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Synthesis of Indolines via Palladium/Norbornene-Catalyzed Reaction of Aziridines with Aryl Iodides

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A Pd- and norbornene-catalyzed domino procedure has been developed to synthesize indoline compounds. This reaction provides efficient access to indolines by employing aryl iodides with aziridines as new electrophiles. The transformation is scalable and tolerates a range of functional groups.

Heterocyclic compounds are ubiquitous and are present in pharmaceuticals, agrochemicals, and biologically active molecules.[1] Transition-metal catalysts for the preparation of heterocyclic compounds, especially palladium-catalyzed reactions have been reported by many research groups in recent years.[2] Palladium/norbornene (NBE) chemistry plays an important role here. Compared with many other strategies, this protocol does not need directing groups (DGs) and performs both *iso* and *ortho*-functionalization of the aryl halides in one step under mild conditions. Significantly, as a key step, the Catellani reaction has been applied to heterocyclic natural products synthesis, such as (±)-goniomitine, aspidospermidine,[3] (+)-linoxepin[4] and rhazinal.[5]

Pd/NBE chemistry was pioneered by Catellani in 1997[6] and has become a powerful tool for performing bi-/tri-functionalization to construct polysubstituted arenes. Over the past two decades, varied termination reagents (**Nu–Y**) have been well studied by the Catellani, Lautens, and other groups.[7] However, electrophiles (**E–LG**) that react with the key five-membered aryl-norbornene-palladacycle (ANP) intermediate to install functional groups at the *ortho*-position were mainly confined to alkyl and aryl halides (Scheme 1a).[8] Until 2013, amino,[9] acyl,[10] and carboxyl[11] electrophiles have been developed to achieve *ortho*-functionalization successively.

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† Electronic Supplementary Information (ESI) available: Details on the experimental procedure, characterization data of all compounds, and CCDC of single crystal X-ray data of compounds 1815728 (**3a**), 1815733 (**3s**), 1815734 (**6k**), 1815739 (***(R)*-5n**), 1815740 (***(S)*-6n**), 1822354 (**E**), and 1815737 (**F**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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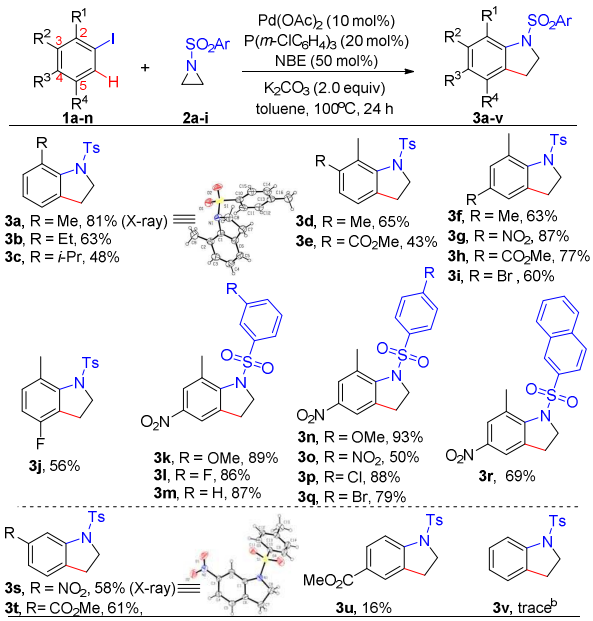
Table 1. Scope of indoline formation[a]

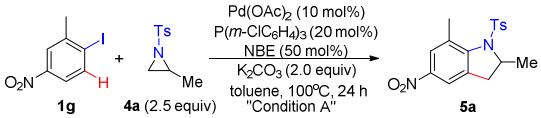


[a] Condition A: **1** (0.15 mol, 1.0 equiv), **2** (2.5 equiv), $Pd(OAc)_2$ (10 mol%), P(*m*-$ClC_6H_4)_3$ (20 mol%), NBE (50 mol%), and K_2CO_3 (2.0 equiv) in toluene (1 mL) at 100°C for 24 h. Isolated yields. [b] Determined by gas chromatography-mass spectrometry (GC-MS).

