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Enantioselective *N*–alkylation of Indoles via an Intermolecular Aza-Wacker-Type Reaction

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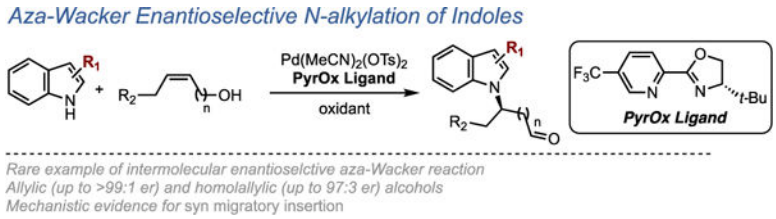
Abstract

The development of an intermolecular and enantioselective aza-Wacker reaction is described. Using indoles as the *N*-source, a selection of alkenols as the coupling partner enables selective β-hydride elimination towards the alcohol. This strategy preserves the newly formed stereocenter by preventing the formation of traditionally observed enamine products. Allylic and homoallylic alcohols with a variety of functional groups are compatible with the reaction in high enantioselectivity. Isotopic-labeling experiments support a *syn* amino-palladation mechanism for this new class of aza-Wacker reactions.

Graphical Abstract:



The indole scaffold is a privileged substructure found in a wide range of natural products, pharmaceuticals, and agrochemicals.[1] In fact, indole is one of the most frequent *N*-heterocycles imbedded in U.S. FDA approved drugs.[2] The most common synthetic modifications of indoles occur at the C2 and C3 positions – owing to their innate nucleophilic nature.[3] In contrast, functionalization of the N–H of indole is less explored due to the mitigated nucleophilicity of this position. This is especially true for the development of reactions which incorporate a stereocenter adjacent to the nitrogen, a structural motif found in a number of bioactive compounds (Scheme 1a).[4] Some progress has been made in intermolecular enantioselective *N*-alkylation of indoles.[5] A relevant approach to our strategy is the trapping of an indole derivative asymmetrically by a transition metal π-allyl

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Supporting Information

Experimental procedures, compound characterization, and NMR spectra. This material is free of charge via the Internet at http://pubs.acs.org.

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intermediate.[6] Nonetheless, a modular method for the direct, enantioselective *N*-alkylation of indoles remains underdeveloped.

In considering complementary strategies to promote enantioselective C–N bond formation from the N−H of indole, an aza-Wacker type reaction was envisioned. Traditionally, intermolecular aza-Wacker reactions are performed on terminal alkenes, and yield enamine products akin to the Wacker oxidation, as exemplified by the initial example reported by Hosokawa and Murahashi (Scheme 1b).[7] In our reaction design, a 1,2-disubstituted alkene is required to set the initial stereocenter. However, to avoid the formation of the enamine, β-hydride elimination of the resulting Pd-alkyl intermediate (A, Scheme 1c) must be biased to migrate away from the newly-formed C–N bond. On the basis of our previous successes in C–C bond-forming enantioselective Heck reactions, we planned to use an alkenol to facilitate the desired β-hydride elimination.[8] Of note, achieving this directional specificity in the chain-walking of an aza-Wacker variant could be difficult. Once the aminopalladation step has occurred, β-H_b elimination must out-compete β-H_a elimination, to avoid the formation of the classic enamine product found in most aza-Wacker reactions (Scheme 1c). This problem is further pronounced if we hope to extend the alkenol chain length (i.e., homoallylic alcohols) where the hydricity of H_a and H_b would presumably be similar, resulting in unselective β-hydride elimination. While the elegant work on asymmetric intramolecular variants of this reaction class have been reported, no intermolecular examples are known, likely as a consequence of these issues.[9]

The use of 1H-indole derivatives adds other key mechanistic challenges: 1) the C2 and C3 positions of the indole could compete with the nitrogen atom as the nucleophile, as exemplified by our use of *N*-protected indole derivatives in an enantioselective, dehydrogenative relay-Heck reaction.[10] 2) Two distinct mechanisms of aminopalladation have been reported in aza-Wacker-type reactions, a *syn*-addition and an *anti*-addition pathway, wherein competing stereoisomers could be formed if both aminopalladation mechanisms are operative.[11] Herein, we report a strategy to overcome a number of these mechanistic challenges through the development of an enantioselective aza-Wacker type reaction. This reaction proceeds through the *N*-alkylation of alkenols with indole derivatives, a rare example of intermolecular aza-Wacker type reaction.

