ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d5cc02682b

Received 12th May 2025,
Accepted 12th July 2025

DOI: 10.1039/d5cc02682b

rsc.li/chemcomm

Palladium-catalyzed tandem cyclization reaction: access to isoxazoline-benzofuran bis-heterocycles†

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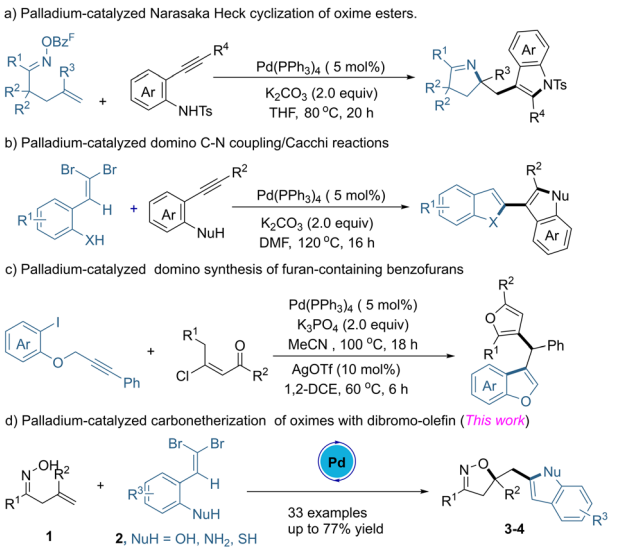
A novel palladium-catalyzed carboetherification reaction of β,γ-unsaturated ketoxime with *gem*-dihaloolefin has been developed. This process offers an efficient route for the assembly of isoxazoline-linked benzofuran/indole bis-heterocycles in moderate to good yields. The scalability of the reaction and subsequent transformations of the products highlight the synthetic potential of this developed method.

Bis-heterocycles represent an important class of molecular frameworks, which are frequently found in a wide variety of pharmaceuticals, natural products and electronic materials.[1] For example, benzimidazole-based oxadiazole (A)[2] serves as a potent inhibitor of EGFR and erbB2. Zopolrestat (B)[3] is an aldose reductase inhibitor and sarolaner[4] has been identified as a promising ectoparasiticide for the treatment of flea and tick infestations. Since diverse bis-heterocycles may possess distinct biological activities, the development of novel strategies for their preparation has attracted considerable attention.

Over the past few decades, significant efforts have been devoted to developing elegant routes for the synthesis of bis-heterocycles focusing on acid-mediated condensations and cross-coupling.[5,6] The harsh reaction conditions limited their further exploration and application. As a remarkable alternative strategy, transition-metal-catalyzed cyclization has proven to be a powerful strategy for the synthesis of bis-heterocycles.[7–11] For example, the group of Lautens developed a novel palladium-catalyzed Narasaka–Heck cyclization cross-coupling for the rapid assembly of unsymmetrical bis-heterocycles by the use of alkene-tethered oxime esters (Scheme 1a).[9] Recently, the same group described the successful realization of this strategy to access a broad class of mixed bis-heterocycles *via* palladium-catalyzed domino Cacchi reactions (Scheme 1b).[10] In 2024, Sun's group described a novel method to access a range of biologically important furan-linked methylene oxindoles utilizing alkyne-tethered carbamoyl chlorides and (*E*)-β-chloroenones as starting materials (Scheme 1c).[11] Despite these achievements, additional efforts in developing new strategies for their efficient synthesis are highly desirable. Herein, we propose a potential palladium-catalyzed carbonetherization strategy involving a tandem intramolecular cross-coupling reaction of dihalogenated alkenes (Scheme 1d). This approach could serve as a



Scheme 1 Strategies for the synthesis of bis-heterocycles. (a) Palladium-catalyzed Narasaka Heck cyclization of oxime esters. (b) Palladium-catalyzed domino C–N coupling/Cacchi reactions. (c) Palladium-catalyzed domino synthesis of furan-containing benzofurans. (d) Palladium-catalyzed carbonetherization of oximes with dibromoolefin.

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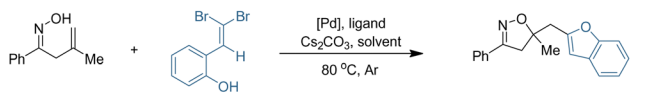
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for the substrates and products. CCDC 2449687. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5cc02682b

viable method for synthesizing benzofuran and isoxazoline-type bicyclic compounds.