(**Y**) were produced during the catalytic cycle process (Scheme 1b). 1) In view of Yu's[16] and Dong's[17] studies; 2) because almost all aziridine ring openings proceed via an S_N2 mechanism;[14e] 3) and the desired indoline product with a configuration inversion was obtained when chiral 2-aryl-aziridine was used, we speculate that the transformation of aryl iodides and aziridines occurs via either a Pd(IV) intermediate (Scheme 1b, *pathway a*) or an S_N2 nucleophilic ring-opening reaction pathway (Scheme 1b, *pathway b*).

Inspired by Lautens' reports,[18] 2-iodotoluene **1a** and 1-tosylaziridine **2a** were used as model coupling partners. With the optimized conditions determined (see the ESI, Tables S1-5), the scope was to further study the assay (Table 1). In particular, it was found that P(*m*-$ClC_6H_4)_3$ had the best combination of electronic and steric properties to give the best yield. [18b] First, different aryl iodides were examined using 1-tosylaziridine **2a** as the aziridine partner. Compared with **3a** (81% yield),[19] which was characterized by single crystal X-ray analysis,[20] moderate yields of **3b** (63% yield) and **3c** (48% yield) were obtained with the more sterically hindered Et and *i*-Pr moieties at the 2-position (R^1) of the benzene ring. Therefore, with the 2-position being methyl, a list of substrates with both electron-deficient and electron-rich groups at the 3-, 4- or 5-positions of the phenyl ring were isolated in good to high yields (**3d-j**), among which the aromatic iodine-bearing 4-nitro group gave the desired indoline product **3g** at a high yield of 87%. For a gram-scale reaction, the indoline **3g** was obtained in comparable yield (see the ESI). Next, when coupled with 1-iodo-2-methyl-4-nitrobenzene **1g**, the aziridines with different arylsulfonyl groups on the nitrogen atom all worked well and

Table 2. New optimization of the reaction conditions



Entry	Change from the Condition A	Yield (%)[a]
1	none	29[b]
2	DME instead of toluene	24[c]
3	toluene/DME (*v/v* 1:1) instead of toluene	36[c]
4	H_2O (2 equiv) + toluene/DME (*v/v* 1:1)	64
5	H_2O (2 equiv) + toluene/DME (*v/v* 1:1)	71[d]
6	EtOH (2 equiv) + toluene/DME (*v/v* 1:1)	61[d]
7	NH_4Cl (2 equiv) + toluene/DME (*v/v* 1:1)	63[d]
8	MX_n[e] (2 equiv) + toluene/DME (*v/v* 1:1)	trace[d]
9	$BF_3{\cdot}Et_2O$ (2 equiv) + toluene/DME (*v/v* 1:1)	trace[d]

[a] Isolated yields. [b] Recovery of **4a** = 74%. [c] Recovery of **4a** < 5%. [d] **4a** (2.0 equiv), 105°C, and 30 h. [e] MX_n = $FeCl_3$, $FeCl_2$, $CuCl_2$, CuCl. DME denotes ethylene glycol dimethyl ether.

afforded their respective indoline products (**3k-r**) in excellent yields (up to 93%). Attempting to further expand the scope, aryl iodides without a substituent group at the 2-position (R^1=H) were carried out. The 3-nitroiodobenzene and methyl 3-iodobenzoate showed good compatibility in this transformation and produced a single isomer in moderate yields (**3s**, 58% yield and **3t**, 61% yield). The configuration of product **3s** was unambiguously determined by X-ray analysis. Methyl 4-iodobenzoate resulted in a lower yield (**3u**, 16% yield). Nevertheless, iodobenzene without any substituent groups was unable to give the corresponding product **3v**. It is likely attributable to "the *ortho* effect" that *ortho*-substituted aryl iodides lead to better yields than those of unsubstituted ones.[21]

