APPENDIX 1

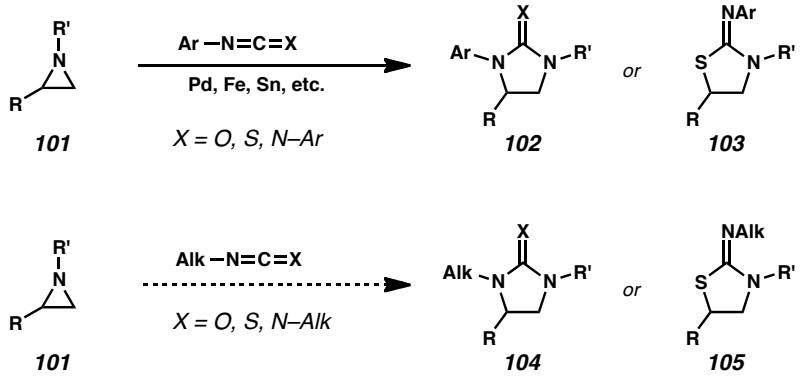
Future Directions for Lewis Acid Mediated (3 + 2) Cyclopropane Cycloadditions[†]

A1.1 RING-EXPANSION REACTIONS OF AZIRIDINES

Aziridines (**101**) are an important class of nitrogen containing heterocycles.[1] Ring expansion reactions of these compounds with aryl-substituted heterocumulenes is well-documented, using palladium and iron catalysts to promote (3 + 2) cycloadditions (Scheme A1.1.1).[2] However, none of the known methods are capable of incorporating alkyl-substituted heterocumulenes into corresponding 5-membered ring products (e.g. **104** and **105**).

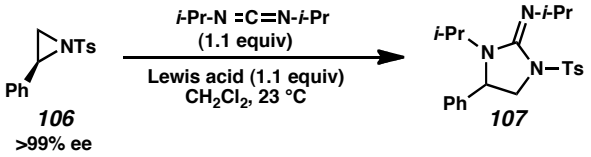
[†] This work was performed in collaboration with Nicholas R. O'Connor and Robert A. Craig, II, graduate students in the Stoltz group.

Scheme A1.1.1. (3 + 2) Cycloadditions of aziridines and carbodiimides



We have found in preliminary work that stoichiometric zinc triflate is a competent Lewis acid for converting enantioenriched aziridines to guanidine products with good retention of stereochemical information (Table A1.1.1). Efforts are ongoing to improve the enantiomeric excess of the products, and to examine the substrate scope of the reaction.

Table A1.1.1. Preliminary Lewis acid optimization for guanidine synthesis

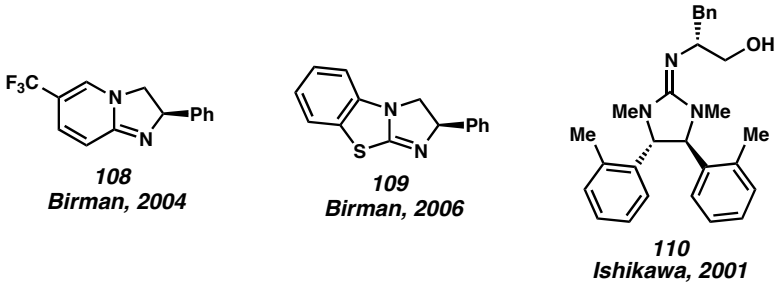


Entry	*Lewis Acid*	*Time (h)*	*Yield (%)*	*ee (%)*
1	$Sn(OTf)_2$ (Sigma)	7	59	24
2	$Sn(OTf)_2$ (Strem)	7	63	36
3	$SnCl_2$	48	>99	42
4	$FeCl_3$	8	80	1
5	$Cu(OTf)_2$	72	>99	55
6	$Zn(OTf)_2$	72	73	82
7	$ZnCl_2$	72	>99	17
8	$ZnBr_2$	24	83	10
9	ZnI_2	72	71	2

