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Organocatalytic oxidative dehydrogenation of aromatic amines for the preparation of azobenzenes under mild conditions

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ABSTRACT

(Diacetoxyiodo)benzene used as stoichiometrically and catalytically in the preparation of azobenzenes under mild reaction conditions was developed. The metal-free oxidation systems demonstrated wide substituents tolerance, alkyls, halogens, and several versatile functional groups, such as amino, ethynyl, and carboxyl substituents are compatible well, and the corresponding products could be formed with good to excellent yields. In this disclosed method, the more large scale formation of azo compounds also could be carried out successfully. Of note that 3-ethynylbenzenamine applied as a very useful cross dehydrogenative partner, which coupled with different anilines, providing asymmetrical azo compounds with acceptable yields in one step under very mild reaction conditions.

1. Introduction

Aromatic azo compounds are ubiquitous motifs and are widely used in industry as organic dyes, indicators, pigments, food additives, radical reaction initiators, and therapeutic agents.[1–12] Their diversified applications continue to make the development of new methods for their preparation of an important objective in chemical synthesis. Therefore, some methodologies for preparation of azobenzenes were developed: (1) oxidation of aromatic primary amines;[13–23] (2) reduction of nitro-aromatic compounds;[24–26] (3) coupling of primary arylamines with nitroso compounds;[27,28] (4) electrophilic reactions of diazonium salts;[29] (5) oxidation of hydrazo derivatives;[30] (6) reduction of azoxybenzene derivatives.[22] Among the many N=N bond formation reactions, the directed dehydrogenation of aromatic anilines emerged recently as uniquely straightforward and potentially one of the most versatile and practical methods. In this context, a number of stoichiometric and transition metal involved oxidants, such as manganese salts, lead salts, mercury salts, or ferrates were previously employed for their preparation.[13,18,31–43] For the consideration of economical and green reaction protocols, Corma disclosed an efficient route to aromatic azo compounds catalyzed by gold nanoparticles using O_2 (3–5 bar) as the oxidant at 100 °C.[44] In addition, Jiao's groups elegantly utilized CuBr/pyridine/O_2 reaction system leading to symmetric and asymmetric aromatic azo compounds under mild reaction conditions.[45] However, there are still great challenges: (1) the stoichiometric procedures, especially, transition metals-mediated systems that afford the corresponding compounds with lower yields and undesirable overoxidation products are inevitable; (2) limited functional groups compatibility and more harsh reaction conditions prevent all of metal-involved methods from further synthetic applications.

In the last decades, hypervalent iodine reagents have enjoyed an increasing popularity in organic synthesis. They can be used for a wide range of chemical transformations, especially as reagents for oxidations.[46–57] For these purposes hypervalent iodine(III) compound, such as (Diacetoxyiodo)benzene (PIDA) is particularly suitable. The advantages of the reagent are as follows: high efficiency, easy availability, mild reaction conditions, and stability against moisture and oxygen. Furthermore, it is environmentally safe and can be regenerated. In 1953, Pausacker described PIDA oxidative anilines to prepare aromatic azo compounds.[58] However, the preliminary research result demonstrated the distinct challenges that the narrow functional groups tolerance; low yields; the necessary of benzene as solvent. Therefore, these disadvantages undoubtedly prevented PIDA from being employed to their full potential. Herein, we wish to report the more details about PIDA oxidized N=N bond formation stoichiometrically and catalytically from easily available amines with only one step under mild reaction conditions, some very useful symmetric and asymmetric aromatic azo compounds were obtained, and the further application was also extended.

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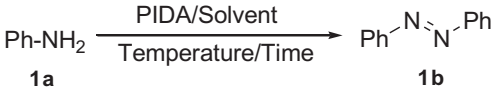
2. Results and discussion

We commenced our studies by testing the conversion of aniline (**1a**) to azobenzene (**1b**) in the presence of PIDA as an oxidation reagent in different solvents and at different temperatures. Unfortunately, the preliminary attempts led to the formation of the desired **1b** in very low yield (<50%) within 1 h (entries 1–5, Table 1) until we discovered that **1b** was produced in 76% yield when the reaction proceeded in the dry CH_2Cl_2 upon exposure of the reaction mixture to air (entry 6, Table 1). In subsequent temperature screening we found that the yield of **1b** decreased greatly as complex mixture in the case of elevated temperature (45 °C, 32% yield, entry 7, Table 1). More importantly, the amount of oxidant was proved as a significant role in the transformation, apparently, with the increase of the amount of PIDA, the yields of **1b** could be enhanced. However, when PIDA used in 0.95 mol ratio to **1a**, the best result was obtained, then the over-submitted PIDA was less favorable to the formation of product resulting in **1b** with declined yield (73% yield, entry 8, Table 1).

Table 1
Test of the conversion of aniline (**1a**) to azobenzene (**1b**)[a]



Entry	Solvents	Oxidant (mol %)	*T* (h)	Yield[b] (%)
1	Benzene	100	1.0	8
2	Toluene	100	1.0	12
3	THF	100	1.0	14
4	$CHCl_3$	100	1.0	25
5	CH_2Cl_2	100	0.5	48
6	CH_2Cl_2	100	0.5	76[c]
7	CH_2Cl_2	100	0.5	32[c,d]
8	CH_2Cl_2	125	0.5	73[c]
9	CH_2Cl_2	95	0.5	80[c]
10	CH_2Cl_2	75	0.5	68[c]

[a] Reaction conditions: Compound **1a** (0.5 mmol), PIDA (75–125 mol %) solvent (4 mL), rt, 20–25 °C.
[b] Yield of isolated product.
[c] In dry CH_2Cl_2.
[d] At 45 °C.

