ChemEurJ

Research Article
doi.org/10.1002/chem.202502660

Chemistry Europe
European Chemical Societies Publishing

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# Palladium-Catalyzed Hydroamination of Vinyl Ethers with Indoles: Efficient Access to *N,O*-Aminal Indoles

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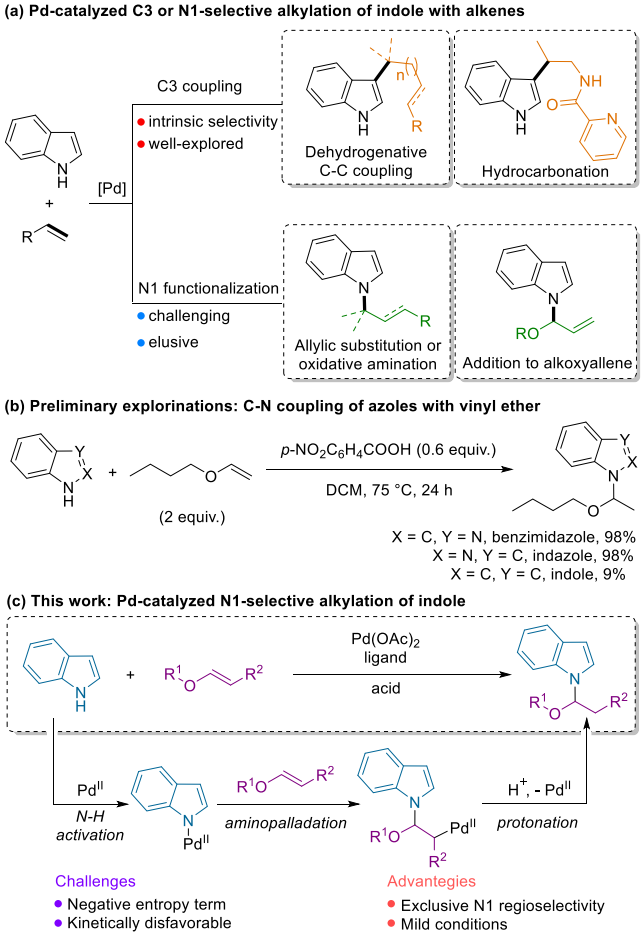
Indole alkaloids represent a privileged class of natural products with significant potential in drug discovery. Herein, an efficient palladium-catalyzed *N*-alkylation of indoles with vinyl ethers has been developed. This atom-economic hydroamination demonstrates good functional group tolerance and broad substrate scope across diverse indole alkaloids, providing straightforward access to valuable *N,O*-aminal indole derivatives. This reaction features mild reaction conditions, complete N1-regioselectivity, operational simplicity, and straightforward product transformation.

## 1. Introduction

Indoles are ubiquitous functionalities in pharmaceuticals, natural products, and organic materials.[1–5] Their significance in both biological systems and industrial fine chemicals has sparked significant research efforts to develop efficient derivatization methodologies.[6–9] In this field, C-N coupling methods have rapidly become a streamlined protocol for the synthesis of *N*-functionalized indoles in recent years.[10–12] Although increasing efforts have been devoted to accommodating diverse indole classes, it remains challenging to achieve N1-regioselective functionalization under palladium catalysis. This difficulty arises from the competing reactivity at both the N1 and C3 positions of the indole substrate, with the latter typically favored due to its inherently higher nucleophilicity.[13–15] Consequently, only a limited number of strategies have been developed to harness the bottleneck *N*-functionalization of indoles, such as oxidative amination,[16–18] allylic amination,[19–21] and addition of allene[22,23] (Scheme 1A). Despite these direct N1-functionalization methodologies above, a general hydroamination cross-coupling between "unbiased" indole and vinyl ether has yet to be reported.[24,25]

To gain insight into the hydroamination between azoles and vinyl ethers, several preliminary investigations were conducted (Scheme 1B). It is revealed that certain azoles, including benzimidazole and indazole, underwent efficient alkylation under acidic conditions with near-quantitative yields.[26–28] In contrast, indole afforded only a marginal yield (9%), highlighting the necessity of employing a suitable catalytic system to facilitate the coupling between indole substrates and vinyl ether electrophiles. This addition reaction exhibits high atom economy and is




**Scheme 1.** (a) Pd-catalyzed approaches for the C3- or N1-alkylated indoles. (b) Preliminary explorations: C-N coupling between azoles and vinyl ether. (c) Pd-catalyzed *N*-alkylation of indole with vinyl ether to access *N,O*-aminal indole.

