CHAPTER THREE

Development of the Direct Acyl-Alkylation of Arynes

3.1 Background and Introduction

3.1.1 A Brief History of Benzyne

In 1953, Professor John D. Roberts published a communication on the existence of benzyne (**117**), an electronically neutral and unstable benzene ring with a triple bond (Figure 3.1.1).[1] During the last 50 years, this discovery has had a profound impact on the field of organic chemistry.

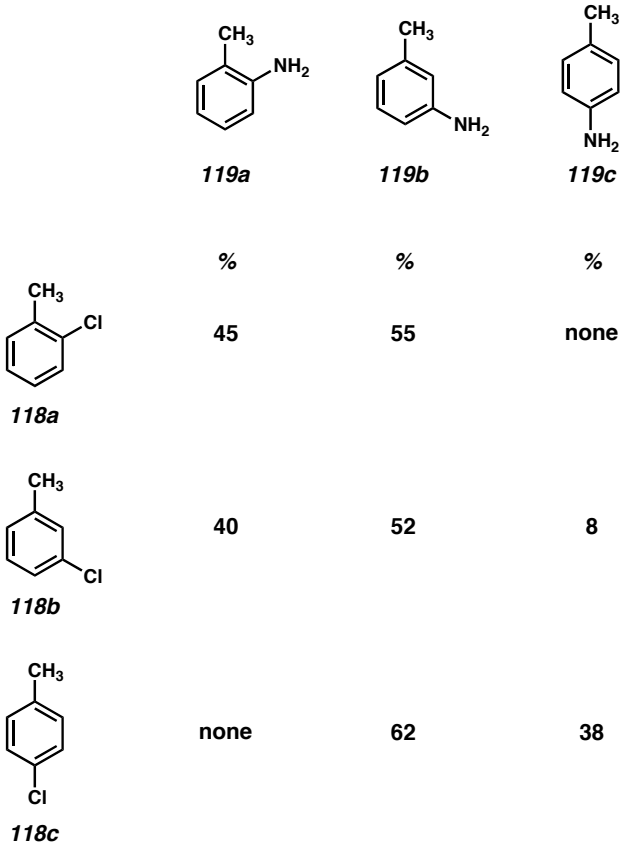
Figure 3.1.1

117

The discovery of benzyne (**117**) was made in the context of Professor Roberts' work to elucidate the mechanism for forming anilines from substituted chloroarenes and metal amides. Before 1953, many chemists believed that metal amides attacked the aromatic ring in an S_NAr fashion, but this mechanism could not account for all of the experimental data on the amination of unsymmetrical haloarenes. For example, while studying the distribution of amination products when sodium amide reacted with

chloromethylbenzenes **118a-c** (Scheme 3.1.1), Professor Roberts observed that both the 2- and 3-chloromethylbenzenes (**118a** and **118b**) formed a mixture of the 2- and 3-methylanilines (**119a** and **119b**).

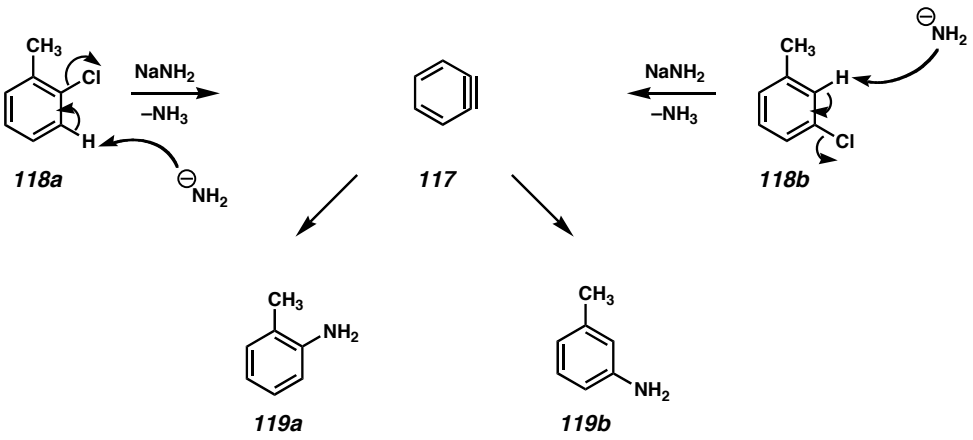
Scheme 3.1.1



Based on this observation and other related studies, Professor Roberts suggested the transient existence of benzyne (**117**) during the amination of halobenzenes (Scheme 3.1.2).[2] Detailed ^{14}C and ^{2}H labeling experiments on the mechanism of aminations of halobenzenes supported this idea.[3] In the last few decades, the existence of benzyne has been proposed to explain the observed reactivity of haloarenes in the presence of other

strong bases.[4] Although there has been some indirect evidence for benzyne based on spectroscopic data and isotope labeling experiments, benzyne was only trapped as a stable guest in hemicarcerand in 2001, 50 years after Professor Roberts' original discovery.[5]

Scheme 3.1.2



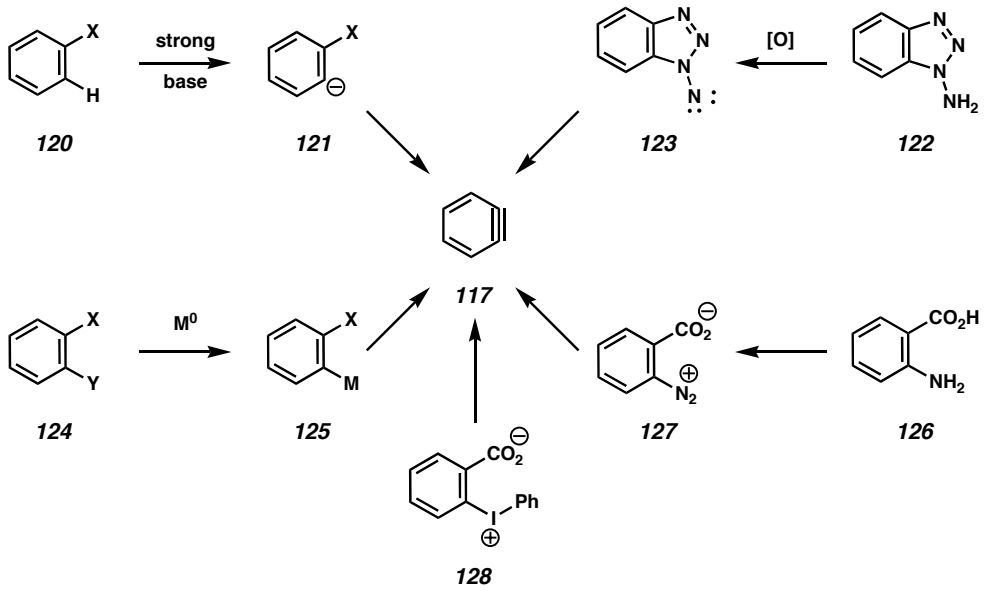
3.1.2 Generation of Arynes

While arynes have historically received much attention from physical organic chemists, their use as reagents in synthetic organic chemistry has been somewhat limited.[6] This is partially attributable to the strongly basic conditions needed to generate arynes and the often uncontrolled reactivity exhibited by these species, even at very low temperatures. Because of their extreme reactivity, arynes must be generated in situ and used immediately. This has limited their use in the development of selective organic

reactions because the harsh conditions that are used to generate arynes may have an adverse effect on other reactants.

Recent advances in the generation of arynes have increased the synthetic utility of these reactive intermediates. The most common methods for generating arynes are summarized in Scheme 3.1.3. Although these are useful methods, in many cases they are still incompatible with certain functionality. Specifically, they may lead to the deprotonation, oxidation, or reduction of other reactants.

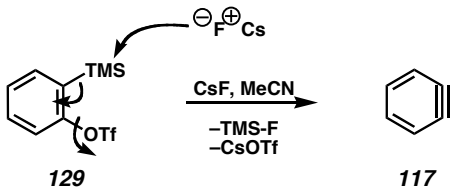
Scheme 3.1.3



In 1983 Kobayashi described a mild method for the in situ preparation of benzyne (**117**) at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (e.g., **129**, Scheme 3.1.4).[7] Recently this method has been used to develop mild reactions involving aryne intermediates. This chapter details the use of

Kobayashi's aryne generation for the direct insertion of arynes into traditionally inert σ-bonds.[8]

Scheme 3.1.4

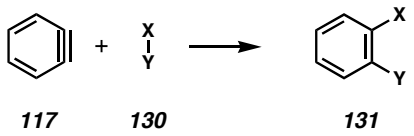


3.1.3 Aryne Insertion into Inert σ-bonds

The direct insertion into traditionally inert σ-bonds is a growing area of chemical research.[9] Specifically, insertions into C-H and C-C bonds are of great interest to synthetic chemists. One strategy for the activation of C-H and C-C bonds relies on the use of reactive reagents that are both kinetically and thermodynamically unstable and therefore more likely to react with these inert σ-bonds. Although Professor Roberts discovered benzyne 50 years ago, only recently have organic chemists realized the potential for this reactive intermediate to insert directly into σ-bonds (Scheme 3.1.5). In 2004, when we began our studies into the reactivity of benzyne, to the best of our knowledge there were still no reported methods on the direct insertion of arynes into C-H or C-C bonds. Nevertheless, there were several examples of aryne insertions into other inert σ-bonds, which produced *ortho*-disubstituted arene systems that would be difficult

to make otherwise (i.e., **131**, Scheme 3.1.5). These insertion reactions are presented in this section.

