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Regioselective Pd-catalyzed indolization of 2-bromoanilines with internal alkynes using phosphine-free ligands

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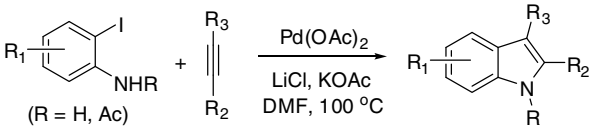
Abstract

The possibility of using phosphine-free ligands to promote Pd-catalyzed indolization of 2-bromoanilines with internal alkynes was examined for the first time. Phenylurea was found to be the optimal ligand, which could mediate the synthesis of 2,3-disubstituted indoles in good yields (ca. 60–85%) with high regioselectivity.

Keywords: Indole; Larock indolization; Palladium catalyst; Phosphine-free ligand; Heteroannulation

The indole ring is prevalent in a wide variety of natural and synthetic products, many of which are capable of binding to biological receptors with high affinity.[1] Accordingly indoles have been referred to as "privileged structures" in pharmaceutical studies, whose synthesis has been a focus in organic chemistry for many years.[2] Up to now numerous methods for the preparation of indoles have been developed. Some famous methods such as Fischer, Bartoli, Nenitzescu, Wittig, and Madelung-Houlihan indole syntheses have found extensive applications.[3] Nonetheless, regioselective synthesis of 2,3-disubstituted indoles remains a challenging problem with all the above classical approaches.

To tackle the problem Larock et al. recently developed a method of Pd-catalyzed indolization which in principal was a heteroannulation reaction of internal alkynes with 2-iodoanilines (Scheme 1).[4] Using this method Konno et al. recently synthesized fluoroalkylated indole derivatives.[5] Watterson et al. synthesized novel indole-based inhibitors of 5′-inosine monophosphate dehydrogenase.[6] Lanter et al. synthesized a potent orally efficacious indole androgen receptor antagonist.[7] Besides, by attaching 2-iodoanilines onto the resins Smith's and Zhang's groups developed interesting solid-phase methods to synthesize 2,3-disubstituted indoles.[8] These applications showed that the Larock indole synthesis allows easy access to a variety of indoles in terms of substitution and functionality.



Scheme 1. Larock indole synthesis.

Noteworthy, Larock's original indolization reaction was performed under 'ligandless' conditions (Scheme 1), which unfortunately only allowed for the use of 2-iodoanilines as reactant. The much cheaper 2-bromo or 2-chloroanilines cannot be applied to the Larock protocol, presumably because the oxidative insertion to C–Br or C–Cl bonds requires electron-rich Pd. To overcome this problem Lu and co-workers recently examined the possibility of using bulky, electron-rich phosphine ligands to improve Larock's protocol.[9] It was found that 2-bromo and 2-chloroanilines

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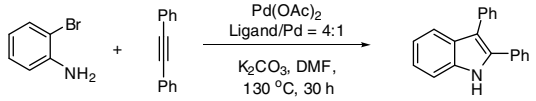
Table 1
Pd-catalyzed indolization of 2-bromoaniline under phosphine-free conditions[a]



Entry	Ligand	Pd loading (mol %)	Yield[b] (%)
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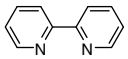
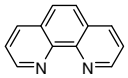
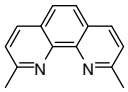
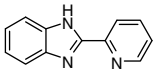
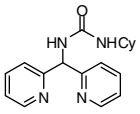
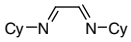
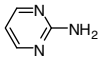
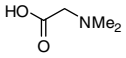
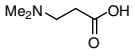
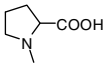
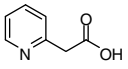
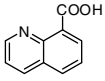
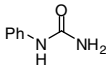
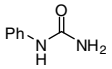
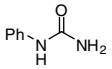
2		1	54
3		1	28
4		1	22
5		1	Trace
6		1	Trace
7		1	50
8		1	40
9		1	32
10		1	61
11		1	25
12		1	37
13		1	16
14		1	16
15		1	45
16		1	84
17		0.5	51
18		5	8

Table 1 (*continued*)

Entry	Ligand	Pd loading (mol %)	Yield[b] (%)
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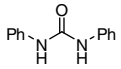
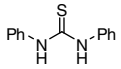
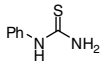
20		1	58
21		1	35
22		1	48
23		1	0
24		1	0

[a] Reaction conditions: 2-bromoaniline (0.25 mmol), alkyne (0.75 mmol), K_2CO_3 (0.75 mmol), $Pd(OAc)_2$:ligand = 1:4, DMF (1 mL), 130 °C, 30 h, under Ar.
[b] Isolated yield.

