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A Facile Construction of Bisheterocyclic Methane Scaffolds through Palladium-Catalyzed Domino Cyclization

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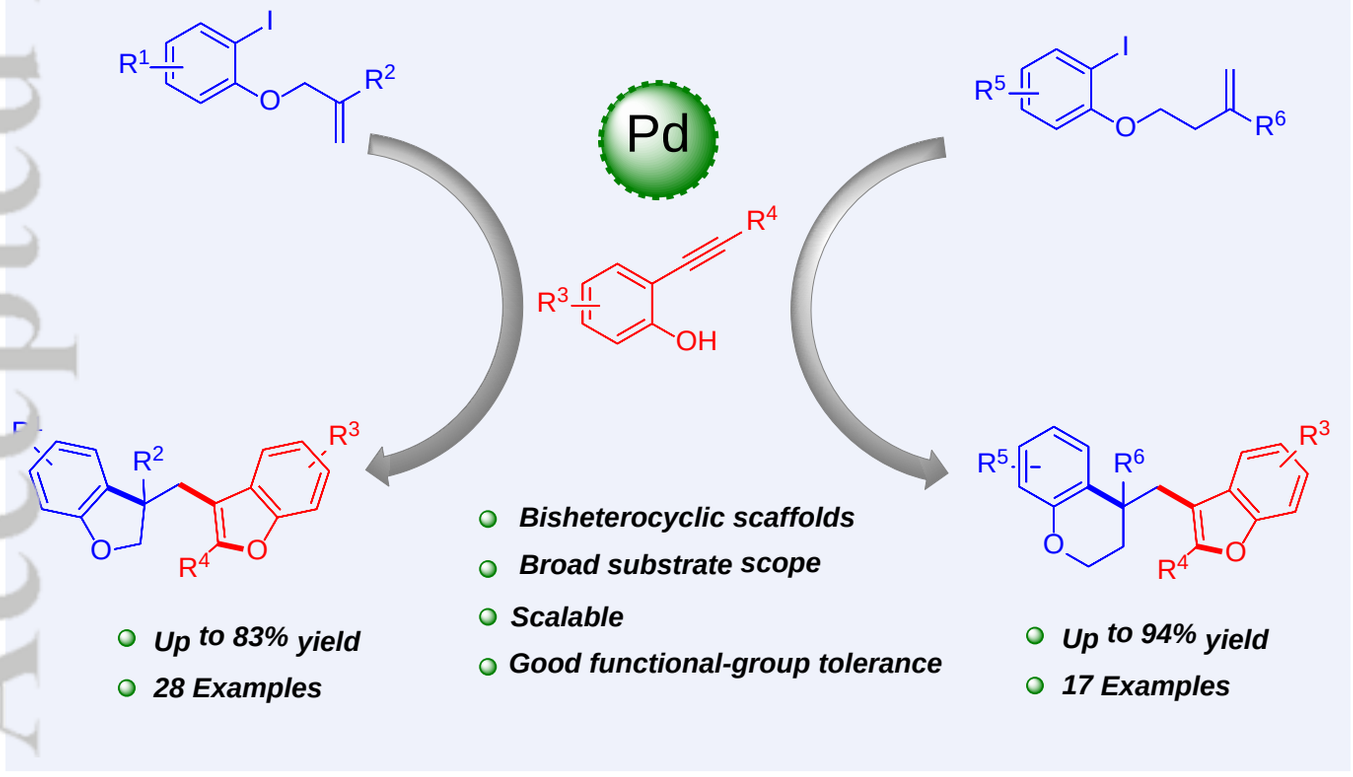
Keywords

Bisheterocyclic methane| Heterocyclic compound | Palladium | Catalysis | Domino cyclization

Main observation and conclusion

A convenient palladium-catalyzed domino cyclization reaction for the construction of bis(benzofuranyl)methane scaffolds bearing an all-carbon quaternary center has been described. In the cascade process, one C(sp^2)–O bond, two C(sp^2)–C(sp^3) bonds as well as two benzofuran rings are formed in a single synthetic sequence. The approach shows wide scope of substrates and good functional-group tolerance. Moreover, this methodology is successfully extended to the synthesis of benzofuranyl methyl chromane derivatives.

