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Selective synthesis of 3-methyleneindolin-2-ones by one-pot multicatalytic processes

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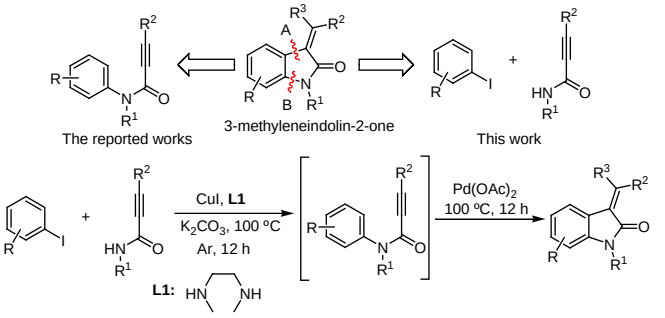
ABSTRACT

A novel one-pot multicatalytic route for the synthesis of 3-methyleneindolin-2-ones has been developed involving sequential copper-catalyzed amination and palladium-catalyzed C–H functionalization processes. In the presence of CuI and $Pd(OAc)_2$, a variety of propiolamides underwent the reaction with iodides to afford the corresponding 3-methyleneindolin-2-ones in moderate yields.

The 3-methyleneindolin-2-one moieties are frequently present in naturally occurring and biologically active compounds that display great potential utilizations in many major therapeutic areas, such as oncology, inflammation, CNS, immunology, and endocrinology.[1] Therefore, attention of organic chemists has been increasingly drawn to the development of efficient methods for their preparation.[2–4] Among the numerous transformations, palladium-catalyzed cyclization of *N*-arylpropiolamide involving an arene C–H functionalization process displayed efficiency particularly for the synthesis of 3-methyleneindolin-2-ones.[2–6] However, only few papers have been reported for this purpose.[2,3] Zhu and coworkers, for example, have first developed the palladium-catalyzed domino carbopalladation/C–H activation/C–C bond-forming reaction that uses an anilide sp^2 C–H bond and an electrophile (aryl iodide) as the coupling partners (Scheme 1).[2] Subsequently, we have demonstrated some new protocols for constructing the 3-methyleneindolin-2-one skeleton by palladium-catalyzed oxidative C–H functionalization of an anilide sp^2 C–H bond with an nucleophile (based on amide, acid, and $ArI(OAc)_2$).[3] Due to continuing interest in this area,[3,4f] we report here a novel one-pot multicatalytic route[7] for the synthesis of 3-methyleneindolin-2-ones involving sequential copper-catalyzed amination and palladium-catalyzed C–H functionalization processes (Scheme 1).[8,9]

The reaction between *N*-(4-methoxyphenyl)-3-phenylpropiolamide (**1a**) and 1-iodo-4-methoxybenzene (**2a**) was investigated to optimize the reaction conditions, and the results are summarized in Table 1. Initially, a series of ligands **L1**–**L7** were examined, and the results showed that **L1**, *N*,*N*′-dimethylethane-1,2-diamine, was the most efficient (entries 1–7). After treatment of amide **1a** with iodide **2a**, CuI, and **L1** in DMF/MeCN for 12 h, the reaction was conducted in the same vessel for another 12 h after the addition of $Pd(OAc)_2$ to afford the target product **3** in a 57% yield (entry 1). However, the other nitrogen-containing ligands **L2–L6** were inferior to **L1** (entries 2–6). The reported effective Buchwald–Hartwig amination phosphine **L7** was also examined for the one-pot reaction, and only 34% yield of **3** was obtained (entry 7). Among the effects of solvents examined, we found that a mixture of DMF/MeCN (1:1) provided the best results (entries 1 and 8–14).



Scheme 1.