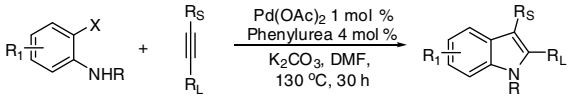
were applicable to the improved protocol. However, the use of bulky, electron-rich phosphine ligands is still not optimal from a cost and throughput perspective.

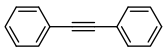
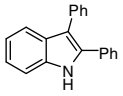
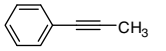
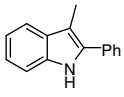
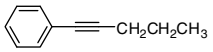
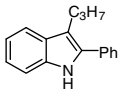
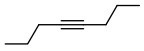
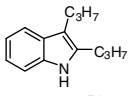
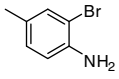
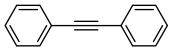
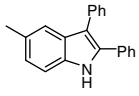
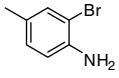
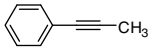
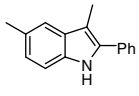
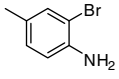
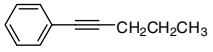
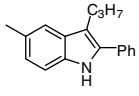
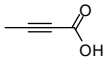
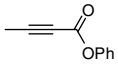
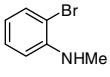
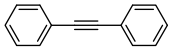
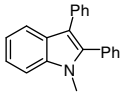
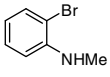
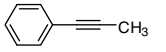
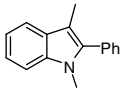
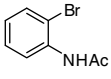
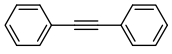
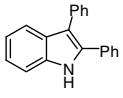
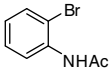
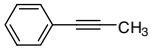
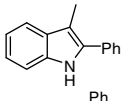
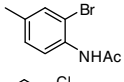
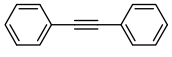
In the present study we search for the further improvement of the Larock indole synthesis method by using low-priced, phosphine-free ligands. These ligands (mainly including oxazolines,[10] imines,[11] diazabutadienes,[12] bis-pyridines,[13] hydrazones,[14] pyrazoles,[15] phenanthrolines,[16] guanidines,[17] quinolines,[18] carbazones,[19] tetrazoles,[20] imidazoles,[21] amino acids,[22] amines,[23] thioureas,[24] and dicarbonyl compounds[25]) were recently found to be sufficiently active to replace expensive phosphines or carbene ligands in many Pd-catalyzed transformations.

To begin the study we focus on the Pd-catalyzed indolization of 2-bromoaniline (Table 1). The solvent, base, and reaction temperature (i.e., DMF, K_2CO_3, and 130 °C) are similar to the conditions previously reported by Lu and co-workers (i.e., NMP, K_2CO_3, 110–130 °C).[9] It is found that in the absence of any ligand, only a trace amount of product can be formed (entry 1). The addition of bipyridine ligands[13] (entries 2–4) leads to the production of some indoles, but the yields remain low. On the other hand, two recently reported bis-pyridine-type Pd-ligands (namely, pyridylbenzoimidazole[26] and di(2-pyridyl)methylamine[27]) are found completely inactive (entries 5 and 6). An additional bis-nitrogen ligand is diazabutadiene (entry 7) developed by Nolan and co-workers,[12] and this ligand gives an isolated yield of 50% for the indolization.

The failure with the bis-nitrogen ligands forced us to examine other ligands including DABCO[23] (entry 8) and guanidines[17] (entries 9 and 10). Unfortunately the yields remain fairly low in a range from 30% to 60%. Besides, it is surprising to find that the amino acid ligands (entries 11–15) that were recently shown to have good perfor-

Table 2
Synthesis of 2,3-disubstituted indoles via Pd/phenylurea-catalyzed heteroannulation of internal alkynes with 2-bromoanilines[a]



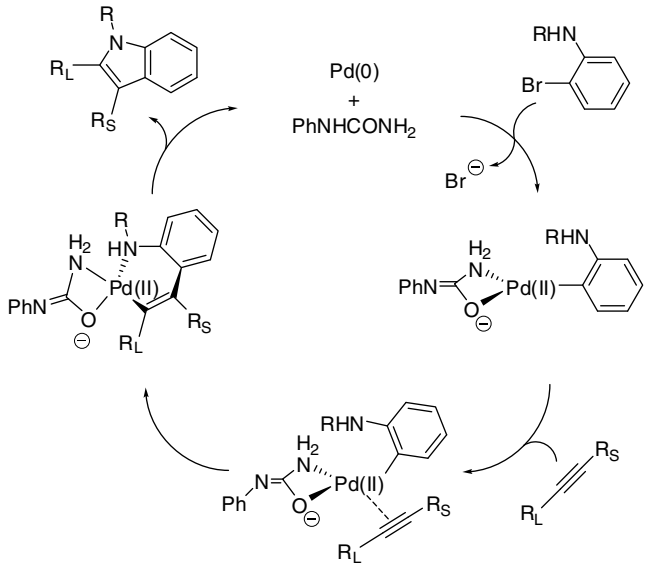
Entry	Aniline derivative	Internal alkyne	Major product	Yield of major product (selectivity)
1				84 (*n*/*a*)
2				62 (96:4)
3				67 (82:18)
4				80 (*n*/*a*)
5				86 (*n*/*a*)
6				65 (88:12)
7				55 (80:20)
8			—	0
9			—	0
10				67 (*n*/*a*)
11				51 (78:22)
12				74 (*n*/*a*)
13				59 (93:8)
14				70 (*n*/*a*)
15			—	0
16				71 (70:30)
17				52 (64:36)