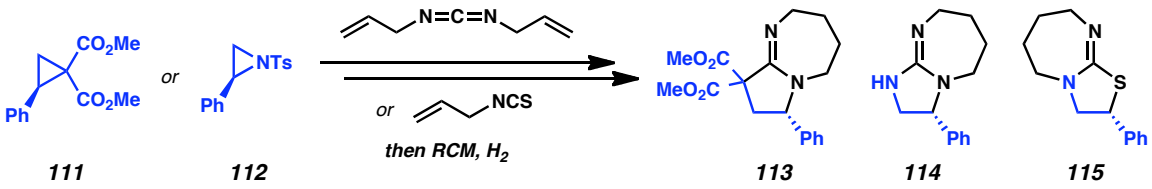
A1.1.1 AMIDINE AND GUANIDINE CATALYSIS

Chiral amidines, guanidines, and isothioureas have been shown to be useful nucleophilic catalysts for an array of asymmetric transformations, including acylations, aldol reactions, among others.[3] Examples of these include Birman's amidine (**108**) and isothiourea (**109**) catalysts,[4,5] and guanidine **110** developed by Ishikawa (Figure A1.1.1).[6] We envision that Lewis acid (3 + 2) cycloadditions of appropriately substituted heterocumulenes could afford access to an array of chiral nucleophilic catalysts (e.g. **113–114)** from readily available enantioenriched aziridines (**112**) or cyclopropanes (**111**, Scheme A1.1.2).

Figure A1.1.1. Examples of chiral nucleophilic catalysts.



Scheme A1.1.2. Potential nucleophilic catalysts accessible via Lewis acid (3 + 2) cycloaddition

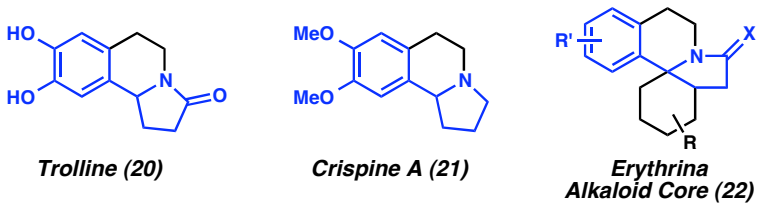


A1.2 NATURAL PRODUCT SYNTHESIS

Several natural products contain the 5-aryl substituted γ-lactam motif accessible via cyclopropane/heterocumulene (3 + 2) cycloaddition, including trolline (**20**), crispine A

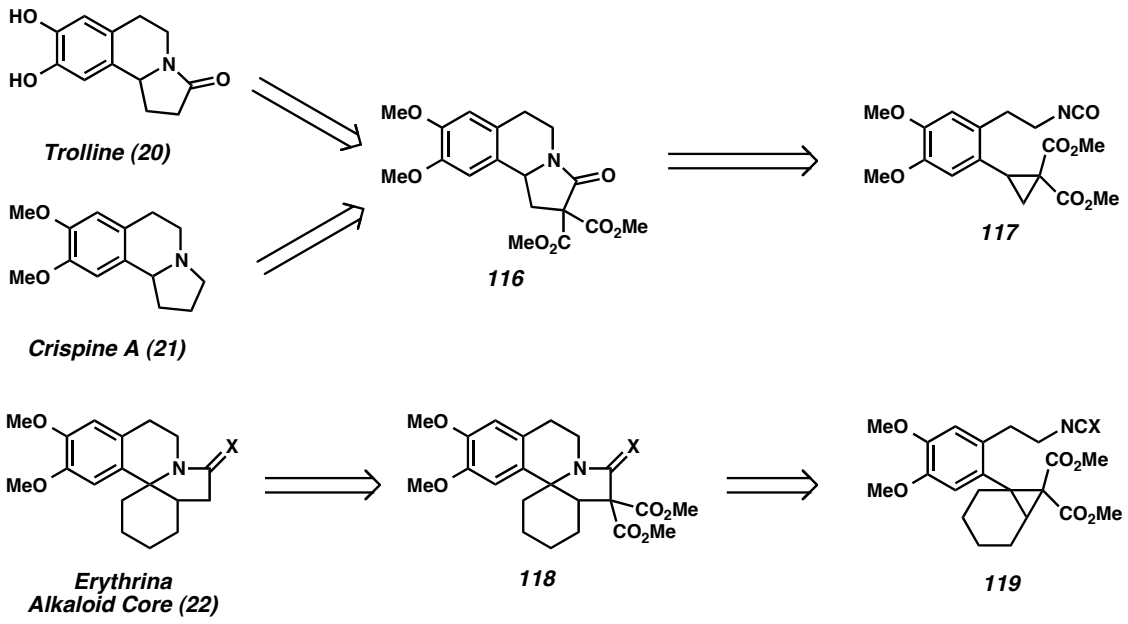
(**21**), and several of the *Erythrina* alkaloids (i.e., **22**, Figure A1.2.1). To demonstrate the utility of the (3 + 2) cycloaddition methodology, proposed is a general route toward this series of natural products.

