Tetrahedron 69 (2013) 4395–4402

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Domino C–H functionalization reactions of *gem*-dibromoolefins: synthesis of *N*-fused benzo[*c*]carbazoles

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ARTICLE INFO

Article history:
Received 23 October 2012
Received in revised form 20 December 2012
Accepted 2 January 2013
Available online 8 January 2013

Keywords:
Domino reactions
C–H functionalization
Palladium
Dibromoolefins
Benzo[*c*]carbazoles

ABSTRACT

A palladium-catalyzed domino transformation of *gem*-dibromoolefins leading to novel polycyclic benzo[*c*]carbazoles is described. A unique feature of the current reaction is the participation of both bromides in C–H functionalization processes. Mechanistic studies were conducted to ascertain the sequence of reaction events, and the results indicate that the (*Z*)-bromide likely reacts in preference to the (*E*)-bromide.

1. Introduction

Development of efficient strategies for the formation of C–C bonds continues to be of prime importance in organic chemistry. Processes wherein a simple C–H bond is directly functionalized have become highly desirable, since they provide higher atom and step economy by obviating the need for pre-activated starting materials necessary in traditional cross-coupling reactions.[1] In the last two decades, direct arylation via C–H bond functionalization has received considerable attention, and remarkable progress has been achieved in the field.

It has long been our goal to develop new methods for heterocycle synthesis, particularly through palladium catalysis. To this end, C–H functionalization represents an efficient and attractive approach. In particular, the combination of C–H functionalization with another C–C bond formation step in a domino fashion would be even more attractive, since domino reactions increase the efficiency and modularity of a synthesis, allowing for rapid generation of molecular diversity.[2] As part of our ongoing research in palladium-catalyzed domino reactions, we have reported extensively on the utility of *gem*-dihalovinyl systems for the preparation of heterocycles.[3] This system presents several attractive features:[4] (1) *gem*-dihaloolefins are more reactive towards oxidative addition than their mono-halogenated counterparts, facilitating cross-coupling chemistry; (2) oxidative addition into the (*E*)-halide is more facile due to steric effects, allowing for selective mono-functionalization and orthogonal functionalization of both halides;[5] and (3) *gem*-dihalovinyl compounds can be easily accessed in a single step from the corresponding aldehydes.[6]

Recently we disclosed an efficient and high-yielding approach towards naphthothiophenes from thiophene-based *gem*-dibromoolefins.[7] In the course of the study we found that benzo[*c*]carbazole **2** could be accessed from indole **1a** in moderate yield (Scheme 1). We speculated that this could pave the way to functionalized benzo[*c*]carbazoles, a scaffold of interest due to demonstrated anti-tumour[8a] and kinase inhibitory activities.[8b] Interestingly, however, when we attempted the reaction of **1a** with an electron-deficient boronic acid, the expected product **4** resulting from Suzuki coupling/C–H functionalization was not observed. Instead, the isolated material was unambiguously identified via X-ray crystallography to be the *N*-fused benzo[*c*]carbazole **3a**.[9] It was apparent that two-fold, domino C–H functionalization had occurred: one at the C-2 position of the indole nucleus, the other at the position *ortho* to the sulfonyl moiety of the tosyl group. Although examples of synthetically useful palladium-catalyzed double C–H functionalization reactions have been reported,[10] to the best of our knowledge this type of reactivity remains unprecedented for *gem*-dibromoolefins. This intriguing transformation also opened the door for developing a modular approach to *N*-fused benzo[*c*]carbazoles, which would be valuable since it could complement the few existing preparative methods towards these challenging targets.[11] In this manuscript, we describe the

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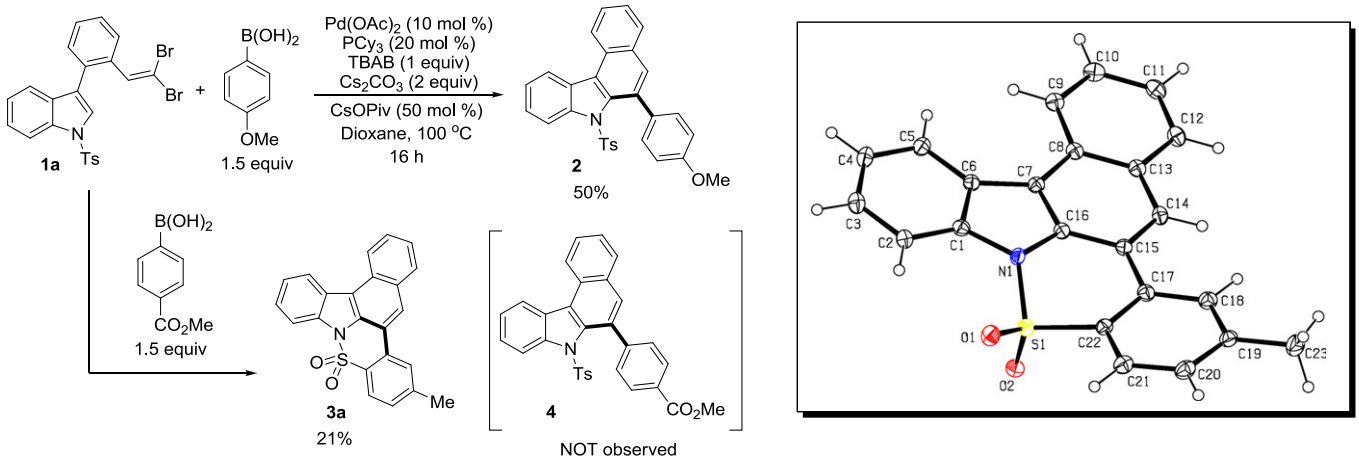
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.01.001



