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Transition-Metal-Free Synthesis of Homo- and Hetero-1,2,4-Triaryl Benzenes by an Unexpected Base-Promoted Dearylative Pathway

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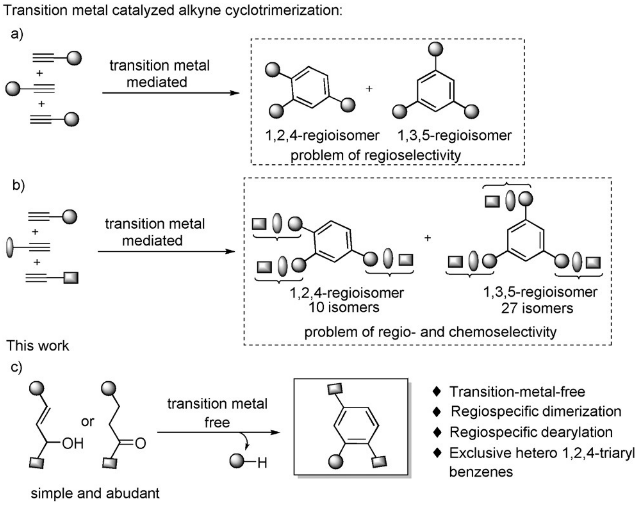
Abstract: *An unprecedented approach for the synthesis of homo- and hetero-1,2,4-triaryl benzenes has been developed using a simple base-mediated reaction of either α-aryl cinnamyl alcohols or α,γ-di-aryl propanones. The salient feature of this strategy involves the sequential hydride transfer, regiospecific condensation, regiospecific dearylation, and aromatization under metal-free reaction conditions. The synthesis of unsymmetrically substituted triphenylenes by oxidative coupling of the synthesized 1,2,4-triaryl benzenes has also been demonstrated.*

The development of novel transition-metal-free organic transformations has been a growing interest in modern chemistry for the reasons of cost, safety, and environmental concerns.[1] Because of this demand, to date, a wide variety of highly efficient and selective transition-metal-free synthetic approaches have been developed.[2] The development of transition-metal-free cascade reactions remains an attractive strategy for efficient synthesis of complex molecular architectures.[3]

The synthesis of multiply substituted aromatic compounds is an issue of great interest in pharmaceutical, as well as in materials science. The [2+2+2] cyclotrimerization of alkynes catalyzed by transition metals is an elegant chemical transformation for the single-step construction of such compounds (Scheme 1 a).[4] After the pioneering work by Reppe in 1948,[5] a large number of transition-metal catalysts were developed for the same reaction.[4] Two major problems associated with these methods are: first is the formation of a mixture of regioisomers (homo-1,2,4- and 1,3,5-triaryl benzenes; Scheme 1 a) by homo-cyclotrimerizations of terminal alkynes. Secondly, the crossed-cyclotrimerization of different alkynes in an intermolecular fashion, without tethering of the starting materials, leads to a mixture of 37 isomers (Scheme 1 b). The first problem is solved in many cases, and results in either the preference for the homo-1,3,5- or homo-1,2,4-substitution pattern, thereby reducing the number of possible products.[6] However, the use of different alkynes and consequently the regio- and chemoselective synthesis of hetero-1,2,4-trisubstituted benzenes still remains an unsolved problem.[7] Herein, we report a transition-metal-free synthesis of both homo- and hetero-1,2,4-triaryl benzenes from homo- and hetero-α-aryl cinnamyl alcohols, respectively (Scheme 1 c). The salient features of this method are that it is 1) transition-metal-free, 2) operationally simple, 3) employs readily available and inexpensive starting materials, and 4) provides either homo- or hetero-1,2,4-triaryl benzenes in a regiospecific manner. The most notable finding is that an unprecedented dearylative aromatization occurs in the presence of a simple KOH/DMSO system.[8] The KOH/DMSO system itself is utilized in various cross-coupling reactions, however, the current reactivity is unprecedented in the literature.[9]



Scheme 1. Synthesis of 1,2,4-triaryl benzenes.

