$ 376.1913, found 376.1916.

*Methyl 2-(3,3-Dimethyl-1-(4-(trifluoromethyl)phenyl)-butyl)-4-(quinolin-2-ylmethoxy)benzoate (**21**).* The title compound **21** was obtained as a colorless viscous liquid (75 mg, 48% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74 (s, 9H), 1.93−2.01 (m, 2H), 3.87 (s, 3H), 5.44 (m, 2H), 5.54 (t, J = 7.5 Hz, 1H), 6.85 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H), 7.14 (d, J = 2.5 Hz, 1H), 7.25 (d, J = 10.0 Hz, 1H), 7.36 (d, J = 10.0 Hz, 1H), 7.57−7.60 (m, 2H), 7.76−7.85 (m, 3H), 8.14 (dd, J = 11.5 Hz, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.2, 31.7, 40.8, 49.9, 52.1, 71.5, 112.9, 114.5, 119.2, 119.3, 121.9, 122.3 (q, J = 257.7 Hz), 123.2, 125.2 (q, J = 3.8 Hz), 126.9, 127.8, 127.9, 128.1 (q, J = 3.8 Hz), 129.0 (q, J = 3.8 Hz), 130.2, 133.1, 137.3, 147.7, 150.1, 150.7, 157.3, 161.0, 167.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.7; IR (neat) cm^{-1}: 2951, 1712, 1600, 1323, 1110; HRMS (ESI): Calcd for $C_{31}H_{31}F_3NO_3$ (M + H)$^+$ 522.2256, found 522.2275.

*Methyl 2-(3,3-Dimethyl-1-(p-tolyl)butyl)-4-(quinolin-2-ylmethoxy)benzoate (**22**).* The title compound **22** was obtained as a colorless viscous liquid (91 mg, 65% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 9H), 1.98 (d, J = 3.0 Hz, 2H), 2.23 (s, 3H), 3.88 (s, 3H), 5.40−5.45 (m, 3H), 6.82 (d, J = 9.0 Hz, 1H), 6.92 (d, J = 9.0 Hz, 2H), 7.19−7.22 (m, 2H), 7.54−7.61 (m, 2H), 7.76−7.84 (m, 3H), 8.14 (dd, J = 9.0 Hz, J = 3.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.0, 30.2, 31.6, 40.6, 50.0, 51.9, 71.4, 112.2, 114.8, 119.2, 122.1, 126.7, 127.7, 127.8, 129.0, 129.1, 130.0, 132.8, 135.2, 137.2, 143.6, 147.7, 151.3, 157.4, 160.9, 168.2; IR (neat) cm^{-1}: 2948, 1712, 1599, 1429, 1123; HRMS (ESI): Calcd for $C_{31}H_{34}NO_3$ (M + H)$^+$ 468.2539, found 468.2536.

*Methyl 2-(3,3-Dimethyl-1-(o-tolyl)butyl)-4-(quinolin-2-ylmethoxy)benzoate (**23**).* The title compound **23** was obtained as a colorless viscous liquid (91 mg, 58% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (s, 9H), 1.79 (dd, J = 15.0 Hz, J = 6.0 Hz, 1H), 1.95 (dd, J = 15.0 Hz, J = 9.0 Hz, 1H), 2.30 (s, 3H), 3.85 (s, 3H), 5.37 (s, 2H), 5.50 (t, J = 7.5 Hz, 1H), 6.82 (dd, J = 9.0 Hz, J = 3.0 Hz, 1H), 6.94−7.01 (m, 2H), 7.04−7.08 (m, 2H), 7.25−7.27 (m, 1H), 7.54−7.60 (m, 2H), 7.73−7.79 (m, 2H), 7.83 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.2, 30.7, 31.9, 38.1, 49.5, 52.0, 71.3, 112.0, 116.3, 119.2, 122.8, 125.5, 125.9, 126.8, 127.6, 127.7, 127.8, 129.0, 130.0, 130.7, 132.8, 136.3, 137.2, 143.1, 147.6, 149.4, 157.4, 160.7, 168.2; IR (neat) cm^{-1}: 2919, 1714, 1598, 1430, 1236, 1122; HRMS (ESI): Calcd for $C_{31}H_{34}NO_3$ (M + H)$^+$ 468.2539, found 468.2560.

