EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201190

A Route to Azafluoranthene Natural Products Through Direct Arylation

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Keywords: Total synthesis / C–H activation / Natural products / Alkaloids / Nitrogen heterocycles / Medicinal chemistry

Microwave-assisted direct arylation reactions were successfully employed in the synthesis of azafluoranthene alkaloids for the first time. Direct arylation reactions on a diverse set of phenyltetrahydroisoquinolines produces the indeno[1,2,3-*ij*]isoquinoline nucleus required towards a high-yielding azafluoranthene synthesis. The method was used as a key step in the efficient preparation of the natural products rufescine and triclisine. As demonstrated herein, this synthetic approach should be generally applicable to the preparation of natural and un-natural azafluoranthene alkaloids as well as azafluoranthene-like isoquinoline alkaloids.

Introduction

Azafluoranthene alkaloids have been identified as secondary metabolites in *Abuta*,[1] *Triclisia*,[2] *Telitoxicum*,[3] *Stephania*,[4] *Cissampelos*[5] and *Pericampylus*[6] species of the Menispermaceae family. Typical members include rufescine (**1**), imeluteine (**2**) and triclisine (**3**; Figure 1). This class of alkaloids shares some structural similarities to aporphine alkaloids such as nantenine (**4**).[7] Naturally-occurring members of both alkaloid classes have oxygenated functionalities (typically hydroxy, methoxy or methylenedioxy groups) decorating the biphenyl sub-structure.

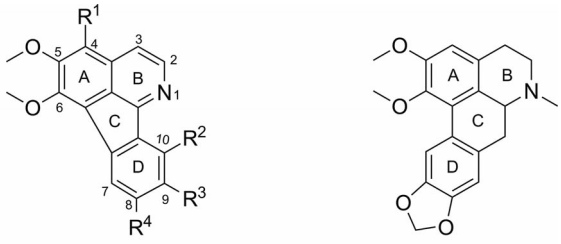

Figure 1. Structures of azafluoranthene alkaloids rufescine (**1**), imeluteine (**2**) and triclisine (**3**) and aporphine alkaloid nantenine (**4**).

Aporphine and azafluoranthene alkaloids have displayed interesting biological activities. Aporphine alkaloids have been shown to possess anticancer activity and there is evidence that this activity is exerted through induction of apoptosis, inhibiting cell proliferation and inhibiting DNA topoisomerase.[8] Some members display acute hypotensive effects[9] and anticonvulsant and antinociceptive activities have also been reported.[10] In the realm of the central nervous system (CNS) activity, aporphines have been studied as ligands for dopaminergic (D_1 and D_2), adrenergic and serotonergic receptors.[11] The dopamine D_1/D_2 receptor-agonist apomorphine is currently used as a treatment for Parkinson's Disease.[10d] A number of aporphines are also known to be inhibitors of acetylcholinesterase, an enzyme that is the biological target of clinically available Alzheimer's disease therapeutics.[12] Our own work on aporphines have explored the synthesis and bioactivity of nantenine derivatives such as serotonin 5-HT_{2A} and α_{1A} adrenergic receptor antagonists,[13] cytotoxic agents[14] and acetylcholinesterase inhibitors.[15]

Relative to aporphines, far fewer azafluoranthene natural products are known. Nevertheless, members of the azafluoranthene class of natural products have shown promising biological activity as anti-HIV,[6] antifungal and cytotoxic[5,16] agents. Recently, the cytotoxic activity of the azafluoranthene eupolauridine was attributed to targeting of DNA topoisomerase II[17] In addition to the biological activities mentioned, the extensive conjugation in molecules containing the azafluoranthene core endow them with interesting spectral properties. For this reason, they have been studied as potentially useful agents in luminescent and electroluminescent applications and devices.[18]

A number of strategies have been investigated for the synthesis of azafluoranthenes. The construction of the aryl-aryl bond is usually a key step in reported methods. Pschorr-based cyclization,[1a,19] photocylization[20] and oxidative biaryl cyclization reactions of isoquinoline precursors with toxic vanadium-based reagents[21] have been successfully implemented in this regard. These methods suffer from low to moderate yields for the biaryl-coupling step. Other strategies include: remote metalation cross-coupling

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201190.

reactions on biaryl precursors,[22] inverse electron demand Diels–Alder reactions of 3-methoxycarbonyl-2-pyrones,[23] intramolecular aza-Wittig condensation reactions on fluorenone derivatives[24] and microwave-assisted electrocyclization reactions of aza-ene intermediates.[25] These latter routes have the drawback of low-yielding steps or require long synthetic sequences. Synthetic approaches with improved efficiencies and overall yields are desirable, especially within the context of accessing diverse libraries of azafluoranthene analogs and to fully exploit their bioactive potential.

We have recently deployed microwave-assisted direct arylation methods to prepare aporphine[13c,13e] and C-homoaporphine alkaloids.[26] By analogy, we expected a similar strategy to be applicable to the synthesis of azafluoranthene alkaloids. It was envisaged that this method could offer improved alternatives to other reported methods in terms of efficiency and yields.

Results and Discussion

The key step in our anticipated synthesis of azafluoranthenes (**5**; Figure 2), required the preparation of phenyltetrahydroisoquinoline intermediate **6**. Such compounds are readily prepared through a Pictet–Spengler reaction with protected amine **7** and bromoaldehyde **8**. This strategy is analogous to the method pioneered by the Fagnou group for the synthesis of aporphine alkaloids in which a intramolecular direct arylation reaction was used to construct the biaryl bond of the aporphine core.[27] In these prior works, the facility of various phosphane ligands for the direct arylation process under thermal conditions was demonstrated. The reaction was shown to be tolerant of a wide variety of substitution patterns (including electron-withdrawing groups) in both aromatic rings. We recently applied a variation of this method in which microwave irradiation was used (instead of thermal conditions) for the biaryl-coupling step in the synthesis of aporphines.[13c]

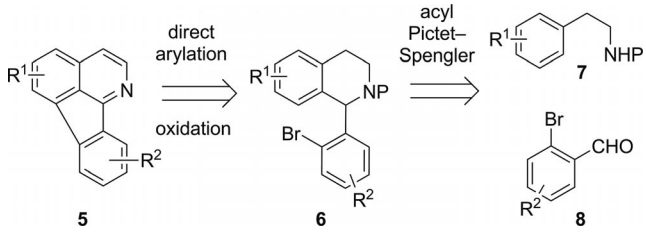
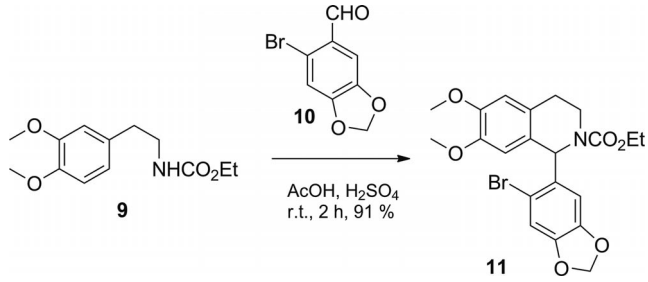


Figure 2. Retrosynthetic analysis for azafluoranthene synthesis.

Efforts initially focused on optimization of the biaryl cyclization reaction of tetrahydroisoquinoline substrate **11**. Our interest in this regard stemmed from a desire to prepare analogs of aporphine alkaloid nantenine (**4**), as part of our ongoing structure-activity relationship studies on nantenine-like molecules as CNS receptors.[13a,13b,13e] Compound **11** was prepared from readily available[28] **9**, and commercially available **10** (Scheme 1).

