Three-Component Coupling Reactions of Arynes for the Synthesis of Benzofurans and Coumarins

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Received: 16 December 2013; in revised form: 7 January 2014 / Accepted: 8 January 2014 / Published: 13 January 2014

Abstract: The domino three-component coupling reaction of arynes with DMF and active methylenes or methines was studied as a highly efficient method for preparing heterocycles. Coumarin derivative 5 was formed when diethyl malonate (2) or α-bromomalonaldehyde (3) were used as a C2-unit. In contrast, dihydrobenzofurans 7a and 7b were obtained by using α-chloroenolates generated from α-chloromalonates 4a and 4b and Et2Zn. The benzofuran 15a could be obtained by using ethyl iodoacetate (14) as a C1-unit. The one-pot conversion of dihydrobenzofurans 7a, 7b and 8a into benzofurans 15a and 15b was also studied. The direct synthesis of benzofuran 15b was achieved by using the active methine 18 having ketone and ester groups.

Keywords: arynes; multi-component reaction; domino reaction; heterocycles; synthesis

1. Introduction

Synthetic strategies involving domino or cascade process offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond formations in a single operation [1]. In recent years, the domino reactions using arynes continue to attract much interest [2–21], since arynes are highly reactive species for constructing the multi-substituted arenes with structural diversity and complexity [22,23].

The recent aryne-based chemistry has achieved some remarkable success in the transition metal-catalyzed reactions [2–10], the transition metal-free reactions and other transformations [11–21]. These advances have shown that the insertion of arynes into various element-element σ-bonds can be
achieved even under the transition metal-free conditions. We have been interested in developing the corresponding π-bond insertion [24–31]. Recently, we reported the efficient insertion into the C=O bond of formamides [32,33], which was successfully applied into the domino process trapping the transient intermediates with nucleophiles [34–36]. In this paper, we describe in detail our approach to prepare coumarin, dihydrobenzofuran and benzofuran derivatives via the three-component coupling process starting from arynes generated from ortho-(trimethylsilyl)aryl triflates.

2. Results and Discussion

2.1. New Approach for the Domino Three-Component Coupling Process

The goal of our study on aryne chemistry is to develop the highly efficient domino reactions for preparing heterocycles. Therefore, we have designed a new approach involving two steps which are induced by the high reactivity related to the strain energy of aryne A and the four-membered intermediate B (Scheme 1) [37].

The insertion of a highly strained aryne A, generated in situ from ortho-(trimethylsilyl)aryl triflate 1 and the fluoride ion [38], into the C=O of N,N-dimethylformamide (DMF) gives the moderately strained [2+2] adduct benzoxetene B, which would undergo isomerized into ortho-quinone methide C (Step 1). The sequential transformation can be achieved by the initial addition of nucleophiles to the transient intermediate C and the subsequent trapping process with electrophiles (Step 2). When nucleophile and electrophile belong to the same molecule as shown in Scheme 1, the use of C2-units (X–Y) leads to the products D and the use of C1-units (X) leads to the products E.

Scheme 1. Three-component coupling reaction.
For the synthesis of products D such as coumarin derivatives, we used enol F and enolate G having both nucleophilic and electrophilic sites, which were derived from malonate 2 and α-bromomalonate 3, respectively (Scheme 2). For the synthesis of products E such as dihydrobenzofurans and benzofurans, α-chloroenolate H having a nucleophilic and electrophilic carbon atom, derived from α-chloromalonate 4, was employed for trapping the unstable intermediate C.

Scheme 2. Substrates for trapping the intermediate C.

2.2. The Synthesis of Coumarin Derivative

In organic synthesis, DMF can react as either an electrophilic or nucleophilic agent [39,40]. At first, we examined the reaction of 3-methoxy-2-(trimethylsilyl)phenyl triflate (1) as an aryne precursor with DMF and diethyl malonate (2) as a C2-unit (Table 1). It is well known that the active methylenes such as diethyl malonate (2) have an excellent reactivity toward arynes giving the σ-bond insertion products [41–45]. To suppress the competitive insertion of aryne into the C–C σ-bond of 2, DMF was employed as a solvent. We were gratified to observe the sufficient reactivity of active methylene 2 toward intermediate B in the absence of base. The effect of fluoride ion sources was studied. In the presence of CsF, treatment of triflate 1 with 2 in DMF at room temperature predominantly gave the desired coumarin 5 in 65% yield, accompanied by a trace amount of salicylaldehyde derivative 6 (entry 1). The replacement of CsF with anhydrous TBAF led to an increase in the chemical yield to give 5 in 86% yield (entry 2). In contrast, no reaction was observed when KF was employed (entry 3).
Table 1. Reaction of aryne precursor 1 with DMF and 2.a.

| Entry | Reagent (3.0 equiv) | Product (% yield) b |
|-------|---------------------|---------------------|
| 1     | CsF                 | 5 (65), 6 (trace)   |
| 2     | TBAF                | 5 (86)              |
| 3     | KF                  | NR c                |

a Reactions were carried out with 1 (1.0 equiv), 2 (1.5 equiv), and reagent (3.0 equiv) in DMF (0.1 M solution of 1). b Isolated yield. c No reaction; Triflate 1 was recovered in 93% yield.

This domino transformation involves the trapping reaction of the unstable intermediate C with enol F giving the intermediate I (Scheme 3). The coumarin 5 was formed via the elimination of a dimethylamino group from the intermediate I.

Scheme 3. Reaction pathway.

