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Free radical reactions for heterocycle synthesis. Part 6: 2-Bromobenzoic acids as building blocks in the construction of nitrogen heterocycles

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Abstract—A general method to construct a variety of nitrogen heterocycles is introduced. 2-Bromobenzoic acids or acid chlorides are used as the common building blocks to couple with appropriate nitrogen-containing compounds. Sequential aryl radical cyclizations including conjugate additions, spirocyclizations, homolytic and *ipso* aromatic substitutions, and 1,5-hydrogen atom transfers are employed to prepare tri- and tetracyclic isoindolinones, benzolactams, isoquinolinones, azabenzoisocoumarins, and bridged-azabicyclic compounds.

1. Introduction

Nitrogen-containing heterocycles as recognized pharmacophores have received great attention in drug discovery and lead optimization.[1] In addition to traditional cycloadditions, cyclizations of nitrogen radicals or nitrogen-containing carbon radicals are the new approaches to *N*-heterocyclics.[2] Between these two radical reactions, the latter one is more general because carbon radicals are easy to generate and carbon–carbon bond formation by radical cyclization is a well-established process.[3] In our continuous effort on the development of free radical reactions,[4] we recently focused our attention on the synthesis of biologically interesting heterocyclic compounds.[5] Described in this paper is a general protocol of aryl radical cyclization to construct benzo-fused heterocycles including isoindolinones, spirolactams, isoquinolinones, azabenzoisocoumarins, and bridged-azabicyclics. Conjugate additions, spirocyclizations, homolytic and *ipso* aromatic substitutions, and 1,5-hydrogen atom transfer reactions are involved in the cyclization process. Readily available 2-bromobenzoic acids or acid chlorides are employed as the common starting materials in a two-step reaction sequence (Scheme 1).

Keywords: nitrogen heterocycles; pharmacophores; radical cyclization.

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2. Result and discussion

2.1. Synthesis of tri- and tetracyclic isoindolinones by intramolecular Michael addition

Many isoindolinone derivatives possess biological activities.[6] Formation of the carbon–nitrogen bond by lactamization is a general method to construct the isoindolinone ring system.[7] Formation of the carbon–carbon bond of the isoindolinone by palladium-catalyzed[8] and free radical[9] cyclizations is an alternative route. Using conjugate alkenes as radical acceptors,[10] we recently reported the synthesis of tricyclic isoindolinones by intramolecular free radical Michael addition of *N*-alkylated benzamides (Scheme 2).[5b] A straightforward 2-step synthesis has been established: *N*-acylation of a cyclic nitrogen compound **1** with a 2-bromobenzoyl chloride was followed by a tris(trimethylsilyl)silane-promoted radical cyclization. The initial radical **5** generated from **2** equilibrated between the *cis* and *trans* amide conformations and only the *cis*-**5** underwent the conjugate radical cyclization. A small amount of direct reduction product **4** was generated from *trans*-**5**.

Examples listed in Table 1 demonstrate the synthesis of tricyclic isoindolinones using uracils (Table 1, entries 1 and 2), pyridinediones (entry 3), and pyridones (entry 4) as starting materials. Uncapped uracils were selectively acylated at the 1-N position using pyridine as a base (entry 2). In a reaction involving dichloropyridone derivative (entry 4), after cyclization, the chlorine atom attached to the carbon 3 was activated by the α-acyl group[11] and readily reduced by the tris(trimethylsilyl)silane to yield **20**.

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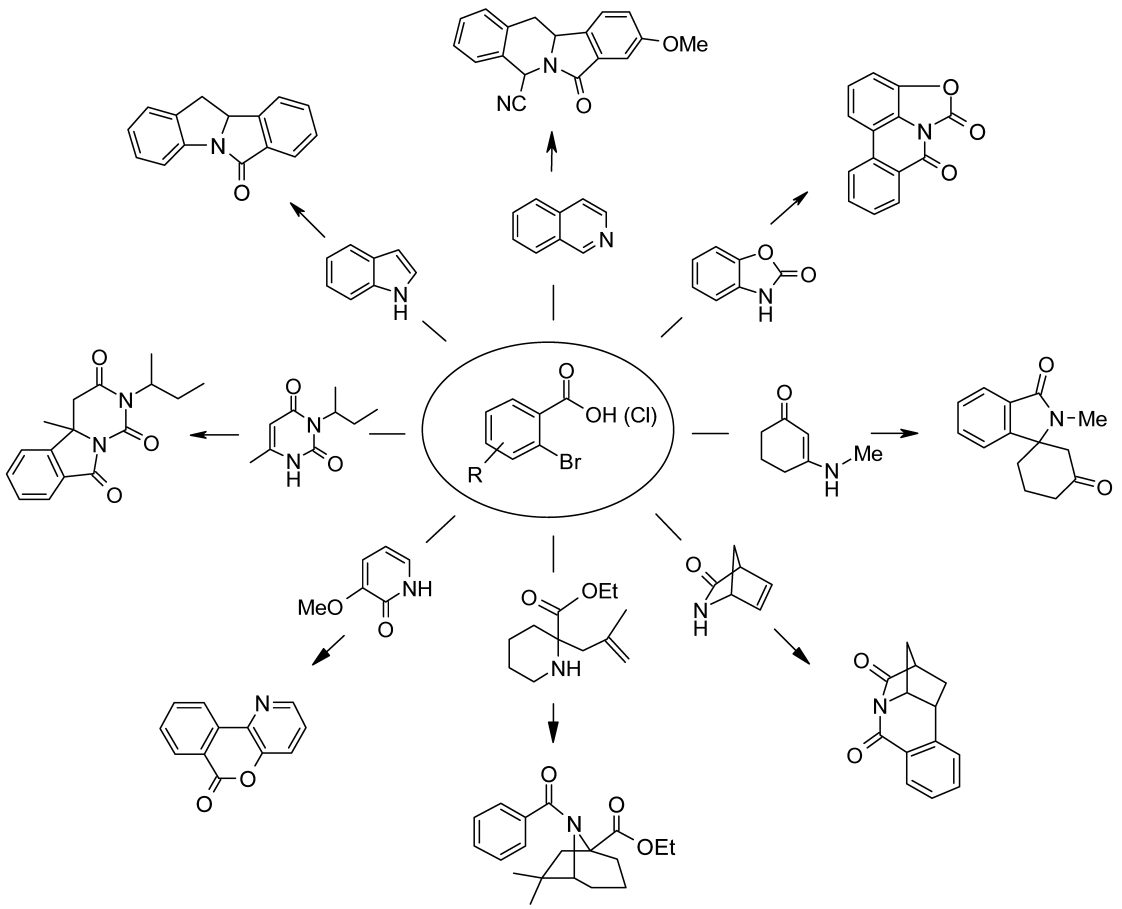
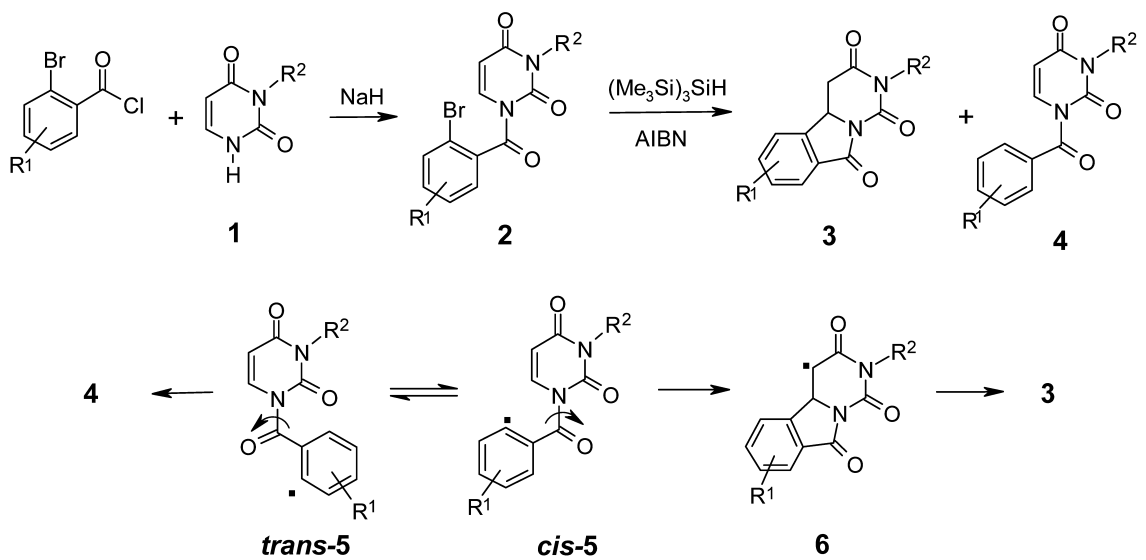