Serendipity plays an important role in the discovery of new reactions. In this particular case, when a solution of α-phenyl cinnamyl alcohol (**1a**) was treated with KO*t*Bu in DMSO at 100 °C, the formation of the 1,2,4-triaryl benzene **3a** was observed (Table 1, entry 1). Encouraged by this result, the screening of various bases, such as Na_2CO_3, K_2CO_3, Cs_2CO_3, DBU, DMAP, pyridine, pipyridine, Et_3N, LiOH, NaOH, NaH, and KOH (entries 2–7) was carried out, and interestingly, KOH provided the best result (83 % of **3a** was isolated; entry 7). Carrying out the reaction employing KOH in other solvents such as DMF, 1,4-dioxane, Et_2O, THF, MeOH, and EtOAc at various temperatures, the reactivity remained less effective compared to using DMSO at 100 °C (see the Supporting Information for details).

Next we focused on the synthesis of homo-1,2,4-triaryl arenes from homo-α-aryl cinnamyl alcohols (Scheme 2). Substrates with electron-donating groups, including *p*-Me (**3b**), *o*-Me (**3c**), *p*-*t*Bu (**3d**), and *p*-MeO (**3e**), and electron-withdrawing groups such as *p*-Cl (**3f**), *p*-Br (**3g**), *p*-F (**3h**),

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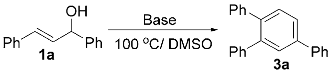
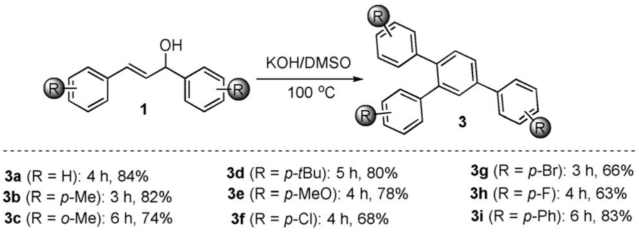
Table 1: Optimization of the reaction conditions.[a]

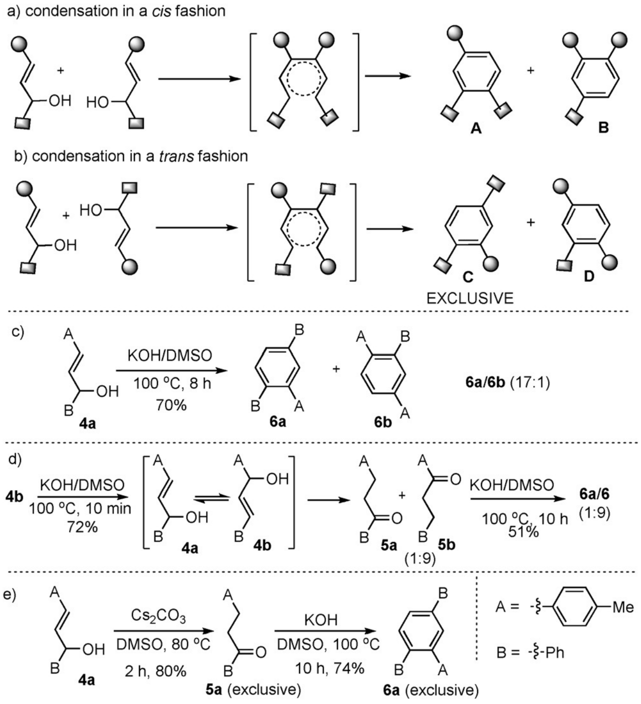


Entry	Base (2 equiv)	Solvent	**3a** [%][b]
1	KO*t*Bu	DMSO	31
2	carbonate[c]	DMSO	–
3	organic bases[d]	DMSO	–
4	LiOH	DMSO	16
5	NaOH	DMSO	26
6	NaH	DMSO	19
7	KOH	DMSO	83

[a] Reaction conditions: **1a** (0.20 mmol), base (2 equiv), 4 h, 1 mL dry DMSO at 100 °C. [b] Yield of product isolated after column chromatography. [c] Carbonates such as: Na_2CO_3, K_2CO_3, Cs_2CO_3. [d] Organic bases such as: DBU, DABCO, pyridine or Et_3N. DABCO = 1,4-diazobicyclo-[2.2.2]octane, DBU = 1,8-diaza- bicyclo[5.4.0] undec-7-ene, DMSO = dimethylsulfoxide.



