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## Graphical Abstract

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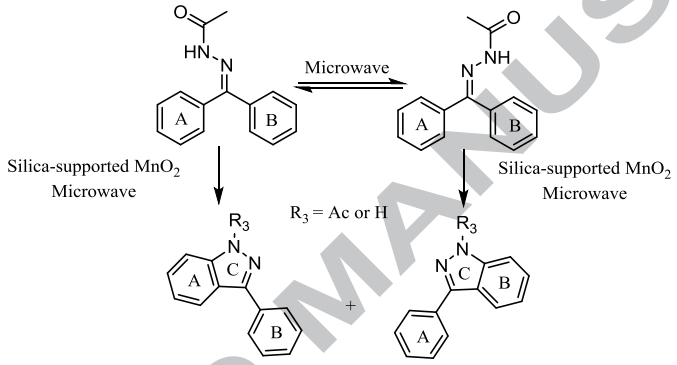
# Microwave assisted solvent-free C–H amination by silica-supported manganese dioxide

Sufen Cao[a] and Wenhu Duan[a,b,*]



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# Microwave assisted solvent-free C–H amination by silica-supported manganese dioxide

Sufen Cao[a] and Wenhu Duan[a,b,*]

[a] *School of Pharmacy, East China University of Science & Technology, Shanghai 200237, PR China*
[b] *Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China*

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ABSTRACT

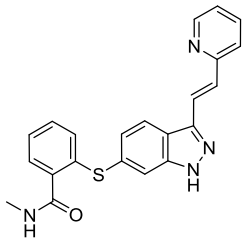
An effective and convenient method has been developed for the preparation of 1-unsubstituted 1*H*-indazoles via C–H amination of *N*-acetylhydrazones in the presence of a catalytic amount of manganese dioxide under microwave irradiation. This new method featured easy operation and relatively short reaction-time.



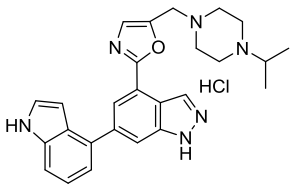
## 1. Introduction

The abundance of 1*H*-indazole ring systems in bioactive agents interests the synthetic community in the synthesis of its derivatives. Axitinib (Fig. 1A) is a launched VEGFR-2 (FLK-1/KDR) inhibitor for cancer treatment;[1] GSK-2269557 (Fig. 1B) selectively inhibits PI3Kδ;[2] LY-2874455 (Fig. 1C) inhibits the FGFR kinase family;[3] and GDC-0810 (Fig. 1D) is an estrogen receptor destabilizer.[4] Syntheses of 1*H*-indazoles via direct C–H amination without palladium catalyst where hydrazones are converted to 1*H*-indazoles by various reagents have been reported (Scheme 1).[5-9] Some methods require an oxygen atmosphere and suffer from long reaction-time.[6, 8] It is noted that a free NH in the indazole moiety can be served as a start point to prepare various *N*-substituted derivatives; more importantly, a NH may also participate in the ligand-protein interactions. For example, the NH in the indazole moiety of pictilisib forms one hydrogen bond with the PI3Kγ (PDB ID: 3DBS).[10] However, these reported palladium-free methods are only applicable to the synthesis of *N*-aryl substituted 1*H*-indazoles (Scheme 1),[5-9] leaving the synthesis of 1-unsubstituted 1*H*-indazoles as an unmet task. Therefore, we wished to develop a new approach to access 1-unsubstitued 1*H*-indazoles.

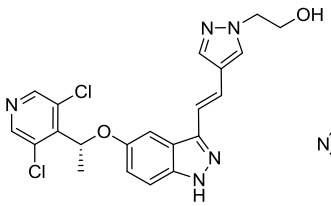
According to Zhang's work,[8] a nitrogen radical was generated by Fe(III) to initiate the reaction and the resulting Fe(II) was oxidized by $O_2$ to regenerate Fe(III). An oxidant that could generate a nitrogen radical without affecting the C=N double bond in a substrate will be suitable for the reaction. Besides,



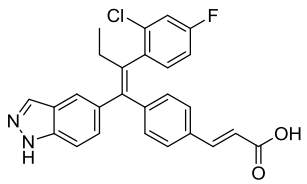
(A)
Axitinib
Launched-2012
VEGFR-2 inhibitor
$IC_{50}$ 0.25 nM