Further investigations using α-bromomalonate 3 and organometallic reagents such as Et₂Zn or Me₃Al were performed (Table 2). In the presence of Et₂Zn, we initially allowed triflate 1 to react with 3 in DMF at room temperature for 12 h (entry 1). The desired coumarin 5 was obtained in 11% yield, accompanied by the recovered triflate 1 in 64%. Although the replacement of CsF with anhydrous TBAF led to an increase in the chemical yield, the new formation of dihydrobenzofuran 7a was observed (entry 2). The reaction did not take place when KF was employed (entry 3). Therefore, Me₃Al was next employed (entries 4 and 5). In the presence of CsF, treatment of 1 with 3 in DMF predominantly gave the desired product 5 in 34% yield (entry 4). Improvement in the chemical yield of 5 was observed when anhydrous TBAF was used (entry 5). The chemical yield increased into 85%. In
this transformation, a suitable combination of \(\alpha\)-bromomalonate 3 and Me\(_3\)Al led to the efficient
generation of the debrominated metal enolate \(G\), which reacted with intermediate \(C\) to give coumarin 5.

Table 2. Reaction of aryne precursor 1 with DMF and 3\(^a\).

| Entry | Reagent (5.0 equiv) | Additive (2.0 equiv) | Product (% yield)\(^b\) |
|-------|---------------------|----------------------|-------------------------|
| 1     | CsF                 | Et\(_2\)Zn           | 5 (11)\(^c\)            |
| 2     | TBAF                | Et\(_2\)Zn           | 5 (41), 7a (23)         |
| 3     | KF                  | Et\(_2\)Zn           | NR\(^d\)                |
| 4     | CsF                 | Me\(_3\)Al           | 5 (34)\(^e\)            |
| 5     | TBAF                | Me\(_3\)Al           | 5 (85)                  |

\(^a\) Reactions were carried out with 1 (1.0 equiv), 3 (1.5 equiv), reagent (5.0 equiv), and additive (2.0 equiv) in DMF (0.1 M solution of 1).\(^b\) Isolated yield.\(^c\) Triflate 1 was recovered in 64% yield.\(^d\) No reaction; Triflate 1
was recovered in 98% yield.\(^e\) Triflate 1 was recovered in 12% yield.

2.3. The Synthesis of Dihydrobenzofurans

We next investigated the domino reaction for the synthesis of dihydrobenzofurans (Table 3). The key issue of this transformation is the efficient generation of \(\alpha\)-halogenated enolate as a C1-unit. However, as mentioned above, the debromination took place when \(\alpha\)-bromomalonate 3 and
organometallic reagents were employed. In remarked contrast to \(\alpha\)-bromomalonate 3, we found that
the use of \(\alpha\)-chloromalonates 4\(_a\)\(_b\) and Et\(_2\)Zn led to the generation of desired \(\alpha\)-halogenated enolates \(H\)
(Scheme 4). Thus, a combination of \(\alpha\)-chloromalonates 4\(_a\)\(_b\) and Et\(_2\)Zn was checked under the
different reaction conditions for the synthesis of dihydrobenzofurans.
Table 3. Reaction of aryne precursor 1 with DMF and 4a,b.

| Entry | Methine | Reagent | T         | Product (% yield)a |
|-------|---------|---------|-----------|-------------------|
| 1 b   | 4a      | TBAF    | rt        | 7a (21), 8a (64)  |
| 2 b   | 4a      | TBAF    | −40 °C to rt | 7a (66), 8a (24) |
| 3 b   | 4a      | CsF     | −40 °C to rt | 7a (63)         |
| 4 c   | 4a      | CsF     | −40 °C to rt | 7a (86)         |
| 5 b   | 4a      | KF      | rt        | NRd              |
| 6 b   | 4b      | CsF     | −40 °C to rt | 7b (70)         |
| 7 c   | 4b      | CsF     | −40 °C to rt | 7b (89)         |

a Isolated yield. b Reactions were carried out with 1 (1.0 equiv), 4a,b (2.0 equiv), reagent (5.0 equiv), and Et2Zn (2.0 equiv) in DMF (0.1 M solution of 1). c Reactions were carried out with 1 (1.2 equiv), 4a,b (1.0 equiv), CsF (6.0 equiv), and Et2Zn (1.0 equiv) in DMF (0.1 M solution of 1). d No reaction; Triflate 1 was recovered in 95% yield.

Scheme 4. Generation of enolates and reaction pathway.

In the presence of anhydrous TBAF, treatment of triflate 1 with 4a in DMF at room temperature gave the desired product 7a in 21% yield, accompanied by 64% yield of undesired dihydrobenzofuran 8a (entry 1). The undesired dihydrobenzofuran 8a having a hydroxy group would be formed as a result of hydrolysis of intermediates B or C with contaminating water. The isolated yield of 7a increased to 66% yield by changing the reaction temperature (entry 2). The formation of undesired product 8a was not observed when CsF was employed (entries 3 and 4). In particular, improvement in the chemical yield of 7a was observed, when 1.2 equivalents of triflate 1 was reacted with 1.0 equivalent of 4a in DMF (entry 4). Similar trend was observed in the reaction using α-chloromalonate 4b (entries 6 and 7). In the presence of CsF and Et2Zn, treatment of triflate 1 (1.2 equiv) with 4b (1.0 equiv) in DMF at −40 °C to room temperature for 12 h gave the desired dihydrobenzofuran 7b in 89% yield (entry 7).

In this transformation, α-chloroenolates H are effectively generated from α-chloromalonates 4a,b and Et2Zn (Scheme 4). These α-halogenated enolates H work as not only a nucleophile to attack to the
intermediate C but also an electrophile to trap intramolecularly the intermediate anion J to give the desired dihydrobenzofurans 7a,b.

The reactivity of α-chloromalonate 4a toward arynes was also investigated (Scheme 5). In the presence of CsF, the direct reaction of triflate 1 with 4a was carried out in CH₃CN without DMF. As expected, the σ-bond insertion product 9 was obtained in 52% yield.

Scheme 5. Reaction of 1 with 4a.

As mentioned above, the competitive insertion of aryne into the C–C σ-bond of 4a was not observed in the domino three-component coupling reaction of bulky triflate 1. Decreasing the steric hindrance around the triple bond of aryne induced the direct insertion of aryne into α-chloromalonate 4a. When sterically less hindered triflate 10 was employed as an aryne precursor, the σ-bond insertion product 12 was obtained in 51% yield (Scheme 6). To suppress the competitive insertion of aryne into 4a, the concentration was evaluated. Under the high diluted concentration (0.02 M solution of 10 in DMF), the σ-bond insertion was mostly suppressed to afford the desired dihydrobenzofuran 11 in 65% yield, accompanied by 14% yield of dihydrobenzofuran 13 having a hydroxy group.

