APPENDIX 6

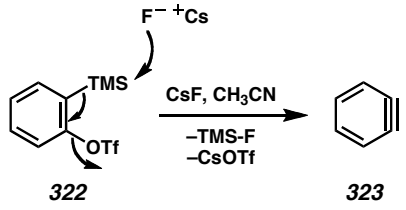
The Development of a Scaleable Acyl-Alkylation of Arynes and Application to the Construction of 1,3-Dihydroxynaphthalenes[†]

A6.1 Background and Introduction

The study of arynes has a rich history in physical organic chemistry. The application of these structures in complex molecule synthesis has, however, been hampered by the harsh conditions for their generation and their high reactivity with a wide variety of organic functionalities. Recent advances in the formation of arynes from readily available precursors have increased the synthetic utility of these reactive intermediates, allowing a broader range of reactions to be developed.[1]

In 1983, Kobayashi reported a mild method for the formation of arynes by the fluoride-mediated elimination of *ortho*-silyl aryltriflates (Scheme A6.1.1).[2] These conditions obviate the need for strongly basic conditions or high reaction temperatures to cleanly generate aryne intermediates.

Scheme A6.1.1 Kobayashi's aryne preparation.

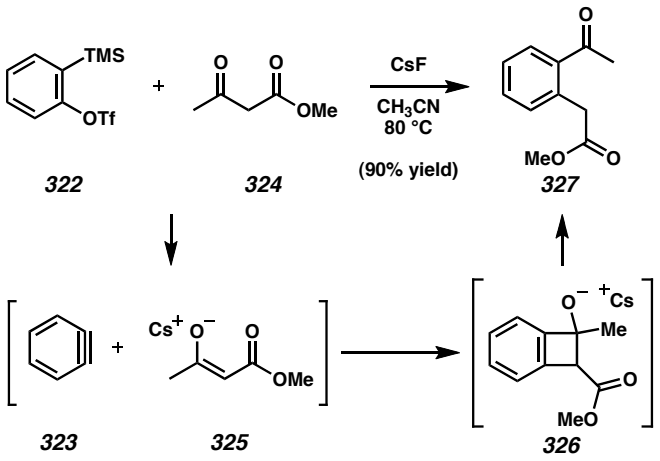


Based on this procedure, we recently developed the acyl-alkylation of arynes.[3,4] Treatment of *ortho*-silyl aryltriflates with CsF and β-ketoesters produced *ortho*-substituted ketoesters in good to excellent yields (Scheme A6.1.2). This reaction is

[†] This work was performed in collaboration with Uttam K. Tambar (Ph.D. 2005), a graduate student in the Stoltz group at California Institute of Technology.

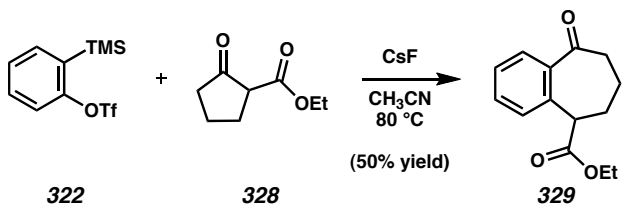
believed to involve initial fluoride-induced aryne formation (**323**). Subsequent formal [2+2] cycloaddition and fragmentation with the cesium enolate of the β-ketoester (**325**) provides the observed product (**327**).

Scheme A6.1.2 Aryne insertion and possible mechanism.



Functionality on the aryne, as well as variation of the β-ketoester, is well tolerated. Furthermore, acyl-alkylation with cyclic β-ketoesters affords ring-expansion products for the construction of a variety of benzannulated ring structures (Scheme A6.1.3). In the next section, we describe a scaleable aryne insertion protocol that allows access to multi-gram quantities of these ketoesters. The synthetic value of these intermediates is demonstrated by their further transformation to 1,3-dihydroxynaphthalenes.

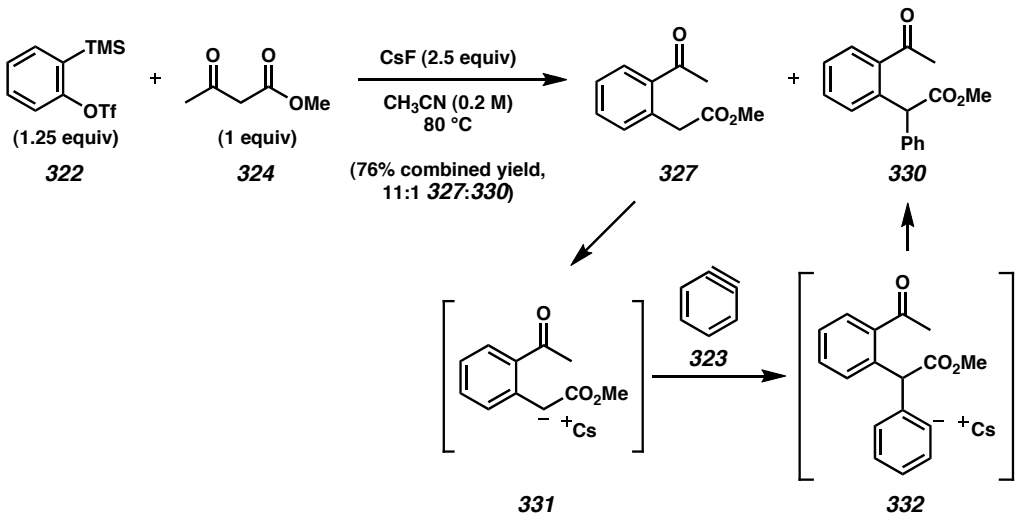
Scheme A6.1.3 Ring expansion by aryne insertion.



