Palladium/Norbornene Chemistry in the Synthesis of Polycyclic Indolines with Simple Nitrogen Sources

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Abstract An efficient procedure has been developed to synthesize indoline derivatives through a palladium-catalyzed Heck reaction/C–H activation/dual amination cascade in one pot. This constitutes the first intermolecular catalytic approach to directly access N-alkylindolines with a broad substrate scope in the absence of any ligands. This method highlights the use of readily available amines and ureas as the required nitrogen sources in building up the indoline core.

Key words amines, N-alkylindolines, norbornene, palladacycle, urea

The synthesis of heterocycles using various methods has been of great interest in recent decades. Indolines are one of the heterocyclics that have undergone various synthetic methods in recent years.1 The main reason for focusing on the synthesis of structures containing indoline scaffold is the unique biological and pharmacological properties of these compounds.2 The structures with indoline skeletons are ubiquitously present in many naturally bioactive alkaloids, such as strychnine,3 (-)-physostigmine,4 and (+)-aspidospermidine5 (Figure 1). It is also a vital intermediate of the pentopril, a drug used for the treatment of hypertension (Figure 1).6 Recently, Du and co-workers have also isolated oleracein from the edible plant Portulaca oleracea used in Chinese traditional medicine (Figure 1).7 Given the importance of these structures, the synthesis of indoline derivatives has been a research topic of great interest to research chemists since the last decade.

One of the most important methods for the construction of indoline scaffolds is the intramolecular Buchwald–Hartwig amination reaction of amine-tethered aryl halides (Scheme 1a).8 Recently, Yu et al.9a pioneered an alternative auxiliary directed indoline synthesis through aryl C–H activation/intramolecular amination process, which was further improved by employing various N-chelating groups and oxidizing agents such as hypervalent iodonium salts (Scheme 1b).9 While these methods provide an attractive entry to these ring systems, they are mostly limited to intramolecular amination reactions and rely on the use of substrates that are preinstalled with amino groups. Furthermore, Kapur et al. communicated a palladium-catalyzed intramolecular amination of silyl enol ethers of β-aminoketones, which led to the formation of the 3-substituted indolines (Scheme 1c).10 However, the multi-step reaction and limitation of product diversity were some drawbacks of the report. Glorius et al. also developed a Rh(III)-catalyzed intramolecular α-arylation of silyl enol ethers of β-aminoketones, which led to the formation of the 3-substituted indolines (Scheme 1c).10 However, the multi-step reaction and limitation of product diversity were some drawbacks of the report. Glorius et al. also developed a Rh(III)-catalyzed directed C–H activation, followed by intramolecular addition of the Csp3–Rh species to the N=N bond to afford 1-aminoindolines using Boc-protected aryl diazenes and alkenes (Scheme 1d).11
In the last decade, the strategy of using norbornene for activation of C–H bonds has been used to synthesize different heterocycles. This technique benefits from the high reactivity of norbornene in the activation of the inactive ortho C–H bonds in aryl halides and palladacycle formation.

This strategy was devised by Catellani and further developed by other research groups.12 Recently the application of palladium/norbornene (Pd/NBE) chemistry for construction of indolines via amination of aryl-norbornene-palladacycle (ANP) intermediates employing three-membered strained N-containing heterocycles have become realistic (Scheme 2). The Shi group pioneered the construction of indolines via oxidative addition of the C,C-palladacycle to di-tert-butyldiaziridinone (Scheme 2a).13

Furthermore, Bi and Liang extended the scope of Pd/NBE chemistry employing sulfonated aziridines as electrophilic reagents for ortho-amination of iodoarenes and construction of N-tosylindolines (Scheme 2b).14

Despite the importance of these communications, the protocols showed a narrow substrate scope while the products were limited to N-tBu and N-Ts indolines, as well as cost issues linked to the use of strained three-membered N-heterocyclic rings. The last report in this context belongs to Dai and Hu who established a decarboxylative annulation of 2-haloaroyloxyacetamides with norbornene for the construction of indolines (Scheme 2c).15 This protocol encountered similar scope limitations on the N-substituent of indolines and required prefunctionalized starting materials. We also recently reported on a regioselective annulation reaction to provide N-arylindolines as a new outcome from the palladium-catalyzed reaction of iodoarenes, norbornene, and anilines.16 Despite significant achievements, however, aliphatic amines remained challenging and more difficult than aromatic amines for this catalytic system. Aliphatic ureas also did not participate in this cascade. Considering the high importance of indole scaffolds in pharmaceutics and remarkable effect of the nature of the N-substituent of N-heterocycles on their biological properties, it would be highly desirable to directly construct complicated indoline molecules from simple and readily available starting materials and more easily diversified nitrogen sources.

