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Synthesis of C3,C4-Disubstituted Indoles via the Palladium/Norbornene-Catalyzed *ortho*-Amination/*ipso*-Heck Cyclization

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Cite This: *Org. Lett.* 2021, 23, 3755−3760 Read Online

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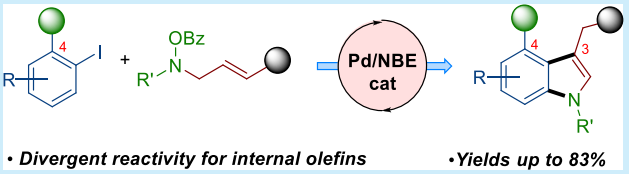
ABSTRACT: Herein, we report the synthesis of C3,C4-disubstituted indoles via the palladium/norbornene cooperative catalysis. Utilizing *N*-benzoyloxy allylamines as the coupling partner, a cascade process involving *ortho*-amination and *ipso*-Heck cyclization takes place with *ortho*-substituted aryl iodides to afford diverse indole products. The reaction exhibits good functional group tolerance, in addition to tolerating a removable protecting group on the indole nitrogen. Divergent reactivity has been observed using the allylamine coupling partner containing more substituted olefins. Construction of the core framework of mitomycin has also been attempted with this strategy.



Indole and its closely related heterocycles are highly prevalent in natural products and drug molecules (Figure 1).[1] Consequently, they have been attractive scaffolds for

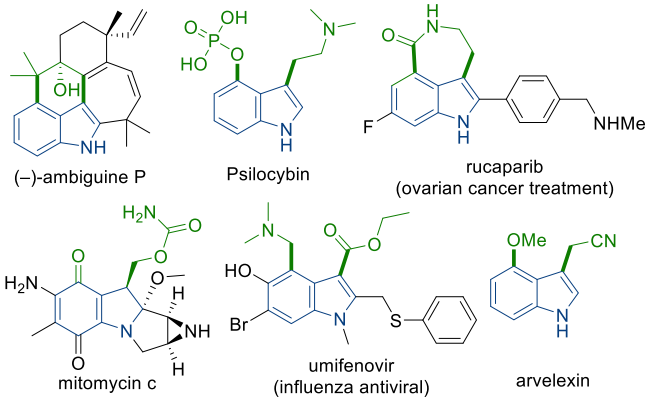


Figure 1. Indoles and their derivatives in natural products and pharmaceuticals

preparation and derivation.[1] While numerous effective indole synthesis methods have been developed to date, it remains nontrivial to prepare C3,C4-disubstituted indoles in a modular manner.[2] On the other hand, the palladium/norbornene cooperative catalysis, first reported by Catellani,[3] represents an emerging useful tool for modular synthesis of polysubstituted arenes.[4] In this transformation, an electrophile and a nucleophile are coupled at the arene *ortho* and *ipso* positions, respectively (Scheme 1a). Seminal work by Lautens in 2010 described a novel preparation of C2,C7-disubstituted indoles through an *ortho*-alkylation/*ipso*-amination cascade of aryl iodides with highly strained 2H-azirines (Scheme 1b).[5] In 2018, the Liang group devised an elegant approach to synthesize indolines using widely available aziridines as the reagent.[6] The development of coupling with *N*-benzoyloxy amines as electrophiles in 2013 allows convenient installation of various amine moieties at the arene *ortho* position via the Pd/NBE catalysis.[7] Recently, the Liang group disclosed an *ortho*-amination of 2-iodoanilines followed by *ipso*-cyclization with norbornadiene and then a retro-Diels−Alder reaction to access 4-aminoindoles.[8] More recently, an *ortho*-amination followed by demethylative annulation with internal alkynes was reported for indole synthesis with moderate efficiency (Scheme 1c).[9]