A6.2 The Development of a Scaleable Aryne Insertion into β-Ketoesters

Initial efforts to produce multi-gram amounts of methyl 2-(2-acetylphenyl)acetate (**327**) involved direct application of the previously developed conditions (Scheme A6.2.1). Purification by silica gel chromatography provided 5.9 g of acetate **327** in 76% yield. However, this material was contaminated with substantial quantities of an unknown byproduct. Repeated crystallization of this material from hexanes or pentane produced reasonably clean acetate **327**. Preparative thin-layer chromatography of the crystallization filtrate provided a pure sample of the byproduct, which was identified as over-arylation product phenylacetate **330**. Unfortunately, the purification of acetate **327** was not reproducible on large scale.

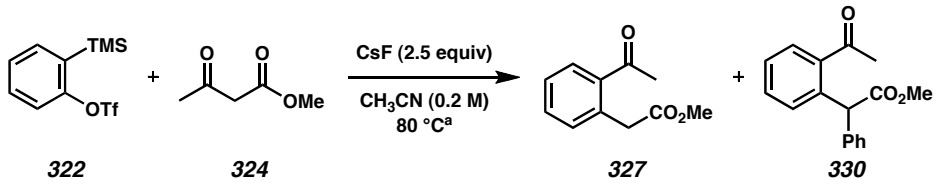
Scheme A6.2.1 Initial procedure with byproduct.



Phenylacetate **330** was expected to arise from α-arylation of desired product **327** by excess benzyne present in the reaction. Thus, we anticipated that fewer equivalents of benzyne precursor **322** would suppress this over-arylation product. Indeed, improved

ratios of **327** relative to **330** were observed, but at the expense of yield, particularly on larger scale (Table A6.2.1).

Table A6.2.1 Screen of reagent ratios in the aryne insertion.



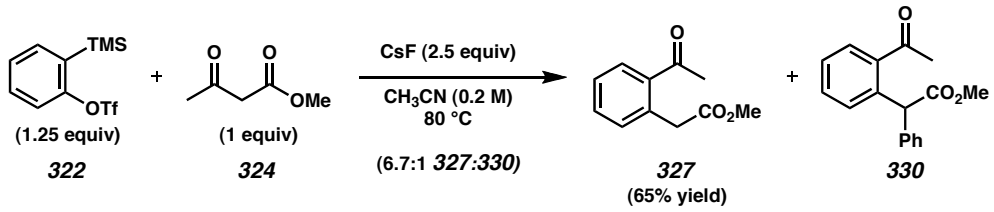
322 ***324*** ***327*** ***330***

entry	equiv ***322***	equiv ***324***	yield[b]	***327***:***330*** ratio[c]
1	1.1	1.0	85%	8:1
2	1.0	1.0	76%	11:1
3	1.0	1.25	82%	12.5:1
4	1.0	2.0	67%	1:0
5[d]	1.0	2.0	58%	99:1

[a] Performed on 0.4 mmol scale, unless otherwise noted. [b] Isolated yield of mixture of **327** and **330**. [c] Ratio determined by ^{1}H NMR. [d] Performed on 2.0 mmol scale.

Ultimately, the initially reported conditions were reinvestigated for this transformation. Again, purification procedures based on recrystallization proved difficult to reproduce. However, distillation under vacuum proved to be a simple and scaleable procedure for obtaining acetate **327** pure in 65% yield (Scheme A6.2.2).

Scheme A6.2.2 Final large scale aryne insertion.

