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Iodine-Promoted Metal-Free Aromatization: Synthesis of Biaryls, Oligo *p*-Phenylenes and A-Ring Modified Steroids

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Abstract: We describe efficient procedures based on the use of iodine for the synthesis of biaryls from arylcyclohexenols or arylcyclohexanols using sub-stoichiometric/catalytic iodine and dimethyl sulfoxide (DMSO) as oxidant. Heteroarylcyclohexanols also produced the corresponding biaryl products. It was proven that biphenyl can also be efficiently obtained when the quantity of iodine was reduced to 0.05 equiv. The method is compatible with different functional groups in the aromatic ring (either electron-donating or electron-withdrawing groups). For substrate scope, apart from cyclohexanone and cyclohexenone, some substituted cyclohexanones were also used to synthesize the starting arylcyclohexanols. The process was applied to the synthesis of oligo *p*-phenylenes and A-ring aromatized steroids, where the combined use of I_2/DMSO not only provoked the necessary migration of the methyl group at C-10, but also further extended the conjugation.

Keywords: aromaticity; biaryls; iodine; metal-free reaction; steroids

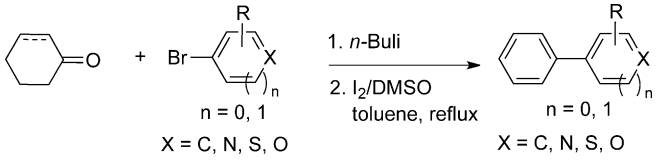
Biaryls are "privileged structures" that occur widely in different forms in such areas as the pharmaceutical industry, natural products and electronic materials.[1] An increase in the number of aromatic rings originates *p*-polyphenes, substances that are considered to possess interesting applications in molecular electronics and other related emerging areas.[2]

A number of methods for the synthesis of biaryls have been reported, among which the palladium-catalyzed cross-coupling reactions are the most widely applied.[3] Also worthy of being underlined is the emergence of methods for the construction of biaryls based on the activation of aromatic C–H bonds[4] or decarboxylative coupling.[5] However, most of these processes require the use of transition metals, which in certain cases is considered undesirable, mainly in terms of purification of the final products.

Favored by the rapid emergence of green chemistry, metal-free strategies such as those published by Shi and others[6] are being reported for the achievement of different aromatizations. In this regard, iodine proved to play a key role in the development of modern synthetic methodologies including some dehydrogenative processes.[7] Furthermore, the combined use of substoichiometric iodine and DMSO was also reported to mediate processes leading to aromatic compounds.[8]

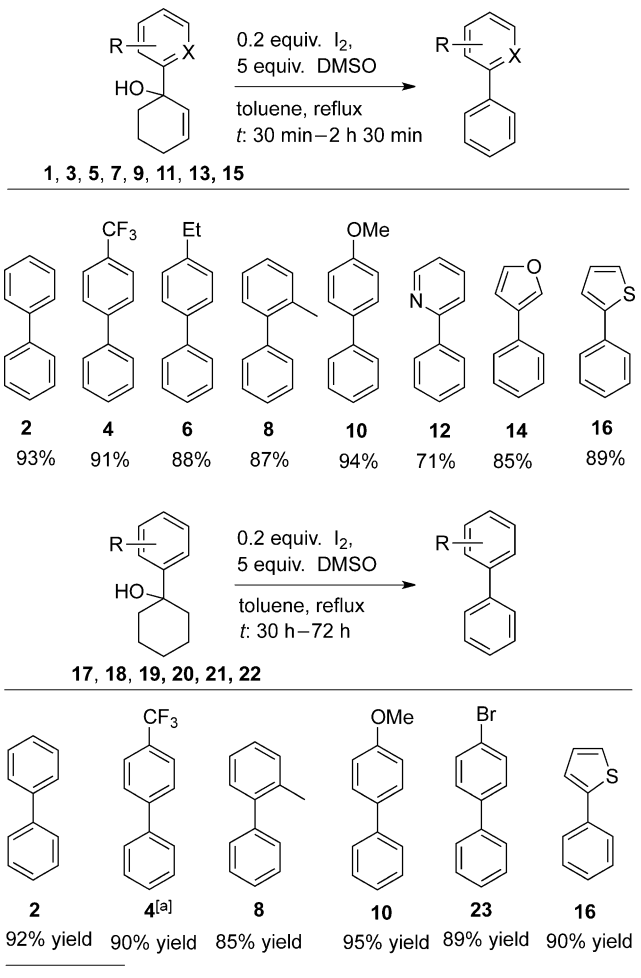
Concerning these iodine-mediated aromatization processes, and having in mind the known capability of iodine to dehydrate tertiary alcohols,[9] we reasoned that iodine could catalyze both the dehydration and subsequent aromatization of arylcyclohexenols, arylcyclohexanols or heteroarylcyclohexanols to produce the corresponding biaryl products (Scheme 1). To the best of our knowledge, to date, no examples of such a transformation have been reported. Herein we present the results reached when this strategy was implemented.

