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Synthesis of Indazoles and Azaindazoles by Intramolecular Aerobic Oxidative C–N Coupling under Transition-Metal-Free Conditions

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Abstract: A transition-metal-free oxidative C–N coupling method has been developed for the synthesis of 1*H*-azaindazoles and 1*H*-indazoles from easily accessible hydrazones. The procedure uses TEMPO, a basic additive, and dioxygen gas as the terminal oxidant. This reaction demonstrates better reactivity, functional group tolerance, and broader scope than comparable metal catalyzed reactions.

Azaindazole and indazole derivatives play an increasingly important role in today's pharmaceutical industry.[1,2] Compounds containing these types of scaffolds are being developed for the treatment of oncological, HIV, CNS, and inflammatory diseases, etc.[3] (Figure 1) Despite the importance of azaindazole and indazole in pharmaceutical development, only a limited number of approaches are available for the synthesis of azaindazoles and indazoles.[4–7] Especially in the case of azaindazole, the major method is employing traditional cycloaddition chemistry, which usually suffers low efficiencies in terms of practicality and overall yields.

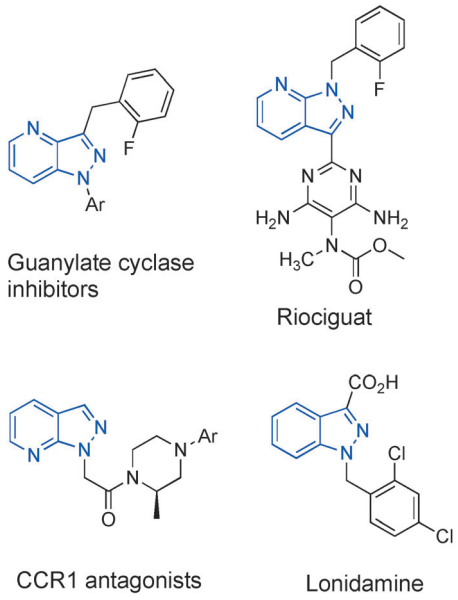

Figure 1. Important azaindoles and indozoles.

Over the last decade, considerable progress has been made towards the development of C–H bond functionalization methods that can be applied to the synthesis of biologically important aromatic and heteroaromatic compounds.[8] As an atom-economic and efficient strategy, constructing a C–N bond through direct C–H functionalization[9] becomes highly attractive in recent years. Nevertheless, these approaches always require the addition of catalytic or stoichiometric amounts of transition metals, most of which are expensive and non-environmentally benign. Moreover, especially for the pharmaceutical industry, the removal of harmful transition-metal contamination is often costly and difficult.[10] In recent years, there has been growing demand for new environmentally benign methods suitable for large-scale synthesis[11] and the use of molecular oxygen[12] as terminal oxidant has received great attention for both environmental and economic prospects. We are particularly interested in the development of an alternative transition-metal-free oxidative C–N bond formation with molecular oxygen as an interesting and practical addition to the transition metal involved protocols. To the best of our knowledge, the development of C(sp^2)–H functionalization for preparing azaindazole and indazole molecules under transition-metal-free conditions remains unexplored. Inspired by the effectiveness of TEMPO-based reagents and cocatalysts in the aerobic alcohol oxidation,[13] we proposed that a proper combination of TEMPO/O_2 with suitable bases might provide an efficient catalytic system for intramolecular oxidative C–N coupling to furnish azaindazoles and indazoles (Scheme 1) through a potential radical process (TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy).[14] Here, we report the first example of the synthesis of azaindazoles and indazoles through aerobic oxidative C–N bond formation without using transition metals.

