Development of an Efficient Palladium-Catalyzed Intramolecular Carbometalation Reaction for the Synthesis of a Dibenzoxapine Containing Tetra-substituted Exocyclic Alkene[†]

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Abstract:

A practical and scaleable synthesis of (*Z*)-3-(1-(8-bromodibenzo[*b,e*]oxepin-11(6*H*)-ylidene)ethyl)aniline hydrochloride (1·HCl), a key intermediate in the synthesis of a selective nuclear hormone receptor modulator, is described. The target compound is prepared in five steps from commercially available (5-bromo-2-iodophenyl)-methanol (5) with a 47% overall yield. The key step involves a palladium-catalyzed intramolecular carbometalation of an alkyne, which affords the dibenzoxapine containing tetrasubstituted exocyclic alkene framework stereoselectively in a single step from readily available building blocks 4-bromo-2-(2-iodo-phenoxym-ethyl)-1-prop-1-ynyl-benzene (3) and 3-nitrophenylboronic acid (4). The development of each step is described. The main focus of the paper is the description and optimization of the intramolecular carbometalation of an alkyne. Eventually, the target compound 1·HCl was prepared in multikilogram quantities with >97% purity.

Introduction

During our program for the development of selective nuclear hormone receptor modulators,[1] a practical and scaleable synthesis of (*Z*)-3-(1-(8-bromodibenzo[*b,e*]oxepin-11(6*H*)-ylide-ne)ethyl)aniline (**1**), was needed. This was a key intermediate used in the late step of our convergent synthetic route. We detail here our efforts for the preparation of **1**, using a palladium-catalyzed intramolecular carbometalation of an alkyne as the key transformation.
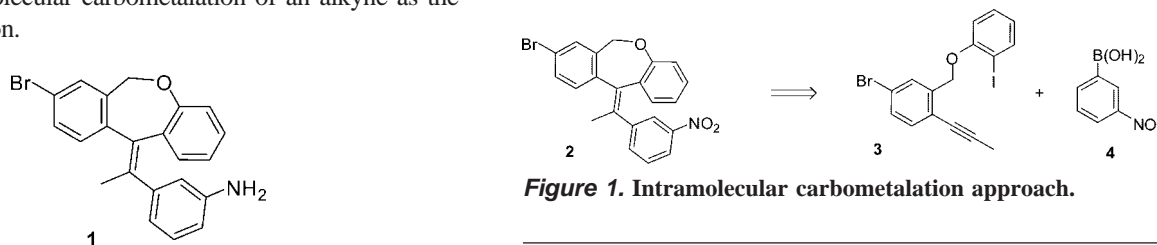

Dibenzoxapine derivatives are an important class of biologi-cally active compounds. The dibenzoxapine derivatives contain-ing tetra-substituted exocyclic alkene moieties represent a novel structure.[1] Despite impressive recent progress, the efficient regio-

and stereoselective synthesis of tetra-substituted alkenes still poses a unique synthetic challenge.[2] Although the classical double-bond-forming methods such as the Wittig reaction or dehydration of a carbinol could be used for the synthesis of tetra-substituted alkenes, they are often limited in scope and lack of stereoselectivity. The carbometalation of alkynes has been developed as a widely used method for the formation of tetra-substituted alkenes.[3] In particular, intramolecular carbo-palladation of alkynes (cyclocarbopalladation) has been used for the formation of various tetrasubstituted alkenes.[4] In 1988, Grigg et al.,[5] shortly followed by Negishi and Zhang,[6] described a cyclocarbopalladation process that afforded exocyclic alkenes stereospecifically. The reaction involved an initial cyclocarbo-palladation to form a vinylpalladium intermediate, followed by terminating the vinylpalladium species with an organometallic reagent. Recently, we published two stereoselective methods for the preparation of tetra-substituted alkenes by intramolecular cyclocarbopalladation of alkynes.[7] These reports represented the first preparations of seven-membered rings through a palladium-catalyzed cascade reaction using organometallics as the termi-nating trapping species. Herein, we describe the first large-scale preparation of **2** using this strategy. The key step involved a palladium-catalyzed intramolecular carbometalation reaction between alkyne **3** and 3-nitrophenylboronic acid **4** to establish the desired geometric relationship (Figure 1).

Figure 1. Intramolecular carbometalation approach.

(2) For a recent review on the stereocontrolled synthesis of tetra-substituted olefins, see: Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698.

(3) For reviews, see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 387–420.

