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Stereoselective Synthesis of Novel Highly Substituted Isochromanone and Isoquinolinone-Containing Exocyclic Tetrasubstituted Alkenes

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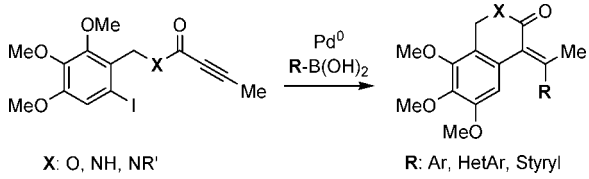


An efficient synthetic route toward the synthesis of highly substituted arylethylidene−isoquinolinones/isochromanones is reported. The tandem carbopalladation/Suzuki−Miyaura coupling sequence stereoselectively provided various functionalized polycyclic compounds in moderate to excellent yields.

The trimethoxyphenyl unit has been established as an essential structural feature found in a variety of molecules that bind at the cochicine site of tubulin and consequently display antitumor properties.[1] Combretastatin A4 (CA4), a natural *cis*-stilbene (3,4,5-trimethoxy-3′-hydroxy-4′-methoxystilbene) discovered by Pettit et al., is one of the most potent tubulin polymerization inhibitors.[2]

In an ongoing project to identify novel tubulin polymerization inhibitors,[3] we have reported the synthesis of 3′-(3,4,5-trimethoxyphenylalkylidene)oxindoles (see Figure 1, oxindole **1**) which may be considered as constrained CA4 analogues.[4] In this study, our attention was focused on the synthesis of six-membered heterocyclic frameworks bearing three methoxy and a substituted ethylidene group:[5] isoquinolinones **A** and isochromanones **B**.

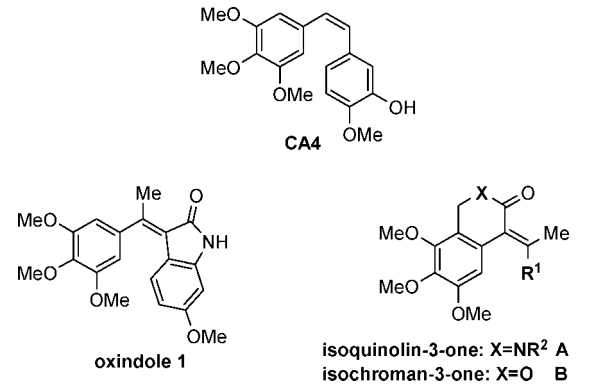
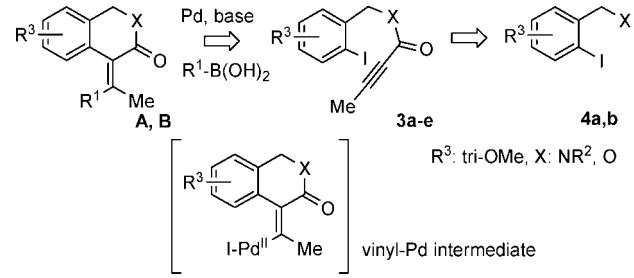


FIGURE 1. CA4, oxindole **1**, and the designed heterocyclic derivatives.

4-Arylideneisochromanones are usually prepared by Knoevenagel condensation of isochromanone with aldehydes.[6] However, in most cases this methodology provides a mixture of (*E*)- and (*Z*)-isomers, in modest yields. Although a few syntheses of arylidenisoquinolinones have been reported, they require troublesome processes.[7] Furthermore, such heterocyclic derivatives bearing a tetrasubstituted *exo* double bond were scarcely reported.