Scheme 6. Reaction of 10 with DMF and 4a.

2.4. The Synthesis of Benzofurans

With these results in mind, the synthesis of benzofurans was next studied (Table 4). At first, ethyl iodoacetate 14 was employed as a C1-unit. The reaction of triflate 1 with 14 was run in DMF in the presence of 3.0 equivalents of TBAF (entry 1). However, the simple O-alkylated product 16 was formed in 28% yield, accompanied by salicylaldehyde derivative 6 in 45% yield. The similar trend was
observed when CsF was used (entry 2). The reaction temperature had an impact on the chemical transformation (entry 3). The desired benzofuran 15a was obtained in 40% yield, when reaction was run at 100 °C. The use of Et2Zn or Me3Al as additive was not effective for this reaction (entries 4 and 5).

Table 4. Reaction of aryne precursor 1 with DMF and 14.

| Entry | Reagent (equiv) | Ethyl iodoacetate | T (°C) | Time (h) | Product (% yield) |
|-------|----------------|-------------------|--------|----------|------------------|
| 1     | TBAF (3.0)     | 1.5 equiv         | rt     | 12       | 16 (28), 6 (45)  |
| 2     | CsF (3.0)      | 1.5 equiv         | rt     | 12       | 16 (44), 6 (34)  |
| 3     | CsF (5.0)      | 2.0 equiv         | 100    | 3        | 15a (40), 16 (trace), 6 (11) |
| 4     | CsF (5.0)      | 2.0 equiv         | rt     | 24       | Complex mixture  |
| 5     | CsF (5.0)      | 2.0 equiv         | rt     | 24       | NR f             |

*Reactions were carried out with 1 (1.0 equiv), 14 (1.5 or 2.0 equiv), and reagent (3.0 or 5.0 equiv) in DMF (0.1 M solution of 1). b Isolated yield. c Reaction was carried out in the presence of Et2Zn (2.0 equiv). d Triflate 1 was recovered in 36% yield. e Reaction was carried out in the presence of Me3Al (2.0 equiv). f No reaction; Triflate 1 was recovered in 79% yield.

To understand the reaction pathway, the formation of benzofuran 15a from the simple O-alkylated product 16 was studied (Scheme 7). As expected, benzofuran 15a was obtained in 32% yield, after being stirred at room temperature for 12 h followed by heated at 100 °C for 12 h. Thus, benzofuran 15a could be obtained from O-alkylated product 16.

Scheme 7. Conversion of 16 into 15a.

For the formation of benzofuran 15a, two possible reaction pathways are shown in Scheme 8. As a direct pathway, benzofuran 15a is assumed to be obtained from ortho-quinone methide C and 14 via intermediate K (path a). Another pathway is the formation of benzofuran 15a from the simple O-alkylated product 16 via intermediates L and M (path b).
As an alternative approach for synthesis of benzofurans, we tried to establish the conversion of dihydrobenzofurans 7a and 7b into benzofurans 15a and 15b (Scheme 9). When dihydrobenzofuran 7a was treated with 2.5 equivalents of EtMgBr followed by SiO₂, the desired benzofuran 15a was obtained in 77% yield without the isolation of adduct 17a. Similarly, benzofuran 15b was formed from dihydrobenzofuran 7b. These transformations would proceed via the retro-aldol type reaction of adducts 17a and 17b followed by the elimination of a dimethylamino group.

Next, we directed our attention into the direct one-pot synthesis of benzofuran 15b (Scheme 10). For this purpose, the active methine 18 having ketone and ester groups was used, since ketone moiety would selectively react with Et₂Zn, leading to the retro-aldol type process. In the presence of CsF, triflate 1 and methine 18 in DMF were treated with Et₂Zn (1.0 equiv + 0.5 equiv) at −60 °C to room temperature for 12 h. As expected, the desired benzofuran 15b having an ester group was directly generated via the addition of an ethyl anion to a ketone group of dihydrobenzofuran O, the retro-aldol type reaction of intermediate P and the elimination of a dimethylamino group of anion Q.
Finally, we investigated the transformation of dihydrobenzofuran \(8a\) having a hydroxy group into benzofuran \(15a\) (Scheme 11) [46]. As a starting substrate, the preparation of dihydrobenzofuran \(8a\) was initially studied. When the domino reaction of triflate \(1\) with \(\alpha\)-bromomalonate \(3\) and DMF was carried out in the presence of water (1.0 equiv), the desired dihydrobenzofuran \(8a\) was obtained in 77% yield instead of dihydrobenzofuran \(7a\) having a dimethylamino group. For the synthesis of benzofuran \(15a\), we next allowed dihydrobenzofuran \(8a\) to react with several bases (Table 5). Treatment of dihydrobenzofuran \(8a\) with 1.0 equivalent of NaH in DMF at room temperature gave the desired benzofuran \(15a\) in 83% yield (entry 1). Probably, this transformation proceeds via the decarboxylation of cyclic intermediate \(R\). In contrast, benzofuran \(15a\) was not obtained when LiHMDS was employed in THF at \(-40^\circ C\) (entry 2). Interestingly, the replacement of LiHMDS with NaHMDS led to the formation of \(15a\) (entry 3). The isolated yield of \(15a\) dramatically increased to 96% yield by replacing NaHMDS with KHMDS (entry 4).

