

An Intra/Intermolecular Suzuki Sequence to Benzopyridyloxepines Containing Geometrically Pure Exocyclic Tetrasubstituted Alkenes

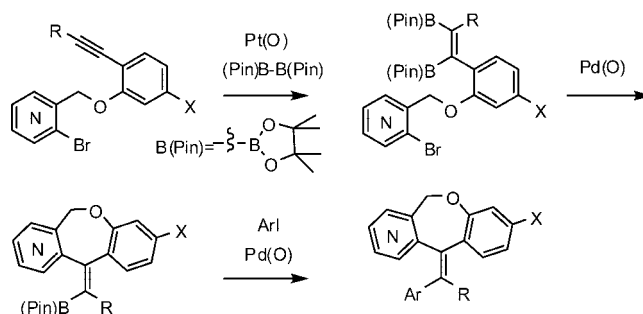
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ABSTRACT



A route to enable the preparation of 5-benzylidenyl-benzopyridyloxepine analogues was developed to continue our research in the field of nuclear hormone receptor modulators. The key steps are 1) a syn-stereoselective dimerization of a tethered aryl alkyne; 2) an intramolecular Suzuki cross-coupling reaction, which forms in a stereo- and regiocontrolled fashion, the 5-exoalkyldienyl 7-membered ring imbedded within the core of the scaffold and; 3) an intermolecular Suzuki to furnish the final tetra-substituted olefinic benzopyridyloxepines.

The highly substituted olefin motif is found in a number of biologically active series including the triphenylethylenes, most notably represented by the SERM tamoxifen,¹ and Lilly's dibenzoxepine nuclear hormone receptor (NHR) modulators.² Recently there has been impressive progress on the regio- and stereoselective syntheses of tetra-substituted alkenes.³ At Lilly, we developed a one-pot procedure to the dibenzoxepines, which contain a tri- or tetrasubstituted exobenzylidene moiety, utilizing an intramolecular carbometalation of an alkyne followed by cross-coupling with a

boronic acid (Heck-Suzuki).^{4,5} In this paper, we report on a complimentary route involving a stereospecific dimetalation of an alkyne followed by regioselective sequential intra/intermolecular cross couplings, which allowed us to synthesize a series of benzopyridyloxepines containing stereodefined tetra-substituted exocyclic alkenes.

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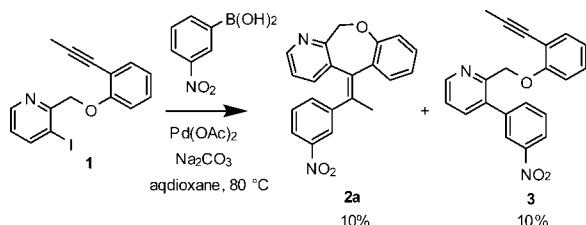
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(5) (a) For previous examples of intramolecular addition of arylpalladium intermediates to tethered alkynes followed by cross coupling to give exocyclic tetrasubstituted alkenes, see Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakum, T. *Tetrahedron Lett.* **1989**, *30*, 1135. (b) Zhang, Y.; Negishi, E-I. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (c) Negishi, E-I; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (d) Wang, R-T; Chou, F-L; Luo, F-T. *J. Org. Chem.* **1990**, *55*, 4846. (e) Cheung, W. S.; Patch, R.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (f) Bour, C.; Blond, G.; Salem, B.; Suffert, J. *Tetrahedron* **2006**, *62*, 10567, and references therein.

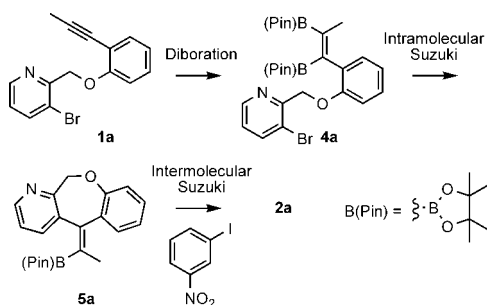
To continue the study of the dibenzoxepine structure–activity relationship (SAR) as NHR modulators, it was our initial desire to apply a route utilizing the key Heck–Suzuki step for the preparation of pyridine analogues. However, to our disappointment, under the ligandless conditions optimal for the phenyl analogues, the palladium-catalyzed reaction of alkyne-tethered aryl iodide **1** in the presence of 3-nitrophenyl boronic acid afforded a low yield of desired pyridyloxepine **2a** (10%) along with direct coupling product **3** (Scheme 1). Based upon mass balance after column chro-

