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A brand-new Pd-mediated generation of benzyne and its [2+2+2] cycloaddition: δ-carbon elimination and concomitant decarboxylation

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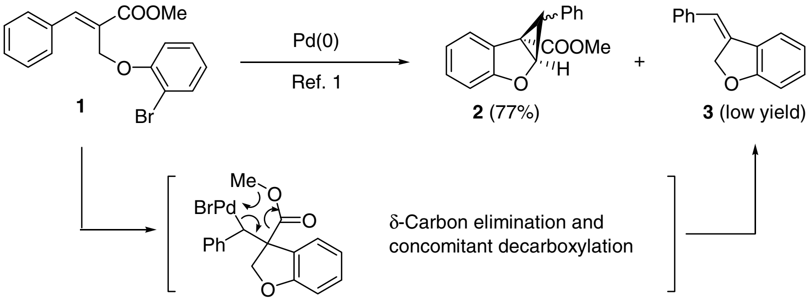
ABSTRACT

We found a brand-new method for the generation of aryne from methyl 2-bromobenzoates via the Pd-mediated concomitant δ-carbon elimination and decarboxylation. The generated arynes underwent Pd-mediated [2+2+2] cycloaddition to give triphenylenes.

Recently, we published the synthesis of cyclopropane-fused dihydrobenzofuran derivatives under Pd-mediated Heck type reaction conditions of 2-bromophenol-attached Baylis–Hillman adducts (Scheme 1).[1] In the reaction, Pd-mediated activation of C(sp^3)–H bond occurred, and the resulting cyclopropane-fused compound **2** was produced in moderate yield.[1] 3-Benzylidene-2,3-dihydrobenzofuran (**3**) was also isolated together in the reaction, albeit in low yield.[1] The mechanism for the formation of compound **3** could be thought as δ-carbon elimination and concomitant elimination of CO$_2$ as in Scheme 1. Palladium-mediated transformations involving β-carbon elimination are well reported in the literature,[2] however, δ-carbon elimination accompanying simultaneous decarboxylation has not been reported, to the best of our knowledge.

Recently, Pd-catalyzed [2+2+2] cycloadditions of arynes for the preparation of polycyclic aromatic hydrocarbons (PAHs) have been developed and studied extensively.[3,4] The corresponding *o*-trimethylsilylaryl triflates were used as adequate aryne precursors,[3–5] which generate arynes by the action of CsF (Kobayashi method).[5] Cyclotrimerization reactions of arynes were carried out directly from the *o*-trimethylsilylaryl triflates, the precursor of arynes, in the presence of CsF/Pd(0) at rt.[3–5]

During the course of our studies,[1] we imagined the possibility of generation of benzyne from methyl 2-bromobenzoate (**4a**) via



Scheme 1.

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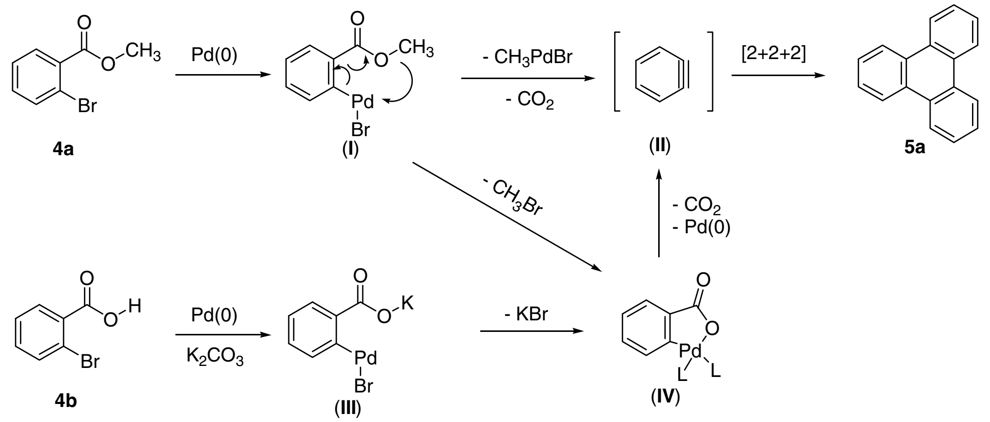


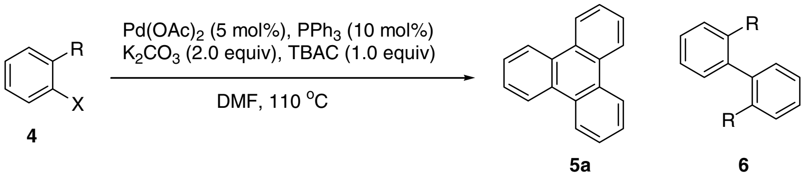
Scheme 2. Postulated reaction mechanism.