Scheme 1. 2-Bromobenzoic acids-based free radical reactions for *N*-heterocycles.

Following the procedure described above, tetracyclic isoindolinones were prepared using indoles (Table 2, entry 1) and isoquinolines[12] (entry 2) as starting materials. The reaction scope has been further extended to include the naphthyl radical cyclization (entry 3).

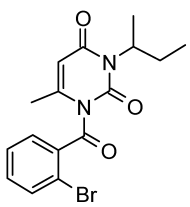
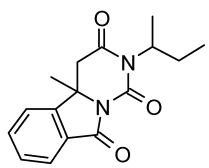
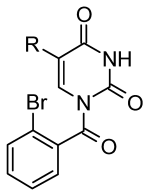
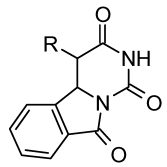
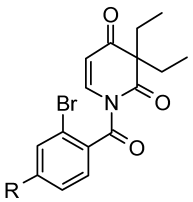
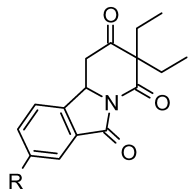
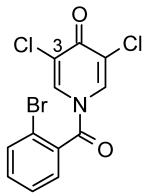
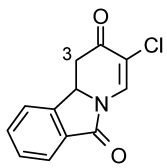
2.2. Formation of spiroisoindolinones by intramolecular Michael additions

Similar to the construction of fused isoindolinones described above, spiro isoindolinones can be prepared by



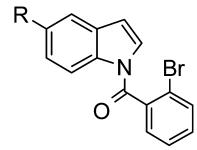
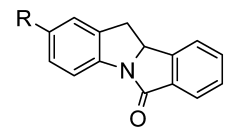
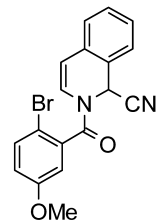
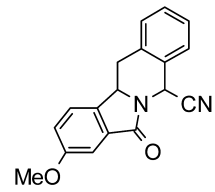
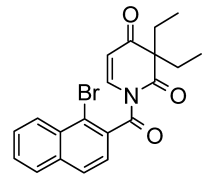
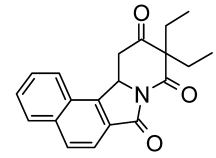
Scheme 2. Formation of tricyclic isoinolinones.

Table 1. Preparation of tricyclic isoindolinones

Entry	Amide[a]	Product[b]
1	 **7,** 80%	 **8**, 50%
2	 R=H, **9,** 46% R=CH_3, **11,** 49% R=CF_3, **13,** 52%	 R=H, **10**, 59% R=CH_3, **12,** 80% R=CF_3, **14,** 59%
3	 R= H, **15,** 62% R= OCH_3, **17,** 92%	 R= H, **16**, 53% R= OCH_3, **18,** 71%
4	 **19,** 98%	 **20,** 43%

[a] *N*-Alkylation with 1.2 equiv. of acid chloride, 1.2 equiv. of NaH, THF.
[b] 1.5 equiv. of $(Me_3Si)_3SiH$, cat. AIBN, benzene, 80°C.

Table 2. Preparation of tetracyclic isoindolinones

Entry	Amide[a]	Product[b]
1	 R= H, **21,** 80% R= OCH_2Ph, **23,** 8%	 R= H, **22,** 53% R= OCH_2Ph, **24,** 71%
2	 **25,** 35%	 **26,** 59%
3	 **27,** 67%	 **28,** 77%

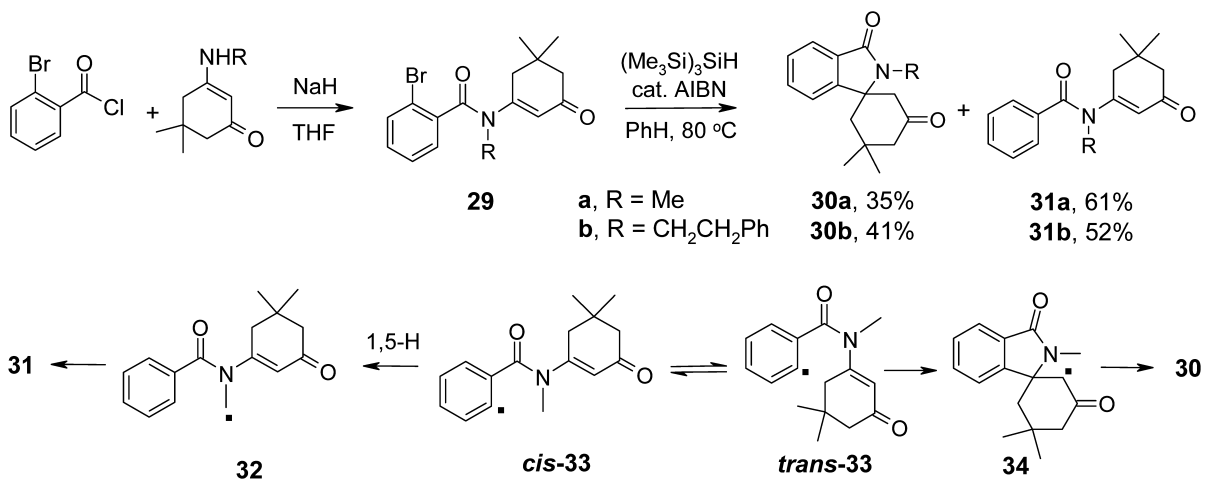
[a] *N*-Alkylation with 1.2 equiv. of acid chloride, 1.2 equiv. of NaH, THF.
[b] 1.5 equiv. of $(Me_3Si)_3SiH$, cat. AIBN, benzene, 80°C.

