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Oxygenative and Dehydrogenative [3 + 3] Benzannulation Reactions of α,β-Unsaturated Aldehydes and γ-Phosphonyl Crotonates Mediated by Air: Regioselective Synthesis of 4-Hydroxybiaryl-2-carboxylates

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Supporting Information

ABSTRACT: Regioselective synthesis of 4-hydroxybiphenyl-2-carboxylates via the base-mediated oxygenative [3 + 3] benzannulation reaction of α,β-unsaturated aldehydes and γ-phosphonyl crotonates is reported. A hydroxyl group is installed in the final product on the originally phosphorus-bound carbon via a novel oxygenative and dehydrogenative transformation. The reaction proceeds rapidly in an open flask, uses atmospheric oxygen as an oxidant, and affords good yields of substituted biaryl phenols.

The biaryl motif is a recurring substructure of a number of natural products, bioactive molecules, chiral catalysts, and functional materials.[1] Development of methods for biaryl synthesis has, therefore, been an important and fertile area of investigation.[2] Transition-metal-mediated reactions such as Suzuki−Miyaura, Negishi, and Stille couplings are among the most commonly used methods of biaryl construction.[3] Directed arylation via metal-catalyzed C−H activation has recently emerged as a powerful method of biaryl synthesis.[4] Both of these approaches, however, rely on the availability of arene building blocks armed with functional or directing groups. Such functionalized arenes are, in turn, mostly prepared from feedstock chemicals by electrophilic and (less frequently) nucleophilic aromatic substitution reactions.[5] Regioselectivity of aromatic substitution reactions is controlled by the electronic nature of the arene and the directing effects of existing substituents. The construction of polysubstituted arenes via aromatic substitution becomes challenging when such directing effects do not favor the desired regiochemistry. *Benzannulation* reactions, the denovo assembly of arenes from acyclic precursors, constitute an alternative and superior approach for the regioselective synthesis of polysubstituted aromatic rings.[6] A vast majority of benzannulation reactions involve two components, and they are classified on the basis of the number of carbon atoms that each of them contributes.[7] The benzannulation approach is characterized by beneficial attributes such as the availability of a variety of acyclic precursors, different modes of annulations, and scope for catalysis. Recent reports by Lee and others on the synthesis of highly substituted phenols and benzene derivatives from acyclic precursors illustrate the synthetic potential of benzannulation reactions.[8] The elegant work of Li on the construction of various terpenoid natural products also showcases the utility of benzannulation reactions.[9]

A careful survey of benzannulation chemistry reveals that the aerial oxidation of cyclohexadiene intermediates to arenes is a frequently encountered mechanistic event. Two such oxidative benzannulation reactions pertinent to the present work are depicted in Scheme 1.

In 2012, Liu and Zhao reported an oxidative [3 + 3] benzannulation reaction of dimethyl glutaconate **1** and α,β-unsaturated carbonyl compounds **2** to afford highly substituted arenes **3** (Scheme 1a).[10] Our recent investigations on the cyclocondensation reactions of unsaturated sulfones led to the discovery of an oxidative [3 + 3] benzannulation reaction for the regioselective synthesis of substituted sulfonylarenes **4** (Scheme 1b).[11] These benzannulations presumably proceed via base-mediated cyclocondensation of a 1,3-bisnucleophile with a 1,3-biselectrophile to generate a cyclohexadiene intermediate **5**. Subsequent aerial oxidation (dehydrogenation) of the latter affords the substituted arene (Scheme 1c). The success of this reaction provided an impetus to explore this area in detail. In this context, the utility of the γ-phosphonyl crotonate **6** as a 1,3-bisnucleophile was examined. Our efforts along this direction culminated in the serendipitous discovery of a novel oxidative benzannulation reaction for the synthesis of substituted biaryl phenols **7** (Scheme 1d).

Interestingly, the overall process may be termed a *dehydrogenative and oxygenative [3 + 3+O] benzannulation* wherein the phosphonate unit of **6** is replaced by a hydroxyl group in the final product **7**. The details of our preliminary investigation that led to the development of this novel transformation are presented in the following sections.