**Scheme 11.** Preparation of \(8a\) and transformation of \(8a\) into \(15a\).
Table 5. Synthesis of benzofuran 15a.

| Entry | Base (1.0 equiv) | Solvent | T (°C) | Time (h) | Yield (%) b |
|-------|------------------|---------|--------|----------|-------------|
| 1     | NaH              | DMF     | rt     | 16       | 83          |
| 2     | LiHMDS           | THF     | −40    | 88       | NR c        |
| 3     | NaHMDS           | THF     | −40    | 88       | 11          |
| 4     | KHMDS            | THF     | −40    | 16       | 96          |

a Reactions were carried out with 8a (1.0 equiv) and base (1.0 equiv). b Isolated yield. c No reaction; Starting substrate 8a was recovered in 84% yield.

3. Experimental

3.1. General

Melting points were taken on a Yanaco MP-J3 and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-4100. 1H-NMR spectra were measured on a JEOL ECX-400 PSK (400 MHz) or Varian NMRS 600 (600 MHz). 13C-NMR spectra were measured on a JEOL ECX-400 PSK (101 MHz) or Varian NMRS 600 (151 MHz) with CDCl3 as an internal standard (77.0 ppm). High resolution mass spectra were obtained by use of a Hitachi M-4100 GC/MS spectrometer or Thermo Fisher Scientific Exactive LC/MS spectrometer. For silica gel column chromatography, SiliCycle Inc. SiliaFlash F60 was used. The anhydrous TBAF was prepared from TBAF·3H2O by heating the hydrate at 40 °C for 6 h, at 60 °C for 12 h, at 80 °C for 6 h, and then at 120 °C for 12 h under reduced pressure [47]. The prepared anhydrous TBAF was used as a solution by addition of appropriate solvent such as DMF.

3.2. Procedure for the Synthesis of Coumarin Derivative 5 using Malonate 2

To a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate (1, 105 µL, 0.40 mmol) and diethyl malonate (2, 91 µL, 0.60 mmol) in DMF (3.4 mL) was added a solution of anhydrous TBAF (314 mg, 1.2 mmol) in DMF (0.6 mL) under argon atmosphere at room temperature. After being stirred at room temperature for 3 h, silica gel (1.0 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane = 1:8–1:0 with 2% CH2Cl2) afforded coumarin derivative 5 (85 mg, 86%).

5-Methoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid, Ethyl ester (5). Pale yellow crystals. mp 132.5–133.5 °C (CH2Cl2-iso-Pr2O). IR (KBr) 2981, 1764, 1704, 1609, 1478 cm⁻¹. 1H-NMR (CDCl3) δ 8.90 (1H, s), 7.55 (1H, t, J = 8.0 Hz), 6.93 (1H, br d, J = 8.0 Hz), 6.73 (1H, dd, J = 8.0, 0.5 Hz), 4.41 (2H, q, J = 7.0 Hz), 3.97 (3H, s), 1.41 (3H, t, J = 7.0 Hz). 13C-NMR (CDCl3) δ 163.3, 157.4, 156.9, 156.2, 144.1, 135.2, 116.0, 109.0, 108.9, 105.2, 61.8, 56.2, 14.3. HRMS (ESI) calcd for C13H13O3 (M+H⁺): 249.0763. Found: 249.0754. Elemental analysis (%) calcd for C13H12O2: C, 62.90; H, 4.87. Found: C, 62.69; H, 5.01.
3.3. Procedure for the Synthesis of Coumarin Derivative 5 using α-Bromomalonate 3

To a solution of diethyl α-bromomalonate (3, 68 µL, 0.40 mmol) in DMF (1.5 mL) was added Me₂Al (1.08 M in hexane, 370 µL, 0.40 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 5 min, 3-methoxy-2-(trimethylsilyl)phenyl triflate (1, 53 µL, 0.20 mmol) and TBAF (264 mg, 1.00 mmol) in DMF (0.5 mL) were added to the reaction mixture. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with saturated NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated at reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane = 1:20–1:1 with 2% CH₂Cl₂) afforded coumarin derivative 5 (42 mg, 85%).

3.4. Typical Procedure for the Synthesis of Dihydrobenzofurans

To a suspension of CsF (183 mg, 1.20 mmol) in DMF (2.0 mL) was added Et₂Zn (1.0 M in toluene, 200 µL, 0.20 mmol) under argon atmosphere at −40 °C. After being stirred at the same temperature for 5 min, diethyl α-chloromalonate 4a (32 µL, 0.20 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl triflate (1, 63 µL, 0.24 mmol) were added to the reaction mixture. After being stirred at −40 °C to room temperature for 12 h, silica gel (0.5 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (EtOAc/hexane = 1:20–1:4) afforded dihydrobenzofuran 7a (58.0 mg, 86%). Under similar reaction conditions, dihydrobenzofurans 7b and 11 were synthesized. Products 8a, 12 and 13 were also formed.

3-(Dimethylamino)-4-methoxy-2,2(3H)-benzofurandicarboxylic acid, 2,2-Diethyl ester (7a). Colorless oil. IR (KBr) 2982, 1741, 1601, 1492, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ 7.18 (1H, t, J = 8.0 Hz), 6.61 (1H, d, J = 8.2 Hz), 6.50 (1H, d, J = 8.0 Hz), 5.17 (1H, s), 4.40–4.12 (4H, m), 3.83 (3H, s), 2.22 (6H, br s), 1.30 (3H, t, J = 7.0 Hz). ¹³C-NMR (CDCl₃) δ 167.3, 165.7, 159.4, 157.5, 130.9, 111.3, 103.8 (2C), 94.6, 69.8, 62.3, 61.7, 55.2, 43.0, 14.1, 13.9. HRMS (ESI⁺) calcd for C₁₇H₂₄NO₆ (M+H⁺): 338.1598, Found: 338.1593.