formation of the quaternary spirocarbon bond via palladium-catalyzed[13] and free radical cyclizations.[14] Scheme 3 outlines a reaction sequence of coupling an amine with the 2-bromobenzoyl chloride followed by the free radical cyclization to generate spiroamide **30**.[5b] The yields of the cyclization products were relatively low (35–41%). Significant amount of direct reduction products **31** were observed (52–61%). It is believed that the equilibrium between *cis*-**33** and *trans*-**33** favors the formation of *cis*-**33**. 1,5-Hydrogen atom transfer of *cis*-**33** led to a relatively stable α-amidomethyl radical **32**.

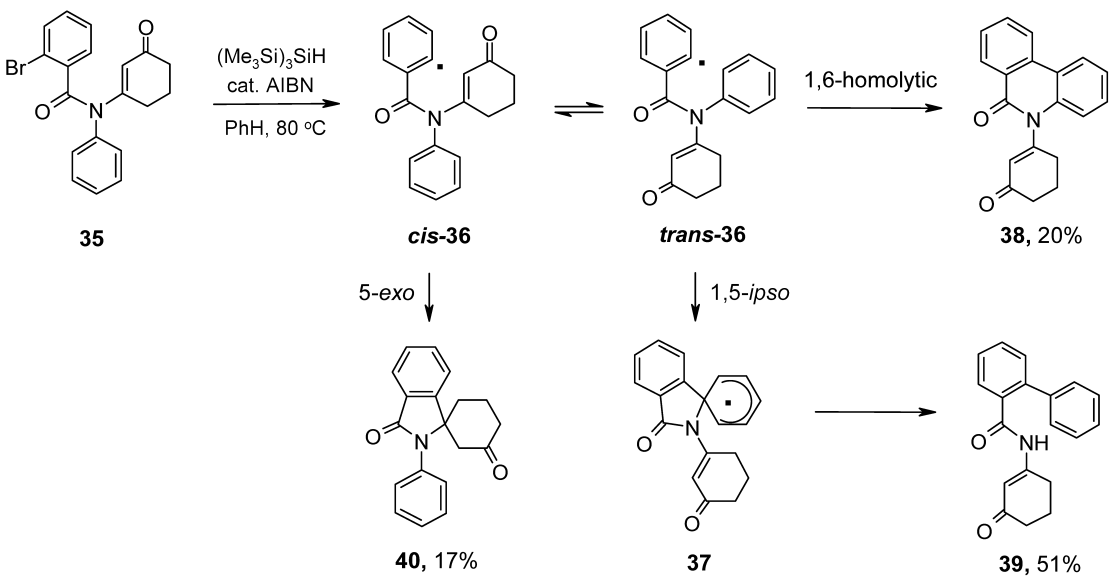
To improve the cyclization yield, a phenyl group was attached to the nitrogen atom (**29**, R=Ph) to block the undesired 1,5-hydrogen atom transfer. As we expected, the reaction of **35** did not produce direct reduction product (Scheme 4). However, two undesired products **38** (20%) and **39** (51%) were isolated together with the spirolactam product **40** (17%). It is believed that *cis*-**36** underwent the expected spirocyclization, while *trans*-**36** underwent the 1,6-homolytic aromatic substitution to form **38** and the 1,5-*ipso* substitution to form **39**, respectively. A similar competitive reaction process has been observed by Crich group in the study of phenyl benzoate systems.[15] The reaction of **35** is of interesting mechanistically, but has limited synthetic utility. More selective and synthetically useful homolytic and *ipso*-substitution reactions will be discussed in Section 2.3.

2.3. Formation of tetracyclic isoquinolinones by homolytic aromatic substitutions and 6-*exo* cyclizations

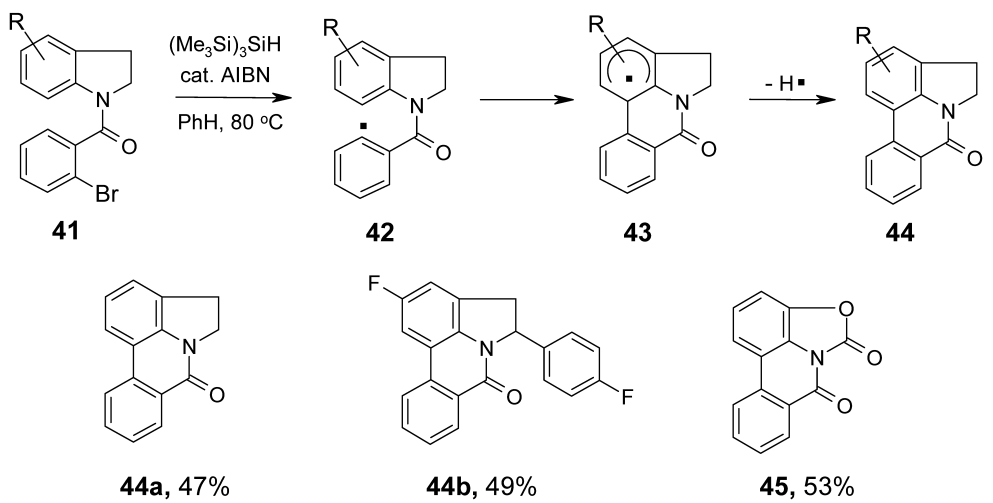
Homolytic aromatic substitutions are useful reactions which can be used to introduce functional groups onto aromatic rings.[16] Scheme 5 demonstrates the synthesis of isoquinolinones by formation of the biaryl carbon–carbon bond. Radical **42** generated from indole derivative **41** cyclized to the aromatic ring to yield a relative stable π-radical **43** that was then oxidized back to the aromatic ring **44** by loss of a hydrogen atom. A reaction of indoline derivative **21** described above (Table 2, entry 1), however, led to a 5-*exo* cyclization product. Additional examples of homolytic substitutions in the preparation of tetracyclic isoquinolinones include reactions of indoline and benzooxazol-2-one derivatives (Scheme 5).[17] Compounds **44a** and **44b** are analogs of pyrrolophenanthrines that have been isolated from various species of *Amaryllidaceae*.[18]