At the outset, we employed ethyl (*E*)-3-methyl-1-phenylbut-3-en-1-one oxime (**1a**) and 2-(2,2-dibromovinyl)phenol (**2a**) as the model substrates to optimize the reaction conditions. Remarkably, the target product **3a** was obtained in 19% yield by the use of $Pd_2(dba)_3$ as a catalyst, and Cs_2CO_3 as a base at 80 °C in toluene for 12 h (Table 1, entry 1). Encouraged by this positive result, we then demonstrated the effect of ligands, and the results revealed that Ruphos improved the yield of **3a** to 62% (Table 1, entries 2–5). Interestingly, replacing the solvent toluene with ethanol, the yield of **3a** could be further increased to 65% (entry 6). Then, several palladium sources such as $[Pd(allyl)Cl]_2$, $Pd(acac)_2$ and $Pd(OAc)_2$, were tested (Table 1, entries 7–9). The yield dramatically reached 72% yield by the use of 10 mol% of $Pd(OAc)_2$ (Table 1, entry 9). Subsequently, other solvents including MeOH, THF and MeCN were used, but all were inferior to ethanol (Table 1, entries 10–12). Replacing Cs_2CO_3 with K_2CO_3 or CsOAc, the product **3a** was not afforded with good results (Table 1, entries 13 and 14). Later, an unexpected discovery was made when screening the ethanol solvents with varying water content. The results indicated that 95% ethanol worked remarkably well, enabling the target product to be isolated in 75% yield (Table 1, entry 16). Notably, 5 mol% $Pd(OAc)_2$ was used in this reaction, and the yield of product **3a** was decreased to 60% (Table 1, entry 17). Moreover, when the reaction was carried out on a 0.3 mmol scale, the yield remained stable (Table 1, entry 18). Additionally, others control experiments did not achieve better results (for details, see ESI†).

Table 1 Optimization of the reaction conditions[a]

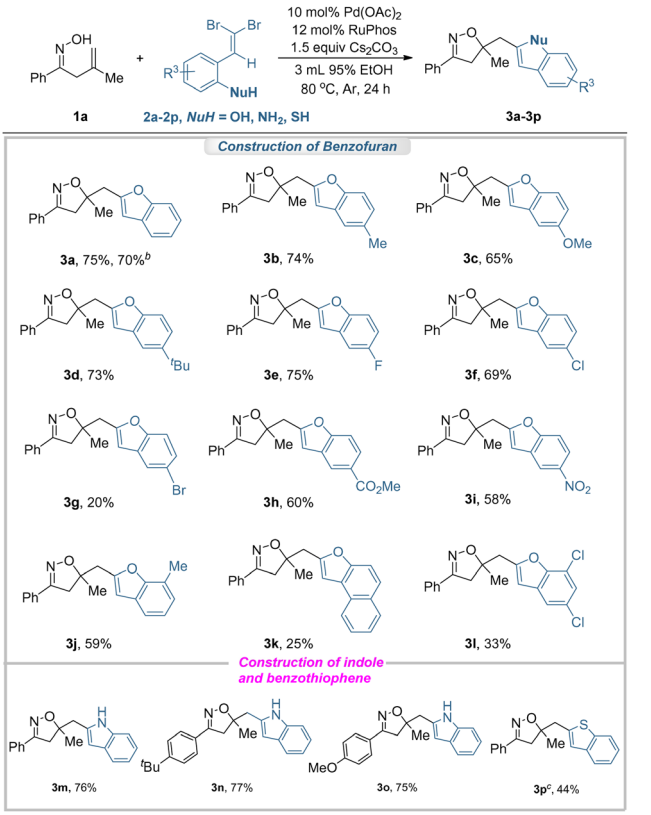


1a 2a 3a

Entry	Pd catalyst	Ligand	Solvent	Yield[b] (%)
1	$Pd_2(dba)_3$	—	Toluene	19
2	$Pd_2(dba)_3$	XantPhos	Toluene	60
3	$Pd_2(dba)_3$	DpePhos	Toluene	33
4	$Pd_2(dba)_3$	CyJohnPhos	Toluene	45
5	$Pd_2(dba)_3$	RuPhos	Toluene	62
6	$Pd_2(dba)_3$	RuPhos	EtOH	65
7	$[Pd(allyl)Cl]_2$	RuPhos	EtOH	63
8[c]	$Pd(acac)_2$	RuPhos	EtOH	68
9[c]	$Pd(OAc)_2$	RuPhos	EtOH	72
10[c]	$Pd(OAc)_2$	RuPhos	MeOH	68
11[c]	$Pd(OAc)_2$	RuPhos	THF	41
12[c]	$Pd(OAc)_2$	RuPhos	MeCN	34
13[cd]	$Pd(OAc)_2$	RuPhos	EtOH	56
14[ce]	$Pd(OAc)_2$	RuPhos	EtOH	31
15[c]	$Pd(OAc)_2$	RuPhos	Dry EtOH	72
16[c]	$Pd(OAc)_2$	RuPhos	95% EtOH	75
17	$Pd(OAc)_2$	RuPhos	95% EtOH	60
18[f]	$Pd(OAc)_2$	RuPhos	95% EtOH	75