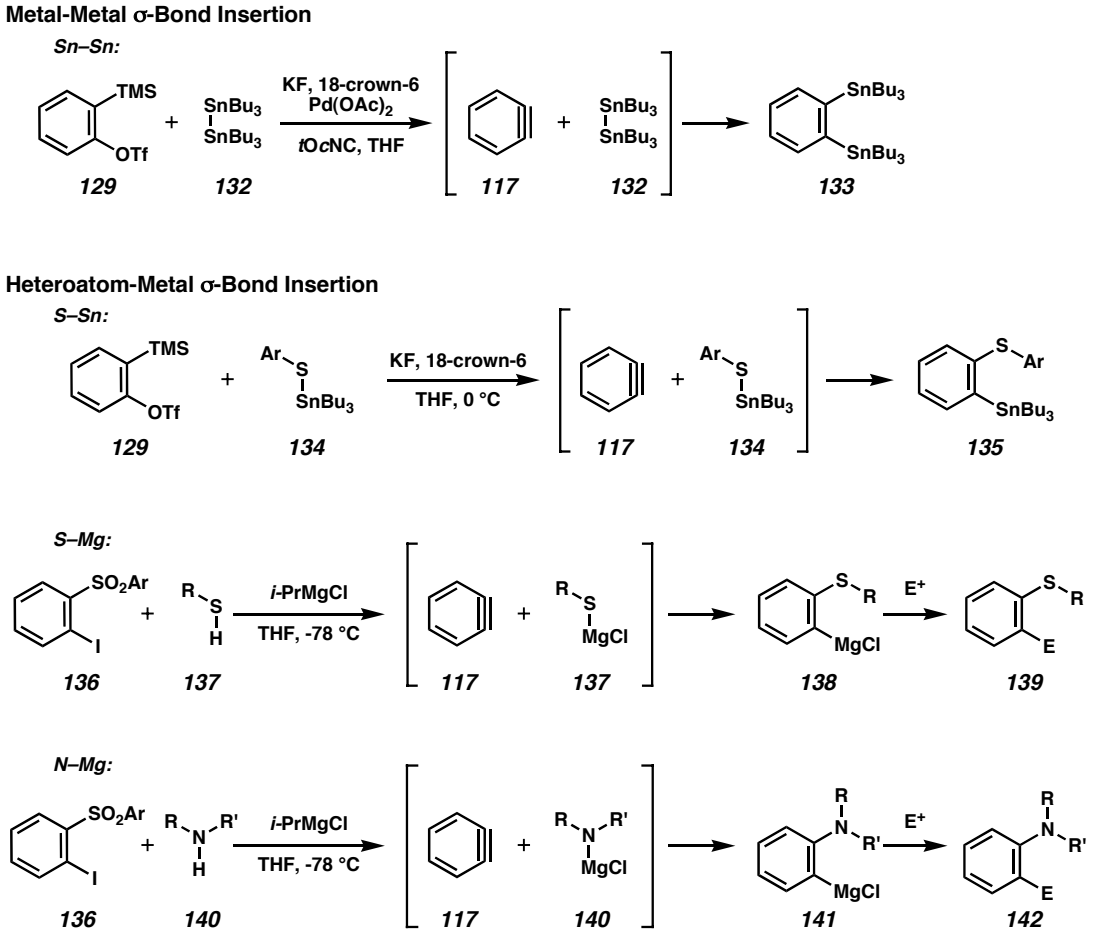
Scheme 3.1.5



117 ***130*** ***131***

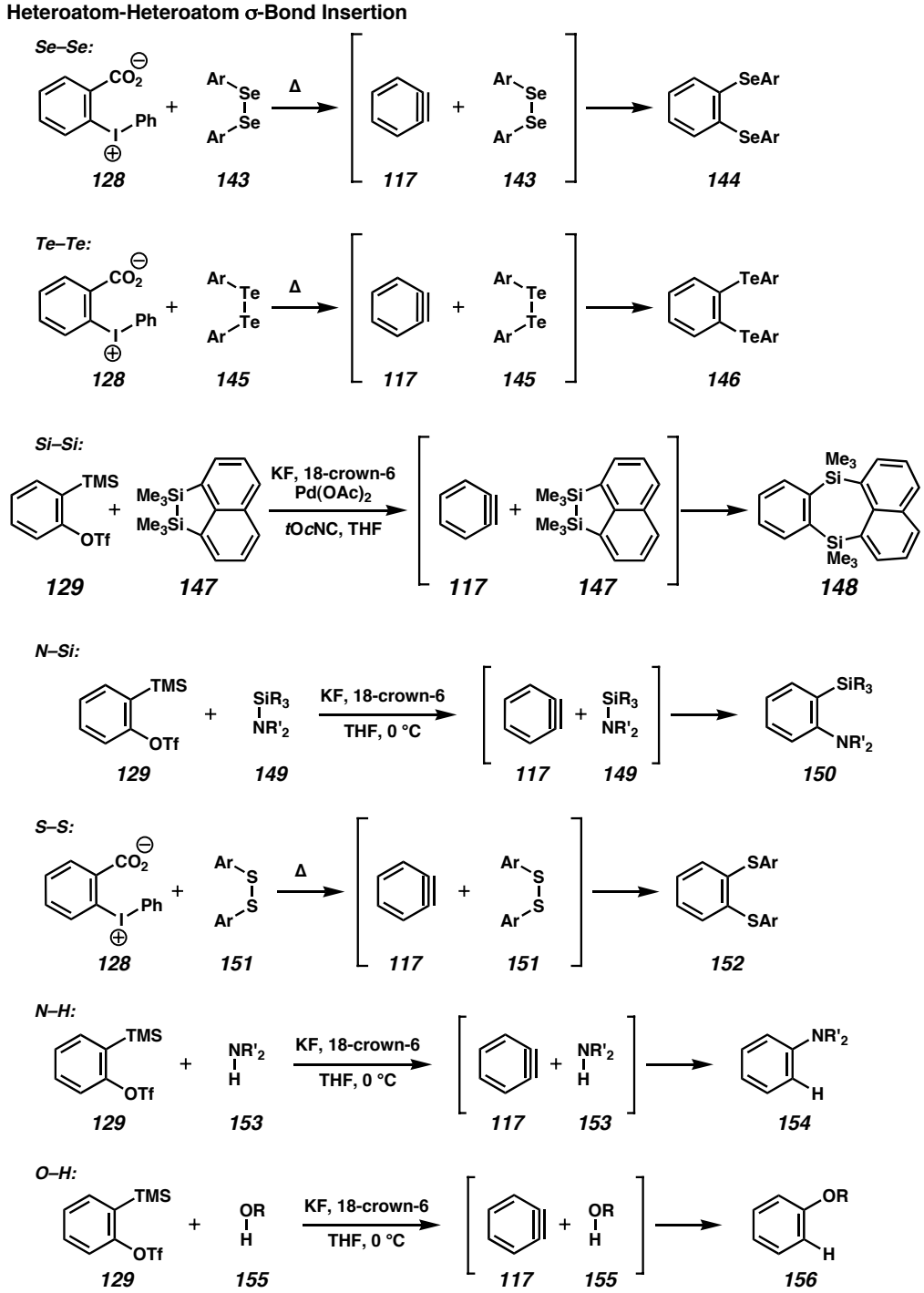
In many cases, σ-bonds containing metal atoms are more susceptible to insertion with arynes. As a result, arynes have been shown to insert into metal-metal σ-bonds, such as Sn-Sn,[10] and heteroatom-metal σ-bonds, such as S-Sn,[11] S-Mg, and N-Mg[12] (Scheme 3.1.6). The products of these reactions contain aryl-metal bonds, which may be further functionalized with electrophiles using known organic transformations (e.g., **139** and **142**).

Scheme 3.1.6



Arynes can also insert into heteroatom-heteroatom σ-bonds, including Se-Se, Te-Te,[13] Si-Si,[14] N-Si,[15] S-S,[16] N-H,[17] and O-H (Scheme 3.1.7).[18] Most notably, the N-H and O-H insertion reactions produce synthetically useful anilines (**154**) and phenols (**156**).

