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Cyclocarbopalladation of Alkynes: A Stereoselective Method for Preparing Dibenzoxapine Containing Tetrasubstituted Exocyclic Alkenes

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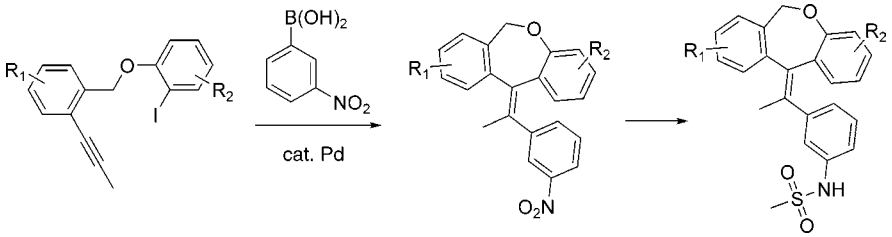
ABSTRACT



A palladium-catalyzed cascade carbometalation-cross coupling of alkyne route was developed for the preparation of tetrasubstituted exocyclic alkenes with high stereo- and regiocontrol. The effectiveness of this novel methodology was demonstrated by the synthesis of a number of dibenzoxapines in sufficient quantities to support their further development.

Dibenzoxapine and dibenzosuberane derivatives have been an interest of the pharmaceutical industry for a number of years. Recently, a novel series of these tricyclic compounds have been identified at Eli Lilly and Company as nuclear hormone receptor modulators.[1] To support their further development, quantities of tetrasubstituted dibenzoxapine derivatives, such as **1a**−**d** (Figure 1), were needed.

The dibenzoxapine derivatives containing tetrasubstituted alkene moieties (**1a**−**d)** represent a novel structure and also pose a unique synthetic challenge. Although these tetrasubstituted dibenzoxapine derivatives could be prepared by methods such as the Wittig reaction[2] or simply dehydration of a carbinol, the synthetic approaches are lengthy and often limited in scope. In addition, a mixture of the (*E*)- and (*Z*)-isomers is often produced. Since each geometric isomer may exhibit different toxicological and pharmacological activities, stereoselective syntheses of these targets are advantageous. Our need to develop a practical stereoselective route led to an investigation of the palladium-catalyzed tandem cyclization of **3a**−**d**. The synthetic strategy was to incorporate a key intramolecular carbometalation of alkynes to establish the desired geometric relationship. The convergent approach involved preparation of cyclization precursors **3a**−**d**, which could be derived from benzyl alcohols **4a**−**c** and phenols **5a** or **5b** through either a one-step Mitsunobu reaction[3] or a two-step alkylation procedure (Figure 1). Benzyl alcohols **4a**−**c** could be easily synthesized from the corresponding aryl halides by using Sonogashira coupling.[4]

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(1) 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.

(2) For a review of Wittig olefination, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(3) (a) Simon, C.; Hosztafi, S.; Makleit, S. *J. Heterocycl. Chem.* **1997**, *34*, 349. (b) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127. (c) Mitsunobu, O. *Synthesis* **1981**, 1.