(4) For representative examples, see: (a) Negishi, E.-I.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (b) Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846. (c) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (d) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525. (e) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579. (f) Cheung, W. S.; Patch, R.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (g) Bour, C.; Blond, G.; Salem, B.; Suffert, J. *Tetrahedron* **2006**, *62*, 10567, and references therein.
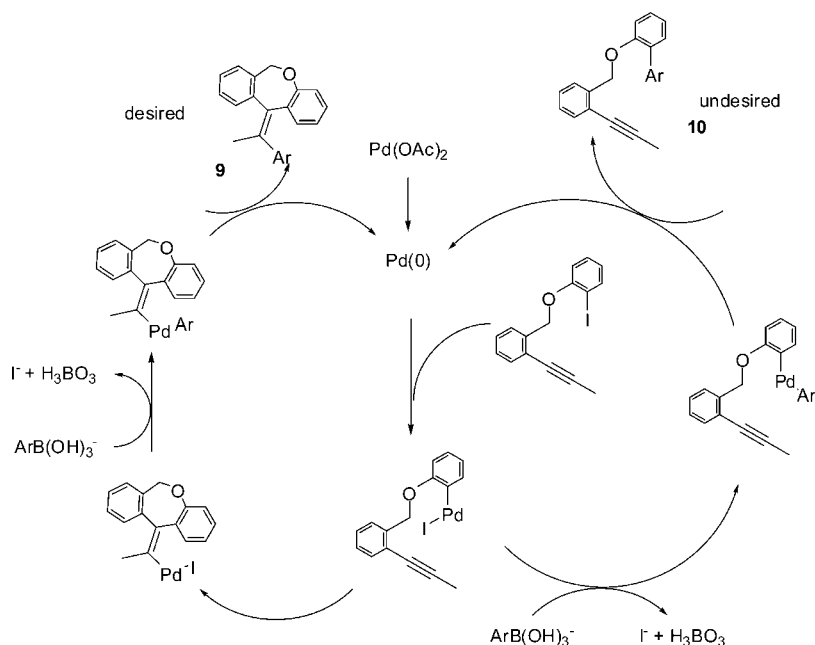
[†] We dedicate this paper to the memory of Dr. Chris Schmid, a colleague, mentor, and friend, who passed away December 26, 2007.

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(1) (a) Coghlan, M. J.; Green, J. E.; Grese, T. A.; Jadhav, P. K.; Matthews, D. P.; Steinberg, M. I.; Fales, K. R.; Bell, M. G. WO 2004/052847 A2, 2004. (b) Carson, M. W.; Coghlan, M. J. WO 2008/008882, A2, 2008.
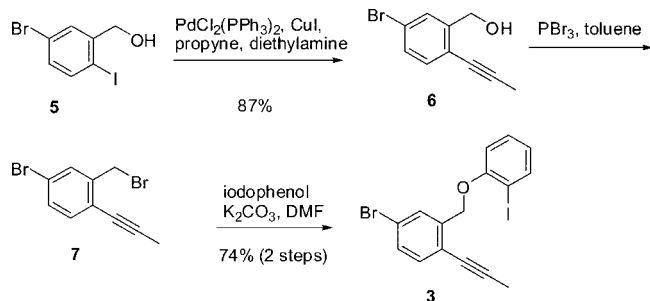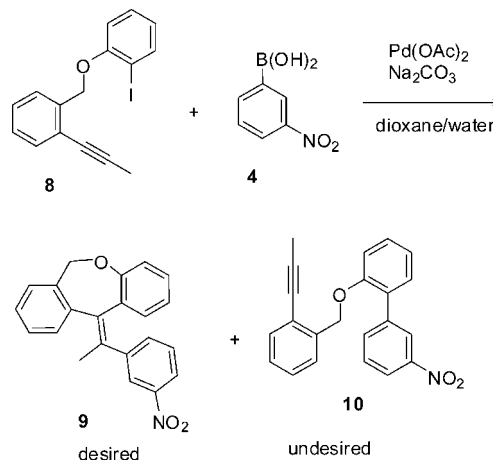
Figure 2. Catalytic cycle for the formation of desired product 9 and undesired byproduct 10.