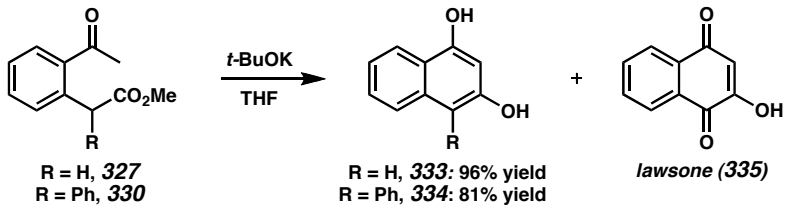


A6.3 Application to the Construction of 1,3-Dihydroxynaphthalenes

With pure acetate **327** and phenylacetate **330** in hand, further transformations to 1,3-dihydroxynaphthalenes were investigated. Reactions involving acetate **327** were

complicated by the instability of the desired 1,3-dihydroxynaphthalene (**333**) to oxygen under basic conditions. Thus, initial attempts to isolate diol **333** resulted in formation of the natural dye lawsone (**335**), presumably due to molecular oxygen exposure during reaction quenching (Scheme A6.3.1). Careful quenching of reactions with degassed HCl allowed isolation of the desired hydroxynaphthalenes **333** and **334** in excellent yields.

Scheme A6.3.1 Base-promoted dihydroxynaphthalene formation.



A6.4 Conclusion

A scaleable methodology for the insertion of arynes into C-C bonds of β-ketoesters has been developed. This procedure allows the preparation of methyl 2-acetylphenylacetate (**327**) in good yield and excellent purity. The transformation of this acetate, as well as the byproduct phenylacetate **330**, to 1,3-dihydroxynaphthalenes has also been demonstrated. These efforts illuminate the utility of this aryne insertion methodology in complex molecule synthesis.

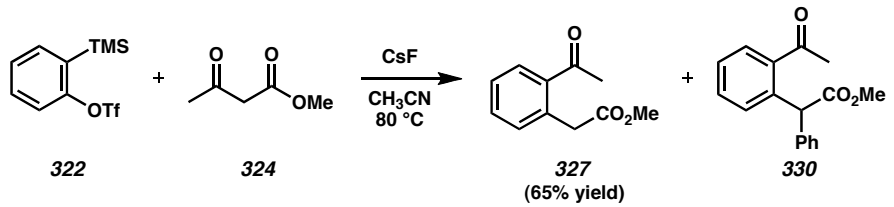
A6.5 Experimental Section

A6.5.1 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. Chemicals were purchased from the Sigma-Aldrich Chemical Company, Milwaukee, WI and were used as received. 2-(Trimethylsilyl)phenyl trifluoromethanesulfonate could also be prepared by the method of Peña and coworkers.[5] Solvents were dried by passage through an activated alumina column under argon. Liquids and solutions were transferred via syringe. Reaction temperatures were controlled using an IKAmag temperature modulator. Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV at 254 nm, *p*-anisaldehyde, and potassium permanganate staining. ICN silica gel (particle size 32-63 μm) or SiliCycle Silia*Flash* P60 Academic silica gel (particle size 40-63 μm; pore diameter 60 Å) was used for flash column chromatography. Bulb-to-bulb distillations were performed with a Büchi Glass Oven B-585 Kugelrohr. ^{1}H NMR spectra were recorded on a Varian Mercury 300 instrument (at 300 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded on a Varian Mercury 300 instrument (at 75 MHz) and are reported relative to Me_4Si (δ 0.0). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm). IR spectra were recorded on a Perkin Elmer Paragon 1000 or Spectrum BX II spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Melting points were determined on a Thomas-Hoover melting point apparatus and are

uncorrected. High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility.

