CHAPTER 2

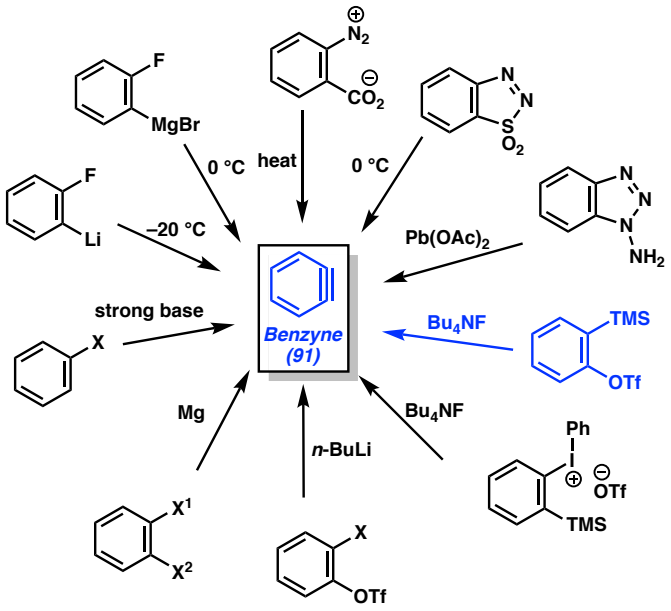
Acyl-Amination of Arenes via Aryne Formation[i]

2.1 INTRODUCTION AND BACKGROUND

Over the past 50 years, arynes have been of considerable interest to synthetic chemists owing to their diverse modes of reactivity. Although numerous procedures for their preparation are known, the majority of these approaches relies on high temperatures or strong base additives (Scheme 2.1.1).[1] However, in 1983 the Kobayashi group disclosed a comparatively mild procedure for *in situ* aryne preparation utilizing *o*-silylaryl triflates (highlighted in blue).[2] Thus, treatment with fluoride will result in desilylation with concomitant triflate elimination, providing a highly reactive benzyne intermediate **91**.

(i) This research was a collaborative effort between A. C. Wright, C. K. Haley, and G. Lapointe, see reference 14.

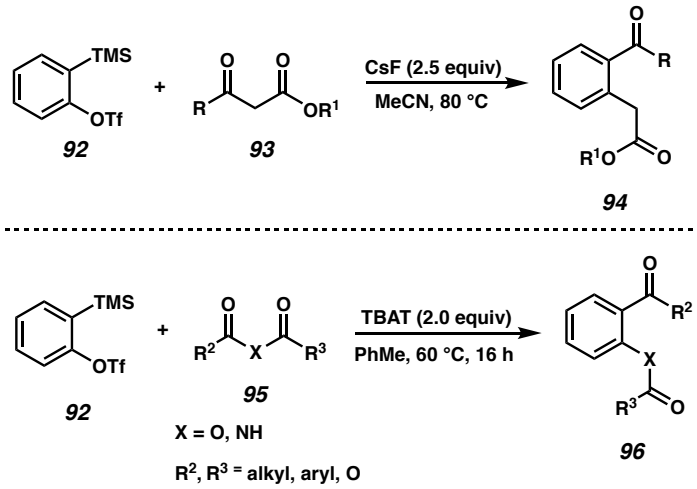
*Scheme 2.1.1. Classical Preparative Procedures for Benzyne (**91**)*



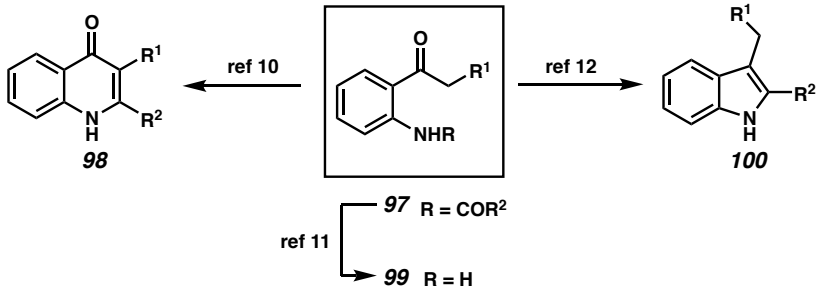
The insertion of aromatic systems into carbon–carbon and carbon–heteroatom σ bonds is a desirable transformation in organic synthesis.[3] In 2005, our group reported an insertion of arenes into β-ketoesters to form acyl-alkylated products using arynes generated *in situ* from *o*-silylphenyl triflates such as **92** under Kobayashi conditions (Scheme 2.1.2).[4] Following this report, other aryne insertions were disclosed using a variety of substrates, including malononitriles,[5] α-cyanocarbonyls,[6] acylated fluorenes[7] and β-ketosulfones.[8] More recently, Saito and co-workers developed a procedure for inserting pyridynes into cyclic ureas in order to construct various bicyclic heterocycles.[9] Herein, we expand the scope of this aryne reaction manifold to include acyclic imides and anhydrides **95** in order to produce ketoamido- and ketoacyloxyarenes **96**. The ketoamide products accessed by this method have been used to generate a variety of valuable structural motifs such as quinolones (**98**),[10] *ortho*-acylanilines (**99**)[11] and indoles[12] (**100**, Scheme 2.1.3). Work from the Greaney group demonstrated that the insertion of amides into arynes

