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Facile synthesis of isoquinolines by imination and subsequent palladacycle-catalyzed iminoannulation of internal alkynes

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ABSTRACT

An efficient and facile synthesis of isoquinolines has been described via a tandem reaction of imination of *o*-halobenzaldehydes with *tert*-butyl amine and subsequent palladacycle-catalyzed iminoannulation of internal alkynes. This tandem reaction could be carried out successively in one pot without any special operation, and the annulation step could afford isoquinolines derivatives in moderate to good yields with high regioselectivity. In addition, the simple synthesis of indoles was realized by palladacycle-catalyzed annulation of *o*-iodoaniline or *o*-bromoanilines with internal alkynes.

1. Introduction

The palladium-catalyzed annulation of internal alkynes has become a reliable and versatile tool for the convenient synthesis of heterocycles derivatives, such as isoquinolines and indoles.[1] Isoquinolines as important alkaloids are abundantly found in numerous natural products and pharmaceutically active compounds, and a substantial number of their applications have been developed at the laboratory and industrial scale.[2] In the last decades, much effort has been devoted to developing transition-metal-catalyzed reactions for the facile construction of the skeleton of heterocycles, and particularly palladium-catalyzed processes have received much attention.[3] Initially, Widdowson,[4] Pfeffer,[5] and Heck[6] reported three palladium-assisted stoichiometric versions of the annulation, respectively. Subsequently, Larock et al. realized the catalytic and simple synthesis of isoquinolines via palladium-catalyzed iminoannulation of internal alkynes with imines.[7] Recently, Konno et al. described an efficient and convenient protocol of this iminoannulation affording fluoroalkylated isoquinolines as the products in a single isomer.[8] Generally, the *tert*-butylimines and internal alkynes were used as the starting materials in the above-mentioned literatures, and the *tert*-butylimines should be prepared in advance. To overcome this limitation, we consider it highly fascinating and desirable to utilize a tandem reaction, which consists of two steps: imination of *o*-halobenzaldehydes with *tert*-butyl amine and palladium-catalyzed iminoannulation of internal alkynes.

Cyclopalladated ferrocenylimines as a family of versatile palladacyclic catalysts, which were described by our research group, have been applied to various reactions (Fig. 1).[9] Inspired by these pioneering reports and our own works, we would like to report for the first time the facile synthesis of isoquinolines by a tandem reaction of imination and following palladacycle-catalyzed iminoannulation of internal alkynes.

2. Results and discussion

In our initial study, effects of bases and additives on the synthesis of 3,4-diphenylisoquinoline were explored and the results are summarized in Table 1. Firstly, the imination of 2-bromobenzaldehyde (**1a**) with *tert*-butyl amine and subsequent

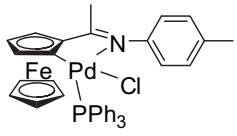

Fig. 1. Palladacycle.

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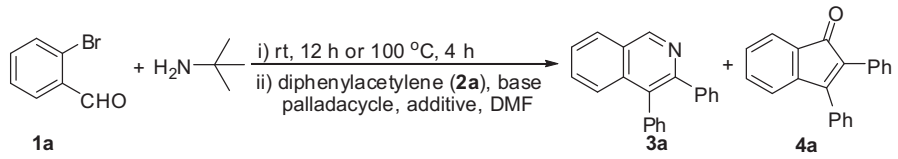
Table 1
Effects of bases and additives on the catalytic synthesis of 3,4-diphenylisoquinoline[a]



