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Nickel catalysed construction of benzazoles *via* hydrogen atom transfer reactions†

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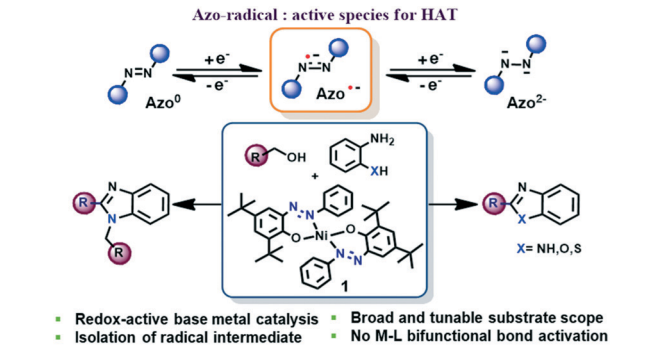
Herein we report a homogeneous, phosphine free, inexpensive nickel catalyst that forms a wide variety of benzazoles from alcohol and diamines by a reaction sequence of alcohol oxidation, imine formation, ring cyclization and dehydrogenative aromatization. A reversible azo/hydrazo couple, that is part of the ligand architecture steers both the alcohol oxidation and dehydrogenation of the annulated amine under fairly mild reaction conditions. Interestingly, both the alcohol oxidation and amine dehydrogenation steps are directly mediated by hydrogen atom transfer (HAT), which is greatly facilitated by the reduced ligand backbone. The k_H/k_D for the amine dehydrogenation step, measured at 60 °C is 5.9, fully consistent with HAT as the rate determining factor during this step. This is a unique scenario where two consecutive oxidation steps towards benzazole formation undergo HAT, which has been substantiated *via* kinetic studies, KIE determination and intermediate isolation.

Introduction

Benzimidazoles and its derivatives are ubiquitously present in natural products and employed widely as antibacterial, antitumor, antihistaminic, and antiviral drugs.[1] Furthermore, substituted benzimidazoles have found applications in pharmaceuticals, agrochemicals, dye industries as well as in material science as thermostable membranes for fuel cells.[2] Previous synthetic strategies for the construction of benzimidazole involved condensation of 1,2-diaminobenzene with a carboxylic acid derivative or formic acid, which required harsh reaction conditions and corrosive acids.[3] To this end, it is highly desirable to find a milder, operationally simple and sustainable method which can be simultaneously environmentally benign.

Toward this direction, the first synthesis of benzimidazole formation *via* dehydrogenative coupling was showcased by Watanabe which required noble metal catalyst ruthenium at a very high temperature, 215 °C.[4] Recent examples from Kempe involve Ir-based catalysts which synthesize benzimidazoles and substituted benzimidazoles at 110 °C.[5] Some heterogeneous systems[6] have also been developed for the synthesis of benzimidazoles but those comprise of precious metals Ir and Ru.[7] On the contrary, there are only a handful of base metal representatives for this important transformation, although cobalt, nickel and manganese catalysts appeared promising in dehydrogenative coupling of diamine and alcohols to realize benzimidazole derivatives.[8] A major drawback of these systems is the requirement of relatively harsh reaction conditions and long reaction time. Additionally, rational design of catalysts is often challenging because of the lack of precise mechanistic understanding. Hence, development of a molecularly-defined, air-stable, base-metal catalyst which can synthesize benzimidazoles or other benzazoles under mild conditions yet in a controllable fashion, is very much desirable.

Herein we communicate a well-defined, phosphine-free, homogeneous nickel catalyst that can construct benzimidazoles under fairly mild conditions in the absence



Scheme 1 $2e^-$ redox in azo–hydrazo couple driven hydrogen atom transfer towards the synthesis of benzazoles.