afforded similar acyl-aminated products.[13] However, the scope of their method was limited to *N*-arylated amide substrates, prohibiting subsequent derivatization.

Scheme 2.1.2. Aryne Insertion Methods



*Scheme 2.1.3. Derivatization of Aryl Ketoamides **97***

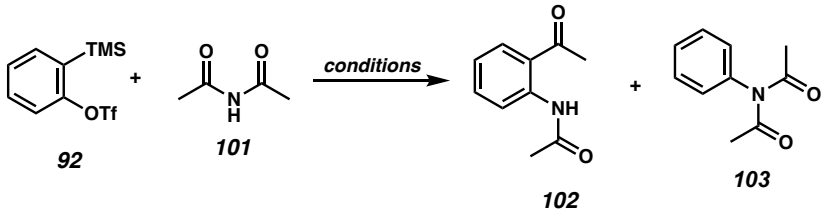


2.2 RESULTS AND DISCUSSION

We initiated our synthetic studies by optimizing conditions for the insertion reaction using acetylacetamide (**101**) and silylaryl triflate **92** (Table 2.2.1).[14] Implementing CsF as the fluoride source to trigger aryne generation, we observed a mixture of the desired ketoamide **102** and undesired imide byproduct **103**. Presumably, **103** is formed via nucleophilic addition of **101** to aryne **91** followed by proton quenching of the resultant aryl anion intermediate (Scheme 2.2.1).

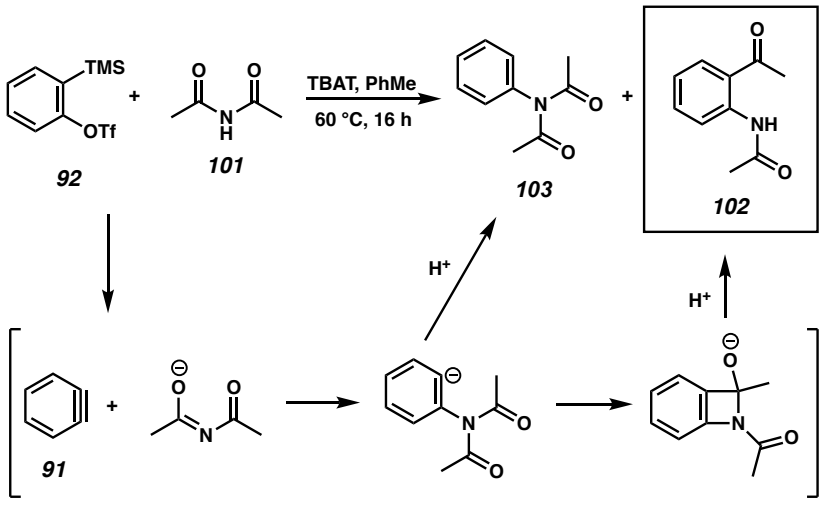
Although all three fluoride reagents afforded the desired product, KF and tetrabutylammonium difluorotriphenylsilicate (TBAT) substantially improved selectivity for the desired amide. Additional screening of solvent and temperature demonstrated that using TBAT in PhMe at 60 °C maximized product yields and minimized byproduct formation (entry 4).