At the beginning, a model study was initiated with hydrazone **1** in the presence of TEMPO in DMSO under one atmos-

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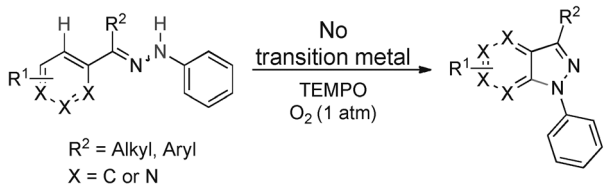
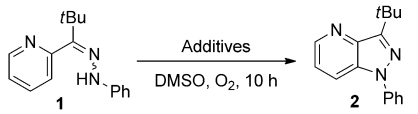


Scheme 1. A new strategy towards azaindazole and indazole through C–H functionalization without using transition metal.

Table 1. Optimization of the reaction conditions.



Entry	Additives	T [°C]	Yield [%]
1	TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)	80	0
2	TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)	110	24
3	TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)	130	48
4	TEMPO (0.1 equiv)/$NaHCO_3$ (1.0 equiv)	140	55
5	TEMPO (0.5 equiv)/$NaHCO_3$ (1.0 equiv)	140	72
6	TEMPO (0.3 equiv)/NaOAc (1.0 equiv)	140	73
7	TEMPO (0.3 equiv)/K_2CO_3 (1.0 equiv)	140	63
8	TEMPO (0.3 equiv)/DMAP (1.0 equiv)	140	75
9	TEMPO (0.3 equiv)/DABCO (1.0 equiv)	140	65
10	TEMPO (0.3 equiv)/NEt_3 (1.0 equiv)	140	57
11	TEMPO (0.3 equiv)/$NaHCO_3$ (0.5 equiv)	140	76
12	**TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)**	**140**	**85**
13	TEMPO (0.3 equiv)/$NaHCO_3$ (2.0 equiv)	140	83
14[b]	TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)	140	33
15[c]	TEMPO (0.3 equiv)/$NaHCO_3$ (1.0 equiv)	140	59
16	**With metals such as Ru, Rh, Pd, Cu, Ni or Fe**	**Low yields (<30%)**	

[a] Isolated yield; [b] under 1 atmosphere air (54% of starting material remained); [c] 2.0 equivalents of H_2O was added

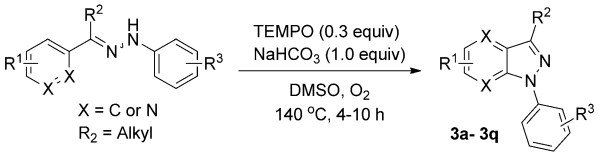
phere of O_2 to test our hypothesis (Table 1). Although no reaction occurred in the initial temperature range (80–100 °C), we were pleased to observe the desired azaindazole **2** in 24% yield after stirring for 10 h (entry 2) at elevated temperature (110 °C). Encouraged by this preliminary result, we started to optimize the reaction conditions. After a comprehensive screening, we found that DMSO was superior over other solvents, such as DMF, DMA, alcohols, and 1,4-dioxane, etc. It was observed that higher temperatures (such as 140 °C) could speed up the reactions and improve the yields. Moreover, we found that the yields notably increased and reactions went to completion in a shorter time with the addition of a base such as $NaHCO_3$ or DMAP (entries 8 and 12; DMAP = 4-dimethylaminopyridine). It was believed that the base would serve as a proton shuttle and assist the transformation. There is only slight differences with higher TEMPO/base loadings in terms of reaction rates and conversion ratios (entry 13). In the absence of base and TEMPO, the yield will suffer a significant drop. Generally, 0.1–0.3 equivalents amount of TEMPO and 1.0 equivalent of base was enough to effectively promote the reaction. Control experiments using various metal catalysts (entry 16), such as Ru, Rh, Pd, Cu, Ni, and Fe were not as efficient as our catalytic system (either serious decomposition of starting materials or only low yields of **2** was observed). Interestingly, a 33% yield of product **2** was also achieved by using air as the oxidant (entry 14). It is noteworthy that this protocol was conducted without the need for moisture-proof conditions (entry 15). Typically the reaction will proceed to completion in DMSO within 6 h, in a clean manner, under one atmosphere of O_2.