SCHEME 1. Retrosynthetic Approach and Postulated Vinyl-Palladium Intermediate



Palladium-catalyzed reactions have proved to be a powerful method for the preparation of a wide variety of heterocyclic compounds in a one-step procedure.[8] Particular attention has been paid to the Heck−Suzuki−Miyaura tandem reaction, which was used for the construction of various fused carbocycles[9−11] or heterocyclic cores (indoline,[12] isoindolinone,[13] indolinone,[4,14] and dibenzoxapine[15]) bearing an exocyclic tri- or tetrasubstituted double bond. This sequence involved alkyne-tethered aryl

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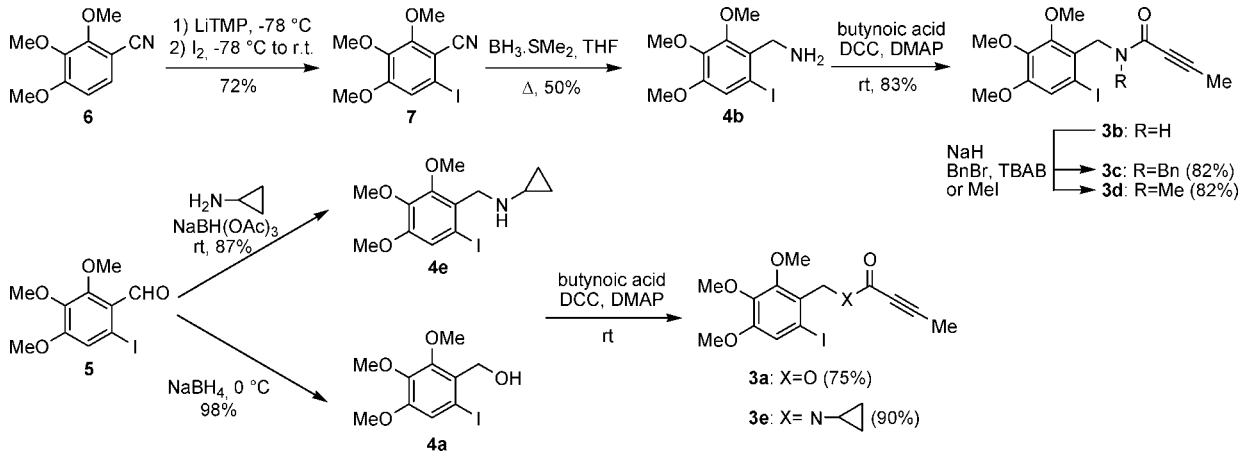
SCHEME 2. Synthesis of Acetylenic Precursors 3a−e



halides and boronic acids. The key step of the domino reaction is the intramolecular *syn*-carbometalation of the triple bond by an arylpalladium halide complex, followed by cross-coupling of the (*E*)-vinyl-palladium intermediate with a boronic species to provide the polycyclic product in a stereocontrolled fashion.[13]

Herein, we wish to report the first synthesis of isoquinolinone **A** and isochromanone **B** via this carbopalladation/cross-coupling sequence. The convergent approach involved preparation of cyclization precursors **3a−e**, which could derive from benzyl alcohol **4a** and benzylamine derivatives **4b** (Scheme 1).

Initially, we planned to synthesize the alkyne precursors **3a−e** from the common 2,3,4-trimethoxy-6-iodobenzaldehyde **5**[16] (Scheme 2). Reduction of **5** by sodium borohydride afforded the benzyl alcohol **4a**, which was subsequently esterified with butynoic acid by a carbodiimide-mediated reaction, to give the acetylenic precursor **3a** in 73% overall yield. Reductive amination of aldehyde **5** with ammonium acetate, in the presence of sodium cyanoborohydride, failed to give the benzylamine **4b**. Thus, the sequence was reconsidered, by using a two-step procedure starting from trimethoxybenzonitrile **6**. Regioselective iodination of nitrile **6** was achieved by a directed ortho-metalation process.[17] Treatment with lithium tetramethylpiperidine (LiTMP), followed by quenching with iodine, gave 2,3,4-trimethoxy-6-iodobenzonitrile **7** in 72% yield. Treatment of iodonitrile **7** with AlH_3[18] failed to provide the amine **4b** (deiodination and reduction occurred concomitantly). To circumvent this problem, borane dimethylsulfide in refluxing THF[19] was used to give the desired amine **4b**, although in moderate yield.

