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Visible-light-mediated direct C3-arylation of 2*H*-indazoles enabled by an electron-donor–acceptor complex†

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A mild visible-light-mediated, photocatalyst-free arylation of 2*H*-indazoles was developed. The formation of an electron donor–acceptor complex by 2*H*-indazoles and aryl diazonium salts in the presence of pyridine allows the direct arylation of 2*H*-indazoles under visible-light irradiation. This process provides an efficient route for the synthesis of C3-arylated-2*H*-indazoles, which are important scaffolds of various bioactive compounds.

Indazoles, which are bioisosteres of indoles and benzimidazoles, are important scaffolds in organic synthesis and medicinal chemistry because of their significant bioactive properties.[1] The synthesis of 2*H*-indazoles in particular has attracted a great deal of attention in the synthetic community due to the prevalence of this structural motif in commercially available pharmaceuticals and other drug candidates (Fig. 1).[2] Recently, the 2*H*-indazole scaffold was found in compounds which exhibit anti-inflammatory properties as well as effective anticancer agents such as pazopanib and niraparib.[2,3]

Various approaches for the synthesis of 2*H*-indazoles starting from acyclic precursors are known.[4] However, direct functionalization of 2*H*-indazoles at the C3 position is less common because of the low reactivity at that position.[5] In spite of this, direct functionalization of 2*H*-indazoles would provide efficient ways to synthesize various 2*H*-indazole derivatives, and some examples have been reported, such as alkenylation,[6] acylation,[5c] phosphonylation,[7] nitration,[8] annulation,[9] and trifluoromethylation.[10]

On the other hand, only a limited number of studies on the direct arylation of 2*H*-indazoles have been reported so far, including arylation by aryl halides, which required transition metal catalysts, ligands, and other organometallic reagents.[11] The above-mentioned methods include concerns regarding the use of toxic and expensive transition metal catalysts, reagents, or both (Scheme 1, I). Very recently, an efficient continuous-flow organo-photocatalytic approach for the arylation of 2*H*-indazoles was reported.[5d,12] However, the substrate scope was limited to phenyl or aryl substituents with an electron-donating group at N2 of the 2*H*-indazole.

Given this background, the development of general and efficient approaches for the arylation of 2*H*-indazoles using environmentally benign processes would still be demanded. Herein, we report the efficient visible-light-promoted direct arylation of 2*H*-indazoles using aryl diazonium salts (Scheme 1, II). Notably, the reaction proceeds under mild reaction conditions without using any catalysts or metal reagents.

With the goal of green chemistry in mind, various reaction conditions were considered, including catalyst-free conditions. We envisaged that the arylation of 2*H*-indazoles might be accomplished *via* a visible-light-induced process in the absence of a photocatalyst through the formation of an electron donor–acceptor (EDA) complex.[13] To test this hypothesis, we employed 2-phenyl-2*H*-indazole **1aa** and 4-methoxybenzenediazonium tetrafluoroborate **2aa** as model substrates. We performed the reaction using various conditions, selected examples of which are summarized in Table 1.

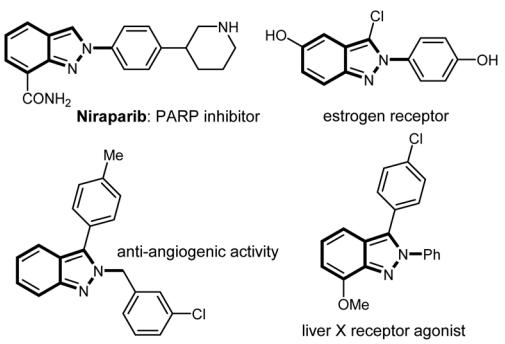

Fig. 1 Bioactive compounds containing the 2*H*-indazole moiety.