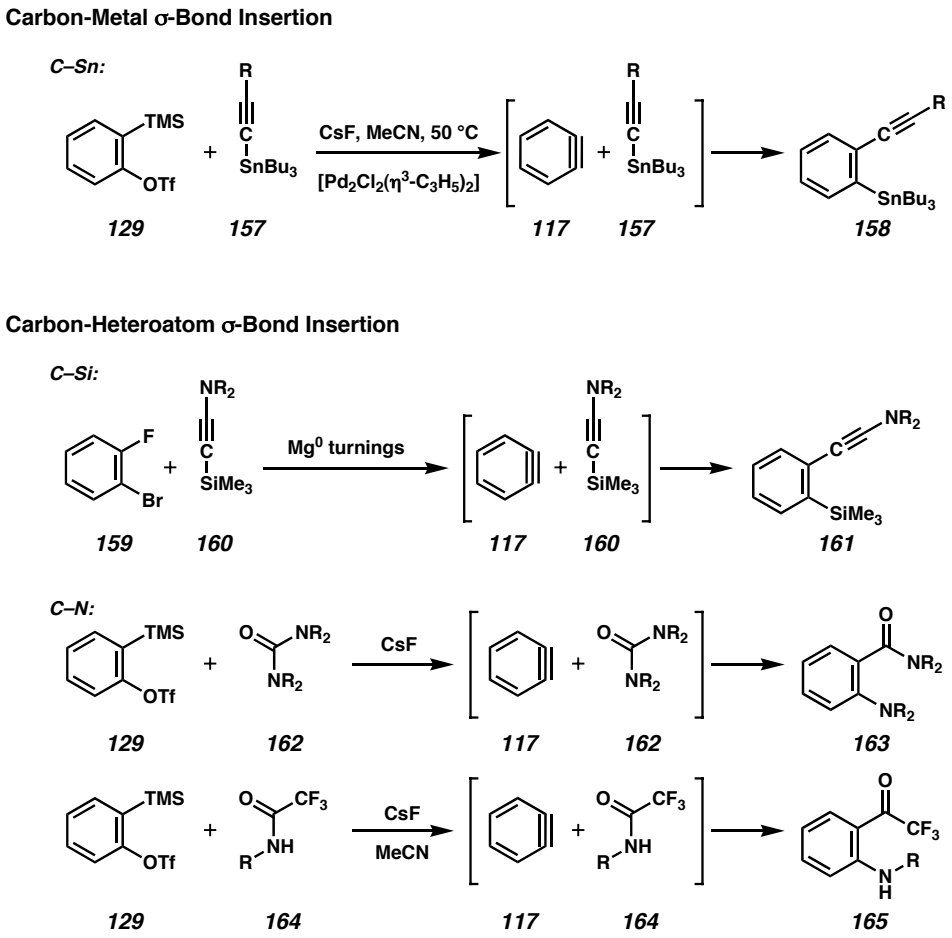
Scheme 3.1.7



The development of mild and direct aryne insertions into carbon containing σ-bonds would produce synthetically useful arenes in an efficient manner. Initial progress

in this area has focused on insertion into carbon-metal σ-bonds, including C-Sn (Scheme 3.1.8).[19] Recently, aryne insertions into carbon-heteroatom σ-bonds, such as C-Si[20] and C-N,[21] have also been reported.

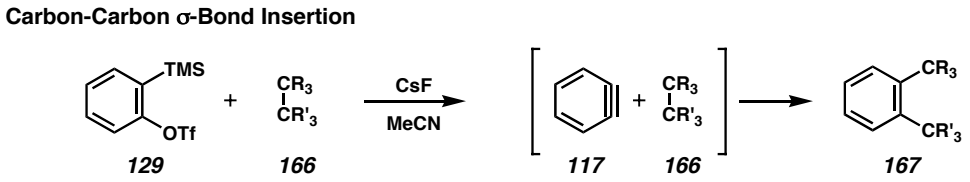
Scheme 3.1.8



Although there have been significant advances in the field of aryne insertion into σ-bonds, at the onset of our explorations into aryne chemistry there were no reports on the direct aryne insertion in C-C σ-bonds. These reactions would construct *ortho*-carbon-substituted arene frameworks (**167**) that are difficult to make by known methods (Scheme

3.1.9). In the next section, we describe our efforts to develop this mild and direct C-C insertion reaction.

Scheme 3.1.9



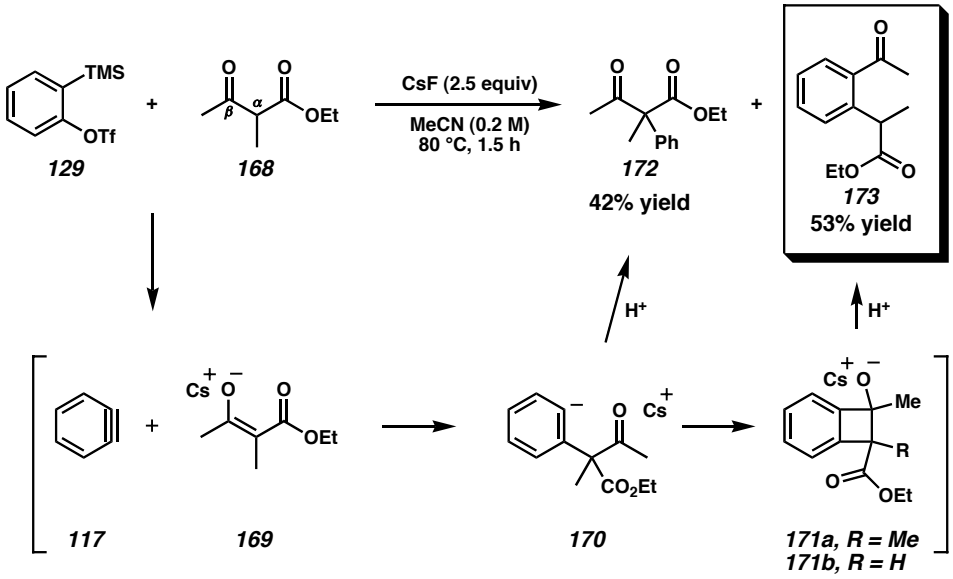
3.2 Development of the Acyl-Alkylation of Arynes

3.2.1 Serendipitous Discovery

As described in the previous section, in 1983 Kobayashi reported a mild method for the in situ preparation of benzyne (**117**) at moderate temperatures that exploits the fluoride-induced elimination of *ortho*-silyl aryltriflates (Scheme 3.1.4). We envisioned that arynes generated by this method could serve as a platform for the production of quaternary benzylic stereocenters. Specifically, we anticipated that the mild conversion of **129** to benzyne (**117**) in the presence of β-ketoester **168** would produce **172** (Scheme 3.2.1). To our surprise, in addition to obtaining the expected β-ketoester **172**, we observed the interesting *ortho*-substituted product **173** in comparable yield. The acyl-alkylation product **173** is the net result of benzyne insertion into the α,β C–C single bond of the β-ketoester, presumably by a formal [2+2] cycloaddition/fragmentation cascade

(i.e., **129→117→170→171a→173**). While aryne insertions into metal–metal, heteroatom-metal, heteroatom-heteroatom, carbon-metal, and carbon-heteroatom σ-bonds have been reported under mild conditions, we were intrigued by our result because it represents the first mild and direct aryne insertion into a carbon–carbon σ-bond.[22,23] The following sections will describe our explorations into the scope of this acyl-alkylation of arynes as an efficient method for the generation of interesting *ortho*-disubstituted arenes and benzannulated carbocycles.

Scheme 3.2.1

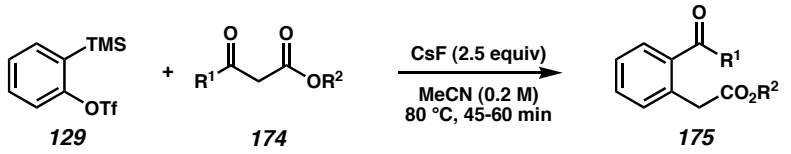


3.2.2 Acyl-Alkylation of Benzyne with Simple β-Ketoesters

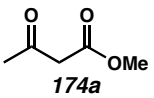
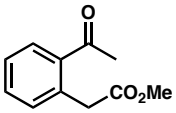
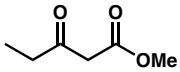
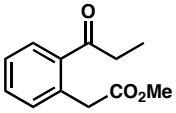
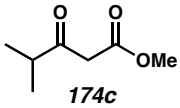
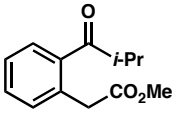
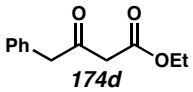
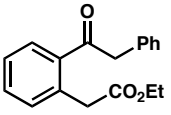
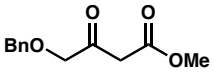
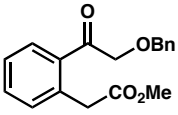
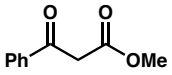
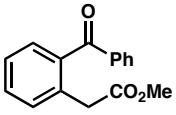
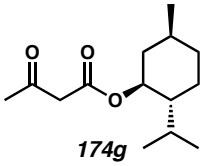
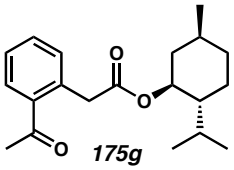
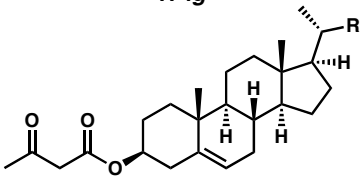
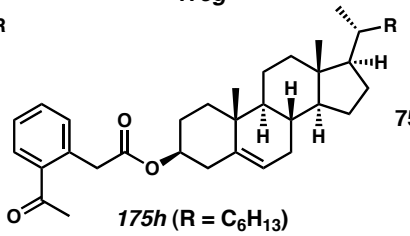
As we began our investigation into the formation of the acyl-alkylation product, we hypothesized that β-ketoesters lacking α-substitution might form the putative