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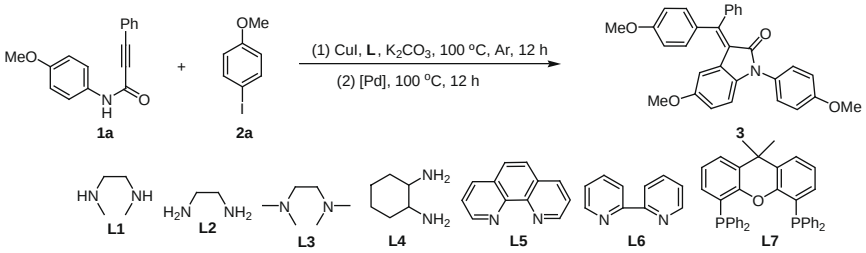
Table 1
Screening optimal conditions[a]



Entry	Ligand	[Pd]	Solvent	Isolated yield (%)
1	**L1**	$Pd(OAc)_2$	DMF/MeCN (1:1)	57
2	**L2**	$Pd(OAc)_2$	DMF/MeCN (1:1)	Trace
3	**L3**	$Pd(OAc)_2$	DMF/MeCN (1:1)	17
4	**L4**	$Pd(OAc)_2$	DMF/MeCN (1:1)	47
5	**L5**	$Pd(OAc)_2$	DMF/MeCN (1:1)	Trace
6	**L6**	$Pd(OAc)_2$	DMF/MeCN (1:1)	18
7	**L7**	$Pd(OAc)_2$	DMF/MeCN (1:1)	34
8	**L1**	$Pd(OAc)_2$	DMF	29
9	**L1**	$Pd(OAc)_2$	MeCN	Trace
10	**L1**	$Pd(OAc)_2$	Toluene	28
11	**L1**	$Pd(OAc)_2$	Toluene/MeCN (1:1)	22
12	**L1**	$Pd(OAc)_2$	DMSO/MeCN (1:1)	24
13	**L1**	$Pd(OAc)_2$	DMF/MeCN (1:4)	20
14	**L1**	$Pd(OAc)_2$	DMF/MeCN (4:1)	32
15	**L1**	$Pd(CF_3CO_2)_2$	DMF/MeCN (1:1)	37
16	**L1**	$PdBr_2$	DMF/MeCN (1:1)	27
17	**L1**	$PdCl_2(PPh_3)_2$	DMF/MeCN (1:1)	32
18	**L1**	$Pd_2(dba)_3$	DMF/MeCN (1:1)	55
19	**L1**	K_2PdCl_4	DMF/MeCN (1:1)	56
20[b]	**L1**	$Pd(OAc)_2$	DMF/MeCN (1:1)	21
21[c]	**L7**	$Pd(OAc)_2$	DMF/MeCN (1:1)	20

Reaction conditions: **1a** (0.2 mmol), **2a** (2.2 equiv), $Pd(OAc)_2$ (10 mol %), **L7** (20 mol %), K_2CO_3 (2.2 equiv), and DMF/MeCN (1:1, 4 mL) at 100 °C for 12 h, then $Pd(OAc)_2$ (10 mol %) at 100 °C for 12 h.

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.2 equiv), CuI (10 mol %), ligand (20 mol %), K_2CO_3 (2.2 equiv), and solvent (4 mL) at 100 °C for 12 h, then [Pd] (10 mol %) at 100 °C for 12 h. Some side products were observed from decomposition of the C–N bonds by GC–MS analysis.

[b] Both CuI (10 mol %) and $Pd(OAc)_2$ (10 mol %) were added at the same time for 24 h.

[c] Reaction conditions: **1a** (0.2 mmol), **2a** (2.2 equiv), $Pd(OAc)_2$ (10 mol %), **L7** (20 mol %), K_2CO_3 (2.2 equiv), and DMF/MeCN (1:1, 4 mL) at 100 °C for 12 h, then $Pd(OAc)_2$ (10 mol %) at 100 °C for 12 h.

Finally, a variety of other Pd catalysts, including $Pd(CF_3CO_2)_2$, $PdBr_2$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$, and K_2PdCl_4, were evaluated (entries 15–19). The screening results demonstrated that the efficiency of $Pd_2(dba)_3$ or K_2PdCl_4 is the same as that of $Pd(OAc)_2$, but $Pd(CF_3CO_2)_2$, $PdBr_2$, and $PdCl_2(PPh_3)_2$ were less effective. It is noteworthy that both CuI and $Pd(OAc)_2$ were added to the mixture of amide **1a** and iodide **2a** at the same time for 24 h providing the product **3** in a low yield (entry 20). The results demonstrated that only a low yield was obtained without Cu catalysts by a Pd-catalyzed amination/C–H functionalization process (entry 21).[9,8e]

