A Rapid Pathway to Molecular Complexity: Palladium-Catalyzed Six-Fold Domino Process to Access Fused Polycyclic Framework

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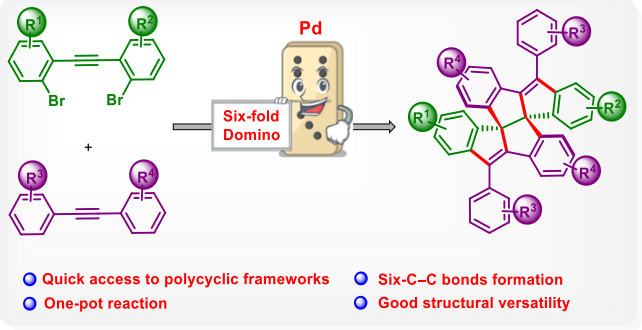
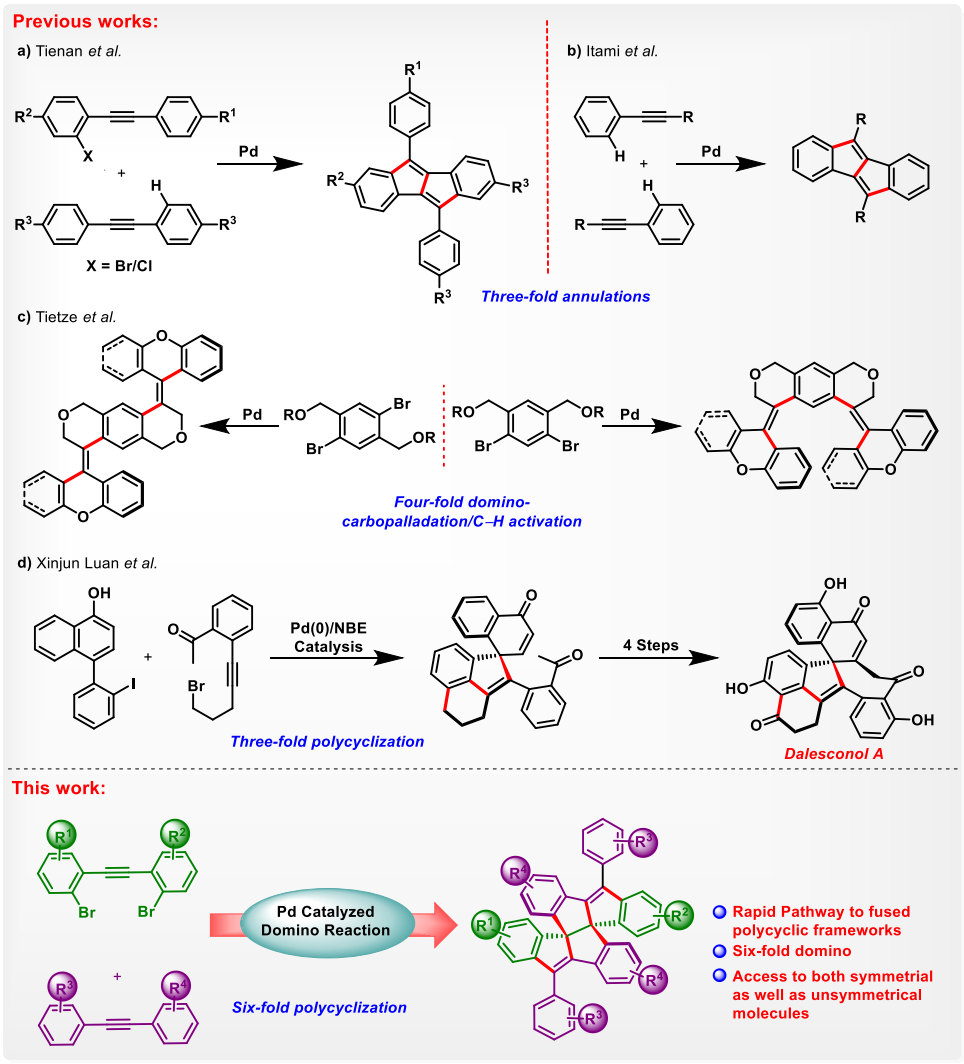
Abstract: This study demonstrates an expedient strategy for the quick access of intriguing fused polycyclic frameworks through palladium-catalyzed six-fold domino crossover annulations of simple 1,2-bis(2-bromoaryl)ethynes and 1,2-diarylethynes. Remarkably, this strategy enables the construction of six-C−C bonds in a single-pot operation. In fact, this synthetic conversion takes up two successive domino pathways (i.e., *via* two consecutive catalytic cycles) to reach the targets and each of it contributes to the formation of three-C−C bonds. Significantly, this strategy exhibited good substrate scope and enabled the construction of C_2-symmetric as well as unsymmetric polycyclic products.