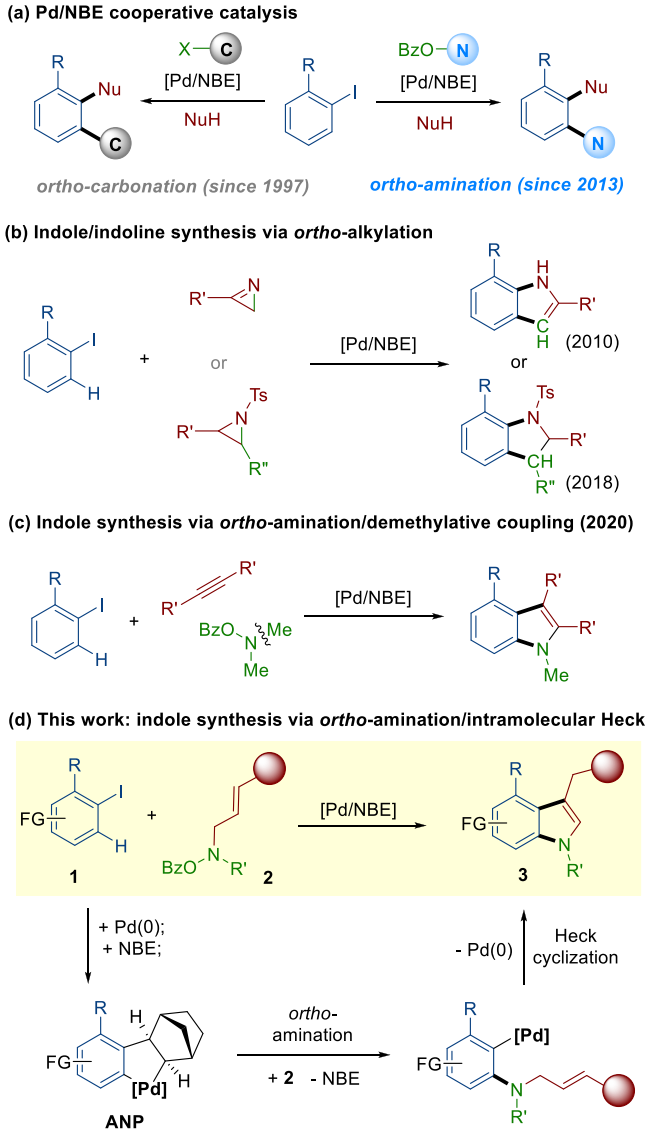
In this communication, we describe a convenient method for preparing C3,C4-disubstituted indoles via an *ortho*-amination/Heck cyclization cascade[10] between common 2-substituted aryl iodides and readily available *N*-benzoyloxy allylamines (Scheme 1d). It can be envisioned that, upon forming the key aryl-norbornyl-palladacycle (ANP), the reaction with the electrophile should install an allylamine moiety at the *ortho* position of the arene. Upon NBE extrusion, an *ipso*-Heck is expected to take place; the resulting exocyclic alkene then isomerizes to the more stable internal position to deliver the indole product.[11]

The investigation started with 2-iodoanisole (**1a**) and an *N*-methyl-allylamine derived coupling partner (**2a**) as the model substrates (Table 1). After careful evaluation of various reaction parameters, the desired indole product (**3aa**) was ultimately formed in 71% yield using $Pd(OAc)_2$ and tri(4-methoxyphenyl)phosphine as the optimal metal/ligand combi-

Received: April 4, 2021
Published: April 26, 2021

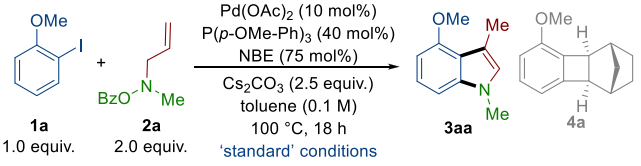
https://doi.org/10.1021/acs.orglett.1c01165
Org. Lett. 2021, 23, 3755−3760