With the optimal conditions in hand, the scopes of both propiolamides **1** and iodides **2** were examined (Table 2).[10] We were pleased to find that the reactions of amide **1a** with various iodides **2b**, **2c**, and **2e** were still conducted smoothly in moderate yields (entries 1, 2, and 4), but the reaction of the electron-deficient aryliodide **2d** gave a mixture of products (entry 3). Treatment of substrate **1a** with iodobenzene (**2b**), CuI, **L1**, and $Pd(OAc)_2$, for instance, selectively afforded two products **4** and **5** in 62% total yield (entry 1). The electron-rich aryliodide **2c** was also suitable for the one-pot reaction under the standard conditions (entry 2). Interestingly, iodomethane (**2e**) could undergo the reaction with amide **1a** to afford the corresponding 3-methyleneindolin-2-one **8** in 47% yield (entry 4). Subsequently, we chose both propiolamides **1** and iodides **2** to control the selectivity (entries 5–9). 3-Phenyl-*N*-*p*-tolylpropiolamide (**1d**), for instance, was reacted with 1-iodo-4-methylbenzene (**2c**) to give the product **11** alone in 53% yield (entry 7). It is noteworthy that 21% yield can still be achieved from the reaction between the two bulk substrates, 3-phenyl-*N*-*o*-tolylpropiolamide (**1f**) and 1-iodo-2-methylbenzene (**2g**) (entry 9). *N*-Alkyl phenylpropiolamides **1g** and **1h** were also investigated under the standard conditions (entries 10 and 11). The results demonstrated that both amides **1g** and **1h** could undergo the one-pot reaction selectively in 36% and 33% yields, respectively.

As shown in Scheme 2, a controlled reaction was conducted. Treatment of *N*-(4-methoxyphenyl)-3-phenylpropiolamide (**1a**) with 1-iodo-4-methoxybenzene (**2a**), CuI, and **L1** afforded the corresponding amination product **16** in 50% isolated yield. Subsequently, the reaction of **16** was carried out under the Zhu's conditions to give the target product **3** in 48% yield.

A possible mechanism was proposed as outlined in Scheme 3 on the basis of the previously reported mechanisms and the present results.[2,3,8,9] Reaction of amide **1** with $CuIL_2$ affords intermediate **A** with the aid of base. Intermediate **A** undergoes the reaction with iodide **2** to yield the product **B** and to regenerate the active Cu species.[8] Subsequently, C–H functionalization of the product **B** occurs after the addition of Pd catalyst to give the target 3-methyleneindolin-2-ones by Zhu's process.[2] We deduced that Pd-catalyzed amination of substrate **1** with iodide **2** may take place to give the product **B** in the multicatalytic processes (entry 21 in Table 1).[9,8e] Based on the present results, the stereoselectivity may mainly depend on the characters of both aryl group on the propiolamide moiety and substituent R^1 of iodides, such as electronic effect and steric effect. Study of the true mechanism is in progress.

In summary, we have developed a novel one-pot protocol for the synthesis of 3-methyleneindolin-2-ones by sequential copper-catalyzed amination and palladium-catalyzed C–H functional-

Table 2
Selective synthesis of 3-methyleneindolin-2-ones by one-pot multicatalytic processes[a]