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*Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202502660*

thermodynamically feasible.[29] Nevertheless, it is kinetically disfavored because both indole and alkene substrates are considered to be electron-rich substrates.[30,31] Moreover, the entropy term of intermolecular hydroamination is highly negative.[32–34]

Through our continuing interest and efforts to develop efficient and selective amination reactions,[35,36] we herein report an efficient palladium-catalyzed hydroamination of indoles with vinyl ethers for the synthesis of *N,O*-aminal indole under mild conditions (Scheme 1C). We envisioned that after the aminopalladation step,[37,38] protonation process[39,40] would take precedence over $\beta$-H elimination of the resulting Pd-alkyl intermediate, thereby affording *N*-alkylated indoles rather than the classic oxidative amination product. Furthermore, the classic efforts to directly construct the *N,O*-aminal indole framework typically require multi-step synthetic sequences[41] or strict reaction conditions,[42–45] such as strong base conditions and elevated reaction temperatures. Our method, hence, offers a catalytic system featuring mild and redox-neutral conditions, moderate reaction temperature, and available substrates.[46,47]

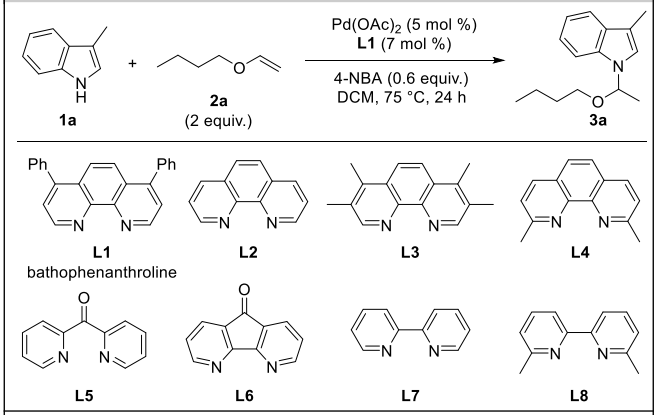
## 2. Results and Discussion

We began our study by evaluating the reactivity of 3-methyl indole (**1a**) with butyl vinyl ether (**2a**) as model coupling partners (Table 1; see Table S1 for more details). After optimization of the reaction parameters, a combination of $Pd(OAc)_2$ (5 mol %), 4,7-diphenyl-1,10-phenanthroline **L1** (7 mol %), *p*-nitrobenzoic acid (4-NBA, 0.6 equiv.) in DCM at 75 °C for 24 hours afforded the best results, delivering **3a** in 86% NMR yield with 83% isolated yield. Ligand screening demonstrated the superiority of **L1**, as alternative phenanthroline derivatives (**L2**-**L8**) afforded substantially lower yields (entries 2–8). In stark contrast, **3a** could not be obtained in the presence of HCl (entry 9). And the addition of acetic acid led to a 41% yield (entry 10). For the benzoic acid additive, the electronic nature influenced reactivity.

For example, 2-$NO_2C_6H_4COOH$ (2-NBA), 4-$CNC_6H_4COOH$ (4-CN-BA), *p*-$ClC_6H_4COOH$ (4-Cl-BA), and 4-$MeOC_6H_4COOH$ (4-MeO-BA) all proved less effective than 4-NBA (entries 11–14). Brief examinations of the amount of the acid indicated that 0.6 equiv. 4-NBA was optimal (entries 15 and 16). Reducing the amount of vinyl ether or increasing the palladium catalyst and ligand loading caused decreased yields (entries 17–19). In the absence of $Pd(OAc)_2$, the reaction proceeded only in marginal yield (9%), highlighting the critical importance of the palladium catalysis (entry 20). Interestingly, aerobic conditions outperformed reactions conducted under $N_2$ atmosphere (entry 21), likely due to facilitated reoxidation of Pd(0) to the catalytically active Pd(II) species during the hydroamination process.[18,36,48,49] A lower temperature led to a significant decrease in yield (entry 22).