Scheme 1. Indole Synthesis via the Pd/NBE Catalysis



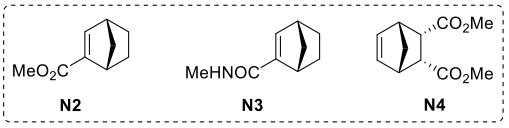
nation with Cs_2CO_3 as the base (Table 1, entry 1). A 1:4 ratio between Pd and the phosphine was found to be necessary to promote reproducibility of the reaction (Table 1, entries **2** and **3**), though the exact reason is unclear (vide infra). Other monodentate phosphine ligands that are less electron-rich than tri(4-methoxyphenyl)phosphine or bidentate phosphine ligands proved to less efficient and generated more four-membered side-product **4a** (Table 1, entries **4**–**6** and Supporting Information, Schemes S1 and S2). It is likely that tri(4-methoxyphenyl)phosphine can significantly suppress undesired off-cycle reactivity observed when using the less electron-rich triarylphosphine ligands. Use of a 5,6-disubstituted norbornene (**N4**) was found to deliver similar results as simple NBE (entry **9**).[12] Other structurally modified NBEs,[13] such as C2-ester-[14] and amide-substituted[15] NBEs, showed much lower reactivity, likely due to their steric hindrance when reacting with bulky electrophile **2a** (entries **7** and **8**). Reducing the NBE loading to 50 mol % only gave slightly lower yield and selectivity (entry **10**). Toluene was found to be the best solvent, which is also consistent with our prior observation with *ortho*-amination.[7a] Increasing the polarity of the solvent by using a mixture of 1,4-dioxane and toluene or 1,4-dioxane

Table 1. Selected Optimization of the Reaction Conditions[a]



entry	change from the "standard" condition	yield of **3aa** (%)[b]	yield of **4a** (%)[b]
1	none	71 (67)[c]	7
2	25 mol% ligand	51	14
3	30 mol% ligand	65	12
4	PPh_3 as the ligand	64	15
5	P(*p*-CF_3-Ph)$_3$ as the ligand	56	13
6	P(2-furyl)$_3$ as the ligand	38	22
7	**N2** instead of NBE	17	–
8	**N3** instead of NBE	n.d.	–
9	**N4** instead of NBE	67	–
10	50 mol% NBE	69	9
11	1:1 1,4-dioxane/toluene as solvent	62	15
12	1,4-dioxane as solvent	52	19

[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol) and **2a** (0.2 mmol), in 1.0 mL of toluene for 18 h. [b]NMR yields determined using 1,1,2,2-tetrachloroethane as the internal standard; n.d. = not detected; – = not determined. [c]Isolated yield on a 0.2 mmol scale.



alone resulted in reduced yield and more side-product formation (entries **11** and **12**).

Meanwhile, the kinetic profile of the reaction was measured (Figure 2). First, the reaction did not show any induction