Introduction:

Chemical synthesis is backbone to organic chemistry, which is the basis for the pharmaceutical industry and many interdisciplinary fields. Hence, in organic synthesis, achieving natural products *or* drugs *or* unnatural products *or* any material of particular interest is vital part in academia and industry. Earlier, attaining good selectivity in synthesizing organic compounds used to be main objective, of course it is very much inevitable; these days, the main motivation is to develop sustainable synthetic strategies with improved efficacy, preserving the resources, without affecting our environment, and with economical advantage. Largely, this sort of synthetic efficiency and molecular complexity can be achieved by implementing domino processes.[1–5] However, arriving at the level of higher structural complexity starting from simple synthetic precursors, in fewer synthetic steps, with great efficiency and practicality is still a challenging task.[6,7] In reality, forming many bonds in general, require number of synthetic steps, generates more waste, consumes more energy, and require more time.[8] In fact, even though the capabilities and limits of contemporary synthetic chemistry have evolved tremendously over the past few decades, the Mother Nature, who has perfected the ability of creating sophisticated and

occasionally unimaginable complex compounds in her own delicate way, is far superior to even the greatest synthetic chemists.[9] Domino reactions are quite common in nature, as multiple enzymes are involved, which can enable the catalysis of diverse steps.[10] However, performing the same experiment in laboratory settings through mimicking the Nature's principles is quite challenging. It demonstrates how difficult and fascinating it is for researchers in synthetic chemistry to replicate the level of perfection seen in nature in order to synthesize complex scaffolds in a single-pot procedure.[11] Much to their inspiration from nature, synthetic chemists get much involved in designing such methodology which involve multiple fold domino process to synthesize complicated fused polycyclic molecules in a single process.[3] In this context, transition metal-catalysis is of growing importance in synthetic organic chemistry, in particular, implementation of domino transformations under such metal-catalyst is quite feasible.[12–14] One such metal that quite frequently employed in enabling domino reactions is palladium.[2,15–18] For instance, in 1993 palladium-catalyzed synthesis of polyspiranes *via* multiple-fold domino was reported by Barry and his colleagues.[19] Later Tienan and his group reported palladium catalyzed three-fold domino for the synthesis of multisubstituted dibenzopentalenes in 2013 using simple acetylene derivatives (Scheme 1a).[20] Also, in same year synthesis of dibenzopentalenes was disclosed by Itami and his coworkers *via* palladium-catalyzed C−H activation pathway (Scheme 1b).[21] Further, in 2014 Tietze and his group unfolds the palladium catalyzed fourfold domino strategy to synthesize complex polycyclic hydrocarbons using simple aromatic system.[22] Later in 2015, same group developed four- and six-fold palladium-catalyzed domino process to synthesize tetrasubstituted alkenes which showed potential application as molecular switches (Scheme 1c).[23] Also, in 2017 bicyclic core was constructed *via* six-step domino reaction of aldehyde and malononitrile by Tsogoeva and coworkers.[24] Recently, in 2021, Luan and his group reported total synthesis of Dalesconol A, in which they successfully employed palladium-catalyzed threefold domino process (Scheme 1d).[25] Since our group has always found multiple-fold domino synthesis to be an intriguing area of study, we have been working on establishing efficient synthetic tools for synthesizing fused complicated molecules utilizing easily accessible building blocks.[26–28] Alkynes are determined to be the most adaptable synthon for multiple C−C bonds construction in this regard, as they readily form π-complexes and subsequently go through migratory insertion processes from their coordination sphere.[29,30] Utilizing these easily synthesized basic alkyne derivatives, we have disclosed a novel six-fold palladium-catalyzed domino approach that employs crossover annulations of two distinct alkyne

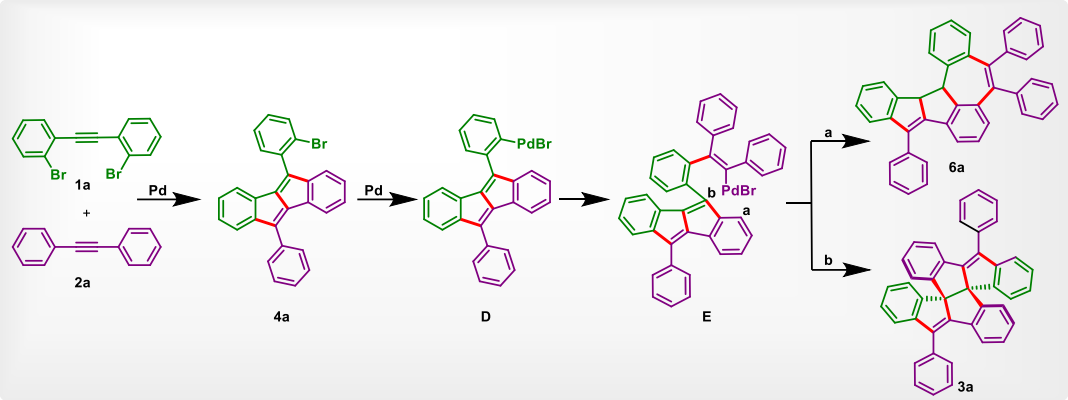


Scheme 1: Reported works *vs.* current work.

derivatives which is 1,2-bis(2-bromoaryl)ethynes and 1,2-diarylethynes to produce fused polycyclic molecules forming six-C–C bond in a single-pot operation.