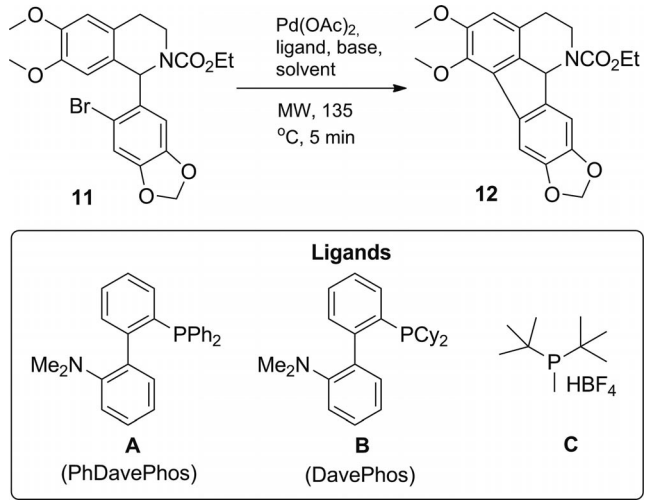


Scheme 1. Synthesis of biaryl coupling substrate **11**.

With **11** in hand, we proceeded to evaluate the optimal combination of ligand, base and solvent required for the microwave-assisted direct biaryl cyclization reaction.

Table 1 summarizes the results of this study. Based on the demonstrated utility of Buchwald phosphane ligands such as PhDavePhos (ligand **A**) and DavePhos (ligand **B**) as well as di-*tert*-butyl(methyl)phosphane tetrafluoroborate (ligand **C**) for direct arylation reactions to prepare similar (aporphine and homoaporphine) scaffolds,[13c,26–27,29] we decided to investigate these ligands.

Table 1. Optimization of direct arylation reaction on **11**.



Entry	Ligand	Base	Solvent	Yield [%][a]
1	**A**	K_2CO_3	DMA	0
2	**B**	K_2CO_3	DMA	26
3	**C**	K_2CO_3	DMA	31
4	**A**	Cs_2CO_3	DMSO	0
5	**B**	Cs_2CO_3	DMSO	0
6	**C**	Cs_2CO_3	DMSO	38
7	**A**	K_2CO_3	DMSO	12
8	**B**	K_2CO_3	DMSO	41
9[b]	**C**	K_2CO_3	DMSO	91

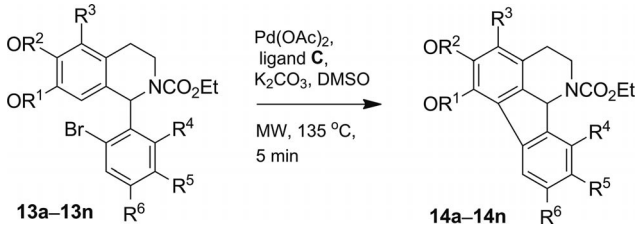
[a] Isolated yields. Reactions run on a 0.1 mmol scale. [b] Under thermal conditions the yield of this combination was 82% after 24 h.

Ligand **A** was ineffective in achieving a high-yielding cyclization reaction irrespective of the solvent or base tried (Table 1, Entries 1, 4 and 7). In the case of the ligand, the best yield (41%; Table 1, Entry 8) was obtained using K_2CO_3 as base and dimethyl sulfoxide (DMSO) as solvent.

Cs_2CO_3 performed poorer than K_2CO_3 with either ligand **A** or **B** with DMSO as solvent (Table 1, Entries 4 and 5). Generally, the combination of K_2CO_3/DMSO gave higher yields than other base/solvent combinations used with a particular ligand (e.g. Table 1, Entries 2 and 8 relative to Table 1, Entries 3 and 9). Yields tended to be higher with ligand **C** relative to the other ligands (Table 1, Entries 3, 6 and 9). The highest yield (91%) was obtained with a ligand **C**/K_2CO_3/DMSO combination.

Having optimized the direct arylation reaction on **11**, we next turned our attention to examining the scope of the reaction with other substrates (**13a**–**13n**, Table 2). These substrates were prepared in a manner similar to that depicted in Scheme 1 (yields ranged from 70%–95%). As shown in Table 2, high yields were obtained consistently with a variety of aryl-ring substitution patterns, highlighting the utility of the method in producing the indeno[1,2,3-*ij*]isoquinoline core as a precursor to azafluoranthene natural products.

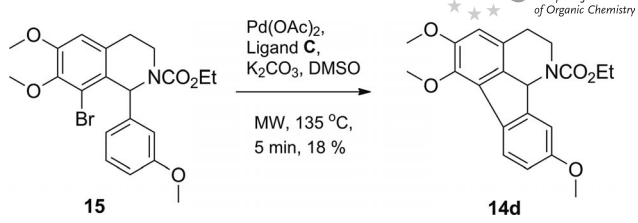
Table 2. Direct arylation with other substrates.



	R^1	R^2	R^3	R^4	R^5	R^6	Yield [%]
14a	Me	Me	H	H	OMe	OMe	89
14b	Me	Me	H	H	F	H	86
14c	Me	Me	H	H	OH	H	81
14d	Me	Me	H	H	OMe	H	83
14e	Me	Me	H	H	H	H	82
14f	Me	H	H	H	F	H	77
14g	Me	H	H	H	OMe	H	82
14h	Me	H	H	H	H	H	81
14i	H	Me	H	H	F	H	76
14j	H	Me	H	H	O	OCH_2	81
14k	H	Me	H	H	OMe	H	77
14l	H	Me	H	H	OMe	OMe	79
14m	Me	Me	OMe	OMe	OMe	H	93
14n	Me	Me	OMe	H	OMe	H	91

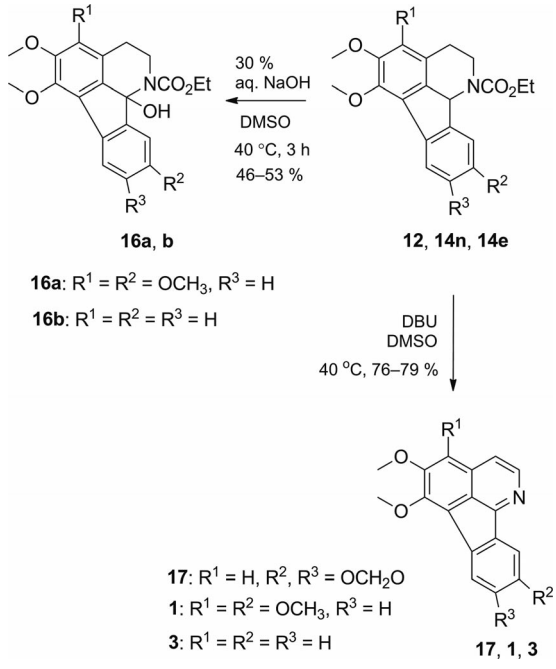
In continued explorations of the direct arylation reaction, coupling of substrate **15** (in which the aryl bromide partner is the incipient ring A of the azafluoranthene nucleus) was attempted. The impetus for inverting the arylation partners in this way was based on the ready availability of several benzaldehydes and heteroaromatic aldehydes (as inputs for the Pictet–Spengler reaction) for later library diversification. We found that this direct arylation reaction proceeded to give **14d** but in poor yield (Scheme 2). This result was unexpected in light of current understanding of the mechanism of direct arylation.

Fagnou and others have provided evidence for a concerted metalation-deprotonation (CMD) pathway in direct arylation reactions with simple or electron deficient aromatics.[30] In this context, electron-deficient aromatic rings (as the non-halide containing coupling partner) react more easily than electron-rich ones.[30b] The acidity of the C–H bond in the unactivated ring is important; the more acidic this proton the more facile is deprotonation and the CMD pathway overall. On the basis of these considerations, we would expect that inversion of the coupling partners as in Scheme 2 should result in a more facile coupling. Because this was not the case, it appears that inversion of partners in this intramolecular framework alters the mechanistic pathway in some way. In the absence of detailed mechanistic studies, we postulate that metalation of substrate **15** is less favorable for steric reasons (the halide is *ortho* to two substituents) and combined with reduced C–H acidity in the arene ring, negatively impacts the CMD process. No attempts were made to optimize this reaction.