benzocyclobutene intermediate (i.e., **171b**, Scheme 3.2.1) more readily, thus suppressing the α-arylation product. In support of this hypothesis, higher yields of the *ortho*-disubstituted product were obtained from the treatment of non α-substituted β-ketoesters (i.e., **174a-h**) with **129** in the presence of CsF (Table 3.2.1). The reaction tolerates substitution at the γ-position (entries 2-6), including aliphatic and aromatic groups. Heteroatoms may also be incorporated into the β-ketoester sidechain, albeit in slightly lower yields (entry 5). Additionally, the ester moiety can be varied while maintaining the efficiency of the reaction. For example, β-ketoesters of more complex alcohols such as menthol and cholesterol provide the desired acyl-alkylation products in good yield (entries 7 and 8). In general, the mild reaction conditions allow for a considerable degree of substitution on the β-ketoester subunit.

Table 3.2.1



129 *174* *175*

entry	*substrate* [a]	*product*	*yield* [b]
1	 *174a*	 *175a*	90%
2	 *174b*	 *175b*	78%
3	 *174c*	 *175c*	84%
4[c]	 *174d*	 *175d*	85%
5	 *174e*	 *175e*	53%
6	 *174f*	 *175f*	99%
7	 *174g*	 *175g*	72%
8	 *174h* (R = C_6H_{13})	 *175h* (R = C_6H_{13})	75%

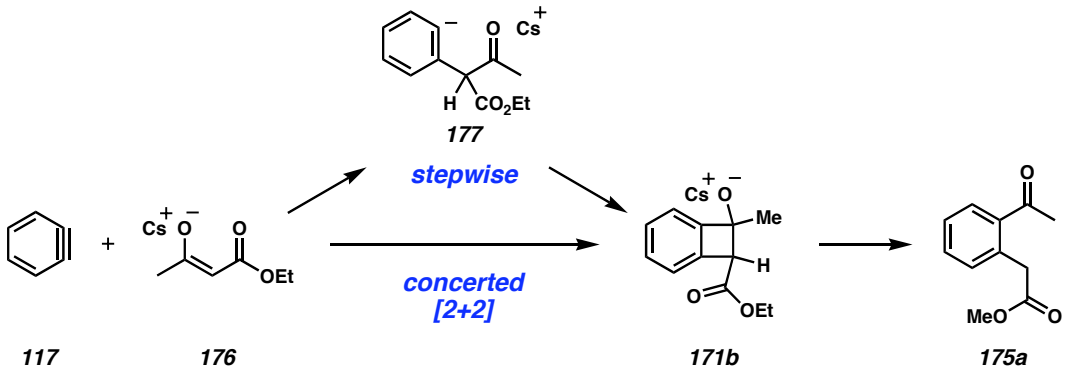
[a] 1.25 equiv of **129** relative to β-ketoester **174**. [b] Isolated yield.

[c] 2 equiv of **129** relative to **174d**.

3.2.3 Mechanistic Insight into the Acyl-Alkylation of Benzyne

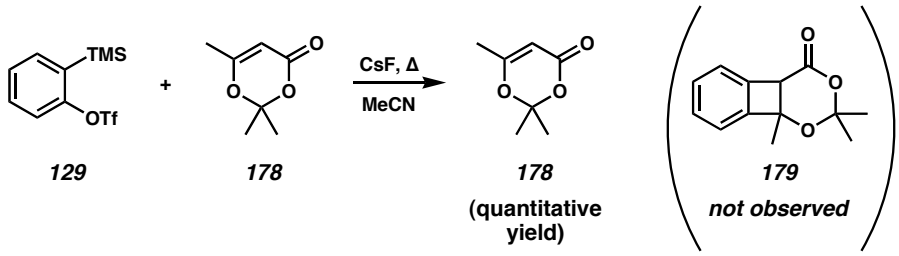
Although we were confident of the need to form the benzocyclobutene **171b** en route to the acyl-alkylated arene product **175a**, we were uncertain whether this four-membered ring structure was formed by a concerted [2+2] cycloaddition or in a more stepwise fashion (i.e., **117**→**177**→**171b**, Scheme 3.2.2).

Scheme 3.2.2



To probe this mechanistic subtlety, we subjected enol ether **178** to the reaction conditions (Scheme 3.2.3). This stable compound is a surrogate for enolate **176**. We reasoned that enol ether **178** would only be able to react with benzyne (**117**) in a concerted [2+2] fasion. Under the optimized reaction conditions, enol ether **178** was recovered in almost quantitative yield. Since the stepwise formation of benzocyclobutene **179** is inaccessible to enol ether **178**, we reasoned that the formation of the four-membered intermediate in the acyl-alkylation reaction must likely proceed in a stepwise fashion.

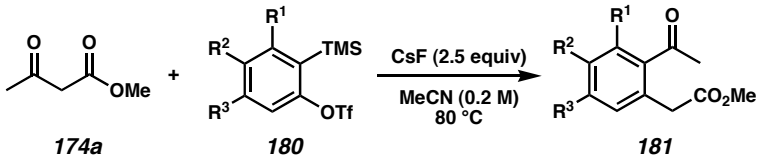
Scheme 3.2.3



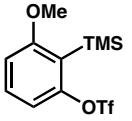
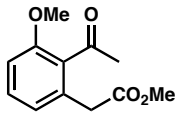
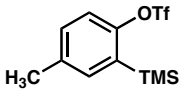
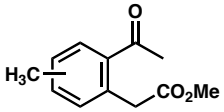
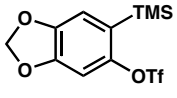
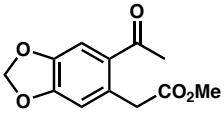
3.2.4 Acyl-Alkylation of Other Arynes

We next examined the coupling of substituted aryne precursors **180a-c** with methyl acetoacetate **174a** (Table 3.2.2). To our delight, this simple β-ketoester reacted with arynes possessing mono-substitution at the *ortho*- and *meta*-positions (entries 1-2) as well as disubstitution (entry 3) to produce high yields of the corresponding acyl-alkylation products (**181a-c**). Additionally, entries 1 and 3 demonstrate that heteroatom substituents are well tolerated. Of particular note is the complete regioselectivity and excellent isolated yield observed in the coupling of methoxy substituted aryne precursor **180a** with **174a**. This high selectivity points toward stepwise production of the key benzocyclobutene intermediate, analogous to the mechanism depicted in Scheme 3.2.3.

Table 3.2.2



174a *180* *181*

entry	*aryne precursor* [a]	*product*	*yield* [b]
1	 *180a*	 *181a*	95%
2[c]	 *180b*	 *181b*	82%[d]
3	 *180c*	 *181c*	75%

[a] 2 equiv of **180** relative to **174a**. [b] Isolated yield. [c] 1.25 equiv of **180b** relative to **174a**.

[d] Mixture of *meta*- and *para*- regioisomers (1.2 : 1).

3.2.5 Acyl-Alkylation of Benzyne with Cyclic β-Ketoesters: Ring Expansion

At this stage, we revisited β-ketoesters with α-substitution. We anticipated difficulty for such reactions based on our original observation that competitive formation of α-arylated products occurred, presumably due to steric congestion en route to the key benzocyclobutene. Nevertheless, we believed that these reactions could provide efficient access to an interesting class of structures that would otherwise be difficult to obtain. Specifically, we envisioned that cyclic β-ketoesters would undergo ring expansion to

furnish medium-sized carbocycles, which continue to be difficult structures to synthesize despite their prevalence in natural products and drug substances.[24] Gratifyingly, the expansion of a 5-membered ring (**182a**) furnished a 7-membered carbocycle (**185a**) in 50% yield (Scheme 3.2.4). We then applied our optimized conditions to a series of cyclic β-ketoesters of varying ring-size (Table 3.2.3). As a result, we were able to synthesize several 7-membered benzannulated structures in synthetically useful yields by employing 5-membered ring β-ketoesters (entries 1-3). While the insertion into a 6-membered ring was less efficient (entry 4), the expansion of a 7-membered ring furnished a 9-membered carbocycle in 69% yield (entry 5).