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of any sacrificial hydrogen acceptor. A thorough literature survey reveals that our reaction conditions are much milder even compared to few well-performing noble metal catalysts. Encouragingly, the catalyst can also regulate the formation of 2-substituted benzimidazole or their 1,2-disubstituted analogues. The precatalyst **1** (Scheme 1), used in this work is an isolable, bench-stable and molecularly-defined entity which helps us to sketch a thorough mechanistic scenario, demonstrating that our reaction pathway is governed by the hydrogen atom transfer (HAT) to the redox active backbone. Fascinatingly, both key steps in the overall reaction rely on HAT, which is unprecedented for dehydrogenative aromatization of N-heterocycles.

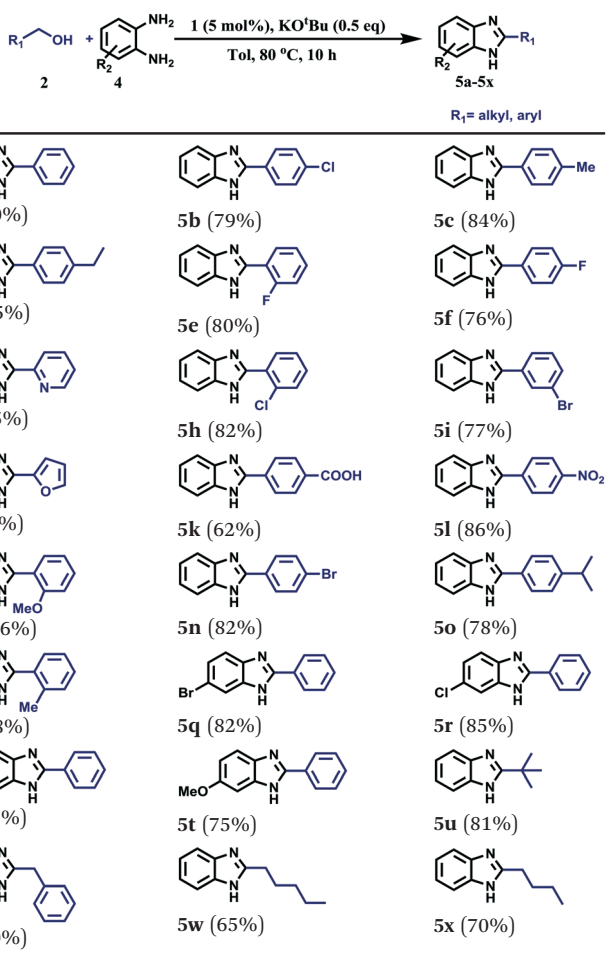
Results and discussion

Our preliminary exploration commenced with 1,2-phenylene diamine coupling with benzyl alcohol in presence of the putative square planar nickel complex, **1** synthesized from azophenolate ligand and $Ni(OAc)_2$ (Scheme 1).[9] To our advantage, the catalyst molecule is air-stable and the entire reaction can be operated under aerobic condition, unlike many catalysts containing phosphine ligands. Optimization of the reaction conditions revealed that the reaction can be performed in presence of 5 mol% of **1**, 0.50 equivalent of base KO^{t}Bu, and the reaction is completed in 10 h at 80 °C giving 90% yield of the desired benzimidazole. A set of control experiments disclose no product formation in absence of the catalyst, or KO^{t}Bu. It has been proved earlier that KO^{t}Bu behaves as a crucial reductant parallel to its reactivity as a base.[10] Furthermore, control experiments prove that the reaction can be considerably expedited by adding an oxygen-filled balloon to the reaction flask whose reason will be clear during mechanistic evaluation. Notably, our conditions are much milder compared to the existing noble and base metal catalysts reported for benzazole formation.