Scheme 2. Alternative coupling approach.

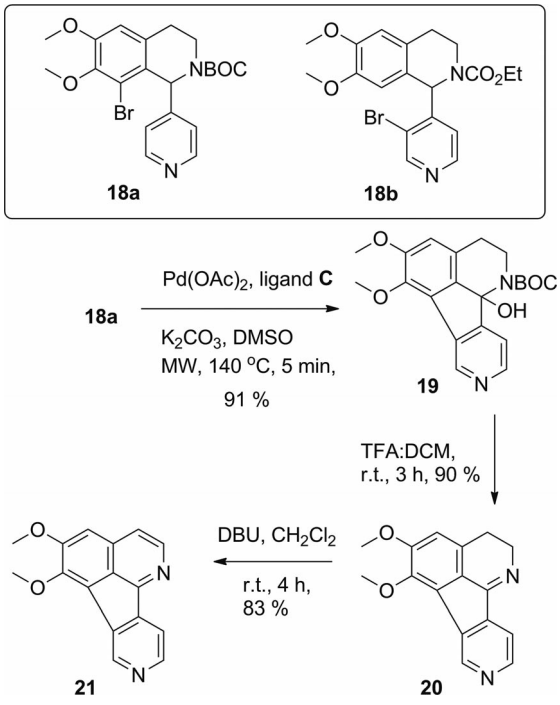
We then turned our attention to the transformation of the cyclized products **12** and **14** to azafluoranthenes. For this task, we focused on synthesis of **17** (Scheme 3) as well as the natural products rufescine (**1**) and triclisine (**3**). Our initial plan was to deprotect the *N*-ethyl carbamate group and then oxidize the resulting tetrahydroisoquinoline moiety to an isoquinoline.



Scheme 3. Synthesis of nantenine analog **17**, rufescine (**1**) and triclisine (**3**).

However, when deprotection of substrates **14n** and **14e** was attempted with aqueous NaOH/DMSO, hydroxylated products **16a** and **16b** were obtained, respectively. After some experimentation, we found that deprotection of the carbamate and oxidation to the isoquinoline moiety could be effected in a single pot by heating the compounds with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in an atmosphere of dry oxygen.[31] Mechanistically, this latter reaction involves removal of a benzylic proton, elimination of the carbamate group and oxidation of the dihydroisoquinoline thus formed. We are uncertain of the mechanism of the benzylic hydroxylation in the formation of **16a** and **16b**; our observations are however consistent with a requirement for oxygen and water for benzylic hydroxylation. A similar benzylic hydroxylation in the synthesis of 5,6,8,12b-tetrahydroisoindolo[1,2-*a*]isoquinolin-8-ones has been reported.[32] Here, formation of a benzylic carbanion under strongly-basic conditions (0.5 M KOH/MeOH, air, reflux temperatures) is thought to precede the formation of a doubly-benzylic radical species through reaction of the carbanion with molecular oxygen.[32] It is possible that this mechanism operates in this case. Interestingly, when **16a** or **16b** was heated with DBU/DMSO no reaction occurred, highlighting the fact that **16a** and **16b** are not formed as intermediates in the oxidation of **14n** and **14e** with DBU/DMSO to **1** and **3**, respectively.

To further examine the utility of this method to construct new azafluoranthene-like isoquinoline-containing heterocycles, we decided to prepare compound **21**. Thus, compounds **18a** and **18b** were prepared using standard methods (see Exp. Section) and subjected to the optimized microwave-assisted arylation reaction conditions (Scheme 4). Although inversion of the arylation partners did not give a high yield of biaryl-coupled product in the synthesis of **14d** (Scheme 2), in the case of **18a**, compound **19** was obtained in 91% yield. (In this case, the increased C–H acidity of the pyridyl moiety relative to the C–H acidity of the anisole moiety of **15**, probably compensates for the increased steric demand in metalation). As observed, the biaryl cyclization reaction was accompanied by a benzylic hydroxylation reaction. Although moisture and air were rigorously excluded from this reaction, the un-hydroxylated cyclized product was not isolated. Presumably, the pyridine moiety increases the propensity for benzylic oxidation of the initially-formed cyclized product. This oxidation seems to occur very rapidly, probably during the work-up procedure. [We also observed similar benzylic hydroxylation of **14a**–**14n** but this was considerably slower; samples of **14a**–**14n** were 20–50% hydroxylated as estimated by thin-layer chromatography (TLC), after exposure to air for 24 h.] All attempts to achieve biaryl cyclization with substrate **18b** using our typical conditions were unsuccessful. The starting material was consumed but cyclized product could not be identified from the complex mixture produced.



Scheme 4. Synthesis of azafluoranthene-like alkaloid **21**.

Compound **19** was transformed to dihydroisoquinoline **20** by treatment with trifluoroacetic acid (TFA). New isoquinoline **21** was prepared by oxidation of **20** in the presence of DBU.

Conclusions

Microwave-assisted direct arylation reactions are a powerful method for assembly of the indeno[1,2,3-*ij*]isoquinoline nucleus of azafluoranthene alkaloids. The arylation reaction under microwave conditions is rapid and is tolerant of a wide variety of substitution patterns in the aryl rings. Azafluoranthenes are easily accessed in three high-yielding steps (Pictet–Spengler reaction, microwave-assisted direct arylation and deprotection/oxidation reactions) from readily available starting materials. This straightforward route offers considerable advantages over existing ones in terms of overall yields, efficiency and accessibility to compound diversity. Further work is continuing on the applicability of the method to other new azafluoranthene-like isoquinoline scaffolds and assessment of the cytotoxicity and CNS receptor activity of these molecules. Our findings will be reported in due course.

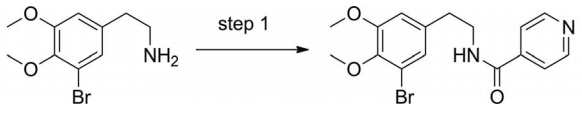
Experimental Section

General: All moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere. Dry DMSO and all other reagents were purchased at the highest commercial quality from Aldrich and Fisher Scientific USA and used without further purification, unless otherwise stated. A CEM Discover microwave reactor was used to carry out all direct arylation reactions. HRMS ESI spectra were obtained by using an Agilent 6520 QTOF instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DPX-500 spectrometer (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C) using $CDCl_3$ as solvent unless stated otherwise. ^{19}F NMR spectra were recorded with a

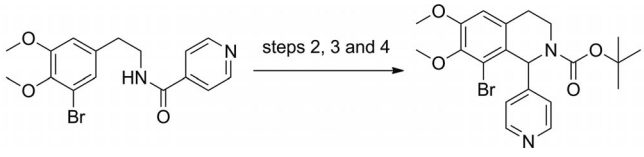
JEOL GX-400 NMR spectrometer operating at 376 MHz. Tetramethylsilane (δ = 0.00 ppm) served as an internal standard for the ^{1}H NMR spectra and $CDCl_3$ (δ = 77.0 ppm) for the ^{13}C NMR spectra unless stated otherwise. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). Reactions were monitored by using TLC with Whatman Flexible TLC silica gel G/UV 254 precoated plates (0.25 mm). TLC plates were visualized by UV (254 nm) and by staining in an iodine chamber. Flash column chromatography was performed with silica gel 60 (EMD Chemicals, 230–400 mesh, 0.063 mm particle size).