For operational simplicity, precursors **1**, **3**, **5**, **7** and **9** were obtained by 1,2 addition over cyclohexenone (25 mL, *ca.* €60) or cyclohexanone (500 mL, *ca.* €29)



Scheme 1. Working hypothesis.

of the corresponding aryllithium or magnesium counterpart. Using arylcyclohexanol **1** as model, extensive work was performed in order to find the optimal reaction conditions. Thus, it was found that the combined use of 0.2 equiv. of iodine and DMSO as oxidant enabled the aromatization of **1** to proceed efficiently, and a 93% yield of biphenyl **2** was obtained after 1 h of reaction in refluxing toluene (Scheme 2). No dry solvent was required and the reaction took place without an inert atmosphere. The starting material remained unaltered with polar solvents such as methanol or water due essentially to the lack of solubility of our starting material. When the quantity of I_2 added to **1** was 100 mol%, only decomposition of the starting material was observed, which could be attributable to the generation of HI in the reaction medium. The use of other iodine species such as KI produced no aromatization of the starting material. Finally, it was also found that no positive results were found with other oxidants such as O_2 or TBHP.[10] In order to ascertain to what extent the quantity of iodine could be reduced, we treated **1** with 0.05 equiv. of iodine and DMSO and, remarkably, biphenyl **2** was generated in 82% yield after 3 h.



[a] 0.1 equiv. of *p*-TsOH was added to accelerate the dehydration step.

Scheme 2. Scope of iodine-promoted aromatization: synthesis of biaryls.

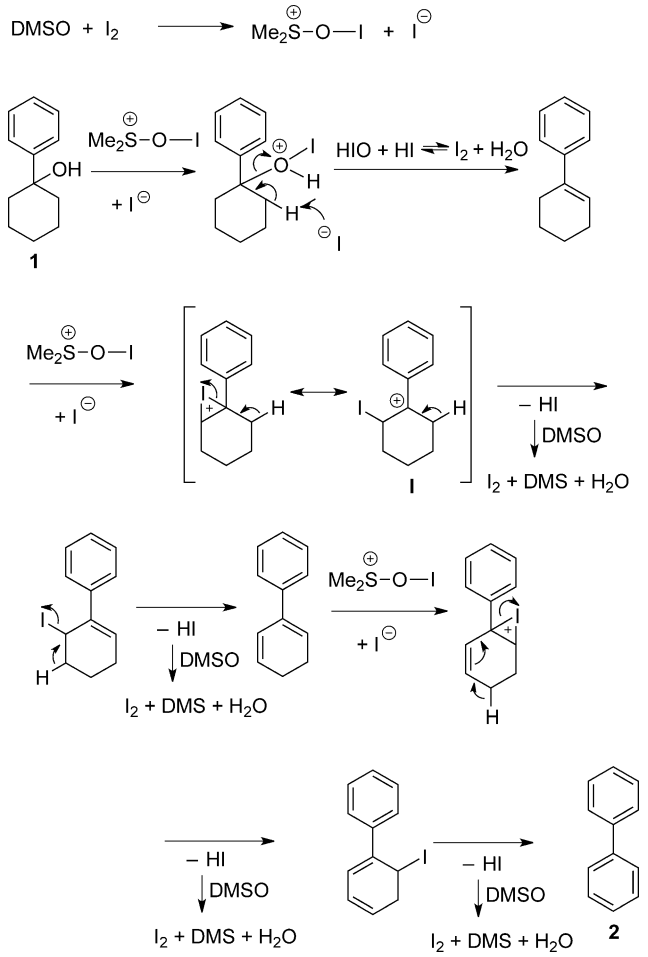
The results summarized in Scheme 2 show that the iodine-DMSO method is compatible with the electron-withdrawing group CF_3 in **4**, an important group in medicinal chemistry. Electron-donating groups gave positive results as well (**6**, **8** and **10**). The methoxy group was perfectly tolerated and no demethylation was observed. Finally, the reaction could be successfully applied to the generation of heterobiaryls **12**, **14** and **16**.[11] Although the results obtained with the pyridine derivative **12** were only modest, it deserves to be noticed that no trace of this biaryl derivative was obtained in a protocol described recently by Li using DDQ.[12]