Scheme 1. Synthesis of cyclization precursor 3

Scheme 2. Synthesis of 9

Results and Discussion

The cyclization precursor **3** was prepared from commercially available (5-bromo-2-iodophenyl)methanol (**5**)[8] in three steps (Scheme 1). The Sonogoshira coupling between **5** and propyne was carried out using PdCl$_2$(PPh$_3$)$_2$ and CuI in diethylamine.[9] Under the treatment of excess propyne, the reaction proceeded to completion at rt after 12 h. After aqueous work up and filtering through silica gel (3×), alkyne **6** was isolated as a pale-yellow solid in 87% yield. Conversion of **6** to **3** could be carried out through either a one-step Mitsunobu reaction or a two-step alkylation procedure. To avoid chromatography purifications, the two-step procedure was adapted. Therefore, alcohol **6** was converted to its tosylate or corresponding halides, and the resulting intermediates were coupled with 2-iodophenol to afford

the cyclization precursor **3**. Benzyl bromide **7** was selected as the intermediate for scale-up since it provided easy purification when forward processed to **3**. Initial bromination of **6** using HBr and acetic acid failed to give any of the desired product **7**.[10] The bromination was then carried out with phosphorous tribromide in toluene. At 60 °C, the reaction proceeded to completion without the presence of an amine.[11] After aqueous workup, benzyl bromide **7** was subjected to the alkylation conditions to couple with 2-iodophenol. Upon treatment with potassium carbonate, the reaction proceeded to completion in DMF at rt, and after the addition of water, the resulting product **3** was crystallized from the reaction mixture. Filtration followed by drying afforded technical grade **3** with >95% HPLC area percentage. Recrystallization of **3** in EtOH further increased its purity to >98%. A 74% yield was obtained over the bromination and alkylation steps.

(5) (a) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 4325. (b) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 5565.

(6) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454.

(7) (a) Yu, H.; Richey, R. N.; Carson, M. W.; Coghlan, M. J. *Org. Lett.* **2006**, *8*, 1685. (b) Yu, H.; Richey, R. N.; Mendiola, J.; Adeva, M.; Somoza, C.; May, S. A.; Carson, M. W.; Coghlan, M. J. *Tetrahedron Lett.* **2008**, *49*, 1915.

(8) We also prepared compound **5** following a modified literature procedure: Frahn, J.; Schlueter, A. D. *Synthesis* **1997**, *11*, 1301.

(9) Sashida, H.; Ohyanagi, K.; Minoura, M.; Akiba, K. *J. Chem. Soc., Perkin Trans. 1* **2002**, 606.

(10) Kaslow, C. E.; Schlatter, J. M. *J. Am. Chem. Soc.* **1955**, *77*, 1054.

(11) Ford-Moore, A. H.; Perry, B. J. *Organic Syntheses IV*; John Wiley & Sins: New York, 1963; p 955.

(12) For a proposed mechanism on an intermolecular carbometalation reaction, see: Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765.

With cyclization precursor **3** in hand, we were ready to attempt the key cyclization reaction. As part of method development efforts, we first optimized reaction conditions using compound **8** as a model substrate (Scheme 2).[7a] As expected, the major byproduct was identified as the direct Suzuki coupling product **10**. A proposed catalytic cycle showing formation of desired product **9** and undesired byproduct **10** is depicted in Figure 2.[12] Thus, the desired pathway consists of the following key steps: (1) reduction of palladium (II) to palladium (0); (2) oxidative addition of aryl iodide to palladium (0); (3) carbopalladation of the alkyne to form a vinylic palladium species; (4) transmetalation of the vinylic palladium species with boronic acid; (5) reductive elimination of palladium (II) to give the desired product **9**. Figure 2 also shows an undesired pathway, in which a direct transmetalation occurs between the boronic acid and the initial palladium (II) intermediate. As a result, the Suzuki cross-coupling byproduct **10** forms. Our extensive ligand screenings suggested that the desired intramolecular cascade reaction was favored over the undesired direct coupling reaction only when a ligandless condition was applied.[7a] In addition, the results indicated that it was critical to use water as a cosolvent to suppress the formation of polymeric byproducts, which were likely formed as a result of slow transmetalation between vinylic palladium and boronic acid. Thus, under our optimized condition, 2 mol % Pd(OAc)$_2$, 1.2 equiv of 3-nitroboronic acid **4**, and 3 equiv of Na$_2$CO$_3$ at 70 °C, the desired product **9** was isolated in 89% yield after column chromatography.[7a]

After fulfilling our initial goals of demonstrating proof of concept on model substrate **8**, we next investigated the carbometalation reaction starting from alkyne **3** and boronic acid **4** (Scheme 3). Our challenges for the preparation of target