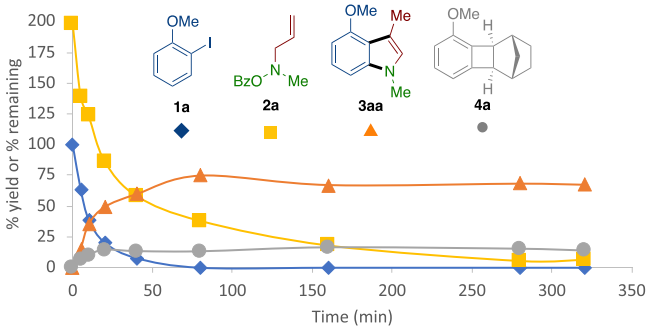


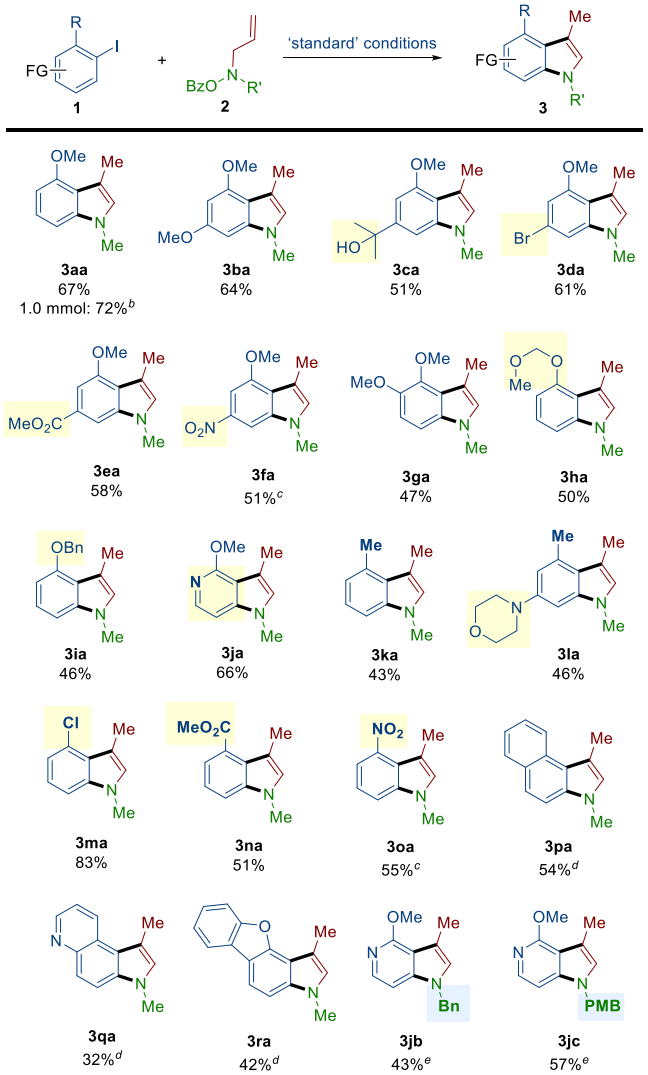
Figure 2. Kinetic profile of the reaction. NBE (1 equiv) was used.

period, which likely benefited from the excess phosphine ligand to enable rapid reduction of Pd(II) to Pd(0). The side-product **4a** was formed from the beginning of the reaction, alongside the desired product **3aa**, which suggests competing pathways with the ANP intermediate: oxidative addition with *N*-benzoyloxy amine **2a** versus direct reductive elimination to give **4a**. The reaction was nearly completed within 1 h, indicating a rapid reaction rate. Afterward, the coupling partner **2a** slowly decomposed, possibly due to the basic reaction condition and elevated reaction temperature.

With these results in hand, we sought to explore the scope of the indole-forming reaction (Scheme 2). First, the isolated

https://doi.org/10.1021/acs.orglett.1c01165
Org. Lett. 2021, 23, 3755–3760

Scheme 2. Substrate Scope of the *ortho*-Amination/Heck Cyclization Cascade[a]

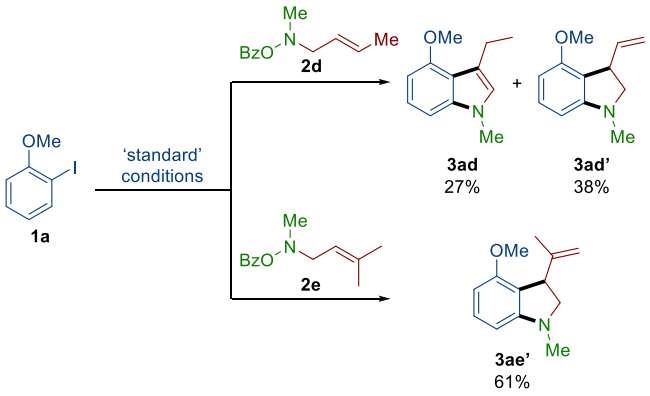


[a]Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol) and **2** (0.4 mmol) in 2.0 mL of toluene for 18 h; all yields are isolated yields. [b]Carried out with $Pd(TFA)_2$ instead of $Pd(OAc)_2$, **1a** (1.0 mmol), and **2a** (2.0 mmol) in toluene (10.0 mL). [c]Carried out with 40 mol % of P(*p*-OMe-Ph)$_3$ as the ligand. [d]Carried out with **2a-2** (see the Supporting Information) instead of **2a** and with PPh_3 as the ligand at 120 °C. [e]Run at 80 °C.

