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Stereoselective synthesis of dibenzoxapine containing tetrasubstituted exocyclic alkenes via cascade methylboronic acid coupling reactions

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Abstract

A stereoselective method for the preparation of dibenzoxapine containing tetrasubstituted exocyclic *E*-alkenes has been developed. The key reaction involves an intramolecular cyclocarbopalladation of alkynes to form a vinylpalladium species and subsequently coupling the vinylpalladium with methylboronic acid. The approach provides a straightforward method for the synthesis of tetrasubstituted exocyclic *E*-alkenes.

The dibenzoxapine framework is commonly found in important pharmaceuticals. A novel series of dibenzoxapine containing tetrasubstituted exocyclic alkene derivatives have been identified at Eli Lilly and Company as nuclear hormone receptor modulators.[1]

Recently, we published a stereoselective method for the preparation of these tetrasubstituted alkenes by intramolecular cyclocarbopalladation of alkynes to form a vinylpalladium species and subsequently coupling the vinylpalladium with arylboronic acids (Scheme 1, strategy A).[2] The strategy was proved to be a highly efficient method for the synthesis of tetrasubstituted exocyclic *Z*-alkenes. To synthesize *E*-alkenes **1b–d** using strategy A, as shown in Scheme 1, quantities of substituted 2-propynylphenols **6a–c** would be needed. To gain access to alkynes **6a–c**, the phenols had to be protected to enable the Sonogashira coupling.[3,4] To avoid the protection and deprotection steps, we envisioned that the tetrasubstituted exocyclic *E*-alkenes could also be prepared from strategy B by carbometallation of alkynes **8a–d** followed by terminating the vinylpalladium species with methylboronic acid **7**. Alkynes **8a–d** could be prepared from benzyl alcohols **9a–b** and phenols **10a–c** through either a one-step Mitsunobu reaction[5] or a two-step alkylation procedure.

The palladium-catalyzed cross-coupling reaction of aryl halides with organoboron compounds has emerged as a powerful method for carbon–carbon bond formation.[6,7] While many types of organoboron compounds[8] are suitable donors, boronic acids are especially popular due to their ease of synthesis. Aryl- and alkenylboronic acids typically afford good yields of cross-coupled products with a wide range of electrophiles. In contrast, the coupling of *n*-alkylboronic acids is much more challenging[9] and thallium or silver bases are often needed.[10] Furthermore, to the best of our knowledge, the use of *n*-alkylboronic acids in the palladium-catalyzed cascade reactions has not been reported. Herein, we reported a stereoselective method for the synthesis of dibenzoxapine containing tetrasubstituted exocyclic alkenes through a palladium-catalyzed