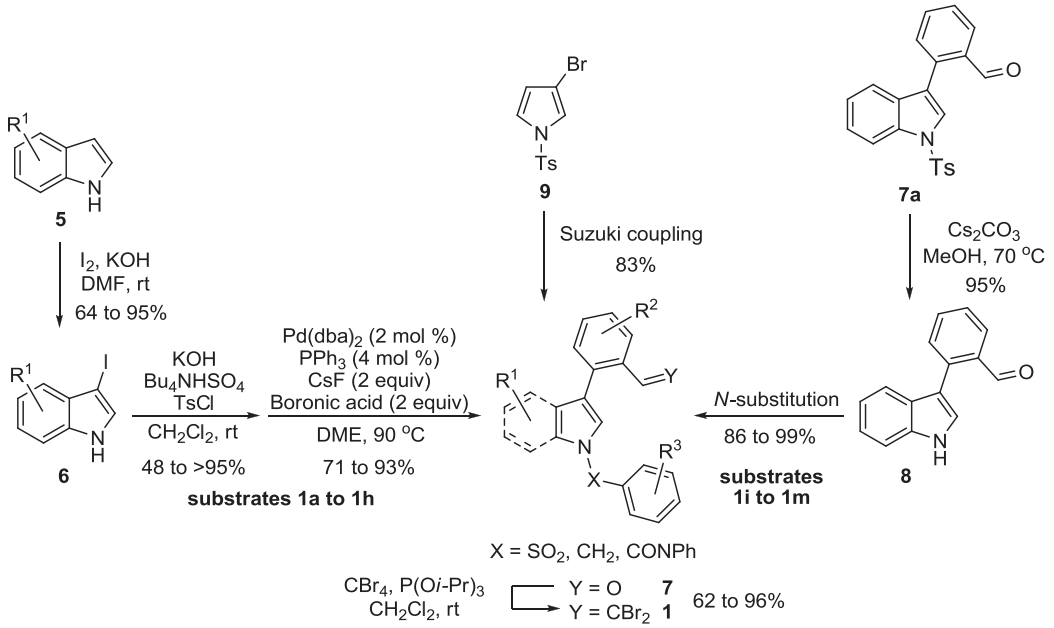
Scheme 1. Serendipitous discovery of a double C–H functionalization product.

development of this methodology, and discuss associated mechanistic insights.

2. Results and discussion

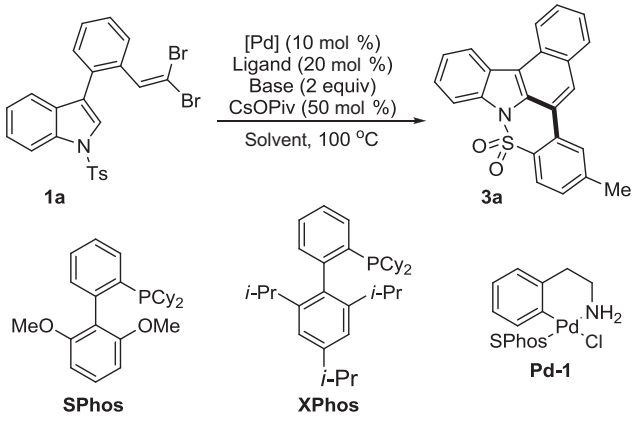
Over the course of this study, we compared several synthetic strategies towards *gem*-dibromoolefins of type **1**. The most modular and divergent sequences are shown in Scheme 2. Starting from commercially available indoles **5**, a sequence of iodination at the 3-position,[12] *N*-tosylation under pseudo-phase transfer conditions,[13] and Suzuki coupling with 2-formylphenyl boronic acid using Larock's conditions[14] afforded aldehydes **7** in fair to excellent yields. While this pathway afforded the most modularity, it proved to be quite laborious, and the yields for the Suzuki coupling were less satisfactory when non-sulfonyl based *N*-substituents were utilized. Thus an alternative strategy was developed. Refluxing aldehyde **7a** with methanolic Cs_2CO_3 cleanly afforded the detosylated product **8**,[15] which gave differentially *N*-substituted aldehydes **7** in a single step and in excellent yields. Finally, Suzuki coupling of known bromide **9**[16] afforded a pyrrole analogue in good yield. The aldehydes were then converted to *gem*-dibromoolefins **1** via our modified Ramirez olefination using $P(Oi\text{-}Pr)_3$,[6c] as we obtained higher yields compared to the more commonly employed PPh_3. Additionally, the oily nature of the phosphorus byproducts allowed for easier purification of the highly crystalline products.

With the desired *gem*-dibromoolefins in hand, we proceeded to examine their utility as precursors for synthesizing benzo[*c*]carbazoles **3**. We began our optimization studies using **1a** as the model substrate (Table 1). Omitting the boronic acid under conditions that led to the initial discovery conferred only marginal benefit (entry 1). We next screened several monodentate, highly electron-rich phosphines, as well as the bidentate ligand dppf (entries 2–5), as these had previously demonstrated superior reactivity in promoting the direct arylation of pyrroles.[5h] Unfortunately, none of them proved to be as effective as PCy_3. However an improvement was seen when the solvent was switched to toluene (entry 6), whilst other polar solvents proved inferior (entries 7–9). We then examined the effects of other palladium catalysts. Of the non-



Scheme 2. Synthesis of *gem*-dibromoolefin substrates **1**.

Table 1
Optimization of the domino C–H functionalization reaction



Entry	[Pd]	Ligand	Solvent	Base	Yield[a] (%)
1	$Pd(OAc)_2$	PCy_3	Dioxane	Cs_2CO_3	21
2	$Pd(OAc)_2$	SPhos	Dioxane	Cs_2CO_3	6
3	$Pd(OAc)_2$	XPhos	Dioxane	Cs_2CO_3	19
4	$Pd(OAc)_2$	t-$Bu_3P{\cdot}HBF_4$	Dioxane	Cs_2CO_3	12
5	$Pd(OAc)_2$	dppf	Dioxane	Cs_2CO_3	18
6	$Pd(OAc)_2$	PCy_3	Toluene	Cs_2CO_3	38
7	$Pd(OAc)_2$	PCy_3	MeCN	Cs_2CO_3	10
8	$Pd(OAc)_2$	PCy_3	DMF	Cs_2CO_3	Trace
9	$Pd(OAc)_2$	PCy_3	DME	Cs_2CO_3	15
10	$Pd(PPh_3)_4$	—	Toluene	Cs_2CO_3	41
11	$Pd_2(dba)_3$	PCy_3	Toluene	Cs_2CO_3	21
12	$PdCl_2$	PCy_3	Toluene	Cs_2CO_3	8
13	Pd–**1**	—	Toluene	Cs_2CO_3	48
14	Pd–**1**	—	Toluene	Na_2CO_3	8
15	*Pd–**1***	—	*Toluene*	*K_2CO_3*	*62 (54)*
16	Pd–**1**	—	Toluene	K_3PO_4	26
17	Pd–**1**	—	Toluene	KOAc	15
18[b]	Pd–**1**	—	Toluene	K_2CO_3	57
19[c]	Pd–**1**	—	Toluene	K_2CO_3	10% Conv.