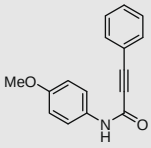
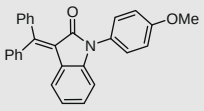
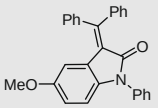
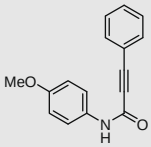
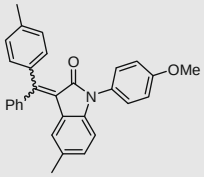
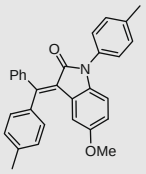
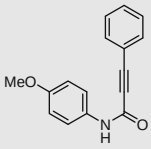
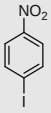
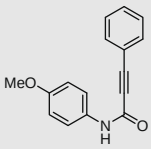
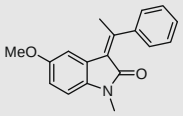
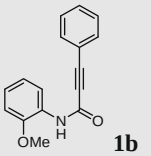
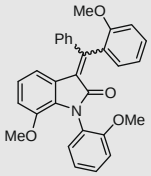
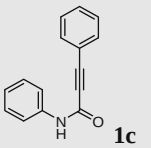
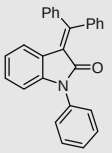
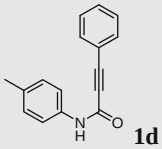
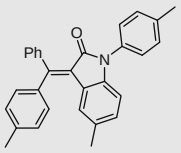
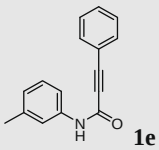
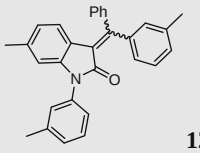
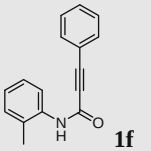
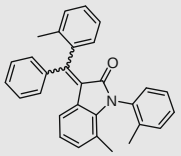
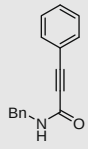
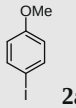
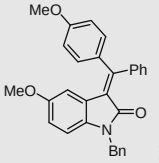
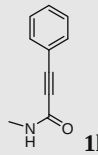
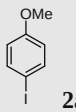
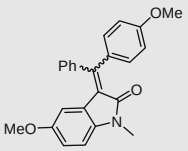
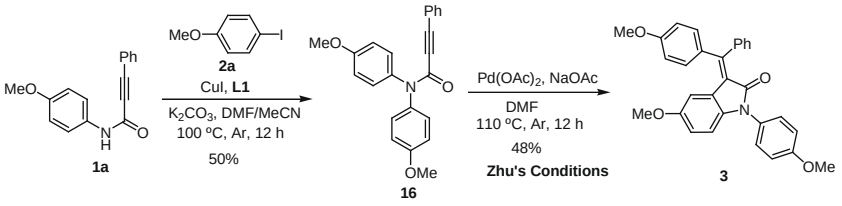
Entry	Amide **1**	Iodide **2**	Product/isolated yield[b] (%)
1	 **1a**	 **2b**	 **4** (27)  **5** (35)
2	 **1a**	 **2c**	 **6** (37; *E*/*Z* = 2 : 1)  **7** (27)
3	 **1a**	 **2d**	Mixture
4	 **1a**	Mel **2e**	 **8** (47)
5	 **1b**	 **2f**	 **9** (32; *E*/*Z* = 1 : 1)
6	 **1c**	 **2b**	 **10** (45)
7	 **1d**	 **2c**	 **11** (53)
8	 **1e**	 **2g**	 **12** (55; *E*/*Z* = 2 : 1)
9	 **1f**	 **2h**	 **13** (21; *E*/*Z* = 3 : 1)

Table 2 (*continued*)

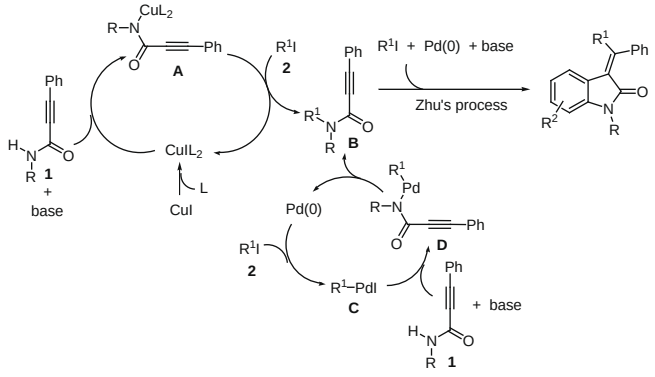
Entry	Amide **1**	Iodide **2**	Product/isolated yield[b] (%)
10	 **1g**	 **2a**	 **14** (36)
11	 **1h**	 **2a**	 **15** (33; *E*/*Z* = 3 : 1)

[a] Reaction conditions: **1** (0.2 mmol), **2** (2.2 equiv), CuI (10 mol %), **L1** (20 mol %), and K_2CO_3 (2.2 equiv) in DMF/MeCN (1:1, 4 mL) at 100 °C for 12 h, then $Pd(OAc)_2$ (10 mol %) at 100 °C for 12 h. Some side products were observed from decomposition of the C–N bonds by GC–MS analysis.