Scheme 3.2.4

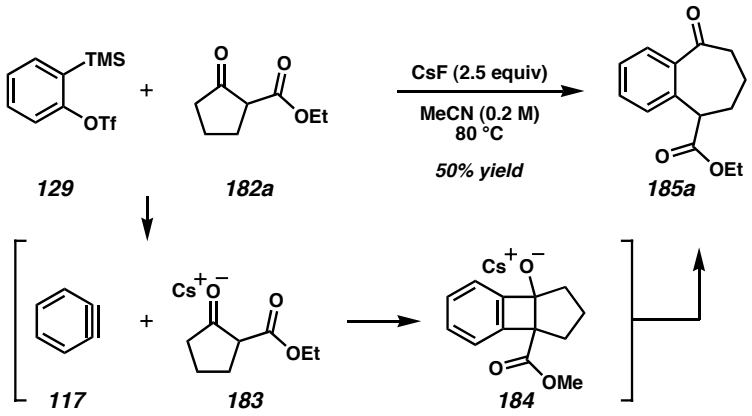
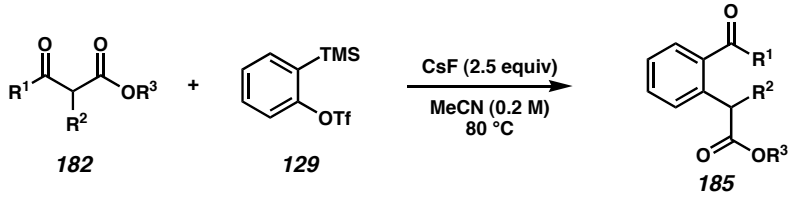
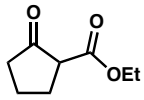
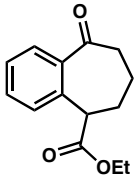
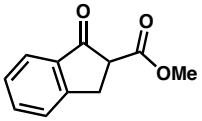
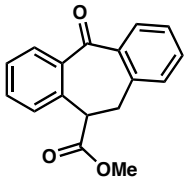
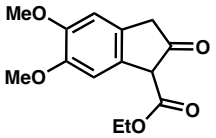
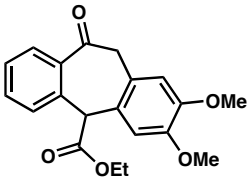
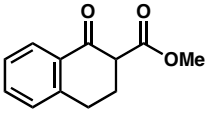
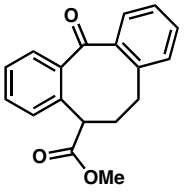
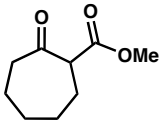
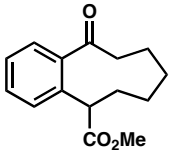


Table 3.2.3



entry	*substrate* [a]	*product*	*yield* [b,c]
1	 *182a*	 *185a*	50%
2	 *182b*	 *185b*	61%
3	 *182c*	 *185c*	65%
4	 *182d*	 *185d*	45%
5	 *182e*	 *185e*	69%

[a] 1.25 equiv of **129** relative to β-ketoester **182**. [b] Isolated yield. [c] In some cases the α-arylated β-ketoester was isolated as the major side product. See experimental section (3.4.3).

3.3 Conclusion

In summary, we have developed a mild, direct, and efficient process for the acyl-alkylation of arynes to produce interesting *ortho*-substituted arenes via an unusual reaction cascade. Overall, the transformation results in the formation of two new C–C bonds by the net insertion of an arene unit into the α,β C-C σ-bond of a β-ketoester. This facile methodology provides convergent, single-step, high-yielding access to a variety of substituted arenes and benzannulated structures that would otherwise be difficult to obtain. Notably, cyclic β-ketoesters can be expanded to generate medium-sized carbocycles.

3.4 Experimental Section

3.4.1 Materials and Methods

Unless stated otherwise, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry, deoxygenated solvents. Commercially obtained reagents were used as received. Cesium fluoride was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E.

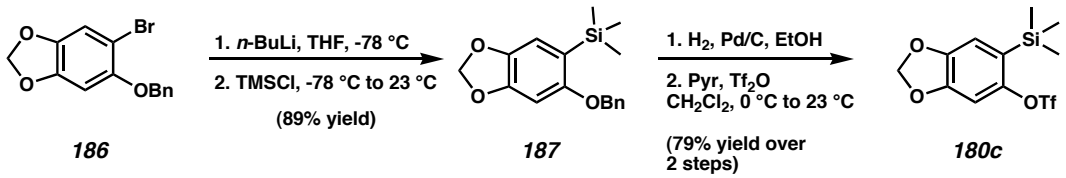
Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized using a combination of UV, anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining. ICN silica gel (particle size 0.032 - 0.063 mm) was used for flash chromatography. ^{1}H NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) or a Varian Inova 500 (at 500 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 75 MHz) or a Varian Inova 500 (at 125 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift. ^{19}F NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz) and are reported relative to CF_3COOH (δ -76.54). Data for ^{19}F NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

3.4.2 Preparative Procedures

Synthesis of Aryne Precursors

Aryne precursor 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) was purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Aryne precursors 3-methoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**180a**)[25] and 4-

methyl-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**180b**)[26] were prepared according to literature procedures.



186 *187* *180c*

Aryl intermediate 187. A flame-dried reaction flask equipped with a magnetic stir bar was charged with benzyl protected sesamol **186**[27] (325 mg, 1.06 mmol, 1.0 equiv) in THF (3.5 mL, 0.3 M), and the mixture was cooled to –78 °C in a dry ice/acetone bath. A 2.5 M solution of *n*-BuLi in hexanes (634 μL, 1.59 mmol, 1.5 equiv) was added slowly at -78 °C. After 15 min, TMSCl (200 μL, 1.59 mmol, 1.5 equiv) was added slowly at -78 °C. After 5 min the cold bath was removed and the reaction mixture was allowed to warm to 23 °C. After 15 min the mixture was quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided aryl intermediate **187** (282 mg, 89% yield) as a clear oil: R_F 0.57 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.29 (m, 5H), 6.85 (s, 1H), 6.53 (s, 1H), 5.91 (s, 2H), 5.01 (s, 2H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 149.6, 141.5, 137.3, 128.7, 128.0, 127.5, 119.3, 113.7, 101.3, 95.2, 71.0, -0.5; IR (thin film/NaCl) 2953, 2894,

1606, 1502, 1473, 1410, 1386, 1243, 1177, 1042 cm^{-1}; HRMS (EI^+) calc'd for $[C_{17}H_{20}O_3Si]^+$: *m/z* 300.1182, found 300.1187.

Aryne Precursor 180c. A reaction flask equipped with a magnetic stir bar was charged with aryl intermediate **187** (1.24 g, 4.13 mmol, 1 equiv) in absolute EtOH (17 mL, 0.25 M). To this mixture was added 10% Pd/C (440 mg, 0.413 mmol, 0.1 equiv), and the reaction vessel was stirred at 23 °C under a balloon of H_2 (1 atm). After 14 h the mixture was filtered through a short pad of celite (Et_2O eluent), and the solvent was evaporated under reduced pressure to afford a colorless oil, which was used immediately without further purification.

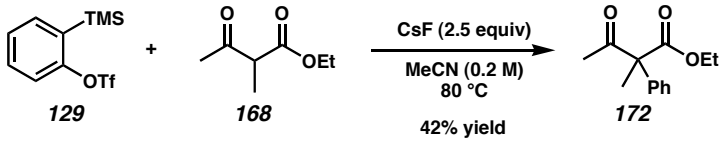
A flame-dried reaction flask equipped with a magnetic stir bar was charged with the *ortho*-silyl phenol in CH_2Cl_2 (20 mL, 0.2 equiv), and the mixture was cooled to 0 °C. Pyridine (1.05 mL, 13 mmol, 3 equiv) and Tf_2O (1.46 mL, 8.67 mmol, 2 equiv) were sequentially added, and the reaction mixture was allowed to warm to 23 °C. After 5.5 h the mixture was extracted with H_2O (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes/CH_2Cl_2 eluent) provided aryne precursor **180c** (1.12 g, 79% yield) as a clear oil: R_F 0.54 (3:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.84 (s, 1H), 6.03 (s, 2H), 0.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 148.8, 147.1, 125.1, 113.4, 113.4, 102.6, 102.5, -0.5; ^{19}F NMR (300 MHz, $CDCl_3$) δ -74.63; IR (thin film/NaCl) 2960, 2903, 1479, 1422, 1247, 1216, 1141, 984, 843 cm^{-1}; HRMS (EI^+) calc'd for $[C_{11}H_{13}O_5F_3SiS]^+$: *m/z* 342.0205, found 342.0211.