Synthesis of Compound 11. Procedure for Acyl Pictet–Spengler Reaction: At 5 °C, concentrated sulfuric acid (0.5 mL) was added dropwise to a solution of carbamate **9**, (0.253 g, 1 mmol) and aldehyde **10** (0.229 g, 1 mmol) in acetic acid (5 mL). After stirring at room temperature for 2 h, the reaction mixture was poured onto crushed ice/water and extracted with dichloromethane (10 mL). The organic layer was washed sequentially with water (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with gradient elution in 10%–30% ethyl acetate/hexanes mixtures to yield **11** (0.360 g, 78%). Compounds **13a**–**13n**, **15** and **18b** were prepared in a similar manner. Compound **18a** was prepared by using a Bischler–Napieralki reaction as described below.

Synthesis of Compound 18a



Step 1: A solution of isonicotinic acid (0.147 g, 1.2 mmol) and 1,10-carbonyldiimidazole (0.194 g, 1.2 mmol) in anhydrous tetrahydrofuran (10 mL) was stirred at 0 °C for 1.5 h and then at room temperature for 1 h. The mixture was cooled in an ice-bath and stirred for 1 h. Then 2-(3-bromo-4,5-dimethoxyphenyl)ethanamine (0.260 g,1 mmol) was added and the solution was stirred at 0 °C for 4 h and left stirring overnight at room temperature. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL) and washed with water (20 mL), saturated $NaHCO_3$ solution (10 mL), and water (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. This gave the crude product as a pale yellow gummy liquid (0.248 g, 68%).



Steps 2–4: To a mixture of the amide above (0.182 g, 0.5 mmol) and P_2O_5 (1 g) in toluene (5 mL) was added $POCl_3$ and the resulting mixture was heated to reflux for 3 h. The solvent was evaporated under reduced pressure. The resulting solid was dissolved in water and carefully basified with solid $NaHCO_3$. Once the liberation of CO_2 had ceased, the aqueous layer was extracted with dichloromethane (10 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure and was used in the next step without further purification.

To a magnetically stirred ice-cooled solution of the crude imine from the previous reaction in a mixture of dry MeOH (10 mL), was added $NaBH_4$ (0.174 g, 0.5 mmol) in three portions over 10 min. The reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with water and extracted with dichloromethane (5 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude amine product was used in the next step without further purification.

To a solution of crude amine (0.174 g, 0.5 mmol) dissolved in dry dichloromethane (5 mL) was added diisopropylamine (0.101 g, 1 mmol), 4-dimethylaminopyridine (0.06 g, 0.05 mmol), and *tert*-butyl carbamate (0.087 g, 0.75 mmol) at room temperature. The reaction mixture was stirred at the same temperature for 24 h, quenched with water (10 mL), and extracted with dichloromethane (10 mL). The organic layer was washed with water (10 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting crude product, after column chromatography over silica gel (EtOAc/Hexanes, 20:80), gave compound **18a** (80 mg, 35.7%).

Compound 11: Yield 0.036 g (78%), white solid. R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4). M.p. 117–119 °C. ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 6.5 Hz, 3 H), 2.75 (m, 1 H), 2.96 (m, 1 H), 3.37 (m, 1 H), 3.75 (s, 3 H), 3.86 (s, 3 H), 4.16 (m, 3 H), 5.92 (s, 1 H), 5.93 (s, 1 H), 6.36 (br. s, 1 H), 6.49 (br. s, 1 H), 6.51 (s, 1 H), 6.65 (s, 1 H), 7.05 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.3, 39.4, 55.9 (×2), 57.2, 61.6, 101.8, 109.2, 110.4, 111.3 (×2), 112.8 (×2), 114.4, 126.6, 127.2, 147.4, 147.7, 148.0, 155.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{23}BrNO_6$ $[M + H]^+$ 464.0703; found 464.0700.

Compound 13a: Yield 0.036 g (76%), colorless oil. R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, J = 6.5 Hz, 3 H), 2.79 (m, 1 H), 2.98 (m, 1 H), 3.40 (m, 1 H), 3.69 (s, 3 H), 3.75 (s, 3 H), 3.89 (s, 6 H), 4.16 (q, J = 6.5 Hz, 2 H), 4.27 (m, 1 H), 6.37 (br. s, 1 H), 6.53 (br. s, 1 H), 6.55 (s, 1 H), 6.67 (s, 1 H), 7.08 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.4, 39.6, 55.87, 55.90, 55.95, 56.1, 57.1, 61.6, 110.5, 111.2, 112.0, 114.3, 115.5, 126.6, 127.4, 135.4, 147.7, 147.9, 148.4, 148.7, 156.0 ppm. HRMS (ESI): calcd. for $C_{22}H_{27}BrNO_6$ $[M + H]^+$ 480.0944; found 480.0938.

Compound 13b: Yield 0.030 g (68%), white solid. R_f = 0.68 (silica gel, hexanes/EtOAc, 6:4). M.p. 126–128 °C. ^{1}H NMR ($CDCl_3$): δ = 1.23 (m, 3 H), 2.82 (m, 1 H), 2.97 (m, 1 H), 3.42 (m, 1 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 4.16 (m, 3 H), 6.41 (br. s, 1 H), 6.55 (s, 1 H), 6.67 (s, 1 H), 6.77 (br. s, 1 H), 6.86 (dd, J = 8.0, 13.7 Hz, 1 H), 7.59 (dd, J = 5.5, 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.4, 39.6, 55.9 (×2), 57.3, 61.7, 110.3, 111.4 (×2), 116.0, 116.2, 126.5, 126.7, 134.2, 147.8, 148.2, 155.9, 161.1, 163.1 ppm. ^{19}F NMR ($CDCl_3$): δ = –114.5 (d, J = 375 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{22}BrFNO_4$ $[M + H]^+$ 438.0638; found 438.0636.

Compound 13c: Yield 0.029 g (67%), colorless oil. R_f = 0.37 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.17 (m, 3 H), 2.03, (br. s, 1 H), 2.72 (m, 1 H), 2.91 (m, 1 H), 3.38 (m, 1 H), 3.71 (s, 3 H), 3.82 (s, 3 H), 4.08 (m, 4 H), 6.31 (s, 1 H), 6.59 (m, 3 H), 7.39 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 28.2, 39.6, 55.8 (×2), 57.3, 61.9, 110.4, 111.2 (×2), 113.4 (×2), 116.5, 126.5, 127.0, 133.7, 144.9, 147.6, 147.9, 156.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_5$ $[M + H]^+$ 436.0681; found 436.0679.

Compound 13d: Yield 0.032 g (72%), colorless oil. R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.23 (m, 3 H), 2.80 (m, 1 H), 2.95 (m, 1 H), 3.43 (m, 1 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 3.89 (s, 3 H), 4.15 (m, 4 H), 6.39 (br. s, 1 H), 6.68 (m, 4 H), 7.52 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 28.3, 39.3, 55.4, 55.86, 55.90, 57.3, 61.6, 110.4, 111.25, 111.28 (×2), 113.7, 126.6, 127.1, 133.6, 147.8, 148.00, 148.02, 156.1, 159.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{25}BrNO_5$ $[M + H]^+$ 450.0838; found 450.0834.

Compound 13e: Yield 0.031 g (73.5%), colorless oil. R_f = 0.60 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.23 (m, 3 H), 2.79 (m, 1 H), 2.98 (m, 1 H), 3.40 (m, 1 H), 3.74 (s, 3 H), 3.89 (s, 3 H), 4.16 (m, 3 H), 6.49 (br. s, 1 H), 6.55 (s, 1 H), 6.67 (s, 1 H), 7.05 (br. s, 1 H), 7.12 (m, 1 H), 7.19 (m, 1 H), 7.63 (d, J = 7.9 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.2, 39.3, 55.9 (×2), 57.3, 61.6, 110.5, 111.3 (×2), 126.7, 127.2, 127.6, 128.8, 130.0, 133.1, 147.7, 148.03, 148.04, 155.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_4$ [M + H]$^+$ 420.0732; found 420.0728.