Encouraged by these results, we applied this substoichiometric in iodine protocol to the generation of biaryls from the corresponding arylcyclohexanols (Scheme 2). Gratifyingly, excellent yields were also obtained for the synthesis of biaryls **2**, **4**, **8**, **10**, **16** and **23** although more prolonged reaction times were required for the reactions to be completed, when compared with the arylcyclohexenol derivatives. The presence of a bromo substituent in the aromatic ring was also tolerated in this aromatization process (**23**), which facilitates further C–C bond forming processes.

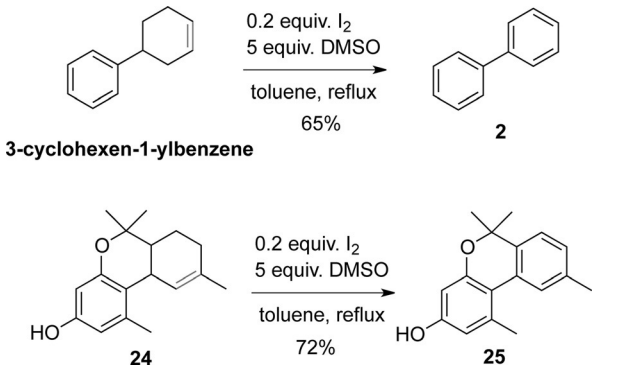
With the aim of checking if the overall transformation could be achieved in one pot, we treated the *in situ* prepared *p*-methoxyarylcyclohexenol **9** with I_2-DMSO, and no reaction was observed. No evolution was also observed after addition of 1 equiv. of H_2O (added to protonate the alkoxy intermediate). The desired transformation was only produced when 1 equiv. of *p*-TsOH was added to the reaction media, and the expected biaryl **10** was thus obtained in 78% yield after 10 h.

A plausible mechanism that rationalizes the generation of biaryls using the iodine-DMSO system is shown in Scheme 3, although the involvement of carbocationic intermediates (e.g., **I**) whose generation at the benzylic position is favored should not be discarded.

The detection of the corresponding arylcyclohexenes during the formation of these biaryls supports the suggested mechanism. Furthermore; it was noted that the aromatization can take place even when the double bond was not placed at the benzylic position, which could be considered as an expansion of the scope on this protocol. Thus, commercial 3-cyclohexen-1-ylbenzene was converted into biaryl **2** in 65% yield when treated with the I_2/DMSO system (Scheme 4).[13] This fact was confirmed when the cannabinoid derivative **24** was found to give **25** in a 72% yield after 65 h (Scheme 4). The inertness of different functions is an additional advantage of this dehydrogenation reaction. In a related process, Stahl has re-



