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Dearomative Indole Bisfunctionalization via a Diastereoselective Palladium-Catalyzed Arylcyanation

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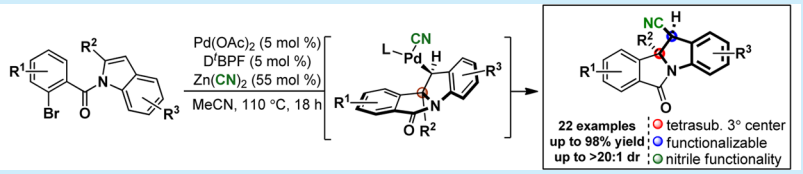
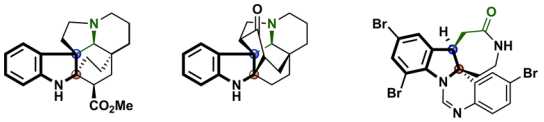
Supporting Information



ABSTRACT: The first Pd-catalyzed dearomative indole bisfunctionalization via a diastereoselective arylcyanation is reported. This method facilitates the formation of diverse indoline scaffolds bearing congested stereocenters with high levels of diastereoselectivity. This also represents the first example of a cyanation mechanism involving a 2° benzylic Pd(II) intermediate.

Indolines represent privileged heterocyclic scaffolds, and due to compounds containing this structural element exhibiting diverse biological activities, they have become highly sought after for use as therapeutic agents.[1] Thus, diverse methods that may expediently access these frameworks have been the focus of intense research effort.[2] Specifically, indolines possessing one or more fully substituted C-centers at C2 and C3 are of particular interest, as these motifs are present in numerous complex natural products (Scheme 1). Yet, general catalytic methods that easily

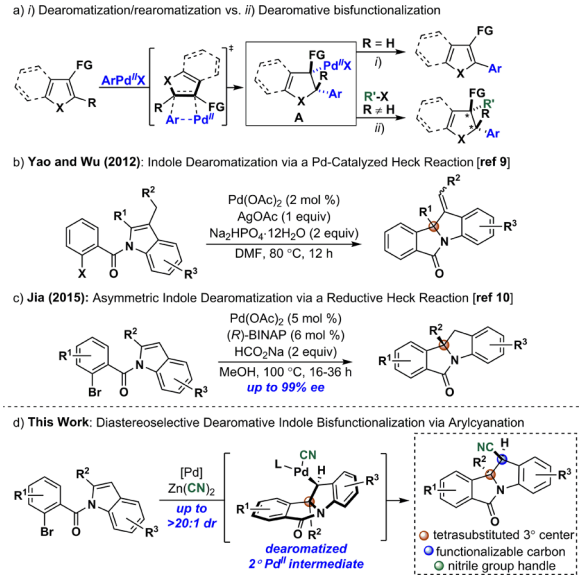
Scheme 1. Complex Indoline-Based Natural Products Bearing Quaternary and Tetrasubstituted Tertiary C-Stereocenters



forge complex cores with this desirable substitution pattern remain scarce in the literature.[2o,q] In light of this situation, we envisioned simple 2-substituted indoles undergoing a highly stereoselective, Pd-catalyzed dearomative bisfunctionalization via a domino arylation/anion capture sequence[3] to set the C2 and C3 stereocenters simultaneously. The transition-metal-catalyzed dearomatization of (hetero)arenes has recently become an attractive strategy that uses simple aromatic substrates to yield products containing a high degree of stereocomplexity.[4] Elegant asymmetric dearomatizations have been reported involving anilines[5a] and phenols,[5b−d] while others have employed indoles[6a−d] and pyrroles[6e] as substrates.