Results and discussion:

The original idea was to synthesize polycyclic products using simple and readily available alkynes. In order to achieve this, it was envisioned that first cross-over annulation between 1,2-bis(2-bromoaryl)ethyne **1a** and 1,2-diarylethyne **2a** would provide bromine-atom containing tetracyclic scaffold **4a** which could further undergo second catalytic cycle in the presence of sufficient amount of 1,2-diarylethyne **2a** with palladium providing intermediate **D**. Then intermediate **D** might be further attacked by second 1,2-darylethyne molecule *via* palladium migration leading to intermediate **E**. From the intermediate **E**, there would be possibility of forming a

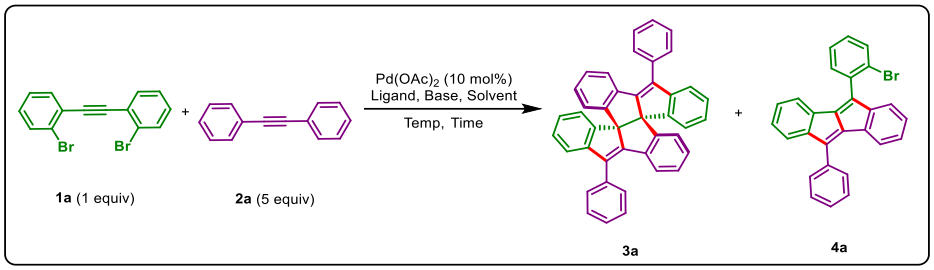


Scheme 2: Anticipated synthetic pathways.

pentacyclic product **6a** (i.e., the formation of seven membered ring through attack at **a** position) or the octacyclic product **3a** (i.e., the consecutive formation of two five membered rings through attack at **b** position) as shown in Scheme 2. The possibility of formation of fused polycyclic product **3a** with five membered rings might be more feasible; however, achieving this polycyclic molecule in one-pot would be rather a challenging task. Of course, a suitable palladium catalyst and conditions would indeed must be instrumental to play a key role to drive the overall anticipated process.

Therefore, 1,2-bis(2-bromophenyl)ethyne **1a** and 1,2-diphenylethyne **2a** were initially selected as model substrates and exposed to palladium catalysis in order to determine the optimal conditions as depicted in Table 1. As expected, the intermediate product **4a** was obtained, but only in 30% of yield when screening was conducted using **1a** (1 equiv) and **2a** (1 equiv) in the presence of $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), and Cs_2CO_3 (3 equiv) at 120 °C for 24 hours in toluene (Table 1, entry 1). Remarkably, yield of **4a** was increased to 45% when DPE-Phos was employed as the ligand (Table 1, entry 2). Further to our delight, the yield (**4a**) was increased to 51% when the temperature was elevated to 140 °C and amount of **2a** was increased to 2 equivalents (Table 1, entry 3). Nevertheless, still, there was no sign of forming the polycyclic molecule even after using two equivalents of acetylene **2a**. It is noteworthy to mention that when the equivalents of **2a** were further increased to 3 and 5, respectively, then along with tetracyclic product **4a** (71% yield), the anticipated fused polycyclic product **3a** was also obtained albeit in trace amounts (Table 1, entries 4 & 5). This intriguing outcome motivated us to investigate more conditions for obtaining high yields of fused polycyclic product **3a**. After an increased catalyst loading to 10 mol%, a slight increase in the yield of 10% of the anticipated product **3a** was noticed along with the significant yield (74%) of **4a** (Table 1, entry 6). While other ligands, including John-Phos, ^{t}Bu-Xphos, and BINAP, were found to be ineffective in producing product **3a**; instead, they

Table 1: Screening conditions for the synthesis of fused polycyclic scaffold **3a**.[a,b,c,d]