Table 2.2.1. Reaction Optimization



entry	fluoride source	solvent	yield (%)	*102*:*103*
1	CsF	MeCN	49	1.25:1
2	KF/18-crown-6	THF	37	10:1
3	TBAT	THF	21	10:1
4	TBAT	PhMe	62	>20:1

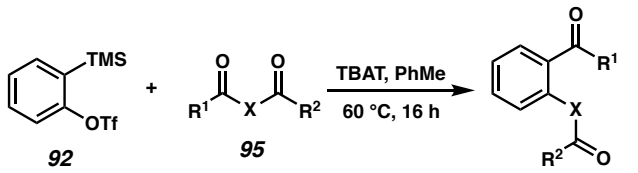
*Scheme 2.2.1. Plausible Mechanism for Formation of Desired **102** and Byproduct **103***



With optimized conditions in hand, we explored the substrate scope with respect to the imide substrate (Table 2.2.2). Imides possessing either aliphatic or aromatic substituents afforded the

corresponding ketoamides in moderate to good yields (entries 1–5). An acylated urethane also underwent insertion, albeit with reduced yield (entry 6). However, *N*-substituted imides afforded no product (entry 7). Acetic anhydride was found to be a suitable substrate, delivering the corresponding ketoacyloxyarene (entry 8) in 54% yield. Unfortunately, benzoic anhydride failed to provide any insertion product (entry 9).

Table 2.2.2. Imide Substrate Scope[a]

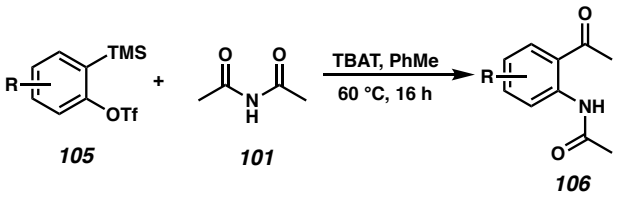


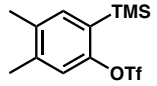
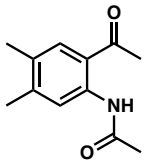
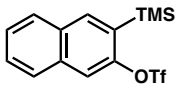
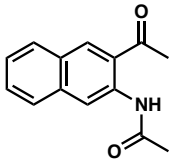
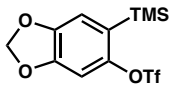
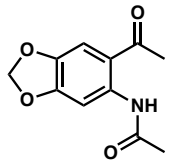
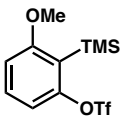
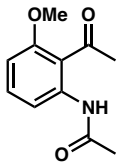
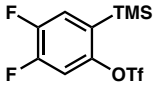
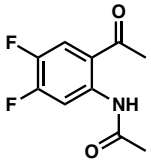
entry	product	R^1	R^2	X	yield (%)[b]
1	***102***	Me	Me	NH	89
2	***104a***	Et	Et	NH	88
3	***104b***	Ph	Ph	NH	68
4	***104c***	*i*-Pr	*i*-Pr	NH	78
5	***104d***	*i*-Bu	*i*-Bu	NH	79
6	***104e***	OMe	Bn	NH	24
7	***104f***	Me	Me	NMe	0
8	***104g***	Me	Me	O	54
9	***104h***	Ph	Ph	O	0

[a]Reaction conditions: TBAT (2.0 equiv), **95** (0.08 M in PhMe), and **92** (1.5 equiv), 60 °C, 16 h. [b]All reported yields are for isolated products.

We next investigated the tolerance of the reaction to other aryne precursors (Table 2.2.3). Gratifyingly, substituted carbocyclic substrates (**105a**–**d**) offered moderate yields of the corresponding aryl ketoamide product (**106a**–**d**). Furthermore, we observed that insertion into an unsymmetrical aryne formed from methoxylated **105d** occurred with good regioselectivity. Unfortunately, the presence of electron-withdrawing fluoride substituents in substrate **105e** failed to undergo insertion.

Table 2.2.3. Aryne Substrate Scope[a]



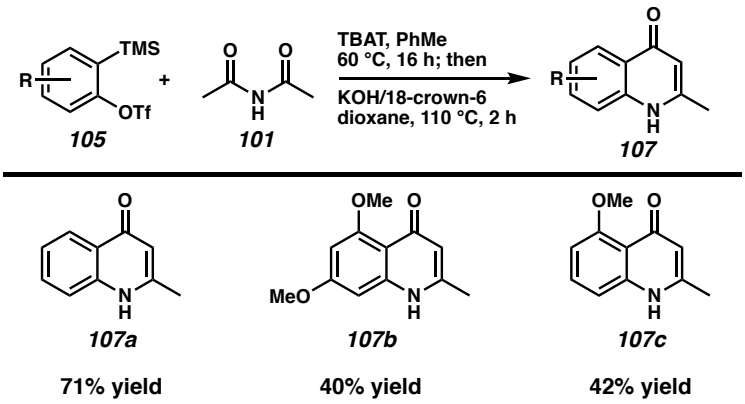
entry	aryne precursor	major product	yield (%)[b]
1	 ***105a***	 ***106a***	31
2	 ***105b***	 ***106b***	44
3	 ***105c***	 ***106c***	65
4	 ***105d***	 ***106d***	47
5	 ***105e***	 ***106e***	0

[a]TBAT (2.0 equiv), **101** (0.08 M in PhMe), and **105** (1.5 equiv), 60 °C, 16 h. [b]All reported yields are for isolated products.