Comprehensive Graphic Content



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Background and Originality Content

Diphenylmethane derivatives are one type of privileged structural motifs, which are widely existed in building blocks,[1] functional materials,[2] pharmaceutical molecules,[3] and biologically active natural products.[4] Moreover, the attractive properties can be obtained when replacing the benzene rings with other aromatic heterocycles, such as indole,[5] pyrazole,[6] and pyrrole.[7] Benzofuran scaffolds,[8] as the bioisosteres of indoles,[9] are also found in an array of natural products and pharmaceuticals with diverse biological and medicinal properties (Fig. 1). Compared with single heterocyclic scaffolds, the compounds with bisheterocyclic scaffolds may lead to more attractive biological activities.[10] To our knowledge, the reported studies on the formation of dibenzofuran scaffolds are scarce,[11] even though several dibenzofuran derivatives possess biological activities.[12] Among these compounds, bis(benzofuranyl)methane framework displayed superior activity against human African trypanosomiasis (HAT).[12a] Therefore, exploring the effective and practical strategies for the construction of bis(benzofuranyl)methanes is still highly desirable and challenging.

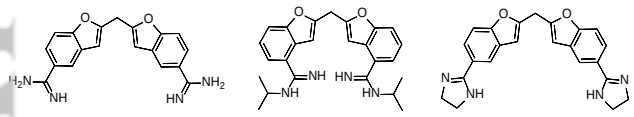
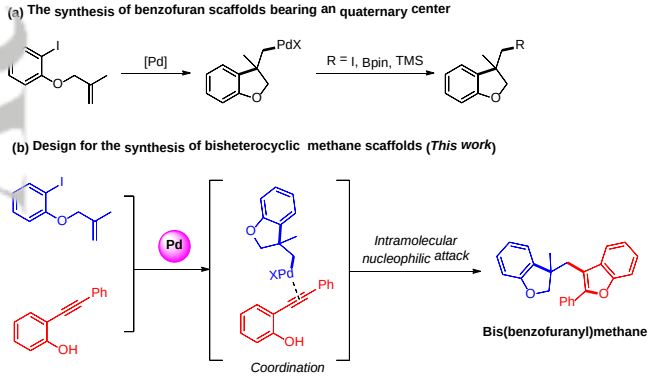


Figure 1 Representative Antileishmanial Activity Bis(benzofuranyl)methane Scaffolds.

On the other hand, transition-metal-catalyzed domino reactions have great advantages for the rapid formation of bisheterocyclic scaffolds via in situ generation of organometallic species in organic synthesis.[13,14] For instance, domino reactions have been extensively developed for the synthesis of biologically useful benzofuran scaffolds (Scheme 1a).[13b, 15] Inspired by these previous studies as well as a continuation of our efforts to develop novel reaction methodologies for the synthesis of heterocyclic derivatives through cascade reactions,[16] we report herein a facile and convenient palladium-catalyzed domino cyclization reaction between allyl ether and *o*-ethynylphenol, providing various bis(benzofuranyl)methane scaffolds. Significantly, one C(sp^2)–O bond, two C(sp^2)–C(sp^3) bonds as well as two benzofuran rings are formed in a single synthetic sequence (Scheme 1b). Moreover, this methodology is successfully extended to the synthesis of benzofuranyl methyl chromane derivatives.

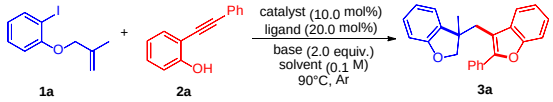
Scheme 1 Pd-Catalyzed Domino Cyclization Reaction



Results and Discussion

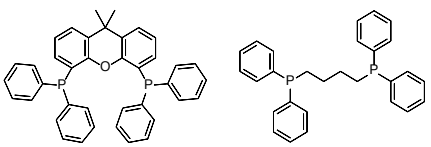
We initiated a systematic study on the palladium-catalyzed domino cyclization using 1-iodo-2-((2-methylallyl)oxy)benzene **1a** and 2-(phenylethynyl)phenol **2a** as model substrates (Table 1). To our delight, the desired product **3a** was formed in 26% yield in the presence of 2.0 equiv. of K_2CO_3 catalyzed by $Pd(OAc)_2$ (10.0 mol %) and P(2-furyl)$_3$ (20.0 mol %) at 90 °C after 15 h in 1,4-dioxane (entry 1). Encouraged by these results, the effect of phosphine ligand was carefully investigated firstly, and P(2-furyl)$_3$ was found to be optimal compared to Xantphos, dppb and PPh_3 (entries 1-4). Next, the effect of base on this domino reaction was also explored. Na_2CO_3 and Cs_2CO_3 were found to be inefficient (entries 5 and 6). The reaction with NaOH provided **3a** in a high isolated yield (entry 7). Switching NaOH to KOH or *t*-BuOLi did not increase the yield of the product (entries 8 and 9). Subsequently, different palladium catalysts were also examined, and $Pd_2(dba)_3$ showed a great performance in comparison with $Pd(TFA)_2$, $Pd(PhCN)_2Cl_2$, and [Pd(η^3-C_3H_5)Cl]$_2$, affording the product **3a** in 83% yield (entries 10-13). In order to further improve the efficiency of the

