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Pd/C-catalyzed synthesis of *N*-aryl and *N*-alkyl isoquinolones via C—H/N—H activation

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ABSTRACT

Pd/C-catalyzed direct synthesis of *N*-aryl and *N*-alkyl isoquinolones was developed via the annulation reactions of benzamides and alkynes in high yields (up to 99%) through the cleavage of C—H/N—H bonds. The reaction was ligand-free and air was used as oxidant. High regioselectivities were found when unsymmetrical alkynes or *meta*-benzamides were used as substrates. The heterocyclic carboxamide substrates, such as furan and thiophene derivatives, also afforded the corresponding products in high yields.

1. Introduction

In the recent years, atom economy and environment friendly are the two hot topics which claim simplifying the steps and decreasing the waste in reactions. Transition-metal-catalyzed C—H activation is one of the most promising methods to access this goal and has achieved a great progress in the past decade. Among them, homogeneous palladium is a common catalyst used for direct C—H activation as its high activity [1–5]. However, an obvious drawback of homogeneous palladium catalysts is hard to recover after reactions. The requirement of precious palladium often hampers commercial access to such methodology. One way to solve this problem is the application of heterogeneous palladium, such as Pd/C (palladium on carbon) [6–13]. As a commercial hydrogenation catalyst, Pd/C has also been widely used in other organic synthesis, including Heck, Suzuki, and Sonogashira reactions; the construction of heterocyclic compound, and other coupling reactions [6–13]. In contrary, Pd/C has only limited applications in C—H activation [14–30], and is a promising catalyst in the transition-metal-catalyzed C—H activation in future.

Isoquinolone skeleton is a basic heterocyclic structure and widely exists in the natural alkaloids. Isoquinolone derivatives have well biological activities used for lower blood pressure, antiviral, and anti-cancer drugs, etc. [31–35] (Scheme 1). The direct synthesis of isoquinolones via annulation reactions of benzamides and alkynes has achieved by homogeneous Rh(III) [36–46], Ru(II) [47–52], Pd(II) [53–55], Ni(II) [56], Co(II) [57], and I(III) [58,59] catalysts in recent years. Different oxidant sources can result in different products. The use of *N*—O group as an internal oxidant will give *N*—H isoquinolones and the use of an external oxidant will afford *N*-substituted isoquinolones [Scheme 2, Eqs. (1) & (2)]. Very recently, our group successfully developed the direct synthesis of *N*-alkoxyl isoquinolones with Pd/C as the heterogeneous catalyst [Scheme 2, Eq. (3)] [30], but we couldn't obtain the corresponding product of low active *N*-aryl/*N*-alkyl benzamides. In this work, we successfully achieved the direct synthesis of *N*-aryl/*N*-alkyl isoquinolones using Pd/C as catalyst and air as external oxidant [Scheme 2, Eq. (4)].

2. Results and discussion

2.1. Optimization of reaction conditions

At the beginning of our study, we used *N*-phenylbenzamide (**1a**) and diphenylacetylene (**2a**) as starting materials, Pd/C as catalyst, air as oxidant, NaI as additive, Cs_2CO_3 and KOAc as base, DMAc (dimethylacetamide) as solvent, and 120 °C as the temperature. The product **3aa** was obtained in 24% yield (Table 1, entry 1). Then, several solvents were tested in this reaction. To our delight, when DMF was used as the solvent, **3aa** was obtained in nearly quantitative yield (Table 1, entry 2). In contrast, when EtOH, toluene, CH_2Cl_2, H_2O, hexane, CH_3CN, THF, and dioxane were used as sol-