Substituent diversity was achieved using a variation on the optimized reaction conditions (Scheme 1). Reaction of anilines substituted at the *ortho* or *meta* or *para* position with more electron-deficient halogens gave the corresponding azobenzenes in different yields. Apparently, *para*-Cl, Br, F-substituented **4a**, **7a**, **8a** provided **4b**, **7b**, **8b** in lower yields (40%, 21%, 55%, respectively). Comparatively, substrates bearing Cl, Br groups in the *meta* position resulted in the corresponding products **3b**, **6b** with excellent yields (88%, 91%, respectively). The sterically demanding *ortho* substituted substrates **2a**, **5a**, **12a** provided the dehydrogenated products in moderate yield (74%, 56%, 46%), indicating that steric congestion around the amino group decreases the reaction efficiency. It was especially noteworthy that not only alkyls, but also ethynyl can be readily utilized in the reaction, giving the symmetrically ethynyl-substituted aromatic azo compound **13b** in excellent yield at ambient temperature. More importantly, the structurally complicated and more useful *para*-aromatic diamines **14a**, **15a**, **16a** can be constructed to the corresponding coupling products in acceptable yields 74%, 59%, 65%, respectively by using this oxidative dehydrogenative method.

After we had expanded the scope of the reactions, we focused on the development of organocatalytic conditions. Since stoichiometric use of PIDA resulted in co-production of an equimolar amount of PhI, which was wasted after product isolation, the catalytic procedure would be achieved by in situ oxidation of iodo(I)arenes to iodine(III) species. Indeed, a similar result was obtained using peracetic acid as an atom-economical and environmentally friendly oxidant provided the target product in average to good yield (Table 2). A series iodine-containing substances were screened in order to improve the yield of the **1b** and to reduce the loading of the catalyst (entries 1–11, Table 2). Besides iodobenzene, substituted iodobenzenes provided access to **1b** in 43–87% yields at a catalyst loading of 15–20 mol %. To our delight, the *o*-iodosylbenzoic acid, which catalyzes the intermolecular dehydrogenation at even lower catalyst loadings, and **1b** in a better yield within a shorter time under mild conditions. However, it is impressive that 15 mol % of simple, cheap, and easily accessible organic substance is sufficient to catalyze oxidation of aniline to azobenzene (**1b**) at room temperature. The byproducts of the developed methodology were just acetic acid and water. The desired **1b** was not formed in the absence of catalyst (entry 12, Table 2).

With the optimized reaction conditions in hand, we then explored the scope and generality of the organocatalytic method (Table 3). In general, we found that the presence of halogens substituents with different electronic properties in various positions had a widely different effect on the formation of azobenzenes. In comparison with above mentioned non-catalytic PIDA intermediated dehydrogenation reactions, the fluoro-substituted **8b** could be formed in more excellent yield of 92%, but longer reaction time was required. However, the reaction of 4-Cl, 4-Br substituted anilines, unsatisfied results were obtained, (**4b**, 20%, **7b**, 18% yields, respectively) and the more fragile functional group Br atom located on the *ortho* position could not be tolerated well, and trace amount of **5b** was produced accompanied by complicated mixture. Meanwhile, the Cl, Br at the *meta* position demonstrated the promoting effect, and the corresponding products **3b** and **6b** were achieved with acceptable yields (63%, 58%, respectively). To our delight, the electron-donating substituents, such as Me, OMe did not adversely affect the reaction, giving the products with better yields of 90% (**9b**), 66% (**10b**), 90% (**11b**) than in the method of using stoichiometric amount of PIDA. However, the most electron-deficient aniline 4-O_2N–C_6H_4–NH_2 did not undergo the coupling reaction under the optimized reaction conditions. In other particular cases, *p*-aromatic diamines **14a**, **15a**, **16b** were very suitable in our presented both of organocatalytic and non-catalytic conditions, resulting in the structurally extraordinary compounds 4,4′-diamines with good to excellent yields, (65%, 92% yields in the organocatalytic condition, 59%, 74% yields in the non-catalytic condition).

These compounds have a variety of potential applications, such as in organic non-linear optics, optical storage media, as chemosensors and as photochemical switches.[59–61] Especially, ethynyl and carboxyl group were also compatible in this organocatalytic reaction system, giving the coupling products in 85% and 95% isolated yields. It was noteworthy that only the azo product was isolated and no other byproducts, such as azoxy, anil, or hydroxylamine compounds were observed, indicating the advantages of our methodology in comparison others. To the best of our knowledge, the very useful compounds **13b**, **14b**, **15b**, **16b**, **17b** cannot be easily accomplished by the previously reported methods. Of note that the **6b**, **13b** have a great potential to further synthetic elaboration, then more large scale of **6a**, **13a** were applied (2 g), the corresponding products were isolated with 50% and 78%, respectively.

In order to further broad the application of this catalytic procedure, asymmetrically substituted azobenzenes, which are typically synthesized through reaction of the diazonium salt with electron-rich aromatic compounds, can be constructed using this metal-free oxidative method. Notably, 3-ethynylbenzenamine was employed as a very useful substrate, which coupled with bromo, chloro, and fluoro, methoxy-anilines to afford asymmetric azo