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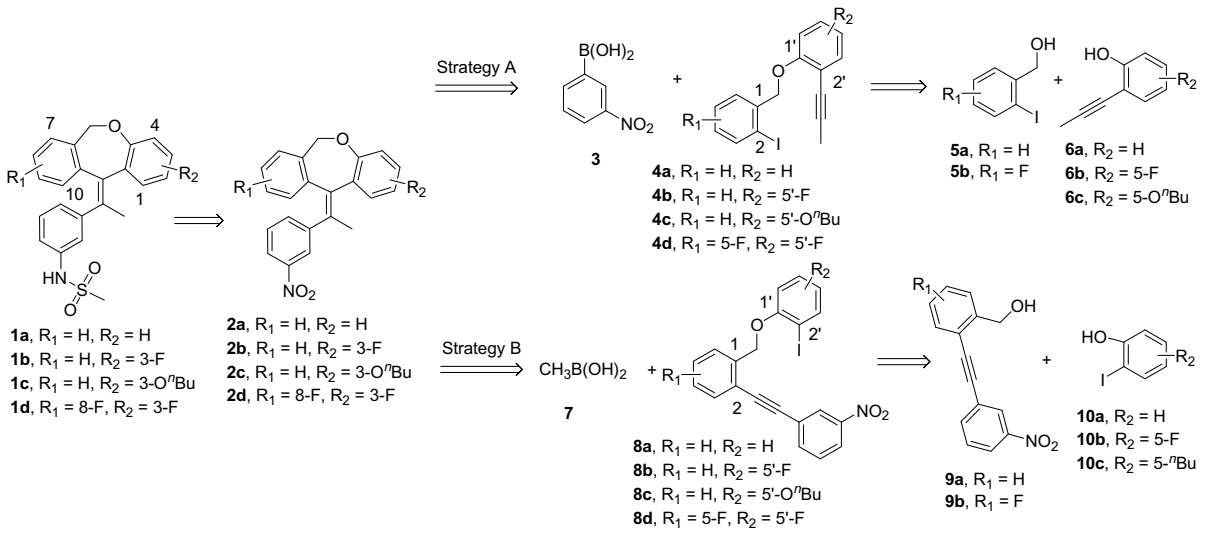
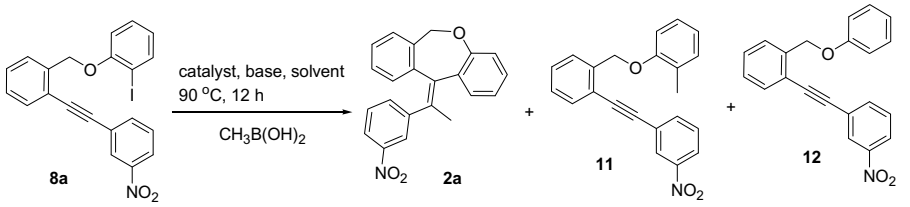


Scheme 1. Synthetic strategies to **1a**–**d**.

Table 1
Optimization studies[a]



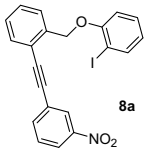
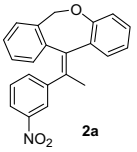
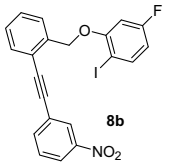
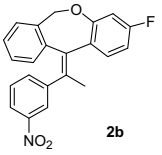
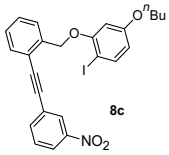
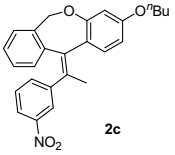
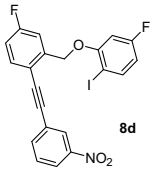
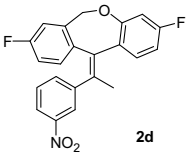
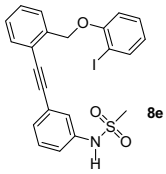
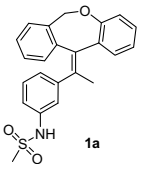
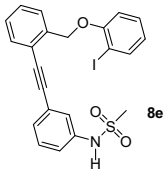
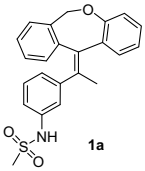
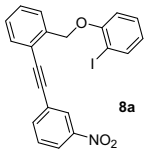
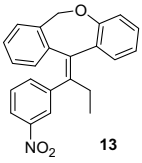
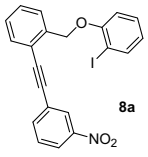
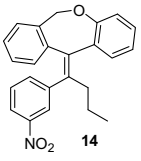
Entry	Catalyst	Base	Solvent	Yield (%) of **8a**[b]	Yield (%) of **11**[b]	Yield (%) of **12**[b]	Yield (%) of **2a**[b,c]
1	$PdCl_2(dppf)\cdot CH_2Cl_2$	K_2CO_3	THF	14	33	1	52
2	$PdCl_2(dppf)\cdot CH_2Cl_2$	K_2CO_3	THF/water[d]	3	71	0	21
3	$PdCl_2(dppf)\cdot CH_2Cl_2$	K_2CO_3	Dioxane	45	6	0	47
4	$PdCl_2(dppf)\cdot CH_2Cl_2$	K_2CO_3	Dioxane/water[d]	13	10	1	65
5	$PdCl_2(dppf)\cdot CH_2Cl_2$	KF	Dioxane	49	3	0	43
6	$PdCl_2(dppf)\cdot CH_2Cl_2$	CsF	Dioxane	5	8	13	67
7	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	DMF	71	3	4	17
8	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	Toluene	0	65	0	25
9	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	THF	0	5	9	83
10	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	Dioxane	0	5	13	75
11	$PdCl_2(dppf)\cdot CH_2Cl_2$	Cs_2CO_3	Dioxane/water[b]	0	2	0	93 (76)
12	$Pd_2(dba)_3$/dppf	Cs_2CO_3	DME	35	4	0	55
13	$Pd(PPh_3)_4$	Cs_2CO_3	DME	9	3	1	78 (58)