1a 3a 4a

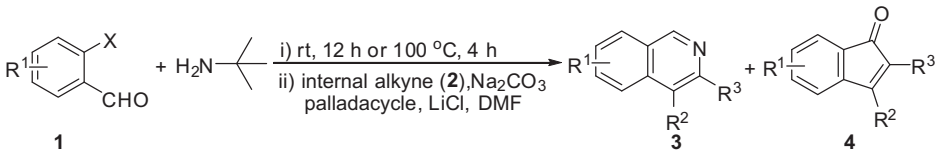
Entry	Base	Additive	Yield[b] [%]	
			3a	**4a**
1	Na_2CO_3	—	61	13
2	**Na_2CO_3**	**LiCl**	81	**9**
3	Na_2CO_3	*n*-Bu_4NCl	20	35
4	Na_2CO_3	*n*-Bu_4NBr	43	29
5	K_2CO_3	LiCl	53	24
6	NaOAc	LiCl	65	23

Bold values in entry 2 represent the optimal conditions.
[a] Reaction conditions: under nitrogen atmosphere, after the mixture of 2-bromobenzaldehyde (0.25 mmol) and *tert*-butyl amine (0.75 mmol) in DMF (1 mL) was stirred at room temperature for 12 h (or 100 °C for 4 h), diphenylacetylene (0.50 mmol), base (0.50 mmol), additive (0.25 mmol), and palladacycle (1 mol %) in DMF (1 mL) were added under stirring at 100 °C for 24 h.
[b] Isolated yields.

palladacycle-catalyzed iminoannulation of diphenylacetylene (**2a**) were carried out using Na_2CO_3 as the base under the additive-free conditions, affording the desired product in a moderate yield of 61% and 2,3-diphenyl-1*H*-inden-1-one (**4a**) as the byproduct (Table 1, entry 1). Interestingly, with the addition of LiCl as the additive, the yield of the product could increase to as high as 81% and the yield of byproduct was decreased to 9% (Table 1, entry 2). However, other additives, such as *n*-Bu_4NCl and *n*-Bu_4NBr did not do good to the reaction process and only relatively low yields were obtained (Table 1, entries 3 and 4). From this point of view, the additive plays a crucial role for the successful reaction. Finally, some other bases, such as K_2CO_3 and NaOAc were also screened and the reactions only gave the corresponding product in moderate yields of 53% and 65%, respectively (Table 1, entries 5 and 6).

Under the optimized conditions, the scope of this tandem reaction was explored (Table 2). For symmetrical internal alkynes, such as diphenylacetylene (**2a**), the reactions proceeded well to afford the desired products in moderate to good yields (Table 2, entries 1–3). For the asymmetrical internal alkynes, this reactions exhibited high regioselectivity with the more sterically hindered group in the 3-position of the isoquinolines as the major isomer (Table 2, entries 4–8). Particularly, if asymmetrical internal alkynes

Table 2
The palladacycle-catalyzed formation of isoquinolines[a]



1 3 4

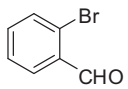
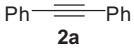
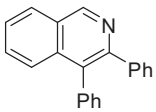
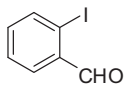
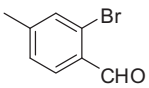
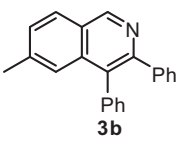
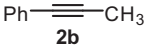
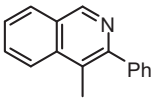
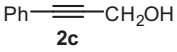
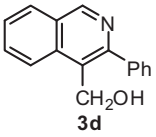
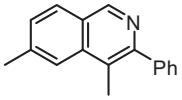
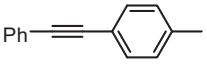
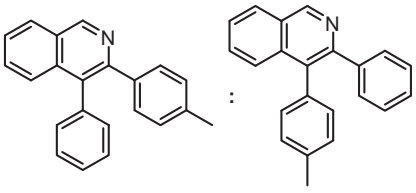
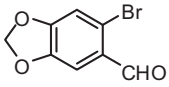
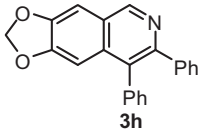
Entry	*o*-Halobenzaldehyde	Alkyne	Product	Yield[b] [%]	
				3	**4**
1	 **1a**	 **2a**	 **3a**	81 (**3a**)	11 (**4a**)
2	 **1b**	**2a**	**3a**	91 (**3a**)	3 (**4a**)
3	 **1c**	**2a**	 **3b**	67 (**3b**)	—