To demonstrate the synthetic utility of this method, we elaborated several of these acylamide insertion products to substituted quinolones via a base-initiated Camps cyclization in a two-step,

one-pot sequence (Figure 2.2.1).[8] Gratifyingly, quinolones **107a–c** were delivered in moderate yield. Moreover, formation of **107b** and **107c** occurred with high regioselectivity for the aryne insertion, producing a single isolable structural isomer in each case.

Figure 2.2.1 Camps Cyclization of Insertion Products to Provide Quinolones



2.3 CONCLUSION

In summary, we have developed a method for inserting arynes into acyclic imides and anhydrides to generate aryl ketoamides and ketoacyloxyarenes, respectively. These products are capable of further derivatization to provide an array of useful scaffolds such as quinolones, indoles, and ketoanilines. Our laboratory is pursuing further development of this technology as it relates to other derivatizations and application in multi-step synthesis.

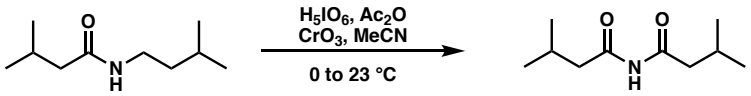
2.4 EXPERIMENTAL SECTION

2.4.1 MATERIALS AND METHODS

Unless otherwise stated, reactions were performed in flame-dried glassware under nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Reaction temperatures were controlled by an IKAmag temperature modulator. Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching. Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.063 mm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded either on a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) or on a Varian Inova 500 (500 MHz and 125 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Preparatory HPLC was performed using an Agilent 1100 Series HPLC utilizing a Zorbax XDB-C18 column purchased from Agilent Technologies. HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI) or mixed (MM) ionization mode or with a JEOL JMS-600H in fast atom bombardment (FAB+).

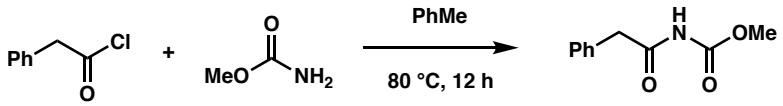
2.4.2 PREPARATIVE PROCEDURES

Imide Synthesis and Characterization Data



108 ***109***

Imide 109: In air, H_5IO_6 (4.42 g, 19.4 mmol, 6.0 equiv), CrO_3 (16.2 mg, 0.16 mmol, 5.0 mol %), and MeCN (46 mL) were sequentially added to a round bottom flask equipped with a magnetic stir bar. The reaction mixture was stirred for 30 minutes at ambient temperature, at which point acetic anhydride (1.8 mL, 19.4 mmol, 6.0 equiv) was added. The mixture was cooled to 0 °C, and **108** (553 mg, 3.23 mmol, 1.0 equiv) was added slowly. The resulting mixture was allowed to warm to ambient temperature over 12 h. The reaction was quenched with ice water and extracted with EtOAc (4 x 40 mL). The resulting organic layers were concentrated in vacuo and purified by column chromatography (20% EtOAc in hexanes) to afford **109** (89 mg, 15% yield) as a white solid; R_f = 0.15 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 2.47 (d, *J* = 9.4, 4H), 2.14 (heptet, *J* = 9.0 Hz, 2H), 0.98 (s, 12 H); ^{13}C (101 MHz, $CDCl_3$) δ 173.9, 46.3, 25.2, 22.4. IR (Neat Film, NaCl) 3272.4, 3170.7, 2957.7, 2871.5, 1728.6, 1505.7, 1466.8, 1386.4, 1367.0, 1294.4, 1246.8, 1181.5, 1160.6, 1120.1, 1090.0 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{10}H_{20}NO_2$ $[M+H]^+$: 186.1494, found 186.1500.

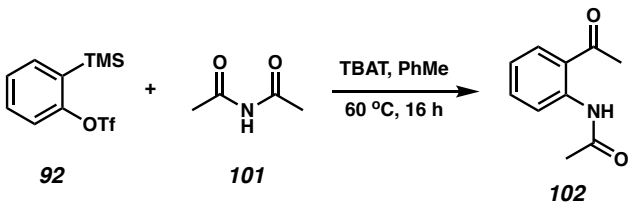


110 ***111*** ***112***

Urethane 112: In air, 2-phenylacetyl chloride (**110**, 309.2 mg, 0.26 mL, 2.00 mmol, 1.0 equiv), methyl carbamate (**111**, 450.4 mg, 6.00 mmol, 3.0 equiv), and PhMe (10 mL) were added.