(B)
GSK-2269557
Phase II
>1000-fold selectivity
vs PI3K α, β, γ



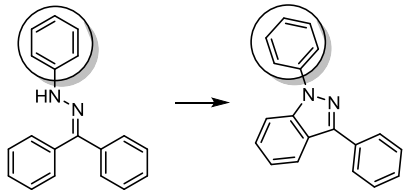
(C)
LY-2874455
Phase II
FGFR1 $IC_{50}$ 2.8 nM
FGFR2 $IC_{50}$ 2.6 nM
FGFR3 $IC_{50}$ 6.4 nM
FGFR4 $IC_{50}$ 6.0 nM



(D)
GDC-0810
Phase II
Selective estrogen receptor destabilizer
ER-α degradation
$EC_{50}$ 0.7 nM

**Figure 1.** 1*H*-Indazole derivatives of pharmaceutical importance.[1-4]

∗ Corresponding author. Tel.: +86-021-50806032; fax: +86-021-50806032; e-mail: whduan@simm.ac.cn



| Author | Oxidant | Catalyst | Additive | Solvent | Temperature (°C) | Reaction time (h) | Yield (%) |
|---|---|---|---|---|---|---|---|
| Kashiwa[5] | oxane | ----- | PhI | TFA | -10 | 0.5 | 90 |
| Li[6] | $O_2$ | Cu(OAc) | DABCO; $K_2CO_3$ | DMSO | 120 | 12 | 84 |
| Yu[7] | $O_2$ | ----- | K-10 | ODCB[a] | 130 | 3 | 87 |
| Zhang[8] | $O_2$ | $FeBr_3$ | ----- | toluene | 110 | 16 | 82 |
| Glandstone[9] | $Pb(OAc)_4$ | $BF_3{\cdot}Et_2O$ | ----- | $Et_2O$ | reflux | --[b] | 85 |

[a]ODCB = 1,2-dichlorobenzene.

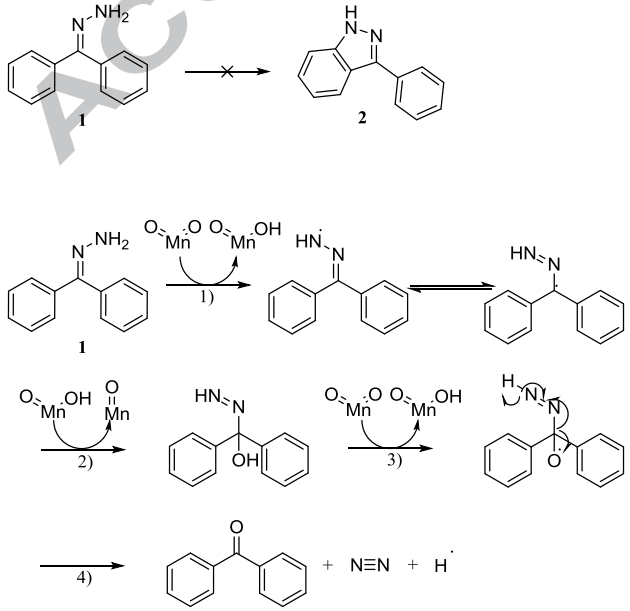
[b]Not reported.

**Scheme 1.** 1-Aryl-1*H*-indazoles constructed by C–H activation reaction.[5-9]

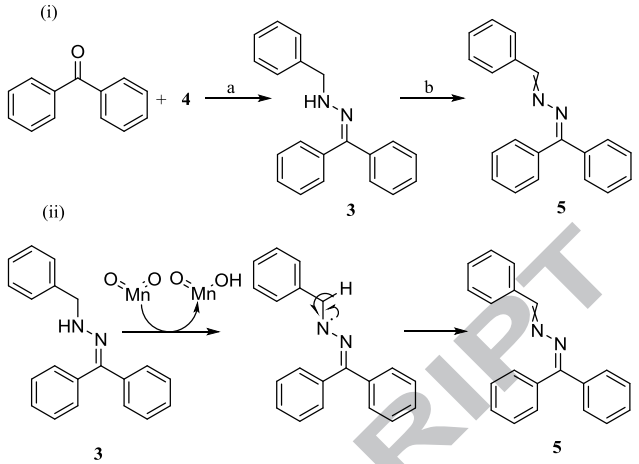
easy removal and storage of the oxidant would also be a practical concern. Pure oxygen was excluded for its gaseous nature.