Synthesis of β-Ketoester Substrates

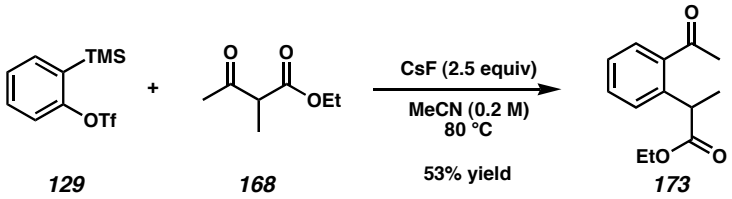
Methyl acetoacetate (**174a**), ethyl 2-methyl-3-oxobutanoate (**168**), ethyl 2-oxocyclopentanecarboxylate (**182a**), and methyl 2-oxocycloheptanecarboxylate (**182e**) were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI. Substrates **174b,**[28] **174c,**[29] **174d,**[30] **174e,**[31] **174f,**[32] **174g,**[33] **174h,**[34] **182b,**[35] **182c,**[36] and **182d**[37] were prepared according to literature procedures.

Representative procedure for the acyl-alkylation of arynes (Tables 3.2.1, 3.2.2, and 3.2.3): A flame-dried 11 cm long reaction tube equipped with a magnetic stir bar was charged with acetonitrile (2 mL). Methyl acetoacetate (**174a**) (43.2 μL, 0.4 mmol, 1.0 equiv), 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**129**) (121.4 μL, 0.5 mmol, 1.25 equiv), and cesium fluoride (152 mg, 1.0 mmol, 2.5 equiv) were sequentially added to the flask. A septum was placed on the reaction vessel, and the mixture was then heated at 80 °C for 45-60 min. When benzyne precursor **129** was consumed by TLC analysis, the mixture was extracted with brine (4 mL). The aqueous layer was extracted with Et_2O (3 x 4 mL). The organics were combined and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and purified by flash chromatography.

3.4.3 Spectral Data

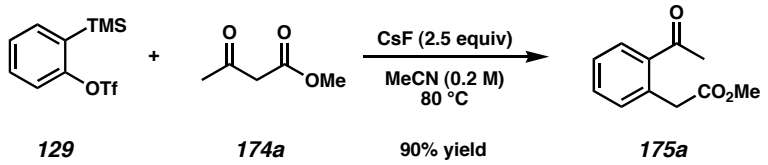


172. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (37.1 mg, 42% yield) as a clear oil: R_F 0.36 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.27 (m, 5H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.10 (s, 3H), 1.77 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 172.1, 138.8, 128.8, 127.9, 127.5, 64.9, 61.8, 27.4, 21.6, 14.2; IR (thin film/NaCl) 2986, 1715, 1251 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1089.

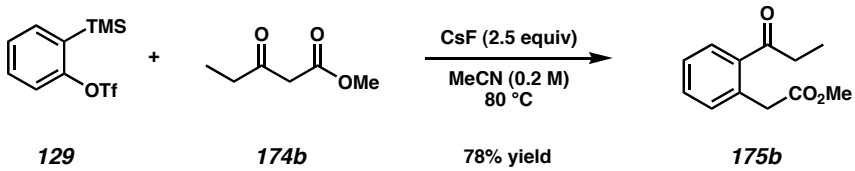


173. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (46.4 mg, 53% yield) as a clear oil: R_F 0.42 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.49-7.29 (m, 3H), 4.41 (q, *J* = 7.0 Hz, 1H), 4.17-4.05 (m, 2H), 2.59 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 174.8, 140.4, 137.8,

132.0, 129.3, 128.8, 126.9, 60.8, 41.7, 29.9, 18.4, 14.3; IR (thin film/NaCl) 2982, 1731, 1687, 1201 cm^{-1}; HRMS (EI^+) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1091.

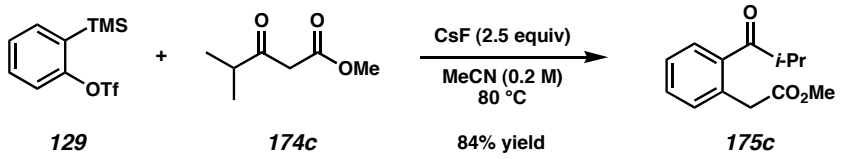


175a. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (69 mg, 90% yield) as a clear oil: R_F 0.46 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.47-7.33 (m, 2H), 7.24-7.20 (m, 1H), 3.91 (s, 2H), 3.66 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 172.0, 137.1, 134.4, 132.8, 132.1, 130.1, 127.5, 51.9, 40.2, 28.8; IR (thin film/NaCl) 3001, 2952, 1739, 1683 cm^{-1}; HRMS (EI^+) calc'd for $[C_{11}H_{12}O_3]^+$: *m/z* 192.0787, found 192.0787.

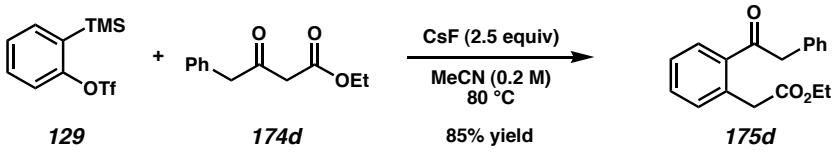


175b. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (64.7 mg, 78% yield) as a clear oil: R_F 0.32 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48-

7.31 (m, 2H), 7.26-7.22 (m, 1H), 3.92 (s, 2H), 3.68 (s, 3H), 2.97 (q, *J* = 7.3 Hz, 2H), 1.18 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 172.2, 137.7, 134.2, 132.7, 131.8, 129.1, 127.5, 52.0, 40.1, 34.0, 8.4; IR (thin film/NaCl) 2979, 2951, 1739, 1685, 1225, 1165 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{12}H_{14}O_3]^+$: *m/z* 206.0943, found 206.0933.

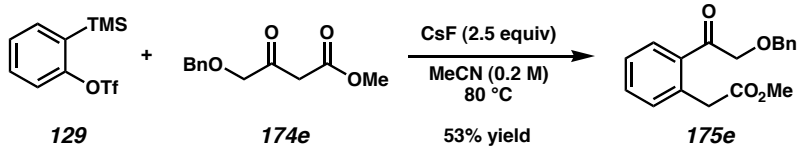


175c. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (71.9 mg, 84% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.4 Hz, 1H), 7.53-7.25 (m, 3H), 3.91 (s, 2H), 3.72 (s, 3H), 3.56-3.44 (m, 1H), 1.21 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.9, 172.2, 137.2, 134.7, 132.9, 131.7, 128.9, 127.5, 52.0, 40.0, 37.7, 19.0; IR (thin film/NaCl) 2973, 1741, 1683, 1229, 1165 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{13}H_{16}O_3]^+$: *m/z* 220.1100, found 220.1094.



129 *174d* 85% yield *175d*

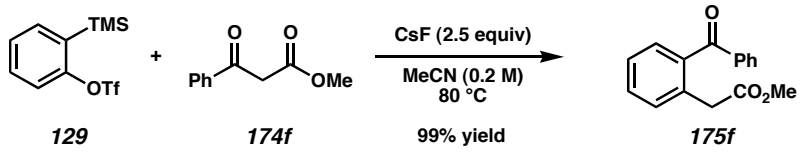
175d. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (95.5 mg, 85% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.49-7.24 (m, 8H), 4.28 (s, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.92 (s, 2H), 1.25 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 171.7, 137.6, 134.7, 132.8, 131.9, 129.8, 129.4, 128.8, 128.7, 127.5, 127.0, 60.9, 47.8, 40.1, 14.4; IR (thin film/NaCl) 3362, 2982, 1732, 1690, 1216, 1175 cm^{-1}; HRMS (EI^+) calc'd for $[C_{18}H_{18}O_3]^+$: *m/z* 282.1256, found 282.1266.



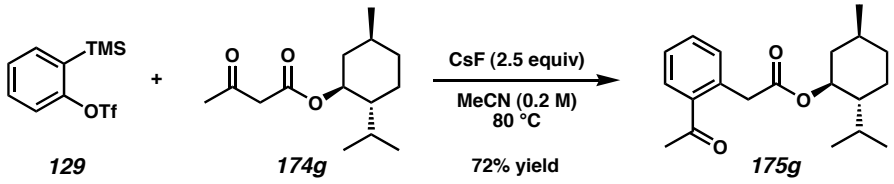
129 *174e* 53% yield *175e*

175e. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (66.2 mg, 53% yield) as a clear oil: R_F 0.28 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.48 (app. dt, *J* = 7.6, 1.4 Hz, 1H), 7.41-7.27 (m, 7H), 4.68 (s, 2H), 4.67 (s, 2H), 3.97 (s, 2H), 3.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 172.1, 137.5, 135.3, 134.7, 132.9,

132.4, 129.0, 128.7, 128.3, 128.2, 127.5, 73.6, 73.4, 52.2, 39.7; IR (thin film/NaCl) 3030, 2950, 1736, 1700, 1230, 1213, 1167, 1110 cm^{-1}; HRMS (EI^+) calc'd for (M-H) $[C_{18}H_{17}O_4]^+$: *m/z* 297.1127, found 297.1136.