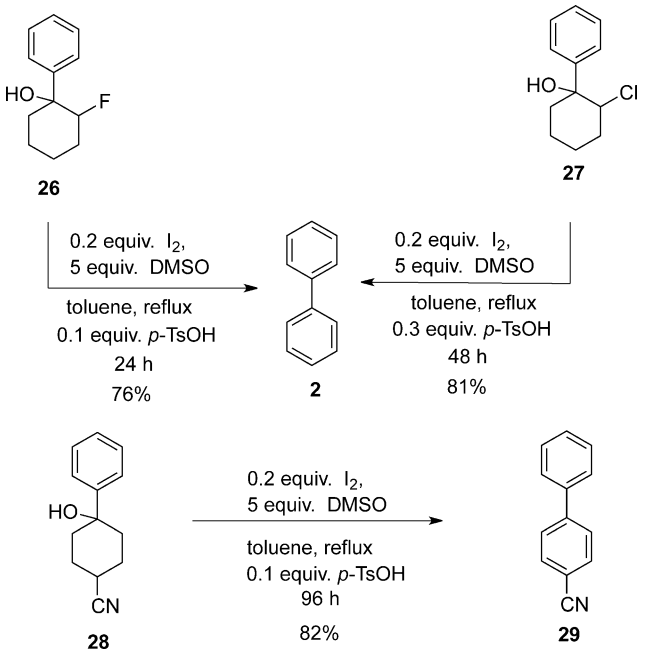
Scheme 3. Mechanism proposed for the iodine-promoted formation of biaryls.



Scheme 4. Iodine-promoted aromatization of substituted arylcyclohexenes.

cently reported the Pd-catalyzed dehydrogenation of cyclohexenes to afford the corresponding arenes.[14]

To gain more data about the scope and limitations of the work, we tested arylcyclohexanols **26–28** with functional groups fluoro, chloro and cyano (Scheme 5), prepared from the corresponding cyclohexanones. In all three cases, catalytic *p*-TsOH was



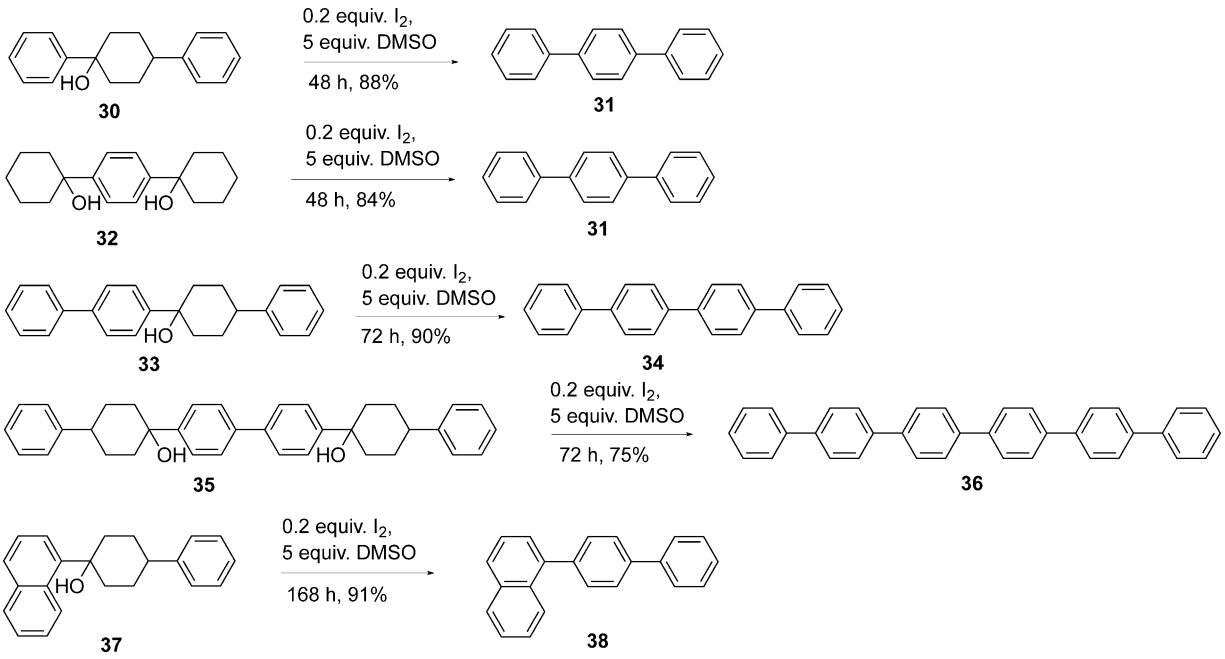
Scheme 5. Iodine/DMSO-based aromatizations of fluoro, chloro and cyano derivatives.