With the optimized conditions in hand, we expanded the scope of the reaction with a diverse set of benzyl alcohol. As described in Table 1, *p*-substituted benzyl alcohols with alkyls, halides (**2b–d**, **2f**, **2n**) all result in high yield of the corresponding benzimidazoles. Similarly, *o*-substituted benzyl alcohols with halides (**2e**, **2h**) or –Me group (**2p**) all provided the product in 80–88% yield. Presence of electron-donating or -withdrawing groups (**2c**, **2l**) in the benzyl alcohol were well tolerated under the optimized reaction conditions and the yield of the final products were similar. Notably, heterocyclic alcohols such as 2-pyridinemethanol (**2g**), 2-furanmethanol (**2j**) smoothly furnished the respective benzimidazole products in moderate to high yields (65–81%). Moreover, during the benzimidazole formation, no *N*-alkylated product was observed to form as a detrimental byproduct.

After successfully using many derivatives of benzyl alcohol for the dehydrogenative cyclization reactions, we tested whether our catalyst can be equally efficient if aliphatic alcohols are chosen as the coupling partner. Gratifyingly, neopentyl alcohol offers high yield (81%) of the 2-substituted benzimidazole (**5u**) under the same reaction conditions. Furthermore, when 1-hexanol was (**2w**) employed as the coupling partner, product 2-pentyl benzimidazole (**5w**) was synthesized in 65% yield. Similarly, for 1-pentanol (**2x**), the corresponding benzimidazole product (**5x**) was also obtained in good (70%) yield. This is much improved yield under milder conditions than many base metal catalyzed 2-benzimidazole formation where aliphatic alcohols with longer chain were used as a coupling partner.[8b,c] We further expanded the scope of our synthetic protocol by having a diverse choice of bis-amine. Accordingly, when –Br, –Cl, –Me, –OMe substituted *o*-phenylenediamines were coupled to benzyl alcohol, all generated the appropriate benzimidazole (**5q–5t**) in good to very good yield (75–85%). We were further delighted to observe that 1,2 disubstituted benzimidazoles can be elegantly synthesized simply by changing the stoichiometry of the alcohol. Accordingly, when **2** was used twice in amount to **4**, corresponding 1,2-disubstituted products formed smoothly under the same reaction conditions with a tiny amount of mono-substituted product

Table 1 Scope of alcohols and diamines: synthesis of benzimidazole



Reaction conditions: **1** (5 mol%), benzyl alcohol (1 mmol), diamine (1 mmol), KO^{t}Bu (0.5 mmol), toluene (2 mL), 80 °C, O_2, 10 h.

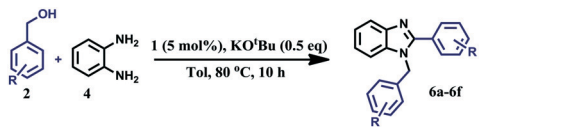
(~13%) formation. The developed protocol was tested for six different alcohols, including heterocyclic 2-furanmethanol and corresponding benzimidazoles were isolated in 66–85% yields (Table 2). Encouragingly, simple control of benzyl alcohol stoichiometry to furnish di- over mono-substituted products add considerable modularity to the developed process. Such tunability prompted us further to expand the scope of this reaction to other benzazoles. Along this direction, we changed the *o*-phenylenediamine with *o*-amino phenol and *o*-amino thiol. Gratifyingly, the corresponding benzoxazoles and benzthiazoles were synthesized in good to excellent yields (Table 3). Furthermore, the diols like quinol and resorcinol offer the disubstituted products in 67 and 56% respectively under the same reaction conditions (Table 4).

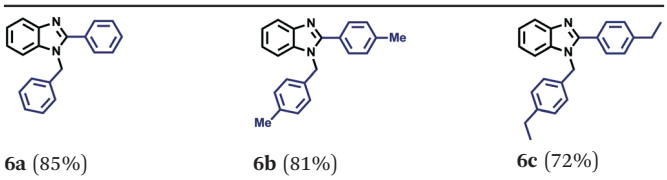
Mechanistically, the benzimidazole formation reaction can be dissected into three major parts: alcohol oxidation, condensation to form imine followed by cyclization, and oxidative dehydrogenation. The plausible intermediates along the reaction sequence have been fully characterized upon their isolation (ESI,† Scheme S1 and S2). Importantly, reaction with d-labelled benzyl alcohol, resulted in d-incorporation (96%) only at the benzylic position of the 1,2-disubstituted benzimidazole (ESI,† Scheme S4 and Table S6). This fact unequivocally establishes that the oxidized alcohol is a source of alkyl group in the final product benzimidazole. The formation of di-substituted benzimidazole upon using two equivalents of alcohols can be easily explained by bisimine formation followed by a ring cyclization and a hydride migration (ESI,† Scheme S2). We have indicated in our previous study that the alcohol oxidation comprises a HAT step where a H-atom from the β-position of the bound alcohol migrates to the mono-reduced azo motif in the ligand backbone.[9]