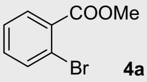
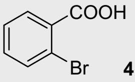
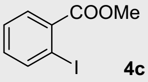
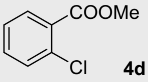
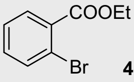
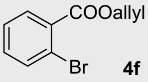
Table 1
Optimization of conditions for the conversion of **4a**–**5a**

Entry	Conditions[a]	Time (min)	Yield(%)
1	$Pd(OAc)_2$ (10 mol%), K_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 110°C	90	52
2	$Pd(OAc)_2$ (5 mol%), PPh_3 (0.1 equiv),K_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 110°C	60	45
3	$Pd(OAc)_2$ (5 mol%), PPh_3 (0.1 equiv),K_2CO_3 (2.0 equiv), D MF, 110°C	240	23
4	$Pd(OAc)_2$ (5 mol%), PPh_3 (0.1 equiv),K_2CO_3 (2.0 equiv),TBAB (1.0 equiv),KI (2.0 equiv),DMF,110°C	210	19
5	$Pd(OAc)_2$ (5 mol%), PPh_3 (0.1 equiv),K_2CO_3 (2.0 equiv),TPAI (1.0 equiv),DMF,110 °C	180	18
6	$Pd(OAc)_2$ (5 mol%), PPh_3 (0.1 equiv) ,K_2CO_3 (2.0 equiv) ,T BAC (1.0 equiv), DMF, 110 °C[6]	0	57[b]
7	$Pd(OAc)_2$ (10mol%) , PPh_3 (0.1 equiv),K_2CO_3 (2.0 equiv),KF(1.0 equiv),DMF,110°C	180	9

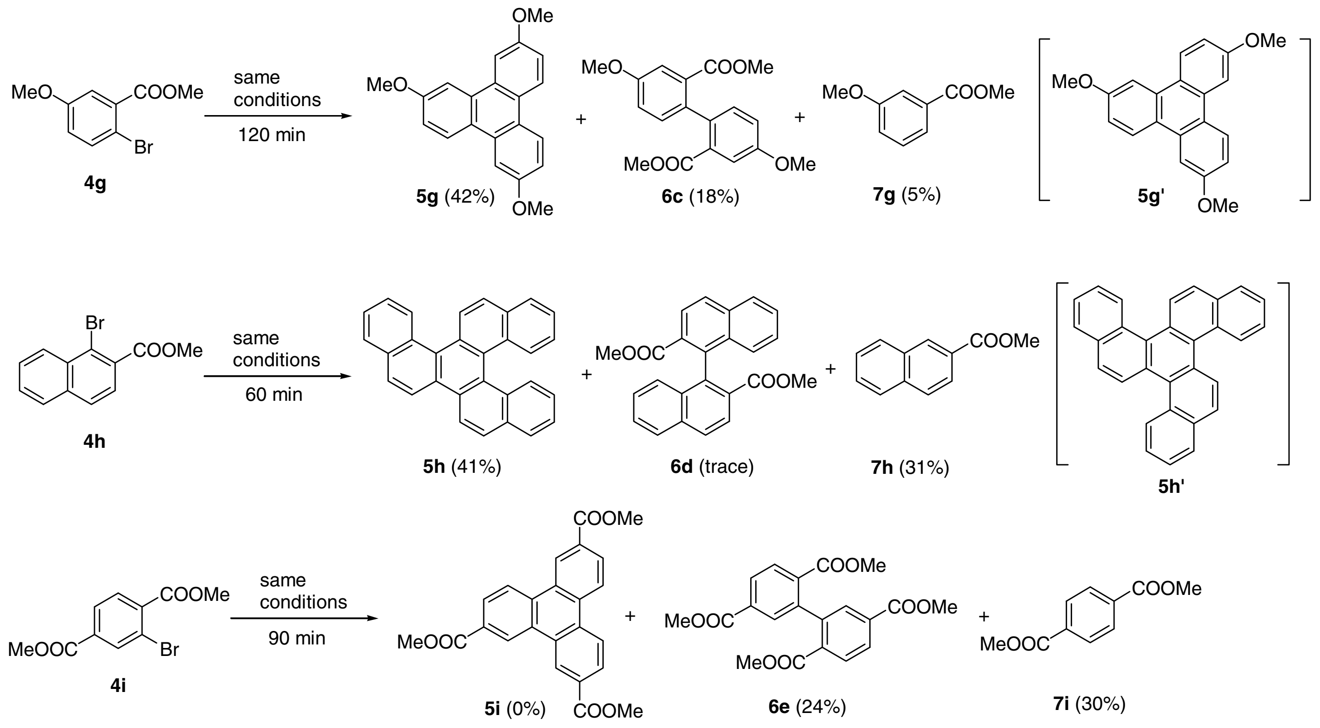
[a] Dimerized compound **6a** was isolated in 8%. Compound **6a** was also observed in other entries in variable amounts.
[b] TBAB is tetrabutylammonium bromide; TPAI is tetrapropylammonium iodide; TBAC is tetrabutylammonium chloride.

Table 2
Relative reactivity of various 2-halobenzoic acid derivatives



Entry	Substrate	Time(min)	**4** (%)	**5a** (%)	**6** (%)
1[a]	 **4a**	60	nd	57	**6a** (8)
2	 **4b**	30	nd	27	nd
3[a]	 **4c**	50	nd	44	**6a** (20)
4	 **4d**	120	15	nd	nd
5[a]	 **4e**	120	nd	21	**6b** (30)
6	 **4f**	30	nd	25	nd

[a] Variable amounts of reduction product, methyl benzoate or ethyl benzoate, were observed.