3-(Dimethylamino)-4-methoxy-2,2(3H)-benzofurandicarboxylic acid, 2,2-Dimethyl ester (7b). Colorless oil. IR (KBr) 2982, 1741, 1601, 1492, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ 7.19 (1H, t, J = 8.2 Hz), 6.61 (1H, d, J = 8.2 Hz), 6.51 (1H, d, J = 8.2 Hz), 5.17 (1H, s), 3.84 (3H, s), 3.77 (3H, s), 2.23 (6H, br s), 1.30 (3H, t, J = 7.0 Hz). ¹³C-NMR (CDCl₃) δ 167.8, 166.1, 159.3, 157.5, 131.0, 111.1, 103.9 (2C), 94.8, 70.1, 55.2, 53.4, 52.7, 43.0 (br). HRMS (ESI⁺) calcd for C₁₅H₁₉NO₆Na (M+Na⁺): 332.1105, Found: 332.1145.

3-Hydroxy-4-methoxy-2,2(3H)-benzofurandicarboxylic acid, 2,2-Diethyl ester (8a). Colorless oil. IR (KBr) 3504, 2983, 1741, 1606, 1494, 1465 cm⁻¹. ¹H-NMR (CDCl₃) δ 7.24 (1H, t, J = 8.0 Hz), 6.63 (1H, d, J = 8.0 Hz), 6.50 (1H, d, J = 8.0 Hz), 6.01 (1H, br d, J = 4.5 Hz), 4.38–4.18 (4H, m), 3.85 (3H, s), 2.68 (1H, br s), 1.31 (3H, t, J = 7.0 Hz), 1.28 (3H, t, J = 7.0 Hz). ¹³C-NMR (CDCl₃) δ 166.2, 165.1, 159.8, 157.2, 132.4, 113.2, 104.6, 103.7, 93.2, 74.5, 62.7, 62.6, 55.6, 14.0, 13.9. HRMS (EI⁺) calcd for C₁₅H₁₉O₃Na (M+Na⁺): 333.0945, Found: 333.0942.
3-(Dimethylamino)-2,2(3H)-benzofurandicarboxylic acid, 2,2-Diethyl ester (11). Colorless oil. IR (KBr) 2982, 2940, 1769, 1742, 1598, 1472, 1462 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.27–7.23 (2H, m), 7.00–6.95 (2H, m), 5.08 (1H, s), 4.38–4.12 (4H, m), 2.18 (6H, br s), 1.31 (3H, t, $J = 7.1$ Hz), 1.25 (3H, t, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 167.2, 165.8, 157.7, 129.9, 125.8, 123.2, 121.6, 110.9, 93.2, 70.7, 62.5, 61.9, 42.4 (br), 14.1, 13.9. HRMS (ESI$^+$) calcd for C$_{16}$H$_{22}$NO$_5$ (M+H$^+$): 308.1492, Found: 308.1586.

α-Chloro-2-(ethoxycarbonyl)benzeneacetic acid, Ethyl ester (12). Colorless oil. IR (KBr) 2983, 2935, 1749, 1716, 1601, 1578, 1466, 1448 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.27–7.23 (2H, m), 7.00–6.95 (2H, m), 5.08 (1H, s), 4.38–4.12 (4H, m), 2.18 (6H, br s), 1.31 (3H, t, $J = 7.1$ Hz), 1.25 (3H, t, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 167.2, 165.8, 157.7, 129.9, 125.8, 123.2, 121.6, 110.9, 93.2, 70.7, 62.5, 61.9, 42.4 (br), 14.1, 13.9. HRMS (ESI$^+$) calcd for C$_{16}$H$_{22}$NO$_5$ (M+H$^+$): 308.1492, Found: 308.1586.

3-Hydroxy-2,2(3H)-benzofurandicarboxylic acid, 2,2-Diethyl ester (13). IR (KBr) 3491, 2984, 1741, 1601, 1477, 1468 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.41 (1H, br d, $J = 7.3$ Hz), 7.31 (br td, $J = 7.8$, 1.4 Hz), 7.04–7.00 (2H, m), 5.91 (1H, br d, $J = 4.6$ Hz), 4.38–4.21 (4H, m), 2.74 (1H, br s), 1.32 (3H, t, $J = 7.1$ Hz), 1.29 (3H, t, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 166.4, 165.3, 131.2, 125.8, 125.7, 122.5, 111.0, 92.8, 76.4, 62.8, 62.7, 14.1, 13.9. HRMS (ESI$^+$) calcd for C$_{14}$H$_{16}$O$_6$Na (M+Na$^+$): 303.0839, Found: 303.0843.

3.5. Procedure for the Insertion into α-Chloromalonate 4a

To a suspension of CsF (183 mg, 1.2 mmol) in MeCN (2.0 mL) were added diethyl α-chloromalonate (4a, 32 µL, 0.20 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl triflate (I, 63 µL, 0.24 mmol) under argon atmosphere at −20 °C. After being stirred at −20 °C to room temperature for 12 h, the reaction mixture was diluted with saturated NaHCO$_3$ and then extracted with AcOEt. The organic phase was dried over Na$_2$SO$_4$ and concentrated at reduced pressure. Purification of the residue by PTLC (AcOEt/hexane = 1:2) afforded the product 9 (31 mg, 52%).

α-Chloro-2-(ethoxycarbonyl)-3-methoxybenzeneacetic acid, Ethyl ester (9). IR (KBr) 2983, 1752, 1736, 1589, 1472, 1442 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.40 (1H, t, $J = 8.2$ Hz), 7.25 (1H, br d, $J = 8.5$ Hz), 6.93 (1H, br d, $J = 8.5$ Hz), 5.50 (1H, s), 4.42 (2H, q, $J = 7.1$ Hz), 4.27–4.15 (2H, m), 3.83 (3H, s), 1.39 (3H, t, $J = 7.1$ Hz), 1.24 (3H, t, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 167.8, 166.5, 156.6, 134.6, 131.2, 123.2, 120.4, 114.8, 62.6, 61.7, 56.1, 55.6, 14.1, 13.9. HRMS (ESI$^+$) calcd for C$_{14}$H$_{16}$O$_6$Na (M+Na$^+$): 323.0657, Found: 323.0642; HRMS (ESI$^+$) calcd for C$_{14}$H$_{16}$O$_6$Na (M+Na$^+$): 323.0657, Found: 323.0642; HRMS (ESI$^+$) calcd for C$_{14}$H$_{16}$O$_6$Na (M+Na$^+$): 323.0657, Found: 323.0642.