Figure A1.2.1. Natural products accessible via cyclopropane (3 + 2) cycloadditions



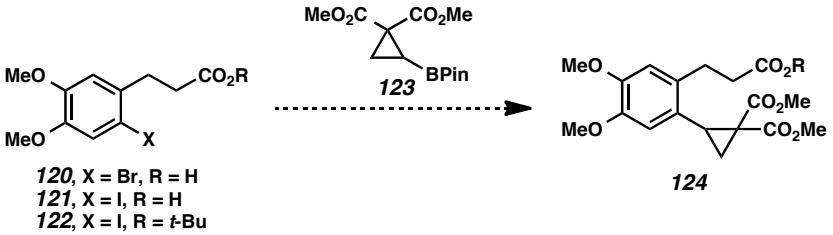
We envisioned that trolline (**20**) and crispine A (**21**) could be derived from common intermediate **116** via decarboxylation followed by demethylation or lactam reduction, respectively (Scheme A1.2.1). The key synthetic intermediate could arise from intramolecular (3 + 2) cycloaddition of isocyanate **117**. The tetracyclic core of the *Erythrina* alkaloids could be rapidly assembled in a similar fashion via intramolecular (3 + 2) cycloaddition of a heterocumulene moiety with a bicyclo[4.1.0]heptane unit (**119**).

*Scheme A1.2.1. Retrosynthetic analysis of alkaloid natural products **20**, **21**, **22***



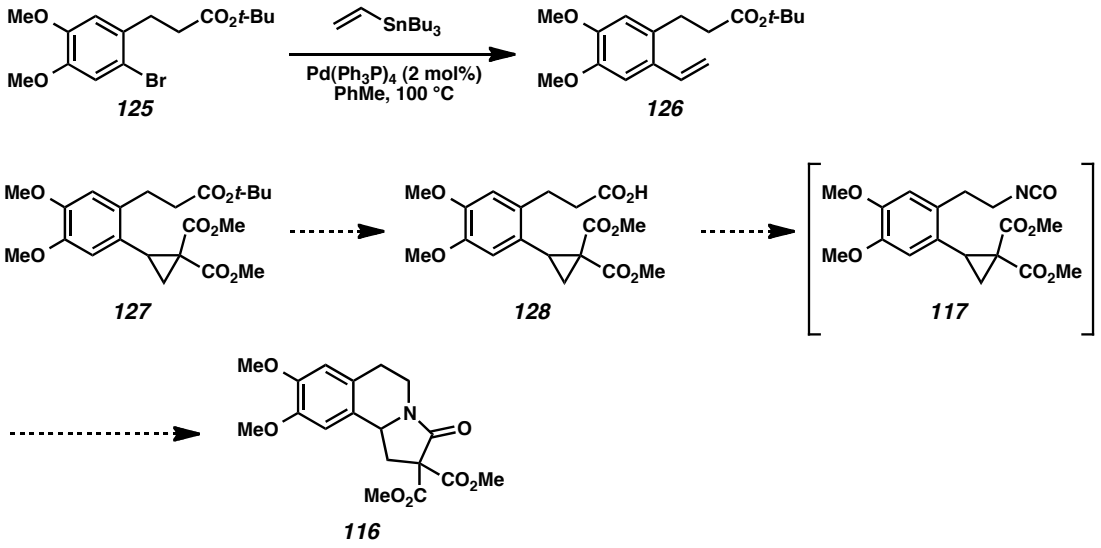
Preliminary work toward the (3 + 2) substrate has been carried out. Our initial efforts focused on a Suzuki cross coupling of cyclopropyl boronate ester (**123**) with haloarenes **120–122** (Scheme A1.2.2). The cyclopropane fragment (**123**) has previously been synthesized in enantiopure form by Gevorgyan and coworkers, and would provide an entry point to asymmetric synthesis.[7] However, under numerous conditions, we failed to observe any cross-coupled product (**124**).