The resulting aldehyde undergoes condensation with *o*-phenylenediamine to form an imine, which upon ring cyclization yields 2,3-dihydrobenzimidazole, **3** (Fig. 2a). In fact, this is the precursor to benzimidazole upon dehydrogenation. The dehydrogenation of different saturated heterocycles is considered to be an important class of reaction, since these heterocycles often serve as liquid organic hydrogen storage material, in commercial fuel cell *etc.*[11] A set of control experiments strongly suggest that the dehydrogenation reactions are very inefficient in absence of **1**, under our reaction conditions. Henceforth, the same catalyst plays a crucial role for the amine dehydrogenation reaction parallel to its function in alcohol oxidation. We posited the dehydrogenation of **3**, being a $2e^-$ process, may undergo a similar cycle of HAT, taking help from the mono reduced azo motif. To examine whether the binding of **3** is necessary during the dehydrogenation process, we performed saturation kinetics experiment with this substrate and observed a clear saturation of rate (k_{obs}) when the concentration of **3** was exceeding 0.8 M (Fig. 1a). An equilibrium constant (K) of 231 M^{-1} and k of 4.5×10^{-4} s^{-1} was derived from the non-linear curve fitting of the saturation plot at 80 °C following the rate law $k_{obs} = kK[\mathbf{3}]/1+K[\mathbf{3}]$. This finding implies that the pathway of dehydrogenation likely follows very similar steps of alcohol oxidation. Furthermore, with a deuterium isotopologue of **3** (labelled isotopically at the benzylic position), a KIE of 5.9 (Fig. 1b) was measured at 60 °C. This considerably large value of KIE again strongly indicates that HAT to the reduced azo backbone is rate- determining for the amine dehydrogenation reaction.

This mode of aromatization is rare and to our knowledge there is not much precedence of HAT based dehydrogenation of N-heterocycles.[12] To unequivocally establish that a radical pathway is involved during this oxidative dehydrogenation step, we used a radical quencher TEMPO and found the reaction is thwarted considerably (ESI,† section 2, III). Very encouragingly, the radical generated upon HAT can cleanly be intercepted by administering TEMPO and can be

Table 2 Scope of alcohols: synthesis of 1,2 di-substituted benzimidazole



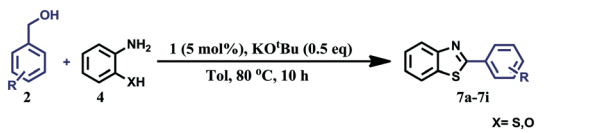


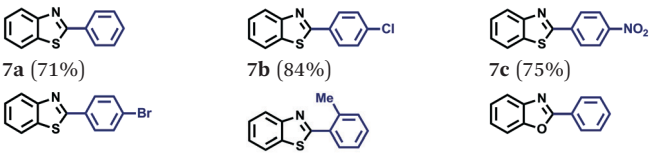
6a (85%) **6b** (81%) **6c** (72%)

6d (84%) **6e** (68%) **6f** (66%)

Reaction conditions: **1** (5 mol%), benzyl alcohol (2 mmol), diamine (1 mmol), KO^{t}Bu (0.5 mmol), toluene (2 mL), 80 °C, O_2, 10 h.