Table 1 Optimization of Reaction Conditions[a]



entry	catalyst	ligand	base	solvent	yield[b]/%
1	$Pd(OAc)_2$	P(2-furyl)$_3$	K_2CO_3	1,4-dioxane	26
2	$Pd(OAc)_2$	Xantphos	K_2CO_3	1,4-dioxane	21
3	$Pd(OAc)_2$	dppb	K_2CO_3	1,4-dioxane	0
4	$Pd(OAc)_2$	PPh_3	K_2CO_3	1,4-dioxane	trace
5	$Pd(OAc)_2$	P(2-furyl)$_3$	Na_2CO_3	1,4-dioxane	0
6	$Pd(OAc)_2$	P(2-furyl)$_3$	Cs_2CO_3	1,4-dioxane	trace
7	$Pd(OAc)_2$	P(2-furyl)$_3$	NaOH	1,4-dioxane	78
8	$Pd(OAc)_2$	P(2-furyl)$_3$	KOH	1,4-dioxane	54
9	$Pd(OAc)_2$	P(2-furyl)$_3$	*t*-BuOLi	1,4-dioxane	67
10	$Pd(TFA)_2$	P(2-furyl)$_3$	NaOH	1,4-dioxane	78
11	$PdCl_2(PhCN)_2$	P(2-furyl)$_3$	NaOH	1,4-dioxane	68
12	$Pd_2(dba)_3$	P(2-furyl)$_3$	NaOH	1,4-dioxane	83
13	[Pd (η^3-C_3H_5)Cl]$_2$	P(2-furyl)$_3$	NaOH	1,4-dioxane	73
14	$Pd_2(dba)_3$	P(2-furyl)$_3$	NaOH	MeCN	54
15	$Pd_2(dba)_3$	P(2-furyl)$_3$	NaOH	DCE	58
16	$Pd_2(dba)_3$	P(2-furyl)$_3$	NaOH	toluene	41
17	$Pd_2(dba)_3$	P(2-furyl)$_3$	NaOH	1,4-dioxane	55[c], 47[d]
18	$Pd_2(dba)_3$	-	NaOH	1,4-dioxane	0

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), catalyst (10.0 mol %), ligand (20.0 mol %), 1,4-dioxane (2.0 mL, 0.1 M), base (0.4 mmol), 90 °C, 15 h, under an argon atmosphere. [b] Isolated yields. [c] $Pd_2(dba)_3$ (5.0 mol %). [d] $Pd_2(dba)_3$ (2.5 mol %).

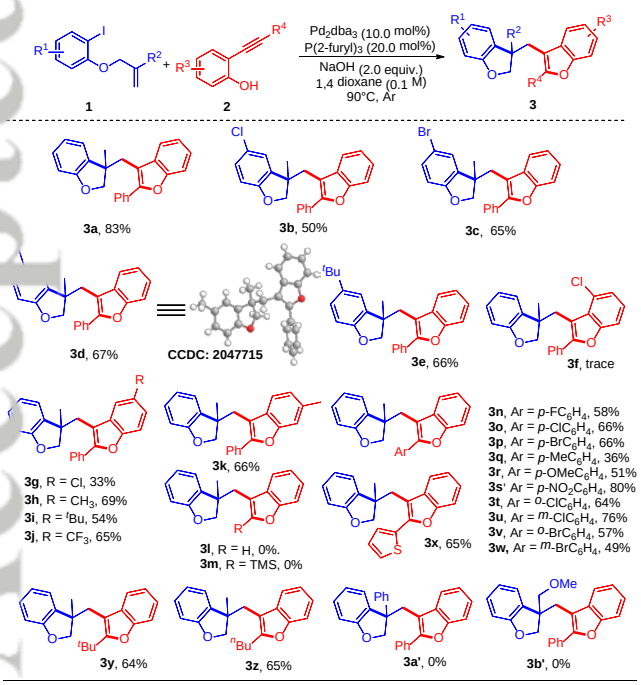


reaction, several solvents other than 1,4-dioxane were investigated. However, the results indicated that CH_3CN, DCE, and toluene were inferior to 1,4-dioxane and generated the desired product in 54%,

58%, and 41% yields, respectively (entries 14-16). In addition, much lower yields were obtained when the catalyst loading was reduced to 5.0 mol % and 2.5 mol % (entry 17). Finally, for comparison, a control experiment revealed that the reaction did not occur in the absence of a phosphine ligand (entry 18).