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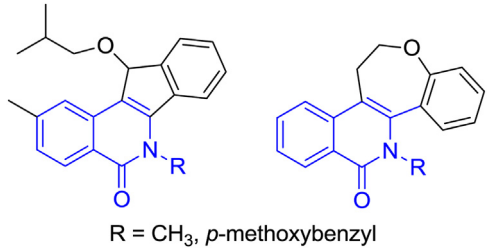
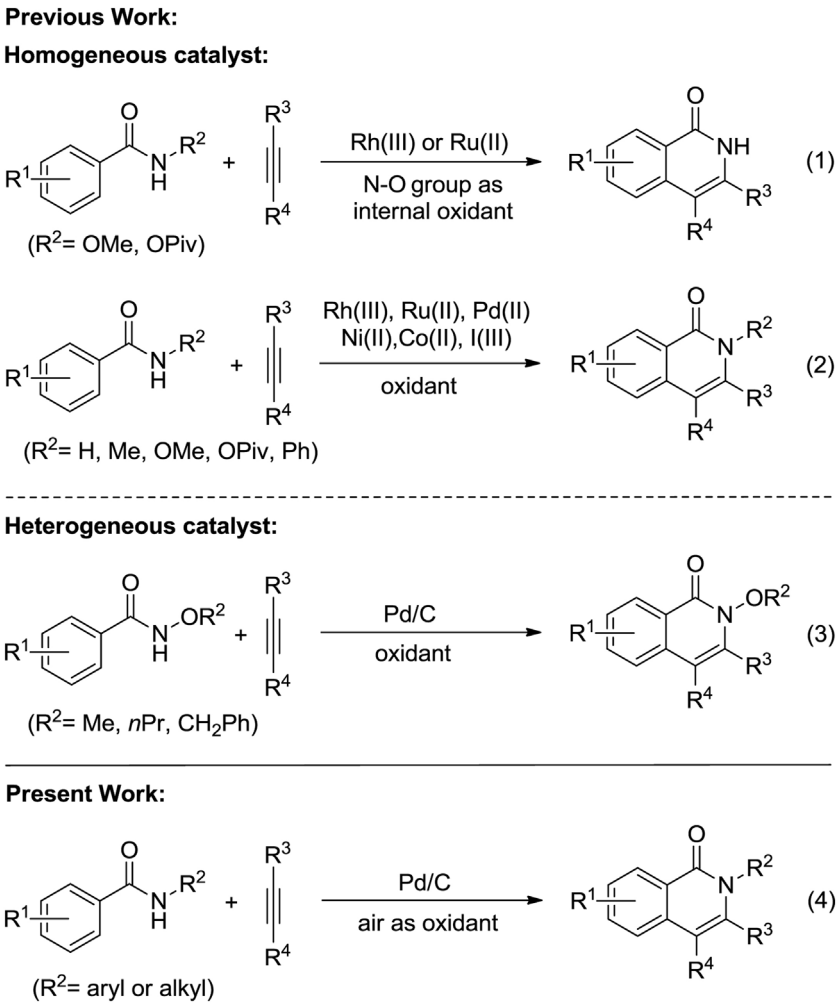


Scheme 1. Some *N*-aryl/*N*-alkyl isoquinolones derivatives used for anti-cancer drugs.

vents, no desired product was obtained (Table 1, entries 3–8, 11, 12), while DMSO and NMP (*N*-methyl-2-pyrrolidone) were used as solvents the product was obtained in 67% and 27% yields, respectively (Table 1, entries 9, 10). Lowering the temperature decreased evidently the yield (Table 1, entries 13, 14). The yield was still quantitative when the ratio of **1a** and **2a** reduced to 1:2 (Table 1, entry 15). Further reduced the ratio, **1a** could not be exhausted (Table 1, entries 16, 17). The reaction could not occur in the absence of Pd/C or NaI and the yield was apparently declined in the absence of Cs_2CO_3 or KOAc (Table 1, entries 18–21). When 3.0 equiv. of KOAc or Cs_2CO_3 was used instead of the mixed bases the yields of **3a** dropped to 73% and 48%, respectively (Table 1, entries 22–23). No product was detected when the reaction underwent in the absence of air (Table 1, entry 24).

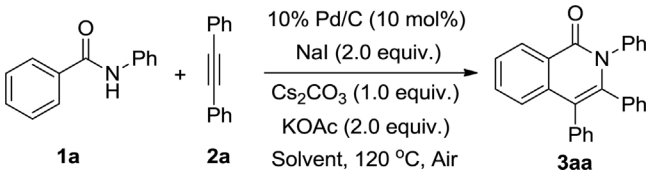
2.2. Scope of N-aryl benzamides and alkynes