[a] Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard; isolated yields in parentheses.
[b] CsOPiv of 1 equiv was used.
[c] CsOPiv omitted from the reaction.

palladacyclic catalysts screened, only $Pd(PPh_3)_4$ had comparable efficiency to $Pd(OAc)_2$ (entry 10), while other Pd(0) and Pd(II) sources gave much reduced yields (entries 11 and 12). Interestingly, the yield increased to 48% when the Buchwald type SPhos palladacycle Pd–**1** was used (entry 13), whereas the previous combination of $Pd(OAc)_2$/SPhos gave one of the worst results (entry 2). Having found the optimal solvent and catalyst, we turned our attention to the choice of base. For the carbonate bases, K_2CO_3 proved superior to Cs_2CO_3, and further increased the yield of the domino reaction to 62% (entry 15). Phosphate and acetate bases were less effective under the reaction conditions (entries 16 and 17). Increasing the loading of CsOPiv had little effect (entry 18), yet omitting it altogether completely shut down the desired reaction, as only 10% conversion was observed (entry 19). This result has certain mechanistic implications and will be discussed later. Attempts to further improve the yield by use of different additives, altering the reaction temperature or concentration did not yield any fruitful results.

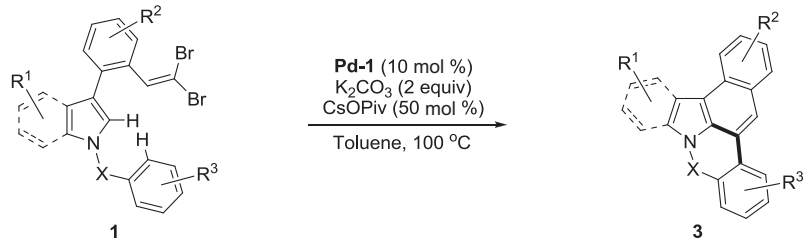
After establishing optimal reaction conditions, we set out to explore the generality of this domino reaction (Table 2). The reaction proved surprisingly sensitive to electronic effects on the indole core, as both electron-donating (**3d**) and electron-withdrawing (**3e**) substituents led to diminished yields, even if they were quite remote from the reactive sites. In the case of nitro substituted substrate **1f**, a complex mixture resulted with no identifiable products. Modification of the benzenoid fragment of the indole ring was unsuccessful, as the 7-azaindole analogue **1g** failed to yield any desired product. However, the fragment could be removed without incident, as product **3n** was obtained in fair yield. While substitution of the tosyl methyl group by fluorine led to a somewhat decreased yield (**3i**), we were delighted to see that a CF_3 group was well tolerated (**3j**). Further, a phenyl to thiophene substitution on the sulfonyl-containing arene also gave benzo[*c*] carbazole **3k** in moderate yield. Interestingly, benzo[*c*]carbazole **3c** bearing a methyl group in proximity to the sulfonyl moiety was formed in 10% lower yield compared to **3b** with a spatially distant methyl group, suggesting that the reaction may also be subject to steric effects. Non-sulfonyl based *N*-substituents ('linkers') were also compatible with this reaction (**3l** and **3m**). Notably, use of a diphenylcarbamoyl linker afforded product **3m** containing a seven-membered ring in 60% yield.

Finally, we sought to gain insight into this interesting transformation through studying the reaction mechanism. From our optimization studies we found that CsOPiv was essential for productive reaction, as in its absence only 10% conversion was achieved (Table 2, entry 19). This dependency on pivalate indicates that C–H bond cleavage may very well proceed via a concerted metallation–deprotonation (CMD) pathway, with pivalate assisting in deprotonation of the aryl ring.[17] However, the order of reaction events remained an open question. Theoretically, the first C–H functionalization could occur at either H^a or H^b; however, the highly strained nature of intermediate **12** makes initial reaction at H^b unlikely (Scheme 3). Yet a third reaction pathway was possible. Base-promoted elimination of **1a** would give bromoalkyne **13**, which could converge on intermediate **11**, the product arising from initial functionalization at H^a, via a 6-*endo-dig* cyclization process. To test this possibility, bromoalkyne **13** was subjected to the reaction conditions for the domino reaction. Although **13** was completely consumed, a complex mixture resulted, and no desired product was detected (Scheme 4). In addition, deuterated substrate **14** led to deuterated benzo[*c*]carbazole **15** with virtually no loss of deuterium, further reinforcing the conclusion that bromoalkyne **13** must not lie on the productive pathway.

Having eliminated bromoalkyne **13** as a potential intermediate, the question now became whether C–H functionalization occurred at H^a or H^b first (see Scheme 3). However, no reaction intermediates from the domino reaction have ever been observed or isolated, thus we turned to indirect methods for studying this question. Since functionalization of H^a and H^b correspond to reaction with the (*Z*) and (*E*)-bromide, respectively, one could probe this indirectly by synthesizing both isomers and evaluating their reactivity in the domino reaction. Thus, both vinyl bromides were prepared as outlined in Scheme 5. The (*Z*)-bromide **16** could be synthesized in 99:1 (*Z*)-selectivity by performing a bromo-Wittig reaction[18] on aldehyde **7a**, while (*E*)-bromide **18** was obtained as the exclusive isomer from the same aldehyde in three steps using Charette's protocol of benzyl bromide homologation and in situ elimination.[19]

With both bromides in hand, we proceeded to examine their reactivity (Scheme 6). When subjected to the reaction conditions, (*Z*)-bromide **16** led to benzo[*c*]carbazole **19** as the sole product in 80% yield. Under identical conditions, (*E*)-bromide **18** gave only a complex mixture of more than six products, none of which corresponded to **19** as judged by TLC and NMR. These results have two important implications. First, (*E*)-bromide **18** by itself does not isomerize under the reaction conditions, as product **19** arising from reaction of (*Z*)-bromide **16** was not detected. Second and more importantly, these results indicate that it is H^a, which first undergoes functionalization. This in turn implies that (*Z*)-bromide of **1a** must react in preference to the (*E*)-bromide, which goes against the natural reactivity of *gem*-dibromoolefins. While such inverse reactivity has been documented, it requires the presence of coordinating functional groups such as amines[3b] or alkynes[20] that are