Table 2 (*continued*)

Entry	*o*-Halobenzaldehyde	Alkyne	Product	Yield[b] [%]	
				3	**4**
4	**1b**	 **2b**	 **3c**	83 (**3c**)	5 (**4c**)
5	**1b**	 **2c**	 **3d**	92 (**3d**)	—
6	**1a**	**2b**	**3c**	54 (**3c**)	15 (**4c**)
7	**1a**	**2c**	**3d**	80 (**3d**)	—
8	**1c**	**2b**	 **3e**	73 (**3e**)	—
9[c]	**1a**	 **2d**	 **3f** (1:1) **3g**	85 (**3f**/**3g**)	—
10	 **1d**	**2a**	 **3h**	12 (**3h**)	68 (**4h**)

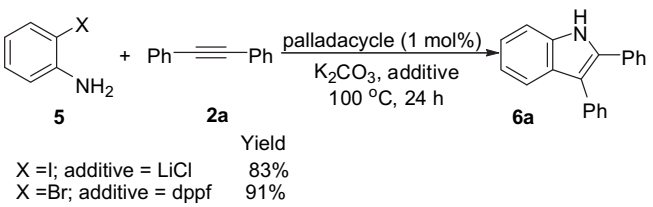
[a] Reaction conditions: under nitrogen atmosphere, after the mixture of *o*-halobenzaldehyde (0.25 mmol) and *tert*-butyl amine (0.75 mmol) in DMF (1 mL) was stirred at room temperature for 12 h (or 100 °C for 4 h), internal alkyne (0.50 mmol), Na_2CO_3 (0.50 mmol), LiCl (0.25 mmol), and palladacycle (1 mol %) in DMF (1 mL) were added under stirring at 100 °C for 24 h.

[b] Isolated yields.

[c] A colon (:) indicates that the products were inseparable.

contain a phenyl group, the phenyl group tends to attach to the carbon atom near to the nitrogen atom in the major isoquinoline products (Table 2, entries 4–8). When the sterical hindrance of two substituents on asymmetrical internal alkynes was almost the same, an inseparable 1:1 mixture of isomers (e.g., **3f** and **3g**) was obtained (Table 2, entry 9). For the *o*-halobenzaldehydes, when the substrate contains two electron-donating groups (**1d**), the side reaction would occur to afford the byproduct as the major product (Table 2, entry 10).

In addition, the facile synthesis of indoles via palladium-catalyzed annulation of *o*-haloanilines with internal alkynes was also investigated, since construction of the indole skeleton would have great importance in heterocyclic chemistry (Scheme 1). The reactions of *o*-iodoaniline and *o*-bromoaniline with diphenylacetylene (**2a**) proceeded smoothly to afford the desired product of 2,3-disubstituted indole (**6a**) in yields of 83% and 91%, respectively.



Scheme 1.

3. Conclusion

In summary, we have accomplished the convenient and efficient synthesis of isoquinolines by a tandem reaction of imination and palladacycle-catalyzed iminoannulation of internal alkynes with high regioselectivity. On the other hand, we also offered a facile protocol for the synthesis of indoles via the catalytic annulation of *o*-iodoaniline or *o*-bromoaniline with internal alkynes. Further investigations on the application of these synthetic methodologies are currently underway in our laboratory.

4. Experimental

4.1. General methods

All commercial materials were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker DPX-400 spectrometer. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. GC analysis was performed on Agilent 4890D gas chromatograph. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were obtained on a Waters Q-Tof MicroTM spectrometer. Ethyl acetate and hexane (analytical grade) were used for column chromatography without purification. The other chemicals were obtained from commercial sources and used as received unless otherwise noted.