Reactions of substituted *N*-aryl benzamides with different alkynes were carried out in the optimal conditions (Table 1, entry 15). The results revealed that the reaction had a good tolerance with both electron-donating and electron-withdrawing groups. High yields of products were obtained generally when electron-rich benzamides were participated in the reaction (Table 2, **3ba–da**, **3ga–ka**, **3oa**). Unexpected, when 4-methoxy-*N*-phenyl benzamide and *N*-(4-methoxyphenyl) benzamide were used slight lower yields were obtained (Table 2, **3ca, 3ka**), probably due to the strong electron-donating effect of methoxy group. In contrast, lower yields were got if the benzamide had an electron-withdrawing group (Table 2, **3ea–fa**, **3la–na**). No obviously steric effect was obtained during the reaction scope (Table 2, **3ga**, **3ia**, **3oa**, **3qa**). Good yields were also obtained when heterocyclic carboxamides were used (Table 2, **3ra–sa**). Then, different alkynes were tested. Substituted diphenylacetylene showed same disciplinarian with substituted benzamides and the electronic effect was more obviously. Diphenylacetylene with an electron-donating group delivered higher yield than that with an electron-withdrawing group (Table 2, **3ab–ac**). Comparable, alkyl phenyl alkynes showed low activities (Table 2, **3ad–ae**). High regioselectivities were found when *meta*-substituted benzamides and unsymmetrical alkynes were used as substrates (Table 2, **3ha–ia, 3ad–ae**).



Scheme 2. Direct synthesis of isoquinolones via annulations of benzamides and alkynes.

Table 1
Optimization of reaction conditions[a].

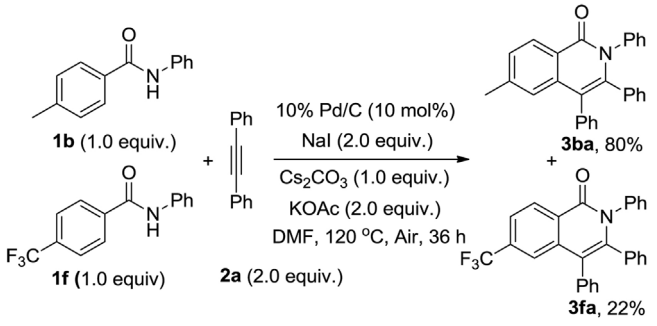


Entry	Solvent	Temp (°C)	**1a**:**2a**	Yield (%)[b]
1	DMAc	120	1:3	24%
2	DMF	120	1:3	99%
3	EtOH	120	1:3	N.R.
4	toluene	120	1:3	N.R.
5	CH_2Cl_2	120	1:3	N.R.
6	H_2O	120	1:3	N.R.
7	hexane	120	1:3	N.R.
8	CH_3CN	120	1:3	N.R.
9	DMSO	120	1:3	67%
10	NMP	120	1:3	27%
11	THF	120	1:3	N.R.
12	dioxane	120	1:3	N.R.
13	DMF	100	1:3	89%
14	DMF	80	1:3	49%
15	DMF	120	1:2	99%
16	DMF	120	1:1.5	98%
17	DMF	120	1:1	88%
18[c]	DMF	120	1:2	N.R.
19[d]	DMF	120	1:2	N.R.
20[e]	DMF	120	1:2	27%
21[f]	DMF	120	1:2	35%
22[g]	DMF	120	1:2	73%
23[h]	DMF	120	1:2	48%
24[i]	DMF	120	1:2	N.R.

[a] Reaction conditions: **1a** (0.3 mmol), 10% Pd/C (10 mol%), NaI (0.6 mmol), Cs_2CO_3 (0.3 mmol), KOAc (0.6 mmol), solvent (1.0 mL), 36 h, air.
[b] Isolated yields. N.R. = no reaction.
[c] Without Pd/C.
[d] Without NaI.
[e] Without Cs_2CO_3.
[f] Without KOAc.
[g] 3.0 equiv. of KOAc was used instead of Cs_2CO_3 (1.0 quiv.) and KOAc (2.0 equiv.) as base.
[h] 3.0 equiv. of Cs_2CO_3 was used instead of Cs_2CO_3 (1.0 quiv.) and KOAc (2.0 equiv.) as base.
[i] Under an atmosphere of argon.