Table 2
Substrate scope of the domino reaction



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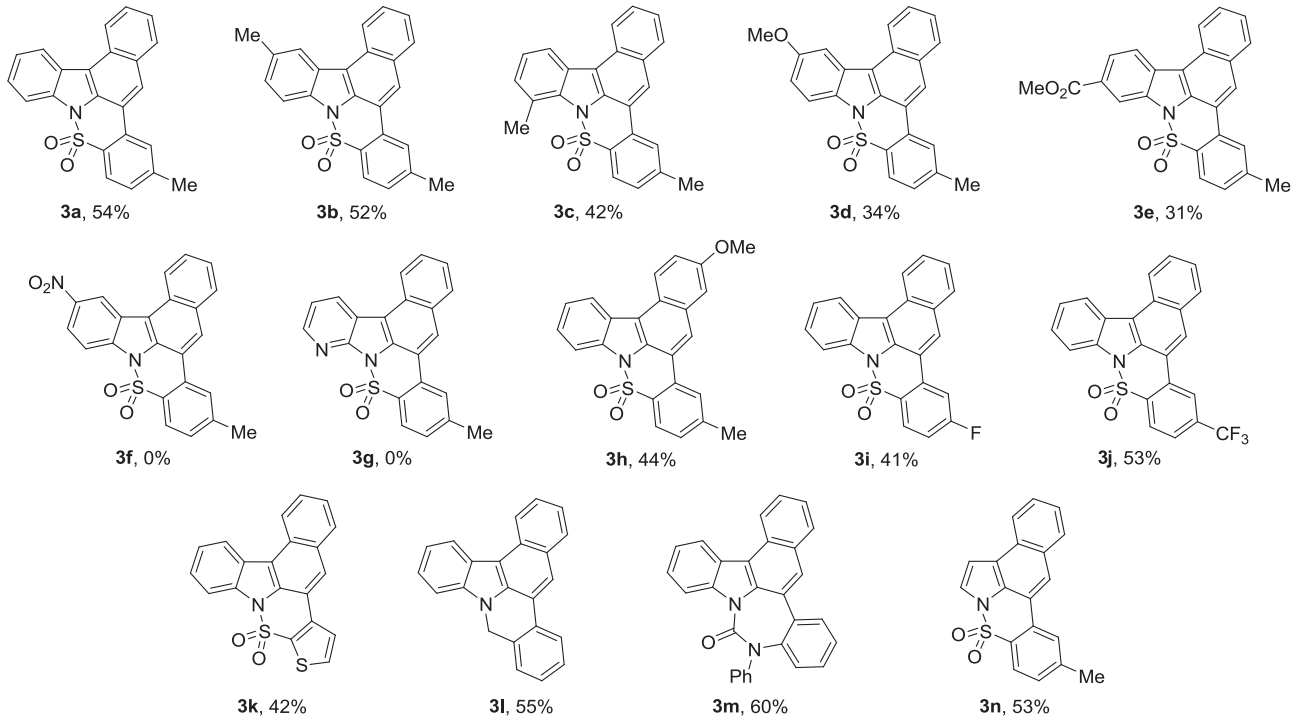
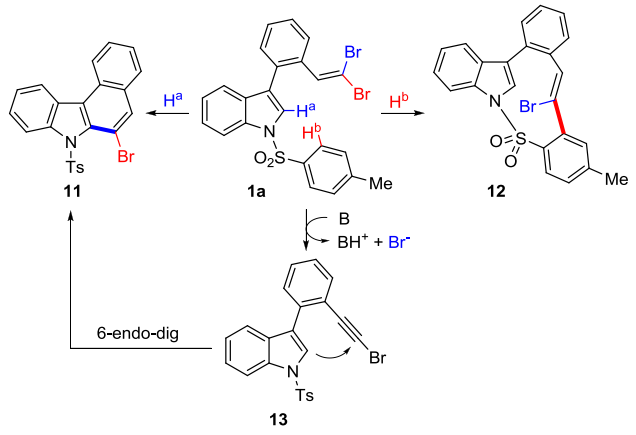
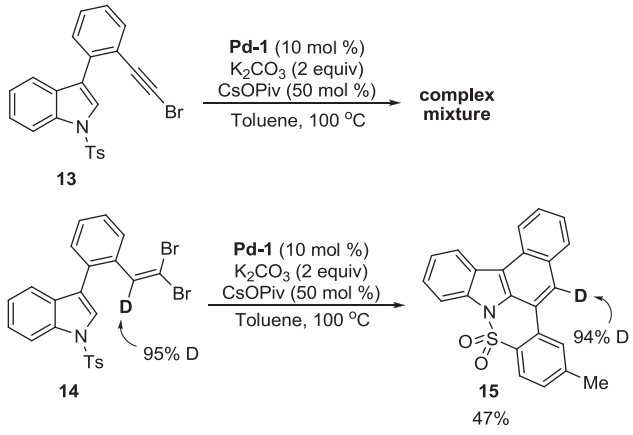




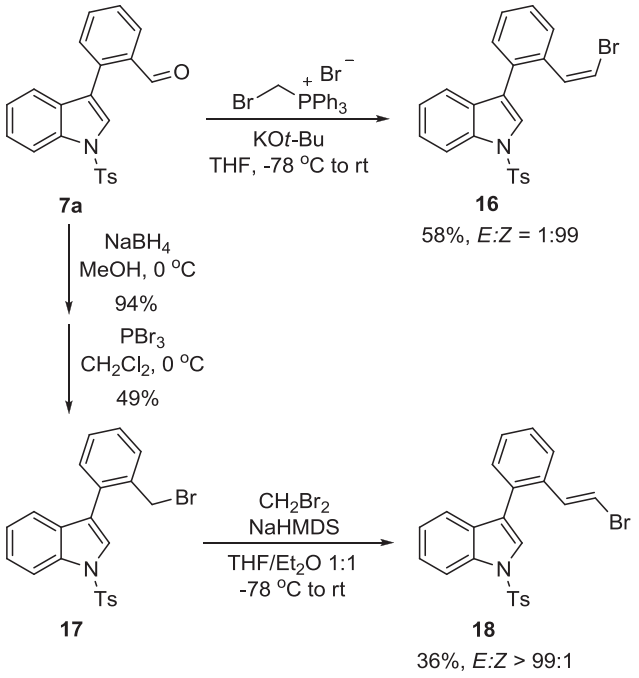
Scheme 3. Mechanistic hypotheses for the domino reaction.



