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# Palladium-catalyzed decarboxylative (4 + 3) cycloadditions of bicyclobutanes with 2-alkylidenetrimethylene carbonates for the synthesis of 2-oxabicyclo[4.1.1]octanes†

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While cycloaddition reactions of bicyclobutanes (BCBs) have emerged as a potent method for synthesizing (hetero-)bicyclo[*n*.1.1]alkanes (usually  $n \leq 3$ ), their utilization in the synthesis of bicyclo[4.1.1]octane derivatives (BCOs) is still underdeveloped. Here, a palladium-catalyzed formal (4 + 3) reaction of BCBs with 1,4-O/C dipole precursors for the synthesis of oxa-BCOs is described. Unlike previous catalytic polar (3 + X) cycloadditions of BCBs, which are typically achieved through the activation of BCB substrates, the current reaction represents a novel strategy for realizing the cycloaddition of BCBs through the activation of the "X" cycloaddition partner. Moreover, the obtained functionalized oxa-BCOs products can be readily modified through various synthetic transformations.

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## Introduction

Bridged ring systems have long been coveted by organic and medicinal chemists due to their versatility as the basic structures of natural products and pharmaceuticals.<sup>1</sup> Given the success of the "escape from flatland" concept in medicinal chemistry,<sup>2</sup> there is a growing interest in bicyclo[*n*.1.1]alkanes as synthetic targets due to their rigid conformation and metabolic stability, which show great potential in replacing benzene rings.<sup>3</sup> For instance, bicyclo[1.1.1]pentanes (BCPs),<sup>4</sup> bicyclo[2.1.1]hexanes (BCHs),<sup>5</sup> and bicyclo[3.1.1]heptanes (BCHeps)<sup>6</sup> can mimic *para*-, *ortho*-, *meta*- and multi-substituted benzenoids in drug design, contingent on their substitution patterns. Additionally, Mykhailiuk's survey showed that incorporating heteroatoms (O- or N-) into BCH and BCHep analogues generally resulted in positive changes in water solubility, metabolic stability, and lipophilicity.<sup>5a-c,6a</sup> Therefore, developing new strategies to synthesize bicyclo[*n*.1.1]alkane derivatives is highly desirable and will expedite their application in new drug discovery.

The first cycloaddition reaction of bicyclo[1.1.0]butanes (BCBs) was reported in 1966 by Blanchard.<sup>7</sup> Only in recent years

has it emerged as a crucial synthetic platform for constructing (hetero-)bicyclo[*n*.1.1]alkane skeletons, owing to the pioneering scientific contributions of Wipf,<sup>8</sup> Glorius,<sup>9</sup> Brown,<sup>10</sup> Leitch,<sup>11</sup> Procter,<sup>12</sup> Molander,<sup>13</sup> Li,<sup>14</sup> Wang,<sup>15</sup> Waser,<sup>16</sup> Studer,<sup>17</sup> L. Deng,<sup>18</sup> Feng,<sup>19</sup> W.-P. Deng,<sup>20</sup> Bach,<sup>21</sup> Jiang<sup>22</sup> and others.<sup>23</sup> Generally, there are five state-of-the-art strategies for the cycloaddition of BCBs to obtain (hetero-)bicyclo[*n*.1.1]alkanes: (a) the formal (3 + 1) cycloaddition of BCBs with dihalocarbenes for synthesizing BCPs pioneered by Applequist,<sup>24a</sup> Mykhailiuk,<sup>24b,c</sup> Ma<sup>24d,e</sup> and Anderson;<sup>24f</sup> (b) thermally-driven (3 + 2) cycloaddition of BCBs for the synthesis of (hetero-)BCHs;<sup>7,8,23a-c</sup> (c) energy transfer [ $2\pi + 2\sigma$ ]<sup>9a-d,10,21</sup> and [ $2\sigma + 2\sigma$ ]<sup>16</sup> photocycloadditions; (d) electron transfer catalysis to construct BCHs and BCHeps *via* formal (3 + 2)<sup>12,14a,15,23d,e</sup> and (3 + 3)<sup>13,14b</sup> cycloaddition of BCBs. (e) Polar cycloadditions of BCBs.<sup>9f,g,11,17-20</sup> Despite substantial advancements, the cycloadditions of BCBs continue to encounter numerous obstacles. For example, (i) in contrast to the well-established formal (3 + 1), (3 + 2), and (3 + 3) cycloadditions of BCBs, the higher-order (3 + *n*) ( $n > 3$ ) cycloaddition of BCBs to saturated bicyclo[*n*.1.1]alkanes is still uncommon in the literature (Scheme 1a).<sup>25</sup> Currently, there is only one documented formal (5 + 3) example of BCBs reacting with thiophenes to form unsaturated bicyclic rings through a photoredox-induced radical pathway (Scheme 1a, left).<sup>9h</sup> This rarity may be attributed to the high degree of transannular strain and unfavorable entropic factors during the formation of medium-sized rings. Although Grygorenko's elegant research has shown that bicyclo[4.1.1]octane frameworks (BCOs) are potential bioisosteres of substituted benzene,<sup>3c</sup> there is no report on the (4 + 3) cycloaddition of BCBs for preparing these valuable C(sp<sup>3</sup>)-rich bridged ring systems. (ii) The seminal contributions of Leitch's