Herein we report an effective method for the synthesis of various polycyclic indolines via Pd/NBE chemistry employing three readily available and easily diversified building blocks including: iodoarenes, norbornene, and readily available nitrogen sources including aliphatic amines and ureas (Scheme 2d). This protocol has the potential for construction of indoline motifs easily diversified on both arene and nitrogen sides, which has not been accomplished yet. Setting the competing ipso-amination versus ortho-amination in the presence of nucleophilic amine sources is the key step for this transformation. This reaction would offer distinct advantages over existing methods, particularly with respect to functional group compatibility on both arene and nitrogen sides, accessible and economical nitrogen sources, and excluding any requisite for phosphine-donor ligands usually necessary in Pd-catalyzed reactions.

In a typical experiment, 2-iodotoluene (1a), propylamine (2a), and norbornene were reacted in the presence of Pd(OAc)2, PPh3, Cs2CO3 in MeCN at 110 °C for 20 hours. Under these conditions, polycyclic indoline 3a was fortunately collected in 21% yield (Table 1, entry 1). The reaction was optimized with respect to Pd sources where Pd(OAc)2 proved to be the most effective catalytic system (entries 1–3). Employing different bases, sodium bicarbonate exhibited the best performance in the annulation reaction (entries 4–7).
However, conducting the reaction in the presence of a stronger base such as NaOH led to a decrease in the yield (entry 6). Gratefully, the transformation proceeded well in the absence of any added ligands rarely achieved in similar methodologies (entry 8). Therefore, the optimization of reaction was continued without using any additional ligands. Next, the effect of different solvents on this transformation was investigated (entries 8–13). Screening of the solvents showed that chlorobenzene was the best choice of solvent and gave the desired product 3a in 69% isolated yield (entry 13). Increasing the amount of norbornene to 4 equivalents did not improve the reaction yield (entry 14). Finally, reducing temperature to 90 °C led to a yield bargain (entry 15).

<table>
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<th>Entry</th>
<th>Catalyst</th>
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<td>Cs₂CO₃</td>
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*Reaction conditions: 2-iodotoluene (1a; 0.1 mmol), norbornene (2 equiv), propylamine (2a; 2 equiv), catalyst (5 mol%), ligand (10 mol%), base (2 equiv), and solvent (1 mL) at 110 °C for 20 h.
* Norbornene: 4 equiv.
* Reaction temperature: 90 °C.

With the optimized condition in hand, the scope of the annulation reaction to construct various polycyclic indolines was examined. As summarized in Scheme 3, a wide range of substituted iodoarenes and amines were found to be compatible with this domino Heck reaction/double C–N bond formation.

First the reactivity of 2-iodotoluene with various alkyl amines was examined and yields were obtained between 57–88%. Fortunately, palladium-catalyzed annulation of iodoarenes and some bulkier amines such as isopropylamine and cyclohexylamine proceeded smoothly under the optimized reaction conditions to afford the desired products 3g and 3i in 81% and 57% isolated yield, respectively. According to the biological importance of N-cyclohexyindoline derivatives, the synthesis of these compounds has received great attention. Intriguingly, even iodoarene containing susceptible halo groups could be well tolerated under the reaction conditions to provide the desired product 3l in promising 89% isolated yield with preserved chloro groups. This adduct can serve as a good precursor for further functionalizations through metal-catalyzed cross-coupling reactions. In addition, the ortho-trifluoromethyl-substituted iodoarene, which due to its lower reactivity is relatively rarely used in palladium-catalyzed coupling reactions, was compatible with the current reaction conditions affording the desired polycyclic indoline 3m in 61% isolated yield. Notably, yields of 58% and 71% were still obtained for compounds 3a and 3c, respectively, when the reactions were scaled up to 4.0 mmol. Unfortunately, nitro-substituted iodoarene did not participate in this transformation.