2.3. Scope of N-alkyl benzamides with alkynes

To extend the reaction scope, reactions of *N*-methyl benzamides with alkynes were carried out (Table 3). The reaction also showed well tolerance with both electron-donating and electron-withdrawing groups (Table 3, **5ba–fa**, **5ab–ac**, **5af–ah**). But strong electronic effect had a bad influence to generate the product. Benzamides and alkynes with —OMe or —CF_3 group afforded relative low yields (Table 3, **5ca**, **5fa**, **5ab**, **5ah**). The use of *N*-*n*Bu benzamide also gave desired product in high yield (Table 3, **5ga**). When unsymmetrical alkynes were used, the corresponding products were obtained in low yields, but with excellent regioselectivities (Table 3, **5ad**, **5ae**).



Scheme 3. Competition reaction of different substrates.

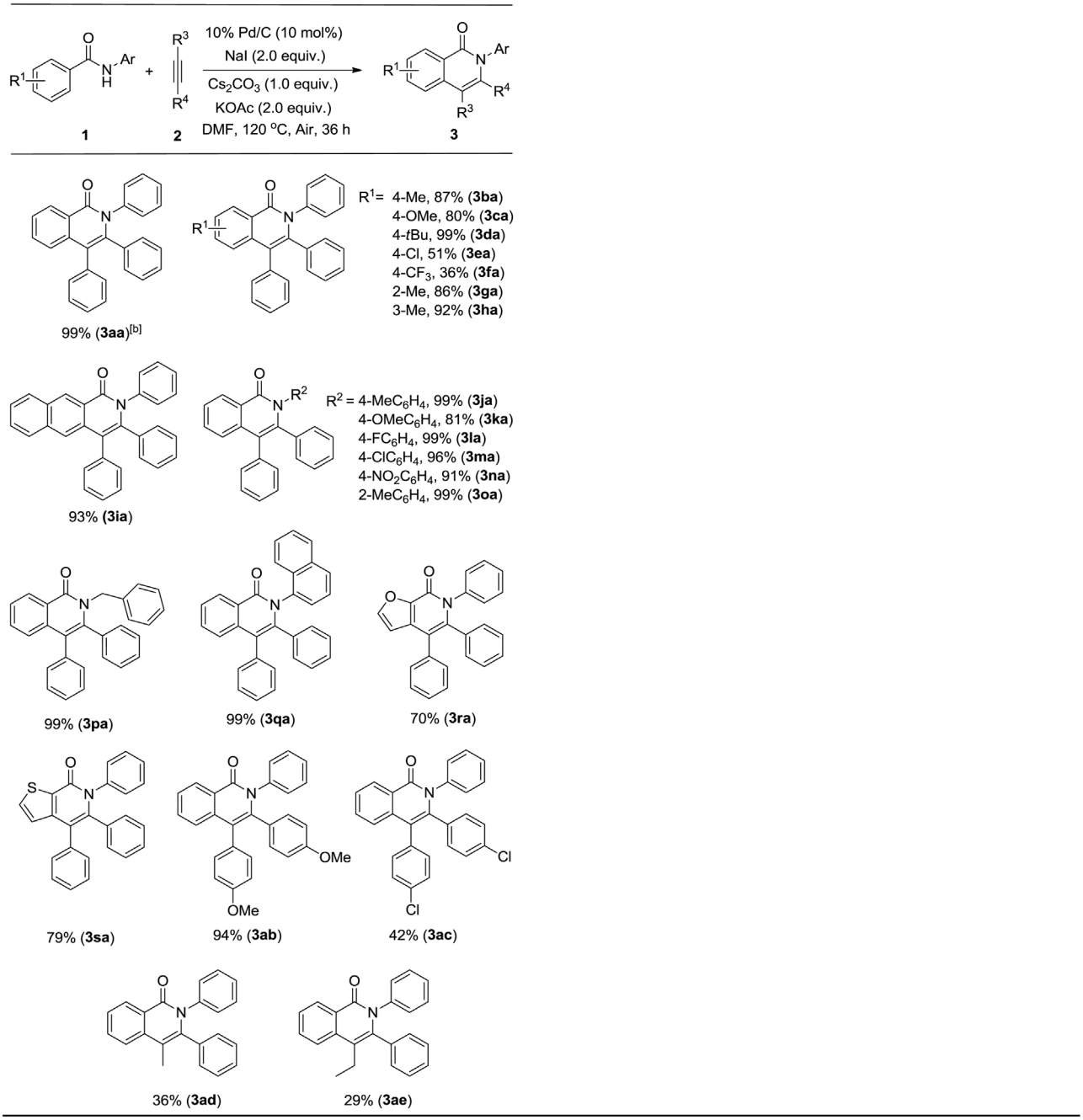
2.4. Competition study

The competition study of **1b** and **1f** in reaction with **2a** was done (Scheme 3). The results further proved that the electron-rich benzamides had higher activity compared to the electron-poor benzamides.