needed to promote the dehydration step. However, whereas the cyano derivative **28** evolved to the corresponding cyanobiaryl **29**, the halo derivatives **26** and **27** produced biaryl **2**. This result can be rationalized on the basis of the mechanism proposed for this iodine-promoted formation of biaryls (Scheme 3), thus the elimination of HCl and HF is postulated in the generation of biphenyl **2**.

At this point, and taking profit of the ready commercial availability of 4-phenylcyclohexanone and different aryl dibromides o diaryl bromides, we reasoned that this iodine-catalyzed process could be easily applied to the synthesis of oligo *p*-phenylenes and other polyaromatic structures.[15] As with biaryls, most of the methods reported for the synthesis of these systems are mediated by metals.[2c,16]

Starting **30**, **33**, **35** and **37** were obtained as mixture of diatereomers.[17] Treatment of these mixtures with the I_2/DMSO system led to the production of terphenyl (**31**), quaterphenyl (**34**), sexiphenyl[18] (**36**) and biphenylnaphthalene **38** in good yields (Scheme 6). Finally, it should be noted that the synthesis of **31** and **36** involved a double dehydration-dehydrogenation process.

The recent interest of organic chemists in modified steroids[19] to evaluate their pharmaceutical relevance prompted us to study the behavior of the arylcyclohexanol **39** generated by addition of aryllithium to testosterone. Although the aromatization of cyclohexanol **39** should involve a migration of the methyl group at C-10, some examples including iodine-mediated rearrangement in the aromatization of friedoo-



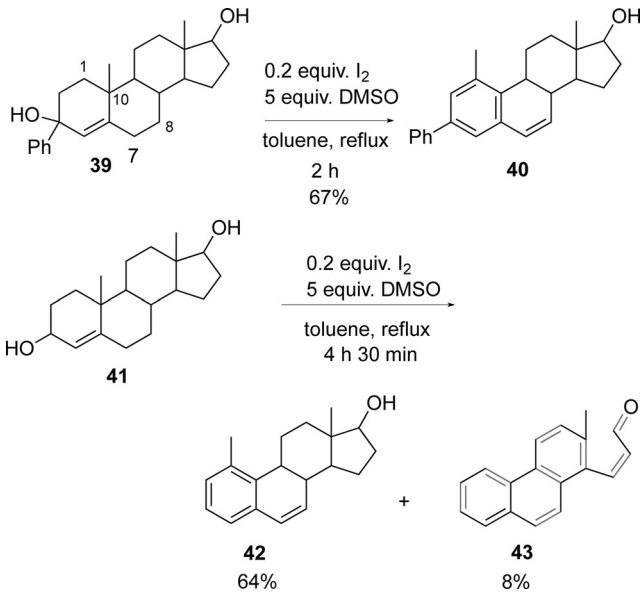
Scheme 6. Synthesis of oligo *p*-phenylenes and biphenylnaphthalene **38**.

leadienes or labdanes were previously reported.[20] Gratifyingly, the treatment of **39** with I_2/DMSO not only provoked the necessary migration of the methyl group at C-10, but also further extended the conjugation to C-6–C-7 to produce the biaryl **40** in acceptable yield (Scheme 7). The migration to C-1 supports the previously suggested intermediacy of carbocationic species.