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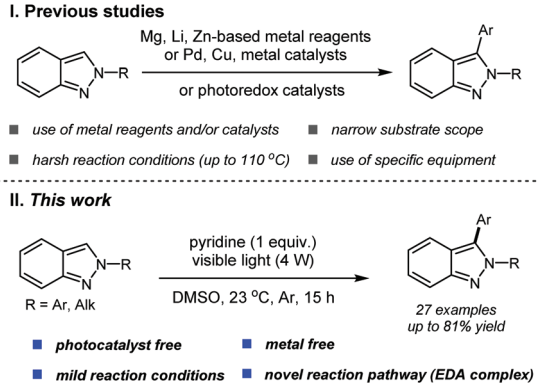
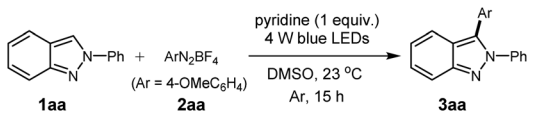


Scheme 1 Synthetic approaches to C3-arylated 2*H*-indazoles.

Table 1 Optimization of the reaction conditions[a]



Entry	Variations in the reaction conditions	Yield[b] (%)
1	None	73
2	With 1.0 equiv. of **1aa**	47
3	DMF instead of DMSO	33
4	CH_3CN instead of DMSO	12
5	CH_2Cl_2 instead of DMSO	Trace
6	Toluene instead of DMSO	No rxn
7	1,4-Dioxane instead of DMSO	No rxn
8	Without pyridine	43
9	With 0.5 equiv. of pyridine	62
10	With 2.0 equiv. of pyridine	72
11	TEA instead of pyridine	47
12	DIPEA instead of pyridine	59
13	TMEDA instead of pyridine	60
14	Green LEDs instead of blue LEDs	68
15	White LEDs instead of blue LEDs	71
16	20 W CFL instead of blue LEDs	65
17	Sunlight instead of blue LEDs	53
18	Under air	54
19	Without light	13

[a] Conditions: **1aa** (1.0 mmol, 2.0 equiv.), **2aa** (0.5 mmol, 1.0 equiv.), and pyridine (1.0 equiv.) in DMSO (2 mL, 0.25 M); irradiation with 4 W blue LEDs (455 nm) at 23 °C for 15 h under Ar. [b] Isolated yield after column chromatography. The yield was obtained based on the amount of consumed **1aa** (0.5 mmol).

We assumed that aryl diazonium salt **2** could act as an electron-acceptor to form the key EDA complex with indazole **1**. We found that direct arylation product **3aa** was obtained in 73% yield in the presence of 1 equiv. of pyridine in DMSO at room temperature under blue LED light irradiation (455 nm) in an Ar environment without using a photocatalyst (Table 1, entry 1). Moreover, the addition of 2 equiv. of indazole **1aa** improved the reaction yield compared with only 1 equiv. of **1aa** (entries 1 and 2, 47% *vs.* 73% yield). Interestingly, only 1 equiv. of **1aa** reacted with aryl diazonium salt **2aa** to afford the desired product; 1 equiv. of starting indazole **1aa** was recovered after the reaction.