Under the above optimal conditions established, the scope of this domino cyclization reaction was investigated by using a series of allyl ethers **1** and *ortho*-alkynylphenol derivatives **2** (Scheme 2). As shown in Scheme 2, various functional groups on the aromatic ring of **1**, such as chloro, bromo, methyl and *tert*-butyl (**3b-e**) were tolerated, readily affording the desired products in moderate to high yields. With respect to R^3 substituents on the phenol ring, the methyl and *tert*-butyl substituted substrates worked well and gave the desired products **3h** and **3i** in 69% and 54% yields, respectively. Chloro group at 4-position of the phenol ring also converted to the corresponding products, albeit with a slightly lower yield (**3g**). However, only trace of the desired product **3f** was detected when a substrate possessing a chloro group at 3-position was employed. The electron-withdrawing substituents were also tested, and it was found that substrate with a trifluoromethyl group could underwent this reaction, providing the corresponding product **3j** in 65% yield. Unfortunately, substrates bearing a terminal alkyne or a trimethylsilyl functionality failed to produce the desired product **3l** and **3m** under the standard conditions, and a complex mixture was observed. Our next objective was to check the scope of R^3 groups of *ortho*-alkynylphenol substrates. Different substituents on the phenyl ring at *para*-positions were tested, and it was found that these substrates could also undergo the cascade reaction smoothly under the optimal conditions to afford the desired

Scheme 2 Synthesis of Bis(benzofuranyl)methane Derivatives [a,b]



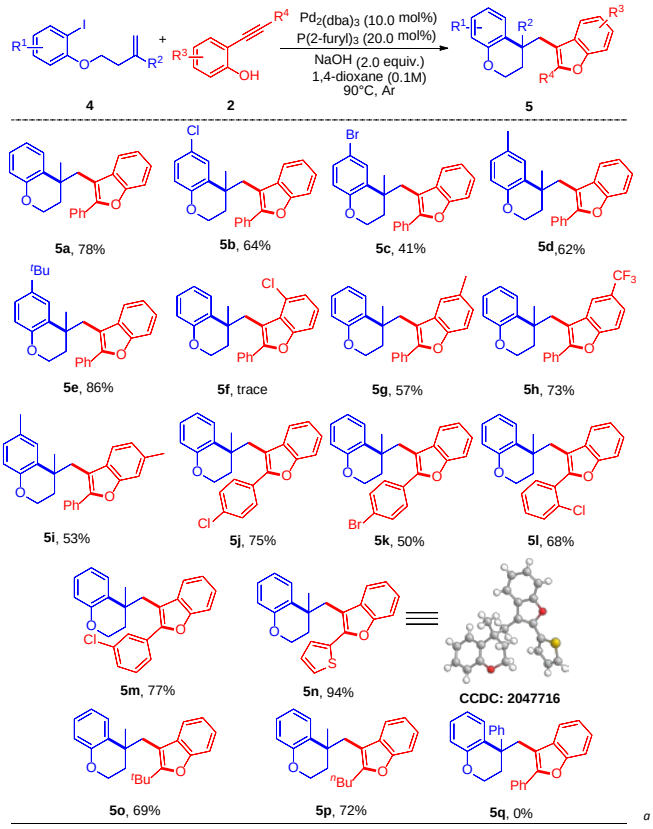
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Pd_2(dba)_3$ (10.0 mol %), P(2-furyl)$_3$ (20.0 mol %), 1,4-dioxane (2.0 mL), NaOH (0.4 mmol), 90 °C, 15 h, under an argon atmosphere. [b] Isolated yields.