3.6. Procedure for the Synthesis of Benzofuran 15a

To a suspension of CsF (304 mg, 2.0 mmol) in DMF (4.0 mL) were added 3-methoxy-2-(trimethylsilyl)phenyl triflate (I, 105 µL, 0.40 mmol) and ethyl iodoacetate 14 (95 µL, 0.80 mmol) under argon atmosphere at 100 °C. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with saturated NaHCO$_3$ and then extracted with CH$_2$Cl$_2$. The organic phase was
dried over Na$_2$SO$_4$ and concentrated at reduced pressure. Purification of the residue by flash silica gel column chromatography (EtOAc/hexane = 1:20–1:4) afforded the product 15a (35 mg, 40%). Product 16 was also formed.

**4-Methoxy-2-benzofurancarboxylic acid, Ethyl ester (15a)**. Colorless oil. IR (KBr) 2981, 1726, 1609, 1570, 1474 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.62 (1H, d, $J = 1.0$ Hz), 7.35 (1H, t, $J = 8.2$ Hz), 7.18 (1H, d, $J = 8.2$ Hz), 6.67 (1H, d, $J = 8.2$ Hz), 4.43 (2H, q, $J = 7.1$ Hz), 3.94 (3H, s), 1.41 (3H, t, $J = 7.1$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 159.5, 156.9, 154.6, 144.4, 128.5, 117.8, 111.6, 105.1, 103.5, 61.4, 55.6, 14.3. HRMS (ESI$^+$) calcd for C$_{12}$H$_{13}$O$_4$ (M+H$^+$): 221.0808, Found: 221.0806.

**2-(2-Formyl-3-methoxyphenoxy)acetic acid, Ethyl ester (16)**. IR (KBr) 2981, 1756, 1689, 1597, 1474 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 10.57 (1H, s), 7.42 (1H, t, $J = 8.5$ Hz), 6.63 (1H, d, $J = 8.5$ Hz), 6.44 (1H, d, $J = 8.5$ Hz), 4.72 (2H, s), 4.26 (2H, q, $J = 7.0$ Hz), 3.90 (3H, s), 1.28 (3H, t, $J = 7.0$ Hz). $^{13}$C-NMR (CDCl$_3$) δ 189.2, 168.2, 161.9, 160.6, 135.6, 114.9, 105.1, 104.8, 66.0, 61.5, 56.1, 14.1. HRMS (ESI$^+$) calcd for C$_{12}$H$_{15}$O$_5$ (M+H$^+$): 239.0920. Found: 239.0912.

### 3.7. Typical Procedure for Conversion of Dihydrobenzofurans into Benzofurans

To a solution of 7a (40.0 mg, 0.12 mmol) in THF (2.4 mL) was added EtMgBr (1.0 M in THF, 300 µL, 0.30 mmol) under argon atmosphere at $-40\ ^\circ C$. After being stirred at $-40\ ^\circ C$ to room temperature for 3 h, the reaction mixture was diluted with saturated NH$_4$Cl and then extracted with AcOEt. The organic phase was dried over Na$_2$SO$_4$ and concentrated at reduced pressure to give quantitatively the crude adduct 17a, which was used for next reaction without further purification. To a solution of 17a (35.2 mg, 0.10 mmol) in AcOEt (1.0 mL) was added silica gel (0.50 g) under the atmosphere at room temperature. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (EtOAc/hexane = 1:10–1:3) afforded the product 15a (16.9 mg, 77%).

**4-Methoxy-2-benzofurancarboxylic acid, Methyl ester (15b)**. Colorless oil. IR (KBr) 2952, 2844, 1733, 1609, 1500 cm$^{-1}$. $^1$H-NMR (CDCl$_3$) δ 7.63 (1H, br s), 7.37 (1H, t, $J = 8.2$ Hz), 7.19 (1H, d, $J = 8.2$ Hz), 6.68 (1H, d, $J = 8.2$ Hz), 3.97 (3H, s), 3.96 (3H, s). $^{13}$C-NMR (CDCl$_3$) δ 160.0, 156.9, 154.7, 144.1, 128.7, 117.9, 111.9, 105.1, 103.5, 66.7, 52.3. HRMS (ESI$^+$) calcd for C$_{11}$H$_{10}$O$_4$Na (M+Na$^+$): 229.0471, Found: 229.0472.

### 3.8. Procedure for Direct Synthesis of Benzofuran 15b

To a suspension of CsF (183 mg, 1.20 mmol) in DMF (2.0 mL) was added Et$_2$Zn (1.0 M in toluene, 200 µL, 0.20 mmol) under argon atmosphere at $-60\ ^\circ C$. After being stirred at the same temperature for 5 min, methyl 2-chloroacetoacetate (18, 24 µL, 0.20 mmol) and 3-methoxy-2-(trimethylsilyl)phenyl triflate (1, 63 µL, 0.24 mmol) were added to the reaction mixture. After being stirred at $-60\ ^\circ C$ to room temperature for 12 h, Et$_2$Zn (1.0 M in toluene, 100 µL, 0.10 mmol) was added to the reaction mixture. After being stirred for 3 h, silica gel (0.5 g) was added to the reaction mixture, and then it was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (EtOAc/hexane = 1:20–1:4) afforded the product 15b (19.9 mg, 48%).
3.9. Procedure for Transformation of Dihydrobenzofuran 8a into Benzofuran 15a

To a solution of dihydrobenzofuran 8a (50 mg, 0.16 mmol) in THF (3.2 mL) was added KHMDS (0.50 M in toluene, 320 µL, 0.16 mmol) under argon atmosphere at −40 °C. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with saturated NaHCO₃ and then extracted with CH₂Cl₂. The organic phase was dried over Na₂SO₄ and concentrated at reduced pressure. Purification of the residue by PTLC (EtOAc/hexane = 1:4 with 2% CH₂Cl₂) afforded benzofuran 15a (33 mg, 96%).