Compound 13f: Yield 0.028 g (67%), white solid. R_f = 0.40 (silica gel, hexanes/EtOAc, 6:4). M.p. 129–131 °C. ^{1}H NMR ($CDCl_3$): δ = 1.30 (m, 3 H), 2.80 (m, 1 H), 2.94 (m, 1 H), 3.41 (m, 1 H), 3.77 (s, 3 H), 4.14 (m, 3 H), 5.68 (s, 1 H), 6.49 (br. s, 1 H), 6.54 (s, 1 H), 6.77 (m, 2 H), 6.87 (m, 1 H), 7.60 (dd, J = 5.5, 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 39.5, 55.9, 57.4, 61.7, 109.7, 114.5, 115.9, 116.1, 117.2, 117.9, 125.9, 127.4, 134.2, 144.9, 145.5, 155.9, 161.9 ppm. ^{19}F NMR ($CDCl_3$): δ = –113.5 (d, J = 360 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{20}BrFNO_4$ [M + H]$^+$ 420.0481; found 420.0477.

Compound 13g: Yield 0.030 g (68%), white solid. R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). M.p. 105–107 °C. ^{1}H NMR ($CDCl_3$): δ = 1.22 (m, 3 H), 2.77 (m, 1 H), 2.93 (m, 1 H), 3.42 (m, 1 H), 3.71 (s, 3 H), 3.77 (s, 3 H), 4.15 (m, 3 H), 5.56 (m, 1 H), 6.39 (br. s, 1 H), 6.56 (s, 1 H), 6.61 (br. s, 1 H), 6.69 (dd, J = 3.5, 8.5 Hz, 1 H), 6.74 (s, 1 H), 7.51 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 39.4, 55.3, 55.9, 57.5, 61.6, 109.9, 113.8, 114.3 (×2), 115.7, 126.5 (×2), 127.4 (×2), 133.5, 143.8, 145.4, 155.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_5$ [M + H]$^+$ 436.0681; found 436.0679.

Compound 13h: Yield 0.028 g (70%), colorless oil. R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.20 (m, 3 H), 2.71 (m, 1 H), 2.90 (m, 1 H), 3.34 (m, 1 H), 3.71 (s, 3 H), 4.14 (m, 3 H), 5.70 (s, 1 H), 6.43 (br. s, 1 H), 6.50 (s, 1 H), 6.72 (s, 1 H), 7.02 (br. s, 1 H), 7.09 (m, 1 H), 7.17 (m, 1 H), 7.60 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.0, 38.4, 55.9, 57.4, 61.6, 109.9, 114.3 (×2), 124.2, 126.7, 127.5, 128.7, 129.8, 130.8, 133.1, 144.6, 145.4, 155.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{21}BrNO_4$ [M + H]$^+$ 408.0630; found 408.0630.

Compound 13i: Yield 0.026 g (62%), colorless oil. R_f = 0.40 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.21 (m, 3 H), 2.82 (m, 1 H), 2.95 (m, 1 H), 3.42 (dd, J = 10.5, 10.5 Hz, 1 H), 3.89 (s, 3 H), 4.14 (m, 3 H), 5.57 (s, 1 H), 6.36 (br. s, 1 H), 6.58 (s, 1 H), 6.66 (s, 1 H), 6.76 (br. s, 1 H), 6.84 (m, 1 H), 7.56 (dd, J = 5.5, 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.6, 39.8, 55.9, 57.2, 61.8, 110.5, 113.5, 115.9, 116.1, 126.3, 127.5, 134.3, 144.0, 146.14, 146.14, 156.3, 160.9, 163.2 ppm. ^{19}F NMR ($CDCl_3$): δ = –114.2 (d, J = 250 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{20}BrFNO_4$ [M + H]$^+$ 424.0553; found 424.0553.

Compound 13j: Yield 0.032 g (70%), white solid. R_f = 0.36 (silica gel, hexanes/EtOAc, 6:4). M.p. 161–163 °C. ^{1}H NMR ($CDCl_3$): δ = 1.24 (m, 3 H), 2.77 (m, 1 H), 2.94 (m, 1 H), 3.39 (m, 1 H), 3.89 (s, 3 H), 4.15 (m, 3 H), 5.48 (s, 1 H), 5.94 (m, 2 H), 6.33 (br. s, 1 H), 6.55 (m, 2 H), 6.64 (s, 1 H), 7.05 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 28.6, 39.7, 55.9, 57.1, 61.7, 101.8 (×2), 109.2, 110.7 (×2), 112.6, 113.6, 114.5, 126.0, 136.2, 144.3, 145.8, 147.4, 155.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{21}BrNO_6$ [M + H]$^+$ 452.0529; found 452.0527.

Compound 13k: Yield 0.032 g (73%), colorless oil. R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3 H), 2.75 (m, 1 H), 2.92 (m, 1 H), 3.40 (m, 1 H), 3.66 (s, 3 H), 3.85 (s, 3 H), 4.11 (m, 3 H), 5.70 (br. s, 1 H), 6.33 (br. s, 1 H), 6.65 (m, 4 H), 7.46 (d, J = 9.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.6, 39.8, 55.3, 55.9, 57.2, 61.7, 110.7, 111.3, 113.7, 114.9, 115.1, 121.4, 126.0, 127.9, 133.6, 144.3, 145.7, 156.0, 158.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_5$ [M + H]$^+$ 436.0681; found 436.0676.

Compound 13l: Yield 0.034 g (73%), colorless oil. R_f = 0.35 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.20 (m, 3 H), 2.25 (s, 1 H), 2.76 (m, 1 H), 2.96 (m, 1 H), 3.39 (m, 1 H), 3.67 (s, 3 H), 3.86 (s, 6 H), 4.14 (q, J = 6.5 Hz, 2 H), 4.28 (br. s, 1 H), 6.29 (br. s, 1 H), 6.55 (s, 1 H), 6.56 (s, 1 H), 6.63 (s, 1 H), 7.03 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 28.8, 39.9, 55.90, 55.95, 56.1, 57.0, 61.6, 110.5 (×2), 112.2, 113.6, 114.6, 115.4, 125.9, 128.1, 144.3, 145.6, 148.5, 148.6, 155.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{25}BrNO_6$ [M + H]$^+$ 466.0787; found 466.0785.

Compound 13m: Yield 0.042 g (82%), colorless oil. R_f = 0.62 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.13 (m, 3 H), 2.62 (m, 1 H), 3.08 (m, 1 H), 3.34 (s, 3 H), 3.51 (m, 1 H), 3.62 (s, 3 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 4.07 (m, 2 H), 4.38 (br. s, 1 H), 6.14 (s, 1 H), 6.33 (br. s, 1 H), 6.75 (d, J = 8.5 Hz, 1 H), 7.34 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 23.3, 39.9, 55.8, 55.9, 57.1, 59.6, 60.90, 60.94, 61.3, 105.7, 112.7, 116.8, 121.3, 127.6, 130.9, 136.8, 140.7, 148.4, 150.6, 151.6, 152.9, 156.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{29}BrNO_7$ [M + H]$^+$ 510.1049; found 510.1048.

Compound 13n: Yield 0.038 g (80%), white solid. R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). M.p. 78–80 °C. ^{1}H NMR ($CDCl_3$): δ = 1.23 (m, 3 H), 2.81 (m, 2 H), 3.35 (m, 1 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 4.16 (m, 3 H), 6.41 (br. s, 2 H), 6.59 (br. s, 1 H), 6.70 (dd, J = 3.0, 8.5 Hz, 1 H), 7.53 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 22.4, 39.2, 55.4, 55.9, 57.4, 60.7, 60.8, 61.6, 106.5, 113.6, 114.8, 115.9, 116.2, 121.1, 130.6, 133.6, 140.9, 150.9, 152.0, 155.9, 158.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{27}BrNO_6$ [M + H]$^+$: 480.0944; found 480.0939.