We first chose active $MnO_2$ as the oxidant. Unfortunately, oxidation of (diphenylmethylene)hydrazine (**1**) by active $MnO_2$ gave benzophenone instead of 1*H*-indazole **2**. The mechanism for this reaction might be (Scheme 2): 1) transferring one electron to $MnO_2$, the substrate transformed into a nitrogen radical intermediate which underwent tautomerism to give a benzhydryl radical; 2) the benzhydryl radical was assumed to abstract one hydroxyl group from O=MnOH generated from the reduction of $MnO_2$, affording diazenyldiphenylmethanol; 3) the subsequent O–H bond cleavage by $MnO_2$ yielded an oxygen radical; and finally 4) accompanied by an emission of nitrogen gas, benzophenone was formed. This was considered as the driving force of this undesired reaction. To this end, the amino group in the substrate **1** was protected to replace the N–H bond with a N–X bond (X could be C or S), which was expected to hamper the formation of nitrogen gas.

It has been reported that by the treatment of $Pb(OAc)_4$ and subsequent $BF_3{\cdot}OEt_2$, *N*-benzoyl-hydrazones could be converted into *N*-benzyl-1*H*-indazoles.[9, 11-13] In these reactions, the nitrogen lone pair electrons attacked the phenyl ring to furnish the indazole skeleton. The model substrate **3** (Scheme 3) was prepared from benzophenone and benzylhydrazine dihydrochloride (**4**). The oxidation of **3** by γ-$MnO_2$[14] gave a dehydrogenation product **5**, which had a large conjugated system.



**Scheme 2.** A proposed mechanism for the formation of benzophenone.



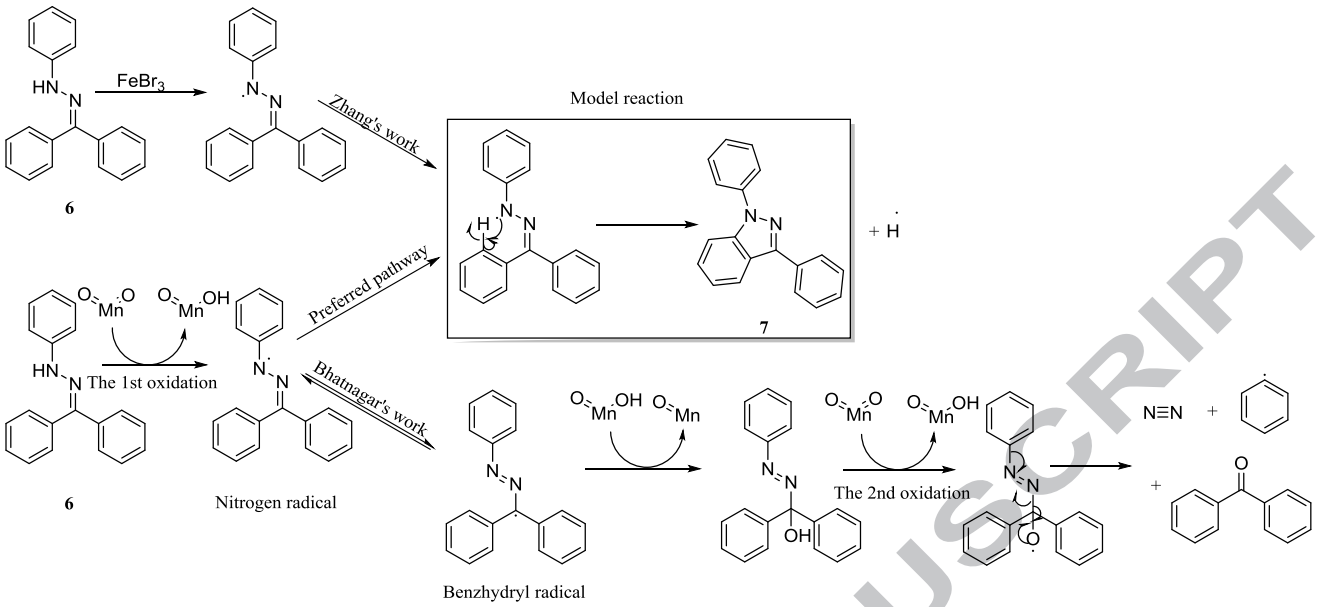
**Scheme 3.** (i) Preparation and oxidation of **3**. Reaction condition: (a) TEA, *n*-BuOH, 120 °C, 4.5 h, argon atmosphere, ground 4Å molecular sieve, 80.0%; (b) $MnO_2$, argon atmosphere, ground 4Å molecular sieve, 60.8%. (ii) A tentative mechanism for the formation of **5**.