Scheme 3.

δ-carbon elimination[2] and concomitant elimination of CO_2. The in situ generated benzyne intermediate must be converted into triphenylene **5a** via the well-known Pd-mediated [2+2+2] cycloaddition mechanism.[3] Our strategy and the proposed mechanism are shown in Scheme 2, with **4a** as an example: (i) oxidative addition of aryl bromide **4a** to Pd(0) generates the intermediate (**I**), (ii) simultaneous δ-carbon elimination and decarboxylation to produce benzyne (**II**), and the final (iii) Pd-mediated [2+2+2] cycloaddition of benzyne to give triphenylene (**5a**).

Initially, we examined the reaction of methyl 2-bromobenzoate (**4a**) in the presence of $Pd(OAc)_2/K_2CO_3$/TBAB in DMF at 110 °C,[1] and obtained triphenylene (**5a**) in 52% isolated yield to our delight.[3a,6] Trials for the optimization of reaction conditions are summarized in Table 1. The use of TBAB (entries 1 and 2) or TBAC (entry 6) showed better yields of **5a** than the cases involving the use of TBAB/KI (entry 4), TPAI (entry 5), or KF (entry 7). Among the examined conditions, the combination of $Pd(OAc)_2/PPh_3/K_2CO_3$/TBAC was found to be the best (entry 6). Under this optimized conditions, compound **5a** was obtained in 57% isolated yield together with aryl–aryl coupling product **6a** (8%, Table 2).[7]

As a next examination, we studied the relative reactivity of various 2-halobenzoic acid derivatives **4b**–**f**, and the results are summarized in Table 2. The reaction of 2-bromobenzoic acid (**4b**) produced **5a** in low yield (27%). In this case, oxapalladacycle intermediate (**IV**)[8] could be the plausible intermediate (vide supra, Scheme 2).[9] As expected, methyl 2-iodobenzoate (**4c**) afforded moderate yield of **5a** (44%), however, the yield of **6a** was increased to 20%. Chloro derivative **4d** was almost un-reactive and severe decomposition was observed. Ethyl ester **4e** and allyl ester **4f** showed lower yields than the corresponding methyl ester **4a**. The smallest methyl group might be eliminated more readily during the δ-carbon elimination stage than the bigger ethyl group (entry 1 vs entry 5). For the allyl ester **4f**, the mechanism might be different from the proposed one: formation of π-allyl palladium intermediate and conversion into the palladacyclic intermediate (**IV**) in Scheme 2 and the generation of CO_2 and benzyne could be regarded as the more plausible mechanism.

The generation of aryne and the following [2+2+2] cycloaddition reaction were examined with related substrates **4g**–**i** as shown in Scheme 3. From the reaction of **4g**, triphenylene derivative **5g** was obtained in 42% yield together with dimeric compound **6c** (18%) and reduction compound **7g** (5%). Trace amount of regioisomeric **5g′** (<5%) was observed in the ^{1}H NMR spectrum of **5g** as in the previous reports of similar compounds.[3a,c,10] Naphthalene derivative **4h** produced **5h** in moderate yield (41%) also. Regioisomeric triphenylene **5h′** was also found (<5%) in the ^{1}H NMR spectrum of **5h**.[3c] In the reaction, we could not isolate **6d** in appreciable amount instead reduction compound **7h** was isolated in 31% yield. The reaction of dimethyl 2-bromoterephthalate (**4i**) did not produce triphenylene **5i** in appreciable amount, instead we isolated dimer **6e** (24%) and reduction compound **7i** (30%), unfortunately. From the results, the generation of arynes from 2-halobenzoates seemed general in part, but sometimes substrate-dependent and needed to be studied more.

In summary, we found a brand-new method for the generation of aryne from methyl 2-bromobenzoates via the Pd-mediated concomitant δ-carbon elimination and decarboxylation. Further studies on the reaction mechanism and the synthetic applicability are actively underway.

Acknowledgments

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9. The formation of (**IV**) from (**I**) by direct elimination of CH$_3$Br (Scheme 2) would also be possible. For this type of reductive cleavage process involving decarboxylation, see: Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2352–2354.
10. *Compound* **5g**: Yellow solid, mp 126–128 °C; IR (film) 1614, 1495, 1217 cm^{-1}; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 3.988 (s, 3H), 3.990 (s, 3H), 4.00 (s, 3H), 7.17 (dd, J = 8.5 Hz and 2.5 Hz, 1H), 7.22–7.25 (m, 2H), 7.89–7.92 (m, 3H), 8.38–8.45 (m, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 55.41, 55.45, 55.47, 105.28, 106.11, 106.12, 114.85, 115.41, 115.61, 122.92, 123.89, 124.28, 124.35, 124.39, 125.00, 129.74, 130.22, 131.32, 158.01, 158.23, 158.78; ESIMS m/z 319 (M$^+$+1). Anal. Calcd for C$_{21}$H$_{18}$O$_3$: C, 79.22; H, 5.70. Found: C, 79.03; H, 5.87.