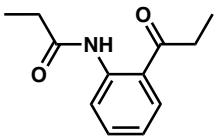
The reaction vessel was heated to 80 °C for 12 h. The reaction was cooled to 23 °C, concentrated, and purified by column chromatography (10% EtOAc in hexanes) to afford **112** (34.1 mg, 9% yield) as white solid; R_f = 0.40 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 7.36–7.33 (m, 2H), 7.31–7.27 (m, 3H), 4.07 (s, 2H), 3.78 (s, 3H); ^{13}C (126 MHz, $CDCl_3$) δ 152.0, 138.5, 133.3, 129.6, 128.6, 127.4, 110.0, 53.1. IR (Neat Film, NaCl) 3246.1, 3172.3, 3014.0, 2259.7, 1788.1, 1757.5, 1686.2, 1520.2, 1455.7, 1257.2, 1216.1, 1192.1, 1144.1, 1049.9, 781.9, 705.3 cm^{-1}; HRMS (ESI-APCI) *m/z* calc'd for $C_{10}H_{12}NO_3$ $[M+H]^+$: 194.0817, found 194.0817.

Aryl Ketoamide Synthesis and Characterization Data



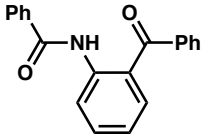
Representative Procedure for Acylamination

A 2-dram vial equipped with a magnetic stir bar was charged with TBAT (144.7 mg, 0.268 mmol, 2.0 equiv) and imide **101** (13.6 mg, 0.134 mmol, 1.0 equiv). The vial was purged with nitrogen, and PhMe (1.6 mL) was added via syringe followed by silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The vial was sealed and placed in an aluminum block preheated to 60 °C. The reaction mixture was stirred at this temperature for 16 h, then it was allowed to cool to 23 °C. The mixture was concentrated in vacuo and purified by column chromatography (10% EtOAc in hexanes) to afford **102** (23.6 mg, 89% yield) as a white solid. Characterization data match those previously reported;[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.70 (s, 1H), 8.74 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 7.3, 8.6 Hz, 1H), 7.12 (dd, *J* = 8.2, 7.3 Hz, 1H), 2.67 (s, 3H), 2.23 (s, 3H).



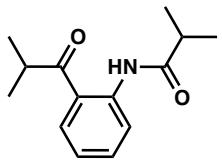
104a

Ethyl ketone 104a: Prepared according to the representative procedure using *N*-propionylpropionamide (17.3 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The reaction was purified by column chromatography (10% EtOAc in hexanes) to afford **104a** (24.0 mg, 88% yield) as a white solid. Characterization data match those previously reported.[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.78 (s, 1H), 8.78 (d, *J* = 9.0 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.57–7.51 (m, 1H), 7.13–7.07 (m, 1H), 3.06 (q, *J* = 7.2 Hz, 2H), 2.50 (q, *J* = 7.6, 2H), 1.31–1.20 (m, 6H).



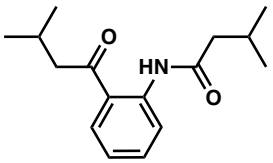
104b

Phenyl ketone 104b: Prepared according to the representative procedure using *N*-benzoylbenzamide (30.2 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The reaction was purified by column chromatography (10% EtOAc in hexanes) to afford **104b** (27.4 mg, 68% yield) as a white solid. Characterization data match those previously reported.[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 8.92 (d, *J* = 8.2 Hz, 1H), 8.11–8.08 (m, 2H), 7.74 (t, *J* = 4.3 Hz, 2H), 7.66–7.59 (m, 3H), 7.56–7.49 (m, 5H), 7.14 (s, 1H).