Compound 15: 1:1 Mixture of rotamers (signals for one rotamer reported). Yield 0.037 g (83%), colorless oil. R_f = 0.7 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.29 (m, 3 H), 2.69 (m, 1 H), 2.96 (m, 1 H), 3.13 (m, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 3.90 (s, 3 H), 4.30 (m, 2 H), 4.38 (m, 1 H), 6.51 (s, 1 H), 6.76 (m, 4 H), 7.20 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 28.2, 55.1, 56.1, 57.2, 57.4, 60.6, 61.7, 111.6, 112.3, 114.4, 119.5, 120.6, 127.5, 129.1, 132.5, 142.3, 145.0, 152.3, 155.0, 159.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{25}BrNO_5$ [M + H]$^+$: 450.0838; found 450.0835.

Compound 18a: Mixture of rotamers (signals for one rotamer reported). Yield 0.080 g (35.7%), colorless oil. R_f = 0.2 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.55 (m, 9 H), 2.64 (m, 1 H), 2.93 (m, 1 H), 3.05 (m, 1 H), 3.83 (m, 1 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 6.63 (s, 1 H), 6.74 (m, 1 H), 7.06 (m, 2 H), 8.51 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.4, 37.3, 38.4, 55.8, 56.1, 60.6, 76.8, 77.1, 80.5, 112.0, 119.0, 119.5, 122.7, 126.5, 126.6, 132.8, 145.3, 149.8, 150.1, 152.8, 154.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{26}BrN_2O_4$ [M + H]$^+$ 449.0998; found 449.0996.

Compound 18b: Yield 0.034 g (82%), colorless oil. R_f = 0.2 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.18 (m, 3 H), 2.93 (m, 2 H), 3.46 (m, 1 H), 3.73 (s, 3 H), 3.86 (s, 3 H), 4.12 (m, 3 H), 6.36 (br. s, 1 H), 6.55 (d, J = 4.5 Hz, 1 H), 6.66 (d, J = 4.5 Hz, 1 H), 7.03 (br. s, 1 H), 8.37 (s, 1 H), 8.75 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.5, 28.3, 40.0, 55.9, 56.7, 61.9, 109.9, 111.44, 122.3, 125.4, 126.7, 148.2, 149.1, 153.4, 156.5 ppm. HRMS (ESI): calcd. for $C_{19}H_{22}BrN_2O_4$ [M + H]$^+$ 421.0685; found 421.0687.

Synthesis of Compound 12. Procedure for Microwave-Assisted Direct Arylation Reaction: In a microwave reaction vial, dihydroisoquin-

oline **11** (0.046 g, 0.1 mmol), $Pd(OAc)_2$ (0.0044 g, 0.02 mmol), ligand **C** (0.0099 g, 0.04 mmol) and K_2CO_3 (0.0276 g, 0.2 mmol) were added and dissolved in Ar-purged anhydrous, degassed DMSO (0.5 mL). The mixture was irradiated in a CEM Discover microwave reactor for 5 min at 135 °C with the power level at 300 W. After cooling to room temperature, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (5 mL). The solvents were evaporated under reduced pressure and the crude product was purified by flash column chromatography (10–20% EtOAc/hexanes) to give cyclized product **12**. Compounds **14a**–**14n**, **16a**, **16b** and **19** were obtained in a similar manner.

Compound 12: Yield 0.034 g (91%), colorless oil. R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.42 (t, J = 7.0 Hz, 3 H), 2.66 (m, 2 H), 2.88 (m, 1 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.38 (m, 2 H), 4.51 (m, 1 H), 5.46 (s, 1 H), 6.02 (d, J = 1.2 Hz, 1 H), 6.03 (d, J = 1.2 Hz, 1 H), 6.61 (s, 1 H), 7.51 (s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.9, 29.8, 44.8, 56.5, 58.5, 60.7, 62.0, 101.3, 104.3, 108.0, 108.6 (×2), 131.3, 132.8, 133.7, 142.1, 142.7, 146.9, 147.6, 153.3, 158.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}NO_6$ [M + H]$^+$ 384.1369; found 384.1365.

Compound 14a: Yield 0.0356 g (89%), colorless oil. R_f = 0.67 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 6.5 Hz, 3 H), 2.67 (m, 2 H), 2.90 (m, 1 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 4.00 (s, 6 H), 4.38 (m, 2 H), 4.52 (m, 1 H), 5.50 (s, 1 H), 6.62 (s, 1 H), 7.58 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.9, 29.9, 44.8, 56.1, 56.2, 56.4, 58.7, 60.6, 61.9, 106.6, 108.8 (×2), 110.3, 131.4, 131.6, 133.7, 140.7, 142.7, 148.3, 149.2, 153.3, 157.9 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_6$ [M + H]$^+$ 400.1755; found 400.1753.

Compound 14b: Yield 0.031 g (86%), colorless oil. R_f = 0.7 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 6.7 Hz, 3 H), 2.69 (m, 2 H), 2.89 (m, 1 H), 3.94 (s, 3 H), 3.99 (s, 3 H), 4.39 (t, J = 6.7 Hz, 2 H), 4.52 (m, 1 H), 5.53 (s, 1 H), 6.67 (s, 1 H), 7.09 (m, 1 H), 7.71 (br. s, 1 H), 7.96 (dd, J = 5.5, 8.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 29.8, 44.6, 56.4, 58.69, 58.71, 60.6, 62.1, 109.4, 114.9, 115.1, 124.4, 131.5, 133.5, 134.9, 143.2, 150.0, 153.4, 157.9, 162.0 ppm. ^{19}F NMR ($CDCl_3$): δ = –114.1 (d, J = 375 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{21}FNO_4$ [M + H]$^+$ 358.1449; found 358.1450.

Compound 14c: Yield 0.029 g (81%), colorless oil. R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, J = 7.0 Hz, 3 H), 1.70 (br. s. 1 H), 2.67 (m, 2 H), 2.89 (m, 1 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 4.49 (m, 1 H), 5.56 (s, 1 H), 6.61 (s, 1 H), 6.90 (dd, J = 2.0, 8.0 Hz, 1 H), 7.65 (br. s, 1 H), 7.86 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 29.9, 44.7, 56.4, 58.8, 60.6, 62.2, 108.5, 114.4, 115.1, 124.51, 131.2, 131.3, 131.6, 133.1, 142.8, 149.7, 153.4, 155.7, 158.5 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ [M + H]$^+$ 356.1492; found 356.1491.

Compound 14d: Yield 0.031 g (83%), colorless oil. R_f = 0.66 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.41 (t, J = 7.2 Hz, 3 H), 2.64 (m, 2 H), 2.86 (m, 1 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 3.96 (s, 3 H), 4.36 (q, J = 7.2 Hz, 2 H), 4.52 (m, 1 H), 5.53 (s, 1 H), 6.59 (s, 1 H), 6.92 (dd, J = 2.4, 8.4 Hz, 1 H), 7.53 (br. s, 1 H), 7.89 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.9, 44.7, 55.5, 56.4, 58.9, 60.6, 61.9, 108.6, 112.4, 113.9 (×2), 124.2, 131.4, 131.6, 133.3, 142.8, 149.7, 153.3, 157.9, 159.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_5$ [M + H]$^+$ 370.1649; found 370.1652.