Amine **4b** was next coupled with butynoic acid (DCC, DMAP) to provide the secondary amide **3b** in 83% yield as a mixture of rotamers. To potentially get a higher proportion of the *cis* conformer, required for the following carbopalladation step,[20] *N*-alkylation of the amide nitrogen with different-sized substituents was investigated. Treatment of **3b** with benzyl bromide or methyl iodide, using NaH as a base, gave the amido derivatives **3c** and **3d** both in 82% yield. Introduction of a cyclopropyl group[21] was unsuccessful by direct alkylation of **3b** with cyclopropylbromide. Instead, reductive amination of iodoaldehyde **5** with cyclopropylamine and sodium triacetoxyborohydride[22] gave the secondary amine **4e** (87% yield), which was directly coupled with butynoic acid following standard conditions to provide amide **3e** in 90% yield.

With alkyne precursors in hand, we then turned our attention to the preparation of trimethoxyisoquinolinones and examined the ability of acetylenic derivatives **3b−e** to be efficient substrates of the projected tandem carbopalladation/coupling sequence, using 4-methoxyphenylboronic acid **8a** as a trapping agent (Table 1). With secondary amide **3b**, the reaction occurred in the presence of CsF (3.3 equiv), $Pd(OAc)_2$ (5 mol %), and PPh_3 (10 mol %) in refluxing THF[4] within 6 h and regio- and stereoselectively provided the (*E*)-cyclized isoquinolinone **9** but in only 29% yield (entry 1). Two other catalyst systems were tested but they both failed to improve the reaction rate or yield (Pd_2dba_3/PPh_3 or PEPPSI-*i*Pr:[23] 12.5% and 26% yields, respectively). We thought that this low efficiency could be ascribed to the high conformational freedom of the starting secondary amide **3b**. As expected, efficiency of the reaction was dramatically enhanced by the use of tertiary amides (compare entries 1 to 2−4). The *N*-cyclopropylamide **3e** led to isoquinolin-3-one **10** in 84% yield within 10 h, whereas with the benzyl amide **3c**, the reaction was accelerated (1 h, 84% yield, entry 3). Finally, *N*-methylbutynamide **3d** gave the best result (3.5 h, 92%, entry 4) and was next chosen to scope the reaction with various boronic acids.

Electron rich 4-*N*-dimethylphenylboronic acid **8b** proved to be more reactive than the electron poor 4-trifluoromethylphenylboronic acid **8c** (62 vs 48%, entry 5 vs 6). The 3-OTBDMS-4-methoxyphenylboronic acid[24] **8d** was also effective in this series, providing the desilylated compound **15**,[25] albeit in a moderate yield (30%, entry 7). 2-Benzofuranboronic acid also

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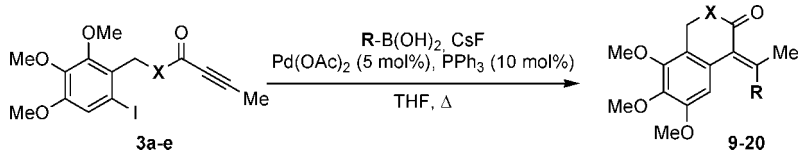
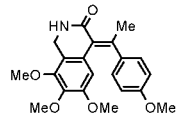
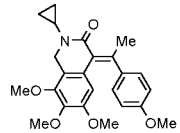
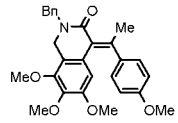
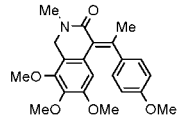
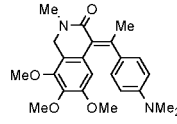
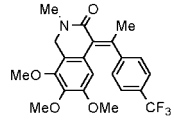
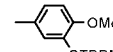
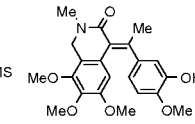
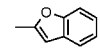
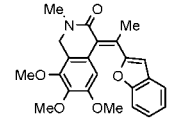
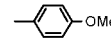
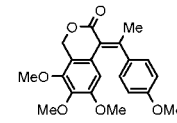
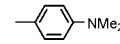
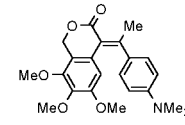
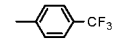
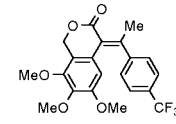
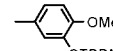
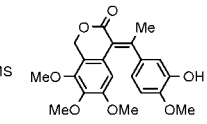
TABLE 1. Tandem Reactions[a]