Although this reaction did not give the desired product, it provided us some useful information: $MnO_2$ was able to oxidize the substrate without affecting the C=N double bond, and a nitrogen radical could be generated.

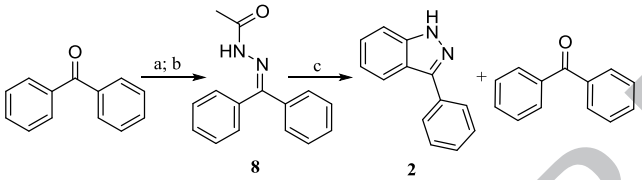
## 2. Result and discussion

To verify this notion, we investigated a model reaction (Scheme 4), the oxidation of benzophenone phenylhydrazone (**6**).[5-9, 15] It has been reported that **6** could be converted to benzophenone (63%) and biphenyl (34%) by 19.7 equiv of active $MnO_2$ at 80 °C in benzene.[15] We proposed that there were two possible ways to control the reaction. 1) As shown in Scheme 4, the reaction pathways diverged at the nitrogen radical intermediate. The crux was the tautomerism between the nitrogen radical and the benzhydryl radical. where the reactivity and stability of the radicals affected their population. 2) According to Bhatnagar's work,[15] the formation of benzophenone required the participation of $MnO_2$ in two oxidative steps. The first oxidation converted the substrate **6** to the common intermediate, a nitrogen radical, and the second oxidation afforded benzophenone. Therefore, we varied the oxidant/substrate ratio and found that when 1.0 equiv of $MnO_2$ was applied, the cyclized product **7** was obtained in a yield of 28.2%, along with benzophenone in a yield of 48.3% under microwave irradiation at 130 °C. In contrast, the unprotected substrate **1** was converted to benzophenone at 50 °C when l.0 equiv of $MnO_2$ was used under microwave irradiation. Compared to substrate **1**, substrate **6** might benefit from the conjugation provided by its aryl group on the nitrogen atom.[8] Therefore, a protecting group should be installed to provide a conjugated system and no vicinal hydrogen which would facilitate the formation of the undesired product. Acetyl, which could be readily removed by acidic hydrolysis, was chosen as the protecting group since a carbonyl could provide p orbitals for conjugation and insulate the radical from methyl hydrogens.

Benzophenone and hydrazine hydrate were heated in ethanol to give hydrazone **1**, and subsequent acetylation afforded **8** (Scheme 5)[16]. A mixture of **8**, γ-$MnO_2$ (1.0 equiv), and ground 4Å molecular sieve subjected to microwave irradiation at 210 °C for 30 minutes afforded **2** in 53.6% yield and benzopheone in 6.5% yield. An attempt to reduce the oxidant/substrate ratio was impeded by the poor homogeneity of the reaction mixture. Thereby, we tried silica-supported $MnO_2$,[17] which would make the oxidant more dispensed.




**Scheme 4.** The reaction pathway diverged at nitrogen radical intermediate.



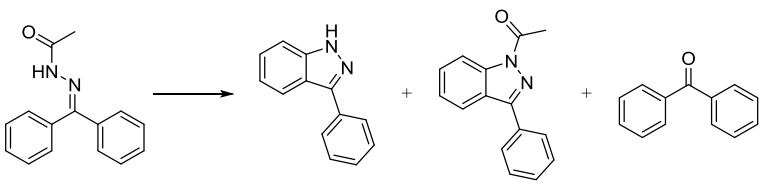

**Scheme 5.** Preparation and oxidation of *N*'-(diphenylmethylene)aceto-hydrazide (**8**). (a) Hydrazine hydrate, EtOH, *p*-TsOH·$H_2O$, reflux, 6.5 h, 88.7%; (b) toluene, acetic anhydride, 100 $^oC$, 1 h, 77.4% (c) $MnO_2$, ground 4Å molecular sieve.