104c

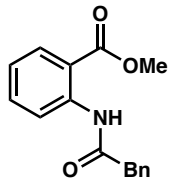
Isopropyl ketone 104c: Prepared according to the representative procedure using *N*-isobutyrylisobutyramide (23.6 mg, 0.150 mmol, 1.0 equiv) and silyl triflate **92** (67.1 mg, 0.225 mmol, 1.5 equiv). Purification was achieved by preparatory HPLC to afford **104c** (27.3 mg, 78% yield) as a white solid; R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.80 (br s, 1H), 8.79 (d, *J* = 6 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 7.53 (t, *J* = 4.5 Hz, 1H), 7.10 (t, *J* = 6 Hz, 1H), 3.65 (sept, *J* = 6 Hz, 1H), 2.62 (sept, *J* = 6 Hz, 1H), 1.28 (d, *J* = 6 Hz, 6H), 1.23 (d, *J* = 6.0 Hz, 6H); ^{13}C (101 MHz, $CDCl_3$) δ 209.2, 176.6, 141.7, 134.8, 130.6, 122.2, 121.1, 120.7, 37.6, 36.3, 19.6 (2 unresolved signals); IR (Neat Film, NaCl) 3251.4, 2970.8, 2903.3, 2872.9, 1700.1, 1653.0, 1604.8, 1583.4, 1521.7, 1517.1, 1467.7, 1450.3, 1383.3, 1356.5, 1350.9, 1301.9, 1239.0, 1211.6, 1157.4, 1099.6, 1083.7, 976.8, 755.1 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1489, found: 234.1490.



104d

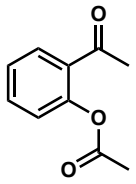
Isobutyryl ketone 104d: Prepared according to the representative procedure using corresponding imide **109** (37.1 mg, 0.200 mmol, 1.0 equiv) and silyl triflate **92** (89.5 mg, 0.300 mmol, 1.5 equiv). Purification was achieved by preparatory HPLC to afford **104d** (41.3 mg, 79% yield) as a white solid. R_f = 0.30 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.73 (br s, 1H), 8.77 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 10.8 Hz, 1H), 7.53 (t, *J* = 9.8 Hz, 1H), 7.10 (t, *J* =

9.8 Hz, 1H), 2.88 (d, *J* = 9.2 Hz, 2H), 2.33–2.19 (m, 4H), 1.03–0.99 (m, 12H); ^{13}C (126 MHz, $CDCl_3$) 205.0, 172.1, 141.0, 134.9, 130.4, 122.2, 121.92, 120.9, 49.0, 48.1, 26.3, 25.6, 22.7, 22.5. IR (Neat Film, NaCl) 3255.4, 2957.6, 2929.9, 2870.7, 1698.8, 1651.9, 1583.5, 1520.0, 1450.7, 1386.2, 1366.0, 1298.9, 1281.3, 1258.1, 1201.8, 1163.5, 1114.3, 1003.9, 947.5, 754.1 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1802, found: 262.1804.



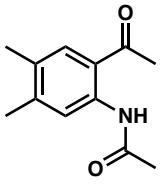
104e

Ester 104e: Prepared according to the representative procedure using carbamate **112** (25.9 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The reaction was purified by column chromatography (10% EtOAc in hexanes) to afford **104e** (8.7 mg, 24% yield) as a white solid. R_f = 0.30 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (br s, 1H), 8.70 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54–7.49 (m, 1H), 7.41–7.28 (m, 5H), 7.08–7.01 (m, 1H), 3.86 (s, 3H), 3.76 (s, 2H); ^{13}C (101 MHz, $CDCl_3$) 170.0, 168.5, 141.4, 134.6, 134.4, 130.8, 129.5, 129.3, 128.9, 127.3, 122.6, 120.4, 52.3, 45.9. IR (Neat Film, NaCl) 2917.9, 1687.6, 1588.4, 1523.0, 1448.6, 1309.3, 1263.3, 1193.6, 1088.9, 756.5 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{16}H_{15}NO_3$ $[M+H]^+$: 270.1125, found: 270.1129.



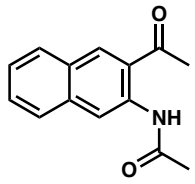
104g

Methyl ketone 104g: Prepared according to the representative procedure using acetic anhydride (13.7 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The reaction was purified by column chromatography (10% EtOAc in hexanes) to afford **104g** (12.8 mg, 54% yield) as a white solid. Characterization data match those previously reported.[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 2.52 (s, 3H), 2.32 (s, 3H).



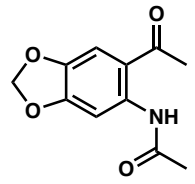
106a

Amide 106a: Prepared according to the representative procedure using imide **101** (8.4 mg, 0.083 mmol, 1.0 equiv) and silyl triflate **105a** (40.5 mg, 0.124 mmol, 1.5 equiv). Purified by column chromatography (10% EtOAc in hexanes) to afford **106a** (6.5 mg, 31% yield) as a white solid. R_f = 0.15 (10% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (br s, 1H), 8.53 (s, 1H), 7.61 (s, 1H), 2.63 (s, 3H), 2.31 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H); ^{13}C (101 MHz, $CDCl_3$) δ 202.4, 169.4, 145.3, 139.1, 132.4, 130.6, 121.5, 119.8, 28.6, 25.6, 20.6, 19.4. IR (Neat Film, NaCl) 3238.4, 2917.3, 1692.5, 1643.4, 1579.0, 1514.1, 1450.2, 1397.3, 1353.6, 1286.8, 1270.0, 1235.1, 1018.7, 876.4, 758.9, 659.3 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1176, found: 206.1171.