We selected 3-phenylindole as a model substrate to avoid the complexity of reacting at the C3 position in the preliminary stages of this reaction development (**1a**, Table 1). A promising starting point for optimization was found using conditions similar to those found for enantioselective phenol addition to allylic alcohols.[12] Specifically, the use of an aprotic solvent, an inorganic base and *p*-benzoquinone (BQ) as the oxidant are required to observe modest levels of product formation (entry 1). Surprisingly, the reactivity was completely suppressed when a more polar solvent (i.e., DMF) was used. This is in contrast with the enantioselective Heck relay reactions developed in our group, which are more efficient in high polarity media.[8] Replacing $Ca(OH)_2$ with an organic base, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), led to an increase in yield to 59% with an er of 8:92 (entry 2). Employing *cis*-**2a** gave a modest increase in yield and enantioselectivity as compared to *trans*-**2a**, and produced the opposite enantiomer of product (entry 3).[11,13] Switching the solvent to 1,2-dichloroethane $(CH_2Cl)_2$ resulted in 72% yield of **3a**, while maintaining good

enantioselectivity (entry 4). A variety of oxidants were also evaluated, and it was found that both O_2 and Cu^{II}/O_2 are less effective than BQ (entries 5 and 6). Removal of the base resulted in a modest enhancement in yield (entry 7). Using PyrOx ligand **L1** under these conditions led to a 93:7 er. Exploring other ligands, we found that the enantioselectivity can be significantly improved by using ligand **L2**, albeit with a modest reduction in yield (Table 1, entries 7 and 8). It should be noted that *N*-alkylation occurs, but the analogous C2-alkylated product was not detected. Only starting materials and **3a** were observed in the analyses of the crude mixture using ^{1}H NMR.

Next, the scope of allylic alcohols was explored using 3-phenylindole as a standardized coupling partner (Table 2). Elongating the alkyl chain (**3b**), introducing a large hydrocarbon substituent (**3c**), or an aryl group (**3d**) did not adversely affect the efficiency and enantioselectivity. Functional group tolerance was explored through incorporation of an ester (**3e**), a protected alcohol (**3f**), a tosylate (**3g**), a protected amine (**3h**), and an alkyl chloride (**3i**). In general, the yields were moderate to good, with the enantioselectivity remaining high in all cases. Overall, the functional-group tolerance is excellent, highlighted by the ability to use reactive electrophiles, such as tosylates (**3g**) and alkyl halides (**3i**).

This process is not limited to allylic alcohols. Further extension of the alcohol from the alkene is tolerated using a homoallylic alcohol, allowing a remote functionalization process to occur (**3j**–**3l**). The enantioselectivity remains excellent in these cases while the reactivity is lower, consistent with our previous studies that demonstrate slower reaction rates for homoallylic with respect to allylic alcohols.[8a] The reaction of a bishomoallylic alcohol does not proceed to the desired product, indicating that competitive β-hydride elimination towards the newly formed C–N bond is more problematic (see Supporting Information for details).

Next, we explored the scope of indole derivatives (Figure 1a). Changing the electronic nature of the 3-phenylindole derivative did not significantly impact the yield and enantioselectivity (**3m**–**3o**). Other C3-substituted indole derivatives are tolerated, highlighted by the use of 3-chloroindole (**3p**), protected tryptamine (**3s**) and other tryptamine derivatives (**3u**, **3v**), which can be further functionalized using conventional approaches.[15] Of note, catalyst controlled diastereoselective addition of protect tryptophan derivatives is achieved (**3t** and **3t'**). Incorporation of a C2-substituent through the use of carbazole derivatives, another common pharmacophore, also leads to the desired product in good yields and enantioselectivity.[15] To test if C3-subsitution is required, indole was evaluated (**3w**) with modest results obtained. The mass balance of this particular substrate is poor, with observation of highly-colored byproducts. Mass spectrometry analyses and control experiments reveal the presence of side reaction between indole and benzoquinone that lead to a consumption of 0.7 equivalents of indole after 12 hours under the reaction conditions (See SI for further details). However, to overcome this synthetic limitation, product **3p** can be readily converted to unsubstituted **3w** through a simple dechlorination process in excellent yield and no loss of stereochemical fidelity (Figure 1b). Finally, the use of simple C3 alkyl derivatives leads to the desired products, albeit in lower yield for the smaller methyl-derived indole (**3w** and **3x**).