yield of the model product **3aa** can reach 72% on the larger 1.0 mmol scale.[16] In addition, a diverse range of functional groups, such as methyl (**3ba**) and benzyl ethers (**3ia**), an unprotected tertiary alcohol (**3ca**), ester (**3ea**), bromide (**3da**), chloride (**3ma**), nitro (**3fa** and **3oa**), acetal (**3ha**), and tertiary amine (**3la**), were tolerated under the reaction conditions, affording various C3,C4-disubstituted indoles. Both electron-rich and -deficient substituents are compatible for this transformation. Notably, the yields for the highly electron-poor nitro-substituted aryl iodides (**3fa** and **3oa**) can be increased by changing the phosphine ligand to the electron-deficient *tris*-(4-trifluoromethylphenyl)phosphine (see Supporting Information for more details). Up to 83% yield can be obtained for the 4-chloroindole product (**3ma**). A clear trend can be observed: the yield of the indole product typically decreases if the *ortho*-substituent is larger in size, indicating that the reaction is sensitive to the steric environment of the Heck cyclization and subsequent aromatization. Moreover, a number of heteroarene-derived iodides were competent substrates, including pyridines (**3ja−c**), quinoline (**3qa**), and benzofuran (**3ra**). Besides forming *N*-methyl indoles, by decreasing the reaction temperature to 80 °C, C3,C4-disubstituted indoles with removable protecting groups on the nitrogen, i.e., −Bn[17] (**3jb**) and −PMB[18] (**3jc**), can be constructed with this method.

Apart from simple allylamine electrophiles, we questioned whether *N*-benzoyloxy amines with a more substituted internal olefin would react in the same manner. Consequently, the coupling reagents containing a 1,2-disubstituted alkene (**2d**) and a trisubstituted alkene (**2e**) were prepared. Interestingly, **2d** provided a separable mixture of the desired indole product (**3ad**) and an indoline isomer (**3ad′**), resulting in a combined yield of 65% (Scheme 3). In contrast, sole indoline product (**3ae′**) was isolated in good yield when using the amine coupling partner with a trisubstituted olefin (**2e**).

Scheme 3. Aminating Reagents with Internal Olefins[a]



[a]All reactions were carried out with **1a** (0.2 mmol) and **2** (0.4 mmol) in 2.0 mL of toluene for 18 h; all yields are isolated yields.

The divergent reactivity with substituted allylamines provides useful insights into the reaction mechanism and selectivity, particularly regarding the *ipso*-Heck cyclization (Scheme 4). During the Heck coupling, the terminal monosubstituted alkene moiety undergoes kinetically favorable *5-exo-trig* cyclization, followed by *β*-hydrogen elimination, to give an exocyclic alkene intermediate, which leads to the desired indole products. When a 1,2-disubstiuted alkene is used, the moderate steric hindrance allows the *β*-hydrogen elimination to occur at either direction (*inward* and *outward*), resulting in a mixture of indole and indoline products. In contrast, in the case of the trisubstituted alkene, the inward elimination would be largely inhibited due to the strong steric repulsion between the *ortho*-substituent (i.e., −OMe) and the nearly coplanar alkene substituent (i.e., −Me). Therefore, high selectivity toward the indoline formation through a less bulky outward elimination is observed with the trisubstituted alkene.

Finally, to explore the potential synthetic application of this method, construction of the core carbon skeleton of the mitomycin family of natural products has been explored (Scheme 5).[19] Utilizing a more complex 2-vinylpyrrolidine derived coupling partner (**2f**), the desired *ortho*-amination/*ipso*-Heck cyclization can indeed take place under the standard condition. On the basis of the crude NMR analysis, the indoline product with an exocyclic olefin was formed in 31%