Scheme 3. Cyclization of 3
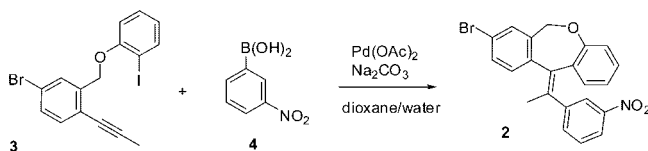
compound **1** were associated with the scale-up of the key cyclization reaction. In particular, the challenges were associated with defining the purification strategy to remove impurities generated from the cyclization. We desired to establish a control strategy that would afford target compound **1** without resorting to chromatography.

The desired cyclization was carried out using ligandless conditions: 2 mol % Pd(OAc)$_2$, 1.2 equiv of 3-nitroboronic acid and 3 equiv of Na$_2$CO$_3$ in dioxane/water at 70 °C. The reaction was first run under brief nitrogen headspace sweep, and it proceeded to give the desired product **2** with 82% in situ HPLC area percentage. In addition to the desired product **2**, we observed several major impurities by HPLC (Scheme 4).[13,14]

(13) Impurities **10** and **11** were isolated by column chromatography. Their structures were determined by ^{1}H NMR.
(14) The corresponding direct Suzuki cross-coupling byproduct was observed in <1%.
(15) (a) Moreno-Manas, M.; Pajuelo, F.; Plexats, R. *J. Org. Chem.* **1995**, *60*, 2346. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034. (c) Marck, G.; Villager, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277. (d) Miller, W. D.; Fray, A. H.; Quatroche, J. T.; Sturgill, C. D. *Org. Process Res. Dev.* **2007**, *11*, 359.

Scheme 4. Major impurities (>1%) detected by HPLC at the end of the reaction
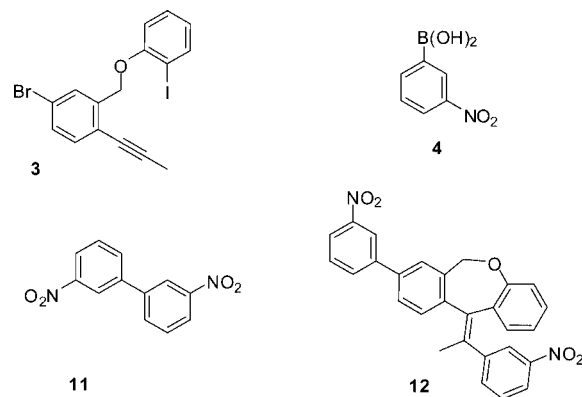
The single largest impurity was identified as dimer **11** (∼5%), which was formed as a result of homocoupling of 3-nitrophenyl boronic acid **4**. It had been reported that the exclusion of oxygen should suppress the homocoupling of boronic acids in Suzuki cross-coupling reactions.[15] Since the second step of our cascade cyclization (coupling of the vinylic palladium species with boronic acid **4**) was essentially a variant of the Suzuki reaction, we next implemented a deoxygenation procedure to suppress the formation of dimer **11**. Thus, subsurface sparging was implemented before and after Pd(OAc)$_2$ addition. The results revealed that this modification reduced the amount of dimer **11** to 1.4% at the end of the reaction.

To consume more expensive starting material **3**, excess (1.2 equiv) of boronic acid **4** was used. Despite the extra boronic acid, ∼4% of starting material **3** remained unreacted after the reaction mixture was stirred at 70 °C for 12 h. Little conversion was observed even if prolonged reaction time was applied. Raising the reaction temperature pushed the reaction to completion; however, significant increase in impurity **12** (∼4% under standard conditions) was observed. Since the remaining starting material **3** could be efficiently rejected through crystallization in the downstream chemistry, we made no further attempt to drive the reaction to completion.

We next focused on monitoring and controlling the formation of polymeric byproducts. The possibility for the formation of polymeric byproducts during the carbometalation of alkynes had been previously documented in the literature.[3a] However, due to the fact that these byproducts could not be detected under a variety of HPLC and NMR conditions, it was extremely difficult to separate and characterize these byproducts. To better monitor the yield of the reactions, we developed a quantitative HPLC assay (measured against a pure standard) to determine the purity of isolated products.[16] Thus, water was added to the reaction mixture at the end of the reaction to precipitate product **2**. After filtration, compound **2** was collected and dried. The potency of the isolated product was determined, and the results are summarized in Table 1. Despite the excellent HPLC area percentage at the end of the reaction, the potency corrected yield with 2 mol % Pd(OAc)$_2$ was only determined as 70% (Table 1, entry 3).