(4) (a) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

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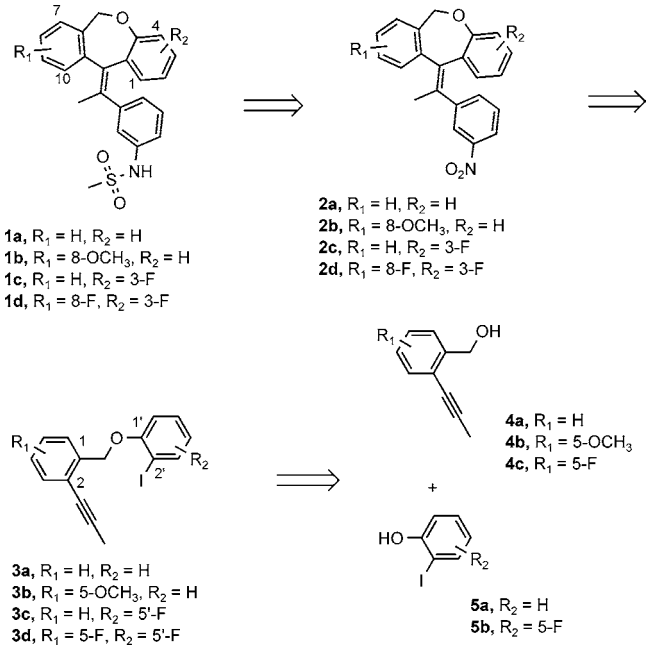
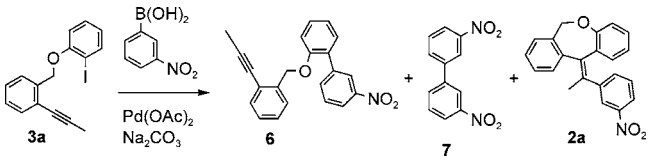


Figure 1. Retrosynthetic approach to **1a**−**d**.

The carbometalation of alkynes by organometallic reagents is now widely used for the stereospecific synthesis of di-, tri-, and even tetrasubstituted alkenes.[5] The major advantage of these reactions lies in their high stereo- and regioselectivity, which enables them to add to the triple bond of various alkynes. Another advantage of this approach is the generation of a new organometallic species, a vinylic metal, which can be further transformed in such a way that the overall result is the one-pot positioning of two new substituents in a cis or trans manner, depending on the organometallic reagent used.[5] In particular, *intramolecular* carbopalladation of alkynes (cyclocarbopalladation) is a versatile approach to various tetrasubstituted alkenes.[6] The reaction generally involves an initial cyclocarbopalladation followed by cross-coupling of the vinylpalladium species with boron, tin, or zinc organometallic species. The termination of the vinylpalladium species effectively converts the Pd(II) to Pd(0), thus completing the catalytic cycle. The initial carbopalladation generally follows the 5-exo-dig, 6-exo-dig, or 7-exo-dig process. However, to the best of our knowledge, there are still no reports on the preparation of seven-membered rings through a palladium-catalyzed carbometalation-cross coupling cascade with use of organometallics as the terminating trapping species.[7]

The commercially available 3-nitrophenylboronic acid was first used as the terminating species. Reaction between alkyne **3a** and 3-nitrophenylboronic acid was attempted to optimize the reaction conditions (Table 1). Modifying a literature procedure[6f] for the carbopalladation reaction, **3a** and 3-nitrophenylboronic acid were heated in toluene at 90 °C for 12 h with 2 mol % $Pd(OAc)_2$, 4 mol % tri-*o*-tolylphosphine, 1 equiv of tetrabutylammonium chloride, and 3 equiv of Na_2CO_3 (Table 1, entry 1). Significant amounts of starting materials **3a** and 3-nitrophenylboronic acid remained unreacted, along with the desired product **2a**, direct Suzuki coupling byproduct **6**,[8] 3-nitroboronic acid dimerization byproduct **7**,[9] and some oligomeric and polymeric byproducts which were formed presumably due to the intermolecular coupling between vinylic palladium intermediate and alkyne

Table 1. Optimization Studies[a]