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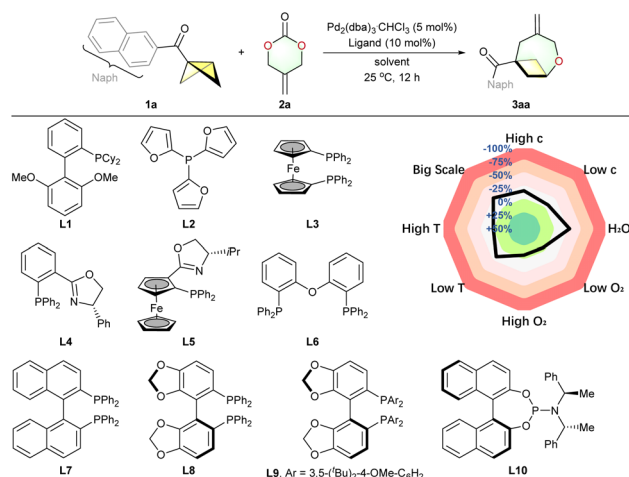
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In the field of O-heterocyclic synthesis, Pd-catalyzed (4 + *n*) dipolar cycloadditions of 2-alkyldienetrimethylene carbonates (ADTMCs)<sup>28</sup> have emerged as a powerful method for synthesizing monocyclic rings,<sup>29a,b</sup> fused rings,<sup>29c-e</sup> and spirocyclic scaffolds.<sup>29f-j</sup> However, their application in constructing bridged ring systems is extremely rare. As part of our ongoing research program on designing new reactions involving strained rings,<sup>19,30</sup> this paper presents the first hetero-(4 + 3) cycloadditions of BCBs with 1,4-O/C dipole species generated catalytically

Although (4 + 2) cycloadditions of ADTMCs are well established,<sup>28</sup> the corresponding (4 + 3) reactions are relatively rare. Currently, there have been only two successful examples.<sup>29g,h</sup> However, the (4 + 3) reactions reported independently by Chen<sup>29g</sup> and Li<sup>29h</sup> are not compatible with substituted ADTMCs. This result can be attributed to the additional challenges in