When 2-substituted aziridine **4a** was combined with aryl iodide **1g** under previously optimized conditions (Condition A), the desired indoline product **5a** was obtained in 29% yield with 74% recovery of starting aziridine **4a** (Table2, entry 1). Meanwhile, the use of DME as solvent gave 24% yield with low recovery of **4a** (entry 2). In a mixed solvent of toluene and DME (*v/v* 1:1), the yield of isolated **5a** slightly increased (36%, entry 3). The addition of 2 equiv of H_2O could remarkably enhance the yield (entries 4-5). Adding EtOH or NH_4Cl, which can provide proton hydrogen, gave moderate yields (entries 6-7). Nevertheless, the use of Lewis acid as an additive dramatically decreased the yields (entries 8-9).

After the new optimized conditions were established (Table 2, entry 5), the scope of the reaction was studied using various substituted aziridines. They tolerated aryl iodide **1g** and afforded the desired products in good yields (Table 3). When R^6 comprised monoalkyl substituents **4a-c**, almost only single isomers **5a-c** derived from ring opening at the unsubstituted carbon atom were observed (>20:1, **5:6**). While 2-aryl-aziridines **4d-j** produced two isomers (**5d-j** and **6d-j,** respectively), products **6d-j** obtained via the regio-selective cleavage of a benzylic C-N bond accounted for the highest

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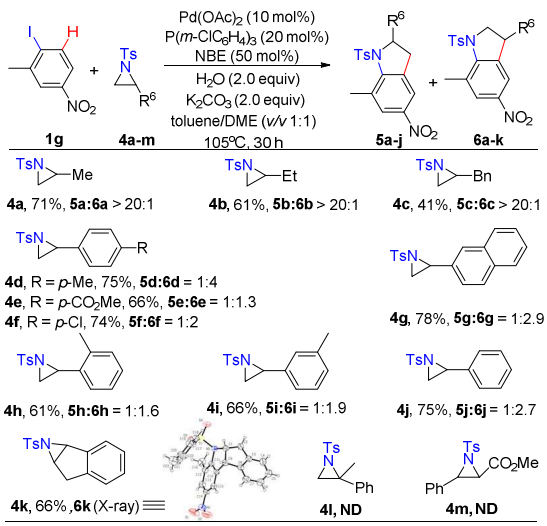
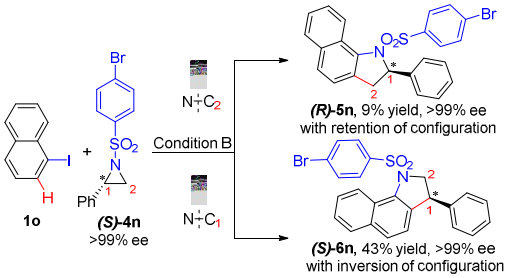
Table 3. New scope of indoline formation[a]



[a] Condition B: **1g** (0.15 mmol, 1.0 equiv), **4** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), P(*m*-$ClC_6H_4)_3$ (20 mol%), NBE (50 mol%), H_2O (2.0 equiv), and K_2CO_3 (2.0 equiv) in toluene/DME (1 mL, *v*/*v* 1:1) at 105°C for 30 h. Isolated yields. Ratios were determined by ^1H NMR. ND denotes not determined.

proportion. The differences between alkyl- and aryl-substituted aziridines probably occurred because the ring opening of aziridines is controlled by a balance between electronic effects and steric hindrance.[14] The results showed good agreement with the S_N2 reaction mechanism under alkaline conditions. The 1-tosyl-1,1*a*,6,6*a*-tetrahydroindeno [1,2-*b*] azirine **4k** was also suitable for this transformation. A single regio-isomer **6k** was isolated in 66% yield. Its configuration was determined by X-ray crystallography. Other poly-substituted aziridines, like *gem*-disubstituted **4l** and 1,2-disubstituted **4m** aziridines were incompatible with aryl iodide **1g**. Nevertheless, no desired products were tested when unsaturated aziridine and heterocyclic substrates were used (see the ESI).