2.5. Recycle of Pd/C catalyst

At last, we carried out the recycle experiment of Pd/C catalyst in the reaction of **1a** and **2a** under the standard conditions. Product **3aa** was obtained in 99%, 65%, and 30% yields after the first, second, and third runs. To investigate the deactivation of Pd/C catalyst, the palladium content was tested in reaction and after reaction. After hot filtration the palladium content in hot solution was tested as high as 2978 ppm, indicating that the true catalyst is homogeneous palladium species which released into solution by aerobic oxidation and stabilized by coordination of iodide and acetate anions. However, the palladium content of the solution is only 26 ppm after reaction. This indicated that the homogeneous Pd species could go back to carbon after reaction. The rapid loss of activity of palladium may be caused by the transformation of palladium into the inactivated Pd-species, rather than running off into the solution. To activate the recovered Pd/C catalyst, N_2H_4 aqueous solution was added as reductant at the end of reaction. After treatment, Pd/C

Table 2
Scope of *N*-aryl benzamides and alkynes[a].



[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), 10% Pd/C (10 mol%), NaI (0.6 mmol), Cs_2CO_3 (0.3 mmol), KOAc (0.6 mmol), DMF (1.0 mL), air, 36 h. [b] Isolated yields.

displayed a better recycle activity. Product **3aa** was obtained in 85%, 80%, and 78% yields after the first, second, and third runs, respectively (Fig. 1).

2.6. Possible mechanism

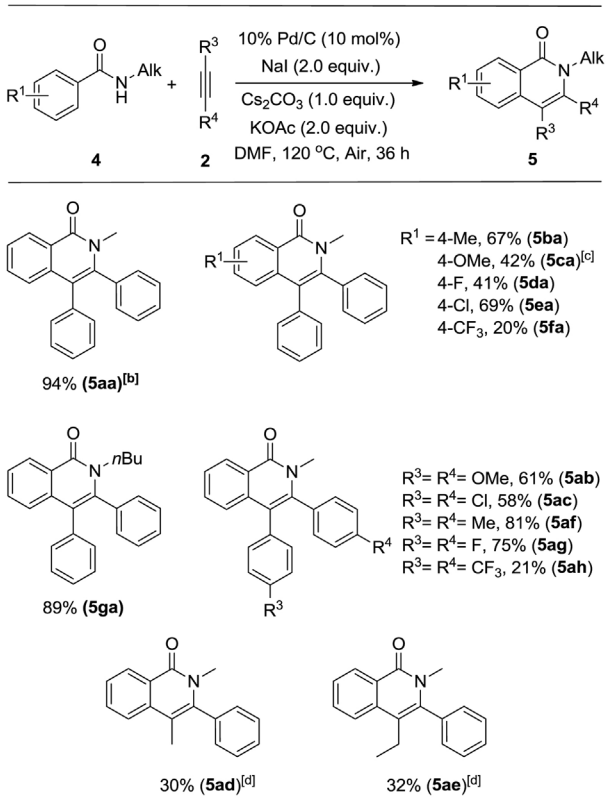
A possible mechanism was proposed on the basis of literature research [30,53–55]. Firstly, Pd(0)/C was oxidized to active homogeneous Pd(II) species **A** by the oxygen of air. Then, reaction of **A** with benzamide in the assistance of NaI and base generated five-membered palladacycle intermediate **B**. Coordination and insertion of an alkyne into the Pd-C bond afforded seven-membered palladacycle intermediate **C**, which was easily converted into the final product and Pd(0) after reductive elimination. The regenerated Pd(0) species can be used for the next catalytic cycle (Scheme 4).