The Rf value of benzophenone and 3-phenyl-N-acetylindazole were close, and multiple development was needed to separate these two compounds on TLC plate. Therefore, we used HPLC to monitor the reactions during the optimization of the reaction conditions. A standard sample of 3-phenyl-*N*-acetylindazole **9** was prepared by acetylation of **2**.

First, we set the reaction times to 45 minutes and varied the oxidant/substrate ratios in the first four entries. The conversion of the starting materials seemed to be practically unchanged in entry 2–4 (Table 1). When more $MnO_2$ was used, the formation of benzophenone increased (Table 1, entry 1–4). We thought a maximum conversion of the starting material together with a minimum formation of the byproduct would give the best outcome of cyclization. Therefore, we fixed the oxidant/substrate ratios to 0.08. Next, we shortened the reaction times (entry 5 and entry 6). No significant difference was observed for these two entries. To determine the isolated yields, we repeated entry 5 and entry 6 (entry 12 and entry 13) and isolated every compounds. To our delight, a mixture of silica-supported $MnO_2$ (0.08 euqiv) and **8** subjected to microwave irradiation at 150 $^oC$ for 15 minutes afforded cyclized products in 87.5% yield (Table 1, entry 12). Heating **8** with silica gel alone under the same condition did not produce a trace of **2** or **9**.

In addition, commercially available $MnO_2$ (Table 1, entry 11) could also oxidize the substrate to the cyclized products under microwave irradiation, but at a higher temperature (210 $^oC$ vs 150 $^oC$ in entry 12) and more $MnO_2$ (34.5 equiv vs 0.08 equiv in entry 12) was needed.

**Table 1**
Optimization of reaction conditions[a]




| Entry | Temperature ($^oC$) | Oxidant/substrate ratio (equiv) | Reaction time (min) | Percentage of **8** | Percentage of **2** | Percentage of **9** | Percentage of benzophenone | Yield of cyclized products (%) | Notes |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 150 | 0.04 | 45 | 11.7 | 17.2 | 67.2 | 3.7 | - | A, B |
| 2 | 150 | 0.08 | 45 | 3.0 | 19.2 | 73.0 | 4.3 | - | A, B |
| 3 | 150 | 0.13 | 45 | 2.8 | 29.4 | 63.2 | 4.3 | - | A, B |
| 4 | 150 | 0.19 | 45 | 3.2 | 37.2 | 52.7 | 6.0 | - | A, B |
| 5 | 150 | 0.08 | 15 | 3.2 | 23.4 | 69.9 | 3.1 | - | A, B |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | 150 | 0.08 | 30 | 2.5 | 20.5 | 71.5 | 5.3 | - | A, B |
| 7 | 170 | 34.5 | 45 | 53.1 | 1.6 | 42.1 | 2.8 | - | B, C |
| 8 | 190 | 34.5 | 45 | 30.2 | 4.0 | 62.1 | 3.4 | - | B, C |
| 9 | 210 | 34.5 | 45 | 4.4 | 12.8 | 74.6 | 7.7 | - | B, C |
| 10 | 210 | 34.5 | 15 | 10.2 | 9.5 | 74.9 | 4.8 | - | B, C |
| 11 | 210 | 34.5 | 30 | 2.4 | 15.1 | 75.2 | 6.8 | - | B, C |
| 12 | 150 | 0.08 | 15 | 6.7 | 27.5 | 60.0 | 2.4 | 87.5 | A, D |
| 13 | 150 | 0.08 | 30 | 0 | 10.9 | 77.3 | 10.9 | 88.2 | A, D |

[a] ZORBAX Eclipse Plus column (C18, 4.6×150 mm, 5 μm); MeCN : $H_2O$ = 45:55 to MeCN : $H_2O$ =70:30 in 50 min; 0.5 mL/min; detecting wavelength: 254 nm; reference wavelength: 360 nm; retention time: **8**: 15.46 min, **2** : 50.65 min, **9** : 17.38 min, benzophenone: 28.22 min.