Scheme A1.2.2. Failed Suzuki cross coupling with cyclopropyl boronate ester ***XX***



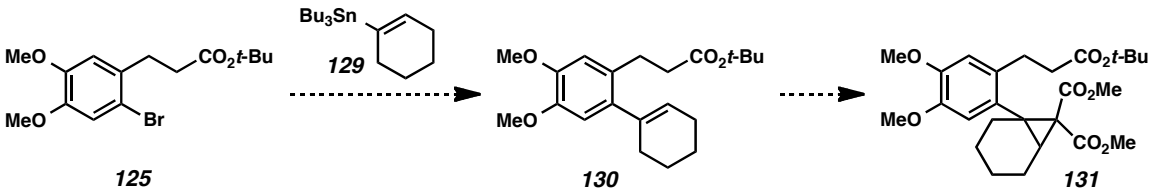
Fortunately, Stille cross-coupling of aryl bromide **125** afforded a styrene derivative (**126**) which may, in future work, be cyclopropanated with diazodimethylmalonate (Scheme A1.2.3). Cleavage of the *tert*-butyl ester followed by a Curtius rearrangement would provide an isocyanate (**117**) that may be treated directly with Lewis acid to afford the desired tricycle **116**.

*Scheme A1.2.3. Stille coupling of bromide **125** and proposed conversion to tricycle **116***



We envision that an appropriate cyclopropane precursor (**131**) to the *Erythrina* alkaloid core would be accessible by a similar route. Stille coupling of aryl bromide **125** with known cyclohexenyl tributyltin (**129**) followed by cyclopropanation would afford a suitable isocyanate precursor for (3 + 2) cycloaddition (Scheme A1.2.4).[8]

*Scheme A1.2.4. Proposed synthesis of cyclopropane **131** via Stille coupling.*



A1.3 CONCLUSION

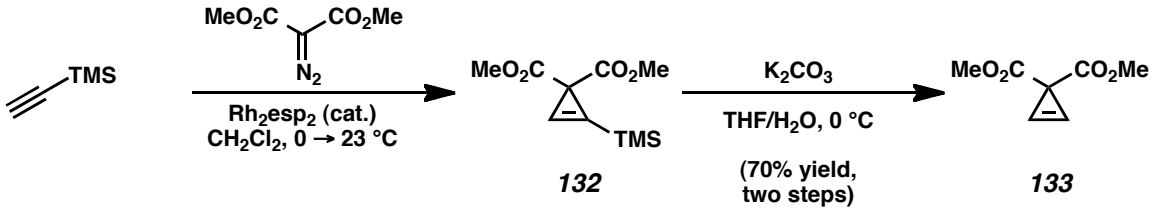
In summary, a variety of methodological and synthetic applications are envisioned based on our original discovery, including guanidine synthesis from chiral aziridines, synthesis of novel chiral nucleophilic catalysts, and total synthesis of polycyclic alkaloids. Efforts are currently ongoing to realize these goals.

A1.4 EXPERIMENTAL SECTION

A1.4.1 MATERIALS AND METHODS

Unless stated otherwise, reactions were performed under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[9] Commercially obtained reagents were used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave reactions were performed with a Biotage Initiator Eight 400 W apparatus at 2.45 GHz. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, or potassium permanganate, iodine, or anisaldehyde staining. 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 on a Varian Inova 500 (at 500 MHz and 126 MHz respectively), Varian 400 (at 400 MHz and 100 MHz, respectively) or on a Varian Mercury 300 (at 300 MHz) and are reported relative to $CHCl_3$ (δ 7.26 & 77.16 respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). 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.

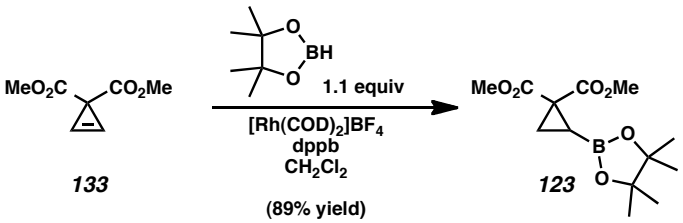
A1.4.2 PREPARATIVE PROCEDURES



Cyclopropene 133. Prepared by an improved procedure based on that reported by Gevorgyan and coworkers.[7] To a flame-dried round-bottom flask equipped with a magnetic stir bar was added bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (0.7 mg, 0.9 μmol, 0.016 mol%) and trimethylsilylacetylene (0.82 mL, 5.75 mmol, 1 equiv). The flask was sealed with a rubber septum, then evacuated and backfilled with argon three times. Dichloromethane was then added (10 mL, 0.6 M) and the flask was cooled in an ice-water bath with stirring. Diazodimethylmalonate (0.9982 g, 6.3 mmol, 1.1 equiv) was added dropwise, then the flask was removed from the bath and allowed to warm to ambient temperature, stirring overnight (13 h). Complete consumption of the starting material was observed (TLC), and the solvent was evaporated in vacuo. The residue was purified by column chromatography on SiO_2 (20:1 → 6:1 hexanes:EtOAc) to afford cyclopropene **132** as a blue oil which was carried forward directly to the next stage.

