Palladium-catalyzed [4 + 4] cycloaddition of homo-TMM all-carbon 1,4-dipole precursors for the construction of benzofu-ro[3,2-b]azocines

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May 31, 2023

Abstract

We developed a novel Pd-catalyzed [4 + 4] cycloaddition of benzofuran-derived azadienes with homo-TMM all-carbon 1,4-dipoles in situ generated from α-allyl malonate derivatives, affording an array of benzofuro[3,2-b]azocines with good to excellent yields (up to 96%) and exclusive regioselectivities. This methodology featured mild reaction conditions and good functional group tolerance. The synthetic utility was demonstrated by a gram-scale reaction. Furthermore, the catalytic asymmetric [4 + 4] cycloaddition version has also been explored.

Cite this paper: *Chin. J. Chem.* **2023** , *41* , XXX—XXX. **DOI: 10.1002/cjoc.202300XXX**

Palladium-Catalyzed [4 + 4] Cycloaddition of Homo-TMM All-Carbon 1,4-Dipole Precursors for the Construction of Benzofuro[3,2-*b*]azocines

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Keywords

Pd-catalyzed | [4 + 4] cycloaddition | Homo-TMM 1,4-dipoles | Benzofuro[3,2-*b*]azocines

Comprehensive Summary

We developed a novel Pd-catalyzed [4 + 4] cycloaddition of benzofuran-derived azadienes with homo-TMM all-carbon 1,4-d

Background and Originality Content

The eight-membered azacycles are widely presented in various natural products and bioactive pharmaceuticals.[1-6] Due to their significant importance, concise and efficient synthetic methods are in high demand for the synthesis of eight-membered azacycles.[7] In recent years, the creation of eight-membered ring systems has been facilitated easily by the implementation of transition-metal-catalyzed high-order

cycloadditions,[8] which has attracted much attention.

Scheme 1 Palladium-catalyzed cycloadditions of TMM 1,n -dipole precursors.

Trimethylenemethane (TMM) is an effective dipole with a wide range of applications that allows for the synthesis of highly functionalized cyclic compounds.[9] To date, an assortment of TMM dipole precursors has been developed to enable the efficient construction of cyclic compounds (Scheme 1a), encompassing methylene cyclopropanes,[10] 2-substituted allyl carbonates (Trost-TMM),[9h,11,12] γ -methylidene-δ -valerolactones,[8g,13]2-methylidenetrimethylene carbonates,[14]pyrrolidines,[15]2-methylene-1-indanols.[16] Among various types of TMM dipole precursors, Trost-TMM is the most extensively investigated one, which served as an efficient three-carbon unit in Pd-catalyzed [3+n] cycloadditions.[9h] In this field, our group successfully realized several asymmetric [3 + 4] cycloadditions of Trost-TMM precursors with different 4-atom synthons, furnishing a series of fused azepines or cycloheptanes with excellent regio-, diastereo- and enantioselectivities in recent years (Scheme 1b).[17] Based on the well-developed conventional Trost-TMM, in 2020, the Trost group developed a novel homo-TMM all-carbon 1,4-dipole precursor, which realized a Pd-catalyzed [4 + 2] cycloaddition to afford chiral cyclohexanes or spiro heptanes (Scheme 1c).[18] However, the transition-metal-catalyzed high-order cycloaddition of this novel homo-TMM all-carbon 1,4-dipole precursor for the synthesis of medium-sized rings has yet to be investigated.

Scheme 2 Design of the Pd-catalyzed [4 + 4] cycloaddition of homo-TMM all-carbon 1,4-dipole precursors with benzofuran-derived azadienes.

Inspired by Trost's work in 2020 and in conjunction with our continuing efforts in the construction of medium-sized rings, we envisaged that the homo-TMM all-carbon 1,4-dipole precursors may undergo a [4 + 4] cycloaddition with azadienes to form azocines (Scheme 2). However, the inhibition of the regioselectivity induced by the potentially rival [4 + 2] cycloaddition of imines or alkenes in azadienes presents considerable difficulty in this process. Herein, we present the Pd-catalyzed [4 + 4] cycloaddition of homo-TMM all-carbon 1,4-dipole precursors with benzofuran-derived azadienes, providing an efficient and convenient approach to access benzofuro[3,2-b]azocines with exclusive regioselectivitives.

