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Phosphine-Mediated Domino Benzannulation Strategy for the Construction of Highly Functionalized Multiaryl Skeletons

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Multiaryl compounds, especially biaryl compounds, represent privileged structural motifs in natural products, pharmaceuticals, polymers, sensors,[1] and functional organic materials.[2] Consequently, efficient methods for the construction of multiaryl compounds are of utmost importance and have been greatly investigated. Traditional strategies have focused on the aryl–aryl bond-formation reaction (Figure 1a) through "the change of partner" methodology, for

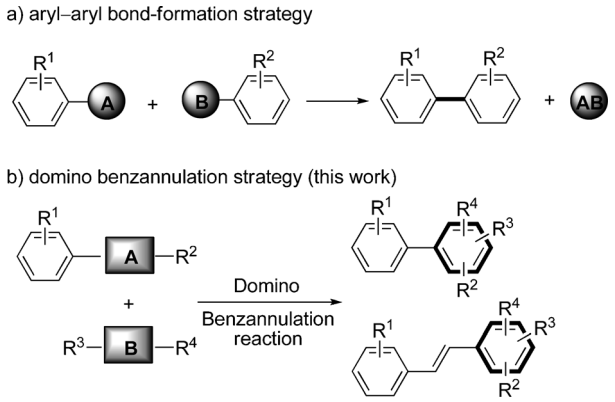

Figure 1. Strategies for the construction of multiaryl compounds: a) the traditional aryl–aryl bond-formation strategy and b) the domino benzannulation strategy investigated in this work.

which various catalytic methods and substrates have been developed.[3–6] Transition-metal-assisted cross-coupling reactions[3] and homolytic aromatic substitution (HAS) with aryl radicals[4] have become the predominant strategies for the aryl–aryl bond-formation reaction. Recently, elegant approaches, such as organocatalyzed direct C–H arylation reactions,[5] have also been developed. Although great strides have been made in the aforementioned aryl–aryl bond formation strategies, with most of those devised to date relying heavily on the activation of aryl halides (Ar–X, X = I, Br, or Cl) through a two-electron or single-electron reduction process.[5e] As a consequence, the construction of multiaryl compounds containing C–X bonds through aryl–aryl bond formation strategies is extremely challenging. Moreover, harsh reaction conditions and difficulties associated with the control of chemo- and regionselectivity are often problematic in the cross-coupling reactions.[6] All of these offer unique opportunities to discover novel strategies for the formation of multiaryl compounds, especially halide-containing and unsymmetrical multiaryl compounds, which could serve as a basic skeleton for further structural modification. Herein, we report a new domino benzannulation strategy (Figure 1b) for the construction of multiaryl skeletons. Diverse aromatic compounds and functional groups will be assembled in a multiaryl molecule through a core domino process.

Although many benzannulation reactions[7] have gradually been used in the construction of aromatic compounds, the asymmetry and complexity of acyclic substrates, as well as the poor regiochemistry of these reactions are always problematic.[7d] In addition, significant domino approaches have recently been developed in the intramolecular benzannulation reaction, some of which have been primarily used in the construction of multiaryl skeletons.[7i–m] However, intermolecular versions[7d,f] of these reactions remain a challenge. On the other hand, phosphine-mediated domino reactions have become powerful tools in the generation of carbo- and heterocycles.[8] In particular, phosphine-catalyzed domino reactions with allenoates or allylic carbonates have emerged as a key platform for the generation of molecular complexity.[9] So far, to the best of our knowledge, no aromatic compound has been directly constructed by this strategy.[10] Based upon these studies, as well as our work concerning phosphine-mediated domino reactions,[11] we now report the first phosphine-mediated benzannulation reaction between β,γ-unsaturated α-ketoester **1** and allyic carbonate **2**. In this reaction, carbonate **2** served as a new kind of C_3 synthon,[12] which is different from its traditional 1,3-zwitterionic intermediate or C_1 manner of reacting.[13]