Previous work by Lautens suggested that inversion of the configuration likely proceeds during the oxidative addition of the enantioenriched secondary alkyl iodides to Pd(II) species to generate the Pd(IV) species.[22] Inspired by this study, an additional experiment was carried out using chiral aziridine ***(S)*-4n** and 1-iodonaphthalene **1o** (Scheme 2). Cleaving of the N-C_2 bond generated ***(R)*-5n** with retention of configuration, while cleaving of the N-C_1 bond gave ***(S)*-6n** with inversion of



Scheme 2. Synthesis of enantioenriched products ***(R)*-5n** and ***(S)*-6n**.

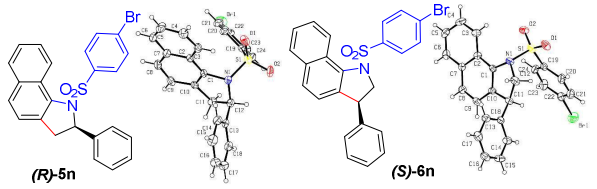


Fig. 1 X-ray structures of products ***(R)*-5n** and ***(S)*-6n**.

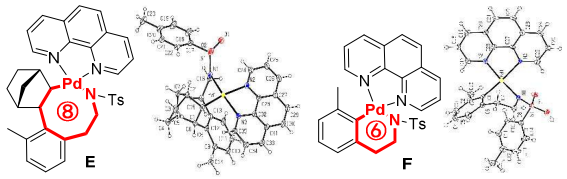


Fig. 2 X-ray structures of products **E** and **F**.

configuration. The two absolute configurations were determined by X-ray crystallography (Fig. 1). Based on the occurrence of Walden inversion and almost all aziridine ring openings proceed via an S_N2 mechanism,[14e] it is likely that a nucleophilic ring-opening process occurs in this reaction.

Mechanistic experiments have been carried out to get a deeper understanding of the reaction pathway. At first, we spent a lot of time isolating possible intermediates with phosphorous ligand, but it didn't work. Several outstanding studies, in the Pd/NBE chemistry field, have been reported by Catellani *et al.* via adding phenanthroline as a ligand to stabilize the reactive palladium intermediates.[23] Inspired by these studies, palladacycle complex **B** (Scheme 1b) bearing phenanthroline was chosen as the substrate. Much to our delight, after nearly a year of effort, two key X-ray crystal structures of intermediates **E** and **F** were obtained (Fig. 2). The two crystal structures are the important evidence that β-carbon elimination of norbornene (norbornene deinsertion) happens to the eight-membered palladacycle **E** to give the six-membered palladacycle **F** in this Catellani reaction. Further mechanistic studies are under investigation.

In summary, we have developed a novel strategy to synthesize indoline compounds from commercial and readily accessible aryl iodides and *N*-sulfonated aziridines. This process involves aziridine ring-opening followed by palladium-catalyzed coupling-cyclization containing C_{alkyl}-C_{aryl} and N-C_{aryl} bond formation in one step. In addition, aziridines were shown to be new electrophilic reagents that further extend the scope of palladium/norbornene chemistry. The occurrence of the Walden inversion suggests that an S_N2 nucleophilic ring-opening process is likely to proceed in this transformation. Further applications of this method to synthesize other heterocycles are underway.

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Conflicts of interest

There are no conflicts to declare.

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20. CCDC 1815728 (**3a**), 1815733 (**3s**), 1815734 (**6k**), 1815739 (***(R)*-5n**), 1815740 (***(S)*-6n**), 1822354 (**E**) and 1815737 (**F**).
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