Numerous metal-catalyzed (hetero)arene monofunctionalizations have also been reported that proceed via distinct dearomatizations/rearomatization sequences (Scheme 2a, path *i*).[7,8] During these processes, catalytic intermediates (i.e., **A**) are produced prior to the ultimate rearomatization step. Although these intermediates possess a high level of stereochemical

Scheme 2. Approaches to Various Indoline Scaffolds via Pd-Catalyzed Indole Dearomatizations



information, there is still a paucity of methods that avoid the final stereoablative rearomatization and retain this information via a further functionalization step (Scheme 2a, path *ii*).

In 2012, Yao and Wu reported a Pd-catalyzed Heck-type indole dearomatization involving carbopalladation of the C2−C3 moiety (Scheme 2b).[9] This reaction facilitated the introduction of a congested tetrasubstituted tertiary carbon center and gave precedence for indole dearomatizations involving a carbopalladation mechanism. More recently, Jia employed a simple $Pd(OAc)_2$/(*R*)-BINAP catalyst system to achieve the first

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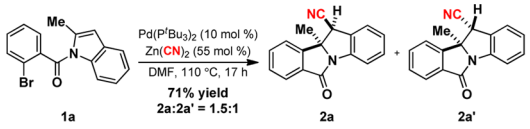
asymmetric indole dearomatization, which proceeded via a reductive Heck reaction (Scheme 2c).[10] This method which is rooted in previously reported reductive radical cyclizations of *N*-(*o*-bromobenzoyl)indoles[11] allows access to highly enantioenriched indolines bearing a similar tetrasubstituted tertiary carbon center. However, despite the exquisite enantioselectivities observed, the simple indoline products possess only a single stereocenter and little functional group content. In line with studies by our group[12] and others,[13] we envisioned that a diastereoselective dearomative indole bisfunctionalization via an arylcyanation would allow streamlined access to diverse indolines bearing both a tetrasubstituted tertiary and a tertiary carbon center at C2 and C3, respectively (Scheme 2d). To the best of our knowledge, the reaction reported herein represents the first example of a dearomative indole C2−C3 *bisfunctionalization* proceeding via a carbopalladation mechanism.

Our studies began by attempting the proposed dearomative arylcyanation of **1a** using previously established catalytic conditions (eq 1).[12] Examination of the crude reaction mixture

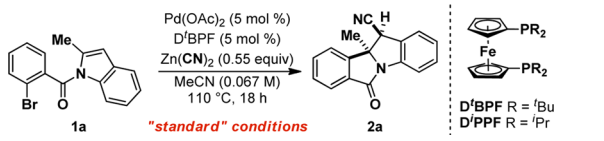


(1)

indicated full conversion of **1a** to a mixture of two products. After isolation, we assigned the structures as the desired indoline **2a** and the corresponding diastereomer **2a**′. Single crystal X-ray analysis later confirmed the relative stereochemistry of **2a**, which represents a *syn*-arylcyanation as anticipated. With this result in hand, we proceeded to optimize the reaction to increase both the yield and ratio of **2a**:**2a**′.

After examining many parameters,[14] Pd(OAc)$_2$ (5 mol %) and D^{t}BPF (5 mol %) with Zn(CN)$_2$ (55 mol %) in MeCN (0.067 M) at 110 °C for 18 h were found to be optimal (Table 1, entry 1). Under these conditions, **2a** was obtained in 98% isolated yield

Table 1. Dearomative Indole Bisfunctionalization via Pd-Catalyzed Arcylcyanation: Effect of Reaction Parameters[a]

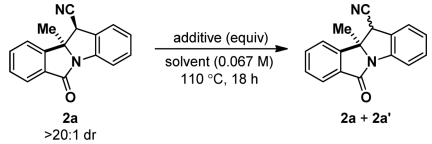


entry	variation from the *"standard" conditions*	dr[a]	yield **2a** (%)[a−c]
1	none	**>20:1**	**99(98)**[d]
2	0.1 M instead of 0.067 M	19:1	95
3	DMF instead of MeCN	1.6:1	90
4	1,4-dioxane instead of MeCN	3:1	92
5	PhMe instead of MeCN	>20:1	5
6	100 °C	>20:1	37
7	ArCl instead of ArBr	13:1	9
8[e]	D^{i}PPF instead of D^{t}BPF	–	<5
9[f]	^{t}BuXantphos instead of D^{t}BPF	–	0
10[e]	K$_4$Fe(CN)$_6$ instead of Zn(CN)$_2$	–	<5
11[e]	no Pd(OAc)$_2$	–	0
12	no D^{t}BPF	–	0