*Methyl 2-(1-(4-Methoxyphenyl)-3,3-dimethylbutyl)-4-(quinolin-2-ylmethoxy)benzoate (**24**).* The title compound **24** was obtained as a colorless viscous liquid (91.2 mg, 63% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 9H), 1.94 (d, J = 6.0 Hz, 2H), 3.70 (s, 3H), 3.87 (s, 3H), 5.37 (t, J = 7.5 Hz, 1H), 5.42 (s, 2H), 6.62 (d, J = 9.0 Hz, 1H), 6.80 (dd, J = 9.0 Hz, J = 2.7 Hz, 1H), 7.16−7.21 (m, 3H), 7.55−7.62 (m, 2H), 7.75−7.79 (m, 2H), 7.84 (d, J = 6.0 Hz, 1H), 8.14 (dd, J = 12.0 Hz, J = 9.0 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.2, 31.7, 40.2, 50.2, 51.9, 52.2, 71.4, 112.3, 113.7, 114.7, 119.3, 122.0, 126.8, 127.7, 127.8, 128.8, 129.1, 130.0, 132.8, 137.2, 138.8, 147.7, 151.5, 157.5, 157.6, 160.9, 168.2; IR (neat) cm^{-1}: 2950, 1712, 1508, 1237, 1038; HRMS (ESI): Calcd for $C_{31}H_{34}NO_4$ (M + H)$^+$ 484.2488, found 484.2476.

*Methyl 2-Bromo-5-hydroxybenzoate (**26**).* Compound **26** was prepared according to a literature procedure.[12] The methyl 2-bromo-5-methoxybenzoate **25** (326 mg, 5.0 mmol) was weighed in a round-bottom flask, dissolved in dichloroethane (50 mL), and the reaction mixture was cooled to −78 °C. BCl_3 (5 mL solution of 1 M BCl_3 solution) was then added dropwise over 20 min, and the reaction mixture was stirred for 30 min at −78 °C before allowing it to slowly warm to room temperature. After stirring for 2 h at room temperature, the reaction mixture was quenched with water (20 mL). The solution was extracted with CH_2Cl_2 (2 × 30 mL), the organic layers were collected, and the solvent was removed in a rotary evaporator. The title compound **26** was obtained as a white solid (954 mg, 83% yield) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:20). The ^{1}H NMR and ^{13}C NMR values match the reported values in the literature.[18] ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 3H), 6.12 (br.s, 1H), 6.86 (dd, J = 10.0 Hz, J = 3.0 Hz, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.47 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.9, 111.8, 118.4, 120.5, 132.6, 135.4, 135.4, 155.1, 167.1; IR (neat) cm^{-1}: 3333, 1684, 1261, 1031.

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Methyl 5-hydroxy-2-vinylbenzoate (27). Compound **27** was prepared according to a literature procedure.[11] $Pd(OAc)_2$ (112 mg, 0.5 mmol), PPh_3 (132 mg, 0.5 mmol), Cs_2CO_3 (4.9 g, 15 mmol), potassiumvinyltrifluoroborate (0.8 g, 6 mmol), and methyl 2-bromo-4-hydroxybenzoate (1.15 g, 5 mmol) were weighed in a sealed tube. THF (15 mL) and H_2O (1.3 mL) were added to the reaction mixture and heated at 85 °C. After 12 h, diethyl ether (20 mL) and water (5 mL) were added to the reaction mixture. The organic layer was separated, and the remaining aqueous fraction was extracted with diethyl ether (4 × 20 mL). The organic layer was collected and the solvent was removed in a rotary evaporator. The title compound **27** was obtained as a white solid (660 mg, 75% yield) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (s, 3H), 5.24 (d, J = 10.0 Hz, 1H), 5.54 (d, J = 15.0 Hz, 1H) 6.13 (s, 1H), 7.00 (dd, J = 10.0 Hz, 5.0 Hz, 1H), 7.33 (dd, J = 20.0 Hz, 10.0 Hz, 1H), 7.37 (d, J = 3.0 Hz, 1H), 7.47 (d, J = 10.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.5, 115.0, 116.8, 119.8, 128.9, 129.5, 132.2, 135.2, 155.2, 168.3; IR (neat) cm^{-1}: 3367, 1693, 1606, 1434, 1297, 1211, 1069; HRMS (ESI): Calcd for $C_{10}H_9O_3$ $(M + H)^+$ 177.0552, found 177.0551.