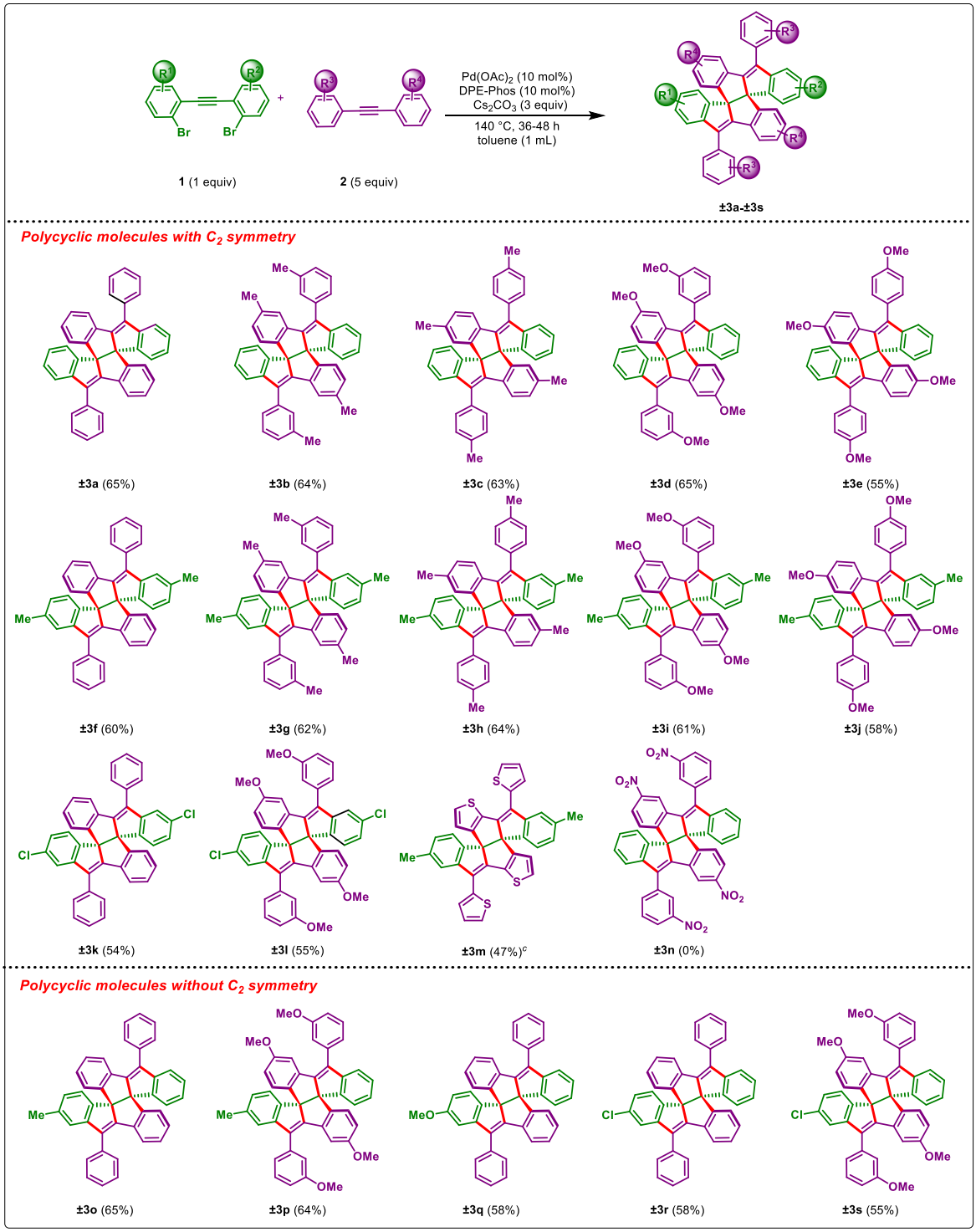
S. No.	**2a** (equiv)	Catalyst (10 mol%)	Ligand (10 mol%)	Base (3 equiv)	Solvent (1 mL)	Additive (1 equiv)	Temp (°C)	Time (h)	Yield **3a**[a] (%)	Yield **4a**[b] (%)
1[c]	1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Toluene	-	120	24	-	30
2[c]	1	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	120	12	-	45
3[c]	2	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	9	-	51
4[c]	3	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	8	trace	60
5[c]	**5**	**$Pd(OAc)_2$**	**DPE-Phos**	**Cs_2CO_3**	**Toluene**	**-**	**140**	**8**	**trace**	**74**
6	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	2	10	76
7[c]	5	$Pd(OAc)_2$	John-Phos	Cs_2CO_3	Toluene	-	140	12	-	50
8[c]	5	$Pd(OAc)_2$	^{t}Bu-Xphos	Cs_2CO_3	Toluene	-	140	17	-	55
9[c]	5	$Pd(OAc)_2$	BINAP	Cs_2CO_3	Toluene	-	140	48	trace	58
10[c]	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	--	140	48	30	50
11	**5**	**$Pd(OAc)_2$**	**DPE-Phos**	**Cs_2CO_3**	**Toluene**	**-**	**140**	**48**	**65**	-
12[d]	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	48	63	-
13	5	$Pd(PPh_3)_4$	DPE-Phos	Cs_2CO_3	Toluene	-	140	24	-	30
14	5	$PdCl_2(PPh_3)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	24	-	28
15	5	$Pd(COOCF_3)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	140	24	-	50
16	5	$Pd(OAc)_2$	DPE-Phos	K_2CO_3	Toluene	-	140	24	22	60
17	5	$Pd(OAc)_2$	DPE-Phos	DBU	Toluene	-	140	24	trace	40
18	5	$Pd(OAc)_2$	DPE-Phos	Na_2CO_3	Toluene	-	140	24	-	55
19	5	$Pd(OAc)_2$	DPE-Phos	CsF	Toluene	-	140	24	trace	40
20	5	$Pd(OAc)_2$	DPE-Phos	K_3PO_4	Toluene	-	140	24	trace	30
21	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	DCE	-	110	24	-	-
22	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	DMF	-	140	48	10	65
23	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Xylene	-	140	48	10	60
24	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Dioxane	-	140	48	trace	54