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.24 mmol, 1.2 equiv.), Cs_2CO_3 (0.3 mmol, 1.5 equiv.), Pd catalyst (5 mol%) and ligand (12 mol%) in solvent (2.0 mL) at 80 °C under Ar for 12 h. [b] Isolated yield. [c] Pd catalyst (10 mol%) was used. [d] K_2CO_3 was used. [e] CsOAc was used. [f] **1a** (0.3 mmol, 1.0 equiv.), **2a** (0.36 mmol, 1.2 equiv.), Cs_2CO_3 (0.45 mmol, 1.5 equiv.), $Pd(OAc)_2$ (10 mol%) and RuPhos (12 mol%) in 95% EtOH (3.0 mL) at 80 °C under Ar for 24 h.

After optimizing the reaction conditions, we next investigated the generality of the current carbon-etherification reaction. As shown in Scheme 2, most of the 2-(2,2-dibromovinyl)phenols bearing an electron-donating group (–Me, –OMe and –^{t}Bu) and electron-withdrawing group (–F, –Cl) at the C4-position reacted smoothly with β,γ-unsaturated ketoxime **1a**, and the corresponding isoxazoline-linked benzofuran bis-heterocycles **3b–3f** were afforded in moderate to good yields (65–75% yields). We found that the reaction proceeded inefficiently when using the 2-(2,2-dibromovinyl)phenol derivative bearing a bromo group because of delivering unidentified by-products (**3g**, 20%). Importantly, strong electron-withdrawing groups including ester and nitro all could be tolerated well to afford the desired products **3h–3i** in 58–60% yields. We were also pleased to find that the *ortho*-substituted substrate was also a good reaction partner, yielding **3j** in 59% yield. Additionally, the disubstituted substrate and naphthyl group were compatible, and the products were formed in low yields (**3k**, 25%; **3l**, 33%). Notably, 2-(2,2-dibromovinyl)aniline exhibited excellent compatibility, and led to the corresponding bis-heterocyclic compound products **3m–3o** in good yields (75–77%). In addition, 2-(2,2-dibromovinyl)benzenethiol and 2-(2,2-dichlorovinyl)phenol were also compatible, the products **3p** and **3a** were obtained in 44% and 70% yields, respectively.



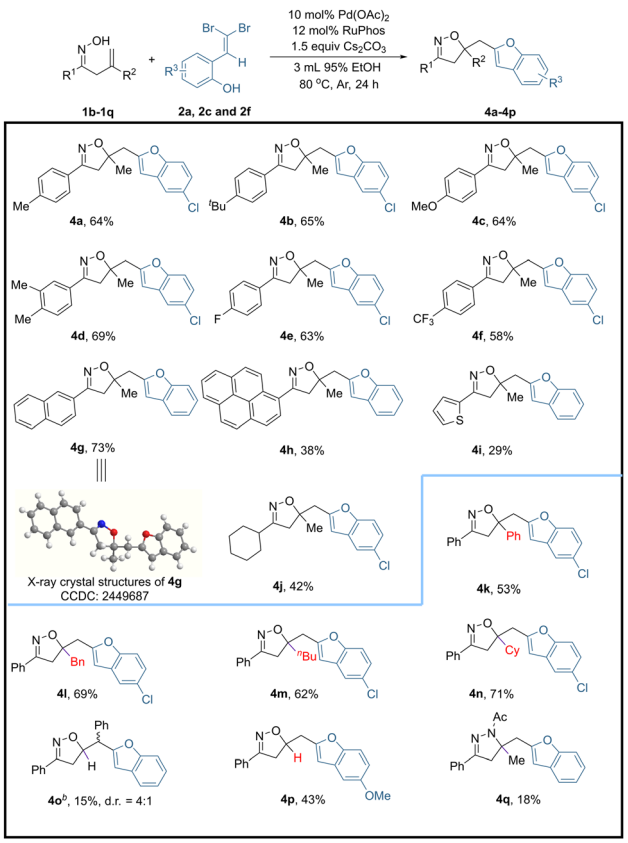
Scheme 2 Substrate scope of *gem*-dihaloolefin.[a] [a] Reaction conditions: **1a** (0.3 mmol, 1.0 equiv.), **2** (0.36 mmol, 1.2 equiv.), Cs_2CO_3 (0.45 mmol, 1.5 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), RuPhos (0.036 mmol, 12 mol%), and 95% EtOH (3.0 mL) at 80 °C under Ar for 24 h. [b] 2-(2,2-Dichlorovinyl)phenol was used. [c] Toluene was used as a solvent.

