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# Palladium-catalyzed direct intramolecular double α-C–H arylation of 1,5-diketone: a strategy for synthesis of Tröger's base analogues

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## ABSTRACT

9-Aryl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diones were straightforwardly prepared via a tandem reaction of easily available *ortho*-chloroacetophenone and *ortho*-chlorochalcone catalyzed by PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>.

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Tröger's base (**TB**, Scheme 1) was first synthesized in 1887,<sup>1</sup> and its structure was finally confirmed in 1935.<sup>2</sup> From the 1980s, studies on the design and synthesis of TB derivatives have been greatly increased, and it was disclosed that these compounds due to their unique structural features could be applied in many fields as chiral reagents and ligands,<sup>3</sup> molecular recognition,<sup>4</sup> and supramolecular chemistry.<sup>5</sup> In addition, the synthesis and application of TB's analogues such as TB-C,<sup>6</sup> TB-O,<sup>6</sup> and TB-CO (2,3:6,7-dibenzobicy-clo[3.3.1]nona-2,6-diene-4,8-dione)<sup>6,7</sup> are also interesting to organic chemists (Scheme 1). In particular, TB-CO has been well studied since it can be easily modified via the transformation of carbonyl groups by traditional reactions.<sup>7</sup>

On the other hand, we have recently been interested in development of high atom-economic reactions by using aryl chlorides as reactants in the Sonogashira coupling,<sup>8</sup> Heck coupling,<sup>9</sup> and synthesis of quinolines.<sup>10</sup> Because palladium-catalyzed intramolecular arylation of ketones has become a general synthetic method for the synthesis of cyclic compounds,<sup>11</sup> and in continuation of our interest in the development of high atom-economic reaction using aryl chloride as reaction partner, we examined the intramolecular double  $\alpha$ -arylation of 1,5-di(2-chlorophenyl)-3-phenyl-1,5-dione (1) under the similar reaction conditions reported in our previous report,<sup>9</sup> with the purpose of establishing a simple synthetic route to access 9-aryl-2,3:6,7-dibenzobicyclo[3,3,1]-nona-2,6-diene-

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Scheme 1. TB's structure and examples of its analogue.

4,8-dione (**2a**), to develop an efficient and simple procedure for the synthesis of 9-substituted derivatives of TB-CO. Fortunately, as shown in Eq. 1 the desired product was obtained in 47% isolated yield,<sup>12</sup> and its structure was confirmed by its spectroscopic data and X-ray crystallography (Fig. 1).<sup>13</sup>

Encouraged by the initial results, we therefore designed a tandem reaction of easily available *ortho*-chloroacetophenone and *ortho*-chlorochalcone for the formation of 9-aryl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-diones involving the sequential intermolecular Michael addition and intramolecular double  $\alpha$ -C-H arylation in the presence of PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub>/Cs<sub>2</sub>CO<sub>3</sub> as shown in Scheme 2. Thus we studied the reaction of 2'-chloroacetophenone (**3**) with 1-(2'-chlorophenyl)-3-phenylprop-2-en-1-one (**4a**) under different conditions to optimize the reaction conditions for the formation of **2a**, and the obtained results are summarized in Table 1.

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Figure 1. X-ray structure of compound 2a.



Scheme 2. A strategy for the synthesis of Tröger's base analogue.

## Table 1

Optimizing the reaction conditions



<sup>a</sup> Unless otherwise noted, reactions were carried out using 1.2 mmol of **3**, 1.0 mmol of **4a**, 0.05 mmol of catalyst, and 3.0 mmol of  $Cs_2CO_3$  in 3.0 mL of solvent under nitrogen atmosphere in a sealed tube for 24 h.

<sup>b</sup> Isolated yield is based on **4a**.