4.2. General procedure for synthesis of isoquinolines

To a solution of *o*-halobenzaldehyde (0.25 mmol) in DMF (1 mL), *tert*-butyl amine (0.75 mmol) was added. The resulting mixture was stirred under a nitrogen atmosphere at room temperature for 12 h (or 100 °C for 4 h). After the haloaldehyde was consumed completely (monitored by TLC), alkynes (0.50 mmol), Na_2CO_3 (0.50 mmol), LiCl (0.25 mmol), palladacycle (1 mol %), and DMF (1 mL) were added to the mixture. Then the vial was placed in a preheated oil bath and heated at 100 °C under stirring for 24 h. After the reaction was complete (monitored by TLC), the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and extracted with CH_2Cl_2. The combined organic phase was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to afford the pure product.

*4.2.1. 3,4-Diphenylisoquinoline (**3a**)*[7a]. White solid, mp 168–169 °C (lit. 170 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19–7.21 (m, 3H), 7.24–7.26 (m, 2H), 7.35–7.38(m, 5H), 7.59–7.62 (m, 2H), 7.67 (dd, J=4.2 and 5.3 Hz, 1H), 8.04 (dd, J=5.1 and 4.2 Hz, 1H), 9.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.6, 126.9, 127.1, 127.3, 127.6, 127.6, 128.3, 130.2, 130.5, 130.6, 131.2, 135.9, 137.2, 140.8, 150.6, 151.7.

*4.2.2. 6-Methyl-3,4-diphenylisoquinoline (**3b**).* White solid, mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 7.18–7.20 (m, 3H), 7.23–7.25 (m, 3H), 7.34–7.37 (m, 5H), 7.42–7.45 (m, 2H), 7.96 (d, J=8.2 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 124.4, 125.8, 126.9, 127.2, 127.4, 127.6, 128.2, 129.1, 130.1, 130.2, 131.2, 136.1, 137.4, 140.9, 150.7, 151.3; HRMS (positive ESI) calcd for $C_{22}H_{18}N$: 296.1439 (M^++H), found: 296.1440.

*4.2.3. 4-Methyl-3-phenylisoquinoline (**3c**)*[7a]. White solid, mp 101–102 °C (lit. 103–104 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (s, 3H), 7.24–7.26 (m, 2H), 7.35–7.38(m, 5H), 7.59–7.62 (m, 2H), 7.67 (dd, J=4.2 and 5.3 Hz, 1H), 8.04 (dd, J=5.1 and 4.2 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 123.6, 124.0, 126.6, 127.2, 127.5, 128.1, 129.8, 130.4, 136.2, 141.3, 150.1, 151.8.

*4.2.4. (3-Phenylisoquinolin-4-yl)methanol (**3d**)*[7b]. White solid, mp 177–178 °C (lit. 175–176 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (s, 2H), 7.43 (m, 1H), 7.48 (t, J=6.8 Hz, 2H), 7.66 (m, 3H), 7.82 (t, J=7.7 Hz, 2H), 8.03 (d, J=8.1 Hz, 1H), 8.31 (d, J=8.5 Hz, 1H), 9.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 59.4, 123.9, 125.7, 127.0, 127.7, 128.1, 128.2, 128.3, 129.7, 131.1, 135.8, 140.1, 152.3, 152.8.

*4.2.5. 4,6-Dimethyl-3-phenylisoquinoline (**3e**).* White solid, mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.61 (s, 3H), 2.63 (s, 3H), 7.26 (s, 1H), 7.40–7.49 (m, 3H), 7.57–7.59 (d, 2H), 7.82 (s, 1H), 7.90 (d, J=8.2 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 22.5, 122.6, 123.4, 125.6, 127.4, 128.0, 128.8, 129.8, 136.4, 140.7, 141.4, 149.7, 151.8; HRMS (positive ESI) calcd for $C_{17}H_{16}N$: 234.1283 (M^++H), found: 234.1279.