entry	catalyst	solvent	temp (° C)	% **3a**[b]	% **6**[b]	% **7**[b]	% **2a**[c]
1[d]	$Pd(OAc)_2$/A[e]	toluene[h]	90	51	4	9	
2	$Pd(OAc)_2$/A[e]	toluene	90	84	0	0	
3	$Pd(OAc)_2$	dioxane	110	88	0	0	0
4	$Pd(OAc)_2$/B[f]	dioxane	90	76	2	3	
5[d]	$Pd(OAc)_2$/A[e]	*n*-BuOH	90	0	0	25	
6[d]	$Pd(OAc)_2$	DMF	110	0	43	4	0
7[d]	$Pd(OAc)_2$/A[e]	DMF	90	0	1	24	32
8	$Pd(OAc)_2$/A[e]	DMF/ H_2O[i]	70	0	74	3	
9	$Pd(OAc)_2$/A[e]	dioxane/H_2O[i]	70	0	76	5	
10	$Pd(OAc)_2$/B[f]	dioxane/ H_2O[i]	70	0	37	2	33
11	$Pd(OAc)_2$/C[g]	dioxane/ H_2O[i]	110	0	19	12	38
12	$Pd(OAc)_2$	dioxane/ H_2O[i]	70	0	3	6	89

[a] All reactions were run with 2% catalyst, 1.2 equiv of 3-nitroboronic acid, and 3 equiv of Na_2CO_3 for 12 h with total concentration at 0.1 M. [b] Determined by reverse-phase HPLC. [c] Isolated yields. [d] Additional oligomers and polymers were formed. Some of the oligomers and polymers may not be HPLC detectable. [e] Ligand A: tri-*o*-tolyphosphine. [f] Ligand B: triphenylphosphine. [g] Ligand C: 2-(dicyclohexylphosphino)biphenyl. [h] 1 equiv of Bu_4NCl was added. [i] 4:1 v/v ratio.

(5) For reviews see: (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Negishi, E. *Acc. Chem. Res.* **1987**, *20*, 65. (c) Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 4, p 865. (d) Marek, L.; Normant, J. F. In *Carbometallation Reactions in Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley VCH: New York, 1998; pp 271−337. (e) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, 5899. (f) Mitchell, D.; Yu, H. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 876.

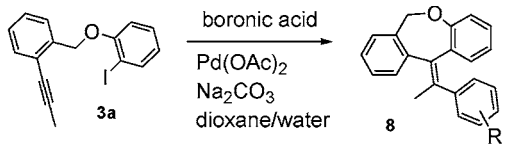
(6) For representative examples, see: (a) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135. (c) Grigg, R.; Sandano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton, P. M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803. (d) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (e) Frewell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525. (f) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845.

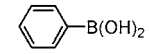
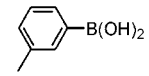
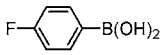
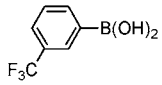
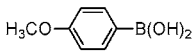
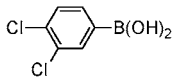
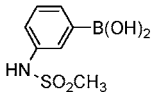
(7) For selective references of seven-membered ring formation through the palladium-catalyzed cascade reaction, see: (a) References 6a and 6d. (b) Grigg, R.; Savic, V.; Sridharan, V.; Terrier, C. *Tetrahedron* **2002**, *58*, 8613.

(8) For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reaction*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 49−97.

(9) (a) Miyaura, N.; Suzuki, A. *Main Group Met. Chem.* **1987**, *10*, 295. (b) Parrish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899. (c) Lei, A.; Zhang, X. *Org. Lett.* **2002**, *4*, 2285. (d) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541.

Table 2. Carbometalation Terminated with Different Boronic Acids[a]



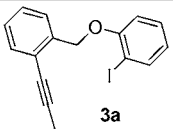
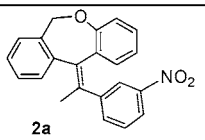
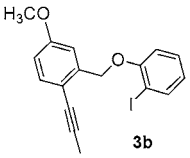
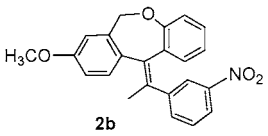
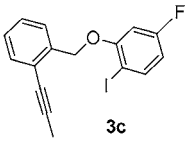
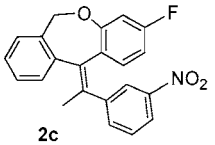
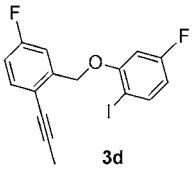
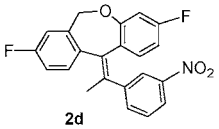
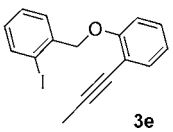
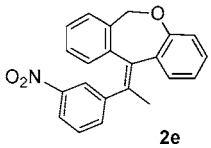
entry	boronic acid	product	% yield[b]
1		**8a**	77
2		**8b**	91
3		**8c**	76
4		**8d**	70
5		**8e**	74
6		**8f**	78
7		**1a**	59