106b

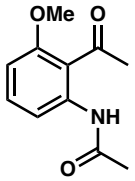
Amide 106b: Prepared according to the representative procedure using imide **101** (29.0 mg, 0.287 mmol, 1.0 equiv) and silyl triflate **105b** (150.0 mg, 0.431 mmol, 1.5 equiv). Purification was achieved by preparatory HPLC to afford **106b** (28.7 mg, 44% yield) as a white solid; R_f = 0.35 (30% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 9.12, (s, 1H), 8.44 (s, 1H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 2.80 (s, 3H), 2.27 (s, 3H); ^{13}C (101 MHz, $CDCl_3$) 203.0, 169.3, 136.7, 136.1, 134.3, 129.7, 128.9, 128.2, 127.7, 125.6, 122.7, 117.7, 28.7, 25.6; IR (Neat Film, NaCl) 3217.8, 1682.2, 1654.4, 1577.0, 1546.1, 1480.7, 1437.2, 1352.5, 1386.4, 1286.3, 1277.9, 1203.7, 1148.0, 1020.5, 953.6, 885.1, 742.1, 656.2 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1019, found: 228.1022.



106c

Dioxolane 106c: Prepared according to the representative procedure using imide **101** (20.4 mg, 0.201 mmol, 1.0 equiv) and silyl triflate **105c** (103.4 mg, 0.302 mmol, 1.5 equiv). Purification was achieved by preparatory HPLC to afford **106c** (28.9 mg, 65% yield) as a white solid; R_f = 0.55 (50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.08 (br s, 1H), 8.37 (s, 1H), 7.25 (s, 1H), 6.02 (s, 2H), 2.57 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 200.6, 169.5, 152.9, 142.4, 139.3, 115.1, 109.6, 102.1, 101.5, 28.8, 25.6. IR (Neat Film, NaCl) 2916.7, 1692.6, 1611.8,

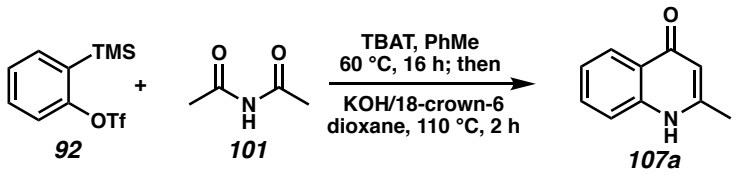
1502.7, 1483.5, 1433.8, 1370.2, 1342.5, 1243.2, 1178.9, 1118.8, 1044.8, 927.0 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{12}NO_4$ $[M+H]^+$: 222.0761, found: 222.0766.



106d

Methyl ether 106d: Prepared according to the representative procedure using imide **101** (13.6 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **105d** (66.0 mg, 0.201 mmol, 1.5 equiv). The reaction was purified by column chromatography (10% EtOAc in hexanes) to afford **106d** (13.0 mg, 47% yield) as a white solid; R_f = 0.20 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.40 (td, *J* = 8.4, 0.5 Hz, 1H), 6.69 (dd, *J* = 8.4, 0.9 Hz, 1H), 2.57 (s, 3H), 3.90 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 169.2, 160.0, 139.2, 133.7, 116.5, 114.0, 106.2, 55.8, 33.7, 25.5; IR (Neat Film, NaCl) 3086.8, 2947.7, 1698.6, 1639.6, 1634.0, 1528.8, 1470.6, 1403.5, 1273.1, 1243.4, 1195.9, 1093.2, 1017.3, 967.4, 802.3, 735.2, 610.8 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{14}NO_3$ $[M+H]^+$: 262.1802, found: 262.1804.