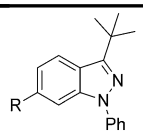
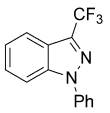
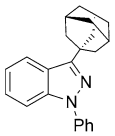
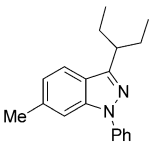
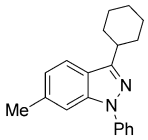
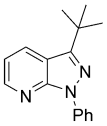
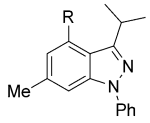
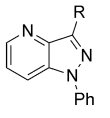
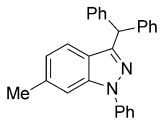
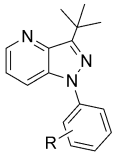
Having identified these optimal conditions, we set out to explore the scope for this new reaction. A variety of aromatic hydrazines, and aromatic ketones were surveyed to prepare different 3-alkyl azaindazoles and indazoles. As displayed in Table 2, the scope of the ring substituents was found to be very broad. Diverse azaindazole and indazole derivatives were prepared readily from corresponding aromatic hydrazones. A variety of *ortho-*, *meta-,* and *para*-substituted aryl groups, as well as the electron-rich and electron-deficient aryl groups were well tolerated. For instance, modest to good yields were observed with substrates which contain strong electron-withdrawing groups, such as NO_2 and CF_3 (**3i** and **n**). Various 3-alkyl groups including adamantyl, tert-butyl, isopropyl, cyclohexyl, trifluoromethyl, diphenylmethyl, and 3-pentyl are compatible with the conditions to afford correponding 3-alkylindazoles (**3a–j**). Pleasingly, 4-azaindazole products (**3l–q**) were prepared with satisfactory yields with 2-acyl pyridine derivatives. Interestingly, when 3-acyl pyridine was employed, only regioisomeric 7-azaindazole product (**3k**) was formed and no corresponding 5-azaindazole counterpart was observed. For some substrates, such as **3g**, **i**, and **l**, steric hindrance, strong electron-withdrawing groups and the low reactivity of pyridine may account for the relative low yields.

Gratifyingly, the scope of this intramolecular cyclization reaction was further successfully expanded to the synthesis of 3-aryl substituted azaindazole and indazole derivatives as well (Table 3). Varied aryl hydrazines were employed to smoothly provide desired products (**4a–p**). Impressively, a broad functional group compatibility was observed with this reaction, including 2,4,6-trichlorophenyl group (**4k**) which is strongly electron-withdrawing and sterically demanding. It is noteworthy that those functional groups (CN, CO_2Et, halides, NO_2 etc.) can readily undergo further chemical manipulations to give very diverse compounds. For unsymmetric diaryl ketone substrates, two regioisomers of indazoles were obtained (**4q–t** and **5**). In most cases, the more electron-rich parts would react preferentially. If phenyl(pyridinyl)methanones were used, both indazoles and azaindazoles would be formed (**4u–y**). Interestingly, in the case of phenyl(pyridin-3-yl)methanone substrate, only two regioisomers of azaindazoles (**4v** and **v′**) were observed and no corresponding indazole product can be found.

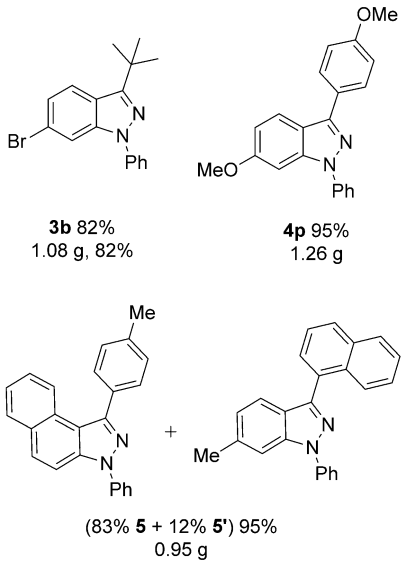
To prove both practicality and effectiveness of this method in the large-scale synthesis, we prepared 3-alkyl and 3-arylindazole products **3b**, **4p** and **5** on a gram-scale (Scheme 2). It was found the large-scale reactions can be smoothly promoted under the optimized conditions in excellent yields. Remarkably, we were very pleased to notice that the yields of large-scale reactions are generally better than their small-scale counter-

Table 2. Scope 1: synthesis of 3-alkyl azaindazole and indazole.



Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
1		63 (**3a**) 67 (**3b**) 79 (**3c**)	6		40 (**3i**)
2		74 (**3d**)	7		91 (**3j**)
3		67 (**3e**)	8		44 (**3k**)
4		55 (**3f**) 22 (**3g**)	9	 R= *i*Pr, Cy	34 (**3l**) 59 (**3m**)
5		75 (**3h**)	10	 R= 4-NO_2, 3-Cl , 3-Me, 2-Cl	80 (**3n**)[b] 72 (**3o**)[b] 53 (**3p**) 54 (**3q**)[b]

[a] Isolated yields; [b] 24 h.



Scheme 2. Gram-scale synthesis of 1*H*-indazoles.

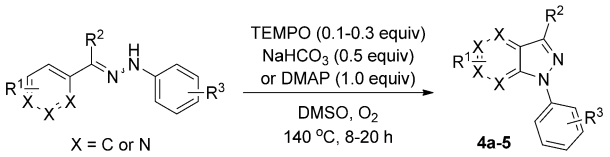
parts. In comparison with conventional approaches, the current method is advantageous for rapid access to these types of molecules because of its operational simplicity, broad availability of starting materials, and transition-metal free conditions.

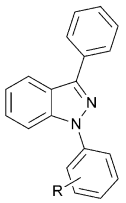
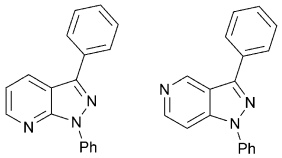
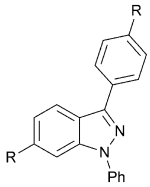
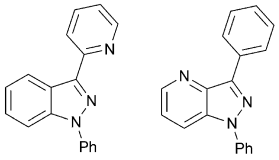
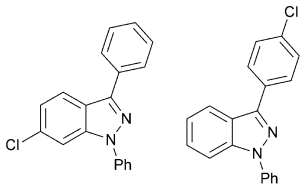
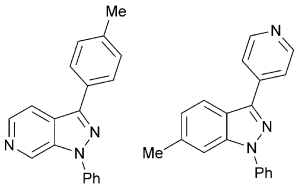
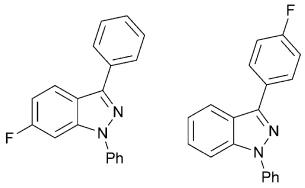
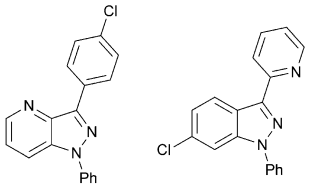
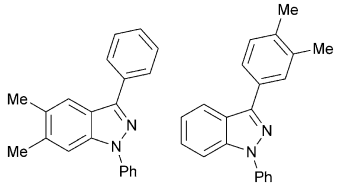
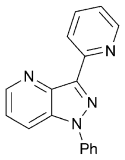
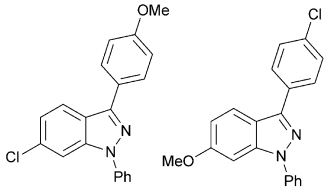
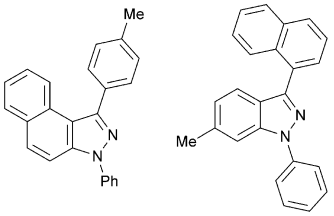
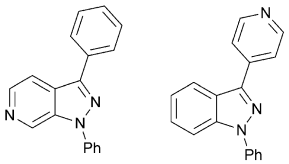
To verify the synthetic utility of this new reaction, both 1-arylazaindazole (**3n**) and 1-arylindazole (**4a**) were readily converted into 1-H azaindazole **7** and indazole **6** through a cleavage of the 4-nitrophenyl group. As illustrated in Scheme 3, a two-step procedure including deprotection and alkylation/benzylation can smoothly transform **3n** and **4a** into the corresponding 1-alkyl substituted products **8** and **9**, respectively, with high efficiency. In addition, as shown in Scheme 4, the applicability and effectiveness of this reaction was further demonstrated in a sequential one-pot C–N formation/deprotection procedure which can directly transform aryl hydrazone into unprotected 1*H*-indazole **6** in a satisfactory yield.