Table 1 Selected examples of the optimization of reaction conditions<sup>a</sup>

Entry	Ligand	Solvent	Conversion of 1a <sup>b</sup> (%)	Conversion of 2a <sup>b</sup> (%)	Yield <sup>b</sup> (%)
1	L1	Toluene	36	100	0
2	L2	Toluene	<5	100	0
3	L3	Toluene	34	100	0
4	L4	Toluene	42	100	11
5	L5	Toluene	58	100	14
6	L6	Toluene	44	100	0
7	L7	Toluene	50	100	0
8	L8	Toluene	10	100	0
9	L9	Toluene	66	100	49
10	L10	Toluene	8	73	0
11	L9	PhCl	75	100	40
12	L9	CH <sub>2</sub> Cl <sub>2</sub>	30	100	10
13	L9	EtOAc	64	100	53
14	L9	THF	85	100	71
15	L9	1,4-Dioxane	>99	100	96

<sup>a</sup> Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (5 mol%) and ligand (10 mol%), solvent (2 mL), 25 °C, under N<sub>2</sub> for 12 h.

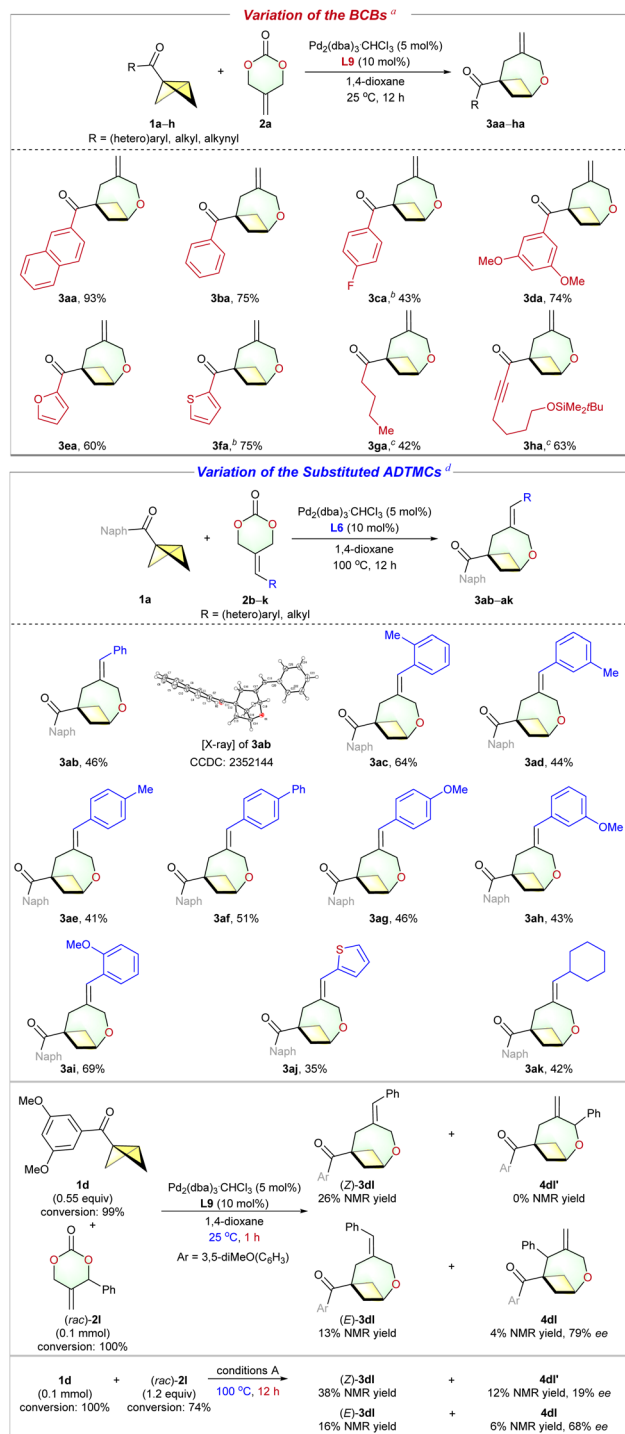
<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> as the internal standard.