4. Conclusions

We have demonstrated that the domino three-component coupling reaction of arynes with DMF and active methylenes or methines gave various heterocycles such as coumarin derivatives, dihydrobenzofurans and benzofurans.

Acknowledgments

This work was partially supported by JSPS KAKENHI Grant-in-Aid for Young Scientists (B) Grant Number 24790032.

Author Contributions

E. Yoshioka performed experiments and analyzed the data. S. Kohtani carried out part of the data analysis and experiments. H. Miyabe contributed to design of the study and manuscript writing.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Ramachary, D.B.; Jain, S. Sequential one-pot combination of multi-component and multi-catalysis cascade reactions: An emerging technology in organic synthesis. Org. Biomol. Chem. 2011, 9, 1277–1300.
2. Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. Efficient palladium-catalyzed cyclotrimerization of arynes: Synthesis of triphenylenes. Angew. Chem. Int. Ed. 1998, 37, 2659–2661.
3. Yoshikawa, E.; Yamamoto, Y. Palladium-catalyzed intermolecular controlled insertion of benzyne-benzyne-alkene and benzyne-alkyne-alkene—Synthesis of phenanthrene and naphthalene derivatives. Angew. Chem. Int. Ed. 2000, 39, 173–175.
4. Liu, Z.; Larock, R.C. Palladium-catalyzed, sequential, three-component cross-coupling of aryl halides, alkynes, and arynes. Angew. Chem. Int. Ed. 2007, 46, 2535–2538.
5. Jayanth, T.T.; Cheng, C.-H. Nickel-catalyzed coupling of arynes, alkenes, and boronic acids: Dual role of the boronic acid. Angew. Chem. Int. Ed. 2007, 46, 5921–5924.
6. Xie, C.; Zhang, Y.; Yang, Y. Gold-catalyzed efficient tandem assembly of terminal alkynes and arynes: Synthesis of alkynylated biphenyl derivatives. Chem. Commun. 2008, 4810–4812.
7. Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. Nickel-catalyzed [2+2+2] cycloaddition of arynes and an unactivated alkene: Synthesis of 9,10-dihydrophenanthrene derivatives. *Chem. Commun.* **2009**, 4284–4286.

8. Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. A cooperative copper- and palladium-catalyzed three-component coupling of benzyynes, allylic epoxides, and terminal alkynes. *Angew. Chem. Int. Ed.* **2009**, 48, 391–394.

9. Gerfaud, T.; Neuville, L.; Zhu, J. Palladium-catalyzed annulation of acyloximes with arynes (or alkynes): Synthesis of phenanthridines and isoquinolines. *Angew. Chem. Int. Ed.* **2009**, 48, 572–577.

10. Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. Silver-mediated trifluoromethylation-iodination of arynes. *J. Am. Chem. Soc.* **2013**, 135, 2955–2958.

11. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. CO₂ incorporation reaction using arynes: Straightforward access to benzoxazinone. *J. Am. Chem. Soc.* **2006**, 128, 11040–11041.

12. Zhao, J.; Larock, R.C. Synthesis of xanthones, thioxanthones, and acridones by the coupling of arynes and substituted benzoates. *J. Org. Chem.* **2007**, 72, 583–588.

13. Gilmore, C.D.; Allan, K.M.; Stoltz, B.M. Orthogonal synthesis of indolines and isoquinolines via aryne annulation. *J. Am. Chem. Soc.* **2008**, 130, 1558–1559.

14. Sha, F.; Huang, X. A multicomponent reaction of arynes, isocyanides, and terminal alkynes: Highly chemo- and regioselective synthesis of polysubstituted pyridines and isoquinolines. *Angew. Chem. Int. Ed.* **2009**, 48, 3458–3461.

15. Cant, A.A.; Bertrand, G.H.V.; Henderson, J.L.; Roberts, L.; Greaney, M.F. The benzyne aza-Claisen reaction. *Angew. Chem. Int. Ed.* **2009**, 48, 5199–5202.

16. Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. Reaction of benzyne with salicylaldehydes: General synthesis of xanthenes, xanthones, and xanthols. *Org. Lett.* **2009**, 11, 169–171.

17. Yoshida, H.; Asatsu, Y.; Mimura, Y.; Ito, Y.; Ohshita, J.; Takaki, K. Three-component coupling of arynes and organic bromides. *Angew. Chem. Int. Ed.* **2011**, 50, 9676–9679.

18. Bhunia, A.; Porwal, D.; Gonnade, R.G.; Biju, A.T. Multicomponent reactions involving arynes, quinolines, and aldehydes. *Org. Lett.* **2013**, 15, 4620–4623.

19. Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P.R.; Biju, A.T. Transition-metal-free multicomponent reactions involving arynes, N-heterocycles, and isatins. *Angew. Chem. Int. Ed.* **2013**, 52, 10040–10043.

20. Ikawa, T.; Takagi, A.; Goto, M.; Aoyama, Y.; Ishikawa, Y.; Itoh, Y.; Fujii, S.; Tokiwa, H.; Sakai, S. Regiocomplementary cycloaddition reactions of boryl- and silylbenzyynes with 1,3-dipoles: Selective synthesis of benzo-fused azole derivatives. *J. Org. Chem.* **2013**, 78, 2965–2983.

21. Stephens, D.; Zhang, Y.; Cormier, M.; Chavez, G.; Arman, H.; Larionov, O.V. Three-component reaction of small-ring cyclic amine with arynes and acetonitrile. *Chem. Comm.* **2013**, 49, 6558–6560.

22. Peña, D.; Pérez, D.; Guitián, E. Insertion of arynes into σ-bonds. *Angew. Chem. Int. Ed.* **2006**, 45, 3579–3581.

23. Yoshida, H.; Ohshita, J.; Kunai, A. Aryne, ortho-quinone methide, and ortho-quinodimethane: Synthesis of multisubstituted arenes using the aromatic reactive intermediates. *Bull. Chem. Soc. Jpn.* **2010**, 83, 199–219.