The study was initiated by screening various bases for the reaction of cinnamaldehyde **8** and the phosphonate **6a**[12] in an

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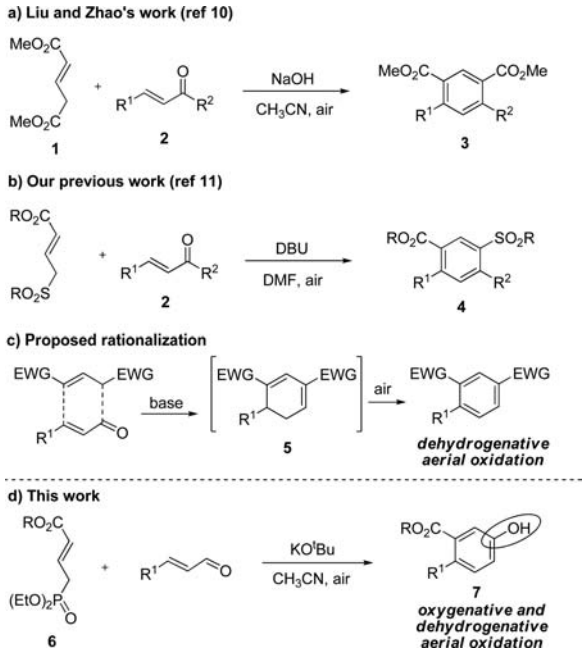
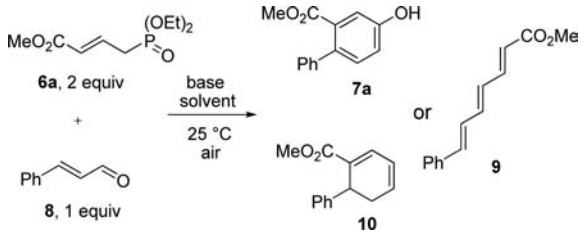
Scheme 1. (a) [3 + 3] Benzannulation of Glutaconates; (b) [3 + 3] Benzannulation of Sulfonyl Crotonates; (c) Common Mechanistic Framework for These Benzannulations; (d) Present Work



open flask at room temperature (Table 1). Although the likelihood of a facile Wadsworth−Emmons reaction was obvious, our recent experience[11] with a similar combination of ambident reactants (Scheme 1b) warranted an exploration. The use of potassium carbonate, DBU, and cesium carbonate led to the consumption of **6a**; however, no stable product could be isolated

Table 1. Optimization of Reaction Conditions for the Base-Mediated Union of Cinnamaldehyde 8 and Phosphonate 6a[a]