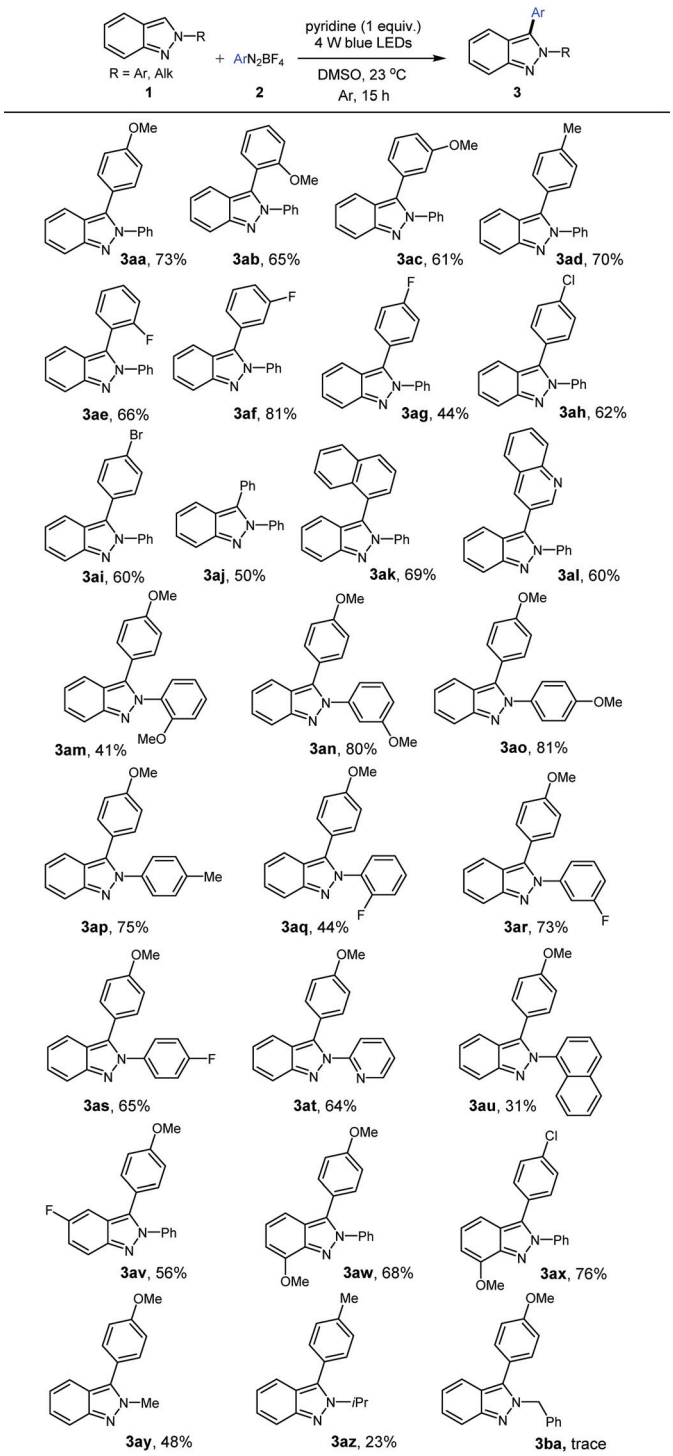
It seems that the additional **1aa** might be helping to accelerate the reaction by controlling the overall reaction profile. In the presence of 2 equiv. of **1aa**, the yield increased smoothly over time. In contrast, in the presence of only 1 equiv. of **1aa**, the yield was around 30% after three hours, and then increased very slowly (see the ESI† for more details). Employing different solvents such as DMF, acetonitrile, or dichloromethane instead of DMSO caused the reaction yield to diminish significantly (entries 3–5). The reaction did not take place in toluene or 1,4-dioxane (entries 6 and 7). Intriguingly, the desired product was obtained in 43% yield in the absence of pyridine, which indicates that formation of the EDA complex might be possible without pyridine (entry 8). However, it seems that pyridine creates a synergistic effect to improve the reaction yield (entry 1). One possible explanation of these results could be the formation of a ternary EDA complex by 2*H*-indazole, the aryl diazonium salt, and pyridine.[14] Varying the amount of pyridine did not improve the reaction yield (entries 9 and 10). In addition, employing different amines instead of pyridine generated the desired product with diminished yield (entries 11–13). Changing the light source did not make a significant difference; the best reaction yield was obtained with blue LEDs (entries 1, 14–17). The reaction yield decreased when the reaction was performed under air (entry 18). Finally, the yield decreased dramatically in the dark; therefore, visible light plays an important role in this transformation (entry 19).

With the optimized reaction conditions in hand, we explored the substrate scope of the synthesis of C3-arylated 2*H*-indazoles. Notably, the reaction was tolerant to various aryl diazonium salts (Table 2). Aryl diazonium salts with either electron-donating (**3aa–3ad**) or electron-withdrawing (**3ae–3ai**) groups provided the desired products in 44–81% yields. The use of naphthyl diazonium salt **2ak** gave the desired product **3ak** in 69% yield. In addition, the reaction with heteroaryl diazonium salt **1al** successfully provided the desired product **3al** in 60% yield.