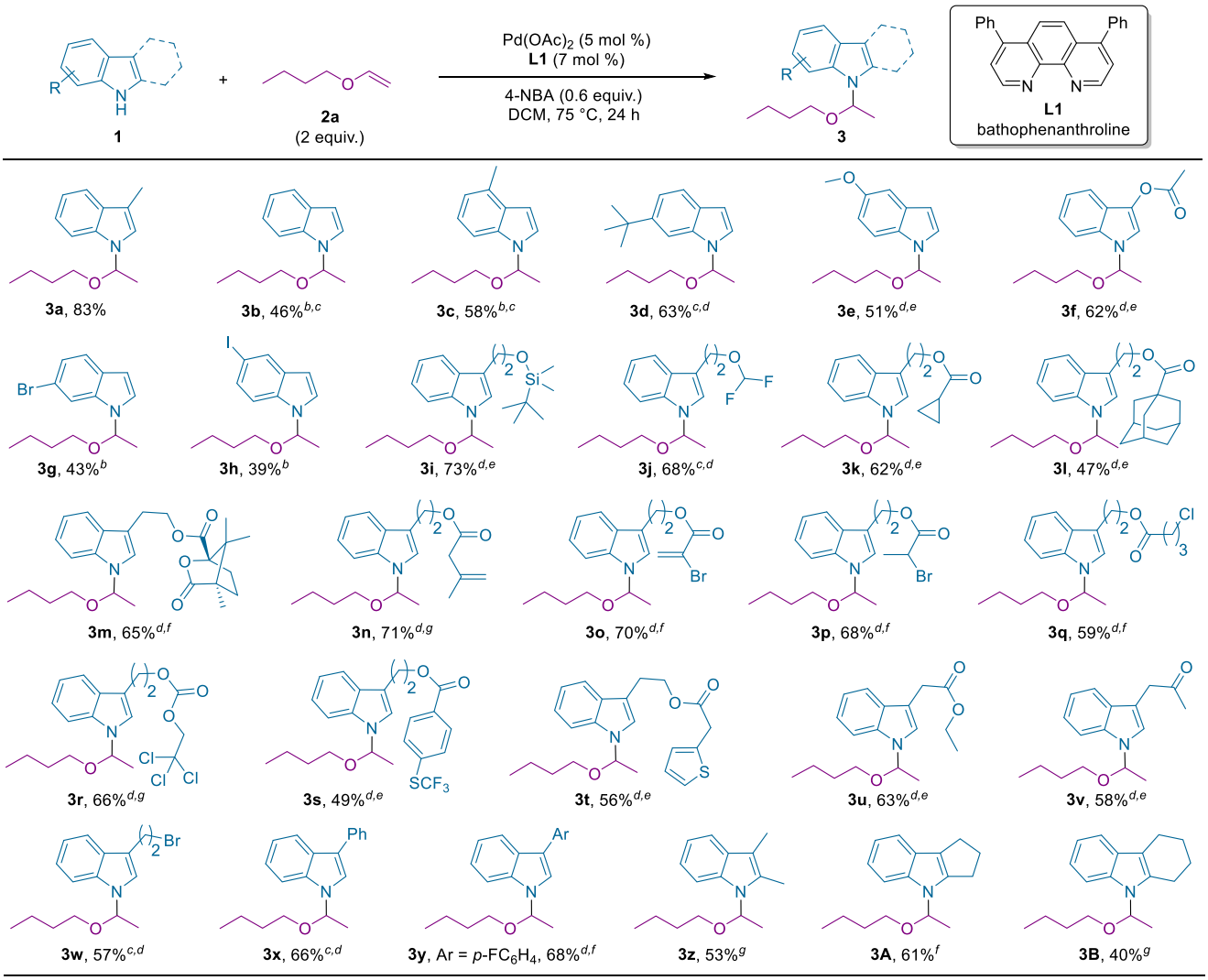
We subsequently investigated the versatility of the indole N-H activation method in alkylation by utilizing the modified reaction conditions (Scheme 2). Pleasingly, the successful N1-selective alkylation of C2- and C3-unsubstituted indoles was achieved, affording products **3b**-**3h** in moderate yields. Furthermore, the introduction of electron-donating substituents (methoxy and acetoxy functionalities, **3e** and **3f**) and moderately electron-withdrawing halogens (bromo and iodo substituents, **3j** and **3h**) at different positions on the indole ring allowed generation of the desired products in moderate yields. The electron-withdrawing nature of the halogen reduces the nucleophilicity of the indole ring, leading to a moderate decrease in reaction yields. And in the absence of a substituent at the C3 position, the indole ring might undergo partial oxidative decomposition under standard reaction conditions. Additionally, the nucleophilicity of the C3 site leads to undesired side reactions, resulting in reduced reaction yields.