Table 3 Scope of alcohols: synthesis of benzthiazole, benzoxazoles





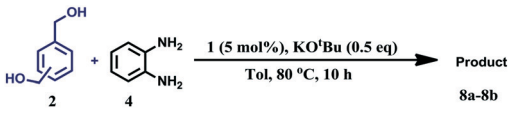
7a (71%) **7b** (84%) **7c** (75%)

7d (73%) **7e** (81%) **7f** (53%)

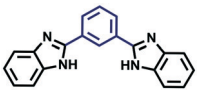
7g (42%) **7h** (40%) **7i** (55%)

Reaction conditions: **1** (5 mol%), benzyl alcohol (1 mmol), *o*-amino phenol/ *o*-amino thiol (1 mmol), KO^{t}Bu (0.5 mmol), toluene (2 mL), 80 °C, O_2, 10 h.

Table 4 Scope of di-alcohol: synthesis of benzimidazole



8a (67%)



8b (56%)

Reaction conditions: **1** (5 mol%), benzyl alcohol (0.5 mmol), diamine (1 mmol), KO^{t}Bu (0.5 mmol), toluene (2 mL), 80 °C, O_2, 10 h.

characterized by high-resolution mass spectrometry. The observed mass of the trapped intermediate, 351.2301 amu and its isotopic distribution match very well with the simulated pattern for the molecule (Fig. 2c). During this dehydrogenative reaction, supposedly a relatively stable carbene radical forms where the stability of the radical is gained by delocalization through the -Ph ring and parallel stability conferred by heteroatoms in the near vicinity. To substantiate this HAT step being operative during dehydrogenation, we further computed the pertinent intermediate and transition state (TS) at M06/lanl2dz (6-31g* for C, H, N, O) level of theory on the model catalyst.[13] In the bound intermediate (**9**, Fig. 2a), the radical character on azo and its proximity to the benzylic hydrogen atom of the substrate makes the H-atom abstraction mechanism very feasible. At the TS, the N—H and C—H distances are 1.38 and 1.30 Å respectively (Fig. 2b). The computed distance between two termini of the HAT was found to be 2.62 Å, that has a close resemblance to many other HAT processes in enzyme catalysis.[14] Not surprisingly, since the reduced azo motif in the ligand backbone is responsible for both HAT steps, the TS for dehydrogenation of **3** is reminiscent of the TS for alcohol oxidation step.[9] Further scrutiny also discloses that the binding of **3** to catalyst **1** is only facilitated when the proton transfer to one phenolate arm leads to detachment of the arm and nickel maintains a distorted square planar geometry (Fig. 2a). This also closely resembles the protonation of an axial tyrosinate arm from the Cu^{II}-bound alcohol in galactose oxidase.[15] Akin to aldehyde or ketone formation from transient ketyl radical the carbene radical also does an intramolecular reduction to the second unreduced azo arm, and readily becomes converted to the benzimidazole. In the context of alcohol oxidation, it is important to note that aliphatic alcohols are difficult to oxidize due to its greater C–H bond strength. The oxidation for this class of substrates is likely facilitated by the reduction of this putative bond strength due to the electronic effect of the alkoxide lone pair.[16]

Overall, the present example is distinctly different from a large body of reports for dehydrogenative benzannulations which are simply directed by traditional metal–ligand cooperativity.[17] As can be easily anticipated, the ligand part of the catalyst traps the borrowed hydrogen both in alcohol oxidation and dehydrogenative aromatization steps and stores in the form of a hydrazo moiety. Interestingly, using O_2 as a terminal oxidant, the catalyst can be revived very easily by formation of H_2O_2. As a conclusive evidence, the formation of H_2O_2 as a byproduct was further traced by iodometry (ESI,† Fig. S3). Indeed, ease of catalyst revival under neat oxygen condition helped the reaction to operate under fairly mild conditions (80 °C, 10 h) that rivals all other catalysts for benzazole formation. As anticipated, the hydrazo form of the catalyst can also be oxidized with simple aerobic oxygen, however, that will make the process sluggish.