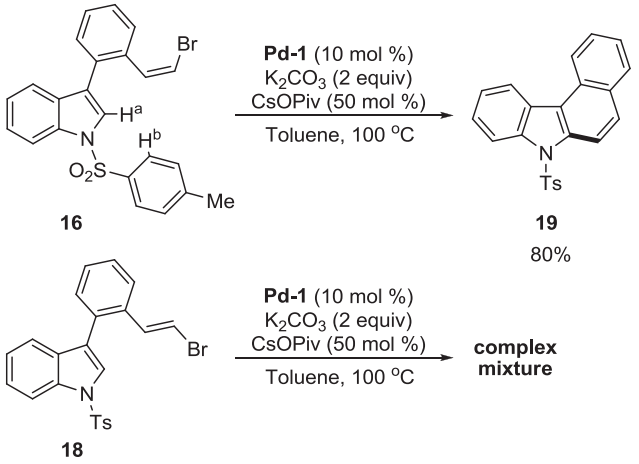
Scheme 4. Evidence against bromoalkyne intermediate **13**.

capable of directing palladium insertion into the (*Z*)-bromide, but such groups are absent in **1a**. Hartwig has demonstrated that oxidative addition can be reversible under certain circumstances,[21] and this remains a second avenue by which reaction at the (*Z*)-bromide may occur even if palladium was inserting into the (*E*)-bromide initially. However we have previously shown that SPhos does not promote reversible oxidative addition.[22] As the SPhos palladacycle is utilized in our domino reaction, oxidative addition is unlikely to be reversible.

If oxidative addition occurs at the (*E*)-bromide initially and is irreversible in our system, then we must consider the possibility of

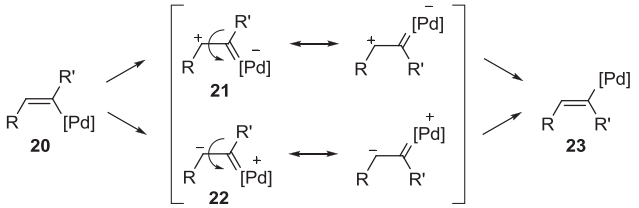


Scheme 5. Synthesis of (*E*) and (*Z*)-vinyl bromides.



Scheme 6. Reactivity of (*E*) and (*Z*)-vinyl bromides.

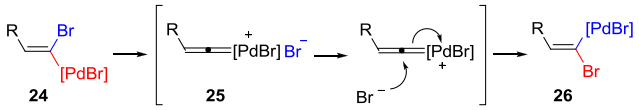
an isomerization process, one, which would give rise to the vinylpalladium intermediate resulting from (*Z*)-insertion and allow the reaction to proceed. Such *E*–*Z* isomerization events have been observed in alkyne carbopalladation reactions,[23] and structures of the type depicted in Scheme 7 are often proposed to rationalize the mixture of *syn* and *anti*-carbopalladation products obtained. The main thrust behind this proposal is that the metal acts either as an



Scheme 7. Proposed structures for isomerization of vinylpalladium species.

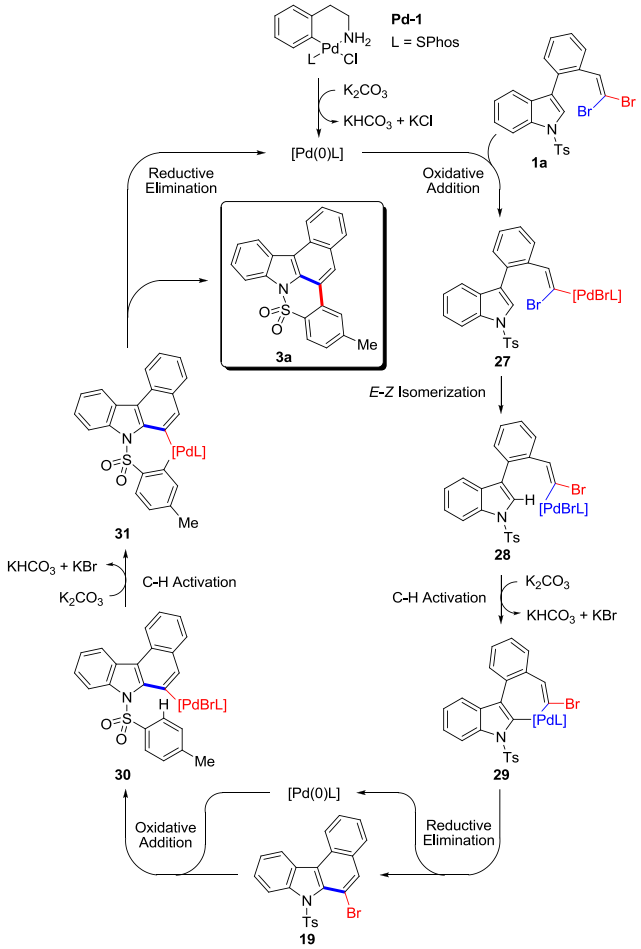
electron sink (**21**) or electron donor (**22**), and this weakens the C=C bond enough to allow free rotation and permit isomerization.

It is certainly conceivable that *gem*-dibromoolefins could isomerize via similar structures as shown in Scheme 7, but a further possibility exists for these systems (Scheme 8). The palladium vinylidene[24] **25** could arise via dissociation of the (*Z*)-bromide from complex **24**. The free bromide could then attack the carbene-like carbon from the more sterically open side opposite the R group to afford isomeric complex **26**. The fact that (*E*)-bromide **18** failed to undergo any productive reaction lends credence to this being a viable pathway, since a decent leaving group alpha to palladium is required. In the case of **18**, this necessitates that hydride acts as a leaving group, which would be very unfavourable.[25]



Scheme 8. Isomerization of vinylpalladium species via vinylidene formation.

While the actual isomerization process remains to be elucidated, there is sufficient information on hand that a plausible catalytic cycle can be proposed (Scheme 9). The cycle initiates with generation of an active Pd(0) species, which would first insert into the (*E*)-bromide of **1a** to give (*E*)-complex **27**. This would now undergo *E*–*Z* isomerization, possibly via a vinylidene intermediate, to give (*Z*)-complex **28**, which provides palladacycle **29** after the first C–H activation event. Reductive elimination then generates the benzo[*c*] carbazole intermediate **19**, which gives arylpalladium(II) species **30**



Scheme 9. Proposed catalytic cycle for the domino reaction.

following oxidative addition. A second C–H activation onto the tethered tosyl group, and subsequent reductive elimination then finally affords the domino C–H functionalization product **3a**.

3. Conclusions

In conclusion, we have developed a novel method for the preparation of functionalized *N*-fused benzo[*c*]carbazoles via a palladium-catalyzed domino C–H functionalization reaction of *gem*-dibromoolefins. The current approach allows these polycyclic heteroaromatics to be prepared from readily available starting materials and with a high degree of modularity. The results from our mechanistic studies indicate that the reaction does not proceed via alkyne carbopalladation. Rather, it likely follows a pathway in which preferential functionalization of the (*Z*)-bromide is achieved through isomerization of the initial (*E*)-vinylpalladium complex, possibly through a cationic vinylidene intermediate.