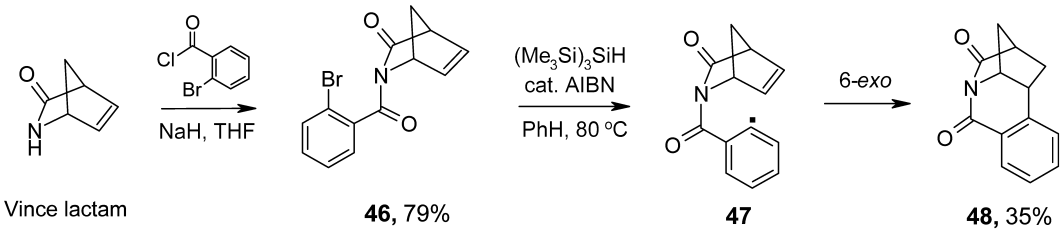
Scheme 3. Synthesis of spirolactams.



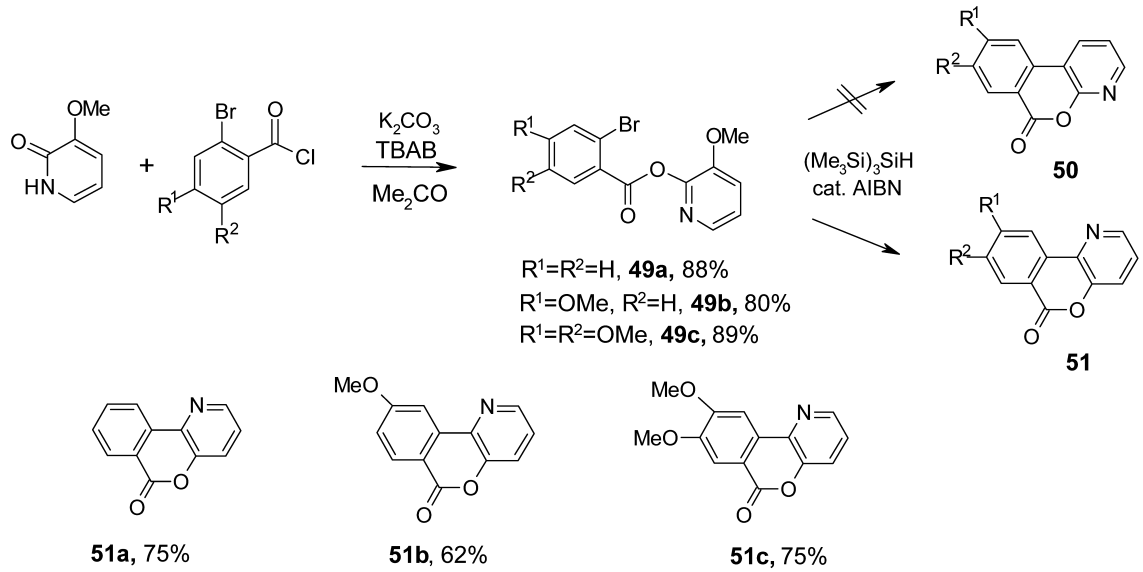
Scheme 4.



Scheme 5. Synthesis of tetracyclic isoquinolinones.



Scheme 6. Synthesis of a bridged-tetracyclic isoquinolinone.



Scheme 7. Synthesis of azabenzoisocoumarins.

A reaction sequence to prepare bridged-tetracyclic isoquinolinone **48** using commercially available Vince lactam is presented in Scheme 6. Radical precursor **46** has two acyl groups next to the nitrogen atom. The cyclic acyl–nitrogen bond is geometrically constrained, while the acyclic acyl–nitrogen bond can be oriented to the conformation **47** for the 6-*exo* cyclization. However, the yield of **48** was low (35%), the major product was the direct reduction product

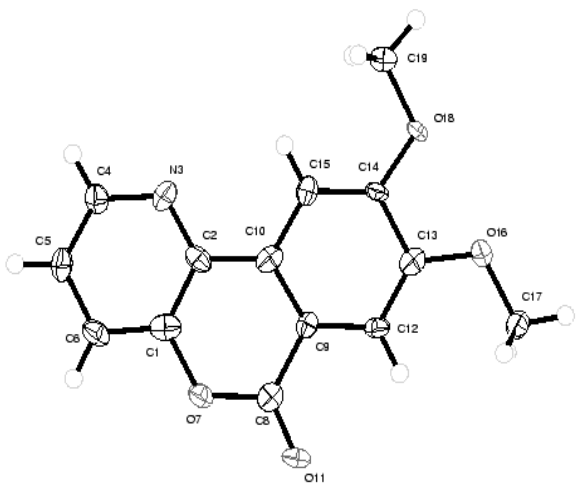
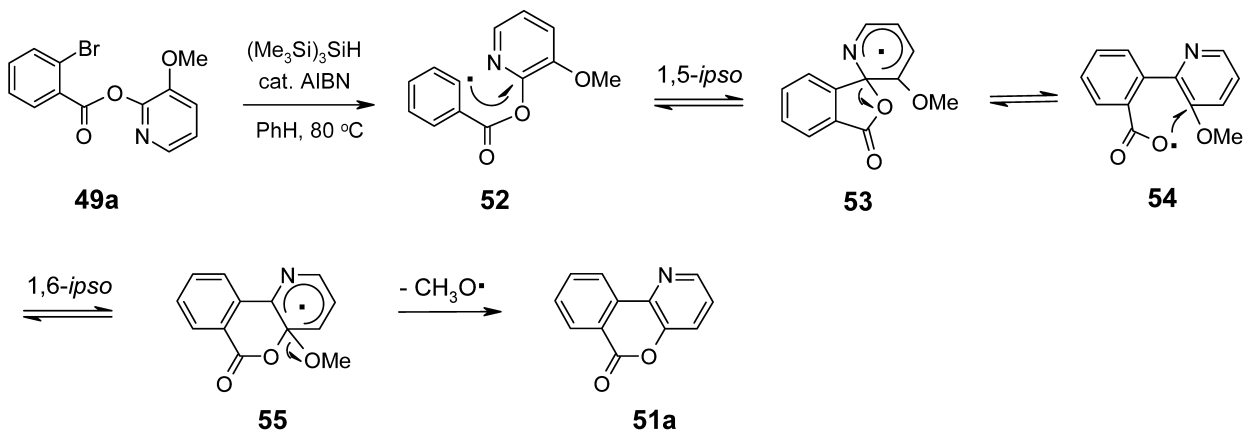


Figure 1. X-Ray structure of **51c**.