We initiated our investigation by subjecting carbonate **2a** to β,γ-unsaturated α-ketoester **1a** in the presence of PPh_3 at room temperature. To our delight, triaryl compound **3a** was obtained in 38% yield (Table 1, entry 1). The use of THF, CH_3CN, or toluene as the solvent led to triaryl compound **3a** as the major compound in moderate or lower yield (Table 1, entries 2–4). DMF as the solvent gave a relatively better result for **3a** with respect to the reaction time and yield (Table 1, entry 5). The yield, to some extent, was sensi-

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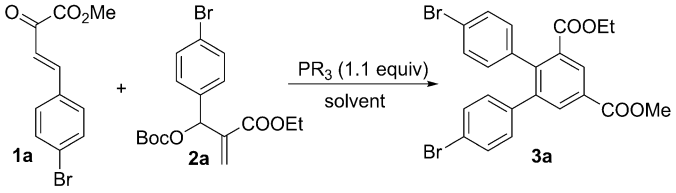
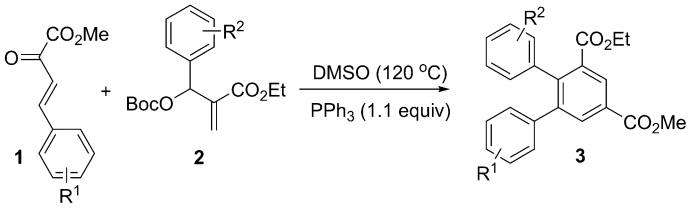
Table 1. Optimization of the phosphine-mediated domino benzannulation reaction.[a]



Entry	PR_3	T [°C]	Solvent	t [h]	Yield [%][b]
1	PPh_3	RT	DCE	24	38
2	PPh_3	RT	THF	24	16
3	PPh_3	RT	CH_3CN	12	44
4	PPh_3	RT	toluene	24	48
5	PPh_3	RT	DMF	12	55
6	PPh_3	80	DMF	1.5	72
7[c]	PPh_3	80	DMF	2	66
8[d]	PPh_3	80	DMF	1	73
9	PPh_3	120	DMF	1.5	80
10	PPh_3	150	DMF	1.5	83
11	PPh_3	120	DMSO	1.5	84
12[e]	PPh_3	120	DMSO	1.5	80
13	PPh_2Et	120	DMSO	1.5	85
14	$PPhEt_2$	120	DMSO	1	72
15	$P(p\text{-}ClC_6H_4)_3$	120	DMSO	4	64

[a] Reaction conditions: **1a** (1.0 equiv, 0.25 mmol), **2a** (1.5 equiv), PPh_3 (1.1 equiv) in a solvent (5.0 mL) at the indicated temperature (DCE = dichloroethene). [b] Isolated yields. [c] **2a** (1.2 equiv) was used. [d] **2a** (2.0 equiv) was used. [e] PPh_3 (2.0 equiv) was used.

Table 2. Phosphine-mediated domino reaction for the construction of triaryl compounds.[a]



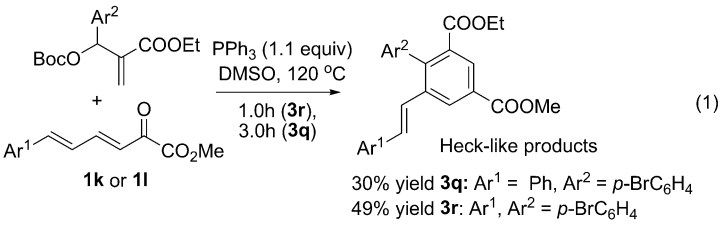
Entry	R^1	R^2	t [h]	Yield [%][b]
1	4-Br	4-Br	1.5	84 (**3a**)
2	4-Br	H	2.0	74 (**3b**)
3	4-Br	4-Me	2.5	65 (**3c**)
4	3-Br	3-Br	1.5	80 (**3d**)
5	3-Br	4-Br	1.5	77 (**3e**)
6	2-Cl	4-Br	2.0	85 (**3f**)
7	2-Cl	3-Br	2.0	80 (**3g**)
8	2,4-Cl	4-Br	0.5	62 (**3h**)
9	2,4-Cl	2,4-Cl	5.0	66 (**3i**)
10	H	4-Br	2.0	76 (**3j**)
11	4-Me	H	2.5	70 (**3k**)
12	4-Me	4-Br	2.0	81 (**3l**)
13	4-OMe	4-Br	2.5	68 (**3m**)
14	$4\text{-}NO_2$	$4\text{-}NO_2$	0.5	49 (**3n**)
15[c]	2-naphthyl	H	3.0	62 (**3o**)
16[d]	furan-2-yl	4-Br	3.0	69 (**3p**)