25	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	TEBAC	140	48	55	10
26	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	TBAI	140	48	30	40
27	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	CuI	140	48	20	50
28	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	PivOH	140	48	32	30
29	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	DMF	-	140 (MW)	45 min	-	68
30	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Toluene	-	130 (MW)	15 min	-	72
31	5	$Pd(OAc)_2$	DPE-Phos	Cs_2CO_3	Dioxane	-	140	30 min	-	70

Reaction conditions: 1a (0.1 mmol), **2a** (0.5 mmol), Pd catalyst (10 mol%), Ligand (10 mol%), Base (0.3 mmol), solvent (1 mL), 140 °C. [a]Isolated yields of **3a**. [b]Isolated yields of **4a**. [c]$Pd(OAc)_2$ (5 mol%). [d]DPE-Phos (20 mol%).

slowed down the reaction and even decreased the yield of the intermediate product **4a** (Table 1, entries 7 to 9). It was clear from the aforementioned explorations that DPE-Phos ligand is best suited for this reaction. Consequently, the reaction with DPE-Phos ligand at 140 °C for 48 h, to our astonishment, generated the desired octacyclic product **3a** in 30% yield along with 50% of **4a** (Table 1, entry 10). Gratifyingly, increased catalyst loading of 10 mol% provided an exclusive polycyclic product **3a** with 65% of yield (Table 1, entry 11). On the other hand, increasing the ligand loading to 20 mol% resulted in drop of yield (Table 1, entry 12). Moreover, screening the reactions using other palladium catalysts proved to be unsuccessful (Table 1, entries 13 to 15). In addition, explorations using other bases, including K_2CO_3, DBU, Na_2CO_3, CsF, and K_3PO_4, were proved to the inferior (Table 1, entries 16 to 20). Moreover, other solvents couldn't be more effective than toluene (Table 1, entries 21 to 24). Additionally, it was supposed that the reaction might work well with some additive so the reaction was also optimized with different additives such as TEBAC, TBAI, CuI, and PivOH, but the results were unsatisfactory (Table 1, entries 25 to 28). Moreover, reactions have also been performed under microwave assisting conditions, but the outcomes were not impressive (Table 1, entries 29 to 31). As a result of above-explored screening study, it can be concluded that the best-optimized conditions for the synthesis of octacyclic product **3a**, is $Pd(OAc)_2$ (10 mol%), DPE-phos (10 mol%), Cs_2CO_3 (3 equiv), in toluene at 140 °C for 48 h (i.e., Table 1, entry 11); with this optimal reaction procedure, the stage is set to test the method's applicability and limitations with other 1,2-bis(2-bromoaryl)ethynes **1** and 1,2-diarylethynes **2**. So, in the beginning, conducted the reactions of 1,2-bis(2-bromophenyl)ethyne **1a** with *meta* and *para* substituted diarylacetylenes [i.e., moderate electron-releasing Me and strong electron-releasing OMe groups (**2b**-**2e**)]; to our delight, furnished the octacyclic products **3a**-**3e**

Scheme 3: Substrate scope of symmetric polycyclic products **±3a-±3s**. [a,b,c]

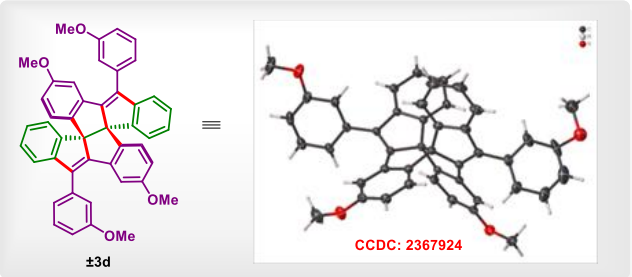


Reaction conditions: [a]Reactions were conducted with **1a-1f** (0.1 mmol) and **2a-2g** (0.5 mmol), $Pd(OAc)_2$ (10 mol%), DPE-phos (10 mol%), Cs_2CO_3 (3 equiv) at 140 °C for 36-48 h in toluene solvent (0.5 mL). [b]Isolated yields of cross-annulated products **±3a-±3s**. [c]Time is 24 h.