4. Experimental section

4.1. General methods

All reagents were purchased from commercial sources and used as received. Solvents were dried according to standard procedures prior to use. Analytical thin later chromatography (TLC) was performed on EMD Silica Gel 60 F_{254} plates (0.2 mm, 60 Å pore size). Flash chromatography was performed employing Silicycle Ultra-Pure 230–400 mesh silica gel. ^{1}H, ^{13}C and ^{19}F NMR were recorded at 25 °C on a Varian Mercury 400 MHz or Bruker Avance III 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) and referenced to solvent residual resonances relative to TMS. High-resolution mass spectra (HRMS) were obtained using an AB/Sciex QStar or AB/Sciex QStar/XL spectrometer operating in positive ESI mode. Infrared spectra were recorded using a Shimadzu FTIR 8400S spectrometer as a thin film on NaCl plates. All melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected.

4.2. General procedure for the palladium-catalyzed domino C–H functionalization reaction

An oven-dried Biotage microwave vial, capped with a septum, was cooled under Ar. To the vial were sequentially added the *gem*-dibromoolefin substrate, Pd–**1** (10 mol %), K_2CO_3 (2 equiv) and CsOPiv (50 mol %), all under an Ar atmosphere. The vial was purged with Ar for 5 min, and toluene was added via syringe. The vial was then sealed under Ar with a Teflon cap, put into an oil bath pre-heated to 100 °C, and stirred overnight. After cooling to room temperature, the crude mixture was filtered over a short plug of Celite, washing liberally with DCM. The solvent was removed in vacuo, and the residue purified by column chromatography.

*4.2.1. Benzo[c]carbazole **3a**.* Following the general procedure, a mixture of *gem*-dibromoolefin **1a** (106.3 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 9:1) afforded **3a** as a cream coloured solid (40 mg, 54% yield). R_f=0.38 (hexanes/EtOAc 4:1). Mp 210–211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J=8.4 Hz, 1H), 8.47 (d, J=7.7 Hz, 1H), 8.40–8.36 (m, 2H), 8.14 (d, J=8.1 Hz, 1H), 8.04–7.99 (m, 2H), 7.71 (t, J=7.6 Hz, 1H), 7.63–7.51 (m, 3H), 7.42 (d, J=8.1 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 137.4, 134.3, 132.3, 131.5, 131.1, 130.2, 129.9, 129.3, 128.4, 127.3, 126.8, 125.3, 125.2, 124.9, 124.2, 123.6, 122.7 (2C), 120.0, 117.4, 115.5, 22.1; IR (NaCl, neat): 3055, 2954, 2923, 2869, 1609, 1448, 1357, 1330, 1228, 1180, 1169, 1079, 947, 751, 748, 734 cm^{-1}; HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{23}H_{19}N_2O_2S$: 387.11672; found: 387.11698.

*4.2.2. Benzo[c]carbazole **3b**.* Following the general procedure, a mixture of *gem*-dibromoolefin **1b** (109.1 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 4:1) afforded **3b** as a light-brown solid (39.6 mg, 52% yield). R_f=0.27 (hexanes/EtOAc 4:1). Mp 228–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J=8.4 Hz, 1H), 8.37 (s, 1H), 8.24 (d, J=8.6 Hz, 2H), 8.14 (d, J=8.1 Hz, 1H), 8.04–8.02 (m, 2H), 7.72 (t, J=7.6 Hz, 1H), 7.54 (t, J=7.6 Hz, 1H), 7.43 (t, J=6.9 Hz, 2H), 2.63 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 135.5, 134.6, 132.3, 131.6, 131.1, 130.2, 129.8, 129.4, 128.3, 128.1, 127.6, 125.2 (2C), 124.2, 123.6, 122.9, 122.5, 120.0, 117.5, 115.1, 22.1, 22.0; IR (NaCl, neat): 3055, 2920, 1603, 1485, 1331, 1233, 1188, 1169, 1150, 1132, 1078, 912, 876, 808, 741, 685, 677, 640, 633 cm^{-1}; HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{24}H_{21}N_2O_2S$: 401.13237; found: 401.13314.

*4.2.3. Benzo[c]carbazole **3c**.* Following the general procedure, a mixture of *gem*-dibromoolefin **1c** (109.1 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 9:1) afforded **3c** as a beige solid (31.9 mg, 42% yield). R_f=0.31 (hexanes/EtOAc 4:1). Mp 257 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J=7.9 Hz, 1H), 8.48–8.46 (m, 2H), 8.20 (d, J=8.2 Hz, 1H), 8.12–8.10 (m, 2H), 7.76 (ddd, J=8.4, 6.9, 1.3 Hz, 1H), 7.60 (ddd, J=8.1, 6.9, 1.1 Hz, 1H), 7.52 (t, J=7.6 Hz, 1H), 7.48 (ddd, J=8.2, 1.5, 0.7 Hz, 1H), 7.44 (d, J=7.1 Hz, 1H), 3.05 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 137.6, 135.5, 132.8, 131.6, 131.2, 130.5, 130.1 (2C), 129.2, 128.4, 127.2, 125.5, 125.4, 125.1, 124.6, 123.7, 122.9, 120.6, 120.2, 118.1, 23.3, 22.1; IR (NaCl, neat): 2975, 2932, 1357, 1323, 1297, 1283, 1270, 1258, 1190, 1164, 1143, 1089, 913, 882, 792, 744, 732 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{18}NO_2S$: 384.10582; found: 384.10547.

*4.2.4. Benzo[c]carbazole **3d**.* Following the general procedure, a mixture of *gem*-dibromoolefin **1d** (112.3 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 4:1) afforded **3d** as a light orange solid (27 mg, 34% yield). R_f=0.37 (hexanes/EtOAc 7:3). Mp 263–265 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J=8.3 Hz, 1H), 8.52 (s, 1H), 8.29 (d, J=9.0 Hz, 1H), 8.19 (d, J=8.1 Hz, 1H), 8.14 (t, J=3.8 Hz, 2H), 8.00 (d, J=2.3 Hz, 1H), 7.79 (t, J=7.6 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.49 (d, J=8.1 Hz, 1H), 7.23 (dd, J=9.0, 2.4 Hz, 1H), 4.03 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 144.3, 135.4, 132.4, 131.9, 131.7, 131.2, 130.3, 130.0, 129.5, 128.6, 128.5, 125.4, 125.3, 124.3, 123.5, 122.9, 120.2, 117.9, 116.2, 114.5, 107.0, 56.24, 22.2; IR (NaCl, neat): 2938, 2833, 1581, 1482, 1429, 1326, 1256, 1167, 1076, 1034, 913, 878, 851, 747, 744 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{18}NO_3S$: 400.10047; found: 400.10154.