Furthermore, the products derived from the *ortho*-, *meta*-, and *para*-substituted aryl diazonium salts were obtained in 44–81% yields (**3aa–3ac**, **3ae–3ag**). A significant electronic effect was not observed with *ortho*-, and *meta*-substituted aryl diazonium salts (**3ab–3ac** *vs.* **3ae–3af**). However, diminished reaction yields were observed with electron-withdrawing substituents at the *para*-position (**3aa**, **3ad** *vs.* **3ag–3ai**). Next, we examined various aryl substituents at N2 of the 2*H*-indazoles (**3am–3au**). Aryl substituents with either electron-donating (**3am–3ap**) or electron-withdrawing (**3aq–3as**) groups afforded the desired products in 41–81% yields. The decrease in the yields of **3am** and **3aq** was likely due to the steric effect of the substituents at the *ortho* position. Similarly, the use of sterically hindered 2-(naphthalen-1-yl)-2*H*-indazole gave the desired product with low yield (**3au**, 31% yield). The reaction with 2-pyridyl substituted 2*H*-indazole **1at** also successfully provided the desired product **3at** in 64% yield.

The electronic effect on the arene structure of 2*H*-indazole was important; 7-methoxy-2-phenyl-2*H*-indazole provided the

Table 2 Substrate scope[a]

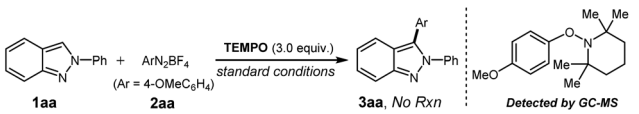


[a] Conditions: **1aa** (1.0 mmol, 2.0 equiv.), **2aa** (0.5 mmol, 1.0 equiv.), pyridine (1.0 equiv.) in DMSO (2 mL, 0.25 M), irradiation with 4 W blue LEDs (455 nm) at 23 °C for 15 h under Ar. Isolated yield after column chromatography. The yield was obtained based on the amount of consumed **1aa** (0.5 mmol).

product with a slightly increased yield compared with 5-fluoro-2-phenyl-2*H*-indazole (**3av**: 56% *vs.* **3aw**: 68%). Notably, alkyl substituted 2*H*-indazoles were also suitable substrates in this transformation even though the reaction yields were relatively low (**3ay**: 48%, **3az**: 23%). However, with benzyl substituted 2*H*-indazole, only a trace amount of the desired product was obtained (**3ba**).

In order to gain mechanistic insight into this transformation, we employed TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a radical inhibitor. When TEMPO was present, none of the desired product was observed, thereby indicating that the reaction proceeds *via* a radical pathway. Furthermore, the aryl radical was trapped by TEMPO, and the TEMPO-adduct was detected by GC-MS (Scheme 2).

To further understand this catalyst-free reaction, we investigated the formation of the plausible EDA complex. First, we analyzed the reaction components by UV-vis absorption spectroscopy (Fig. 2a). When a solution of **2aa** in DMSO was treated with **1aa**, the color of the mixture turned yellow, and a significant bathochromic shift was observed in the UV-vis spectrum, which is diagnostic of an EDA complex.[13] A clear bathochromic shift was also observed with a mixture of **2aa** and pyridine in DMSO. Interestingly, a mixture of **1aa**, **2aa**,



Scheme 2 Radical trapping experiment.

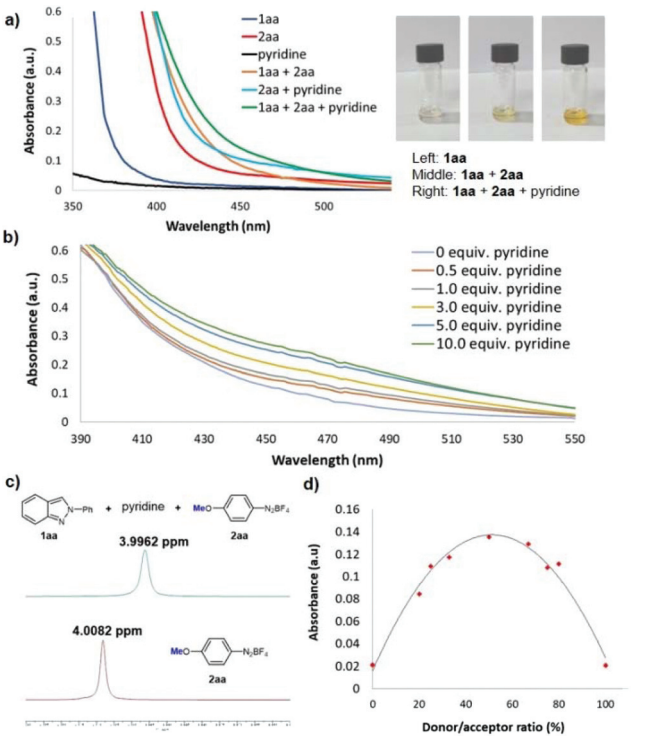
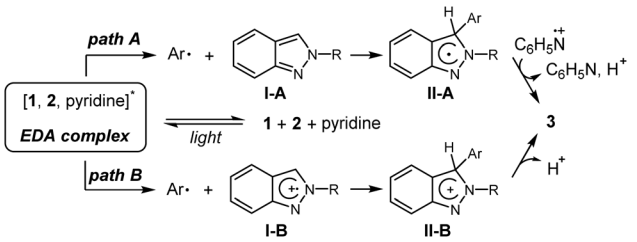