When a mixture of **3** (1.2 mmol), **4a** (1.0 mmol),  $Cs_2CO_3$  (3.0 mmol), and PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (0.05 mmol) in 1,4-dioxane (3.0 mL) in a sealed tube was heated at 120 °C with stirring under nitrogen atmosphere for 24 h, **2a** was isolated from the reaction mixture in 45% yield (entry 1), accompanied with the formation of dechlorinated by-products of starting materials. Decreasing the reaction temperature to 100 °C resulted in a very low yield of the desired product (entry 2). The screening of solvents disclosed that when the reaction was carried out in toluene, **2a** was isolated in 27% yield (entry 3), and however, the use of THF, DMSO, and DMF resulted in a very low yield or no formation of **2a** (entries 4–6). In addition, other palladium catalysts such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>,

 $Pd(PPh_3)_4$ , and  $Pd_2(dba)_3$  did not show any catalytic activity for the formation of **2a** (entries 7–10).

Under the reaction conditions indicated in entry 1 of Table 1, we then investigated the generality of the present procedure by the reaction of 3 with ortho-chlorochalcone derivatives 4, and the results concluded in Table 2 are disclosed: (1) The corresponding diones 2 could be obtained in fair to moderate yields with the use of various substituents on aryl rings in 4. (2) The reactions with the use of **4** bearing either electron-donating groups (**4b**-**d**) or electron-withdrawing groups (4f, 4i, and 4l) at para-position on aryl rings afforded the corresponding products in moderate yields (38-51%), and the cases at meta- (4e, 4j) or ortho-position (4k), gave relatively low yields, probably due to steric hindrance. An exception was the reaction of **4m**, which has a cyano group at para-position, but the yield of **2m** was low, probably due to the coordinative ability of the cyano group to obstruct the reaction: (3) in the reaction of **4g** and **4h**, the former with the substituted position at  $\beta$ -position was significantly more reactive than at  $\alpha$ position. (4) The heterocyclic groups of thiophenyl (**4n**) and furyl (40) could be also introduced to the 9-position of 2 for further transformation. The limit of the present catalytic reaction appears to be the unsatisfactory yields of the desired diones 2, since the formation of 2 requires a high selective process of intramolecular double  $\alpha$ -C–H arylation simultaneously.

In addition, under the optimized conditions, the reactions of **3** with **4** bearing alkyl group such as 1-(2'-chlorophenyl)-2-penten-1-one (**4p**) and 1-(2'-chlorophenyl)-4,4-dimethyl-2-penten-1-one (**4q**), as well as 1-(2'-chlorophenyl)propen-1-one (**4r**, without substituent) have also been examined. Unfortunately, the reactions did not afford the corresponding desirable cyclic dione derivative **2** at all. On the basis of GC and GC–MS analyses of the reaction mixture, it was found that **3** and **4q** were almost recovered, **4p** was recovered in 46%, and **4r** was completely consumed. No by-product(s) could be identified, and only small amount of acetophenone could be confirmed resulting possibly from the dechlorination of **3**.



In summary, we have developed a one-pot synthetic reaction to construct 9-aryl-2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4, 8-diones via a palladium-catalyzed tandem reaction of *ortho*-chloroacetophenone and *ortho*-chlorochalcone derivatives includ-ing intermolecular Michael addition and intramolecular double