A number of other *N*-heterocyclic nucleophiles ranging in pK_a values were evaluated for this reaction, including a few selected examples depicted in Figure 1c (see Supporting Information for a comprehensive list). Most *N*-heterocyclic compounds resulted in <5% yield of the desired *N*-alkylated product according to analyses of the crude mixture using ^{1}H NMR. However, oxazolidinone was identified as another modestly suitable nucleophile, (32% yield, 90:10 er). Interestingly, the *N*-nucleophiles that are efficient for this coupling have a very similar pK_a value although the precise reason for effective catalysis is not yet understood.

Considering the *N*-alkylation is the major product observed in this reaction, the nature of the amino-palladation step was evaluated. Specifically, as outlined in the introduction, intramolecular variants of aza-Wacker processes have been shown to undergo both *syn*- and *anti*- enantioselective processes.[11] A deuterium-labeled allylic alcohol (**2y-*d*$_2$**) was subjected to our optimized conditions to differentiate these mechanisms of amino-palladation (Scheme 2b). Depending on which mode of amino-palladation is operative, two possible diastereomers of the product **3y** can be obtained (Scheme 2a). According to previous mechanistic studies, the deuterium label adjacent to the newly formed aldehyde reflects the relative stereochemistry of the initial [Pd]–C bond.[8] This is a result of the Pd-hydride remaining coordinated to the alkene during the chain walking process. In the event, a single stereoisomer is observed from the reaction, and the relative stereochemistry was confirmed by ^{1}H NMR studies after conversion of **3y** to **4** by an intramolecular Friedel-Crafts acylation. Specifically, ^{1}H NMR coupling constants (both experimental and calculated) as well as 1D nOe experiments support a *syn*-amino-palladation pathway for this reaction. Additionally, the absolute configuration of product **3r** was determined to be (*R*) by X-ray crystallography. Taken together, the *syn*-nature of the amino-palladation and the observation of the (*R*) product are both consistent with the same mode of asymmetric catalysis for the previously reported C–C bond-forming processes reported from our group.[16]