Results and Discussion

Initially, the reaction of benzofuran-derived azadiene **1a** , derived from benzofuran, with dimethyl malonate derivative **2a**was conducted to screen the reaction conditions. In the presence of 5 mol% $Pd_2(dba)_3$ as the catalyst, 11 mol% diphosphine ligand **L1** or **L2** in DCM for 1 h**,** no desired target product **3a** was detected (Table 1, entries 1 and 2). Subsequently, the screening of preliminary monophosphine ligands showed that ligand **L3** turned out to be a suitable ligand, providing **3a** in 91% yield with exclusive regioselectivity (Table 1, entries 3-5). It is noteworthy that using $Pd(PPh_3)_4$ instead of the combination of $Pd_2(dba)_3$ with ligand **L3**further enhanced the reaction efficiency, affording **3a** in 95% yield (Table 1, entry 6). A series of commercial solvents, including DCE, THF, and toluene, were used in the [4 + 4] cycloaddition reaction, but none of them afforded better results than DCM (Table 1, entries 7-9). Lowering the catalyst loading from 10 mol% to 2.5 mol% did not affect the reaction efficiency, and achieved optimal reaction outcomes in terms of yield (95% NMR yield and 95% isolated yield) (Table 1, entries 10-12).

Table 1 Optimization of reaction conditions of the reaction.[a]

entry	catalyst	**ligand**	solvent	yield (%)[b]
1	$Pd_2(dba)_3$	**L1**	DCM	ND
2	$Pd_2(dba)_3$	**L2**	DCM	ND
3	$Pd_2(dba)_3$	**L3**	DCM	91
4	$Pd_2(dba)_3$	**L4**	DCM	89
5	$Pd_2(dba)_3$	**L5**	DCM	87
6[c]	$Pd(PPh_3)_4$	-	DCM	95
7[c]	$Pd(PPh_3)_4$	-	DCE	93

entry	catalyst	**ligand**	solvent	yield (%)[b]
8[c]	$Pd(PPh_3)_4$	-	THF	94
9[c]	$Pd(PPh_3)_4$	-	toluene	72
10[d]	$Pd(PPh_3)_4$	-	DCM	95
11[e]	$Pd(PPh_3)_4$	-	DCM	95 (95)[g]
12[f]	$Pd(PPh_3)_4$	-	DCM	88

[a] Reaction conditions: **1a** (0.10 mmol),**2a** (0.15 mmol), $Pd_2(dba)_3$ (5 mol%) and **ligand** (11 mol%) in 1.0 mL of solvent under an N_2 atmosphere at 25 °C for 1 h.[b] Yield of **3a** was determined by^{1}H NMR spectroscopic analysis of the crude product with 1,3,5-trimethoxybenzene as an internal standard.[c] $Pd(PPh_3)_4$ (10 mol%).[d] $Pd(PPh_3)_4$ (5 mol%).[e] $Pd(PPh_3)_4$ (2.5 mol%).[f] $Pd(PPh_3)_4$ (2.0 mol%). [g] Isolated yield of **3a** on a 0.2 mmol-scale reaction.

Under the optimal reaction conditions in hand, the substrate scope of benzofuran-derived azadienes **1** was investigated and the results were summarized in Scheme 3. Benzofuran-derived azadienes **1**bearing different *N* -protecting groups participated in the reaction smoothly, leading to the corresponding products **3b**(77% yield) and **3c** (90% yield), respectively. In addition, azadienes **1** bearing various electron-withdrawing groups (fluoro, chloro, bromo, and cyano) or electron-donating (methyl and methoxy) at the *para* , *meta* or *ortho* position of the aryl ring were well accommodated. The target products**3d -3n** were delivered in 79-96% yields. It was noteworthy that 2-Cl and 2-Me-substituted substrates **1l** and**1m** underwent the reaction smoothly, affording the target products **3l** (80% yield) and **3m** (79% yield), respectively, which is presumably attributed to the steric effect. Naphthyl and furanyl moieties also facilitated the formation of**3o** (92% yield) and **3p** (90% yield), respectively. In a similar fashion, the reactions of benzofuran-derived azadienes**1** bearing various substituents (bromo, methoxy, and chloro) at the C4-C7 positions of the benzofuran ring also efficiently proceeded to afford the target products **3q -3u** in 83-92% yields.

Scheme 3 Substrate scope for Pd-catalyzed [4 + 4] cycloaddition of benzofuran-derived azadienes **1** and dimethyl malonate derivative **2a** .