controlling regioselectivity (such as the by-products **4ab** and **5ab** in Scheme 3) and *Z/E* selectivity when using the substituted ADTMCs as oxa-1,4-dipole synthons. Under conditions A, **1a** and phenyl-2-alkylidenetrimethylene carbonate **2b** were converted into product **3ab**, but the yield was low (13% NMR yield). The structure and *E/Z* geometry of the C=C bond in **3ab** were determined using X-ray single crystal diffraction.<sup>35</sup> After numerous attempts, the optimized reaction conditions B successfully facilitated the (4 + 3) cycloaddition of **1a** and **2b**, resulting in a 53% NMR yield of the desired **3ab** together with some unidentified by-products (<10% NMR yield) (Scheme 3 bottom, see the ESI for details). Next, we investigated the reaction of the substituted ADTMCs with substituents at the *ortho*-, *meta*- or *para*-position of the phenyl ring (Scheme 2, middle, **3ab-ai**). In general, substrates (**3ac** and **3ai**) with a substituent group at the *ortho*-position of the phenyl ring showed higher yields compared to substrates with *meta*- or *para*-substituted phenyl rings. Gratifyingly, the reaction was not limited to ADTMCs with substituted phenyl group; the heteroaryl substrate **2j**, and the cycloalkyl substrate **2k** also underwent the

reaction smoothly. Moreover, the reaction between BCB **1d** (0.55 equiv.) and racemic 5-methylene-4-phenyl-1,3-dioxan-2-one **2l** yielded a mixture of (*Z*)-**3dl** and (*E*)-**3dl**, along with chiral (4 + 3) cycloadduct **4dl**, with a 4% NMR yield and 79% ee after 1 hour at room temperature. When the reaction was conducted at 100 °C with 1.2 equivalents of (*rac*)-**2l**, it produced four isomers, namely (*Z*)-**3dl**, (*E*)-**3dl**, **4dl'** (19% ee), and **4dl** (68% ee), in a ratio of about 52 : 24 : 16 : 8. The unreacted ADTMC **2l** was obtained with an enantiomeric excess of 1% (Scheme 2 bottom).

To demonstrate the synthetic utility of these (4 + 3) cycloadducts, several transformations of **3aa** were investigated (Scheme 4). Firstly, we found that the dihydroxylation of the *exo*-methylene moiety of **3aa** using K<sub>2</sub>OsO<sub>4</sub>·2H<sub>2</sub>O/NMO afforded diol **6** in 93% yield. Moreover, the epoxidation of the double bond was accomplished with *m*-CPBA (**3aa** → **7**). Alternatively, the double bond could be hydrogenated to produce the corresponding **8** in good yield. In addition, adduct **3aa** could be converted into a variety of oxa-bicyclo[4.1.1]octane derivatives by Wittig olefination (**9**), reduction (**10**) and condensation reaction (**11**).

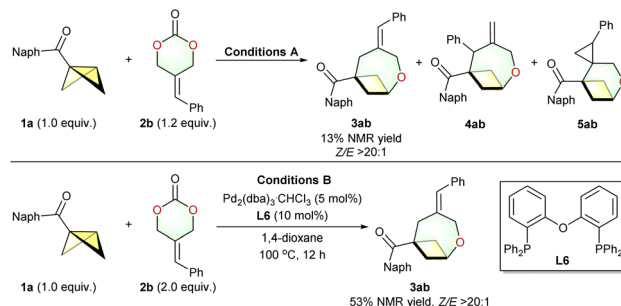




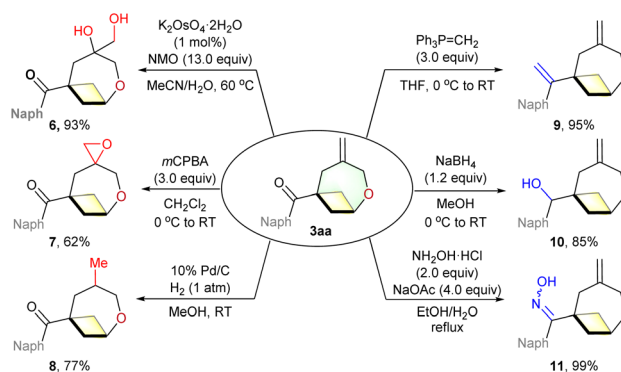
Scheme 2 Substrate scope of the Pd-catalyzed (4 + 3) cycloaddition.