2.4. Formation of azabenzoisocoumarins by double *ipso* substitutions

Intramolecular homolytic *ipso* substitutions have been widely used in phenyl migrations and biaryl syntheses.[16,19] This reaction has been further applied in the preparation of benzo-fused ring systems such as phenanthridinones[15b,20] and benzochromenes.[21] Described herein is a novel double *ipso* substitution process for the synthesis of azabenzoisocoumarins (Scheme 7).[5a] The radical precursor **49** was prepared by selective *O*-acylation of 3-methoxy-2(1*H*)-pyridone with 2-bromobenzoyl chlorides in the presence of K_2CO_3 and tetrabutylammonium bromide (TBAB). The free radical reaction of **49** produced an *ipso* substitution product. The structure of the product was found to be 10-oxa-4-azaphenanthren-9-one **51**[22] instead of the direct 1,6-*ipso* substitution product 10-oxa-1-azaphenanthren-9-one **50** as confirmed by X-ray analysis of compound **51c** (Fig. 1).

A mechanism for the radical transformation is outlined in Scheme 8. The rearrangement started with a 1,5-*ipso* substitution of radical **52**. The radical attack at 2-position of the pyridine ring generated the carbonyloxy radical **54**. Since the decarboxylation rate of aromatic carbonyloxy radicals ($k=10^4-10^5\ s^{-1}$) is significantly slower than that of alkyl carbonyloxy radicals ($k=10^8-10^{10}\ s^{-1}$),[23] radical **54** survived and underwent a second 1,6-*ipso* substitution to displace the methoxy group.[24] The essentially irreversible extrusion of the methoxy radical promoted the *ipso*



Scheme 8. Double *ipso* rearrangement for azabenzoisocoumarins.

rearrangement processes. A comparison reaction using a radical precursor without the methoxy group gave less than 10% yield of the rearrangement product **51a**. This result confirmed the role of the methoxy group in the promotion of the double *ipso* rearrangement. This reaction has been employed in the synthesis of benzocoumarins.[5a] The yields were low compared to the synthesis of azabenzoisocoumarins because the benzene ring is usually a less active system than the pyridine ring for the *ipso* substitution.

2.5. Formation of bridged-azabicyclics by a 1,5-hydrogen atom transfer/cyclization sequence

α-Amidoalkyl and α-amidoacyl radicals have important synthetic utilities in the preparation of nitrogen-containing heterocycles. An efficient way to generate such radicals is 1,5-hydrogen atom transfers.[25] This method has been used to transfer the aryl radicals to pyrrolidine and piperidine rings in the construction of bridged azabicyclic compounds.[26] Following a procedure reported by Ikeda,[26c] we introduced a 2-methylallyl side chain α to the ester group to investigate the regioselectivity of radical cyclizations. Under a general reaction condition, only the 5-*exo* cyclization product **59** was isolated (Scheme 9), no 6-*endo* cyclization product was observed.

In summary, we have demonstrated the synthetic utility of 2-bromobenzoic acid derivatives in the preparation of a variety of nitrogen-containing heterocycles. This general reaction process can be used for parallel and combinatorial synthesis of structurally diversified ring systems.

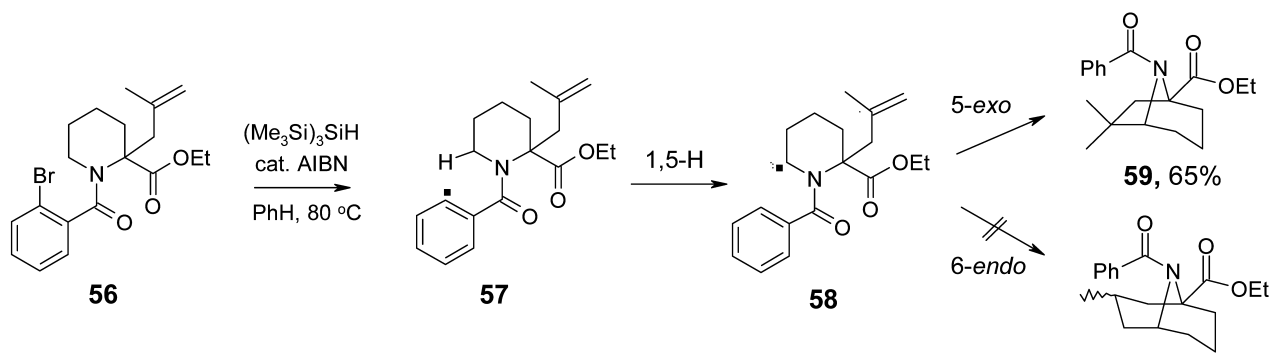
3. Experimental

3.1. General

2-Bromobenzoic acids, 2-bromobenzoyl chlorides and nitrogen-containing compounds for the coupling reactions were obtained from commercial sources unless otherwise stated. Compounds **25**[12] and **56**[26c] were prepared following the literature procedures. Radical initiator 2,2′-azobis-(2-methylpropionitrile) (AIBN) and tris(trimethyl-silyl)-silane were purchased form Aldrich and Fluka, respectively. Anhydrous benzene obtained from Fluka was used without further purification.

3.2. Preparation of radical precursors

3.2.1. General procedure for *N*-acylation of pyridinediones, pyridones, indoles, indolines and related compounds. To a suspension of NaH (60% in mineral oil, 7.2 mmol) in 5 mL of anhydrous THF was added a solution of the substrate (6 mmol) to be acylated in 15 mL of anhydrous THF at room temperature. After stirring for 45 min, 2-bromo-5-methoxybenzoyl chloride (7.2 mmol) was added dropwise. The reaction mixture was stirred at room temp overnight and then quenched with ice water. The mixture was extracted with ethyl acetate. The combined organic layer was washed with NH_4Cl aq. and brine, dried over $MgSO_4$, and concentrated in vacuo to afford the *N*-acylation product. Most *N*-acylation compounds were used for the next step of radical reaction without further purification. If the *N*-acylation product was not



Scheme 9. Synthesis of a bridged azabicyclic compound.

pure enough, a flash column chromatography was performed.

3.2.2. General procedure for *N*-acylation of uncapped uracils. To a solution of 5-trifluoromethyl-1*H*-pyrimidine-2,4-dione (20 mmol) and 2-bromobenzoyl chloride (23 mmol) in 35 mL of dry CH_3CN was added 4.0 mL of pyridine. The mixture was stirred at room temperature for 14 h. To the concentrated reaction mixture was added 20 mL of 1.0N NaOH followed by extraction with AcOEt and then with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was triturated with a small amount of CH_2Cl_2 to remove the unreacted uracil as a solid by filtration. The filtrate was concentrated and triturated with CH_2Cl_2/BuCl (1/1) to give the acylated product.