Scheme 2. Substrate scope: homo-1,2,4-triaryl benzene. Reaction conditions: **1a** (0.30 mmol), KOH (2 equiv), dry DMSO (1 mL), 4 h at 100 °C. Yield is that of the product isolated after column chromatography.



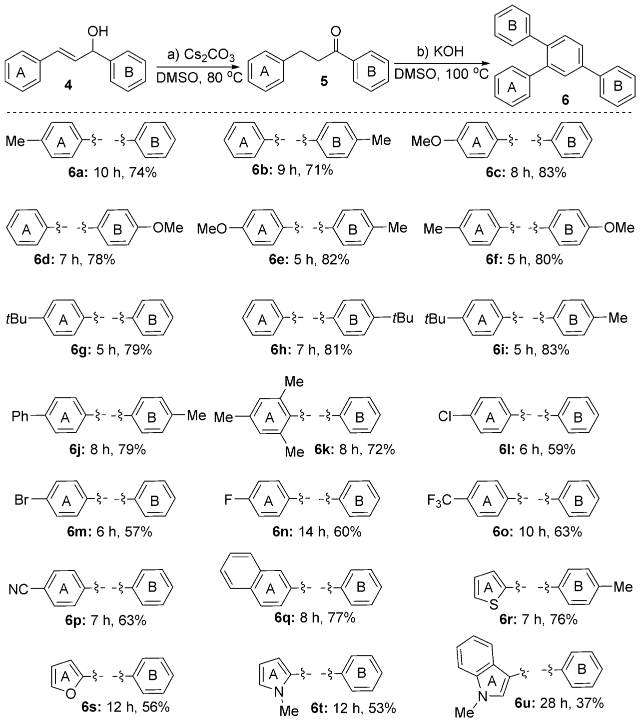
Scheme 3. Condensation of unsymmetrical α-aryl cinnamyl alcohols.

and *p*-Ph (**3i**), on the aryl moiety were effectively converted into the corresponding homo-1,2,4-triaryl benzenes in good to excellent yields (63–83 %).

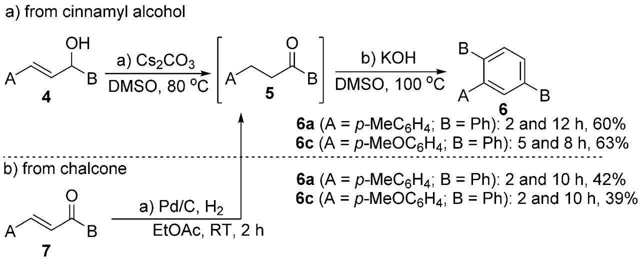
The successful synthesis of homo-1,2,4-triaryl benzenes led us to wonder if hetero-1,2,4-triaryl benzenes could be synthesized by this strategy. However, compared with the homo-α-aryl cinnamyl coupling process, the corresponding heterocoupling could be more complicated because of serious competition between the *cis* and *trans* C−C bond-formation processes (Schemes 3a and b). The condensation in a *cis* fashion is followed by dearylative aromatization and would provide the 1,2,4-triaryl benzenes with the homo-1,2-biaryl products **A** and **B**, depending on which aryl group is removed. In contrast, condensation in a *trans* fashion would give the 1,2-heterodiaryl products **C** and **D** (Scheme 3b). Keeping in mind the above possibilities, the α-phenyl *p*-methyl-cinnamyl alcohol (**4a**) was treated under the optimized reaction conditions, and interestingly, 1,4-diphenyl 2-*p*-tolyl benzene (**6a**; Scheme 3c) was formed (resembles **C** in Scheme 3b). In addition, a small amount of 1,4-di-*p*-tolyl 2-phenyl benzene (**6b**; resembles **D** in Scheme 3b) is formed. A closer look at the reaction revealed that a transiently formed mixture of the ketones **5a** and **5b**, in turn, regiospecifically converted into the products **6a** and **6b**, respectively (Scheme 3d). Probably, in the presence of KOH/DMSO, **4a** first undergoes partial OH transposition to provide a mixture of the regioisomeric alcohols **4a** and **4b**, which follow a base-mediated hydride transfer to generate the mixture of ketones **5a** and **5b**, respectively. Encouragingly, such OH transposition was completely ceased by using Cs_2CO_3 instead of KOH at 80 °C and a single regioisomer of **5a** was obtained (Scheme 3e). However, continuation of the reaction for a longer reaction time did not lead to the formation of **6a**. Furthermore, the treatment of the **5a** in KOH/DMSO at 100 °C provided the single regioisomer **6a** by a regiospecific dearylation.