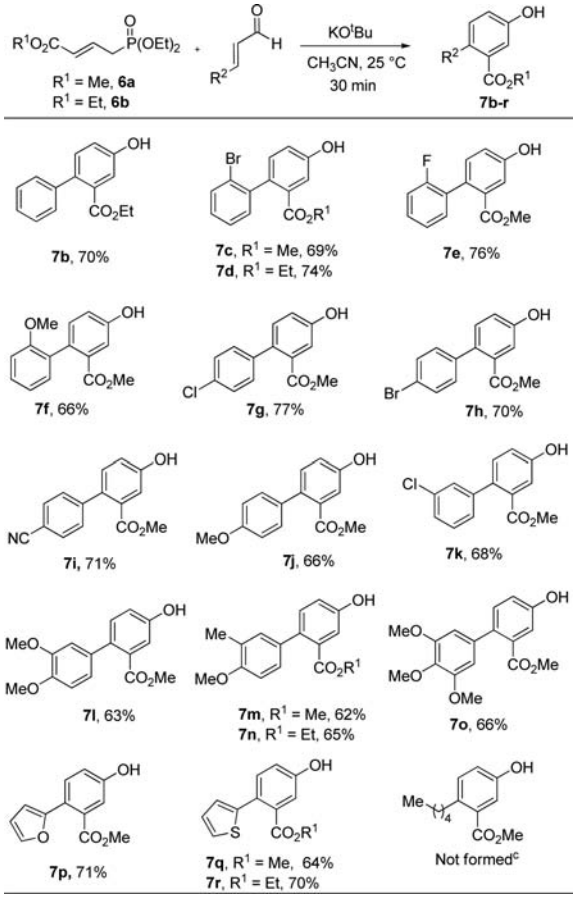
entry	base (equiv)	solvent	time (h)	product (yield, %)[b]
1	K_2CO_3 (3)	CH_3CN	2	
2	K_2CO_3 (2)	DMF	2	
3	DBU (2)	DMF	1	
4	Cs_2CO_3 (2)	CH_3CN	2	
5	NaH (2)	THF	2	**9** (35)
6	KO^{t}Bu (2)	MeOH	2	
7	**KO^{t}Bu (2)**	**CH_3CN**	**0.5**	**7a (67)**
8	KO^{t}Bu (3)	CH_3CN	0.5	**7a** (60)
9	KO^{t}Bu (1)	CH_3CN	0.5	**7a** (52)
10[c]	KO^{t}Bu (2)	CH_3CN	0.5	**7a** (44)
11[d]	KO^{t}Bu (2)	CH_3CN	0.5	**10** (62)
12[e]	KO^{t}Bu (2)	CH_3CN	0.5	**7a** (66)

[a]Reaction conditions: **6a** (0.50 mmol), **8** (0.25 mmol), base, CH_3CN (2 mL). [b]Isolated yield after chromatography. [c]Reaction at 0 °C. [d]Reaction under deoxygenated conditions. [e]Reaction under an oxygen balloon.

(entries 1−4). It was observed that only sodium hydride in THF promoted the Wadsworth−Emmons reaction to afford 35% of the triene ester **9**[13] (entry 5). On the other hand, the reactions mediated by potassium *tert*-butoxide (entries 7−10) furnished an unexpected product that was assigned the structure **7a** based on its spectroscopic data (see the SI for details). The best yield for **7a** was obtained when **8** was reacted with 2 molar equiv each of the phosphonate **6a** and base in acetonitrile in an open flask (entry 7). Interestingly, the substituted cyclohexadiene **10** was obtained in 62% yield when the reaction was run at carefully deoxygenated conditions (entry 11). The yield of the benzannulation reaction was practically unchanged when the reaction was carried out under a balloon filled with oxygen.

The unexpected formation of a phenol derivative prompted us to explore the scope of this reaction. A variety of α,β-unsaturated aldehydes were prepared, and they were treated with the phosphonates **6a**,**b** under the optimized reaction conditions. The results are summarized in Scheme 2.

Scheme 2. Scope of the Oxidative Benzannulation Reaction[a,b]



[a]Reaction conditions: **6a**,**b** (1 mmol), enal (0.5 mmol), KO^{t}Bu (1 mmol), acetonitrile (4 mL), 25 °C, air, 0.5 h. [b]Yields of products isolated after column chromatography. [c]Expected product for the reaction of **6a** and (*E*)-oct-2-enal.

An array of 2-carboxy-4-hydroxy biaryls **7a**−**r** was obtained from readily available starting materials. The β-aryl rings of enals can accommodate electron-releasing as well as electron-withdrawing substituents without compromising the efficiency of the oxidative benzannulation reaction. A cyano group on the enal−aryl ring is tolerated under the reaction conditions as illustrated