Scheme 3 Reaction scope for construction of indolines
Gratefully, when expanding the scope of amines to their amide derivatives, we found that ureas could also serve as the nitrogen sources of indolines through C–N bond cleavage. Once aliphatic amines were replaced with 1,3-bis(alkyl)ureas, the annihilation reactions proceeded well under the same optimized reaction conditions to afford the polycyclic indolines in comparable yields (Scheme 4).

Remarkably, when an asymmetric N-alkyl,N-arylurea was picked as a coupling partner in this transformation, a high regioselectivity was observed in the conversion. It is interesting to note that in this catalytic system, selectivity favored N-alkylation versus N-arylation of C–H bonds for construction of N-alkylindoline 3a in 59% yield and phenyl isocyanate was removed from the reaction pot as the byproduct (Scheme 5).

A mechanistic rationale is summarized in Scheme 6. In the catalytic cycle, when amine is used as the coupling partner, the oxidative addition of aryl halide to Pd(0), followed by a carbbadaladation reaction with NBE and subsequent intramolecular C–H activation, results in the C,C-palladacycle intermediate 5. Next a transmetalation between two Pd(II) centers, palladacycle 5 and Pd(II) coordinated to the nitrogen sources of indolines through C–N bond cleavage. The oxidative addition of aryl halide to Pd(0), followed by a carbopalladation reaction with NBE and subsequent intramolecular C–H activation, results in the C,C-palladacycle intermediate 5. Next a transmetalation between two Pd(II) centers, palladacycle 5 and Pd(II) coordinated to the nitrogen sources of indolines through C–N bond cleavage. This approach provides a general platform to introduce various N-alkyl groups to the arene ortho-position and to provide various N-alkyl-substituted indolines. The reaction features broad substrate scope and proceeds smoothly without additional phosphine-donor ligands usually as a prerequisite in palladium-catalyzed reactions. Employing unsymmetrical N-alkyl,N-arylurea, a high regioselectivity via ortho N-alkylation versus N-arylation of iodoarene was perceived.

All reagents were commercially available and used as received. Column chromatography was carried out on silica gel (230–400 mesh). 1H NMR spectra were recorded at r.t. on a Bruker 500 MHz spectrometer using DMSO-d_6 and CDCl_3 as solvent. Chemical shifts are reported in ppm with TMS as an internal standard. 13C NMR spectra are referenced from the solvent central peak. Chemical shifts are given in ppm. Elemental analyses (CHN) were recorded on a Thermo Finnigan Flash EA 1112 elemental analyzer.

5-Methyl-9-propyl-2,3,4,4a,9a-hexahydro-1H-1,4-methanocarbazole (3a); Typical Procedure

A vial equipped with a stir bar was charged with 2-iodotoluene (1a; 21.8 mg, 0.10 mmol), propylamine (2a; 11.8 mg, 0.2 mmol, 2 equiv), Pd(OAc)_2 (1.1 mg, 5 mol%), norbornene (18.8 mg, 0.2 mmol, 2 equiv), NaHCO_3 (21.8 mg, 0.10 mmol), propylamine (2a; 11.8 mg, 0.2 mmol, 2 equiv), Pd(OAc)_2 (1.1 mg, 5 mol%), norbornene (18.8 mg, 0.2 mmol, 2 equiv), NaHCO_3 (21.8 mg, 0.10 mmol, 2 equiv), norbornene (18.8 mg, 0.2 mmol, 2 equiv).
NaHCO₃ (16.8 mg, 0.2 mmol, 2 equiv), and chlorobenzene (1 mL) was added, and the vial was capped. The resulting mixture was heated in a sand bath at 110 °C for 20 h, then filtered through a short plug of silica gel. Removal of the solvent gave a crude mixture, which was purified by column chromatography (hexane/EtOAc gradient) to give indoline 3a; yield: 17 mg (69%); yellow oil.

EI-MS:

m/z (%): 303 (M⁺, 100), 235 (57), 198 (41).