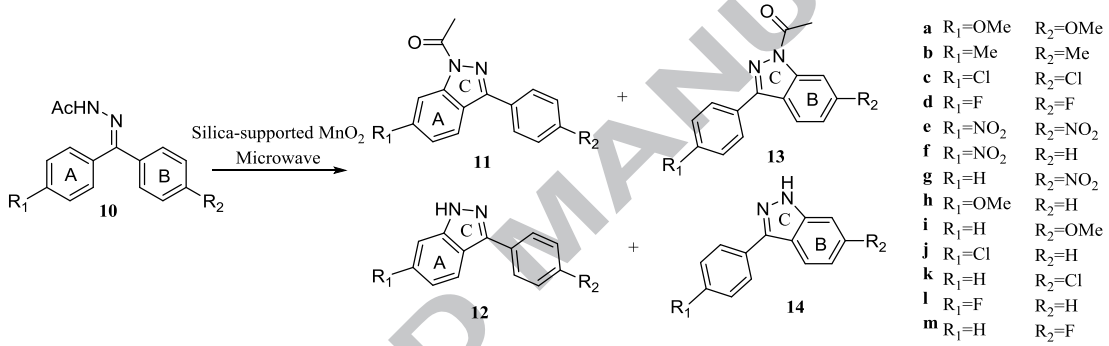
A: $MnO_2$ prepared according to the known procedure with minor modificaiton[17] (for detail, see supplementary material)

B: The content of the reaction mixture was determined by HPLC and expressed as percentage of peak area

C: $MnO_2$ purchased from Sinopharm Chemical Reagent Co., Ltd. (China)

D: Isolated yield

**Table 2**
Synthesis of 3,6-disubstitued idazoles

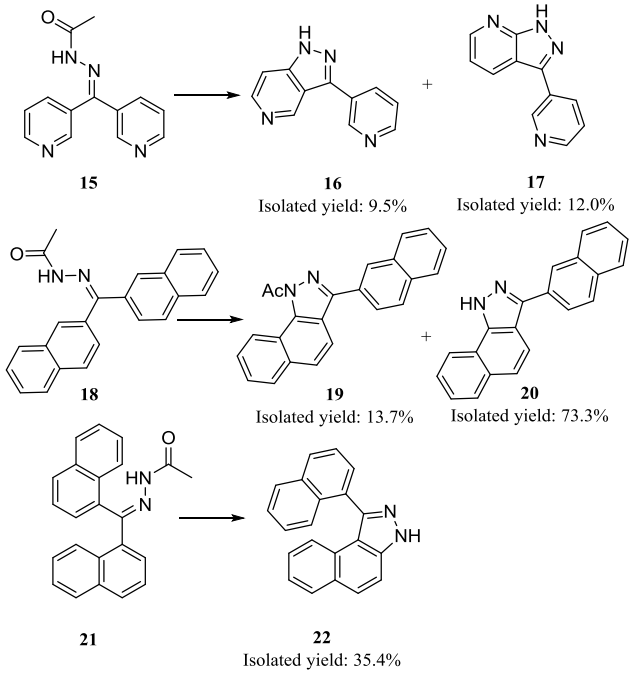



| Entry | $R_1$ | $R_2$ | Temperature ($^oC$) | $MnO_2$ (equiv) | Reaction time (min) | Yield of **11** (%)[a] | Yield of **12** (%)[a] | Yield of **13** (%)[a] | Yield of **14** (%)[a] | (A/C ring fused product): (B/C ring fused product) | Yield of cyclized products (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | OMe | OMe | 150 | 0.08 | 5 | 61.8 | 27.2 | - | - | - | 89.0 |
| 2 | Me | Me | 150 | 0.08 | 5 | 66.7 | 18.1 | - | - | - | 84.8 |
| 3 | Cl | Cl | 150 | 0.08 | 5 | 50.1 | 31.3 | - | - | - | 81.4 |
| 4 | F | F | 150 | 0.08 | 5 | 50.7 | 27.1 | - | - | - | 77.8 |
| 5 | $NO_2$ | $NO_2$ | 230 | 0.08 | 30 | - | 33.9 | - | - | - | 33.9 |
| 6 | $NO_2$ | H | 210 | 0.20 | 10 | - | 13.3 | - | 53.2 | 20:80 | 66.5 |
| 7 | H | $NO_2$ | 210 | 0.20 | 10 | - | 51.2 | - | 14.3 | 78:22 | 65.5 |
| 8 | OMe | H | 150 | 0.08 | 10 | 43.4 | 19.3 | 14.4 | 9.7 | 72:28 | 86.8 |
| 9 | H | OMe | 150 | 0.08 | 10 | 16.6 | 12.0 | 32.9 | 27.6 | 32:68 | 89.1 |
| 10 | Cl | H | 150 | 0.08 | 10 | 17.4 | 19.1 | 22.6 | 19.1 | 47:53 | 78.2 |
| 11 | H | Cl | 150 | 0.08 | 10 | 33.0 | 14.3 | 21.4 | 14.3 | 57:43 | 83.0 |
| 12 | F | H | 150 | 0.08 | 10 | 30.8 | - | 24.4 | - | 56:44 | 55.2 |
| 13 | H | F | 150 | 0.08 | 10 | 21.7 | - | 20.3 | 4.9 | 46:54 | 46.9 |