Fig. 2 Mechanistic studies. (a) UV-vis absorption spectra of the reaction components. (b) UV-vis absorption spectra with different amounts of pyridine. (c) ^{1}H NMR spectra of **2aa**. (d) Job plot of **1aa** and **2aa**.



Scheme 3 Proposed reaction pathway.

and pyridine showed a further bathochromic shift, thereby suggesting the formation of a ternary EDA complex (Fig. 2a).[14] To further clarify the role of pyridine in forming the EDA complex, a 1 : 1 mixture of **1aa** and **2aa** in DMSO was treated with different amounts of pyridine (0–10 equiv.), and the absorption was analyzed by UV-vis spectroscopy (Fig. 2b). The intensity of the absorption increased upon increasing the pyridine concentration. These results suggest that pyridine is involved in the formation of the EDA complex.[14c] This ternary EDA complex would enhance the reactivity of the reaction; therefore, an improved yield was observed in the presence of pyridine in our optimization experiments (Table 1, entries 1 and 8). In addition, ^{1}H NMR studies showed that the aryl diazonium salt acts as an electron-acceptor in the EDA complex; a noticeable chemical shift of the methoxy group of **2aa** was observed in the presence of **1aa** and pyridine in DMSO-d_6 (Fig. 2c). Additional NOESY studies showed possible correlations between **1aa**–**2aa**, and **2aa**-pyridine in the mixture. Furthermore, we found that the diffusion coefficient decreased in the mixture of **1aa**, **2aa**, and pyridine in DOSY studies (see the ESI† for more details).

In our previous report, we found that an aryl diazonium salt could form an EDA complex with pyridine in a 1 : 1 ratio.[15,16] We were curious about the ratio of **1aa** and **2aa** in the EDA complex. A Job plot of the UV-vis spectroscopy results indicated a 1 : 1 ratio of **1aa**/**2aa** in the EDA complex (Fig. 2d, see the ESI† for more details).[17]

A plausible reaction pathway is proposed based on the present study and previous reports (Scheme 3).[5d,7,18] The reaction would start with the formation of an EDA complex of 2*H*-indazole **1**, aryl diazonium salt **2**, and pyridine. Next, photoexcitation of the EDA complex would trigger SET to generate an aryl radical, which would then react with **I-A** (path A) or **I-B** (path B), affording intermediates **II-A** or **II-B**, respectively. After oxidation of **II-A** by pyridinium radical cation and subsequent deprotonation (path A) or deprotonation of **II-B** (path B), the aromaticity would be regenerated to afford the desired product **3**.

Conclusions

In summary, we have developed a photocatalyst-free, visible-light-mediated arylation reaction of 2*H*-indazoles. The desired products were obtained under mild reaction conditions without using any catalysts or metal reagents. This environmentally friendly process is an efficient method for the synthesis of C3-arylated 2*H*-indazoles, which are important scaffolds of many bioactive compounds. In addition, the novel reaction pathway for the arylation of 2*H*-indazoles through the formation of a ternary EDA complex would provide new opportunities to expand the field of organic photochemical reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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