[a] Reaction conditions: aniline (0.25 mmol), alkyne (0.75 mmol), K_2CO_3 (0.75 mmol), $Pd(OAc)_2$:ligand = 1:4, DMF (1 mL), 130 °C, 30 h, under Ar.

mances in both Pd-catalyzed Heck and Suzuki reactions[22] also fail to promote the indolization reaction. At this point it is interesting to find that the addition of phenylurea provides an indolization yield of 84% (entry 16). This yield is comparable to that of Lu's protocol (63–99% for 2-bromoanilines)[9] which utilized 10 mol % of expensive 1,1′-bis(di-*tert*-butylphosphino)ferrocene as the ligand. Noteworthy, Lu's protocol requires a Pd loading of 5 mol %, whereas our Pd/phenylurea protocol[28] only requires 1 mol % of Pd. It is also interesting to find that the change of the Pd loading to either 0.5 or 5 mol % causes a much lower indolization yield (entries 17 and 18).

The applicability of the Pd/phenylurea protocol was next examined for the coupling between various 2-bromo-anilines and internal alkynes (Table 2). It is found that the indolization can smoothly take place with diaryl alkynes (entries 1 and 5), aryl alkyl alkynes (entries 2, 3, 6, and 7), and dialkyl alkynes (entry 4). The yields range from 55% to 86%. Note that electron-deficient alkynoic acid and ester cannot be used in the present protocol (entries 8 and 9). On the other hand, 2-bromoaniline derivatives with an alkyl or acyl substituent on the nitrogen are also good substrates in the indolization (entries 10–14), which afford N-alkylated or N-deacylated indoles as the final product. Lastly, it is found that the Pd/phenylurea protocol cannot activate 2-chloroaniline (entry 15), whose indolization was only accomplished with bulky electron-rich phosphine ligands.[9]

Mechanistically phenylurea must be explicitly involved in the catalytic cycle, because in its absence the reaction does not take place with 2-bromoaniline. On the basis of our previous examination of phenylurea as a phosphine-free ligand in Pd-catalyzed Heck and Suzuki reactions,[29] we propose that the indolization reaction proceeds through the following steps (Scheme 2): (a) oxidation insertion of C–Br bond to Pd(0) producing a Pd(II)–aryl complex; (b) coordination and regioselective addition of the Pd(II) complex to the alkyne; and (c) Pd extrusion and product formation via reductive elimination. The role of phenylurea is to stabilize the Pd(II) intermediates and transition states by using its deprotonated form.[29] Other ureas (such as *N*-methylurea, Table 1, entry 22) cannot effectively promote the same reaction, presumably because *N*-methylurea is less acidic than *N*-phenylurea by about 5 pK_a units[30] and therefore, cannot use its deprotonated form in the catalysis. The proposed mechanism is consistent with the regioselectivities observed in the Pd/phenylurea-catalyzed indolization reactions (see Table 2), where the insertion of the Pd(II)-aryl bond into the alkyne prefers to place the aryl group (which is geometrically more bulky than Pd(II)) near the smaller substituent.



Scheme 2. Possible catalytic cycle of Pd/phenylurea catalyzed indolization of 2-bromoaniline with an internal alkyne.

In conclusion, the possibility of using phosphine-free ligands to mediate palladium-catalyzed indolization of 2-bromoanilines with internal alkynes is examined here for the first time. Most of the recently popularized phosphine-free ligands fail to promote the indolization reaction except for phenylurea. By using the optimized Pd/phenylurea protocol, 2,3-disubstituted indoles can be successfully produced in good yields (ca. 60–85%) with high regioselectivity. This study provides an additional example to illustrate the advantage of using urea derivatives as potential phosphine-free ligands to promote Pd-catalyzed transformations.[31] Further studies to evolve phosphine-free ligands to promote the indolization of 2-chloroanilines are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.112.

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