[b] Ratios of *Z*/*E* isomers were determined by ^1H NMR.



Scheme 2. A controlled reaction.



Scheme 3. A possible mechanism.

ization reactions. In the presence of CuI and $Pd(OAc)_2$, a variety of propiolamides underwent the multicatalytic processes with iodides to afford the corresponding 3-methyleneindolin-2-ones in moderate yields. Efforts to extend the application of the transformation in organic synthesis are underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.066.

References and notes

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10. *Typical procedure*: A mixture of propiolamide **1** (0.2 mmol), iodide **2** (2.2 equiv), CuI (10 mol %), *N,N′*-dimethylethane-1,2-diamine **L1** (20 mol %), and K_2CO_3 (2.2 equiv) was stirred in DMF/MeCN (v/v 1:1, 4 mL) at 100 °C for 12 h, then $Pd(OAc)_2$ (10 mol %) was added to the mixture, and stirred at 100 °C for another 12 h until complete consumption of starting material which was monitored by TLC. After the reaction was complete, the mixture was washed with saturated NaCl, and was extracted with diethyl ether. The organic layers were dried with Na_2SO_4 and were evaporated under vacuum, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure product.

(E)-5-Methoxy-1-(4-methoxyphenyl)-3-((4-methoxyphenyl)(phenyl) methylene)-indolin-2-one (**3**): Red oil; ^{1}H NMR (500 MHz) δ: 7.36–7.30 (m, 9H), 6.97 (d, J = 4.5 Hz, 1H), 7.28 (t, J = 4.5 Hz, 3H), 7.27–7.18 (m, 4H), 7.17–7.15 (m, 1H), 7.02 (t, J = 6.5 Hz, 1H), 6.99 (t, J = 6.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 4.90 (s, 2H), 2.37 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz) δ: 166.5, 160.8, 158.7, 155.7, 154.9, 140.2, 137.5, 133.5, 131.6, 130.5, 129.2, 128.1, 127.8, 127.7, 124.4, 123.6, 114.6, 114.3, 114.1, 109.3, 109.2, 55.5 (2C), 55.4; IR (KBr, cm^{-1}): 1699, 1508, 1247; LRMS (EI, 70 eV) m/z (%): 464 (33), 463 (M^+, 100), 448 (13), 420 (2), 386 (3), 340 (1), 232 (19), 195 (2); HRMS (EI) for $C_{30}H_{25}NO_4$ (M^+): calcd 463.1784, found 463.1783.

5-Methoxy-3-((4-methoxyphenyl)(phenyl)methylene)-1-methylindolin-2-one (***15***): ^{2}*E*/*Z* = 3:1; Yellow oil, ^{1}H NMR (500 MHz) δ: 7.49 (s, 1H), 7.42–7.28 (m, 6H), 7.10 (d, J = 7.0 Hz, 2.3H), 7.06 (d, J = 7.0 Hz, 0.7H), 6.97–6.87 (m, 1H), 6.75–6.64 (m, 1H), 3.86 (s, 3H), 3.83 (s, 1H), 3.54 (s, 3H), 3.44 (s, 1H), 3.20 (s, 1H), 3.17 (s, 3H) ; ^{13}C NMR (125 MHz) δ 166.9, 160.7, 154.9, 154.7, 140.3, 137.2, 137.0, 133.3, 132.5, 131.6, 130.3, 129.7, 129.2, 129.1, 128.9, 127.7, 124.4, 123.9, 114.1, 114.0, 113.8, 113.0, 109.5, 109.2, 107.8; IR (KBr, cm^{-1}): 1684, 1507, 1490; LRMS (EI, 70 eV) m/z (%): 372 (21), 371 (M^+, 100), 356 (18), 341 (4), 328 (3), 294 (5), 264 (3), 178 (8).