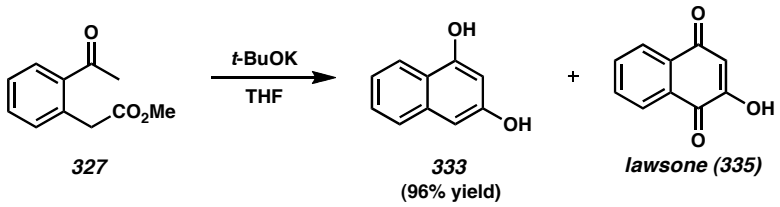
A6.5.2 Preparative Procedures



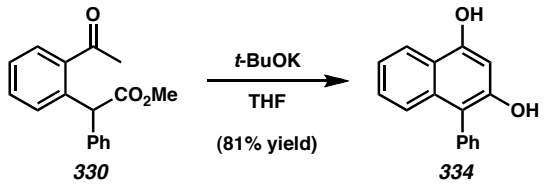
322 *324* *327* (65% yield) *330*

Methyl 2-(2-Acetylphenyl)acetate (327) and Methyl 2-Phenyl-2-(2-acetylphenyl)acetate (330). To a solution of methyl acetoacetate (**324**, 5.59 mL, 6.01 g, 51.8 mmol, 1.0 equiv) and 2-trimethylsilylphenyl trifluoromethanesulfonate (**322**, 15.7 mL, 19.31 g, 64.7 mmol, 1.25 equiv) in CH_3CN (260 mL) was added anhydrous CsF (19.66 g, 129.4 mmol, 2.5 equiv). The reaction mixture was submerged in an 80 °C oil bath and allowed to reflux for 30 min. After cooling to 23 °C, saturated aq NaCl (200 mL) was added. The phases were separated, and the aqueous phase was extracted with Et_2O (3 x 200 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (9:1→4:1→2:1 hexanes:EtOAc) to provide a mixture of **327** and **330** (8.00 g, 87:13 ratio) as an off-white solid. Bulb-to-bulb distillation (1-2 torr, 159-165 °C) afforded **327** (6.49 g, 65% yield, 98.4:1.6 **327**:**330** ratio) as a white crystalline solid. The characterization data matched the data in the literature:[6] R_f 0.46 (3:1 hexanes:EtOAc); mp 53-55 °C (lit.[7] mp 57-59 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, J = 7.6, 1.5 Hz, 1H), 7.47-7.33 (comp. 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 (*m*/*z*): $[M]^+$ calcd for $[C_{11}H_{12}O_3]^+$, 192.0787; found 192.0787. The distillation residue was found to be mainly **330** (1.36 g, 10% yield, 89:11 **330**:**327** ratio) as a viscous amber oil, which solidified upon standing. An analytically pure sample of **330** was obtained by preparative TLC (3:2 hexanes:Et_2O). The characterization data matched the data in the literature:[8] R_f 0.46 (3:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.73 (m, 1H), 7.40-7.25 (comp. m, 5H), 7.25-7.18 (comp. m, 2H), 7.09-7.04 (m, 1H), 5.76 (s, 1H), 3.71 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 173.3, 138.7, 138.1, 137.1, 131.8, 130.6, 129.6, 129.3, 128.7, 127.3, 127.0, 53.7, 52.2, 29.3; IR (thin film/NaCl) 1735, 1681, 1254, 1201, 1161 cm^{-1}; HRMS-EI (*m*/*z*): $[M]^+$ calcd for $[C_{17}H_{16}O_3]^+$, 268.1100; found 268.1105.



1,3-Dihydroxynaphthalene (333). To a solution of potassium *tert*-butoxide (112.2 mg, 1.0 mmol, 2.0 equiv) in THF (4 mL) was added dropwise a solution of ester **327** (96.1 mg, 0.50 mmol, 1.0 equiv) in THF (1 mL). After 5 min, the reaction was complete by TLC analysis. 1 N aq HCl (degassed with argon, 5 mL) then saturated aq NaCl (2.5 mL) was added. Use of non-degassed HCl resulted in formation of substantial quantities of lawsone (**335**). The mixture was extracted with $CHCl_3$ (3 x 8 mL). The organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford **333** (77.0 mg, 96% yield) as a tan solid. The characterization data matched that for a commercially available sample.



1,3-Dihydroxy-4-phenylnaphthalene (334). To a solution of potassium *tert*-butoxide (112.2 mg, 1.0 mmol, 2.0 equiv) in THF (4 mL) was added dropwise a solution of ester **330** (134.2 mg, 0.50 mmol, 1.0 equiv) in THF (1 mL). After 5 min, the reaction was complete by TLC analysis. 1 N aq HCl (degassed with argon, 5 mL) then saturated aq NaCl (2.5 mL) was added. The mixture was extracted with $CHCl_3$ (3 x 8 mL). The organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure and purified by flash chromatography (3:1 hexanes:EtOAc) to afford **334** as a brown oil contaminated with EtOAc. Et_2O (1 mL) then pentane (4 mL) was added to this oil. The resulting solution was concentrated under reduced pressure to afford **334** (contaminated with Et_2O, 7:2 **334**:Et_2O by ^1H NMR, 104.8 mg total, 96.2 mg **334**, 81% yield) as an off-white foamy solid: R_f 0.24 (7:3 hexanes:EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 8.17-8.11 (m, 1H), 7.61-7.54 (comp. m, 2H), 7.52-7.45 (m, 1H), 7.43-7.29 (comp. m, 5H), 6.65 (s, 1H), 5.42 (s, 1H), 5.13 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 150.3, 134.1, 131.6, 129.7, 128.3, 127.2, 124.5, 122.7, 121.7, 120.1, 114.3, 108.2, 100.2; IR (thin film/NaCl) 3399, 1628, 1596, 1387, 765, 706 cm^{-1}; HRMS-FAB (*m/z*): $[M]^+$ calcd for $[C_{16}H_{12}O_2]^+$, 236.0837; found 236.0833.

A6.6 Notes and References

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(2) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211-1214.

(3) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340-5341.

(4) Subsequent to our report, similar aryne insertions into C-C bonds were disclosed, see: (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292-3294. (b) Yoshida, H.; Watanabe, M.; Ohshita, F.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729-6731. (c) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505-1507. (d) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965-3968.

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(8) Breslow, R.; Kivelevich, D. *J. Org. Chem.* **1961**, *26*, 679-681.