This strategy was found to be extremely effective and provided a single regioisomer of hetero-1,2,4-triaryl benzenes (Scheme 4). The methodology was extended to an array of substrates. Various hetero-1,2,4-triaryl benzenes having various substitutents (**6a–k**) have been synthesized from the corresponding cinnamyl alcohols. Notably, the results obtained in the case of **6a** versus **6b**, **6c** versus **6d**, **6e** versus **6f**, and **6g** versus **6h** are most impressive because by changing the position of two aryl groups on the cinnamyl alcohols, different regioisomers were isolated. An electron-deficient substituent on one of the aryl rings provided the desired products (e.g., **6l–p**) with good yields. The naphthyl moiety (**6q**) and heteroaryl rings, such as 2-thiofuryl (**6r**), 2-furyl (**6s**), 2-*N*-methyl pyrrole (**6t**), and 3-*N*-methyl indole (**6u**) are also compatible with the current reaction conditions and afforded the desired products. Some of the structures, such as **6d**, **6g**, and **6q** were confirmed by X-ray analysis of the crystal structure (see the Supporting Information).[10]

Finally, a one-pot, sequential hydride transfer of an α-aryl cinnamyl alcohol using Cs_2CO_3, thus affording the corresponding ketone **5**, followed by KOH/DMSO-mediated cross-condensation/dearylation to provide the hetero 1,2,4-triaryl benzene **6** has been demonstrated (Scheme 5a). Additionally, a sequential reduction of the chalcone **7**, the synthetic



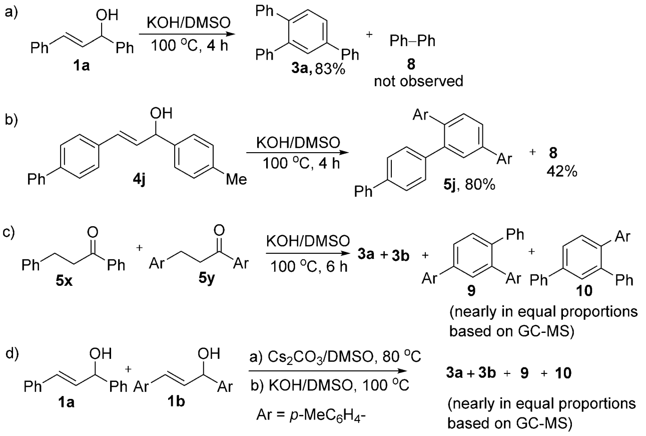
Scheme 4. Synthesis of hetero 1,2,4-triaryl benzene. Reaction conditions: a) **4** (0.50 mmol), Cs_2CO_3 (1.0 mmol), dry DMSO (2 mL) at 80 °C; b) **5** (0.20 mmol), KOH (2 equiv), DMSO (1 mL) at 100 °C. Yield is that of the product isolated after column chromatography (from the reaction of **5**).



Scheme 5. Sequential synthesis of hetero-1,2,4-triaryl benzenes.

precursor of cinnamyl alcohol **4**, using Pd/C and H_2, to the ketone **5** followed by a KOH/DMSO-mediated reaction also gave the hetero-1,2,4-triaryl benzene **6** (Scheme 5 b).

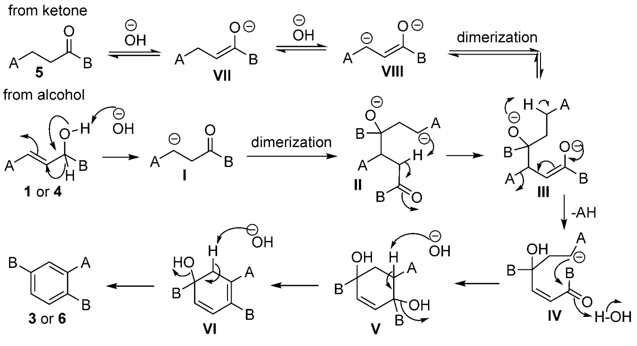
The photophysical properties of selected products (**3a** versus **6b**, **6c**, **6d**, and **6p**) were investigated with UV/Vis spectrophotometry and fluorescence spectroscopy (see the Supporting Information). The absorption spectra for all the structures are attributed to the structural rigidness of the chromophoric moiety. For the case of **6d** and **6p** the absorption peak is most red-shifted because of the involvement of the labile electrons of the methoxy and cyano groups, respectively. Interestingly, **6c** and **6p** are highly fluorescent with the absolute quantum yield of 0.92 and 0.94, respectively, in MeOH, thus implying the distinct substituent effect of the methoxy and cyano group on the conjugated 1,2,4-triaryl benzene moiety.