Entry	X	Time	Yield[b]	R	Product
1	**NH** **3b**	6h	29%	 **8a**	 **9**
2	 **3e**	10h	84%	 **8a**	 **10**
3	**NBn** **3b**	1h	84%	 **8a**	 **11**
4	**NMe** **3d**	3.5h	92%	 **8a**	 **12**
5	**NMe** **3d**	4h	65%	 **8b**	 **13**
6	**NMe** **3d**	2h	48%	 **8c**	 **14**
7	**NMe** **3d**	10h	30%	 **8d**	 **15**
8	**NMe** **3d**	2h	73%	 **8e**	 **16**
9	**O** **3a**	4h	76%	 **8a**	 **17**
10	**O** **3a**	5h	70%	 **8b**	 **18**
11	**O** **3a**	17h	34%	 **8c**	 **19**
12	**O** **3a**	2h	50%	 **8d**	 **20**

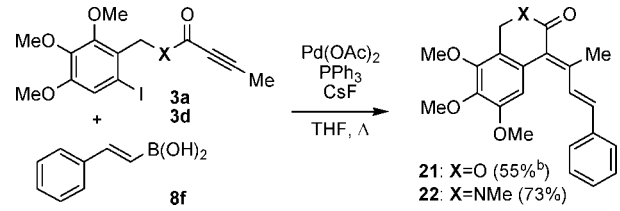
[a] All reactions were carried out with boronic acid (1.1 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and CsF (3.3 equiv), THF reflux (0.03 M) until complete conversion. [b] Isolated yield.

participated well in this reaction to give the corresponding isoquinolinone **16** (73%, entry 8).

Afterward, we explored the tandem reaction with ester **3a** (entries 9−12). The cyclization/alkylation reaction with boronic acid **8a** occurred smoothly, exclusively providing the (*E*)-isochromanone **17** in good yield[26] (entry 9). Similar efficiency was obtained with arylboronic acid **8b** (70%, entry 10), whereas coupling with boronic acid **8c** bearing the 4-trifluoromethyl group needed a longer reaction time and furnished compound **19** with a lower yield (entry 17, 34%). Reaction with **8d** gave the phenol derivative **20** in moderate yield (entry 12, 50%).

Finally, a tandem reaction was attempted with a vinyl boronic acid (Scheme 3). We were pleased to observe that the tandem reaction between ester **3a** and *trans*-styrylboronic acid **8f** stereoselectively provided (*E*,*E*)-isochromanone **21** in 55% yield within only 20 min. It is noteworthy that direct Suzuki coupling occurred concomitantly in 29% yield, probably due to the high reactivity of the boronic acid. Butynamide **3d** reacted more slowly (4 h for complete conversion) but exclusively gave the (*E*,*E*)-dienic derivative **22** in 73% yield. NOESY experiments supported the *E* configuration of the newly formed double bond of both compounds (Figure 2 and Supporting Information).

SCHEME 3. Synthesis of Conjugate Dienic Derivatives[a]



[a] Reagent and conditions: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), CsF (3.3 equiv), THF refux (0.03 M), 0.3 h for **21**, 4 h for **22**. [b] Direct Suzuki coupling byproduct was also recovered in 29% yield.