[a] All reactions were run using 3 mol % catalyst, 1.5 equiv of methylboronic acid **7**, 3 equiv of base for 12 h with total concentration at 0.1 M.
[b] Reversed-phase HPLC area percents.
[c] Isolated yields are reported in parentheses.
[d] 4:1 v/v.

carbometallation-cross-coupling reaction with the use of methylboronic acid as the terminating trapping species.

As shown in Table 1, alkyne **8a** was initially chosen to test the feasibility of this sequence. Therefore, exploration of tetrasubstituted dibenzoxapine formation was probed by heating 1.5 equiv of methylboronic acid, 3 mol % of palladium catalyst and 3.0 equiv of base in 0.1 M solvent at 90 °C for 12 h. $PdCl_2(dppf)\cdot CH_2Cl_2$ was used as the catalyst in most of our screenings, since it has been described as an effective catalyst in promoting coupling reactions involving alkylboronic acids.[9a] When K_2CO_3 was used as the base, incomplete reactions were observed under a variety of solvents (entries 1–4). In addition, significant amounts of direct coupling byproduct **11** was also detected under these conditions. Using Cs_2CO_3 as the base provided better reactivity in general. In solvents such as toluene, THF, dioxane and dioxane/water, reactions proceeded to completion at 90 °C within several hours (entries 8–11). In particular, when dioxane/water was used, both direct coupling byproduct **11** and des-iodo byproduct **12** were well controlled (entry 11). Therefore, under this optimized condition, 3 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$, 1.5 equiv of

Table 2
Synthesis of dibenzoxapine derivatives

Entry	ArI	Product	Yield[c] (%)
1	 8a	 2a	76[a]
2	 8b	 2b	71[a]
3	 8c	 2c	69[a]
4	 8d	 2d	65[a]
5	 8e	 1a	38[a]
6	 8e	 1a	58[b]
7	 8a	 13	11[a]
8	 8a	 14	0[a]

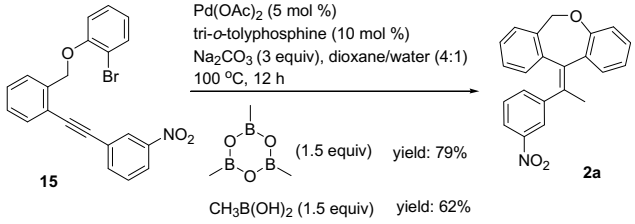
[a] Condition A: $PdCl_2(dppf)\cdot CH_2Cl_2$ (3 mol %), boronic acid (1.5 equiv), Cs_2CO_3 (3 equiv), dioxane/water (4:1), 90 °C, 12 h.
[b] Condition B: $PdCl_2(dppf)\cdot CH_2Cl_2$ (3 mol %), methylboronic acid **7** (1.5 equiv), K_2CO_3 (3 equiv), dioxane, 90 °C, 12 h.
[c] Isolated yield.

methylboronic acid and 3.0 equiv of Cs_2CO_3, the desired product **2a** was isolated in 76% yield.