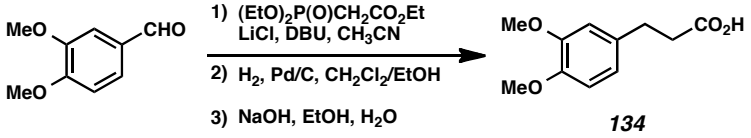
Cyclopropene **132** was dissolved in tetrahydrofuran (30 mL) in a round-bottom flask, and the solution was cooled in an ice-water bath. To this solution was added K_2CO_3 (10 mL, 10% in water) with stirring. After 10 minutes, TLC indicated complete consumption of starting material (3:1 hexanes:EtOAc, SM = 0.62, prod = 0.21). The phases were separated and the organic phase was concentrated to an approximate volume

of 5 mL. The aqueous and organic phases were recombined and diluted with water (10 mL) and diethyl ether (25 mL). The phases were separated and the aqueous layer was extracted with additional diethyl ether (25 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography to afford cyclopropene **133** (634.1 mg, 70% yield) as an amorphous white solid. The characterization data matched those reported by Gevorgyan and coworkers.[7]

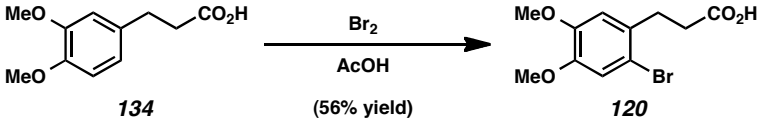


Cyclopropane 123. In a nitrogen filled glove-box, an oven-dried scintillation vial was charged with bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (5.2 mg, 0.013 mmol, 0.02 equiv) and dppb (6.0 mg, 0.014 mmol, 0.022 equiv), and the solids were dissolved in dichloromethane, affording an orange solution. A separate one dram vial was charged with cyclopropene **133** (99.5 mg, 0.64 mmol, 1 equiv) and pinacolborane (0.1 mL, 0.7 mmol, 1.1 equiv). The mixture was dissolved in dichloromethane (0.5 mL) and transferred into the first vial; the second vial was then washed with additional dichloromethane (0.3 mL) and transferred into the first vial. The reaction was stirred for 17 h and complete conversion of the starting material was observed (TLC: 3:1 hexanes:EtOAc, R_F: SM = 0.21, product: 0.46). The reaction mixture was dry-loaded onto SiO_2 (~1 mL) and purified by column chromatography on SiO_2 (8:1 hexanes:EtOAc)

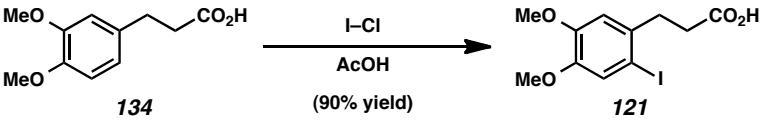
to afford cyclopropane **123** (160.7 mg, 89% yield). The characterization data matched those reported by Gevorgyan.[7]



3-(3,4-Dimethoxyphenyl)propionic acid 134. Prepared according to the method of Lebel and coworkers without modification.[10]

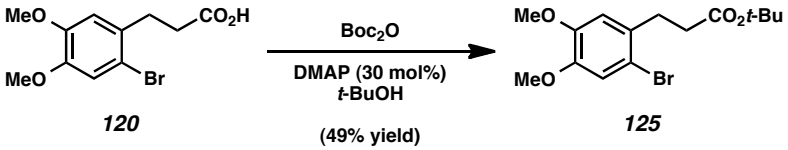


3-(2-bromo-3,4-dimethoxyphenyl)propionic acid 120. Prepared according to the method of Lebel and coworkers with minor modifications:[10] pre-cooling the acetic acid solution in an ice-water bath resulted in a frozen mixture; therefore, the solution was cooled until it began to freeze, and bromine was added thereafter, with continued cooling in the ice-water bath.