3.2.3. General procedure for selective *O*-acylation of pyridones. To a suspension of 3-methoxy-2-(*1H*)-pyridone (10 mmol) in 10 mL of acetone was added K_2CO_3 (20 mmol) and TBAB (1.0 mmol). After stirring at room temperature for 30 min, 2-bromobenzoyl chloride (10 mmol) was added carefully. The mixture was stirred overnight. To the concentrated reaction mixture was added water and the mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous NH_4Cl, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash column chromatography with Hex/AcOEt (80/20) to give the *O*-acylation product.

3.3. General procedure for free radical reactions

To a refluxing solution of bromide (1 equiv.) in dry benzene (20 mL per mmol of bromide) was added $(CH_3Si)_3SiH$ (1.5 equiv.) and AIBN (0.05 equiv.). After 2 h, a second portion of AIBN (0.05 equiv.) was added and the reaction mixture was refluxed for an additional 4–10 h. The concentrated reaction mixture was triturated with BuCl or further purified by flash chromatography to give the cyclization product.

3.3.1. Compound 8. 83% Yield as a white solid mp 107–112°C; IR ν_{max} (neat) 1776, 1713, 1368, 1239, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=8.5 Hz, 3H), 1.45 (d, J=7.0 Hz, 3H), 1.67 (s, 3H), 1.80–2.15 (m, 2H), 2.68 (d, J=16.1 Hz, 1H), 3.18 (dd, J=16.1, 2.8 Hz, 1H), 4.78 (m, 1H), 7.45 (d, J=7.7 Hz, 1H), 7.60 (t, J=7.7 Hz, 1H), 7.75 (t, J=7.7 Hz, 1H), 8.00 (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.1, 15.9, 23.6, 24.2, 42.0, 50.6, 38.3, 119.6, 124.5, 127.3, 128.2, 133.2, 147.1, 166.7, 166.8; LRMS (AP+) *m/z*(rel. intensity) 287 (M^++H, 100); HRMS calcd for $C_{16}H_{18}N_2O_3$ 286.1317, found 286.1317.

3.3.2. Compound 10. 59% Yield; IR ν_{max} (neat) 1766, 1721, 1406, 1260, 1191, 759 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.78 (dd, J=16.0, 13.3 Hz, 1H), 3.20 (dd, J=16.0, 3.8 Hz, 1H), 5.43 (dd, J=13.5, 3.8 Hz, 1H), 7.62 (t, J=7.2 Hz, 1H), 7.76 (m, 2H), 7.85 (d, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) *?*δ 34.0, 53.1, 122.0, 123.0, 127.8, 128.6, 132.7, 142.5, 146.3, 163.6, 168.7; LRMS (AP+) *m/z*(rel. intensity) 217 (M^++H, 100), 172 (48); HRMS calcd for $C_{11}H_8N_2O_3$ 216.0535, found 216.0545.

3.3.3. Compound 12. 80% Yield; IR ν_{max} (neat) 1766, 1397, 758 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) 1.45 (d, J=6.9 Hz, 3H), 2.80 (m, 1H), 5.18 (d, J=12.2 Hz, 1H), 7.62 (t, J=7.2 Hz, 1H), 7.7 (m, 2H), 7.90 (d, J=7.5 Hz, 1H), 10.94 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.6, 38.9, 57.8, 123.0, 123.1, 127.9, 129.0, 132.6, 141.7, 146.2, 163.4, 171.2; LRMS (AP+) *m/z*(rel. intensity) 231 (M^++H, 100), 169 (34); HRMS calcd for $C_{12}H_{10}N_2O_3$ 230.0691, found 230.0696.

3.3.4. Compound 14. 59% Yield as a light yellow solid mp 210–213°C; IR ν_{max} (neat) 1778, 1726, 1390, 1262, 1221, 1125, 1043, 756, 610, 582, 450 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 4.82 (m, 1H), 6.00 (br s, 1H), 7.66 (t, J=7.7 Hz, 1H), 7.90–8.00 (m, 3H), 11.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.6, 45.3, 52.8, 123.1, 123.2, 128.2, 128.5, 132.9, 138.8, 145.1, 161.6, 163.2; LRMS (AP+) *m/z* (rel. intensity) 285 (M^++H, 100), 275 (13), 265 (8), 232 (8); HRMS calcd for $C_{12}H_7F_3N_2O_3$ 284.0409, found 284.0429.

3.3.5. Compound 16. 53% Yield as a clear oil; IR ν_{max} (neat) 1762, 1719, 1367, 1293, 1261, 758 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.80 (t, J=7.5 Hz, 3H), 0.94 (t, J=7.5 Hz,, 3H), 1.80–2.20 (m, 4H), 2.43 (dd, J=15.8, 13.5 Hz, 1H), 3.38 (dd, J=15.8, 3.0 Hz, 1H), 5.18 (dd, J=13.5, 3.0 Hz, 1H), 7.50 (d, J=7.7 Hz, 1H), 7.60 (t, J=7.7 Hz, 1H), 7.78 (t, J=7.7 Hz, 1H), 8.01 (t, J=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 28.5, 29.3, 44.0, 52.0, 62.8, 120.8, 124.4, 128.3, 128.5, 133.0, 141.7, 164.2, 169.1, 205.4; LRMS *m/z*(rel. intensity) 271 (M^+, 100); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1208.

3.3.6. Compound 18. 71% Yield as white solid mp 183–184°C; IR ν_{max} (neat) 1762, 1719, 1498, 1367, 1261, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (t, J=7.5 Hz, 3H), 0.95 (t, J=7.5 Hz, 3H), 1.80–2.30 (m, 4H), 2.41 (dd, J=15.8, 13.5 Hz, 1H), 3.28 (dd, J=15.8, 3.0 Hz, 1H), 3.90 (s, 3H,), 5.08 (dd, J=13.5, 3.0 Hz, 1H), 7.30 (d, J=7.7 Hz, 1H), 7.37 (d, J=7.7 Hz, 1H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.0, 8.2, 28.3, 29.2, 44.1, 51.6, 54.3, 62.6; LRMS (AP+) *m/z* (rel. intensity) 302 (M^++H, 100); HRMS calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1322.

3.3.7. Compound 20. 2.2 equiv. of $(Me_3Si)_3SiH$ was used for the radical reaction; 43% yield as a white solid mp 200°C (dec); IR ν_{max} (neat) 1721, 1680, 1406, 1293, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.66 (dd, J=16.0, 15.3 Hz, 1H), 3.30 (dd, J=16.0, 4.2 Hz, 1H), 5.23 (dd, J=15.3, 4.2 Hz, 1H), 7.50 (d, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 1H), 7.72 (t, J=7.5 Hz, 1H), 7.97 (d, J=7.5 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.9, 58.4, 116.7, 123.5, 126.6, 130.8, 131.6, 135.2, 137.5, 144.5, 164.7, 186.9; LRMS (AP−) *m/z* (rel. intensity) 232 (M^+−1, 100); HRMS calcd for $C_{12}H_8Cl^{35}NO_2$ 233.0244, found 233.0251.