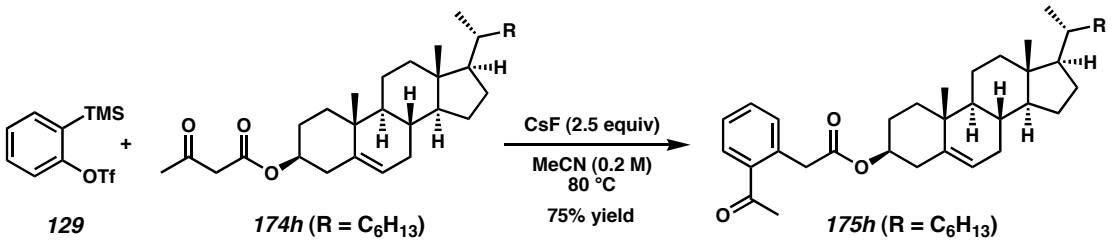


175f. Purification by flash chromatography (10:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (101 mg, 99% yield) as a clear oil: R_F 0.38 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.84-7.79 (m, 1H), 7.61-7.54 (m, 1H), 7.50-7.30 (m, 7H), 3.90 (s, 2H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 171.8, 138.4, 137.9, 134.1, 133.1, 131.9, 131.0, 130.5, 130.2, 128.4, 126.7, 52.0, 38.8; IR (thin film/NaCl) 2951, 1739, 1662, 1270 cm^{-1}; HRMS (EI^+) calc'd for $[C_{16}H_{14}O_3]^+$: *m/z* 254.0943, found 254.0952.



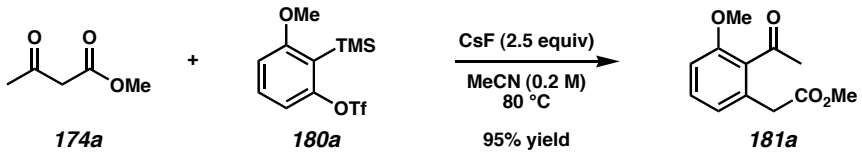
175g. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (90.7 mg, 72% yield) as a clear oil: R_F 0.50

(3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.51-7.34 (m, 2H), 7.28 (dd, *J* = 7.4, 1.1 Hz, 1H), 4.76-4.66 (m, 1H), 3.97 (s, 2H), 2.62 (s, 3H), 2.11-2.02 (m, 1H), 1.98-1.86 (m, 1H), 1.75-1.64 (m, 2H), 1.58-1.33 (m, 3H), 1.11-1.00 (m, 2H), 0.93 (d, *J* = 4.3 Hz, 3H), 0.91 (d, *J* = 5.1 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 171.3, 137.7, 134.6, 132.7, 131.9, 129.8, 127.4, 74.8, 47.2, 41.0, 40.6, 34.4, 31.6, 29.0, 26.3, 23.6, 22.2, 20.9, 16.5; IR (thin film/NaCl) 2955, 2929, 2870, 1732 1687, 1258, 1172 cm^{-1}; HRMS (EI^{+}) calc'd for $[C_{20}H_{28}O_3]^{+}$: *m/z* 316.2039, found 316.2034.

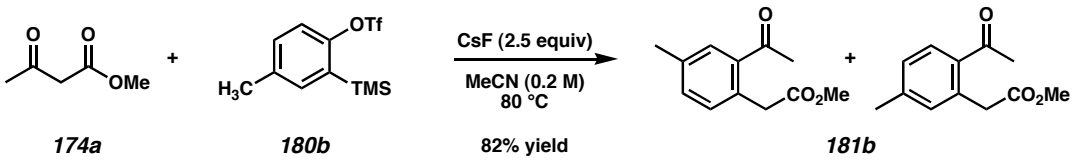


175h. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (163.5 mg, 75% yield) as a clear oil: R_F 0.50 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.48-7.33 (m, 2H), 7.24 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.36 (d, *J* = 5.1 Hz, 1H), 4.72-4.55 (m, 1H), 3.91 (d, *J* = 1.6 Hz, 2H), 2.59 (s, 3H), 2.35 (d, *J* = 7.7 Hz, 2H), 2.05-1.76 (m, 5H), 1.70-1.05 (m, 21H), 1.02 (s, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (dd, *J* = 6.5, 1.2 Hz, 6H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 171.2, 139.9, 137.5, 134.7, 132.8, 132.1, 130.0, 127.5, 122.7, 74.6, 56.9, 56.3, 50.2, 42.5, 40.7, 39.9, 39.7, 38.2, 37.2, 36.8, 36.4, 36.0, 32.1, 32.0, 29.0, 28.4, 28.2, 27.9, 24.5, 24.0, 23.0, 22.8, 21.2, 19.5, 18.9, 12.0; IR

(thin film/NaCl) 3451, 2946, 2868, 1732, 1686, 1258, 1170 cm^{-1}; HRMS (EI^+) calc'd for $[C_{37}H_{54}O_3]^+$: *m/z* 546.4073, found 546.4080.

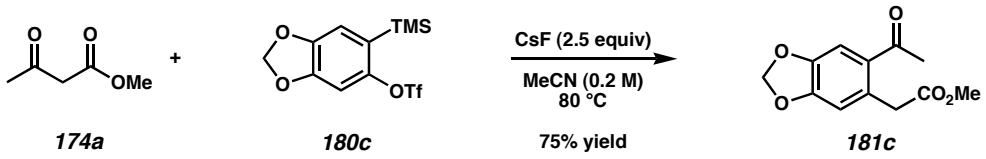


181a. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (84.6 mg, 95% yield) as a clear oil: R_F 0.29 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.2 Hz, 1H), 6.90-6.81 (m, 2H), 3.84 (s, 3H), 3.68 (s, 2H), 3.66 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 171.9, 157.3, 132.7, 131.2, 130.8, 123.6, 110.4, 55.8, 52.2, 38.3, 32.3; IR (thin film/NaCl) 3005, 2952, 2842, 1738, 1691, 1598, 1583, 1471, 1438, 1351, 1267 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{14}O_4]^+$: *m/z* 222.0892, found 222.0892.

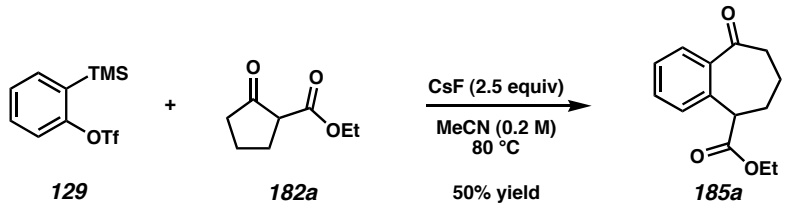


181b. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation products as a 1.2:1 mixture of inseparable isomers (67.9 mg, 82% yield) as a clear oil: R_F 0.26 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz,

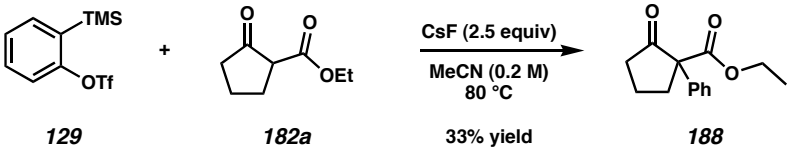
$CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.61 (s, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.9 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.05 (s, 1H), 3.90 (s, 2H), 3.89 (s, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 2.58 (s, 3H), 2.56 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 200.7, 172.4, 172.3, 143.0, 137.3, 137.1, 134.9, 134.3, 133.9, 132.9, 132.7, 131.5, 130.9, 130.8, 129.6, 128.2, 52.0, 40.6, 39.9, 28.9, 28.8, 21.6, 21.2; IR (thin film/NaCl) 2952, 1740, 1680 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{14}O_3]^+$: *m/z* 206.0943, found 206.0945.



181c. Purification by flash chromatography (7:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (70.7 mg, 75% yield) as a clear oil: R_F 0.18 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 6.70 (s, 1H), 6.03 (s, 2H), 3.84 (s, 2H), 3.69 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 172.2, 150.6, 146.9, 131.2, 130.7, 113.0, 110.5, 102.2, 52.0, 40.7, 28.9; IR (thin film/NaCl) 1738, 1678, 1613, 1507, 1491, 1375, 1274, 1245 cm^{-1}; HRMS (EI^+) calc'd for $[C_{12}H_{12}O_5]^+$: *m/z* 236.0685, found 236.0692.