In summary, we have established a rare example of enantioselective, intermolecular aza-Wacker-type reaction thereby avoiding the traditional formation of enamine products in these reaction types. This transformation allows the direct *N*–alkytaltion of indoles to alkenols in a regio-, stereo-, and enantioselective manner with significant functional group compatibility. Coupling with a homoallylic alcohol exemplifies the ability to form products with a remote stereocenter. Further assessment of this reaction type and understanding the underlying mechanistic consequences of Pd-chain walking are currently under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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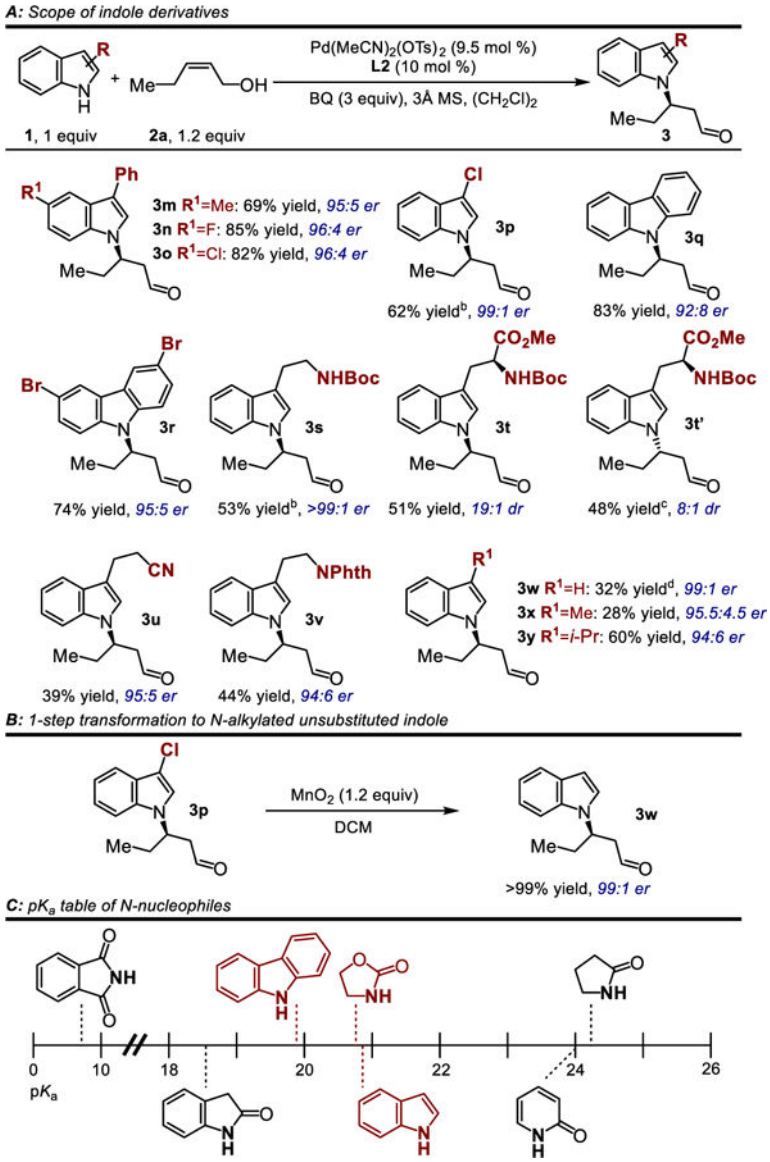
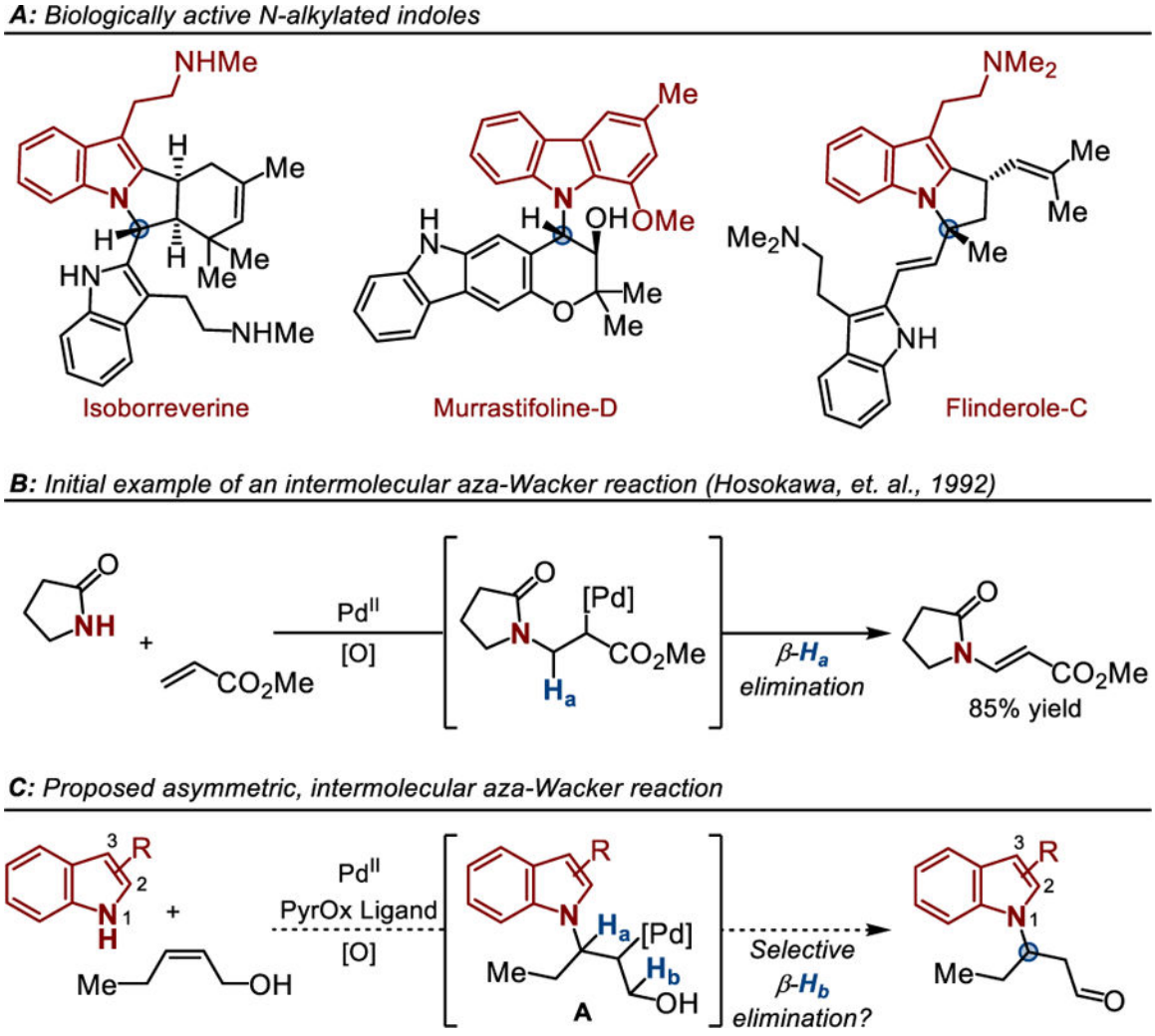