Subsequently, the electronic effect on the aromatic ring in the β,γ-unsaturated ketoximes was tested in this transformation (Scheme 3). Similarly, a large range of the corresponding bis-heterocyclic products bearing a methyl, methoxyl, *tert*-butyl, fluoro or trifluoromethyl were formed in satisfactory yields (**4a–4f**, 58–69%). In addition, the naphthyl-substituted β,γ-unsaturated ketoxime proceeded smoothly, delivering **4g** in 73% yield. Meanwhile, the structure of **4g** was confirmed through X-ray crystal structure analysis.[12] Notably, the fused ring, heterocycle and alicyclic ring were all tolerated well, and the corresponding products **4h**, **4i** and **4j** were afforded 38%, 29% and 42% yields, respectively. It is particularly worthy of note that both aryl-substituted alkenes and alkyl-substituted alkenes were applicable, and the corresponding products **4k–4n** were all formed in acceptable yields (53–71%). Moreover, an internal alkene gave the product **4o** in low yield (15%) with *d.r.* 4 : 1. Notably, alkenyl hydrazone was also tolerated, and the dihydropyrazole link benzofuran product **4q** was obtained in 18% yield.

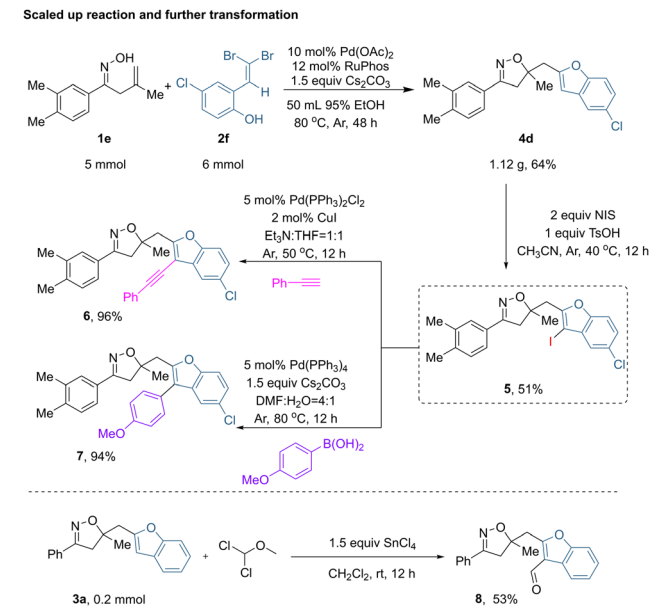
To demonstrate the practical value of this reaction, a Gram-scale reaction of **1e** with **2f** was conducted, and 1.12 g of the product **4d** was formed with a yield of 64% (Scheme 4). Furthermore, iodination of **4d** in the presence of NIS resulted in the formation of **5** in 51% yield, which then underwent Sonogashira and Suzuki coupling reaction to access alkyne-substituted product **6** and aryl-substituted product **7** in the yields of 96% and 94%, respectively. Besides, formylation product benzofuran-isoxazoline bis-heterocycle **8** was obtained in a moderate yield of 53% from **3a** and 1,1-dichlorodimethyl ether in the presence of tin tetrachloride, which could be further transformed into more complex structures.

Moreover, mechanistic studies detailing the Pd(0)-catalyzed isoxazoline-benzofuran bis-heterocycle-forming sequence were explored. When **2a** was subjected to Cs_2CO_3 under standard conditions, 23% yield of **9** was afforded (Scheme 5, eqn (1)). In addition, β,γ-unsaturated ketoxime **1a** and 2-bromobenzofuran **9** were tested under the standard conditions, affording 74% yield of **3a** (Scheme 5, eqn (2)). Moreover, alkenyl ketoxime **(*Z*)-1q-D** and **(E)-1q-D** with **2c** were conducted respectively in (Scheme 5, eqn (3) and (4)). The product **4p-D** had 3 : 2 d.r. indicating that both *syn*- and *anti*-addition pathways operate in this carbonetherization procedure.[13] The major product showed a *syn*-addition pathway in this reaction,[14] supported by the J_{H-H} coupling constant (for additional details, please see ESI†).