in yields ranging from 55% to 65% (Scheme 3). On the other hand, methyl-substituted 1,2-bis(2-bromo-4-methylphenyl)ethyne **1b** was also successful with internal acetylenes **2a-2e** and

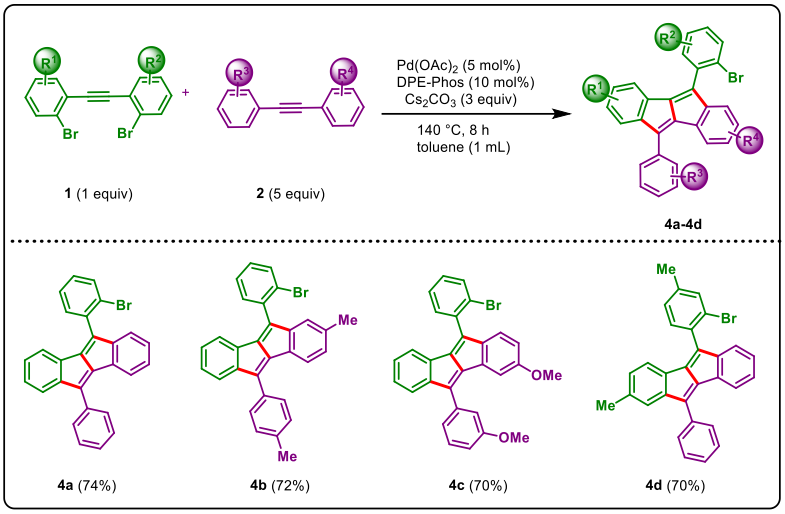
afforded the corresponding polycyclic products [**3f** (60%), **3g** (62%), **3h** (64%), **3i** (61%), and **3j** (58%)], as shown in Scheme 2. Furthermore, 1,2-bis(2-bromo-4-chlorophenyl)ethyne **1c** underwent annulations with diarylacetylenes **2a** and **2d**, which resulted in the formation of products **3k** and **3l** in yields 54% and 55%, respectively (Scheme 3). Notably, the reaction of **1c** was also well tolerated with heteroaromatic ring containing acetylene i.e., 1,2-di(thiophen-2-yl)ethyne **2f**, delivering the product **3m** in 47% of isolated yield (Scheme 3). However, the reaction with strong electron withdrawing nitro substituted diarylacetylene **2g** wasn't successful in producing **3n**. It is worth noting that all of these polycyclic products **3a**-**3m** are C_2-symmetric possessing a vertical axis of symmetry. Remarkably, as demonstrated in Scheme 3, unsymmetrical 1,2-bis(2-bromoaryl)ethynes such as **1d**, **1e**, and **1f** with simple and OMe-substituted diarylacetylenes **2a** and **2d** were also well tolerated, yielding the corresponding unsymmetrical products **3o-3s** in moderate to fair yields, which unlike **3a-3m** devoid the C_2-axis of symmetry (Scheme 3). Also, it is noteworthy to mention that the excess of acetylenes that were utilised to accelerate the reaction were retrieved and repurposed. Moreover, the crystal structure of the product **±3d** was confirmed by its X-ray diffraction analysis (CCDC: 2367924) as shown in Figure 1. Additionally, the goal was also set to accomplish unsymmetrical products concerning external acetylenes **2** starting from symmetrical 1,2-bis(2-bromoaryl)ethynes **1**.

Figure 1: X-ray structure of polycyclic molecule **±3d**.