Methyl 5-(Quinolin-2-ylmethoxy)-2-vinylbenzoate (28). Compound **28** was prepared according to a literature procedure.[19] In a round-bottom flask, methyl 5-hydroxy-2-vinylbenzoate (920 mg, 4 mmol) was weighed and dissolved in DMF (10 mL). K_2CO_3 (828 mg, 6 mmol) and KI (996 mg, 6 mmol) were then added, and the reaction mixture was stirred at room temperature. 2-(Chloromethyl)quinolin-1-ium chloride (1.02 g, 4.8 mmol) was added to the reaction mixture and stirred at room temperature. After 12 h, EtOAc (20 mL) and water (15 mL) were added to the reaction mixture. The organic layer was separated and washed with water (3 × 5 mL). The organic layer was collected, and the solvent was removed in a rotary evaporator. The title compound **28** was obtained as a white solid (1.12 g, 88% yield) after purification by silica gel column chromatography using ethyl acetate/hexanes (1:5). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (s, 3H), 5.25 (d, J = 10.0 Hz, 1H), 5.40 (s, 2H), 5.54 (d, J = 15.0 Hz, 1H), 7.14 (dd, J = 10.0 Hz, 5.0 Hz, 1H), 7.38 (dd, J = 15.0 Hz, J = 10.0 Hz, 1H), 7.50−7.56 (m, 3H), 7.64 (d, J = 10.0 Hz, 1H), 7.71−7.74 (m, 1H), 7.81 (d, J = 10.0 Hz, 1H), 8.08 (d, J = 10.0 Hz, 1H), 8.17 (d, J = 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 52.2, 71.5, 115.1, 116.2, 119.1, 126.7, 127.7, 127.8, 128.6, 129.0, 129.7, 129.9, 132.8, 135.1, 137.2, 147.6, 157.3, 157.6, 167.5; IR (neat) cm^{-1}: 1711, 1598, 1496, 1427, 1218, 1050; HRMS (ESI): Calcd for $C_{20}H_{18}NO_3$ $(M + H)^+$ 320.1287, found 320.1286.

Methyl 2-(3,3-Dimethyl-1-phenylbutyl)-5-(quinolin-2-ylmethoxy)benzoate (29). The title compound **29** was obtained as a colorless viscous liquid (76 mg, 56% yield) after purification by silica gel column chromatography using THF/hexanes (1:10). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (s, 9H), 2.05 (d, J = 6.0 Hz, 2H), 3.90 (s, 3H), 5.17 (t, J = 6.0 Hz, 1H), 5.35 (s, 2H), 7.08−7.13 (m, 2H), 7.20−7.25 (m, 2H), 7.34 (d, J = 6.0 Hz, 2H), 7.40 (d, J = 3.0 Hz, 1H), 7.45 (d, J = 9.0 Hz, 1H), 7.55 (m, J = 7.5 Hz, 1H), 7.64 (d, J = 9.0 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.82 (d, J = 4.5 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 30.3, 31.7, 40.9, 50.1, 52.3, 71.5, 116.0, 118.6, 119.2, 125.8, 126.6, 127.7, 127.8, 128.0, 128.4, 129.0, 129.9, 130.9, 137.2, 140.3, 147.0, 147.7, 155.9, 157.7, 168.6; IR (neat) cm^{-1}: 2918, 1719, 1600, 1492, 1207, 1071; HRMS (ESI): Calcd for $C_{30}H_{32}NO_3$ $(M + H)^+$ 454.2382, found 454.2390.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00199.

NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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