We next applied the optimized conditions to the formation of tetrasubstituted dibenzoxapine derivatives, using methylboronic acid **7** as the terminating species. As illustrated in Table 2, several different functional groups could be incorporated into the aromatic rings to afford the tetrasubstituted exocyclic *E*-alkenes **2a–d** as a single stereoisomer[11] using optimized condition A (entries 1–4).[12] **2a–d** were further converted to the desired nuclear hormone modulators **1a–d** via a nitro group reduction followed by a sulfonation procedure.[2]

Surprisingly, when the same condition was applied to the cyclization of alkyne **8e**, in which a methylsulfonamide group was present, significant amounts of wrong stereoisomer was observed[13] and a poor yield was obtained as a result (entry 5). To overcome the issue, an alternative condition B was developed for substrate **8e**. Thus, when K_2CO_3 was used as the base and dioxane as the solvent, the formation of the wrong isomer was reduced to less than 4% (entry 6). It is worth noting that when condition B was applied to the cyclization of **8a**, significant amounts of starting material remained (Table 1, entry 3). Unfortunately, when ethylboronic acid was used as the terminating species, very low yield of desired product **13** was isolated (Table 2, entry 7). No product was isolated when *n*-propylboronic acid was used (Table 2, entry 8).[14]

The methodology was not limited to aryl iodide substrates. We had also obtained excellent results using aryl bromide **15** as the starting substrate (Eq. 1). An improved yield was observed when trimethylboroxine instead of methylboronic acid was used as the terminating species for aryl bromide **15**.[15]



(1)

In summary, we have developed a palladium-catalyzed cascade reaction for the synthesis of a series of nuclear hormone modulators using methylboronic acid as the terminating species. The synthesis provided a straightforward approach to the dibenzoxapine containing tetrasubstituted exocyclic *E*-alkenes.

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11. The undesired diastereomers were not detectable by NMR in crude reaction mixtures.
12. General procedure for the preparation of **2a**–**d**: To a round bottom flask was added alkyne **8a** (500 mg, 1.10 mmol), methylboronic acid **7** (99 mg, 1.65 mmol), Cs_2CO_3 (1.08 g, 3.30 mmol), 8.8 mL of dioxane and 2.2 mL of water. The flask was purged with N_2 and $PdCl_2(dppf)\cdot CH_2Cl_2$ (27 mg, 0.033 mmol) was added. The reaction mixture was stirred at 90 °C under N_2 for 12 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc (10 mL) and water (10 mL). EtOAc layer was washed with brine (10 mL) and dried with $MgSO_4$. The residue after evaporation was subjected to silica gel chromatography (9:1 hexane/CH_2Cl_2) to give dibenzoxapine **2a** (287 mg, 0.84 mmol, 76% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.96 (m, 2H), 7.37–7.29 (m, 4H), 7.23–7.18 (m, 2H), 6.89 (m, 3H), 6.67 (d, $J = 7.5$ Hz, 1H), 5.89 (d, $J = 12.5$ Hz, 1H), 4.99 (d, $J = 12.5$ Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 147.8, 145.0, 143.2, 137.3, 134.4, 133.2, 132.8, 131.1, 129.6, 128.8, 128.6, 128.2, 127.9, 127.6, 124.9, 123.2, 121.4, 120.2, 119.7, 70.1, 22.0; IR (KBr) ν 3069, 3032, 2935, 1607, 1532 cm^{-1}; MS (EI) m/z (rel intensity) 344 (M^+, 100); HRMS (ES) m/z (M+1) calcd for $C_{22}H_{17}NO_3$, 344.1287; found, 344.1294.
13. The *E*/*Z* isomerization could occur at either the vinylpalladium or the product stage. When dibenzoxapine **1a** was stirred under the reaction conditions overnight, no isomerization was observed. Therefore, we suspected that isomerization occurred at the vinylpalladium stage under condition A.
14. Examination of alternative ethylboronic acid and *n*-propylboronic acid mediated reaction conditions also revealed poor results.
15. For substrate **15**, replacing methylboronic acid with trimethylboroxine reduced the amount of direct coupling byproduct **11**. For aryl iodide substrates **8a**–**e**, <2% of direct coupling products were formed under our optimized conditions and very similar results were obtained when trimethylboroxine was used to replace methylboronic acid.