Compound 14e: Yield 0.028 g (82%), colorless oil. R_f = 0.61 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3 H), 2.68 (m, 2 H), 2.89 (m, 1 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.40 (q, J = 7.1 Hz, 2 H), 4.55 (m, 1 H), 5.60 (s, 1 H), 6.69 (s, 1 H), 7.30 (dd, J = 7.6, 7.6 Hz, 1 H), 7.41 (m, 1 H), 7.97 (s, 1 H), 8.05 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.9, 44.7, 56.5, 58.9, 60.6, 61.9, 109.8, 123.7, 126.4, 126.9, 128.2 (×2), 131.5, 133.8, 138.9, 143.7, 147.7, 153.3, 157.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_4$ [M + H]$^+$ 340.1543; found 340.1549.

Compound 14f: Yield 0.026 g (77%), colorless oil. R_f = 0.41 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 2.67 (m, 2 H), 2.89 (m, 1 H), 4.00 (s, 3 H), 4.39 (m, 2 H), 4.52 (m, 1 H), 5.55 (s, 1 H), 5.78 (s, 1 H), 6.74 (s, 1 H), 7.12 (m, 1 H), 7.79 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.7, 44.6, 58.8, 61.5, 62.1, 112.2, 114.4, 114.9, 115.2, 123.8, 132.7, 133.5, 134.2, 141.0, 149.7, 150.7, 157.8, 162.1 ppm. ^{19}F NMR ($CDCl_3$): δ = –114.4 (d, J = 360 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{19}FNO_4$ [M + H]$^+$ 344.1220; found 344.1217.

Compound 14g: Yield 0.029 (82%), colorless oil. R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 2.66 (m, 2 H), 2.87 (m, 1 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 4.38 (q, J = 7.0 Hz, 2 H), 4.52 (m, 1 H), 5.56 (s, 1 H), 5.78 (br. s, 1 H), 6.68 (s, 1 H), 6.97 (dd, J = 1.5, 8.5 Hz, 1 H), 7.60 (br. s, 1 H), 7.75 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.8, 44.7, 55.6, 59.0, 61.4, 61.9, 111.3, 112.7, 113.9, 123.7, 130.9, 132.5, 133.2, 140.5, 149.4, 150.0, 158.0, 159.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ [M + H]$^+$ 356.1492; found 356.1497.

Compound 14h: Yield 0.026 g (81%), colorless oil. R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 2.67 (m, 2 H), 2.89 (m, 1 H), 4.02 (s, 3 H), 4.39 (t, J = 7.0 Hz, 2 H), 4.54 (m, 1 H), 5.59 (s, 1 H), 5.79 (s, 1 H), 6.75 (s, 1 H), 7.31 (m, 2 H), 7.43 (dd, J = 7.5, 7.5 Hz, 1 H), 7.87 (d, J = 7.5 Hz, 1 H), 7.98 (br. s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.8, 44.7, 59.1, 61.6, 61.9, 112.6, 123.2, 126.5, 127.1, 128.4, 130.5, 132.7, 133.8, 138.3, 141.2, 148.1, 149.3, 157.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{20}NO_4$ [M + H]$^+$ 326.1314; found 326.1313.

Compound 14i: Yield 0.026 g (76%), colorless oil. R_f = 0.41 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.1 Hz, 3 H), 2.65 (m, 2 H), 2.86 (m, 1 H), 3.95 (s, 3 H), 4.40 (q, J = 7.1 Hz, 2 H), 4.53 (m, 1 H), 5.56 (s, 1 H), 5.99 (s, 1 H), 6.62 (s, 1 H), 7.08 (m, 1 H), 7.67 (br. s, 1 H), 7.96 (dd, J = 5.4, 8.2 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 29.6, 44.9, 56.7, 58.9, 61.9, 107.5, 114.7, 114.9, 124.5, 127.1, 133.8, 135.1, 139.9, 147.2, 149.5, 157.9, 160.8, 162.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{19}FNO_4$ [M + H]$^+$ 344.1220; found 344.1227.

Compound 14j: Yield 0.030 g (81%), colorless oil. R_f = 0.38 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.42 (m, 3 H), 2.64 (m, 2 H), 2.85 (m, 1 H), 3.94 (s, 3 H), 4.38 (m, 2 H), 4.52 (m, 1 H), 5.48 (s, 1 H), 5.92 (s, 1 H), 6.00 (s, 1 H), 6.02 (s, 1 H), 6.57 (s, 1 H), 7.53 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7, 29.6, 44.8, 56.6, 58.7 (×2), 61.9, 101.2 (×2), 104.5, 106.8, 126.9, 133.1, 134.1, 139.3, 141.5, 146.5, 147.1, 147.5, 157.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{20}NO_6$ [M + H]$^+$ 370.1285; found 370.1289.

Compound 14k: Yield 0.027 g (77%), colorless oil. R_f = 0.39 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.44 (t, J = 7.0 Hz, 3 H), 2.65 (m, 2 H), 2.85 (m, 1 H), 3.87 (s, 3 H), 3.94 (s, 3 H), 4.40 (q, J = 7.0 Hz, 2 H), 4.53 (m, 1 H), 5.58 (s, 1 H), 5.94 (s, 1 H), 6.57 (s, 1 H), 6.95 (dd, J = 2.0, 8.3 Hz, 1 H), 7.55 (br. s, 1 H), 7.92 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 29.7, 44.8, 55.5, 56.5, 59.0, 61.8, 106.8, 112.4, 113.6, 124.2, 126.9 (×2), 131.9, 133.6, 139.4, 147.1, 149.1, 157.9, 158.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ [M + H]$^+$ 356.1492; found 356.1491.

Compound 14l: Yield 0.030 g (79%), colorless oil. R_f = 0.36 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (m, 3 H),

2.65 (m, 2 H), 2.88 (m, 1 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 4.00 (s, 3 H), 4.41 (m, 2 H), 4.52 (m, 1 H), 5.51 (s, 1 H), 5.92 (s, 1 H), 6.57 (s, 1 H), 7.59 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.9, 29.8, 44.9, 56.07, 56.14, 56.7, 58.9, 61.9, 106.7 (×2), 110.4, 126.9, 131.9, 134.1, 139.3, 139.9, 147.2, 147.9, 149.1, 158.0 ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_6$ $[M + H]^+$ 386.1598; found 386.1597.

Compound 14m: Yield 0.040 g (93%), colorless oil. R_f = 0.61 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.10 (m, 3 H), 2.65 (m, 1 H), 2.90 (m, 1 H), 3.79 (m, 2 H), 3.89 (s, 6 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 3.98 (s, 3 H), 4.06 (m, 2 H), 5.40 (s, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 7.56 (d, J = 8.0 Hz,1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.3, 22.7, 45.5, 56.2, 60.5, 60.7, 60.8, 61.1, 61.2, 61.4, 76.8, 112.6, 118.1, 122.5, 126.2, 132.6, 137.7, 146.3, 146.6, 147.3, 150.3, 151.7, 157.1 ppm. HRMS (ESI): calcd. for $C_{23}H_{28}NO_7$ $[M + H]^+$ 430.1860; found 430.1861.

Compound 14n: Yield 0.036 g (91%), colorless oil. R_f = 0.62 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.43 (t, J = 7.0 Hz, 3 H), 2.63 (m, 2 H), 2.99 (m, 1 H), 3.87 (s, 3 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 4.03 (s, 3 H), 4.40 (q, J = 7.0 Hz, 2 H), 4.55 (m, 1 H), 5.53 (s, 1 H), 6.93 (dd, J = 2.5, 8.5 Hz, 1 H), 7.53 (br. s, 1 H), 7.83 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 24.6, 44.3, 55.6, 59.2, 60.9, 61.3, 61.8, 62.0, 112.2, 113.9, 123.5, 124.8, 126.8, 131.8, 136.6, 146.0, 147.5, 149.0, 149.2, 157.8, 158.6 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_6$ $[M + H]^+$ 400.1755; found 400.1757.