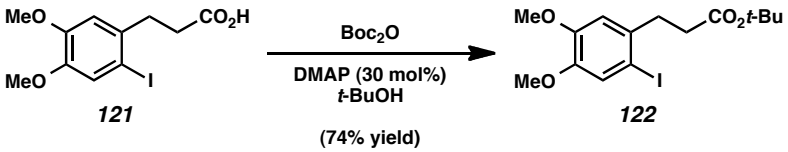


3-(2-iodo-3,4-dimethoxyphenyl)propionic acid 121. Carboxylic acid **134** (1.0812 g, 5.14 mmol, 1 equiv) was dissolved in acetic acid (6 mL) in a round-bottom flask. Iodine monochloride (1.1370 g, 6.94 mmol, 1.35 equiv) was added in portions at ambient temperature to afford an orange solution. After at least 20 minutes, a precipitate was observed. After 85 minutes, the suspension was poured over water (10 mL) and a

saturated solution of aqueous sodium thiosulfate was slowly added until the orange color disappeared. The suspension was filtered, washed with water, and air-dried to afford iodide **121** (1.5503 g, 90% yield) as a white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.80 (s, 1H), 3.85 (s, 6H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H).

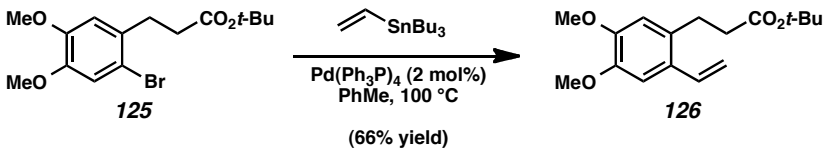


***tert*-butyl ester 125.** According to the procedure of Takeda and coworkers.[11] To a suspension of acid **120** (1.0007 g, 3.4 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (2.2544 g, 10.4 mmol, 3 equiv) in *tert*-butanol (8.5 mL, 0.4 M) was added 4-(*N*,*N*-dimethylamino)pyridine (127.3 mg, 1.02 mmol, 0.3 equiv). Vigorous bubbling was observed and the solution became yellow. After one hour, the reaction mixture was dry-loaded directly onto SiO_2 (~10 mL) and purified by column chromatography on SiO_2 (20:1 → 10:1 hexanes:EtOAc) to afford *tert*-butyl ester **125** (581.6 mg, 49% yield): ^{1}H NMR (300 MHz, Chloroform-d) δ 6.99 (s, 1H), 6.77 (s, 1H), 3.85 (s, 6H), 2.95 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.7 Hz, 2H), 1.43 (s, 9H).



***tert*-butyl ester 122.** According to the procedure of Takeda and coworkers.[11] To a suspension of acid **121** (340 mg, 1 mmol, 1 equiv) and di-*tert*-butyl dicarbonate (652 mg,

3 mmol, 3 equiv) in *tert*-butanol (2.5 mL, 0.4 M) was added 4-(*N*,*N*-dimethylamino)pyridine (36.6 mg, 0.3 mmol, 0.3 equiv). Vigorous bubbling was observed and the solution becomes yellow. After one hour, the reaction mixture was dry-loaded directly onto SiO_2 and purified by column chromatography on SiO_2 (hexanes → 10:1 hexanes:EtOAc) to afford *tert*-butyl ester **122**.



Styrene 126. In a nitrogen-filled glovebox, a flame-dried Schlenk bomb was charged with tetrakis(triphenylphosphine) palladium(0) (30 mg, 0.03 mmol, 0.02 equiv). The bomb was sealed, removed from the glovebox, and placed under an atmosphere of argon. To a vial containing bromide **125** (455.1 mg, 1.30 mmol, 1 equiv) was added dry toluene, which was then removed in vacuo; this procedure was repeated twice to remove traces of water from the substrate. Under an atmosphere of argon, the bromide was dissolved in toluene (3 mL) and transferred to the Schlenk bomb under a high flow of argon. Finally, vinyl tributyltin (0.4 mL, 1.37 mmol, 1.05 equiv) was added as a neat oil to the Schlenk bomb under a high flow of argon. The bomb was sealed and lowered into an oil bath which was preheated to 100 °C. After 17 hours, the bomb was cooled to ambient temperature, and a crude product was obtained by a workup procedure that was not properly recorded. The crude product was purified by column chromatography to afford styrene **126** as a yellow solid (253.1 mg, 66% yield). ^{1}H NMR of the crude material showed complete consumption of the starting material and clean signals corresponding to the vinyl group: 5.87 (dd, J = 17.2, 10.5 Hz, 1H), 5.09 (d, J = 10.5 Hz, 1H), 5.04 (d, J =

17.2 Hz, 1 H). ^{1}H NMR of the purified product was poorly shimmed or had paramagnetic impurities.

A1.5 NOTES AND REFERENCES

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