3. Experimental section

3.1. General information

^{1}H NMR (400 MHz), ^{19}F (376 M Hz), and ^{13}C NMR (101 MHz) were recorded on a NMR spectrometer with $CDCl_3$ as solvent. Column chromatography was performed on silica gel 200–300 mesh or alumina 200–300 mesh. IR spectra were recorded as KBr disks on a FT-IR spectrometer. High-resolution mass spectrometry (HRMS) was done on a FTICR-mass spectrometer. Palladium content was

Table 3
Scope of *N*-alkyl benzamides and alkynes[a].



[a] Reaction conditions: **4** (0.3 mmol), **2** (0.9 mmol), 10% Pd/C (10 mol%), NaI (0.6 mmol), Cs_2CO_3 (0.3 mmol), KOAc (0.6 mmol), DMF (1.0 mL), air, 36 h. [b] Isolated yields. [c] 140 °C was used. [d] 2 equiv of CsOAc was used instead of KOAc.

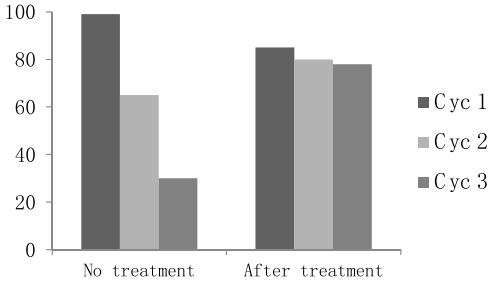
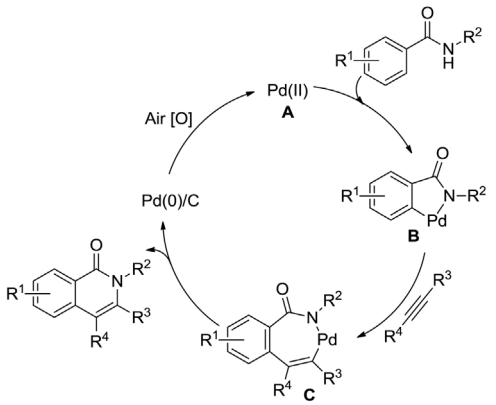


Fig. 1. Recycle of Pd/C catalyst.



Scheme 4. Proposed mechanism.

tested by TAS-990 Atomic Absorption Spectrophotometer (AAS) (Pd absorption wavelength = 244.8 nm). The *N*-aryl and *N*-alkyl benzamides [37–39,47,53] and substituted alkynes [60] were prepared following the literature procedures. All other compounds are commercially available without any further purification.

3.2. General procedure

A mixture of a substituted benzamide (**1**) (0.3 mmol, 1.0 equiv), an alkyne (**2**) (0.6 mmol or 0.9 mmol, 2.0 equiv or 3.0 equiv), 10% Pd/C (0.03 mmol, 10 mol%, Alfa Aesar, No. 044696, eggshell, reduced), $NaI{\cdot}2H_2O$ (0.6 mmol, 2.0 equiv), Cs_2CO_3 (0.3 mmol, 1.0 equiv), and KOAc (0.6 mmol, 2.0 equiv) was weighted in a Schlenk tube equipped with a stir bar. DMF (1.0 mL) was added and the mixture was stirred at 120 °C for 36 h under air. Afterwards, the mixture was filtered and washed with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried with anhydrous Na_2SO_4. After removal of solvents under reduced pressure, the residue was absorbed to small amounts of silica. The purification was performed by flash column chromatography on silica gel with EA:PE (Petroleum ether) = 1:5 or 1:10 as eluent.

3.3. Recycle of Pd/C catalyst

After reaction, the mixture was cooled down to 0 °C and 0.5 mL of 80% N_2H_4 aqueous solution was added dropwise. Stirred for 20 min, the mixture was filtered. The residue (Pd/C and base) was washed with ethanol (2*5 mL) and water (2*5 mL). All the organic phase was combined. The purification was performed by flash column

chromatography on silica gel. The washed residue (Pd/C) was used for next cycle of reaction after dried in vacuum.

4. Conclusions

In summary, we have successfully realized the direct synthesis of *N*-aryl/*N*-alkyl isoquinolones from the annulation reactions of benzamides and alkynes using Pd/C as catalyst. The reaction is through the cleavage of C—H/N—H bonds and air is used as oxidant. The reaction has a broad substrate scope and high regioselectivities when the unsymmetrical alkynes or *meta*-benzamides were used as substrates.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cattod.2017.02.005.

These data include characterization and NMR spectra of products **3** and **5**.

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