For isoquinolinone **9** and isochromanone **17**, a cross peak between H-5 of the heterocyclic moieties and H-2′/H-6′ of the 4-methoxyphenyl, unambiguously confirmed the *E* configuration of the tetrasubstituted double bond (Figure 2 and Supporting Information). Furthermore, chemical shift of the olefinic methyl group (2.55 and 2.56 ppm for **9** and **17**) could be used as a

(26) For precursor **3a**, ester function favors a *Z* configuration, providing the triple bond next to the PdI in the carbopalladation step.

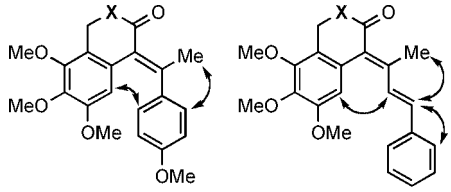


FIGURE 2. NOESY correlations of cyclized compounds.

diagnostic signal[27] for assignment of stereochemistry of all other compounds (δ methyl group: 2.50−2.57 ppm).

The structure of compounds **9**−**22** confirmed the postulated mechanism of the tandem reaction: intramolecular *syn*-carbopalladation in a 6-*exo*-*dig* process followed by cross coupling with retention of configuration of the (*E*)-Pd-vinyl intermediate.

In conclusion, the tandem Heck−Suzuki−Miyaura reaction has proved to be a diversity-oriented strategy for rapid construction of various highly functionalized new arylalkylidene-isoquinolinones and isochromanones of biological interest. In all cases, the reaction proceeded regio- and stereoselectively to provide the cyclized products as a single isomer in moderate to high yields. Consequently, this domino approach could be extended to the synthesis of new substituted benzo-fused heterocyclic compounds.

Experimental Section

Representative Procedure: Example of (*E*)-1,2-Dihydro-6,7,8-trimethoxy-4-[1-(4-methoxyphenyl)ethylidene]-2-methylisoquinolin-3(4*H*)-one (12). A flask, flame-dried under high vacuum, was charged with amide **3d** (106 mg, 0.263 mmol), 4-methoxyphenylboronic acid **8a** (44 mg, 0.289 mmol), and CsF (132 mg, 0.867 mmol, flame-dried under high vacuum prior to use) and purged 3 times with argon. Anhydrous THF was added (0.03 M) and the resulting mixture was degassed (argon bubbling, 15 min) before $Pd(OAc)_2$ (2.9 mg, 0.013 mmol) and PPh_3 (6.9 mg, 0.026 mmol) were added. After refluxing under argon for 3.5 h, the reaction was cooled to rt, quenched with water, and extracted twice with diethyl ether. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 6/4) and recrystallization (dichloromethane/hexane) to give **12** as a yellow solid (92 mg, 92%): mp 115−116 °C; IR ($CHCl_3$, cm^{-1}) ν 3005, 2938, 2838, 1719, 1639, 1609, 1509, 1463, 1245, 1107; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, $J = 8.7$ Hz, 2H), 6.76 (d, $J = 8.7$ Hz, 2H), 5.87 (s, 1H), 4.38 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H) 3.76 (s, 3H), 3.22 (s, 3H), 3.15(s, 3H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 158.6, 151.6, 148.1, 144.6, 139.9, 136.2, 130.3, 129.5 (2C), 126.7, 119.3, 113.7 (2C), 108.7, 61.2, 60.9, 55.4, 55.2, 46.5, 30.9, 23.2; MS (ES^+) *m*/*z* 406.2 $[M + Na]^+$; HRMS (ES^+) *m*/*z* calcd for $C_{22}H_{25}NO_5Na$ $[M + H]^+$ 406.1630, found 406.1636.

(27) This diagnostic signal would appear at a lower field for *Z* isomers due to the anisotropic effect of the carbonyl group.

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Supporting Information Available: Synthetic procedures, characterization data, and copies of the ^1H NMR, ^{13}C NMR, and NOESY experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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