[a] Reaction conditions: **1** (1.0 equiv, 0.25 mmol), **2** (1.5 equiv), PPh_3 (1.1 equiv), DMSO (5.0 mL), 120 °C. [b] Isolated yields. [c] $R^1C_6H_4$ = 2-naphthyl. [d] $R^1C_6H_4$ = furan-2-yl.

tive to the temperature and thus the reaction benefitted from higher temperatures (Table 1, entries 5 and 6). Furthermore, DMSO was proven to be the best solvent (Table 1, entries 9 and 11). Altering the ratio of **1a** to **2a** or increasing the amount of PPh_3 had little effect on the yield (Table 1, entries 6–8). Next, the effect of the nucleophilicity of the phosphine on this reaction was studied. PPh_3 and PPh_2Et gave similar results (Table 1, entries 11 and 13), suggesting that adjusting the nucleophilicity could not result in a higher yield (Table 1, entries 14 and 15).

Under the optimized reaction conditions, we evaluated the generality of this domino reaction. The results showed that these processes serve as a general and efficient method to prepare a variety of triaryl compounds (**3**) in modest to high yields. Furthermore, the electronic properties and position of substitution on **1** and **2** were found to have a limited effect on these processes (Table 2). For the β,γ-unsaturated α-ketoester **1** and substrate **2** bearing a strong electron-withdrawing group on the aromatic ring, such as a nitro group (Table 2, entry 14), the desired product could also be obtained in moderate yield. However, increased steric hindrance on substrates **2** was found to negatively influence the reaction time (Table 2, entry 9). More importantly, halide-substituted mixed triaryl compounds could be constructed by this method (Table 2, entries 1–13 and 16). The presence of C–X bonds in multiaryl skeletons increases the possibility for structural modification and thereby enhances the synthetic utility of this reaction. Furan-2-yl- and 2-naphthyl-substituted β,γ-unsaturated α-ketoesters **1** were also successfully employed in this reaction (Table 2, entries 15 and 16).

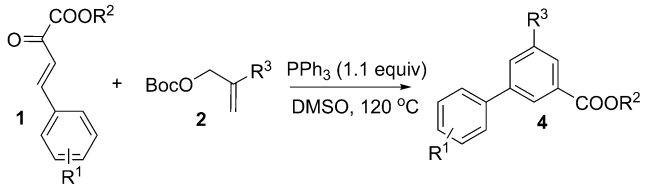
Inspired by these results, we envisaged that Heck-like products might be obtained by this strategy. Indeed, this hypothesis was proven by further investigation [Eq. (1)]. For example, the reaction of **1k** with **2** was sluggish, but gave the desired product **3q** in 30% yield with 16% recovered **1k**. Pleasingly, **1l** gave the corresponding Heck-like product **3r** in 49% yield, indicating that to some extent the yield and reaction time was sensitive to the reactivity of β,γ,δ,ε-unsaturated α-ketoester **1**. To our knowledge, this was the first time the construction of Heck-like products had been achieved in a metal-free manner.