3.3.8. Compound 22. 53% Yield as a white solid mp 136–137°C; IR ν_{max} (neat) 1699, 1604, 1479, 1371, 1303, 1212, 1140, 1101, 1014, 913, 753, 689, 528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (dd, J=15.2, 10.4 Hz, 1H), 3.45 (dd, J=15.2, 8.7 Hz, 1H), 5.61 (dd, J=10.4, 8.7 Hz, 1H), 7.05 (t, J=7.5 Hz, 1H), 7.26 (m, 2H), 7.52 (m, 2H), 7.58 (m, 1H), 7.61 (d, J=7.7 Hz, 1H), 7.87 (d, J=7.7 Hz, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 32.3, 63.9, 114.9, 121. 4, 122.9, 123.3, 123.8, 126.5, 127.2, 131.0, 1327, 134.5, 139.1, 144.5, 166.9; LRMS (AP+) *m/z* (rel. intensity) 222 (M^++H, 100); HRMS calcd for $C_{15}H_{11}NO$ 211.0841, found 211.0843.

3.3.9. Compound 24. 71% Yield as a yellow solid mp 164–165°C; IR ν_{max} (neat) 1699, 1487, 1370, 1279, 1226, 1138, 1065, 1016, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.02 (dd, *J*=15.2, 10.4 Hz, 1H), 3.41 (dd, *J*=15.2, 8.7 Hz, 1H), 5.05 (s, 2H), 5.60 (dd, *J*=10.4, 8.7 Hz, 1H), 6.90 (m, 2H), 7.38–7.59 (m, 9H), 7.85 (d, *J*=7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 64.3, 69.1, 111.6, 112.0, 115.3, 121.2, 123.2, 125.9, 126.5, 127.1, 130.8, 132.8, 133.0, 135.4, 136.1, 144.4, 154.7, 166.8; LRMS (AP+) *m/z* (rel. intensity) 328 (M^++H, 88), 153 (100); HRMS calcd for $C_{22}H_{17}NO_2$ 327.1259, found 327.1259.

3.3.10. Compound 26. 59% Yield; IR ν_{max} (neat) 1705, 1640, 1494, 1453, 1435, 1398, 1328, 1286, 1244, 1142, 1026, 777, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (dd, *J*=15.0, 3.3 Hz, 1H), 3.42 (dd, *J*=15.0, 3.1 Hz, 1H), 3.89 (s, 3H), 4.80 (dd, *J*=13.3, 3.1 Hz, 1H), 7.20–7.55 (7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9, 40.8, 51.6, 54.2, 105.6, 116.0, 119.2, 121.8, 125.3, 126.0, 126.5, 127.6, 128.3, 130.6, 136.3, 158.9, 165.1; LRMS (AP+) *m/z* (rel. intensity) 291 (M^++H, 100); HRMS calcd for $C_{18}H_{14}N_2O_2$ 290.1055, found 290.1065.

3.3.11. Compound 28. 77% Yield; IR ν_{max} (neat) 1760, 1717, 1354, 1260, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (t, *J*=7.3 Hz, 3H), 1.03 (t, *J*=7.3 Hz, 3H), 1.80–2.03 (m, 2H), 2.08–2.33 (m, 2H), 2.52 (dd, *J*=16.1, 13.4 Hz, 1H), 2.75 (dd, *J*=16.1, 2.8 Hz, 1H), 5.55 (dd, *J*=13.4, 2.8 Hz, 1H), 7.72 (m, 2H), 7.90–8.10 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 8.4, 28.4, 29.3, 45.2, 52.1, 62.7, 119.0, 121.9, 125.7, 126.4, 126.6, 127.6, 128.3, 129.5, 135.0, 140.6, 164.6, 168.9, 205.6; LRMS (AP+) *m/z* (rel. intensity) 322 (M^++H, 100); HRMS calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1378.

3.3.12. Compound 30a. 35% Yield; IR ν_{max} (neat) 2958, 1694, 1470, 1418, 1387, 1277, 1943, 764, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.27 (s, 3H), 1.97 (d, *J*=15.6 Hz, 1H), 2.08 (d, *J*=15.6 Hz, 1H), 2.43 (d, *J*=15.6 Hz, 1H), 2.50 (d, *J*=15.6 Hz, 1H), 2.64 (d, *J*=16.5 Hz, 1H), 2.76 (d, *J*=16.5 Hz, 1H), 3.04 (s, 3H), 7.38–7.60 (3H), 7.80 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.0, 28.8, 30.7, 30.8, 42.9, 44.9, 50.6, 63.7, 120.0, 122.2, 126.8, 128.7, 130.6, 150.1, 165.3, 207.3; LRMS (AP+) *m/z* (rel. intensity) 258 (M^++H, 100); HRMS calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1420.

3.3.13. Compound 30b. 41% Yield; IR ν_{max} (neat) 2960, 1690, 1469, 1399, 1275, 751, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.21 (s, 3H), 1.83 (d, *J*=15.6 Hz, 1H), 1.94 (d, *J*=15.6 Hz, 1H), 2.40 (d, *J*=15.6 Hz, 1H), 2.45 (d, *J*=15.6 Hz, 1H), 2.52 (d, *J*=16.5 Hz, 1H), 2.62 (d, *J*=16.5 Hz, 1H), 3.00 (m, 1H), 3.23 (m, 1H), 3.39 (m, 1H), 3.78 (m, 1H), 7.20–7.37 (6H), 7.40–7.55 (m 2H), 7.83 (d, *J*=8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.1, 28.4, 30.1, 30.6, 31.3, 33.3, 41.4, 43.5, 45.6, 50.7, 64.8, 120.3, 122.0, 125.1, 126.8, 127.1, 127.4, 129.0, 130.5, 137.5, 150.0, 165.9, 207.3; LRMS (AP+) *m/z* (rel. intensity) 348 (M^++H, 100); HRMS calcd for $C_{23}H_{25}NO_2$ 347.1885, found 347.1889.

3.3.14. Compound 38. 20% Yield as a semisolid; IR ν_{max} (neat) 2952, 1658, 1608, 158, 1320, 1234, 750, 725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10–2.80 (6H), 6.20 (s, 1H), 7.15 (d, *J*=8.3 Hz, 1H), 7.37 (m, 1H), 7.47 (m, 1H), 7.64 (t, *J*=7.7 Hz, 1H), 7.82 (t, *J*=7.7 Hz, 1H), 8.32 (d, *J*=7.8 Hz, 2H), 8.52 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 28.7, 37.2, 118.0, 119.1, 121.9, 123.3, 123.6, 125.3, 128.3, 128.6, 129.7, 131.0, 133.2, 133.8, 136.1, 158.9, 160.0, 199.1; LRMS (AP+) *m/z*(rel. intensity) 290 (M^++H, 100); HRMS calcd for $C_{19}H_{15}NO_2$ 289.1103, found 289.1108.

