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Synthesis of Indolines and Derivatives via Aza-Heck Cyclization

Feiyang Xu, Katerina M. Korch, and Donald A. Watson*

Abstract: For the first time, an aza-Heck cyclization that allows the preparation of indoline scaffolds is described. Using *N*-hydroxy anilines as electrophiles, which can be easily accessed from the corresponding nitroarenes, this method provides indolines bearing pendant functionality and complex ring topologies. Synthesis of challenging indolines, such as those bearing fully substituted carbons at C2 is also possible using this method.

The indoline scaffold is found in numerous natural products and biologically active complex molecules.[1] Synthetic pharmaceuticals containing this ring system are used to treat a wide variety of diseases, including migraines, hypertension, cancer, and chronic inflammatory and neurodegenerative conditions.[2] Notable examples of indoline-containing natural products and drugs are shown in Figure 1,[3] many of which bear a fully substituted carbon at C2 and/or unsaturation adjacent to the indoline nitrogen.

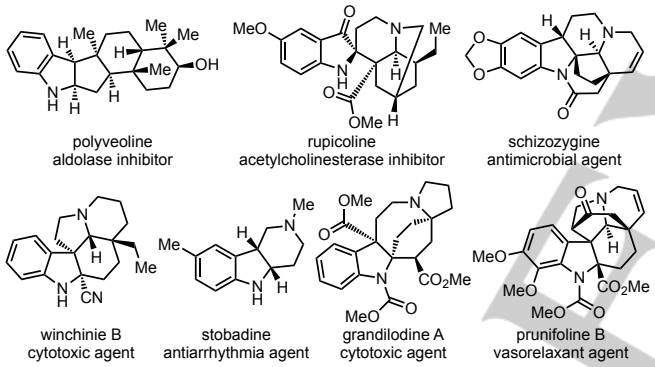

Figure 1. Notable Natural Products and Drugs Containing Indoline Scaffolds.

Because of the prevalence of indolines in bioactive molecules, the discovery of new methods to prepare this heterocycle has attracted substantial research interest.[1] One attractive strategy involves cyclization of an aniline equivalent onto a pendant alkene. Aza-Wacker approaches to indoline synthesis using this general strategy have been previously described;[4] however, in general they are highly limited in terms of alkene substitution of the substrate. The vast majority of such cyclizations require substrates bearing either a terminal or 1,2-disubstituted alkene and result in mono-cyclic indolines or related heterocycles. Using aza-Wacker approaches, there has been only one isolated example of the formation of a fused bicyclic indoline,[4f] and one example of the cyclization to form an indoline bearing a fully substituted C2 carbon.[4i][5] In general, access to indolines bearing full substitution at C2 is challenging, and most often requires manipulation of a preformed indole core.[1a] Tsuji-Trost and related allylation reactions are capable of accessing such molecules;[6] however, they require more highly functionalized allylic electrophiles, which introduces difficulty in starting material preparation and limits the accessible product ring topologies. Thus, there is a clear need to develop a cyclization technology that can produce a wide range of indoline topologies, including more challenging product structures, from easily available starting materials.

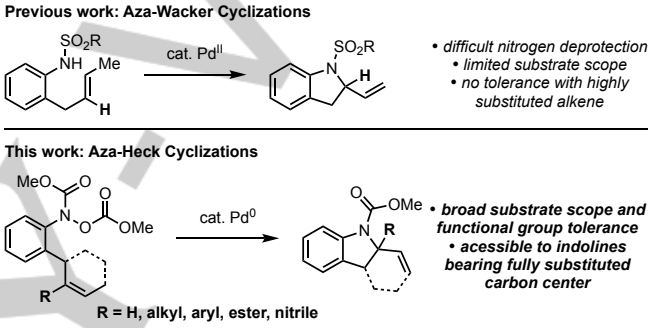

Figure 2. Prior Art and Our Method.