*4.2.6. 4-Phenyl-3-(p-tolyl)isoquinoline (**3f**) with 3-phenyl-4-(p-tolyl) isoquinoline (**3g**) (1:1)*[3a]. White solid, mp 93–100 °C (**3g** lit. 129 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.39 (s, 3H), 7.00–7.02 (m, 2H), 7.14–7.28 (m, 16H), 7.36–7.39 (m, 4H), 7.58–7.60 (m, 2H), 8.02–8.04 (m, 1H), 9.36 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 21.3, 125.5, 125.6, 126.7, 126.8, 126.9, 127.2, 127.5, 127.6, 128.3, 128.4, 130.1, 130.2, 130.4, 131.0, 131.2, 136.7, 137.4, 150.5, 151.5, 151.7; HRMS (positive ESI) calcd for $C_{22}H_{18}N$: 296.1439 (M^++H), found: 296.1437.

*4.2.7. 7,8-Diphenyl-[1,3]dioxolo[4,5-g]isoquinoline (**3h**)*[7b]. White solid, mp 231–233 °C (lit. 234–235 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (s, 2H), 7.00 (s, 1H), 7.17–7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.8, 102.1, 103.0, 124.9, 127.1, 127.5, 128.2, 130.1, 131.1, 134.5, 137.9, 140.9, 148.3, 149.5, 150.2, 151.4.

*4.2.8. 2,3-Diphenyl-1H-inden-1-one (**4a**)*[10]. Red solid, mp 147–149 °C (lit. 152–153 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, J=7.3 Hz, 1H), 7.25–7.28 (m, 6H), 7.37–7.42 (m, 6H), 7.59 (d, J=7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.2, 122.9, 127.7, 128.0, 128.5, 128.7, 128.9, 129.2, 129.9, 130.7, 132.3, 132.7, 133.4, 145.1, 155.2, 196.5.

*4.2.9. 2-Methyl-3-phenyl-1H-inden-1-one (**4c**)*[11]. Orange solid, mp 80–82 °C (lit. 83–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H, C-2 methyl), 7.07 (d, J=7.2 Hz, 1H), 7.17–7.54 (m, 3H), 7.49 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.6, 120.4, 122.5, 128.0, 128.1, 128.7, 129.1, 131.0, 131.1, 132.7, 133.1, 145.7, 154.7, 198.3.

*4.2.10. 6,7-Diphenyl-5H-indeno[5,6-d][1,3]dioxol-5-one (**4h**).* Purple solid, mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (s, 2H), 6.65 (s, 1H), 7.09 (s, 1H), 7.22–7.26 (s, 5H), 7.32–7.35 (m, 2H), 7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.1, 104.0, 105.3, 124.7, 127.5, 128.0, 128.4, 128.9, 129.3, 129.8, 130.8, 131.4, 132.7, 141.8, 147.7, 151.6, 153.7, 195.2; HRMS (positive ESI) calcd for $C_{22}H_{14}O_3Na$: 349.0841 [M+Na]$^+$, found: 349.0840.

4.3. General procedure for synthesis of indole

o-Halobenzaldehyde (0.25 mmol), diphenylacetylene (0.50 mmol), palladacycle (1 mol %), additive (0.25 mmol), and K_2CO_3 (0.50 mmol) were dissolved in DMF (1.50 mL) in a 10 mL vial under air and heated at 100 °C for 24 h. After the reaction was complete (monitored by TLC), the mixture was diluted with CH_2Cl_2 (10 mL), filtered through a pad of Celite, and washed multiple times with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to afford the pure product.

*4.3.1. 2,3-Diphenyl-1H-indole (**6a**)*[12]. White solid, mp 113–114 °C (lit. 120–121 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.15(m, 13H), 7.67 (d, J=7.9 Hz, 1H), 8.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 110.9, 115.0, 119.7, 120.4, 122.7, 126.2, 127.7, 128.2, 128.5, 128.7, 130.1, 132.7, 134.1, 135.0, 135.9.

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