3.3.15. Compound 39. 51% Yield; IR ν_{max} (neat) 3278, 3232, 1693, 1628, 1511, 1237, 1181, 1132, 745, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70–2.05 (m, 4H), 2.28 (t, *J*=6.3 Hz, 2H), 6.40 (s, 1H), 6.58 (br s, 1H), 7.40–7.60 (9H),7.83 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 28.0, 36.5, 111.6, 127.8, 128.2, 128.7 (2C), 128.9 (2C), 129.4, 130.3, 131.2, 134.3, 139.5, 139.8, 154.9, 168.0, 199.9; LRMS (AP+) *m/z* (rel. intensity) 292 (M^++H, 100), HRMS calcd for $C_{19}H_{17}NO_2$ 291.1259, found 291.1259.

3.3.16. Compound 40. 29% Yield; IR ν_{max} (neat) 1698, 1493, 1467, 1382, 763, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92–2.40 (m, 6H), 2.58 (m 2H), 2.88 (d, *J*=13.7 Hz, 1H), 7.23–736 (3H), 7.50–7.60 (5H), 7.98 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 32.7, 38.3, 48.6, 66.7, 121.1, 123.1, 127.3, 127.5, 128.3 (2C), 129.1, 129.4 (2C), 130.5, 133.3, 146.8, 165.9, 206.6; LRMS (AP+) *m/z* (rel. intensity) 292 (M^++H, 100); HRMS calcd for $C_{19}H_{17}NO_2$ 291.1259, found 291.1266.

3.3.17. Compound 44a. 47% Yield; analytical data is consistent with those reported in literature.[17c]

3.3.18. Compound 44b. 49% Yield; IR ν_{max} (neat) 1641, 1607, 1515, 1484, 1393, 1254, 1160, 840, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (dd, *J*=12.5, 3.7 Hz, 1H), 3.95 (dd, *J*=12.5, 10.2 Hz, 1H), 5.99 (dd, *J*=10.2, 3.7 Hz, 1H), 6.99 (t, *J*=8.9 Hz, 2H), 7.11 (d, *J*=8.1 Hz, 1H), 7.13 (m, 2H), 7.63 (m, 2H), 7.78 (t, *J*=8.0 Hz, 1H), 8.16 (d, *J*=8.0 Hz, 1H), 8.48 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.3, 63.4, 107.4, 114.2, 116.9, 117.9, 123.4, 128.7, 128.8, 129.8, 131.8, 133.4, 134.3, 137.2, 138.4, 160.1, 162.2, 164.6; LRMS (AP+) *m/z* (rel. intensity) 334 (M^++H, 100); HRMS calcd for $C_{21}H_{13}F_2NO$ 333.0965, found 333.0965.

3.3.19. Compound 45. 53% Yield; IR ν_{max} (neat) 1806, 1697, 1313, 1141, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 2H), 7.51 (t, *J*=6.2 Hz, 2H), 7.65 (t, *J*=6.2 Hz, 1H), 7.80–7.90 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.5, 113.7, 123.5, 123.9, 127.0, 128.0, 130.7, 132.0, 141.3, 149.5, 166.3; LRMS (AP+) *m/z* (rel. intensity) 238 (M^++H, 80), 196 (100); HRMS calcd for $C_{14}H_7NO_3$ 237.0426, found 237.0428.

3.3.20. Compound 48. 35% Yield; IR ν_{max} (neat) 1694, 1335, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (m, 1H), 1.85 (m, 1H), 2.12 (m, 1H), 2.56 (m, 1H), 3.18 (m, 1H),

3.39 (dm, 1H), 4.54 (s, 1H), 7.24 (d, J=7.5 Hz, 1H), 7.39 (t, J=7.5 Hz, 1H), 7.53 (t, J=7.4 Hz, 1H), 8.14 (d, J=7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5, 33.7, 38.3, 48.1, 61.9, 124.6, 126.7, 127.2, 128.3, 132.8, 142.7, 164.2, 175.2; LRMS (AP+) m/z (rel. intensity) 214 (M^++H, 100); HRMS calcd for $C_{13}H_{11}NO_2$ 213.0790, found 213.0799.

3.3.21. Compound 51a. 49% Yield; analytical data is consistent with those reported in the literature.[22]

3.3.22. Compound 51b. 62% Yield; IR ν_{max} (neat) 1731, 1611, 1449, 1352, 1275, 1028, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (s, 3H), 7.38 (m, 1H), 7.49 (dd, J=8.8, 2.8 Hz, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.79 (d, J= 2.8 Hz, 1H), 8.58–8.62 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3, 109.4, 122.2, 122.7, 122.9, 123.7, 127.3, 135.4, 144.3, 145.1, 158.6, 159.9; LRMS (AP+) m/z (rel. intensity) 228 (M^++H, 100); HRMS calcd for C13H9NO3 227.0582, found 227.0585.

3.3.23. Compound 51c. 75% Yield; IR ν_{max} (neat) 1719, 1608, 1518, 1465, 1435, 1383, 1320, 1264, 1154, 1079, 1024, 873, 792, 752, 618 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3H), 4.14 (s, CH_3), 7.25 (m, 1H), 7.64 (d, J=8.2 Hz, 1H), 7.70 (s, 1H), 8.04 (s, 1H), 8.59 (d, J= 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.8, 55.0, 102.4, 108.4, 114.1, 122.4, 123.0, 129.1, 135.1, 144.0, 145.7, 149.8, 153.8, 158.3; LRMS (AP+) m/z (rel. intensity) 258 (M^++H, 100); HRMS calcd for $C_{14}H_{11}O_4N$ 257.0688, found 257.0688.

3.3.24. Compound 59. 65% Yield; IR ν_{max} (neat) 2963, 1739, 1641, 1446, 1401, 1367, 1277, 1189, 1122, 1085, 1052, 912, 749, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 1.13 (s, 3H), 1.27 (t, 3H), 1.40 (s, 3H), 1.63–2.08 (8H), 2.40 (m, 1H), 3.61 (br s, 1H), 4.20 (q, 2H), 7.41 (m, 3H), 7.52 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.5, 15.8, 20.8, 26.2, 27.4, 30.2, 39.0, 46.0, 58.8, 64.1, 67.1, 125.8 (2C), 126.2 (2C), 128.5, 134.9, 168.1, 170.6; LRMS (AP+) m/z (rel. intensity) 316 (M^++H, 100), 270 (15); HRMS calcd for $C_{19}H_{25}NO_3$ 315.1834, found 315.1831.

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