5-Methyl-9-propyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3b)

Yield: 22 mg (76%); pale oil.

EI-MS:

5-Methyl-9-phenyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3c)

Yield: 21 mg (68%); brown oil.

EI-MS:
m/z (%): 303 (M⁺, 100), 235 (57), 198 (41). Anal. Calcd for C₁₈H₂₅N: C, 84.65; H, 9.87; N, 5.48. Found: C, 85.02; H, 9.74; N, 5.71.

5-Methyl-9-phenethyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3e)

Yield: 25 mg (88%); yellow oil.

EI-MS:
m/z (%): 303 (M⁺, 100), 235 (57), 198 (41). Anal. Calcd for C₁₉H₂₇N: C, 84.75; H, 10.31; N, 4.94. Found: C, 85.06; H, 10.43; N, 4.43.

5-Isopropyl-9-methyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3f)

Yield: 20 mg (81%); pale oil.

EI-MS:
m/z (%): 291 (M⁺, 100), 223 (51), 198 (30). Anal. Calcd for C₁₉H₂₇N: C, 84.75; H, 10.31; N, 4.94. Found: C, 85.06; H, 10.43; N, 4.43.

5-Isobutyl-9-methyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3g)

Yield: 25 mg (88%); yellow oil.

EI-MS:
m/z (%): 303 (M⁺, 100), 235 (57), 198 (41). Anal. Calcd for C₁₉H₂₇N: C, 84.75; H, 10.31; N, 4.94. Found: C, 85.06; H, 10.43; N, 4.43.

5-Methyl-9-phenethyl-2,3,4a,9a-hexahydro-1H-1,4-methano-carbazole (3e)

Yield: 21 mg (68%); brown oil.

EI-MS:
m/z (%): 303 (M⁺, 100), 235 (57), 198 (41). Anal. Calcd for C₁₉H₂₇N: C, 84.75; H, 10.31; N, 4.94. Found: C, 85.06; H, 10.43; N, 4.43.

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9-Cyclohexyl-5-methyl-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazole (3i) yield: 16 mg (57%); pale oil.

EI-MS: m/z (%) = 343 (M•+, 100), 285 (72), 269 (34).

1H NMR (500 MHz, CDCl3): δ = 1.01–1.09 (m, 3 H), 1.13–1.20 (m, 2 H), 1.27 (t, J = 7.3 Hz, 3 H), 1.31–1.34 (m, 1 H), 1.36–1.40 (m, 2 H), 1.53–1.58 (m, 6 H), 2.33–2.42 (m, 2 H), 2.55–2.65 (m, 2 H), 3.11–3.18 (m, 2 H), 3.67 (d, J = 8.3 Hz, 1 H), 6.13 (d, J = 7.7 Hz, 1 H), 6.35 (d, J = 7.5 Hz, 1 H), 6.91 (t, J = 7.6 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 14.1, 14.7, 20.5, 24.9, 25.1, 29.1, 30.0, 32.6, 41.4, 41.9, 47.2, 49.9, 71.8, 102.0, 115.2, 127.9, 128.9, 140.0, 153.5.

EI-MS: m/z (%) = 269 (M•+, 100), 201 (55), 212 (34).


9-Isobutyl-5-(trifluoromethyl)-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazole (3m) yield: 19 mg (61%); pale oil.

1H NMR (500 MHz, CDCl3): δ = 0.93 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.28 (s, 3 H), 1.55–1.60 (m, 2 H), 1.97–2.0 (m, 1 H), 2.39–2.44 (m, 1 H), 2.51 (s, 1 H), 2.89–2.99 (m, 3 H), 3.44 (d, J = 8.8 Hz, 1 H), 3.69 (d, J = 8.3 Hz, 1 H), 6.34 (d, J = 8 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 7.05 (t, J = 7.9 Hz, 1 H).

13C NMR (125 MHz, CDCl3): δ = 18.3, 24.9, 28.9, 32.5, 41.0, 41.5, 47.1, 50.3, 58.9, 70.7, 72.3, 102.0, 117.7, 127.7, 129.5, 133.9, 153.1.

EI-MS: m/z (%) = 309 (M•+, 100), 241 (59), 252 (33), 240 (14).


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Supporting Information
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References