Compound 16a: Yield 0.019 g (46%), colorless oil. R_f = 0.46 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.15 (t, J = 7.5 Hz, 3 H), 3.20 (m, 2 H), 3.43 (m, 2 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 3.95 (s, 3 H), 3.98 (s, 3 H), 4.05 (m, 2 H), 5.03 (br. s, 1 H), 6.95 (dd, J = 2.5, 8.0 Hz, 1 H), 7.13 (d, J = 2.5 Hz, 1 H), 7.63 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.6, 24.5, 29.7, 41.6, 55.6, 60.4, 60.5, 60.8, 61.2, 109.1 (×2), 120.0, 124.1 (×2), 127.3, 131.3, 134.7, 136.4, 147.3, 152.2, 156.7, 160.1 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NO_7$ $[M + H]^+$ 416.1631; found 416.1632.

Compound 16b: Yield 0.019 g (53%), colorless oil. R_f = 0.46 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.21 (m, 3 H), 3.22 (m, 2 H), 3.50 (m, 2 H), 3.97 (s, 6 H), 4.11 (q, J = 7.1 Hz, 2 H), 6.56 (s, 1 H), 7.31 (m, 2 H), 7.50 (m, 1 H), 7.62 (d, J = 7.4 Hz, 1 H), 7.87 (d, J = 7.4 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.67, 31.6, 41.7, 56.2, 60.4, 60.7, 113.4, 123.6, 123.9, 124.6, 128.77, 134.5, 135.4, 137.9, 141.9, 143.7, 156.8, 158.7 ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1492; found 356.1491.

Compound 19: Yield 0.035 g (91%), colorless oil. R_f = 0.1 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 1.41 (s, 9 H), 3.23 (m, 2 H), 3.44 (m, 2 H), 3.98 (s, 3 H), 4.01 (s, 3 H), 4.77 (br. s, 1 H), 6.64 (s, 1 H), 7.48 (d, J = 4.5 Hz, 1 H), 8.70 (d, J = 4.5 Hz, 1 H), 9.16 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2, 32.1, 41.1, 56.0, 60.5, 114.5, 116.9, 124.1, 135.6, 139.6, 141.5, 143.9, 144.9, 151.5, 156.2, 159.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{25}N_2O_5$ $[M + H]^+$ 385.1758; found 385.1758.

Synthesis of Compound 17. Procedure for Deprotection and Oxidation to Azafluoranthenes: To a solution of azafluoranthene **12** (0.038 g, 0.1 mmol) in dry DMSO (1 mL) was added DBU (0.152 g, 1 mmol) under N_2 and the reaction mixture was purged with oxygen by using a balloon. The reaction mixture was stirred at 40 °C for 8 h. Water (5 mL) was added to the reaction mixture and extracted with dichloromethane (5 mL). The organic layer was washed sequentially with water (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (30% ethyl acetate/hexanes) to yield **17** (79%). Similar procedures were used to synthesize compounds **1** (76%) and **3** (77%).

Compound 17: Yield 0.030 g (79%), pale yellow oil. R_f = 0.3 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 3 H), 4.11 (s, 3 H), 6.10 (s, 2 H), 6.96 (s, 1 H), 7.37 (d, J = 6.0 Hz, 1 H), 7.53 (s, 1 H), 7.57 (s, 1 H), 8.55 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.3, 61.3, 101.7, 103.2, 104.1, 106.0, 116.5, 123.1, 126.1, 130.1, 133.0, 133.9, 145.4, 147. 0, 148.0, 149.1, 158.7, 159.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}NO_4$ $[M + H]^+$ 308.0917; found 308.0918.

Compound 1: Yield 0.025 g (76%), colorless oil. R_f = 0.32 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 3.96 (s, 3 H), 4.07 (s, 3 H), 4.13 (s, 3 H), 4.15 (s, 3 H), 6.99 (dd, J = 2.5, 8.5 Hz, 1 H), 7.66 (d, J = 6.0 Hz, 1 H), 7.70 (d, J = 2.5 Hz, 1 H), 7.85 (d, J = 8.5 Hz, 1 H), 8.62 (d, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.7, 61.45, 61.49, 62.1, 107.3, 113.8, 116.0, 122.2, 124.1, 124.6, 126.3, 131.1, 140.3, 144.6, 148.4, 149.9, 150.6, 159.0, 159.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}NO_4$ $[M + H]^+$ 324.1230; for 324.1231.

Compound 3: Yield 0.021 g (77%), colorless oil. R_f = 0.34 (silica gel, hexanes/EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 3 H), 4.12 (s, 3 H), 7.02 (s, 1 H), 7.45 (m, 3 H), 8.04 (m, 1 H), 8.10 (m, 1 H), 8.60 (dd, J = 5.0, 5.0 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.4, 61.4, 104.7, 117.1, 121.9, 123.3, 124.8, 126.6, 128.4, 129.8, 131.1, 138.2, 139.2, 145.7, 147.8, 159.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}NO_2$ $[M + H]^+$ 264.1019; found 264.1020.

Synthesis of Compound 20: Compound **19** (44 mg, 0.1 mmol), which was synthesized following the general procedure for direct arylation, was dissolved in dichloromethane: TFA (1:1, 1 mL) and stirred at room temperature for 3 h. The solvents were evaporated under reduced pressure and the residue dissolved in dichloromethane (5 mL). The dichloromethane layer was washed with 5% $NaHCO_3$ solution (5 mL), water (5 mL), brine (5 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give **20** (31 mg, 90%).

Compound 20: Yield 0.030 g (90%), colorless oil. R_f = 0.51 (silica gel, 100% EtOAc, 6:4). ^{1}H NMR ($CDCl_3$): δ = 2.83 (t, J = 8.5 Hz, 2 H), 3.93 (s, 3 H), 3.99 (s, 3 H), 4.27 (t, J = 8.5 Hz, 2 H), 6.62 (s, 1 H), 7.69 (d, J = 5.0 Hz, 1 H), 8.64 (d, J = 5.0 Hz, 1 H), 9.11 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.6, 50.8, 56.4, 60.8, 110.8, 116.6, 121.2, 128.4, 129.9, 136.3, 143.5, 144.33, 145.0, 149.7, 157.9, 165.0 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1128; found 267.1130.

Synthesis of Compound 21: Compound **20** (0.017 g, 0.05 mmol) was dissolved in dichloromethane (0.5 mL) and DBU (0.015 g, 0.1 mmol) was added to the reaction mixture at room temperature. The resulting dark brown solution was stirred at room temperature and open to the air for 4 h. Water (5 mL) was added to the reaction mixture and extracted with dichloromethane (5 mL). The dichloromethane layer was washed with water, brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (50% ethyl acetate/hexanes) to afford **21** (0.014 g, 83%).

Compound 21: Yield 0.014 g (83%), pale yellow oil. R_f = 0.52 (silica gel, 100% EtOAc). ^{1}H NMR ($CDCl_3$): δ = 4.09 (s, 3 H), 4.18 (s, 3 H), 7.10 (s, 1 H), 7.57 (d, J = 5.5 Hz, 1 H), 8.10 (dd, J = 1.0, 5.0 Hz, 1 H), 8.71 (d, J = 5.5 Hz, 1 H), 8.73 (d, J = 5.0 Hz, 1 H), 9.28 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 56.6, 61.7, 105.3, 116.4, 116.6, 118.8, 123.8, 124.2, 131.2, 132.8, 145.3, 146.2, 148.5, 149.8, 156.6, 159.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}N_2O_2$ $[M + H]^+$ 265.0977; found 265.0978.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

This publication was made possible by the National Institute of General Medical Sciences (NIGMS), a component of the National Institutes of Health (NIH), (grant number 1SC1GM092282). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or its divisions.

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Received: September 4, 2012
Published Online: January 3, 2013