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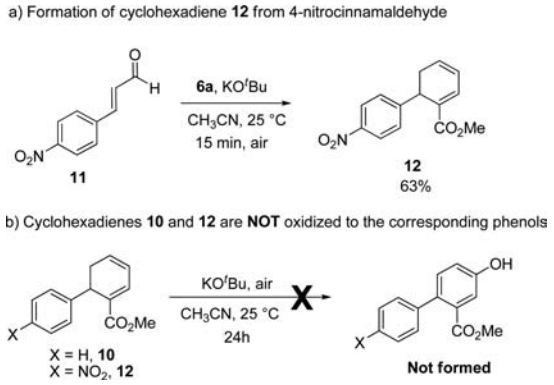
by the formation of phenol **7i**. Heterobiaryls **7p**−**r** endowed with 2-furyl and 2-thienyl rings are produced from β-heteroaryl enals. It is noteworthy that palladium-mediated coupling reactions of the bromine-carrying biaryls **7c**,**d**,**h** could potentially lead to the formation of valuable *p*- and *m*-terphenyls. Attempted reactions of β-alkyl enals and α,β-unsaturated ketones, however, failed to deliver the benzannulation products. Although both the starting materials were consumed, no identifiable products could be isolated in these cases.

Interestingly, treatment of 4-nitrocinnamaldehyde and **6a** under benzannulation conditions did not afford the phenol product. Instead, the substituted cyclohexadiene **12** was obtained in 63% yield (Scheme 3a). It may be recalled that analogous

Scheme 3. (a) 4-Nitrocinnamaldehyde Affords the Cyclohexadiene 12 under Benzannulation Conditions. (b) Compounds 10 and 12 Are *Not* Converted to the Corresponding Phenols under Benzannulation Conditions

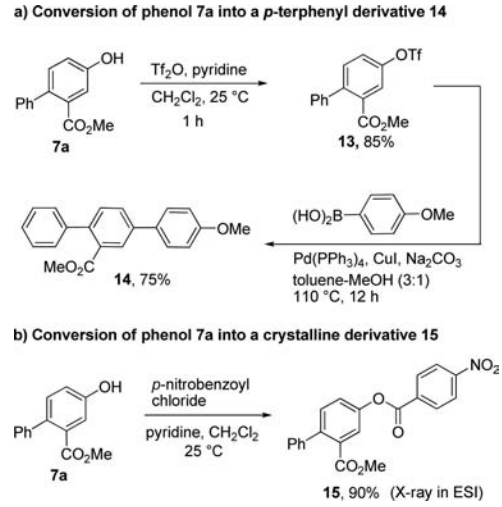


cyclohexadiene **10** was obtained from cinnamaldehyde during optimization studies when oxygen was excluded from the reaction mixture (Table 1, entry 11). Moreover, the formation of similar cyclohexadienes in the reaction of tetrazolylacroleins and methyl (2*E*)-4-(triphenylphosphoranylidene)but-2-enoate has been reported.[14] Isolated samples of cyclohexadienes **10** and **12** were largely unchanged even after 24 h when they were subjected to the conditions of benzannulation under air (Scheme 3b). Evidently, the cyclohexadienes **10** and **12** are not intermediates in the formation of the phenol products. Presumably, the cyclohexadienes are generated as a result of a parallel reaction pathway.

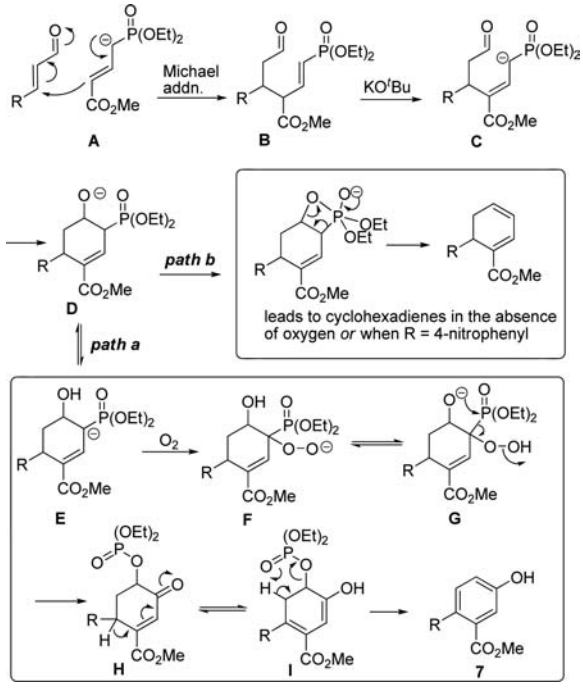
It is clear from the aforementioned results that a convenient protocol for the synthesis of substituted phenols has been developed. Such methods are extremely important as phenols are versatile building blocks for industrial chemicals, pharmaceuticals, and polymers.[15] The synthetic malleability of the biaryl phenols generated in the present study is evident in the transformations depicted in Scheme 4a. The triflate **13** derived from the phenol **7a** was employed in a Suzuki−Miyaura coupling to obtain the *p*-terphenyl derivative **14** in 75% yield. Additionally, base-mediated acylation of the representative phenol **7a** with *p*-nitrobenzoyl chloride afforded a crystalline derivative **15** (Scheme 4b). Single-crystal X-ray analysis of the latter confirmed the structural assignment and the regiochemical outcome of the benzannulation reaction.[16]