Next, investigations were performed to gain some insight of the reaction mechanism. As shown in Scheme 5, both an intramolecular and intermolecular isotope effect studies were conducted and a small KIE values (1.09 and 1.16) were consistently obtained (KIE = kinetics isotope effects). These results indicate that C–H bond cleavage did not involve in the rate-limiting step of this transformation.

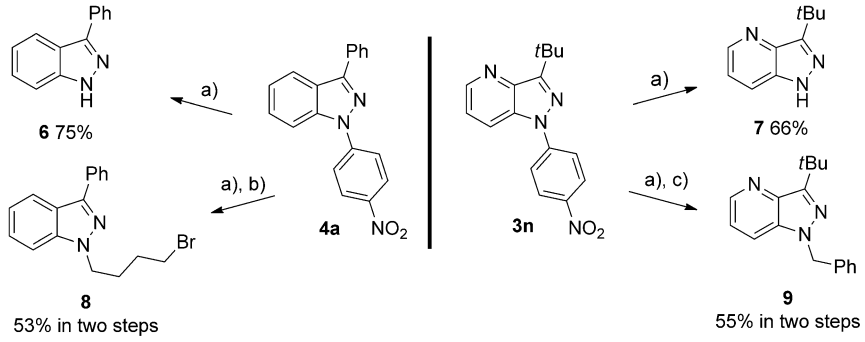
To further probe the reaction mechanism, the reaction was monitored by electron paramagnetic resonance (EPR) spectroscopy with PBN (Z-*N*-benzylidene-2-methylpropan-2-amine oxide) as the radical trap (Figure 2). A group of six peaks were labeled **a**. The calculated hyperfine splittings are g_0 (2.0021)

Table 3. Scope 2: synthesis of 3-aryl azaindazole and indazole.

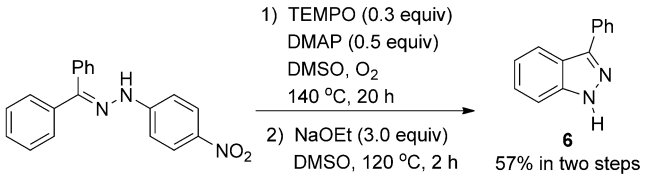


Entry	Product	Yield [%][a]	Entry	Product	Yield [%][a]
1	 R= 4-NO2, 4-CN, 4-CO2Et, 4-F, 4-Cl, 3-F, 3-Cl, 3-NO2, 3-Me, 2-F, 2,4,6-Trichloro	89 (**4a**)[c] 68 (**4b**)[c] 65 (**4c**)[c] 61 (**4d**) 79 (**4e**) 62 (**4f**) 85 (**4g**) 81 (**4h**)[c] 58 (**4i**) 73 (**4j**) 59 (**4k**)[c]	8		52 (41% **4v**+11% **4v′**)
2	 R= H, Cl, F, Me, OMe,	78 (**4l**) 62 (**4m**) 67 (**4n**) 65 (**4o**) 82 (**4p**)	9		84 (56% **4w**+28% **4w′**)
3		77 (35% **4q**+42% **4q′**)	10		77 (23% **4x**+54% **4x′**)
4		71 (40% **4r**+31% **4r′**)	11		69 (31% **4y**+38% **4y′**)
5		71 (26% **4s**+45% **4s′**)	12		53 (**4z**)[c]
6		79 (27% **4t**+52% **4t′**)	13		92 (80% **5**+12% **5′**)
7		74 (13% **4u**+61% **4u′**)			

[a] Isolated yields; [b] reactions were conducted at 150 °C.