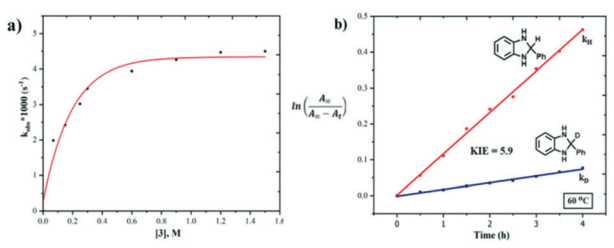


Fig. 1 a) Saturation kinetics plot of k_{obs} *vs.* [**3**], b) kinetic isotope effect for amine dehydrogenation at 60 °C by **1**.

Conclusions

In summary, we report an inexpensive nickel catalyst that forms a variety of benzazoles in a tunable manner, utilizing hydrogen borrowing from alcohols. The redox-active azo backbone present in the catalyst system helps both alcohol oxidation and a dehydrogenative aromatization *via* a common hydrogen atom transfer pathway. The success of the catalyst hinges on the easy reversible $2e^-$-redox of the azo–hydrazo couple, which is part of the ligand utilized in this system. Both the alcohol oxidation and aromative dehydrogenation reactions are governed by a radical housed in the azo backbone, that makes this class of catalyst entirely different from previously evaluated systems relying on metal–ligand cooperativity. We hope this catalytic process will be considered as a new avenue toward the formation of heterocycles and will be a nice addition to the repertoire of HAT catalysis. Our current effort is focused on furnishing a wide variety of heterocycles using this methodology to prove the prowess of the catalyst to promote HAT-based dehydrogenations.

Experimental section

General considerations

All the starting compounds employed in this study were procured from commercial suppliers and were used without further purification. Potassium *tert*-butoxide, potassium hydroxide and *o*-phenylene diamine were purchased from Sigma Aldrich. Glassware were dried overnight at 160 °C prior to use. Solvents such as methanol, ethanol and toluene were used as received from the suppliers. For thin layer