(1)

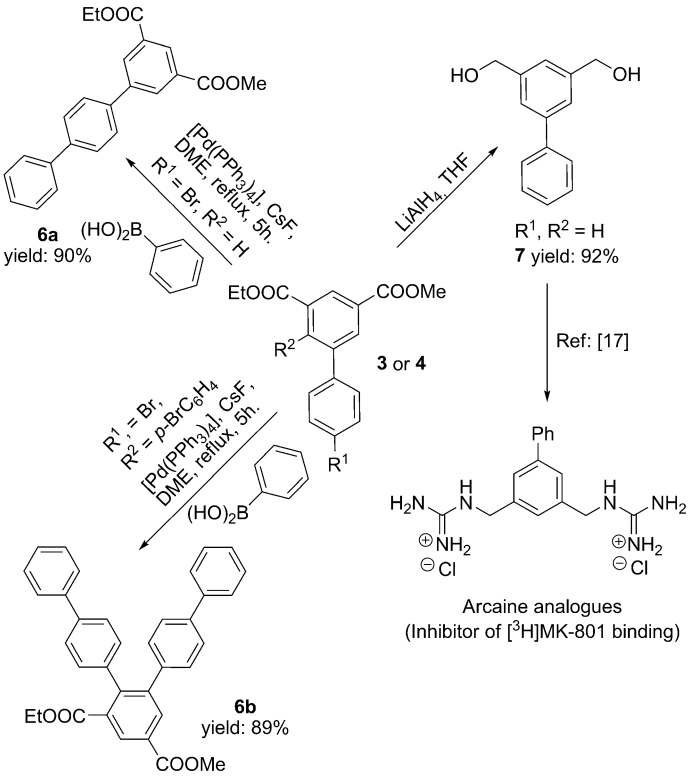
Subsequently, the reaction of unsubstituted carbonate **2** was examined under the optimal conditions to obtain biaryls **4**. This reaction also showed good tolerance of electronic properties and the position of the aryl-substitution on **1**,

Table 3. Phosphine-mediated domino reaction for the construction of biaryl compounds.[a]



Entry	R^1	R^2	R^3	t [h]	Yield [%][b]
1	4-Me	Me	COOEt	1.5	71 (**4a**)
2[c]	4-Br	Me	COOEt	1.0	52 (58; **4b**)
3[c]	4-Cl	Me	COOEt	1.0	51 (57; **4c**)
4[c]	4-Br	*i*Pr	COOEt	1.5	46 (56; **4d**)
5	3-Me	Me	COOEt	1.5	61 (**4e**)
6	H	Me	COOEt	1.5	66 (**4f**)
7[d]	2-naphthyl	Me	COOEt	1.5	57 (**4g**)
8	4-Me	Me	CN	2.0	50 (**4h**)
9	4-Me	Me	COOBu	1.5	61 (**4i**)
10	4-Me	Me	COOMe	1.5	70 (**4j**)
11[e]	furan-2-yl	Me	COOEt	2.0	49 (**4k**)
12[c]	2-Cl	Me	COOEt	1.0	58 (63; **4l**)

[a] Reaction conditions: **1** (1.0 equiv, 0.5 mmol), **2** (1.5 equiv), PPh_3 (1.1 equiv), DMSO (5.0 mL), 120 °C. [b] Isolated yields. [c] The yields in parentheses are for the reactions carried out at 80 °C. [d] $R^1C_6H_4$ = 2-naphthyl. [e] $R^1C_6H_4$ = furan-2-yl.