Table 2 The sumthesis of 0 and 2 2007 dile

*m*-MeOC<sub>6</sub>H<sub>4</sub> 4e

2-Naphthyl 4g

1-Naphthyl 4h

p-PhC<sub>6</sub>H<sub>4</sub> 4f

The synthesis of 9-aryl-2,3:6,7-dibenzobicyclo[3.3.1]-nona-2,6-diene-4,8-diones

0 + 3 1.2 mmol	CI 4 1.0 mmol	$Ar \frac{PdC}{Cs_2}$	Cl <sub>2</sub> (PCy <sub>3</sub> ) <sub>2</sub> (5 mol%) CO <sub>3</sub> (3.0 equiv) 4-dioxane 20 °C, 24 h, N <sub>2</sub>		
Ar		Yield (%)	Ar		Yield (%)
p-Tolyl <b>4b</b>	2b	43	<i>p</i> -FC <sub>6</sub> H <sub>4</sub> <b>4i</b>	2i	51
<i>p</i> - <i>t</i> BuC <sub>6</sub> H <sub>4</sub> <b>4c</b>	2c	43	m-FC <sub>6</sub> H <sub>4</sub> <b>4j</b>	2j	35
<i>p</i> -MeOC <sub>c</sub> H₄ <b>4d</b>	2d	38	0-FCcH₄ <b>4k</b>	2k	26

p-F3CC<sub>6</sub>H<sub>4</sub> 4

2-Furyl 40

p-NCC<sub>6</sub>H<sub>4</sub> 4m

2-Thiophenyl 4n

23

36

48

14

2e

2f

2g

2h

21

2m

2n

20

41

10

22

20

2

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 $\alpha$ -C–H arylation. Although the yields of products remain to be improved, the present method provides an alternative, efficient, and simple procedure for the synthesis of 9-substituted derivatives of TB-CO compared to traditional methods which often need long synthetic steps and harsh reaction conditions. Also the synthesized 9-substituted derivatives of TB-CO (polycyclic diones) have high potential application in supramolecular chemistry via further transformation.

A typical experimental procedure (Table 1, entry 1): a mixture of 2'-chloroacetophenone (3) (185.0 mg, 1.2 mmol), 1-(2'-chlorophenyl)-3-phenylprop-2-en-1-one (242.0 mg, 1.0 mmol) (4a), PdCl<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> (36.8 mg, 0.05 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (977.5 mg, 3.0 mmol) in 1,4-dioxane (3 mL) in a thick-walled screw-capped Pyrex tube was heated with stirring at 120 °C (oil bath temperature) for 24 h under nitrogen atmosphere. After the reaction mixture was cooled to room temperature. CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added, and the GCMS analysis was performed. After removal of volatiles under reduced pressure, the residue was subjected to column chromatography isolation (silica gel, eluted with a mixture solvent of petroleum ether and ethyl acetate (50:1)) to give 2a as a yellow solid (145.9 mg, 0.45 mmol, 45%). Data for 2a: yellow solid, mp 170–172 °C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.91 (1H, d, J = 7.9 Hz), 7.75 (1H, d, J = 7.9 Hz), 7.45–7.37 (3H, m), 7.36–7.33 (2H, m), 7.29-7.23 (2H, m), 7.12-7.08 (4H, m), 4.32 (2H, s), 4.25 (1H, s);  $^{13}\mathrm{C}$  NMR (75 MHz, CDCl\_3)  $\delta$  194.4, 193.8, 140.5, 139.1, 137.3, 135.2, 134.7, 129.4, 129.1, 128.9, 128.9, 128.8, 128.7, 128.6, 127.7, 127.3, 127.2, 54.4, 54.3, 46.3; GC-MS m/z (% rel inten.) 324 (M<sup>+</sup>, 94), 281 (36), 253 (30), 207 (100), 73 (84); IR (neat) 1691, 1678 cm<sup>-1</sup> ( $v_{CO}$ ); HRMS (ESI) calcd for C<sub>23</sub>H<sub>17</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 325.1223, found: 325.1223.

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## Supplementary data

Supplementary data (general method, characterization data, charts of <sup>1</sup>H, <sup>13</sup>C NMR for all products, and the data of X-ray crystal structure of **2a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04.069.

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- 12. It should be noted that when aryl bromides or aryl iodides were used, the desirable product 2 could not be obtained. The main side-reaction is the intramolecular Heck coupling reaction of 4.
- Crystals for X-ray diffraction analysis were obtained by recrystallization from a mixture of CH<sub>2</sub>Cl<sub>2</sub> and cyclohexane. CCDC 936765 contains supplementary crystallographic data for compound 2a.