Over the past several years, the discovery of Heck-type reactions using heteroatomic electrophiles has greatly enhanced carbon-heteroatom bond construction.[7] Within the context of alkaloid synthesis, aza-Heck cyclizations employing nitrogen electrophiles has proven to be a powerful strategy for nitrogen-containing heterocycle synthesis.[8] To date, we and others have described a few classes of such electrophiles that allow access to pyrroles and pyridines,[9] cyclic imines,[10] saturated pyrrolidines and piperidines,[11] lactams,[12] and imidazolidinones.[13] However, the use of nitrogen electrophiles bearing aromatic substitution has not been demonstrated. Moreover, only two prior examples of aniline electrophiles have been shown in cross-coupling reactions, making this a highly underdeveloped area of study.[14],[15]

Herein, we report that *N*-aryl-*N*-hydroxy carbamates undergo facile palladium-catalysed cyclization onto pendant alkenes to deliver indolines, and related heterocycles, bearing allylic unsaturation. Unlike earlier methods, broad scope of alkene substitution and functional group compatibility are observed, allowing the preparation of indolines with complex ring topologies and substitution patterns and making this a general approach to this important ring system.

Towards development of the aza-Heck reaction, our initial studies investigated the cyclization of **1** bearing an ester leaving group, which has been widely utilized in cross-couplings of nitrogen electrophiles (including those of anilines). We focused on the easily reduced palladium pre-catalyst (COD)Pd(CH_2SiMe_3)$_2$, and selected P(OCH_2CF_3)$_3$ as ligand, as it has shown success in previous aza-Heck reactions (Table 1, Entry 1). Disappointingly, under these and other conditions, only trace conversion and none of the desired aza-Heck product **3a** was observed. We then sought a leaving group that might favor greater reactivity. We

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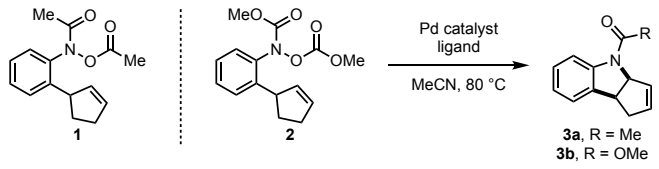
speculated that a carbonate leaving group might serve such as role, as decarboxylation might lead to irreversible oxidation addition.[16]

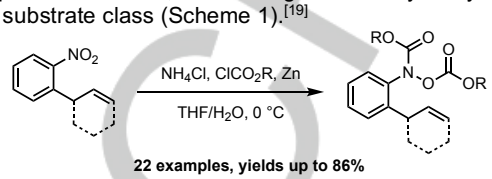
Table 1. Reaction Optimization.



Entry	Pd Catalyst [mol %]	Ligand [mol %]	Yield [%, **3**] [a]
1 [b]	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P(OCH_2CF_3)_3$ [12.5]	0
2	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P(OCH_2CF_3)_3$ [12.5]	25
3	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ [12.5]	53
4	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P(4\text{-}CF_3\text{-}C_6H_4)_3$ [12.5]	85
5	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P(4\text{-}F\text{-}C_6H_4)_3$ [12.5]	65
6	(COD)Pd(CH_2SiMe_3)$_2$ [5]	PPh_3 [12.5]	61
7	(COD)Pd(CH_2SiMe_3)$_2$ [5]	$P(C_6F_5)_3$ [12.5]	0
8	Pd_2dba_3•$CHCl_3$ [1.5]	$P(4\text{-}CF_3\text{-}C_6H_4)_3$ [7.5]	84 [c]

[a] Yield calculated by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b] **1** as starting material instead of **2**. [c] Isolated Yield.