Although the mechanistic underpinnings of the oxidative benzannulation reaction are not clear at this stage, a plausible rationalization may be advanced as follows (Scheme 5). The initial carbon−carbon bond-forming event is a Michael addition

Scheme 4. Synthetic Transformations of Representative Phenol 7a



Scheme 5. Mechanistic Hypothesis for the Oxidative Benzannulation



of the phosphonate anion **A** to the enal to afford an acylic intermediate **B**. The preferential addition at the less hindered end of the allylic anion **A** sets the regiochemistry of the overall transformation. Deprotonation of **B** and subsequent intramolecular nucleophilic attack of the resultant carbanion **C** on the aldehyde would produce β-hydroxyphosphonate **D**. Such β-hydroxyphosphonates are generally stable and isolable in the absence of an electron-withdrawing group at the β-position.[17] Here, **D** presumably generates the stabilized carbanion **E** via proton shift (path a), and the latter interacts with atmospheric oxygen to furnish the peroxide **F**. Incidentally, the reaction of stabilized carbanions with oxygen is well-known and has been employed in targeted synthesis, most notably by Stork in the synthesis of quinine.[18] Peroxide **F** may undergo internal proton transfer to form the alkoxide **G**, which then attacks the adjacent

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phosphonate group. Transfer of the phosphonate moiety from carbon to oxygen[19] may then occur along with concomitant cleavage of the labile peroxide bond. This generates the enone **H**, which is tautomeric with the dienol **I**. Elimination of the phosphonate group from **I** at ambient temperature is presumably driven by the formation of the aromatic product **7**. Additionally, the proton that is abstracted from **I** is acidic by virtue of its allylic relationship with the ester group.

In the absence of atmospheric oxygen, an intramolecular Wadsworth−Emmons reaction ensues from **D** to generate cyclohexadiene products (such as **10**). The presence of a nitrophenyl ring presumably stabilizes anionic intermediates in the Wadsworth−Emmons reaction pathway[19] leading to the selective formation of cyclohexadiene **12** (path b).

In summary, a regioselective and oxidative [3 + 3] benzannulation protocol for the facile synthesis of substituted 4-hydroxybiphenyl-2-carboxylates from readily available cinnamaldehydes has been developed. It is interesting to note that the combination of an aldehyde and a widely used Wadsworth−Emmons reagent leads to the formation of a phenol framework. The reaction is operationally simple, proceeds rapidly under mild, metal-free conditions, and uses atmospheric oxygen as an oxidant. The substituted biaryl phenols thus obtained can be readily transformed further into valuable products. A parallel reaction pathway leading to the formation of substituted cyclohexadienes was also observed in an isolated case. It is conceivable that the oxygenative benzannulation method will find applications in the synthesis of designer biphenyl and terphenyl phenol derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00016.

Detailed experimental procedures and characterization data for all compounds (PDF)

X-ray data for **15** (CIF)

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Notes

The authors declare no competing financial interest.

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