[a] Isolated yield

With the optimized reaction condition, we then investigated the substrate scope of the reaction (Table 2 and Table 3). Since the reaction is a redox reaction, the electronegativity of the substituents affected the reaction substantially. The electron-donating substituents favored the reaction while the electron withdrawing substituents retarded the cyclization. The substrate **10a**, with two methoxy substituents, gave cyclized products in 89.0% yield after 5 minutes of microwave irradiation at 150 $^oC$ (Table 2, entry 1). The mononitro-substituted substrates, **10f** and **10g** (Table 2, entries 6 and 7), required longer reaction time and elevated temperature to achieve complete conversion, and the yields of the cyclized products dropped to 66.5% and 65.5%, respectively. The dinitro-substituted substrate **10e** (Table 2, entry 5) gave a low yield (33.9%), albeit a harsh reaction condition was employed. The electron-deficient dipyridine compound **15** also gave a low yield (21.5%, Table 3). β-Substituted naphthelene derivative **18** gave a higher yield (87%) than the sterically crowded α-substituted naphthelene derivative **21** (35.4%, Table 3). Moderate regioselectivity (Table 2, entries 6–13) was observed for the asymmetric substrates. The electronegativity of the substituents rather than the configuration of the starting materials seemed to govern the orientation of the cyclization,

**Table 3**
Amination of different aryl hydrogens




| Substrate | Temperature (°C) | Reaction time (min) | Yield of cyclized product (%) |
|---|---|---|---|
| **15** | 150 | 45 | 21.5 |
| **18** | 150 | 45 | 87.0 |
| **21** | 190 | 45 | 35.4 |

which implied an *E-Z* isomerization prior to the cyclization. Microwave irradiation of **10f** and silica-supported $MnO_2$ at 150 °C for 5 minutes gave a mixture of isomers, **10f** and **10g**. In this reaction, **10f** would encounter three energy barriers (Table 2, entry 6) : first, when the temperature rose to 150 °C, **10f** overcame the energy barrier of the isomerization, equilibrium between **10f** and **10g** was expected; second, the mixture was further heated to a higher temperature and eventually overcame the potential barrier of the cyclization of the more electron-rich ring, the unsubstituted ring in this case, giving **14f**; and finally, the third energy barrier was overcome at an even higher temperature, both **12f** and **14f** were accessible at this stage while **14f** had the higher reaction rate. The regioselectivity of this reaction was an overall result of isomerization and cyclization affected by reaction temperature and the substituents on the phenyl rings.

Deprotection of cyclized products was exemplified by the acidic hydrolysis of 1-acetylindazole **9**. After cyclization, the crude product was added to a mixture of MeOH and 6N HCl and heated at reflux for an hour, giving 1*H*-indazole **2** in 83.6% yield in two steps.

## Conclusion

In conclusion, we developed an efficient and simple method to synthesize 1-unsubstituted 2-aryl-1*H*-indazoles via direct C–H amination. All reagents could be easily handled in open air.

## Acknowledgments

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## Supplementary Material

Supplementary data (experimental procedures and characterization data for the compounds **1**, **2**, **3**, **5**, **7**–**9**, **10a**–**10m**, **11a**–**11d**, **11h**–**11m**, **12a**–**12k**, **13h**–**13m**, **14f**–**14k**, **14m** and **15**–**22**) can be found, in the online version, at

Highlights

- Solvent and palladium free microwave-assisted direct C–H aminiation was reported.
- *N*-Unsubstituted 1*H*-indazoles instead of *N*-aryl 1*H*-indazoles were constructed.
- Tuning the reaction condition and substrates altered the reaction pathway.