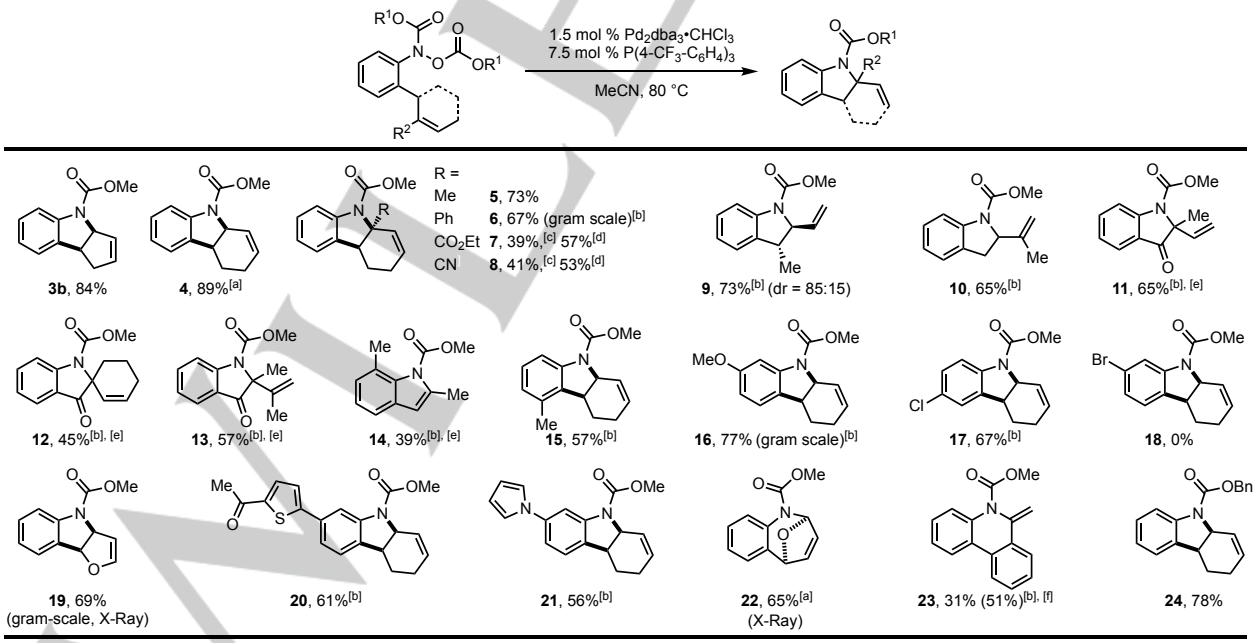
Previously, the single-step semi-reduction of nitroarenes to *N*-aryl-*N*-hydroxy carbamates had been reported.[17] Although these products have not been explored in cross-coupling reactions, we envisioned that these might make outstanding substrates, not only for their potential carbonate leaving group, but also for their ease of preparation. Moreover, substrate assembly would be aided by the vast chemistry of nitroarene synthesis.[18] Gratifyingly, we found that known protocols were well-suited to substrates bearing pendant alkenes,[17a] allowing for a ready entry into the required substrate class (Scheme 1).[19]



Scheme 1. Synthesis of *N*-aryl-*N*-hydroxy Carbamate Substrates.

Excitingly, and in validation of our hypothesis, using a substrate bearing the carbonate leaving group (**2**), the desired product **3b** was observed in 25% yield (Table 1, Entry 2). Ligand optimization revealed that $P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$ provided **3b** in 53% yield (Entry 3).[11b] Ultimately, the related ligand to $P(4\text{-}CF_3\text{-}C_6H_4)_3$ proved to have the optimal balance of electronic and steric properties, providing product **3b** in 85% yield (Entry 4). Other similarly sized, but electronically varied ligands proved inferior (Entries 5–7). Finally, we found that the more readily available and bench-stable pre-catalyst (Pd_2dba_3•$CHCl_3$) provided similar yields at lower catalyst loading (Entry 8), making this a highly practical method for indoline synthesis. Notably, although acyl, sulfonyl, or phenoxy leaving groups have been previously used in aza-Heck cyclizations, this is the first reported example of using a carbonate leaving group in a heteroatomic cross-coupling.

These conditions enabled synthesis of a broad scope of indolines. The model product **3b** was isolated in 84% yield. Using



[a] Average of two runs. [b] Run with 5 mol % Pd_2dba_3•$CHCl_3$, 25 mol % $P(4\text{-}CF_3\text{-}C_6H_4)_3$. [c] Run with 5 mol % Pd_2dba_3•$CHCl_3$, 25 mol % $P(4\text{-}CF_3\text{-}C_6H_4)_3$, DCE. [d] Run with 7.5 mol % Pd_2dba_3•$CHCl_3$, 37.5 mol % $P(4\text{-}CF_3\text{-}C_6H_4)_3$, DCE. [e] Run at 100 °C. [f] Parenthetical yield calculated by ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard.