[a] All reactions were run with 1.2 equiv of boronic acid, 3.0 equiv of Na_2CO_3, and 1 mol % $Pd(OAc)_2$ in 4:1 dioxane/water (0.1 M) at 100 °C for 12 h. [b] Isolated yields after column chromatography.

starting material.[10] Increasing the catalyst loading to 10 mol % $Pd(OAc)_2$ and 20 mol % tri-*o*-tolylphosphine and raising the temperature to 110 °C did consume all of the starting material **3a**; however, a much lower yield of the desired product was observed. As anticipated, elimination of the tetrabutylammonium chloride resulted in a more incomplete reaction (entry 2). Next, we investigated several additional solvents, under both ligand and ligandless conditions (entries 3−7). Although none of these reactions gave a satisfactory result, this initial screening indicated that substrate **3a** is more reactive in solvents with higher dielectric constants. With 2 mol % of catalyst, toluene and dioxane led to a significant amount of starting material **3a**, indicating that the insertion of palladium to alkyne did not take place under the reaction conditions. *n*-BuOH and DMF led to a faster palladium insertion process and completed reactions. However, significant amounts of oligomers and polymers were observed. It is likely that under these conditions, the initial palladium insertion was activated, but the subsequent transmetalation between vinylic palladium and boronic acid did not occur at a reasonable rate.

Since the coupling of a vinylic palladium species with arylboronic acids is essentially a variant of the Suzuki cross-coupling reaction, which is known to proceed much faster in water when a hydroxide is present, we examined the possibility of using water as the cosolvent (entries 8 and 9).[7a,11,12] In fact, a significant enhancement in the reaction rate was observed when the reactions were conducted in DMF/water (4:1 v/v) and dioxane/water (4:1 v/v). Both reactions went to completion at 70 °C in less than 1 h accompanied by only trace amounts of polymerization. However, under these conditions the direct Suzuki coupling product **6** predominated.

Table 3. Synthesis of Dibenzoxepin Derivatives **2a**−**e** from **3a**−**e** and 3-Nitroboronic Acid[a]

entry	alkyne	product	yield (%)[b]
1	 **3a**	 **2a**	89
2	 **3b**	 **2b**	70
3	 **3c**	 **2c**	77
4	 **3d**	 **2d**	73
5[c]	 **3e**	 **2e**	67

[a] All reactions were run with 1.2 equiv of boronic acid, 3.0 equiv of Na_2CO_3, and 1 mol % $Pd(OAc)_2$ in 4:1 dioxane/water (0.1 M) at 70 °C for 12 h unless otherwise indicated. [b] Isolated yields after column chromatography. [c] 4:1 DMF/water (0.1 M) was used as solvent.

In an effort to find conditions where the alkyne insertion would be faster than the direct Suzuki coupling, we continued our investigation by using dioxane/water (4:1) as the solvent with various ligands (entries 9−11). None of the ligands gave the desired **2a**/**6** ratios, but we were pleased to find that under the ligandless condition (entry 12), desired product **2a** and direct Suzuki coupling product **6** were obtained in an excellent ratio of 29:1. Therefore, under this optimized condition, 2 mol % $Pd(OAc)_2$, 1.2 equiv of 3-nitroboronic acid, and 3 equiv of Na_2CO_3[13] at 70 °C for 12 h, the desired product **2a** was isolated in 89% yield.