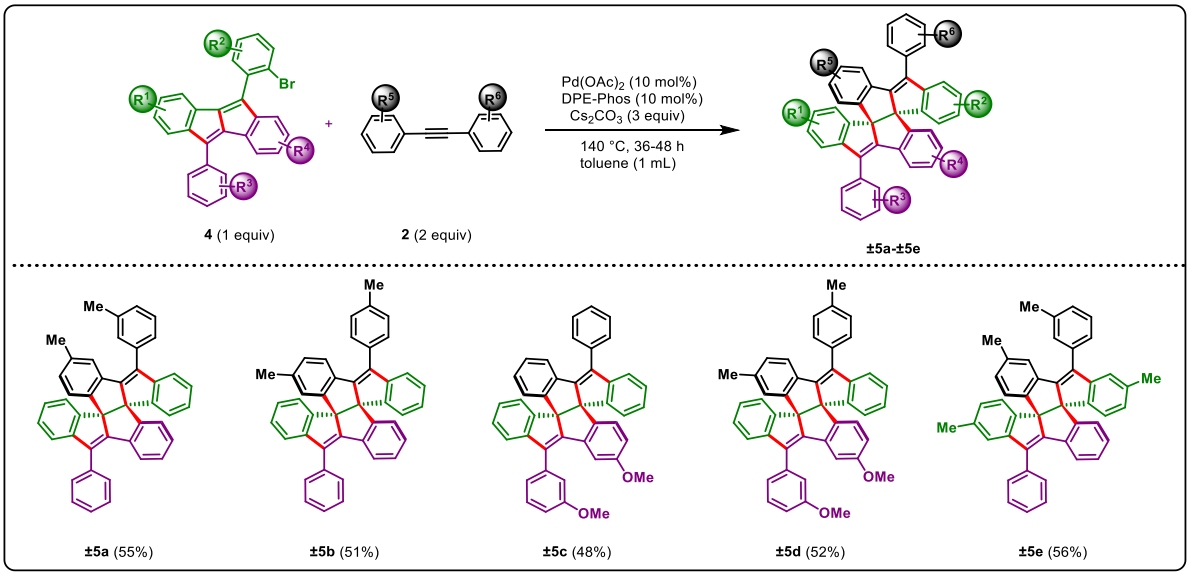
This indeed could become possible by selectively stopping the reaction right after forming the tetracyclic intermediate products **4** in accordance to the conditions of Table 1, entry 5. Thus, as anticipated, led to the isolation of tetracyclic intermediate products **4a-4d** starting from **1a**/**1b** and **2a**/**2c**/**2d** as depicted in Scheme 4 [**4a**, $R^1 = R^2 = R^3 = R^4 = H$ (74%); **4b**, $R^1 = R^2 = H$ & $R^3 = R^4 =$ *p*-Me (72%); **4c**, $R^1 = R^2 = H$ & $R^3 = R^4 =$ *m*-OMe (70%); and **4d**, $R^1 = R^2 =$ *p*-Me & $R^3 = R^4 = H$ (70%)]. Subsequently, these tetracyclic intermediate products **4a-4d** were then subjected to other substituted internal acetylenes **2a**/**2b**/**2c** in reference to the conditions of Table 1 and entry 11, which gave the desired unsymmetrical products [**5a**, $R^1 = R^2 = R^3 = R^4 = H$ & $R^5 = R^6 =$ *m*-Me (55%); **5b**, $R^1 = R^2 = R^3 = R^4 = H$ & $R^5 = R^6 =$ *p*-Me (51%); **5c**, $R^1 = R^2 = H$, $R^3 = R^4 =$ *m*-OMe & $R^5 = R^6 = H$ (48%); **5d**, $R^1 = R^2 = H$, $R^3 = R^4 =$ *m*-OMe & $R^5 = R^6 =$ *p*-Me (52%); **5e**, $R^1 = R^2 =$ *p*-Me, $R^3 = R^4 = H$ & $R^5 = R^6 =$ *m*-Me (56%)] as shown in Scheme 5. A viable reaction mechanism for the synthesis of polycyclic product **±3a** based on our analysis and previous

Scheme 4: Substrate scope of tetracyclic products **4a-4d**. [a,b]