Scheme 1



matography, apparent oligomerization was the main outcome of the reaction.⁶ To circumvent the issue of a low yielding cyclization step for the preparation of NHR modulator targets, we then envisioned a route highlighted by an intramolecular Suzuki coupling to synthesize the seven-membered ring containing the geometrically pure exocyclic alkene. A similar approach involving an intramolecular Stille coupling to trisubstituted exocyclic alkenes of benzopyridyloxepines was reported by Finch and co-workers.⁷ Scheme 2

Scheme 2



illustrates the new sequence commencing with a platinum-catalyzed syn diboration of tethered alkynyl aryl pyridyl bromide **1a** with bis(pinacolato)diboron to cleanly give bis(vinylpinacol boronic ester **4a**, which was used in the next

(6) This result is reminiscent of our previous findings in which we conducted exploratory Heck–Suzuki reactions of phenyl analogues in the presence of a ligand. The fact that the pyridine resulted in much lower yields than the phenyl analogue under the ligandless conditions suggests that another molecule of **1** or resultant intermediates function as a ligand. In other words, the complexation of the pyridyl nitrogen to organopalladium intermediates disfavors the desired intramolecular Heck–Suzuki compared to side reactions such as 1) direct coupling to give **3** and; 2) intermolecular Heck reaction leading to high molecular weight products.

step without further purification.⁸ It should be noted that the use of bromopyridine is required as an attempted diboration of the aryl iodide **1** resulted in recovery of starting material due to the likely C–I insertion of the platinum. With the bis boronic ester **4a** in hand, we investigated conditions for the intramolecular Suzuki cross coupling to give vinyl boronic ester **5a** (Scheme 2). Optimization of this step revealed that dilute (0.01 M **4a** in anhydrous dioxane) conditions, using PdCl₂(dppf)•CH₂Cl₂ and K₃PO₄, delivered the desired vinyl boronic ester **5a**. To complete the synthesis of **2a**, we were faced with the challenge of coupling a bulky boronic ester with an aryl iodide. Prior art reveals that cross coupling of aryl halides with sterically hindered boronic esters under standard Suzuki conditions (e.g., Pd(PPh₃)₄, aqueous weak

Scheme 3

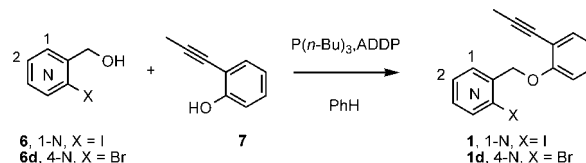
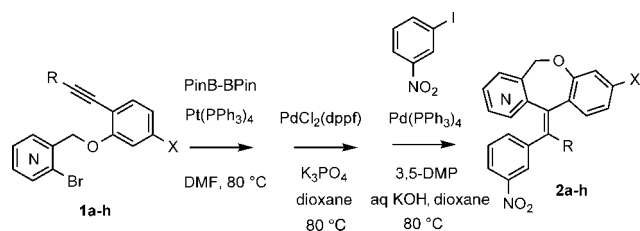


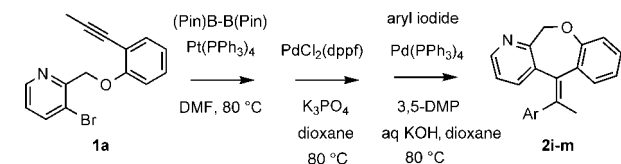
Table 1. Synthesis of Benzopyridyloxepines **2a–h** from Tethered Alkynyl Aryloxy Pyridyl Bromides **1a–h**^a



entry	starting material	product	% yield ^b
1			45
2			32
3			30
4			0
5			40
6			38
7			45
8			45

^a Diboration: 1.1 equiv of bis(pinacolato)diboron and 8 mol % of Pt(PPh₃)₄ in DMF (0.1 M) at 80 °C for 24 h. Intramolecular Suzuki: 10 mol % PdCl₂(dppf)·CH₂Cl₂ and 3 equiv of K₃PO₄ in dioxane (0.01 M) at 80 °C for 24 h. Intermolecular Suzuki: 1.5 equiv of 3-iodonitrobenzene, 5 mol % of Pd(PPh₃)₄, 6 M aqueous KOH (0.4 M), and 5 equiv of 3,5-dimethoxyphenol in dioxane (0.15 M) at 80 °C for 18 h. ^b Isolated yields (**1** to **2**, three steps) after column chromatography.