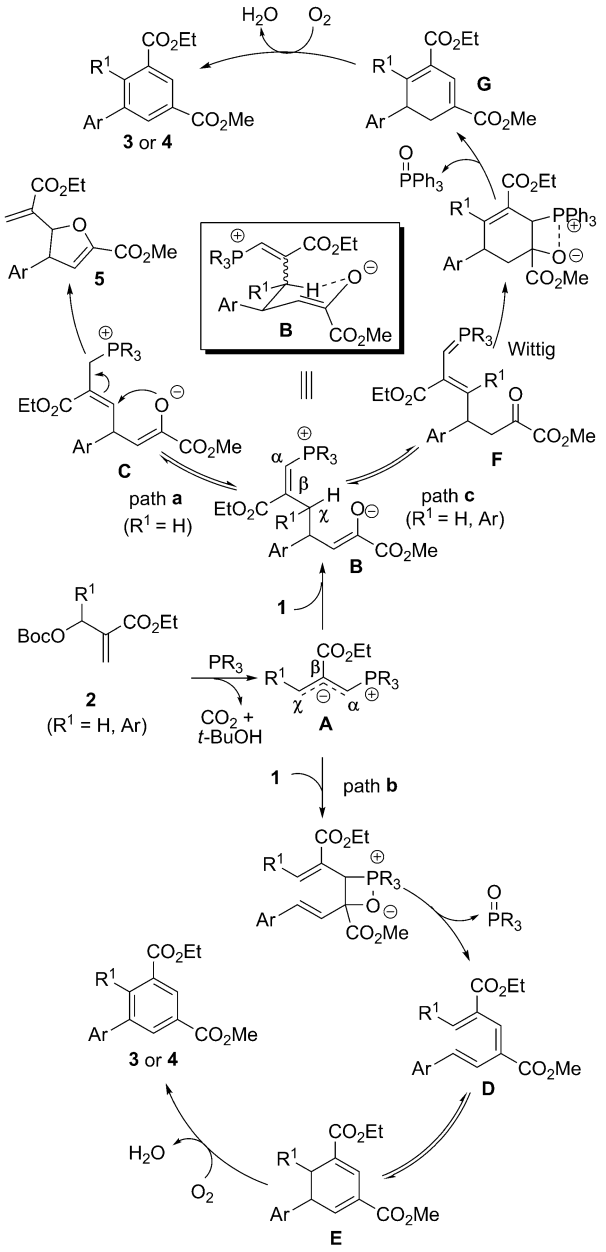
Scheme 1. The application of the synthesized multiaryl compounds (DME = dimethoxyethane).

giving compounds **4** in modest to good yields. However, the reaction was sensitive to the size of the ester substituent R^3 (Table 3, entries 1, 9, and 10). Moreover, *tert*-butyl(2-cyanoallyl) carbonate was also able to accomplish the formation of **4**, albeit with a slightly lower yield (Table 3, entry 8). The structures of **3** and **4** were characterized by a combination of NMR and HRMS spectra and single-crystal X-ray analysis (**4b**).[14] In addition, unsubstituted carbonate **2** was much more active than the Ar-substituted analogue. However, some side reactions resulted in the formation of the desired product in relatively lower yields when it reacted with more active β,γ-unsaturated α-ketoesters **1** (Table 3, entries 2–4). For instance, in Table 3, entries 2 and 3, a trace amount of dihydrofurans **5** (**5a** and **5b**) was isolated or could be detected by NMR spectroscopy (Table 3, entry 4) as by-products.[15] It should be noted that at a lower temperature (80 °C) more active β,γ-unsaturated α-ketoesters **1** performed better than at 120 °C (Table 3, entries 2–4 and 12).

This phosphine-mediated domino reaction strategy is complementary to the traditional cross-coupling methods. The combination of these two methods could provide a powerful platform for generating complex multiaryl compounds, which is especially powerful for the construction of asymmetric multiaryl skeletons, such as **6a** and **6b** (Scheme 1). These skeletons are often exploited in the design of organic electroluminescent (OEL) devices and liquid crystalline materials.[16] Moreover, after transformation from **3** or **4** in a few steps, the biologically active molecular arcaine analogues, which act as inhibitors of [^{3}H]MK-801 binding, can be obtained.[17]

The detailed mechanisms of these selective domino reactions have not yet been clarified. However, according to our experimental results[13b,15] and some related studies,[18] the formation of the dihydrofuran byproducts was through a [4+1] annulation reaction, in which allyic carbonate **2** served as a C_1 synthon. The aforementioned reaction was initiated by the formation of the allylic phosphorus ylide **A** through the commonly accepted addition–elimination and deprotonation processes (Scheme 2). Subsequently, ylide **A** underwent the sterically favored γ-carbanion addition to β,γ-unsaturated α-ketoester **1a**, yielding intermediate **B**. Intermediate **B** interconverts with **C** through proton transfer (path **a**, between the γ- and α-carbon atoms). Then, intramolecular annulation involving oxygen-anion addition to the olefinic double bond delivers the 2,3-dihydrofurans.[15]