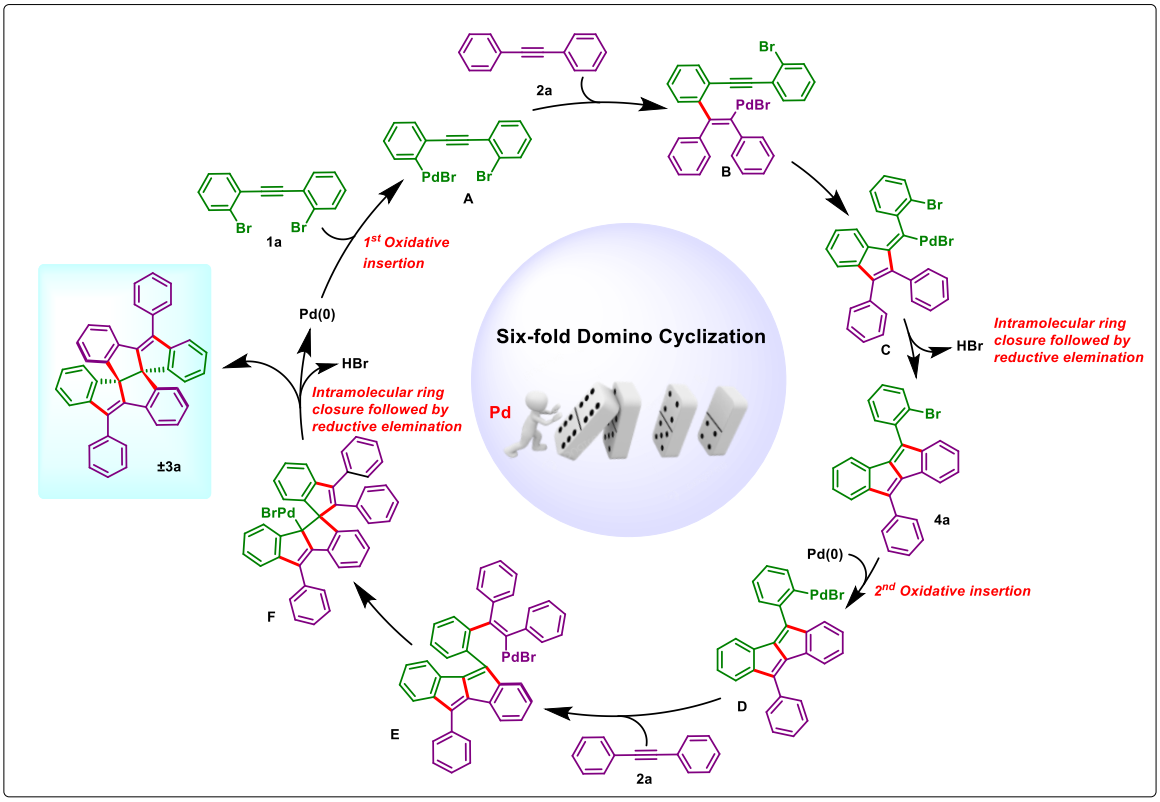
Reaction conditions: [a]Reactions were conducted with **1a** & **1b** (0.2 mmol) and **2a**, **2c** & **2d** (1 mmol), $Pd(OAc)_2$ (5 mol%), DPE-phos (10 mol%), Cs_2CO_3 (3 equiv) at 140 °C for 8 h in toluene solvent (1 mL). [b]Isolated yields of cross-annulated products **4a-4d**.

Scheme 5: Substrate scope of asymmetric polycyclic products **±5a-±5e**. [a,b]



Reaction conditions: [a]Reactions were conducted with **4a**, **4c** & **4d** (0.1 mmol) and **2a**, **2b** & **2c** (1 mmol), $Pd(OAc)_2$ (10 mol%), DPE-phos (10 mol%), Cs_2CO_3 (3 equiv) at 140 °C for 36-48 h in toluene solvent (1 mL). [b]Isolated yields of cross-annulated products **±5a-±5e**.

literature precedence of palladium-catalyzed domino reactions is depicted in Scheme 6. Primarily, the C−Br bond of 1,2-bis(2-bromophenyl)ethyne **1a** undergoes oxidative insertion by the active Pd(0)-catalyst and forms the intermediate **A**. The Pd(II) intermediate **A** is subsequently inserts *via* first *syn*-addition onto the triple bond of 1,2-diphenylethyne **2a** and gives the intermediate **B**. Subsequently, this intermediate **B** migrates palladium entity intramolecularly to the proximal triple bond of 1,2-bis(2-bromophenyl)ethyne **1a** *via* second *syn*-addition, which produces the bicyclic intermediate **C**.



Scheme 6: Feasible reaction pathway for the formation of **±3a**.

Now **C** could further undergo a second intramolecular ring-closure step with the aromatic ring originated from external 1,2-diphenylethyne **2a** that generates the tetracyclic intermediate product **4a** containing bromine-atom, which completes the first catalytic cycle and reforms the active Pd(0)-catalyst. This intermediate product **4a** would now serve as a suitable intermediate to take up the second catalytic cycle *via* the attack by a second molecule of 1,2-diphenylethyne **2a** to yield the desired product **3a**. Thus, the tetracyclic product **4a** then undergoes a second oxidative insertion with the active Pd(0)-catalyst, and affords the intermediate **D**, which then couple with second molecule of 1,2-diphenylethyne **2a** *via* third *syn*-addition and leads to the formation of **E**. Subsequent palladium migration furnishes the hexacyclic intermediate **F** *via* fourth *syn*-addition. Ultimately, **F** undergoes reductive elimination and delivers the desired octacyclic product **3a** that concludes the second catalytic cycle and regenerates the active Pd(0)-catalyst.

Conclusion:

In conclusion, we have developed a successful six-fold domino technique that uses palladium as a catalyst to enable the creation of fused-polycyclic frameworks in a single-pot. Remarkably, in every reaction, the surplus unreacted 1,2-diarylethynes were retrieved and repurposed. The approach demonstrated a broad range of substrate compatibility and produced symmetrical as well as unsymmetrical polycyclic products. Overall, this method provided a practical, effective, and innovative

synthetic tool for constructing structurally complex polycyclic frameworks.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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