Table 2. Synthesis of Benzopyridyloxepine Derivatives **2i–m** from **1a**^a



entry	aryl iodide	product	% yield ^b
1			36
2			42
3			31
4			37 ^c
5			22

^a Diboration: 1.1 equiv of bis(pinacolato)diboron and 8 mol % of Pt(PPh₃)₄ in DMF (0.1 M) at 80 °C for 24 h. Intramolecular Suzuki: 10 mol % of PdCl₂(dppf)·CH₂Cl₂ and 3 equiv of K₃PO₄ in dioxane (0.01 M) at 80 °C for 24 h. Intermolecular Suzuki: 1.5 equiv of aryl iodide, 5 mol % of Pd(PPh₃)₄, 6 M aqueous KOH (0.4 M), and 5 equiv of 3,5-dimethoxyphenol in dioxane (0.15 M) at 80 °C for 18 h. ^b Isolated yields (**1** to **2**, three steps) after column chromatography. ^c (*E*)-**2l** and (*Z*)-**2l** were isolated as single isomers via column chromatography in 21% and 16% yield, respectively.

commercially available iodophenol (Scheme 3). However, the intra/intermolecular Suzuki route allowed us to target bromopyridines as intermediates which shortened the syntheses and allowed for later structural divergence. As shown in Scheme 4, Mitsunobu reaction between bromopyridyl methanols **6a–c** and iodophenols **8a–c** afforded bromobenzyl iodoaryl ethers **9a–e** which undergo regioselective Sonogashira reactions at the C–I locus to give alkynes **1a–h**.

It should be noted that bromopyridines with reactive C–Br bonds (see **6d**) were outside the scope of the selective Sonogashira reaction, therefore Mitsunobu between **6d** and

7 using *tri*-*n*-butylphine and 1,1'-(azodicarbonyl)-dipiperidine (ADDP) afforded the desired bromopyridine **1d** (Scheme 3).

With intermediates **1a–h** in hand, we applied the intra/intermolecular Suzuki technology to prepare compounds for the SAR studies. The methodology worked in moderate yields, calculated at the end of the three-step diboration, intra/intermolecular coupling sequence, to afford the 1,2, and 3-pyridyl isomers **2a–c** (Table 1, entries 1–3). To our disappointment, the sequence failed in the case of the 4-pyridyl analogue **1d** (Table 1, entry 4). Both the fluoro and methoxy substituted examples (Table 1, entries 5–6) resulted in similar yields suggesting a lack of electronic effect in the alkynyl phenyl ring. We successfully expanded the series to propylidenyl **2g** and isobutylidenyl **2h** analogues as well (Table 1, entries 7–8) resulting in yields similar to the ethylidenyl analogue **2a** (Table 1, entry 1).

The intra/intermolecular Suzuki route allowed for access to substituted aryl rings at the vinyl position with late divergence in the synthesis. Analogues phenyl **2i**, *p*-fluorophenyl **2j**, and *p*-aminophenyl **2k** were prepared in moderate yields (Table 2, entries 1–3). However, the conditions of the coupling reaction in some cases gave undesired results. For example, unlike the *m*-NO₂ analogue **2a** (Table 1, entry 1), the coupling of **5a** with 4-iodonitrobenzene afforded both the *E*- and *Z*- isomers of **2l** (Table 2, entry 4). We attempted to synthesize the *p*-cyanophenyl derivative, but could only isolate the primary amide **2m** in low yield (Table 2, entry 5). Despite the aforementioned limits, one could conclude that the three-step diboration, inter/intramolecular Suzuki cross coupling methodology has the potential to be a viable

alternative to the intramolecular carbometalation for the stereoselective preparation of tetra-substituted exocyclic alkenes.

In summary, a diboration, inter/intramolecular Suzuki cross-coupling sequence enabled the synthesis of pyridyl-benzoxepines with a highly substituted stereodefined olefinic moiety at the five-position. Highlights of the sequence include (1) an intramolecular Suzuki cross coupling to give a seven-membered ring and (2) an example of an intermolecular Suzuki in a sterically congested environment. The route allowed us to synthesize a diverse set of targets for our NHR program, and it serves as complimentary route to the Heck–Suzuki cascade. In future work, we will expand the scope of this technology to biologically active exocyclic alkenes outside the scope of dibenzoxepines.

Supporting Information Available: Detailed experimental procedures and NMR of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Due to instability, boronic acid intermediates **4a** and **5a** as well as analogous intermediates (*vide infra*) were difficult to purify, therefore the material was used in subsequent steps in crude form and the yield was calculated over three steps.