<sup>a</sup> Standard conditions A: **1** (0.20 mmol), **2** (0.24 mmol),  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (5 mol%), and **L9** (10 mol%) in 1,4-dioxane (4 mL) at 25 °C under a  $\text{N}_2$  atmosphere for 12 h. Isolated yields of **3** were reported. <sup>b</sup> Reaction was run at 0.15 mmol scale. <sup>c</sup> Run at 100 °C. <sup>d</sup> Standard conditions B: **1** (0.10 mmol), **2** (0.20 mmol),  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (5 mol%), and **L6** (10 mol%) in 1,4-dioxane (2 mL) at 100 °C under a  $\text{N}_2$  atmosphere for 12 h.

Based on our experimental observations and relevant literature studies, we proposed a plausible mechanism to illustrate the catalytic cycle (Scheme 5). First,  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  and the P-

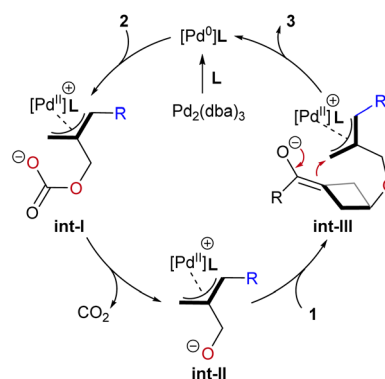


Scheme 3 Optimized reaction conditions B for the (4 + 3) cycloadditions of BCBs with the substituted ADTMCs.



Scheme 4 Synthetic transformations.

ligand formed a  $[\text{Pd}^0]/\text{L}$  complex. Then, oxidative addition of the ADTMCs **1** to palladium(0) gives  $\pi$ -allylpalladium carbonate **int-I**. Successive decarboxylation forms  $\pi$ -allyl palladium 1,4-O/C dipole species **int-II**. The oxygen anion in the zwitterionic allylpalladium intermediates **int-II** facilitates nucleophilic ring-opening of BCBs, generating intermediate **int-III**. Finally, intramolecular allylation of **int-III** affords the target (4 + 3) product **3** and regenerates the palladium catalyst. Therefore, in the O-homoconjugate addition process (**int-II**  $\rightarrow$  **int-III**), the monosubstituted BCB ketones could serve as more effective electrophiles compared to the 1,3-disubstituted BCB ketones for producing the desired cycloadducts.



Scheme 5 Proposed mechanism.



## Conclusions

In conclusion, a new strategy based on the palladium catalysis toward the atom-economic synthesis of uncommon yet significant 2-oxabicyclo[4.1.1]octane frameworks (oxa-BCOs) has been presented. This represents the first hetero-(4 + 3) cycloaddition of BCBs.<sup>36</sup> The utilization of easily accessible starting materials, gentle reaction conditions, broad functional group tolerance, and versatile functionalizations of the functionalized oxa-BCOs products renders this approach highly practical and appealing. The increasing significance of bicyclo[4.1.1]octanes in the quest for new bridged bicyclic molecules with bioisosteric properties leads us to believe that our protocol would not only enrich the toolkit of synthetic chemists but also greatly enlarge the (hetero-)bicyclo[*n*.1.1]alkanes library accessible for drug discovery.

## Data availability

The data supporting this article have been included as part of the ESI.† All detailed procedures, characterization data and NMR spectra are available in the ESI.†

## Author contributions

X.-Y. G. and L. T. performed all of the experiments and analysed their results. X.-Y. G., X. Z. and J.-J. F. wrote the manuscript. J.-J. F. conceived the catalytic system and directed the project.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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