Figure 1.

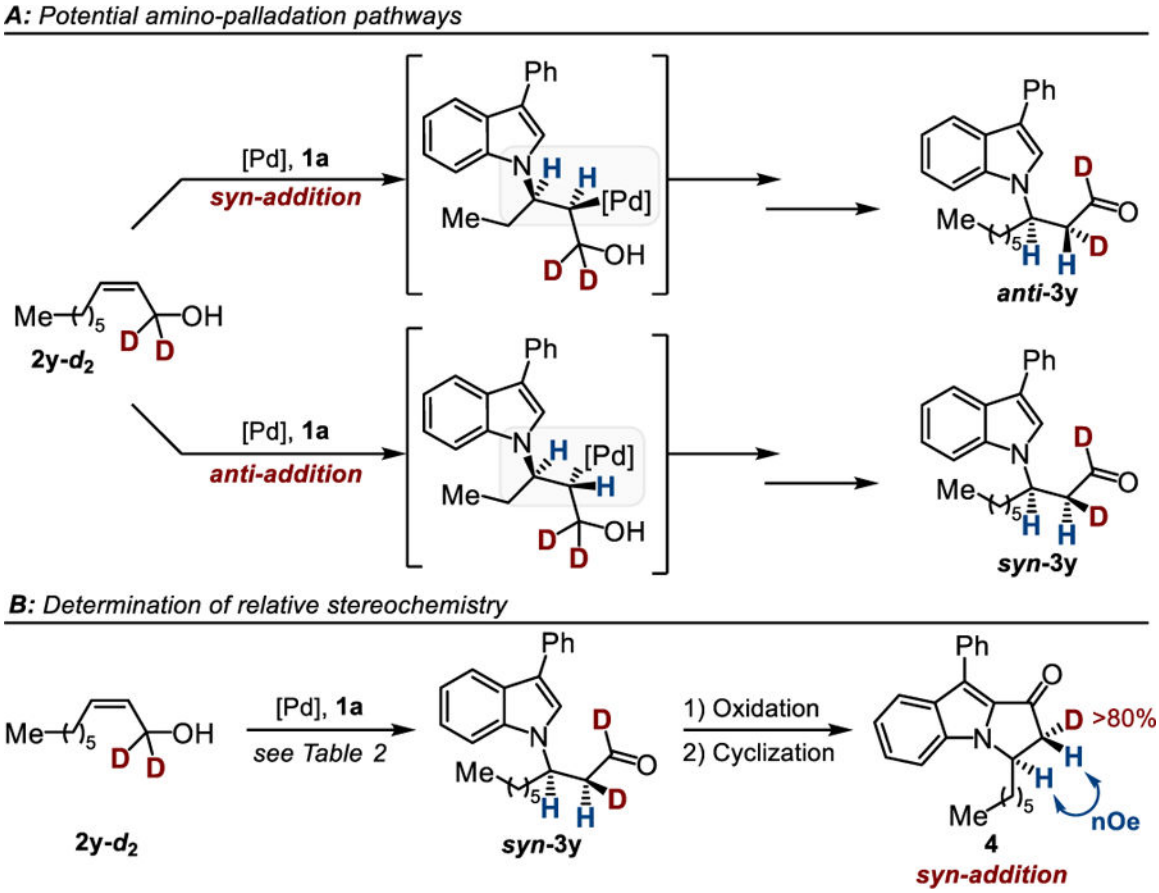
Scope of *N*-heterocyclic Nucleophiles[a]