products **3n-3s** in moderate to good yields, regardless of the electron-withdrawing groups and the electron-donating groups on the aromatic rings. It should be noted that a substrate bearing a strong electron-withdrawing substituent on the aromatic ring, such as a nitro group, performed satisfactorily, giving the corresponding product **3s** in high yield. Moreover, halides (Cl and Br) at *ortho*- and *meta*- positions were also investigated, and the corresponding products were obtained in 49-76% yields (**3t-3w**). Significantly, substrate containing a heteroaryl group was also found to be a suitable reaction partner affording the corresponding product **3x** in 65% isolated yield. Furthermore, in addition to aromatic ring groups, the alkyl substituents could also be introduced to the furan moiety with moderate yields (**3y and 3z**). Unfortunately, substrates **1a'** and **1b'** with an aryl and ether group at the α-position of the double bond failed to complete this transformation, none of the desired products **3a'** and **3b'** were detected. Finally, the exact structure of **3d** was further unambiguously identified by single-crystal X-ray analysis.

Moreover, this domino cyclization reaction was successfully applied to the synthesis of chroman-containing bisheterocyclic methane derivatives (Scheme 3). Integration of a chromanmoiety into heterocyclic methanes is synthetically valuable because both of them are widely utilized in the synthesis of natural products and biologically active molecules.[17] However, the synthetic methods to access these complex polyheterocyclic frameworks are very limited.

We found that under the same reaction conditions, the palladium-catalyzed domino cyclization of 1-iodo-2-((3-methylbut-3-en-1-yl)oxy)benzene **4a** with

Scheme 3 Synthesis of Chroman-Containing Bisheterocyclic Molecules [a,b]



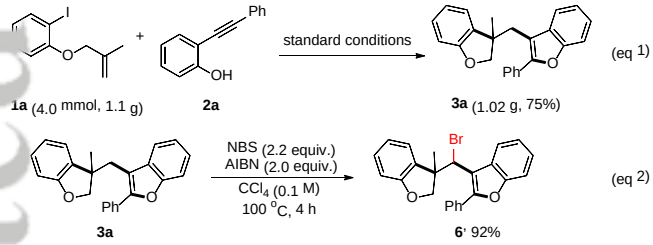
Reaction conditions: **4** (0.2 mmol), **2** (0.3 mmol), $Pd_2(dba)_3$ (10.0 mol %), P(2-furyl)$_3$ (20.0 mol %), 1,4-dioxane (2.0 mL), NaOH (0.4 mmol), 90 °C, 15 h, under an argon atmosphere. [b] Isolated yields.

ortho-alkynylphenol **2a** led to the formation of chroman-containing bisheterocyclic product **5a** in 78% yield. Subsequent investigations indicated that halogen and alkyl groups on the chroman ring at 4-

position were well-tolerated, affording the corresponding products in moderate to good yields (**5b-e**). Similarly, the generality of *ortho*-alkynylphenol partners were also evaluated. It was found that a variety of substituted *ortho*-alkynylphenols underwent the reactions successfully to afford the corresponding bisheterocyclic products **5g-m** in 50-77% yields except for the substrate with a chloro group at 3-position, which only afforded the trace of corresponding product **5f**. Notably, when an *ortho*-alkynylphenol containing a heteroaromatic functionality such as thienyl group was used as a substrate, the domino reaction proceeded well and afforded the desired product **5n** in excellent yield. The exact structure of **5n** was further unambiguously identified by single-crystal X-ray analysis. Moreover, substrates bearing a *tert*-butyl or an *n*-butyl group were also furnished this reaction smoothly, generating the desired products **5o** and **5p** in 69% and 72% yields. Furthermore, substrate **1q** with an aryl group at the α-position of the double bond was confirmed not suitable for this transformation and no desired product **5q** was detected.

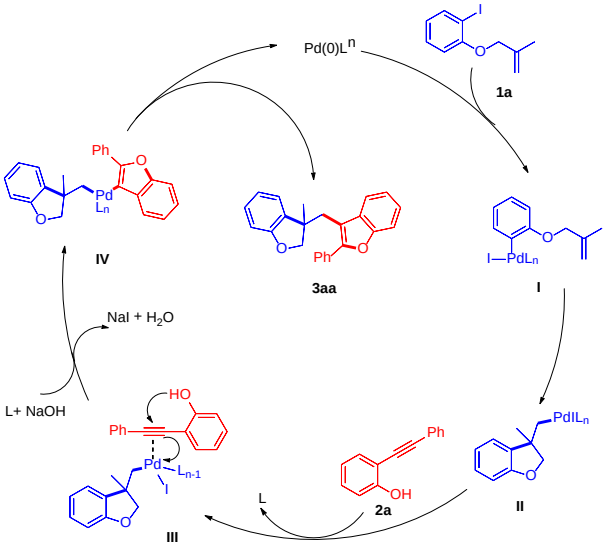
In order to evaluate the efficiency and practicality of this method, a gram-scale experiment of **1a** with **2a** was carried out, and 75% yield of desired product **3a** was isolated on the 4.0 mmol scale under the standard conditions (Scheme 4, eq 1). Moreover, a synthetic transformation of **3a** was then performed. The bromo-substituted bis(benzofuranyl)methane **6** was obtained in high yield when **3a** reacted with *N*-bromosuccinimide (NBS) in the presence of azodiisobutyronitrile (AIBN) in carbon tetrachloride at 100 °C for 4 h (Scheme 4, eq 2).