We subsequently investigated the possibility of improving the yield by suppressing the formation of polymeric byproducts.

(16) Because a heterogeneous reaction mixture was observed at the end of the reaction, in situ quantitative HPLC assay was not used.

Table 1. Determination of potency corrected isolated yields[a]

entry	Pd loading (mol %)	% dimer 11	in situ HPLC area[b] (%)	yield[c] (%)
1	0.1	0.8	89.3	83
2	0.5	1.1	87.6	77
3	2	1.4	87.4	70
4	10	14.6	85.6	61

[a] All reactions were run with 1.2 equiv of boronic acid **4**, 3.0 equiv of Na$_2$CO$_3$, and Pd(OAc)$_2$ in 4:1 dioxane/water (0.1 M) at 70 °C with subsurface sparging. [b] Remaining boronic acid **4** and dimer **11** were excluded from the calculations since they were attributed to the extra boronic acid used. [c] Yield was determined from the weight and potency of the isolated product. The product was isolated by addition of water to the reaction mixture, followed by filtration to collect the product. See Experimental Section for details.

Whereas the desired cascade reaction presumably was first order in palladium concentration, it occurred to us that the undesired polymer formation reactions were likely higher order in palladium concentration. We therefore explored the options of reducing palladium catalyst loading. When the catalyst loading was reduced from 2 mol % to 0.5 mol %, the in situ HPLC area percentage remained unchanged at the end of the reaction. However, 77% potency corrected yield was obtained (Table 1, entry 2). Further reducing the catalyst loading to 0.1 mol % again afforded similar HPLC area percentage (entry 1). In this case, we were delighted to observe 83% potency corrected yield. To further demonstrate the trend, we tested the cyclization with 10 mol % of Pd(OAc)$_2$. Although similar HPLC area percentage was observed at the end of the reaction, significantly lower isolated yield was obtained (Table 1, entry 4). The results from Table 1 clearly revealed the trend that higher-level palladium loading was correlated to higher level of polymeric byproduct. It was also noteworthy that higher-level of dimer impurity **11** was observed when 10 mol % Pd(OAc)$_2$ was employed, despite the fact that the same subsurface sparging procedure was applied to all reaction conditions. It was also worth mentioning that the similar levels of impurity **12** and starting material **3** were observed when the catalyst loading was changed from 0.1 mol % to 10 mol %.

As described, technical grade **2** was isolated by water addition followed by filtration at the end of the reaction. The procedure provided an efficient rejection of remaining boronic acid **4**. However, little rejection of starting material **3**, cross-coupling impurity **12**, and dimer **11** occurred during the process. To further purify technical grade **2**, attempts were made to recrystallize the material under a variety of solvent systems. Although starting material **3** could be easily rejected through crystallization, the removal of impurity **12** proved to be inefficient. To maximize the overall yield of **1**, technical grade **2** was then forward processed to the next step.

To complete the synthesis of **1**, compound **2** was reduced under hydrogenation conditions. Sulfided platinum on carbon (5% wt.) was selected as the catalyst to avoid the reduction of the bromo functionality (Scheme 5). The reaction proceeded to completion in THF at 50 psi within 2 h. The reaction mixture was then filtered to remove residual platinum and palladium catalysts. The solvent was then switched from THF to EtOAc and an aqueous workup was applied. As expected, impurity **12**, which was carried over from the previous step, was also reduced under the reduction conditions. Fortunately, this

impurity was removed to the aqueous layer during an aqueous HCl wash. Final HCl salt formation further rejected impurity **3** (<0.2%) and afforded target compound **1** with >97% potency. In addition, both palladium and platinum levels were determined to be below <10 ppm in the isolated HCl salt. The strategy of carrying out the majority of the impurity rejection at compound **1** stage controlled all of the impurities and afforded 74% overall yield in the last two steps.