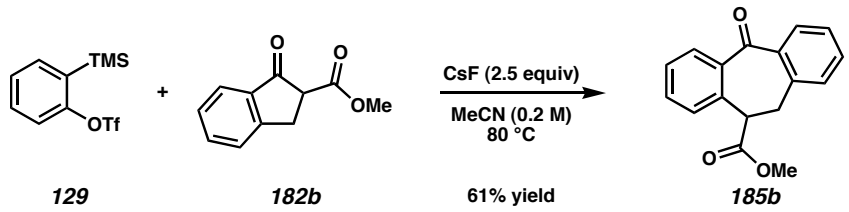


185a. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (46.9 mg, 51% yield) as a clear oil: R_F 0.32 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.51-7.40 (m, 1H), 7.42-7.35 (m, 1H), 7.22-7.18 (m, 1H), 4.25-4.16 (m, 2H), 4.02 (dd, *J* = 7.4, 5.6 Hz, 1H), 2.84-2.73 (m, 1H), 2.70-2.57 (m, 1H), 2.47-2.33 (m, 1H), 2.16-2.03 (m, 1H), 1.92-1.76 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 173.4, 139.7, 136.8, 132.1, 128.8, 128.7, 127.8, 61.4, 49.0, 41.0, 28.5, 20.4, 14.2; IR (thin film/NaCl) 2939, 1730, 1681, 1254, 1188 cm^{-1}; HRMS (EI^+) calc'd for $[C_{14}H_{16}O_3]^+$: *m/z* 232.1100, found 232.1095.

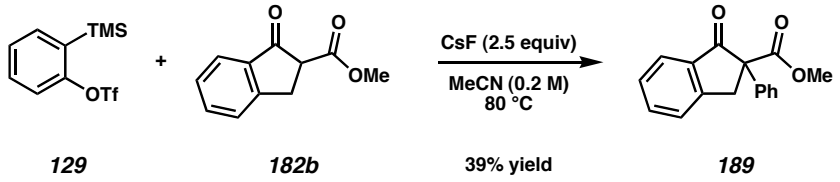


188. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the α-arylated product (30.3 mg, 33% yield) as a clear oil: R_F 0.42 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.94-2.82 (m, 1H), 2.59-2.44 (m, 2H), 2.42-2.27 (m, 1H), 2.10-1.86 (m, 2H), 1.21 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 170.9, 136.4, 128.7, 127.8, 127.6, 65.2, 62.1, 38.0, 35.1, 19.5, 14.2; IR (thin film/NaCl) 2976, 1747, 1712, 1445, 1212 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{14}H_{16}O_3]^+$: *m/z* 232.1100, found 232.1099.

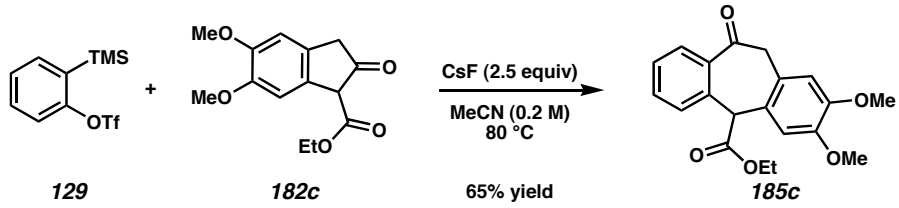


185b. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (63.9 mg, 61% yield) as a clear oil: R_F 0.31 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53-7.30 (m, 4H), 7.24-7.18 (m, 2H), 4.26 (t, *J* = 4.8 Hz, 1H), 3.56 (d, *J* = 5.1 Hz, 2H), 3.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 172.5, 138.8, 138.6, 138.4, 137.5, 132.7, 131.5, 130.6, 130.3, 129.6, 128.9, 128.0, 127.4, 52.4, 50.6, 37.8; IR (thin film/NaCl) 2951, 1737, 1649, 1599, 1292, 1240, 1170 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{17}H_{14}O_3]^+$: *m/z* 266.0943, found 266.0941.



129 *182b* 39% yield *189*

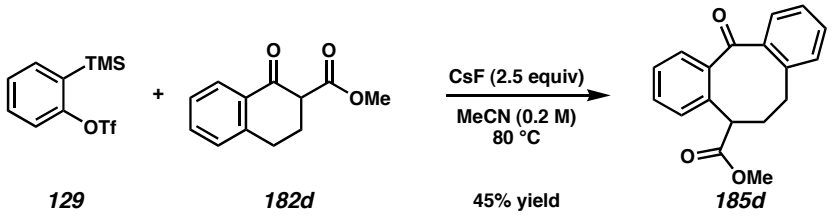
189. Purification by flash chromatography (25:1 hexanes/EtOAc eluent) provided the α-arylated product (42 mg, 39% yield) as a clear oil: R_F 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.54 (app. dt, *J* = 7.4, 1.2 Hz, 1H), 7.42-7.14 (m, 7H), 4.13 (d, *J* = 17.3 Hz, 1H), 3.6 (s, 3H), 3.47 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 171.2, 138.9, 135.9, 135.2, 128.9, 128.5, 128.2, 127.8, 127.5, 126.4, 125.3, 65.6, 53.5, 41.0; IR (thin film/NaCl) 2952, 1745, 1716, 1606, 1211 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{17}H_{14}O_3]^+$: *m/z* 266.0943, found 266.0934.



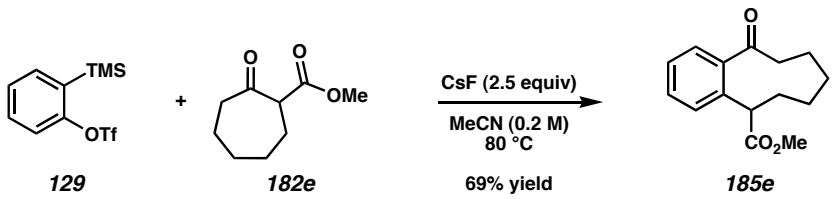
129 *182c* 65% yield *185c*

185c. Purification by flash chromatography (1:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (75.7 mg, 65% yield) as a clear oil: R_F 0.12 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.52-7.30 (m, 3H), 6.87 (s, 1H), 6.76 (s, 1H), 4.88 (s, 1H), 4.43 (d, *J* = 14.8 Hz, 1H), 4.24-4.13 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.72 (d, *J* = 15.4 Hz, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 194.8, 171.4, 148.8, 148.0, 139.9, 134.8, 133.1, 131.3, 131.0, 129.8, 128.3, 124.7, 114.0, 113.8, 62.1, 59.4, 56.3, 56.2, 49.5, 14.4; IR (thin film/NaCl) 2978, 2937, 1728, 1673, 1598, 1518, 1262, 1230, 1201, 1112, 1025 cm^{-1}; HRMS (EI^+) calc'd for $[C_{20}H_{20}O_5]^+$: *m/z* 340.1311, found 340.1326.



185d. Purification by flash chromatography (15:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (50 mg, 45% yield) as a clear oil: R_F 0.39 (3:1 hexanes/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.94 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.57-7.49 (m, 2H), 7.47-7.30 (m, 2H), 7.24-7.16 (m, 2H), 3.88 (dd, *J* = 11.6, 4.9 Hz, 1H), 3.62 (s, 3H), 2.71-2.53 (m, 2H), 2.20-1.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 173.7, 141.3, 140.7, 139.2, 136.7, 133.9, 133.0, 131.3, 131.1, 130.8, 127.7, 127.2, 126.3, 52.3, 45.3, 35.6, 30.6; IR (thin film/NaCl) 2951, 1736, 1638, 1595, 1292, 1254, 1219 cm^{-1}; HRMS (EI^+) calc'd for $[C_{18}H_{16}O_3]^+$: *m/z* 280.1100, found 280.1108.



129 *182e* 69% yield *185e*

185e. Purification by flash chromatography (20:1 hexanes/EtOAc eluent) provided the desired acyl-alkylation product (67.6 mg, 69% yield) as a clear oil: R_F 0.29 (3:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (m, 4H), 3.95 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.66 (s, 3H), 2.96-2.85 (m, 1H), 2.84-2.72 (m, 1H), 2.07-1.80 (m, 4H), 1.77-1.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.4, 174.5, 143.3, 134.9, 130.1, 127.9, 127.2, 124.9, 52.3, 46.0, 43.5, 32.3, 26.0, 25.4, 23.8; IR (thin film/NaCl) 2936, 2860, 1732, 1693, 1435, 1249, 1201 cm^{-1}; HRMS (EI$^+$) calc'd for $[C_{15}H_{18}O_3]^+$: *m/z* 246.1256, found 246.1255.

3.4.4 Independent Chemical Correlation / Structural Proof

Acyl-alkylation product **175a** was independently prepared according to a literature procedure.[38] The product obtained through our methodology was identical by all spectroscopic data to the compound prepared by this alternative method. Spectroscopic data for acyl-alkylation product **175f** was identical to all the reported data in the literature.[39]

3.5 Notes and References

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