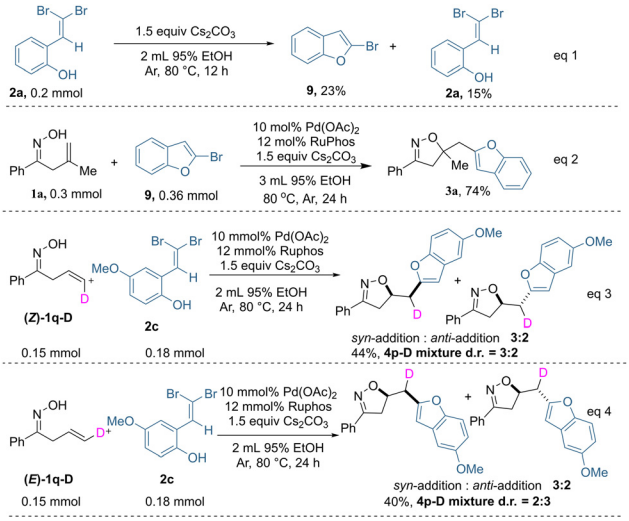
Based on our experimental results and previous work,[14–16] the possible mechanism is proposed in Scheme 6. The initial oxidative addition of Pd(0) to 2-(2,2-dibromovinyl)phenol (**2a**) gave the Pd^{II} intermediate **I**. Then intermediate **I** followed by a C–O coupling sequence delivers the benzofuran intermediate **II**. However, Cs_2CO_3-mediated **1a** to generate 2-bromobenzofuran **9**, where Pd(0) undergoes an oxidative addition to generate intermediate **II**. Then ligand exchange occurs between complex **II** and **1a** resulting in complex **III**. Then, complex **III** undergoes a *syn*-addition pathway through olefin insertion to give complex **IV** (path a). Another complete *anti*-addition pathway catalytic cycle by Pd(II) complex **II** electrophilic activation of alkene and oxime ether attack of the alkene afford Pd complex **IV** in path b. Finally, reductive elimination of **IV** generates the coupling product **3a**.



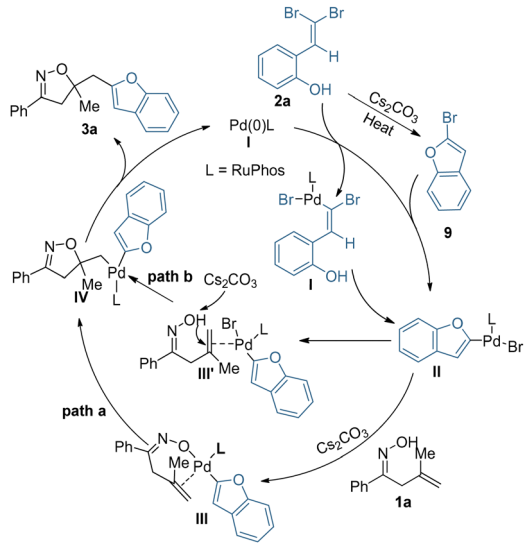
Scheme 3 Substrate scope of β,γ-unsaturated ketoxime. [a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.36 mmol, 1.2 equiv.), Cs_2CO_3 (0.45 mmol, 1.5 equiv.), $Pd(OAc)_2$ (0.03 mmol, 10 mol%), RuPhos (0.036 mmol, 12 mol%), and 95% EtOH (3.0 mL) at 80 °C under Ar for 24 h. [b] Toluene was used as a solvent.



Scheme 4 Gram-scale and synthetic transformations.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed mechanism.

In summary, we have developed a novel palladium-catalyzed carboetherification reaction of β,γ-unsaturated ketoxime with *gem*-dihaloolefin for the efficient synthesis of isoxazoline-link-benzofuran/indole bis-heterocycles. A wide range of functional groups bearing different electron-donating or electron-withdrawing groups were well tolerated under the standard reaction conditions. Furthermore, the scalability of the reaction and subsequent transformations of the products highlight the synthetic potential of this method. The asymmetric exploration of this strategy is ongoing in our lab.

We are grateful to the National Natural Science Foundation of China (22471236, 22101249), Natural Science Foundation of Jiangsu Province (BK20200918), and Lvyang Jinfeng Talents Attracting Plan.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included in the ESI.†

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