Scheme 5. Synthesis of **1·HCl**
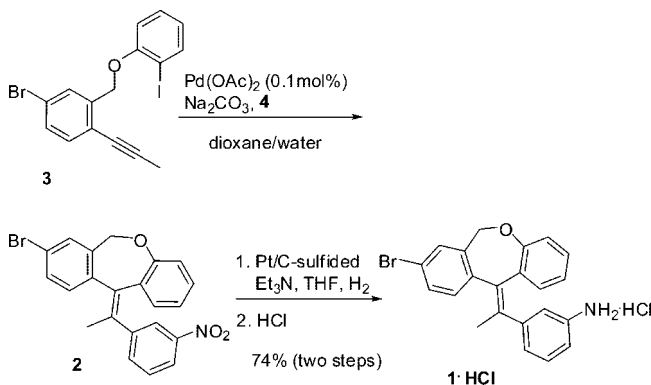
Conclusion

In conclusion, we have identified and developed an efficient and scaleable route for the synthesis of key intermediate (Z)-3-(1-(8-bromodibenzo[b,e]oxepin-11(6H)-ylidene)ethyl)aniline hydrochloride (**1·HCl**) to support our selective nuclear hormone receptor modulator program. The key reaction involved a palladium-catalyzed intramolecular carbometalation of an alkyne to form the desired dibenzoxapine-containing tetrasubstituted exocyclic (Z)-alkene. Target compound **1·HCl** was prepared in 48% overall yield in five steps from commercially available (5-bromo-2-iodophenyl)methanol (**5**). The impurity control strategy was established in the final HCl salt formation step. Furthermore, palladium and platinum levels were sufficiently controlled to <10 ppm. The reactions described were successfully scaled up at 12 L scale to provide 2.0 kg of target compound. We believe this is the first large-scale pharmaceutical application described in the literature for a palladium-catalyzed intramolecular carbometalation of an alkyne.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded as specified for each experiment with chemical shift recorded as parts per million. Elemental analysis and high-resolution mass spectrometry data were provided by the Physical Chemistry group of Lilly Research Laboratories. Commercially available reagents and solvents were used without further purification. Compounds **1**, **3**, **6**, and **8** were monitored using an Agilent 1100 series instrument equipped with a UV using the following conditions: 40% acetonitrile 0.1% aqueous trifluoroacetic acid/60% 0.1% aqueous trifluoroacetic acid to 70% acetonitrile 0.1% aqueous trifluoroacetic acid/30% 0.1% aqueous trifluoroacetic acid; flow rate: 1.0 mL/min; column temperature: 30 °C; column: Zorbax SB-C8, 4.6 mm × 250 mm, 5 μm; detector: 254 nm. Compound **2** was monitored using an Agilent 1100 series instrument equipped with a UV using the following

conditions: 5% acetonitrile 0.1% formic acid/95% 0.1% formic acid in water to 100% acetonitrile 0.1% formic acid; flow rate: 0.5 mL/min; column: Zorbax SB-C8, 3.0 mm × 150 mm, 3.5 μm; detector: 254 nm.

(5-Bromo-2-prop-1-ynyl-phenyl)-methanol (6). To a 12-L three neck round-bottom flask equipped with an overhead stirrer apparatus, a thermometer/thermocouple, and a nitrogen inlet was charged alcohol **5** (480 g, 1.53 mol) and diethylamine (5.4 L, 52.2 mol). Copper (I) iodide (5.88 g, 30.8 mmol) was added, followed by bis(triphenylphosphine)palladium(II) chloride (10.8 g, 15.3 mmol). Propyne gas was bubbled into the reaction mixture for 45 min while the reaction temperature was increased from rt to 32 °C. The reaction mixture was stirred at rt overnight. HPLC analysis indicated that <1% of alcohol **5** remained. The reaction mixture was filtered through water-wet Celite. The residual catalyst on the Celite was washed with 1 L of EtOAc. The combined filtrate was concentrated under reduced pressure to a total volume of 500 mL. Additional EtOAc (3 L) was added, and the mixture was washed with water (2 × 3 L) followed by 10% brine solution (1 L). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give 358 g of a dark-brown solid. The solid was purified via silica gel filtration (975 g of silica gel, 5% EtOAc/hexanes as eluents) to afford compound **6** as a pale-yellow solid (299 g, 1.33 mol, 87%). ^{1}H NMR (DMSO-d_6) δ 7.60 (d, 1 H, J = 2.0 Hz), 7.39 (m, 1 H), 7.26 (d, 1 H, J = 8.0 Hz), 5.38 (t, 1 H, J = 6.0 Hz), 4.57 (d, 2 H, J = 6.0 Hz), 2.06 (s, 3 H). ^{13}C NMR (DMSO-d_6) δ 146.8, 133.7, 129.8, 129.4, 121.7, 120.1, 93.2, 76.5, 61.1, 4.5. HRMS calcd for $C_{10}H_9OBrNa$ [M + Na] 246.9734, found 246.9729.