*4.2.5. Benzo[c]carbazole **3e**.* Following the general procedure, a mixture of *gem*-dibromoolefin **1e** (117.9 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 2:1) afforded **3e** as a light orange solid (26.5 mg, 31% yield). R_f=0.28 (hexanes/EtOAc 7:3). Mp 277–278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.73 (d, J=8.4 Hz, 1H), 8.59–8.57 (m, 2H), 8.30 (dd, J=8.4, 1.4 Hz, 1H), 8.21 (d, J=8.1 Hz, 1H),

8.16–8.15 (m, 2H), 7.82 (t, *J*=7.6 Hz, 1H), 7.65 (t, *J*=7.5 Hz, 1H), 7.52 (d, *J*=8.1 Hz, 1H), 4.04 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 144.6, 137.0, 136.2, 132.3, 131.4, 131.2, 130.9, 130.5, 130.2, 129.5, 129.0, 128.4, 126.2, 125.9, 125.3, 124.4, 124.2, 123.7, 122.4, 119.4, 117.6, 116.9, 52.6, 22.2; IR (NaCl, neat): 2952, 1714, 1432, 1334, 1300, 1292, 1273, 1250, 1168, 1096, 980, 913, 847, 748, 743, 668 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{25}H_{18}NO_4S$: 428.09565; found: 428.09666.

4.2.6. Benzo[c]carbazole ***3h***. Following the general procedure, a mixture of *gem*-dibromoolefin **1h** (112.3 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 7:3) afforded **3h** as a light orange solid (34.9 mg, 44% yield). R_f=0.31 (hexanes/EtOAc 7:3). Mp 240–242 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J*=9.0 Hz, 1H), 8.48 (d, *J*=7.3 Hz, 1H), 8.39 (dd, *J*=7.4, 1.2 Hz, 1H), 8.37 (s, 1H), 8.18 (d, *J*=8.1 Hz, 1H), 8.07 (s, 1H), 7.64–7.56 (m, 2H), 7.47 (d, *J*=8.1 Hz, 1H), 7.43–7.38 (m, 2H), 3.97 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 144.2, 137.5, 133.2, 132.5, 132.4, 131.7, 129.8, 127.4, 126.8, 125.2, 124.9, 124.8, 124.5, 124.2, 122.6, 121.5, 120.8, 120.3, 117.8, 115.6, 108.4, 55.5, 22.1; IR (NaCl, neat): 1600, 1372, 1316, 1243, 1232, 1168, 1144, 1117, 1032, 938, 891, 878, 810, 754, 740, 717, 692 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{24}H_{18}NO_3S$: 400.10047; found: 400.10145.

4.2.7. Benzo[c]carbazole ***3i***. Following the general procedure, a mixture of *gem*-dibromoolefin **1i** (107 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 15 h. Subsequent workup and column chromatography (hexanes/DCM 1:1) afforded **3i**, which co-eluted with an orange impurity. The chromatographed material was triturated with hexanes (0.5 mL×3) to wash away the impurity and afford **3n** as an off-white solid (30.3 mg, 41% yield). R_f=0.22 (hexanes/DCM 1:1). Mp 220–223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J*=8.4 Hz, 1H), 8.50 (dd, *J*=7.0, 1.7 Hz, 1H), 8.41–8.34 (m, 2H), 8.30 (dd, *J*=8.8, 5.2 Hz, 1H), 8.08 (d, *J*=8.2 Hz, 1H), 7.92 (dd, *J*=9.6, 2.4 Hz, 1H), 7.77 (ddd, *J*=8.3, 6.9, 1.3 Hz, 1H), 7.66–7.57 (m, 3H), 7.36 (ddd, *J*=8.8, 7.7, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5 (d, *J*=255.4 Hz), 137.3, 135.0 (d, *J*=9.2 Hz), 134.2, 131.1 (d, *J*=3.1 Hz), 131.0, 130.4, 129.7, 129.0, 127.3, 127.2 (d, *J*=9.9 Hz), 127.1, 125.7, 125.2, 123.7, 123.3, 122.8, 120.4, 116.7 (d, *J*=2.6 Hz), 116.6 (d, *J*=23.3 Hz), 115.5, 111.8 (d, *J*=24.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −104.13 (td, *J*=8.2, 6.0 Hz); IR (NaCl, neat): 3075, 1605, 1586, 1481, 1447, 1337, 1287, 1225, 1173, 1119, 1078, 922, 824, 787, 752, 635 cm^{-1}; HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{22}H_{16}FN_2O_2S$: 391.09195; found: 391.09119.

4.2.8. Benzo[c]carbazole ***3j***. Following the general procedure, a mixture of *gem*-dibromoolefin **1j** (117 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (40% DCM in hexanes) afforded **3j** as a golden yellow solid (44.8 mg, 53% yield). R_f=0.37 (hexanes/DCM 1:1). Mp 250–252 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J*=8.4 Hz, 1H), 8.59–8.50 (m, 3H), 8.43 (d, *J*=8.3 Hz, 1H), 8.37 (d, *J*=7.1 Hz, 1H), 8.15 (d, *J*=8.2 Hz, 1H), 7.93 (d, *J*=8.2 Hz, 1H), 7.81 (t, *J*=7.2 Hz, 1H), 7.68–7.57 (m, 3H); ^{13}C NMR (100 MHz, CDC_3) δ 137.6 (q, *J*=1.2 Hz), 137.3, 135.4 (q, *J*=33.2 Hz), 134.0, 132.9, 131.2, 130.5, 129.8, 129.2, 127.4, 127.3, 125.9, 125.6 (q, *J*=3.5 Hz), 125.4, 125.3, 123.8, 123.5, 123.3 (q, *J*=273.6 Hz), 122.9, 122.2 (q, *J*=3.9 Hz), 120.6, 116.4, 115.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.1; IR (NaCl, neat): 3073, 1476, 1416, 1341, 1283, 1221, 1175, 1134, 1088, 1069, 947, 912, 887, 808, 787, 748, 741 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{13}F_3NO_2S$: 424.06191; found: 424.06097.