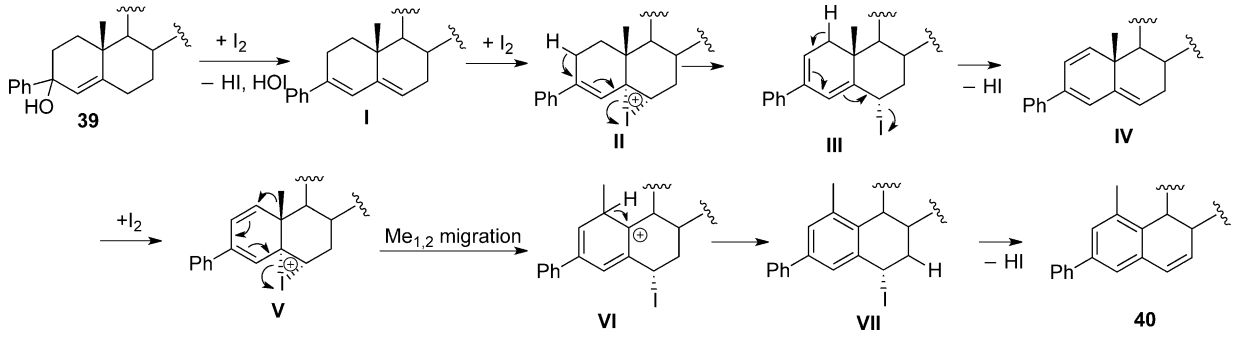
A plausible mechanism for the formation of **40** is depicted in Scheme 8. Once starting **39** is dehydrated, the action of I_2 on diene **I** would provoke to the generation of 1,3,5-trienic intermediate **IV**. A new addition of I_2 would cause methyl rearrangement from C-10 to C-1 *via* carbocation **VI** to give **VII**. Then, **VII** would evolve to biphenyl derivative **40** *via* HI elimination.

Finally, we were intrigued to invesitagte the behavior of allylic alcohol **41** – obtained from direct reduction of testosterone, when treated with I_2/DMSO. In the event, aromatization of the A-ring took placed again after migration of the methyl group at C-10, and compound **42** was produced as major product (Scheme 7). Most remarkably the fully conjugated aldehyde **43** was also generated in this process, although in very low yield (8%). The production of aldehyde **43**, where up to eight new unsaturations were formed, supports the high potentiality of this method.

In conclusion, we have found a new metal-free way of constructing biaryls or heterobiaryls from both arylcyclohexenols and arylcyclohexanols, a process which also has a potentially wide range of applications in the construction of molecular electronics or drug design. Thus, the method was applied to the formation of different oligo *p*-phenylenes. Experimental conditions using 0.2 equiv. of iodine and DMSO as oxidant were obtained for the preparation of these biaryls, although it was found that biphenyl **2** can also be efficiently obtained from **1** by using only 0.05 equiv. of iodine. Finally, iodine also proved to mediate the dehydrogenation of testosterone derivatives **39** and **41** to afford A-ring aromatized steroids.



Scheme 7. Iodine/DMSO-based aromatizations of testosterone derivatives.



Scheme 8. Mechanism proposed for the iodine-promoted formation of biphenyl **40**.

Experimental Section

General Procedure for the Aromatization Promoted by Iodine/DMSO

To a solution of the corresponding starting material (1 mmol, 1 equiv.) in toluene (0.1 M) heated under reflux was added iodine (0.2 equiv.) and DMSO (5 equiv.). The solution was stirred at reflux and monitored by thin-layer chromatography analysis. Upon consumption of the starting material the reaction was diluted in *t*-BuOMe (100 mL), washed with a saturated solution of sodium thiosulfate (1 × 100 mL), and brine (1 × 100 mL). The organic layer was dried over sodium sulfate and evaporated under vacuum. Purification was performed by silica gel chromatography to yield chromatographically and spectroscopically pure product.

Acknowledgements

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