4-Bromo-2-(2-iodo-phenoxy)methyl-1-(prop-1-ynyl)benzene (3). To a 2000 mL round-bottom flask equipped with an overhead stirrer apparatus, a thermometer/thermocouple, and a nitrogen inlet was charged (5-bromo-2-prop-1-ynyl-phenyl)-methanol (**6**) (46.0 g, 204 mmol) and toluene (460 mL). The resulting mixture was cooled to 5−10 °C with an ice bath. Phosphorus tribromide (25.0 mL, 264 mmol) was added dropwise so the temperature did not rise above 15 °C. The reaction mixture was then heated to 60 °C for 18 h. The reaction mixture was then cooled to 5 °C in an ice/water bath and was quenched slowly with ice water (200 mL) followed by saturated aqueous sodium carbonate (300 mL). The biphasic reaction mixture was then filtered through a thin bed of Celite, and the residue was washed with ethyl acetate (120 mL). The filtrate was separated, and the aqueous layer was extracted with ethyl acetate (200 mL). The combined organic extracts were washed with brine (400 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give benzyl bromide **7** as a yellow oil, which solidified upon standing (58.7 g, 204 mmol, 100%). The crude mixture was used in the next step without further purification. ^{1}H NMR (DMSO-d_6) δ 7.74 (d, 1 H, J = 2.0 Hz), 7.47 (m, 1 H), 7.32 (d, 1 H, J = 8.5 Hz), 4.68 (s, 2 H), 2.08 (s, 3 H). ^{13}C NMR (DMSO-d_6) δ 141.8, 134.4, 133.0, 132.0, 123.1, 121.4, 94.3, 76.4, 32.1, 4.7.

To a 1000 mL round-bottom flask equipped with a nitrogen inlet, magnetic stirrer, and a thermocouple were charged benzyl bromide **7** (58.7 g, 204 mmol), 2-iodophenol (40.5 g, 184 mmol), powdered potassium carbonate (63.4 g, 460 mmol), and DMF (400 mL). The resulting slurry was stirred at rt for 18 h.

HPLC analysis indicated that the reaction was complete. The reaction mixture was filtered through Celite, and the residue was rinsed with 100 mL of DMF. The filtrate was transferred to a 2000 mL round-bottom flask and was allowed to stir at rt. Water (1 L) was added to the filtrate slowly to form a thick slurry. The resulting slurry was stirred at rt for 2 h and filtered. The solid was rinsed with water (150 mL), dried in vacuo at 45 °C to give 73.1 g of technical grade **3** as a yellow solid. To a 1000 mL round-bottom flask equipped with a condenser, nitrogen inlet, magnetic stirring, and a thermocouple were charged technical grade **3** (73.1 g) and ethanol (365 mL). The resulting slurry was heated at 80 °C, and a solution formed. The solution was allowed to cool to room temperature. At ∼60 °C the product began to crystallize from solution. The mixture was aged at room temperature overnight (∼18 h) and was cooled to 5 °C for an additional 2 h. The solid was isolated by filtration and washed with 200 mL of cold ethanol. The solid was dried in vacuo at 45 °C to give the title compound **3** as an off-white solid (64.7 g, 152 mmol, 74% from **6**). ^{1}H NMR (DMSO-d_6) δ 7.81−7.78 (m, 2 H), 7.51−7.49 (m, 1 H), 7.38−7.35 (m, 2 H), 7.06 (m, 1 H), 6.79−6.76 (m, 1 H), 5.21 (s, 2 H), 2.03 (s, 3 H). ^{13}C NMR (DMSO-d_6) δ 156.9, 140.7, 139.5, 134.0, 131.2, 130.5, 130.2, 123.6, 121.6, 121.5, 113.5, 94.0, 87.2, 76.4, 68.5, 4.7. Anal. Calcd for $C_{16}H_{12}BrIO$ C, 45.00, H, 2.83, found C, 45.20, H, 2.79.