4.2.9. Benzo[c]carbazole ***3k***. Following the general procedure, a mixture of *gem*-dibromoolefin **1k** (104.7 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 3:1) afforded **3k** as a red-brown solid (30 mg, 42% yield). R_f=0.31 (hexanes/EtOAc 7:3). Mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J*=8.4 Hz, 1H), 8.53 (d, *J*=7.5 Hz, 1H), 8.35 (d, *J*=8.0 Hz, 1H), 8.26 (s, 1H), 8.07 (d, *J*=8.2 Hz, 1H), 7.85 (d, *J*=5.1 Hz, 1H), 7.78–7.75 (m, 2H), 7.65–7.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 136.5, 134.2, 131.8, 131.4, 130.7, 130.0, 129.2, 128.5, 126.8, 126.7, 125.3, 124.6, 123.7, 123.2, 123.1, 122.8, 118.6, 115.0, 114.8; IR (NaCl, neat): 1319, 1308, 1281, 1229, 1169, 1123, 932, 908, 880, 843, 781, 745, 729, 702 cm^{-1}; HRMS (ESI) $[M+NH_4]^+$ calcd for $C_{20}H_{15}N_2O_2S_2$: 379.05749; found: 379.05777.

4.2.10. Benzo[c]carbazole ***3l***. Following the general procedure, a mixture of *gem*-dibromoolefin **1l** (93.4 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/EtOAc 20:1) afforded **3l**, which co-eluted with an impurity. The chromatographed material was triturated with a minimal amount of hexanes to wash away the impurity and afford **3l** as a yellow solid (33.6 mg, 55% yield). R_f=0.28 (hexanes/EtOAc 15:1). Mp 247–249 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J*=8.2 Hz, 1H), 8.48 (d, *J*=7.9 Hz, 1H), 8.11 (dd, *J*=7.7, 0.7 Hz, 1H), 8.06 (s, 1H), 7.96 (d, *J*=8.0 Hz, 1H), 7.62 (ddd, *J*=8.2, 7.0, 1.3 Hz, 1H), 7.51 (dd, *J*=4.5, 0.8 Hz, 2H), 7.44–7.42 (m, 3H), 7.36 (td, *J*=7.4, 1.3 Hz, 1H), 7.31 (d, *J*=7.5 Hz, 1H), 5.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 134.8, 130.4, 130.3, 130.1, 129.9, 129.4, 128.5, 128.0, 127.7, 126.9, 124.1, 124.0, 123.3, 123.1, 123.0, 122.2, 120.4, 119.2, 118.6, 113.3, 109.3, 45.4; IR (NaCl, neat): 3047, 1620, 1593, 1588, 1531, 1498, 1489, 1471, 1442, 1410, 1386, 1377, 1313, 1226, 1016, 913, 876, 785, 744, 719 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{23}H_{16}N$: 306.12827; found: 306.12936.

4.2.11. Benzo[c]carbazole ***3m***. Following the general procedure, a mixture of *gem*-dibromoolefin **1m** (114.5 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/DCM/EtOAc 85:10:5) afforded **3m** as a yellow-orange solid (49.1 mg, 60% yield). R_f=0.25 (hexanes/DCM/EtOAc 85:10:5). Mp 237–238 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J*=8.4 Hz, 1H), 8.46 (d, *J*=7.0 Hz, 1H), 8.26–8.22 (m, 2H), 8.12 (d, *J*=8.1 Hz, 1H), 7.72 (t, *J*=7.5 Hz, 1H), 7.61–7.57 (m, 2H), 7.53–7.45 (m, 4H), 7.38 (t, *J*=7.7 Hz, 2H), 7.29–7.25 (m, 3H), 7.11–7.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3, 143.4, 142.1, 141.2, 140.1, 133.2, 131.9, 130.5, 129.5, 129.2, 129.0 (2C), 128.6, 128.1, 127.7, 127.5, 127.2, 126.5, 125.9, 125.7, 125.3, 124.6, 124.4, 123.8, 121.8, 121.0, 120.3; IR (NaCl, neat): 3060, 1692, 1490, 1471, 1447, 1362, 1340, 1323, 1311, 1261, 908, 790, 779, 764, 743, 731, 668 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{29}H_{19}N_2O$: 411.14974; found: 411.14776.

4.2.12. Benzo[e]indole ***3n***. Following the general procedure, a mixture of *gem*-dibromoolefin **1n** (96.3 mg, 0.2 mmol), Pd–**1** (13.5 mg, 0.02 mmol, 10 mol %), K_2CO_3 (55.3 mg, 0.4 mmol, 2 equiv) and CsOPiv (23.4 mg, 0.1 mmol, 50 mol %) in toluene (4 mL) was heated to 100 °C for 18 h. Subsequent workup and column chromatography (hexanes/DCM 35:65) afforded **3n** as a dark yellow solid (33.7 mg, 53% yield). R_f=0.28 (hexanes/EtOAc 4:1). Mp 248–250 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.24 (d, *J*=8.2 Hz, 1H),

8.16–8.14 (m, 2H), 8.07 (d, J=8.2 Hz, 1H), 7.86 (d, J=3.4 Hz, 1H), 7.67 (t, J=7.2 Hz, 1H), 7.57 (t, J=7.5 Hz, 1H), 7.46 (d, J=8.3 Hz, 1H), 7.41 (d, J=3.4 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 132.1, 131.8, 131.0, 130.8, 129.9, 129.8, 128.4, 127.9, 125.6, 125.4, 125.1, 124.6, 123.6, 121.0, 120.1, 116.8, 109.6, 22.1; IR (NaCl, neat): 3130, 3054, 2918, 1604, 1362, 1331, 1200, 1171, 1139, 913, 878, 812, 798, 748, 743, 684 cm^{-1}; HRMS (ESI) $[M+H]^+$ calcd for $C_{19}H_{14}NO_2S$: 320.0739; found: 320.0727.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council (NSERC), Merck for an Industrial Research Chair, and the University of Toronto for financial support. We also thank Dr. Alan Lough of the University of Toronto for X-ray analysis. P.T.F. and N.N. gratefully acknowledge the Deutscher Akademischer Austauschdienst (DAAD) for postdoctoral fellowships.

Supplementary data

Experimental procedures and characterization data for all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.01.001.

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25. Electronic variations on the indole core may also negatively impact the rate of formation of the palladium vinylidene, which may explain why indoles with both electron-donating and electron-withdrawing substituents gave lower yields in this domino reaction (see Table 2).