Quinolone Synthesis and Characterization Data

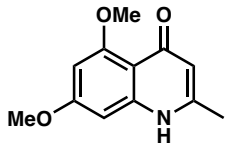


92 ***101*** ***107a***

Representative Procedure for Quinolone Synthesis

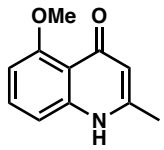
A 2-dram vial equipped with a magnetic stir bar was charged with TBAT (144.7 mg, 0.268 mmol, 2.0 equiv) and imide **101** (13.6 mg, 0.134 mmol, 1.0 equiv). The vial was purged with

nitrogen, and PhMe (1.6 mL) was added via syringe followed by silyl triflate **92** (60.0 mg, 0.201 mmol, 1.5 equiv). The vial was sealed and placed in an aluminum block preheated to 60 °C. The reaction mixture was stirred at this temperature for 16 h, then it was allowed to cool to 23 °C. The mixture was concentrated in vacuo and then charged with dioxane (1.6 mL), KOH (22.6 mg, 0.402 mmol, 3.0 equiv), and 18-crown-6 (106.3 mg, 0.402 mmol, 3.0 equiv). The reaction vial was sealed and heated to 110 °C and stirred for 2 h. The reaction was allowed to cool, diluted with CH_2Cl_2 (10 mL), neutralized to pH ~7, and washed with brine (10 mL). The layers were separated, and the aqueous layer was back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by column chromatography (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to provide **107a** (15.1 mg, 71% yield) as a yellow solid. Characterization data match those previously reported.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.04 (s, 1H), 7.79 (d, *J* = 10.8 Hz, 1H), 7.65–7.62 (m, 2H), 7.40–7.36 (m, 1H), 6.74 (s, 1H), 2.61 (d, *J* = 1.4 Hz, 3H).



107b

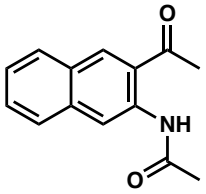
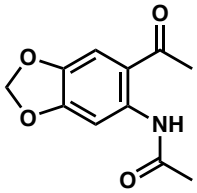
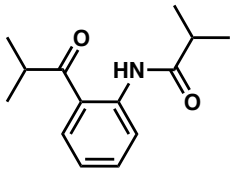
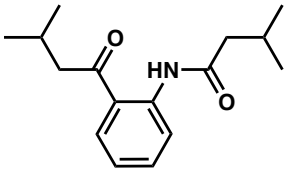
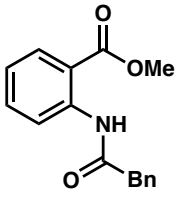
Quinolone 107b: Prepared according to the representative procedure using imide **101** (13.6 mg, 0.134 mmol, 1.0 equiv) and 3,5-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (66.0 mg, 0.201 mmol, 1.5 equiv) to provide quinolone **107b** (11.8 mg, 40% yield) as a brown solid. Characterization data match those previously reported.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.75 (s, 1H), 6.74 (s, 1H), 6.24–6.23 (m, 1H), 3.78 (s, 6H), 2.17 (s, 3H).



107c

Quinolone 107c: Prepared according to the representative procedure using imide **101** (13.6 mg, 0.134 mmol, 1.0 equiv) and silyl triflate **105d** (66.0 mg, 0.201 mmol, 1.5 equiv) to provide quinolone **107c** (10.6 mg, 42% yield) as a beige solid. $R_f = 0.35$ (10% MeOH in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27 (m, 1H), 7.21 (t, *J* = 8.2, 1H), 7.11 (br s, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.67 (dd, *J* = 12.0, 11.2 Hz, 1H), 3.81 (s, 3H), 2.18 (s, 3H); ^{13}C (126 MHz, $CDCl_3$) 168.2, 160.2, 139.1, 134.8, 129.7, 111.8, 110.1, 105.6, 100.0 55.3, 24.8. IR (Neat Film, NaCl) 2920.7, 1664.8, 1598.3, 1548.7, 1492.8, 1425.9, 1369.9, 1252.6, 1156.1, 1044.1, 775.1 cm^{-1}; HRMS (MM: ESI-APCI) *m/z* calc'd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0863, found: 190.0866.

Preparatory HPLC Conditions

Entry	Product	Conditions	Retention Time (min)
1	 ***106b***	HPLC Zorbax XDB-C18 column 20% to 60% MeCN in H_2O 15 min, 30.0 mL/min	13.90
2	 ***106c***	HPLC Zorbax XDB-C18 column 20% to 60% MeCN in H_2O 15 min, 30.0 mL/min	12.75
3	 ***104c***	HPLC Zorbax XDB-C18 column 40% to 80% MeCN in H_2O 15 min, 30.0 mL/min	14.36
4	 ***104d***	HPLC Zorbax XDB-C18 column 40% to 80% MeCN in H_2O 20 min, 30.0 mL/min	17.35
5	 ***104e***	HPLC Zorbax XDB-C18 column 0% to 80% MeCN in H_2O 10 min, 15 mL/min	9.79

2.5 NOTES AND REFERENCES

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