4-Bromo-2-((2-iodophenoxy)methyl)-1-(prop-1-ynyl)benzene (2). To a 12-L three neck round-bottom flask equipped with a condenser, nitrogen inlet, mechanical stirring, and thermocouple were charged aryl iodide **3** (300 g, 0.702 mol), 3-nitrophenylboronic acid **4** (140.6 g, 0.842 mol), and sodium carbonate (223 g, 2.11 mol). A solution of 5.6 L of 1,4-dioxane and 1.4 L of water was added to the mixture. The resulting slurry was sparged with subsurface nitrogen for 20 min. $Pd(OAc)_2$ (158 mg, 0.702 mmol) was added, and the reaction was sparged with subsurface nitrogen for an additional 20 min. The reaction mixture was warmed to 70 °C under nitrogen for 22 h. The reaction mixture was cooled to rt, and a slurry was formed upon cooling. Water (7.5 L) was slowly added to the reaction mixture, and the resulting thick slurry was stirred at rt for 2 h. The reaction mixture was filtered, and the solid was washed with water (900 mL). The solid was collected, vacuum-dried at 40 °C to give compound **2** (302 g with 81% potency, 0.583 mol, 83% potency corrected yield). The material was forward processed without further purification. ^{1}H NMR (DMSO-d_6) δ 8.15 (t, 1 H, J = 1.5 Hz), 8.02 (AB, 1 H, J = 8.1 Hz, 2.4 Hz), 7.81 (d, 1 H, J = 2.1 Hz), 7.74 (d, 1 H, J = 8.1 Hz), 7.64 (AB, 1 H, J = 7.8 Hz, 2.1 Hz), 7.51 (t, 1 H, J = 8.1 Hz), 7.37 (d, 1 H, J = 7.8 Hz), 6.95 (m, 1 H), 6.69 (d, 1 H, J = 7.2 Hz), 6.47 (m, 2 H), 5.80 (d, 1 H, J = 12.6 Hz), 5.00 (d, 1 H, J = 12.6 Hz), 2.075 (s, 3 H).

(Z)-3-(1-(8-Bromodibenzo[b,e]oxepin-11(6H)-ylidene)ethyl)aniline hydrochloride (1·HCl). A hydrogenation vessel was charged with **2** (76.5 g with 81% potency, 0.147 mol), tetrahydrofuran (700 mL), triethylamine (20.5 mL, 14.9 g, 0.147 mmol), and platinum, 5% wt on C, sulfided (6.2 g, 1.6 mmol). The reactor was sealed, evacuated and purged with hydrogen. The reaction mixture was stirred under 50 psi hydrogen

atmosphere at rt for 2 h. The reaction vessel was evacuated and flushed with nitrogen. HPLC analysis indicated that the reaction was complete. The reaction mixture was filtered through GFF paper, and the catalyst residue was washed with 150 mL of ethyl acetate. The filtrate was solvent exchanged to 1.2 L of ethyl acetate, and 900 mL of water was added. The pH of the aqueous layer was adjusted to ∼1 through addition of concentrated HCl solution. The mixture was transferred to a separatory funnel, and the layers were separated. The organic layer was washed with 1.2 L of saturated aqueous sodium bicarbonate, followed by 600 mL of brine. Seventeen milliliters of HCl (37 wt % in water) was added dropwise to the organic layer. The mixture was heated at 50 °C, and 50% of the ethyl acetate was removed by distillation. The resulting slurry was then cooled to rt and stirred for 1 h. The slurry was filtered, and the solid was washed with ethyl acetate (150 mL). Off-white crystals were collected and dried to a constant weight to afford **1·HCl** (56.1 g, 0.131 mol, 89% yield from **2**, 74% yield from **3**). ^{1}H NMR (DMSO-d_6) δ 9.77 (bs, 2 H), 7.80 (d, 1 H, $J = 2.5$ Hz), 7.62 (m, 1 H), 7.36 (d, 1 H, $J = 8.0$ Hz), 7.25−7.18 (m, 3 H), 7.07 (d, 1 H, $J = 7.5$ Hz), 6.96−9.92 (m, 1 H), 6.67 (m, 1 H), 6.55 (m, 1 H), 6.45 (m, 1 H), 5.73 (d, 1 H, $J = 12.0$ Hz), 5.00 (d, 1 H, $J = 12.0$ Hz), 2.01 (s, 3 H). ^{13}C NMR (DMSO-d_6) δ 154.8, 144.6, 142.5, 135.8, 135.7, 134.0, 132.8, 131.88, 131.87, 129.8, 129.7, 129.3, 129.0, 125.2, 123.6, 121.7, 120.9, 120.5, 119.3, 68.2, 22.4. HRMS calcd for $C_{22}H_{19}BrNO$ [M + H] 392.0645, found 392.0642.