Scheme 3. Synthesis of N-free 1*H*-azaindazole and indazole and further transformations. a) NaOEt (3.0 equiv), DMSO, Ar, 120 °C, 2 h; b) NaH (3.0 equiv), DMF/DMSO, 0 °C, 10 min, Ar, $Br(CH_2)_4Br$ (4.0 equiv), 0 °C–RT, 12 h; c) NaH (3.0 equiv), DMF/DMSO, 0 °C, 10 min, Ar, BnBr (2.0 equiv), 0 °C–RT, 12 h.

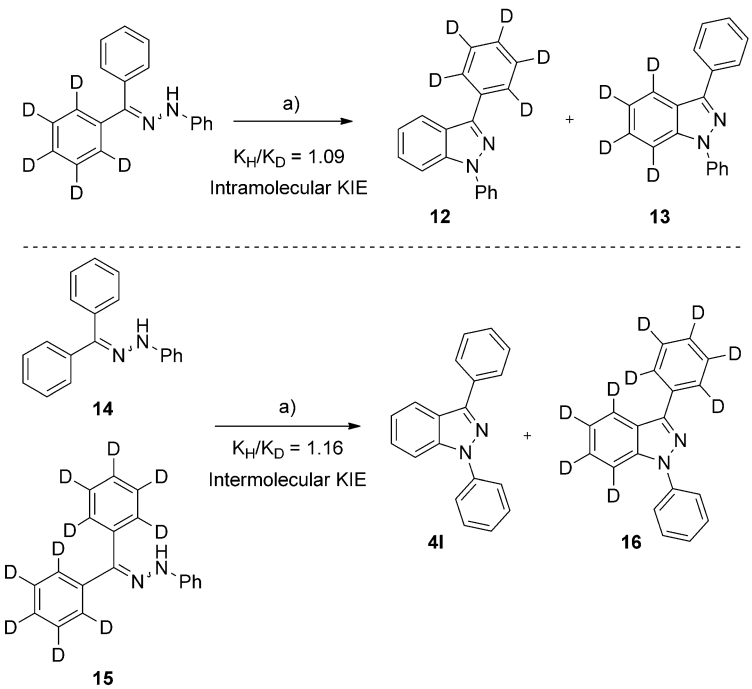


Scheme 4. One-pot-synthesis of N-free 1*H*-indazole.

and $a_{N1} = 1.489$ mT, $a_{H1} = 0.275$ mT, which indicates the presence of carbon radicals during the transformation. Another group of peaks were labeled **b**. The corresponding calculated hyperfine splittings are $a_{N1} = 1.489$ mT, $a_{H1} = 0.350$ mT, which potentially indicates the presence of superoxide anion radicals during the transformation. Three groups of small peaks were labeled **c**. The calculated hyperfine splittings are $a_{N1} = 1.489$ mT, $a_{H1} = 0.275$ mT, $a_{N2} = 0.149$ mT, which indicates the presence of nitrogen radicals[15] during the transformation (for more details see the Supporting Information). Additionally, the reaction mixtures were monitored by Mass Spectra during the reaction course. As shown in Figure 3, the MS data of the potential nitrenium radical intermediate **B** could be observed with 253.17 for the corresponding substrate **A** (for more details see the Supporting Information).

Although details about the mechanism remain to be ascertained, on the basis of these observations, a possible overall mechanism of this new and transition-metal-free oxidation can be delineated as followings. Step (i) involves TEMPO/O_2-promoted N–H oxidation of the substrate which will afford a nitrenium radical intermediate. In the following steps (ii) and (iii), an intramolecular C–N bond formation and base-directed deprotonation could afford the desired product. Molecular oxygen serves as the terminal oxidant to transform TEMPOH back into TEMPO. (Scheme 6)

In summary, an unprecedented transitional-metal-free, aerobic oxidative C–N coupling method has been developed for heterocycle synthesis. Dioxygen gas (1 atm) is employed as the oxidant in this transformation. This method has been found to be generally useful for the preparation of a variety of multi-substituted azaindazole and indazole derivatives from easily accessible starting materials. Most azaindazole products are difficult to make by conventional approaches. Mechanistic studies suggest a potential TEMPO/O_2 promoted radical pathway for this reaction. Compared with metal-catalyzed reactions, this reaction demonstrates better reactivity, functional group tolerance, and broader scope. Further studies into the mechanism and synthetic applications of this method are currently underway in our laboratory.