However, this reaction was highly chemoselective in favor of the formation of the multiaryl compounds. Presumably, the intermolecular Wittig reaction first occurs between allylic phosphorus ylide **A** and **1** to produce intermediate **D**. Then, intermediate **D** accomplishes an electrocyclization reaction, generating intermediate **E**. Intermediate **E** subsequently undergoes an oxidative aromatization processes to give product **3** or **4** (path **b**). In this mechanism, the aryl rings are attached to the carbon centers directly involved in the 6p-electrocyclization step. Thus, it allows for a logical explanation for the observed effects relating to the electronic properties of the aryl substituents. In addition, in another possible reaction pathway (path **c**), which could not be com-



Scheme 2. Plausible mechanisms for the formation of multiaryl compounds.

pletely ruled out, the factors that control the chemoselectivity might be due to a preference in the proton transfer (path **c**, between the γ-carbon atom and the oxygen anion) in a six-membered transition state from intermediate **B**. Thus, the equilibrium between intermediates **C**, **B**, and **F** would lie overwhelmingly on the side of **F** under these reaction conditions. Intermediate **F** would subsequently undergo an intramolecular Wittig reaction to yield intermediate **G**, followed by an oxidative aromatization processes to give product **3** or **4**. We tried to obtain the intermediates **E** or **G** by quenching the reaction under the acid conditions. However, we failed in this effort and neither intermediates **E** nor **G** were obtained. The instability of intermediate **E** or **G** might be the driving force in losing hydrogen by air oxidation to form the aromatic compound easily.[7i]

In conclusion, we have developed a novel domino benzannulation reaction strategy for the construction of multiaryl compounds in moderate to high yields. In these reactions, diverse aromatic compounds and functional groups (C–X) can be assembled in a multiaryl molecule through a core domino process, which increases the possibilities for structural modification. This approach has also been applied to the synthesis of Heck-like products. Furthermore, the allyic carbonate **2** serves as a new kind of C_3 synthon, which is different from its traditional 1,3-zwitterionic intermediate reaction mode. Further effort towards the application of this strategy in organic synthesis and the detailed mechanism will be investigated by our group.

Experimental Section

Experimental details: PPh_3 (1.1 equiv) was added to a mixture of β,γ-unsaturated α-keto ester **1** (1.00 equiv, 0.25 mmol) and allylic carbonate **2** (1.50 equiv) in DMSO (5.0 mL). The resulting suspension was kept at 120 °C until completion of the reaction (the reaction was monitored by TLC). Dichloromethane (20 mL) was then added to the reaction mixture and it was washed with water (3×10 mL). The organic layer was separated and dried over sodium sulfate. After filtration and concentration on a rotary evaporator, the residue was purified by column chromatography on silica gel (gradient eluent: petroleum ether/ethyl acetate 30:1–20:1) to afford the multiaryl compound.

Acknowledgements

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Keywords: benzannulation reactions · domino reactions · multiaryls · organocatalysts · phosphine

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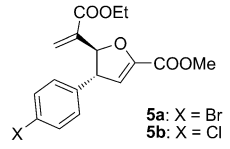
[14] CCDC-835163 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] The structures of **5a** and **5b** were characterized by a combination of NMR and HRMS spectra (for the details see the Supporting Information). The yields of the dihydrofurans were less than 5%. Dihydrofurans could be detected at both 80 and 120 °C.



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Domino Reactions

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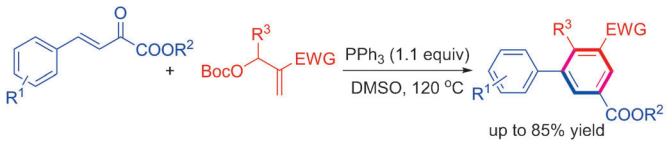
Phosphine-Mediated Domino Benzannulation Strategy for the Construction of Highly Functionalized Multiaryl Skeletons



A skeleton crew: A phosphine-mediated domino benzannulation strategy was developed for the synthesis of multiaryl skeletons (see scheme). A wide range of aromatic compounds and functional groups can be assembled into a multiaryl molecule through a core domino process.