Scheme 2. Scope of the Indoline-Forming Aza-Heck Cyclizations.

a substrate bearing a larger cyclohexene ring, **4** was produced in 89% yield. More substituted alkenes can also be utilized. These include both trisubstituted alkenes (**10**-**12**), tetrasubstitutedalkenes (**13**), and those bearing a range of groups, including alkyl, aryl, ester, and nitrile (**5**-**8**). Many of these examples provide indolines bearing fully substituted C2 carbons adjacent to nitrogen.[20] As mentioned, this is a motif that appears widely in bioactive natural products but is often challenging to prepare (Figure 1).[1a] Benzylic substitution is also well tolerated. With stereogenic benzylic substitution, good levels of diastereoselectivity are observed (**9**); with benzylic ketones, pseudoindoxyls arise (including those bearing fully substituted carbon centers, **11**-**13**). These oxidized heterocycles appear in many natural products, but typically must be prepared by the oxidative rearrangement of indoles.[21] It is also notable that these cyclizations proceed via 5-*exo* cyclization onto an electron-deficient alkene opposite to its inherent electronic bias.

A range of functional groups are compatible with this cyclization, including ethers (**16**, **19**, **22**), carbonyls (**7**, **11**–**13**, **20**), nitrile (**8**), aryl chloride (**17**), and various appended heterocycles (**19**–**22**). Unfortunately, aryl bromide is not tolerated (**18**). *N*-hydroxy aniline bearing an allylic ether can also cyclize under these conditions, resulting in the fused vinyl ether **19** on gram scale.

A range of bicyclic ring topologies can also be prepared, including fused (**3b**, **4**–**8**, **15**–**17**, **19**–**21**, **24**), spirocyclic (**12**), and bridged (**22**) systems. Again, this starkly contrasts aza-Wacker cyclizations, where most examples result in mono-cyclic products (see above). There are no reported examples of bridged indolines formed by aza-Wacker cyclization. 6-*exo* cyclization is also possible. For example, bridged bicyclic hemiaminal **22** can be prepared in this fashion; this is the first metal-catalyzed approach to access such a scaffold. Similarly, dihydrophenanthridine **23** can be prepared via 6-*exo* cyclization of a biaryl substrate.[22] Finally, the carbamate group can be varied. For example, the Cbz-protected indoline (**24**) was prepared in good yield, indicating that other protecting and leaving groups can be utilized in this chemistry.

In summary, we have developed a general method for the synthesis of indoline derivatives using an aza-Heck approach. This marks the first use of aniline electrophiles and carbonate leaving groups in such a cyclization. This reaction offers distinct advantages over existing methods, particularly with respect to functional group compatibility, accessible ring topologies, and tolerance of alkene substitution. The ease of access to the required substrates by semi-reduction of nitroarenes, along with the highly adaptable nature of the reaction, should make this process highly applicable to the synthesis of indoline-containing natural products and bioactive molecules.

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Keywords: catalysis • palladium • indolines • aza-Heck • cyclization

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[22] In this case, the isolated yield was suppressed due to product instability.

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Layout 2:

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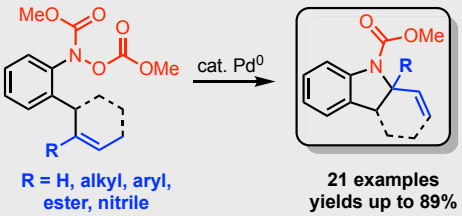

- ***easily prepared substrates***
- ***broad substrate scope and functional group tolerance***
- ***acessible to indolines bearing fully substituted carbon center***

Feiyang Xu, Katerina M. Korch and Donald A. Watson

Page No. – Page No.

Synthesis of Indoline Derivatives via Aza-Heck Cyclizations