[a]Reported yields are of isolated material on a 0.5 mmol scale. Enantiomeric ratios were determined by SFC equipped with a chiral stationary phase. [b]Slow addition of 1 using a syringe pump over 12 hours. 1 (1.2 equiv), 2a (1 equiv).[c](R)-enatiomer of the ligand L2 used. [d]Indole (2 equiv), 2a (1 equiv), BQ (0.5 equiv), O_2 balloon, and L1 was used as the ligand. NPhth = phthalimide.



Scheme 1.

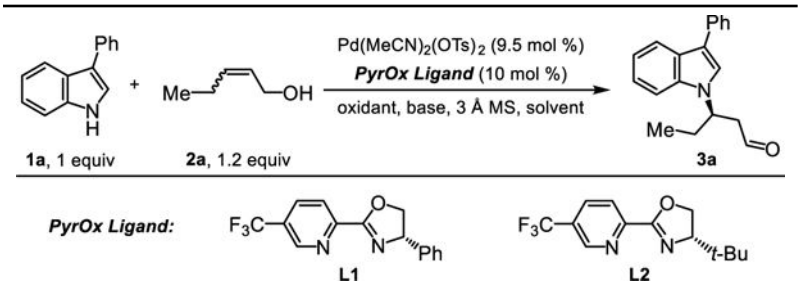
Enantioselective *N*-alkylation via an aza-Wacker-type Mechanism



Scheme 2.
Mechanistic Experiments

Table 1.

Optimization of Reaction Conditions with 3-Phenylindole



Entry	Base	2a isomer	Solvent	Oxidant	Ligand	Yield(%)[a]	er
1	$Ca(OH)_2$	trans	$PhCF_3$	BQ	**L1**	44	n.d.
2	DTBMP	trans	$PhCF_3$	BQ	**L1**	59	8:92
3	DTBMP	cis	$PhCF_3$	BQ	**L1**	66	95:5
4	DTBMP	cis	$(CH_2Cl)_2$	BQ	**L1**	72	93:7
5	DTBMP	cis	$(CH_2Cl)_2$	O_2	**L1**	9	n.d.
6	DTBMP	cis	$(CH_2Cl)_2$	Cu^{II}/O_2[b]	**L1**	25	n.d
7	-	cis	$(CH_2Cl)_2$	BQ	**L1**	86 (84)[c]	93:7
8	-	cis	$(CH_2Cl)_2$	BQ	**L2**	**76 (78)**[c]	**98:2**

[a] Reactions were performed on a 0.2 mmol scale. Yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. 3Å MS were added at a concentration of 225 mg/mmol. BQ = *p*-benzoquinone (3 equiv).

[b] Cu^{II} = $Cu(OTf)_2$ (10 mol %).

[c] Yields in parentheses are of isolated material. Enantiomeric ratios were determined by SFC equipped with a chiral stationary phase.

Table 2.

Scope of Alkenol Derivatives[a]

[a]Reported yields are of isolated material on a 0.5 mmol scale. Enantiomeric ratios were determined by SFC equipped with a chiral stationary phase.

[b]**1a** (2 equiv), **2** (1 equiv), BQ (4 equiv). NPhth = phthalimide.