Then, the protocol generality was explored by extending the substrate scope of homo-TMM donors **2** (Scheme 4). The analog of**2a** , that is, substituted malononitrile **2b** , exhibited a good reactivity to form the target products **3v** (91% yield) and**3w** (75% yield), respectively. Compared to the symmetrical malonate-type substrates, the cyano-substituted ester enolate**2c** obviously deteriorated the reaction efficiency, leading to**3x** in a moderate yield (41% yield). Unfortunately, the more sterically hindered *t* -butyl ester counterpart **2d** was used, and only a trace amount of the desired 8-membered product**3y** was detected. The bis(phenylsulfonyl)methane derivative**2e** also proved to be unreactive in the [4 + 4] cycloaddition reaction. The molecular structure of compound **3a**was further confirmed by the *X* -ray single crystal crystallographic determination (CCDC 2235088, see the SI for details).

Scheme 4 Substrate scope for Pd-catalyzed [4 + 4] cycloaddition of benzofuran-derived azadienes **1** and dimethyl malonates derivatives **2** .

To further demonstrate the versatility and effectiveness of this catalytic system, a gram-scale reaction of compound **3a** with a 2.5 mol% catalyst loading was performed, providing an acceptable yield (91% yield) (Scheme 5a). Subsequently, the 4-toluenesulfonyl (Ts) group of **3a** could be removed in the presence of Mg in MeOH, yielding the corresponding benzofuro[3,2-*b*]azocine **4** in 86% yield.[19]

Scheme 5 Demonstration of the synthetic utility.

Furthermore, the catalytic asymmetric [4 + 4] cycloaddition version has also been explored, and several chiral ligands were screened (see Table S1 for the details). The reaction provided moderate enantioselectivity (61% ee) with $Pd_2(dba)_3$ as the catalyst in the presence of chiral ligand **L*** (Scheme 6).

Scheme 6 The asymmetric [4 + 4] cycloaddition.

A mechanism was proposed to illustrate the Pd-catalyzed [4 + 4] cycloaddition (Scheme 7). First, the initial oxidative addition of a catalytically active Pd(0) species with substrate **2a** and the deproton process by the *tert* -butoxy anion forms the key Pd^{II}-π-allyl complex intermediate **A** . Then, the attack by the carboanion of intermediate **A** to azadiene**1a** provides aromatization intermediate **B** . Subsequently, the addition of a nitrogen anion to π-allyl-palladium in aromatization intermediate **B** affords the eight-membered ring**3** by intramolecular cyclization and regenerates the active palladium catalyst for the next catalytic cycle.

Scheme 7 Proposed mechanism.

Conclusions

In summary, we have developed an efficient Pd-catalyzed [4 + 4] cycloaddition of homo-TMM all-carbon 1,4-dipoles with benzofuran-derived azadienes, affording various benzofuro[3,2-*b*]azocines in good to excellent yields (up to 96% yield) with exclusive regioselectivities. The reaction proceeded with broad substrate scope and excellent functional group tolerance. The high-order cycloaddition of homo-TMM all-carbon 1,4-dipoles provided a convenient and mild route to the synthesis of 8-membered rings. Further investigations on the asymmetric [4 + 4] cycloaddition are currently underway in our laboratory.

Experimental

Under a nitrogen atmosphere, benzofuran-derived azadienes **1** (0.2 mmol) and $Pd(PPh_3)_4$ (15.4 mg, 0.005 mmol) were added sequentially into a flame-dried Schlenk tube equipped with a magnetic stir bar. The tube was evacuated and back-filled with nitrogen for three times. Then the anhydrous DCM (2.0 mL) was added *via*syringe sequentially and the resulting mixture stirred at 25 . Then, TMM precursors **2** (0.3 mmol) was added. After completion, the mixture was concentrated and purified by column chromatography (petroleum ether/ dichloromethane = 4:1) to give the corresponding cycloadducts **3** .

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

Acknowledgement

We are grateful for financial support from National Key Research and Development Program of China (2021YFA0804900), the NSFC (22171082, 21971062), the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (No. 2022R01007), and Shanghai Frontiers Science Center of Optogenetic Techniques for Cell Metabolism.

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Manuscript received: XXXX, 2023 Manuscript revised: XXXX, 2023 Manuscript accepted: XXXX, 2023 Accepted manuscr

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Palladium-catalyzed [4 + 4] cycloaddition of homo-TMM all-carbon 1,4-dipole precursors for the constructi
We developed a novel Pd-catalyzed [4 + 4] cycloaddition of benzofuran-derived azadienes with homo-TMM all-carbon 1,4-d