**Table 1.** Optimization of the reaction conditions.[a]




| Entry | Deviation from standard conditions | Yield (%) |
|---|---|---|
| **1** | **none** | **86(83)** |
| 2 | **L2** instead of **L1** | 53 |
| 3 | **L3** instead of **L1** | 60 |
| 4 | **L4** instead of **L1** | 38 |
| 5 | **L5** instead of **L1** | 50 |
| 6 | **L6** instead of **L1** | 63 |
| 7 | **L7** instead of **L1** | 55 |
| 8 | **L8** instead of **L1** | 40 |
| 9 | HCl as additive | trace |
| 10 | AcOH as additive | 41 |
| 11 | 2-NBA as additive | 64 |
| 12 | 4-CN-BA as additive | 81 |
| 13 | 4-Cl-BA as additive | 78 |
| 14 | 4-MeO-BA as additive | 40 |
| 15 | 0.5 equiv. 4-NBA | 82 |
| 16 | 0.8 equiv. 4-NBA | 51 |
| 17 | 1.5 equiv. butyl vinyl ether | 52 |
| 18 | 1.8 equiv. butyl vinyl ether | 79 |
| 19 | 7 mol % $Pd(OAc)_2$ & 9 mol % **L1** | 70 |
| 20 | Without $Pd(OAc)_2$ | 9 |
| 21 | Under $N_2$ atmosphere | 73 |
| 22 | 65 °C | 48 |

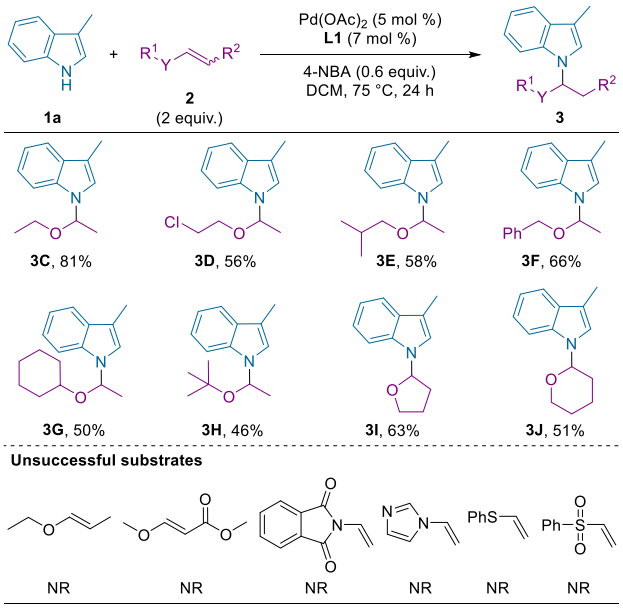
[a] Yields were determined by $^1H$ NMR with $CH_3NO_2$ as an internal standard based on **1a**. Value in parentheses is isolated yield. 2-NBA, 2-$NO_2C_6H_4COOH$. 4-CN-BA, 4-$CNC_6H_4COOH$. 4-Cl-BA, *p*-$ClC_6H_4COOH$. 4-MeO-BA, 4-$MeOC_6H_4COOH$. 4-NBA, 4-$NO_2C_6H_4COOH$.