24. Heaney, H.; McCarty, C.T. Reactions of arynes with carbonyl compounds. *J. Chem. Soc. Chem. Commun.* **1970**, 1970, 123a.
25. Heaney, H.; Jablonski, J.M.; McCarty, C.T. Aryne chemistry. Part XXXI. Reactions of arynes with αβ-unsaturated aldehydes. *J. Chem. Soc. Perkin Trans. 1*, 1972, 2903–2910.

26. Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. A 2:1 coupling reaction of arynes with aldehydes via *o*-quinone methides: Straightforward synthesis of 9-arylxanthenes. *Org. Lett.* 2004, 6, 4049–4051.

27. Hamura, T.; Ibusuki, Y.; Uekusa, H.; Matsumoto, T.; Siegel, J.S.; Baldridge, K.K.; Suzuki, K. Dodecamethoxy- and hexaoxotricyclobutabenzene: Synthesis and characterization. *J. Am. Chem. Soc.* 2006, 128, 10032–10033.

28. Feltenberger, J.B.; Hayashi, R.; Tang, Y.; Babiash, E.S.C.; Hsung, R.P. Enamide-benzyne-[2+2] cycloaddition: Stereoselective tandem [2+2]-pericyclic ring-opening-intramolecular *N*-tethered [4+2] cycloadditions. *Org. Lett.* 2009, 11, 3666–3669.

29. Biswas, K.; Greaney, M.F. Insertion of arynes into thioureas: A new amidine synthesis. *Org. Lett.* 2011, 13, 4946–4949.

30. Chakrabarty, S.; Chatterjee, I.; Tebben, L.; Studer, A. Reactions of arynes with nitrosoarenes—An approach to substituted carbozoles. *Angew. Chem. Int. Ed.* 2013, 52, 2968–2971.

31. Li, R.; Wang, X.; Wei, Z.; Wu, C.; Shi, F. Reaction of arynes with vinylogous amides: Nucleophilic addition to the *ortho*-quinodimethide intermediate. *Org. Lett.* 2013, 15, 4366–4369.

32. Yoshioka, E.; Kohtani, S.; Miyabe, H. Sequential reaction of arynes via insertion into the π-bond of amides and trapping reaction with dialkylzincs. *Org. Lett.* 2010, 12, 1956–1959.

33. Yoshioka, E.; Miyabe, H. Insertion of arynes into the carbon-oxygen double bond of amides and its application into the sequential reactions. *Tetrahedron* 2012, 68, 179–189.

34. Yoshioka, E.; Kohtani, S.; Miyabe, H. A multicomponent coupling reaction induced by insertion of arynes into the C=O bond of formamide. *Angew. Chem. Int. Ed.* 2011, 50, 6638–6642.

35. Yoshioka, E.; Tanaka, H.; Kohtani, S.; Miyabe, H. Straightforward synthesis of dihydrobenzofurans and benzofurans from arynes. *Org. Lett.* 2013, 15, 3938–3941.

36. For a related example, see: Yoshida, H.; Ito, Y.; Ohshita, J. Three-component coupling using arynes and DMF: Straightforward access to coumarins via ortho-quinone methides. *Chem. Commun.* 2011, 47, 8512–8514.

37. Meier, H. Benzoxetes and benzothietes—Heterocyclic analogues of benzocyclobutene. *Molecules* 2012, 17, 1548–1570.

38. Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-elimination of *o*-trimethylsilylphenyl triflate to benzyne under mild conditions. *Chem. Lett.* 1983, 12, 1211–1214.

39. Muzart, J. *N,N*-Dimethylformamide: Much more than a solvent. *Tetrahedron* 2009, 65, 8313–8323.

40. Ding, S.; Jiao, N. *N,N*-Dimethylformamide: A multipurpose building block. *Angew. Chem. Int. Ed.* 2012, 51, 9226–9237.

41. Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. Straightforward construction of diarylmethane skeletons via aryne insertion into carbon-carbon σ-bonds. *Chem. Commun.* 2007, 1505–1507.

42. Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. Fluorenes as new molecular scaffolds for carbon-carbon σ-bond cleavage reaction: Acylfluorenylation of arynes. *Chem. Commun.* 2008, 5963–5965.
43. Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. Selective synthesis of o-acylbenzylphosphonates by insertion reactions of arynes into β-ketophosphonates. *J. Org. Chem.* **2009**, *74*, 5691–5694.

44. Tadross, P.M.; Virgil, S.C.; Stoltz, B.M. Aryne acyl-alkylation in the general and convergent synthesis of benzannulated macrolactone natural products: An enantioselective synthesis of (−)-curvularin. *Org. Lett.* **2010**, *12*, 1612–1614.

45. Tadross, P.M.; Gilmore, C.D.; Bugga, P.; Virgil, S.C.; Stoltz, B.M. Regioselective reactions of highly substituted arynes. *Org. Lett.* **2010**, *12*, 1224–1227.

46. Witiak, D.T.; Newman, H.A.I.; Poochikian, G.K.; Fogt, S.W.; Baldwin, J.B.; Sober, C.L.; Feller, D.R. Diethyl (4bα,4cα,9aα,9bα)-3,6-dichlorocyclobuta[1,2-b:3,4-b']bisbenzofuran-9a,9b(4bH,4cH)-dicarboxylate: The cis,syn photodimer of ethyl 5-chlorobenzofuran-2-carboxylate, an analogue related to the antilipidemic drug clofibrate. *J. Med. Chem.* **1978**, *21*, 833–837.

47. Generation of anhydrous TBAF is likely to lead to certain amounts of decomposition via Hofmann elimination. See: Sharma, R.K.; Fry, J.L. Instability of anhydrous tetra-n-alkylammonium fluorides. *J. Org. Chem.* **1983**, *48*, 2112–2114.

Sample Availability: Not available.

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