Scheme 5. KIE studies. a) TEMPO (0.3 equiv), $NaHCO_3$ (1.0 equiv), DMSO (1.5 mL), O_2, 1 h.

Experimental Section

General procedure

To a solution of hydrazone (0.2 mmol, 1.0 equiv) in DMSO (1.0–1.5 mL) was added TEMPO (0.1–0.3 equiv) and $NaHCO_3$ or DMAP (0.5–1.0 equiv). The reaction mixture was then stirred at 140 °C under 1 atmosphere of O_2 for 4–24 h, which was monitored by TLC. The resulting mixture was quenched with water and extracted with CH_2Cl_2 (2×10.0 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration, the crude product was purified by flash column chromatography with petroleum ether/Et_2O or petroleum ether/DCM or petroleum ether/ethyl acetate or DCM/acetone to afford product.

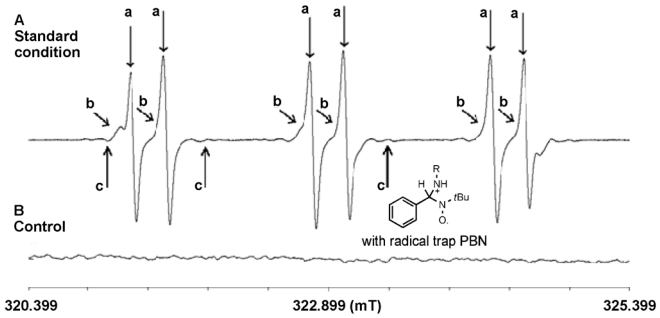


Figure 2. The EPR spectra (9.44 GHz, 120 °C): A) A reaction mixture (substrate 0.1 mmol, DMAP 0.05 mmol, DMSO 1 mL, O_2) in the presence of the radical trap (0.2 mmol). B) A control reaction (DMAP 0.05 mmol, DMSO 1 mL, O_2) in the presence of the radical trap (0.2 mmol).

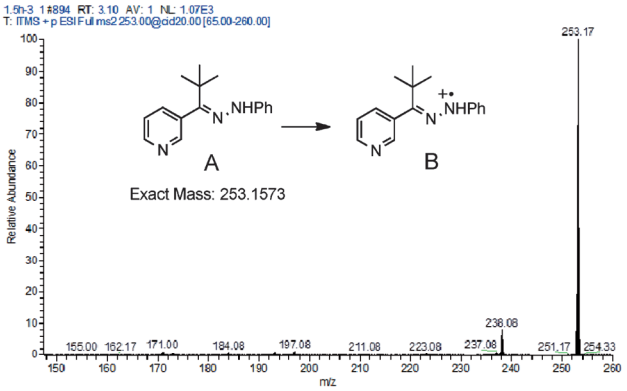
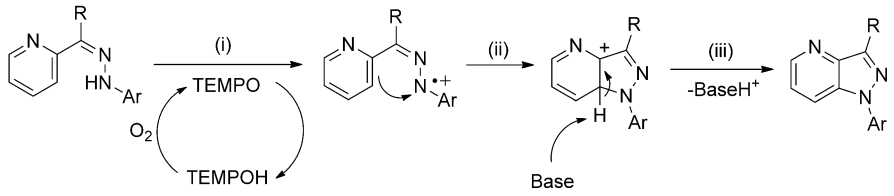


Figure 3. Mass spectra analysis.



Scheme 6. Plausible mechanism.

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Keywords: aerobic oxidative C–N coupling · azoindazole · heterocycles · indazole · metal-free condition

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