(10) (a) Wu, G.; Rheingold, A. L.; Geig, S. L.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Reddy, K.; Rajender, S. K.; Lee, G. H.; Peng, S. M.; Liu, S. T. *Organometallics* **2001**, *20*, 5557.

(11) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(12) After the completion of this work, Larock et al. reported the synthesis of tetrasubstituted olefins through an *intermolecular* carbopalladation process. Water as cosolvent and ligandless conditions were also proved to be critical, see: (a) Zhou, C. Z.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 3765. (b) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259. (c) Zhang, X.; Larock, R. C. *Org. Lett.* **2003**, *5*, 2993. (d) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579.

To understand the scope of this cyclization, alkyne **3a** was next reacted with different arylboronic acids bearing both electron-donating and electron-withdrawing groups. The results summarized in Table 2 indicated that the reaction was fairly general in scope as electron density in boronic acid had little effect on reaction yield. In all cases, excellent ratios of desired compounds (**8a**−**f**, **1a**) versus direct coupling products were obtained (>25:1). The excellent selectivity could be explained by assuming that the desired cascade reaction is sterically favored over the undesired direct coupling reaction. A moderate yield (59%) was obtained when *m*-methylsulfonylaminophenyl boronic acid was used (Table 2, entry 7). The reduced yield resulted from competitive deboronation,[14] which was observed only in this case where a sulfonamide group was present.

Similar reaction conditions used for the preparation of **2a** were applied to the formation of nuclear hormone modulators **2b**−**e**[15] (Table 3). Both electron-donating groups (entry 3) and electron-withdrawing groups (entry 4) could be employed in the aromatic ring directly connected to the alkyne to afford the desired dibenzoxapine derivatives. The same strategy was also used in the synthesis of dibenzoxapine derivative with the opposite olefin isomer (entry 5). In all cases, the desired compounds were isolated as single stereoisomers. As anticipated, the eight-membered-ring product was not observed, indicating the regioselectivity was dictated by the 7-exo-dig nature of the process rather than the steric effect as in the *intermolecular* reactions.[16] It was also noteworthy that the reaction proceeded with high catalyst turnover rate. The reaction was more efficient with 0.5 mol % than 5 mol % $Pd(OAc)_2$.

With stereodefined tetrasubstituted exocyclic alkenes **2a**−**d** in hand, the final targets **1a**−**d** were prepared uneventfully via a nitro group reduction followed by a sulfonation procedure (79−89% yield). Because of steric hindrance, the tetrasubstituted alkenes were generally inert to various hydrogenation conditions.

In summary, the palladium-catalyzed intramolecular alkyne carbometalation reaction has proven to be a practical means for preparing dibenzoxapine containing tetrasubstituted exocyclic alkenes. High regio- and stereocontrol was obtained in all cases. Employing phosphine-free Pd(0) catalyst and water as the cosolvent afforded the target compounds in excellent yields. The practical utility of this novel method was demonstrated on the kilogram scale to afford the desired dibenzoxapine with over 70% yield.

Acknowledgment. We would like to thank Professors Marvin Miller and William Roush and Drs. Tony Zhang, Scott May, Carmen Somoza, Marvin Hansen, Stan Kolis, and David Mitchell for helpful discussions.

Supporting Information Available: Complete experimental details along with spectroscopic data for all new molecules synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Since all of the above optimization was carried out with Na_2CO_3 as base, we also investigated the effect of base on the reaction results. CsF, $NaHCO_3$, K_2CO_3, and $KHCO_3$ were used to replace Na_2CO_3 under the optimized conditions. They all afforded good **2a**/**6** selectivity, but the yield is generally lower.

(14) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207.

(15) It was necessary to convert **2b** to final target **1b** soon after isolation. **2b** could undergo a light-catalyzed isomerization during storage.

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