Scheme 4 Gram-Scale Experiment and Synthetic Transformations



On the basis of the above results and related literature,[13a, 18] we proposed a plausible mechanism to account for the palladium-catalyzed domino cyclization, as shown in Scheme 5. The catalytic cycle is initiated by oxidative addition of the carbon−halogen bond to Pd (0). Subsequently, the intermediate Ⅰ preferentially undergoes an intramolecular Heck cyclization, generating a primary alkylpalladium species Ⅱ. Coordination of the alkylpalladium intermediate Ⅱ to the triple bond of **2a** is accompanied by the intramolecular nucleophilic attack of the oxygen atom and generates the intermediate Ⅲ. Then, assisted by a base, intermediate Ⅲ could easily convert to the intermediate Ⅳ. Finally, reductive elimination of intermediate Ⅳ produces the product **3a** while regenerating the Pd (0) species for the catalytic cycle.

Scheme 5 Proposed Mechanism.



Conclusions

In conclusion, we have successfully developed a novel palladium-catalyzed domino cyclization reaction, which constructs bisheterocyclic methane scaffolds bearing an all-carbon quaternary center. This protocol is an effective and practical strategy to preparing new bisheterocyclic methane frameworks with potential biological and medicinal properties. Good functional group tolerance, broad substrate scope and moderate to good yields make the present protocol attractive for academia and industry. Further investigations toward this reaction for the synthesis of other bisheterocyclic methane compounds are in progress in our lab.

Experimental

A sealed tube was charged with compounds **1** or **4** (0.2 mmol, 1.0 equiv.), compounds **2** (0.3 mmol, 1.5 equiv.), $Pd_2(dba)_3$ (18.31 mg, 10.0 mol %), P(2-furyl)$_3$ (9.28 mg, 20.0 mol %) and NaOH (16.0 mg, 0.4 mmol) in 1,4-dioxane (2.0 mL) under an argon atmosphere. Then, the reaction mixture was stirred at 90 °C for 15 h. After cooling at room temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate = 100: 1, v/v)) to afford the products **3** or **5.**

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

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A Facile Construction of Bisheterocyclic Methane Scaffolds through Palladium-Catalyzed Domino Cyclization

Hongbo Qi, Kaiming Han, Shufeng Chen*

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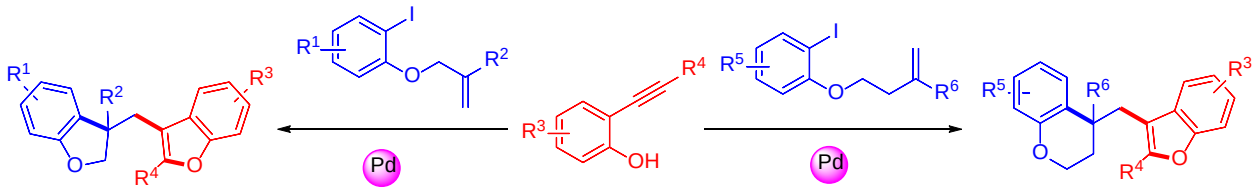

- ***Bisheterocyclic scaffolds***
- ***Broad substrate scope***
- ***Scalable***
- ***Good functional-group tolerance***
- ***Up to 94% yield***
- ***45 Examples***

A convenient palladium-catalyzed domino cyclization reaction for the construction of bis(benzofuranyl)methane scaffolds bearing an all-carbon quaternary center has been described. In the cascade process, one C(sp^2)–O bond, two C(sp^2)–C(sp^3) bonds as well as two benzofuran rings are formed in a single synthetic sequence. This methodology is also successfully extended to the synthesis of benzofuranyl methyl chromane derivatives.