**Scheme 2.** [a] Reaction conditions: **1** (0.2 mmol), **2a** (2 equiv.), $Pd(OAc)_2$ (5 mol %), **L1** (7 mol %), 4-NBA (0.6 equiv.), DCM (1 mL), 75 °C, 24 h. [b] $Pd(OAc)_2$ (3 mol %), **L1** (4 mol %), 4-NBA (0.5 equiv.). [c] 27 h. [d] $Pd(OAc)_2$ (3 mol %), **L1** (4 mol %), 4-NBA (0.8 equiv.). [e] 30 h. [f] 40 h. [g] 48 h.

Given the prevalence of tryptophol as a privileged structural motif in natural products and pharmaceuticals, we next examined its derivatives as substrates. As expected, tryptophol-derived compounds **1i** and **1j**, modified with a silyl ether and a difluoromethoxy group (prepared via etherification of tryptophol with silyl chloride and $TMSCF_2Br$, respectively), proved to be effective starting materials for the *N*-alkylation, giving rise to the corresponding *N*,*O*-aminal indole in 68–73% yields. Further studies revealed the successful incorporation of protected tryptophol derivatives **3k**-**3t** bearing diverse functional groups, including cyclopropyl, adamantyl, camphenyl, alkenyl, bromo, chloro, trichloro, trifluoromethanethiyl, and thiophenyl moieties, highlighting the robustness of the strategy for derivatizing bioactive molecules. Additionally, the protocol was also compatible with various C3-substituted indole alkaloids, accommodating substituents such as acetate (**3u**), ketone (**3v**), bromoethyl (**3w**), phenyl (**3x**), and fluorophenyl (**3y**). The reaction demonstrated good steric tolerance at the C2 position, proceeding smoothly with 2,3-dimethylindole, 1,2,3,4-tetrahydrocyclopenta[*b*]indole, and 2,3,4,9-tetrahydrocarbazole, albeit with reduced yields (**3z**-**3B**).

Next, we turned our attention to assessing the generality of the hydroamination of vinyl ethers (Scheme 3). Under the standard reaction conditions, ethoxyethene and (2-chloroethoxy)ethene underwent efficient coupling with the indole substrate, yielding products **3C** (81%) and **3D** (56%), respectively. However, steric hindrance influenced reactivity, as manifested by diminished yields in the case of isobutyl- (**3E**), benzyl- (**3F**), cyclohexyl- (**3G**), and *tert*-butyl-substituted (**3H**) vinyl ethers, likely due to reduced binding affinity to the Pd catalyst. Notably, the reaction remained effective with internal olefins as coupling partners (**3I** and **J**). Additionally, when the linear and internal olefin, such as (*E*)-1-ethoxyprop-1-ene or methyl (*E*)-3-methoxyacrylate, was employed, only trace amounts of the target product could be detected by GC-MS, with the majority of the indole substrate remaining unreacted. These results are mainly attributed to the steric hindrance of alkene substrates. When the bulky internal vinyl ethers were employed