https://doi.org/10.1021/acs.orglett.1c01165
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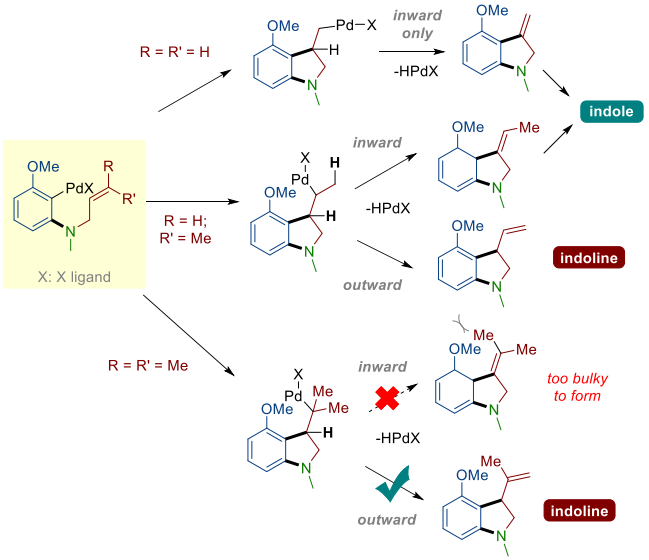
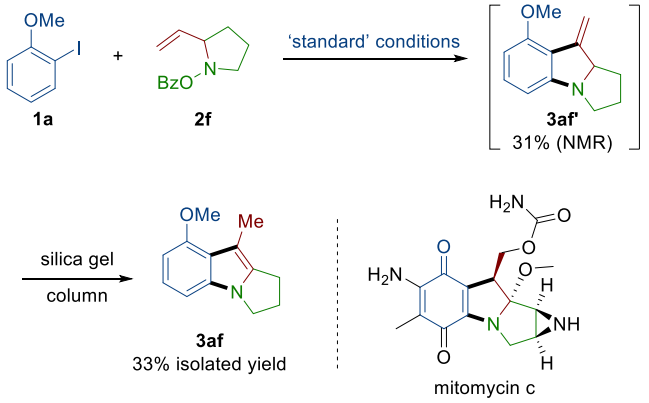
Scheme 4. Divergent Reaction Pathways for Substituted Alkene Coupling Partners



Scheme 5. Attempt to Access the Skeleton of Mitomycin[a]



[a]Conducted with **1a** (0.1 mmol) and **2f** (0.15 mmol) in 1.0 mL of toluene for 18 h.

yield. Unsurprisingly, during the chromatography purification on silica gel, the alkene was fully isomerized to deliver the more stable tricyclic indole product (**3af**). Efforts on systematically optimizing this transformation, trapping the indoline intermediate, and ultimately applying this method to mitomycin synthesis are ongoing.

In summary, an *ortho*-amination, *ipso*-Heck cyclization cascade of aryl iodides for the synthesis of C3,C4-disubstituted indoles has been developed. The reaction appears to be general for a diverse range of aryl iodides, typically with smaller *ortho* substituents delivering the desired indole products in greater yields than larger substituents. A broad range of functional groups and heterocycles can be tolerated. Additionally, a steric effect has been found to be responsible for the divergent reactivity with more substituted alkene-derived coupling partners. Currently, expansion of this platform toward synthesis of other pharmaceutically relevant heterocycles is underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01165.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the University of Chicago and NIGMS (1R01GM124414-01A1) are acknowledged. Dr. Xin Liu (the University of Chicago) is acknowledged for checking the experimental procedures. Mr. Marcelo de la Mora (the University of Chicago) is acknowledged for the preparation of some starting materials.

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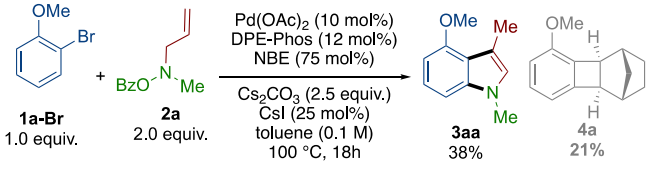
(16) Substituting aryl iodides with aryl bromides proved to be a more challenging transformation. Our preliminary result showed that the desired product **3aa** can be obtained in 38% yield (NMR) with 21% yield of **4a** under the modified reaction conditions.



(17) For one-step indole N−Bn deprotection, see: Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. An efficient method for the *N*-debenzylation of aromatic heterocycles. *Tetrahedron Lett.* **2002**, *43*, 399−402.
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