Scheme 6. Control experiments.

To gain insight into the current triaryl benzene formation process, control experiments were performed. As shown in (Scheme 6 a), along with the desired 1,2,4-triaryl benzene **3a**, the dimerization of dearylated species [e.g., Ph–Ph; (**8**)] was not observed under the standard reaction conditions. Instead, a protonated dearylated moiety (Ph–Ph) was isolated (Scheme 6 b). Treating an equimolar mixture of two different α-aryl cinnamyl ketones, **5x** and **5y** (Scheme 6 c), as well as a mixture of the α-aryl cinnamyl alcohols **1a** and **1b** (Scheme 6 d), leads to the formation of the four possible products **3a**, **3b**, **9**, and **10** (by homo and heterocondensation).

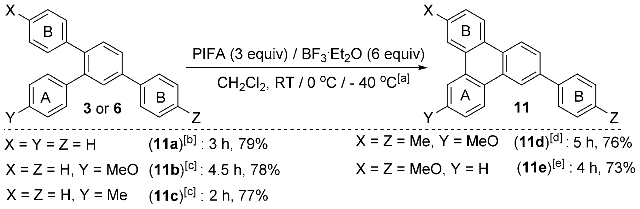
Based on the above preliminary control experiments as well as the literature reports,[11] a possible reaction pathway is depicted in Scheme 7. The initial step involves the base-mediated hydride transfer of the cinnamyl alcohol **1** or **4** to generate the β-carbanion **I**. Further, a self-condensation of **I** affords the corresponding species **III** via intermediate **II** by a protonation-deprotonation pathway. The enolate **III** probably undergoes β-dearylation to provide the conjugated species **IV**, which undersoes intramolecular condensation followed by base-promoted aromatization to afford either the desired 1,2,4-triaryl benzene **3** or **6**. In contrast, the ketone **5** could also provide **III** by generation of the β-carbanion enolate **VIII** and enolate **VII** under KOH/DMSO conditions. This proposal probably does not represent the transformation



Scheme 7. Proposed mechanism.

fully as it features an unusual and unprecedented step, that is, the loss of the aryl ring A as an anion (**III**→**IV**). The full mechanism remains to be elucidated to provide a fuller picture of this intriguing transformation.

Intrigued by the prevalence of triphenylenes in materials science,[12] an oxidative coupling of the synthesized 1,2,4-triaryl benzenes was demonstrated for the synthesis of substituted triphenylenes using PIFA/$BF_3{\cdot}Et_2O$ as shown in Scheme 8. Notably, unsymmetrically substituted triphenylenes, such as **11b–e**, wherein the two aryl rings bear different substitutions, were isolated and are the first of this kind of compound.[13]



Scheme 8. Synthesis of substituted triphenylenes from 1,2,4-triaryl arenes. [a] Yield is that of the isolated product. [b] Reaction was carried out at RT. [c] Reaction was carried out at 0°C. [d] Reaction was carried out at −40°C. PIFA = phenyliodine bis(trifluoroacetate).

In summary, we have developed a novel transition-metal-free method for the synthesis of homo- and hetero-1,2,4-triaryl benzenes from easily accessible starting substrates using KOH in DMSO. The reaction displays a broad substrate scope and good tolerance to a variety of substituents including electron-rich and electron-deficient aryls, and heteroaryls. This method would be particularly attractive from economical and environmental points of view. The photophysical outcome of the synthesized hetero-1,2,4-triaryl benzenes derivatives showed that such molecules might have a potential application in materials chemistry. Currently, we are focusing on additional studies to understand the mechanism in detail.

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Keywords: arenes · cyclizations · materials science · regioselectivity · synthetic methods

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