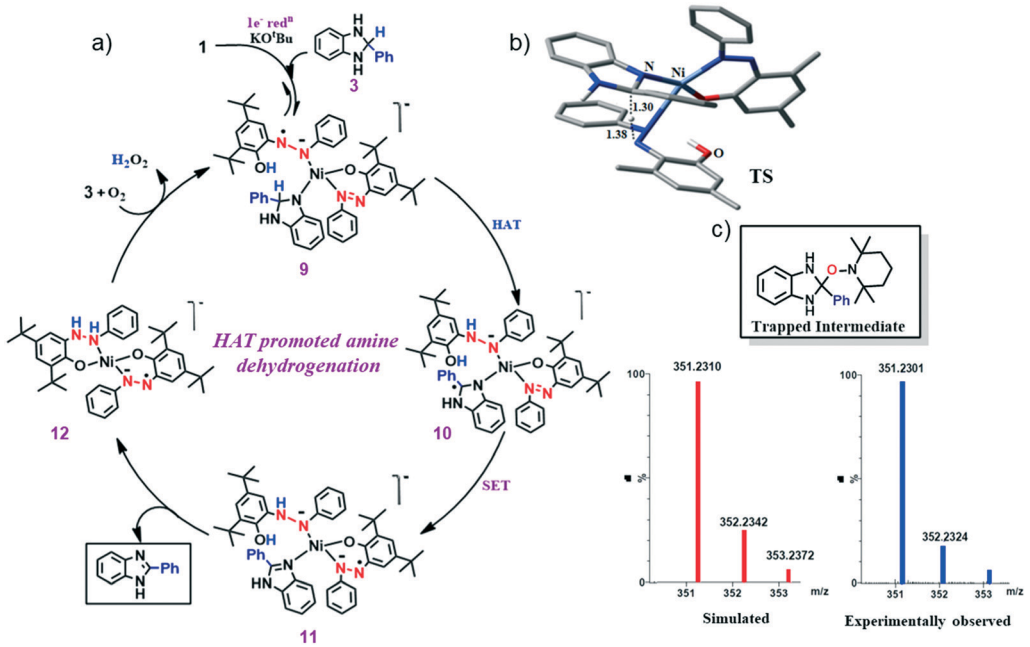


Fig. 2 a) Plausible mechanistic scheme for HAT promoted amine dehydrogenation reaction. b) DFT optimized transition state for HAT. All hydrogens except chemically important ones are removed for clarity (^{t}Bu groups in the model ligand are truncated to Me). c) Mass spectrum of trapped radical intermediate by TEMPO.

chromatography (TLC), aluminium foils coated with silica and fluorescent indicator (from Merck) were used. Column chromatography was performed using SD fine silica gel 60–120 mesh using a gradient of ethyl acetate and hexane as mobile phase. High-resolution mass spectra were recorded on a Waters QTOF mass spectrometer. IR spectra were recorded on a Perkin–Elmer FT IR spectrometer using KBr pellet, and presented as ν_{max} in inverse centimetres. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker Biospin Advance III FT-NMR spectrometer. NMR shifts are reported as delta (δ) units in parts per million (ppm) and coupling constants (J) are reported in Hertz (Hz). The following abbreviations are utilized to describe peak patterns when appropriate: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Chemical shifts (δ) are quoted to the nearest 0.01 ppm relative to tetramethylsilane (δ 0.00 ppm) in $CDCl_3$ (δ 7.26 ppm) or $(CD_3)_2SO$ (δ 2.50 ppm). To improve solubility of the probe molecule, sometimes small amount of $(CD_3)_2SO$ has been mixed in the primary solvent $CDCl_3$. Carbon chemical shifts are internally referenced to the deuterated solvent signal of $CDCl_3$ (δ 77.1 ppm).

Synthesis of 1

The synthesis of **L** was performed following a reported procedure in our previous work.[9] A methanolic solution of 0.1 mmol of **L** was taken in a 100 mL round-bottom flask and to it 0.1 mmol of KOH was added and the mixture was stirred at rt for 30 min. Then, 0.05 mmol of $Ni(OAc)_2$ was added to the reaction mixture and refluxed for another 30 min. Immediate precipitate was obtained during the reflux. After completion of the reaction, the solution was filtered to obtain dark brown coloured product in 82% yield. The desired product was fully characterized by ^{1}H, ^{13}C NMR and IR spectroscopies.

General procedure for the synthesis of benzazoles

In a typical reaction 5 mL vial was charged with alcohols (1 mmol), *o*-phenylenediamine/2-aminothiophenol/2-aminophenol (1 mmol), KO^{t}Bu (0.5 mmol), **1** (5 mol%) in 2 mL toluene and was closed with rubber septum. The resulting solution was purged with O_2. The reaction mixture was stirred at 80 °C for 10 h. The reaction mixture was cooled to room temperature upon completion and concentrated *in vacuo*. The residue was purified by column chromatography using ethyl acetate/petroleum ether (5–10%) as eluent to afford pure products. The desired coupling products were fully characterized by ^{1}H, ^{13}C NMR spectroscopies.

General procedure for the synthesis of 1,2 di-substituted benzimidazole

In a typical reaction 5 mL vial was charged with alcohols (2 mmol), *o*-phenylenediamine (1 mmol), KO^{t}Bu (0.5 mmol), **1** (5 mol%) in 2 mL toluene and was closed with rubber septum. The resulting solution was purged with O_2. The reaction mixture was stirred at 80 °C for 10 h. The reaction mixture was cooled to room temperature upon completion and concentrated *in vacuo*. The residue was purified by column chromatography using ethyl acetate/petroleum ether (5–10%) as eluent to afford pure products. The desired coupling products were fully characterized by ^{1}H, ^{13}C NMR spectroscopies.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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