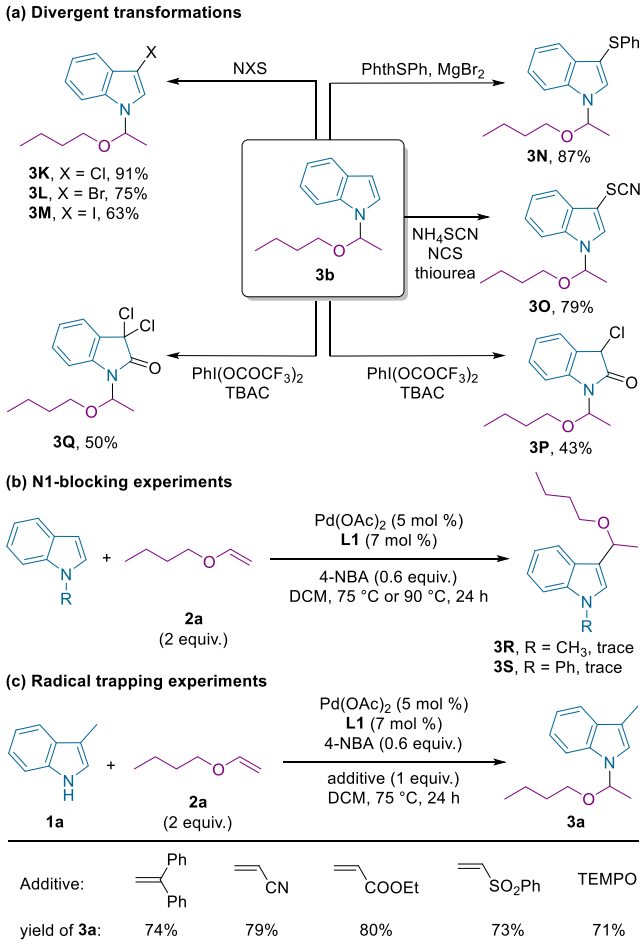

**Scheme 3.** Substrate scope of vinyl ethers. Reaction conditions: **1a** (0.2 mmol), **2** (2 equiv.), $Pd(OAc)_2$ (5 mol %), **L1** (7 mol %), 4-NBA (0.6 equiv.), DCM (1 mL), 75 °C, 24 h.

in the hydroamination, the compromised coordination hindered the critical aminopalladation step, thereby preventing the C-N bond-forming process. Moreover, substrates such as *N*-vinylphthalimide, *N*-vinylimidazole, phenyl vinyl sulfide, and phenyl vinyl sulfone proved incompatible with this alkylation protocol.

The synthetic potential of this protocol was exemplified by a series of transformations of *N*,*O*-aminal indole **3b** (Scheme 4a). The halogenation reaction of **3b** with *N*-halo electrophiles (NCS, NBS, and NIS) provided halogenated products **3K**-**3M** in 73–91% yields. Using $MgBr_2$ as the catalyst, the sulfenylation of **3b** led to sulfide **3N** in 87% yield. The thiocyanation reaction of **3b** with $NH_4SCN$, NCS, and thiourea resulted in the formation of thiocyanated product **3O** in 79% yield. In the presence of oxidant $PhI(OCOOCF_3)_2$ and TBAC, **3a** could be transformed into chlorinated oxindole **3P** and dichlorinated oxindole **3Q**. To gain insight into the reaction mechanism, mechanistic studies were performed. Firstly, the C-3 vinylation of indole was tested, and only trace mount of the C-3 alkylated product could be detected by GC-MS analysis when utilizing *N*-methyl and *N*-phenyl indole (Scheme 4b). The results indicated that C-3 alkylation would be difficult to occur in the current reaction system. In addition, to reveal whether a radical process was involved in the transformation, a stoichiometric amount of radical scavenger was added to the standard reaction, and **3a** was formed in 71–80% yields (Scheme 4c). The experiments suggest that a radical pathway is excluded.

## 3. Conclusion

In summary, we have developed an efficient palladium-catalyzed coupling protocol for the preparation of *N*,*O*-aminal indoles from




**Scheme 4.** Synthetic transformations of *N*,*O*-aminal indole and mechanism investigations.

indoles with vinyl ethers. This reaction proceeds under mild conditions, affording products in moderate to high yields with excellent regioselectivity. The protocol is operationally simple and displays good functional group tolerance, thereby suggesting that it can be a practical alternative to established protocols. Furthermore, the utility of the products was demonstrated through direct C-H functionalization and oxidation of the indole core.

## Supporting Information

Experimental procedures and characterization data are available in the Supporting Information. The authors have cited additional references within the Supporting Information.[50–55]

## Acknowledgments

This work was supported by the National Key Research and Development Program of China (2022YFB4101800), the National Natural Science Foundation of China (22231002, 22571094), the Guangdong Basic and Applied Basic Research Foundation (2024B1515040027), and the Postdoctoral Fellowship Program of CPSF under Grant Number (GZC20250695).

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** C-N coupling · hydroamination · indole · palladium catalysis · vinyl ether

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Manuscript received: August 27, 2025
Revised manuscript received: September 21, 2025
Version of record online: ■■, ■■