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Combined yield of **2a** and **2a**′. [c]Value in parentheses represents isolated yields. [d]Average value over three experiments. [e]Quantitative recovery of **1a**. [f]0.22 equiv of K$_4$Fe(CN)$_6$ used.

in >20:1 dr. Increasing the concentration to 0.1 M in MeCN showed no serious deleterious effects on yield (95%); yet, the dr decreased to 19:1 (entry 2), which presumably results from epimerization (cf. Table 2). Solvents such as DMF and dioxane

Table 2. Epimerization Studies for 2a



entry	solvent	additive (equiv)	dr[a]	% yield (**2a**+**2a**′)[b]
1	DMF	–	1.8:1	90
2	MeCN	–	>20:1	92
3	1,2-DCE	–	>20:1	91
4	PhMe	–	>20:1	96
5	Dioxane	–	>20:1	99
6	PhMe	HNBu$_2$ (0.5)	1:3	89
7	DMF[c]	–	>20:1	99
8	Dioxane	Zn(CN$_2$) (0.55)[d]	1.2:1	91
9[e]	Dioxane	–[d]	1:3	93
10[e]	Dioxane	Pd(OAc)$_2$ (0.05)	4.7:1	83

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yields. [c]Reaction sparged with N$_2$ for 18 h. [d]Run in the presence of Pd(OAc)$_2$ (5 mol %) and D^{t}BPF (5 mol %). [e]Reaction run for 4 h.

were less effective and resulted in a higher level of epimerization than MeCN (entries 3 and 4). PhMe was not an effective solvent in this transformation and led to only 5% of the desired products, albeit as a single stereoisomer (entry 5). Lowering the temperature to 100 °C led to only partial conversion of **1a** (entry 6). Use of the Cl analog of **1a** proved to be ineffective, and **2a** was obtained in only 9% yield in 13:1 dr (entry 7). Other bulky phosphine ligands such as the D^{i}PPF and ^{t}BuXantphos were not effective, and **1a** was recovered quantitatively in both instances (entries 8 and 9). The less toxic potassium hexacyanoferrate(II) was ineffective in this transformation, providing only traces of **2a** (entry 10). Finally, in the absence of Pd(OAc)$_2$ or D^{t}BPF the reaction failed to provide **2a**, and **1a** was recovered quantitatively (entries 11 and 12).

We sought to gain insight into the origin of **2a**′ which was only observed in reactions run in DMF and dioxane (Table 2). Initially, when a sample of **2a** (>20:1 dr) was resubjected to the conditions from eq 1, epimerization occurred, producing a 1.6:1 mixture of **2a** and **2a**′ in 88% yield. However, in the absence of catalyst, ligand, and Zn(CN)$_2$, a 1.8:1 mixture of **2a** and **2a**′ was still obtained in 90% yield (entry 1). Conversely, when **2a** was heated in neat MeCN, 1,2-DCE, PhMe, or dioxane, it was recovered in high yield with no observable epimerization (entries 2−5), ruling out a strictly thermal process. Since DMF is known to thermally decompose and hydrolyze in the presence of moisture to products including HNMe$_2$,[15] we considered the prospect of this byproduct facilitating epimerization. Accordingly, when **2a** was heated in PhMe in the presence of HNBu$_2$[16] (0.5 equiv), indeed a 1:3 mixture of **2a** and **2a**′ was obtained in 89% yield (entry 6). In addition, epimerization was completely suppressed when **2a** was heated in DMF for 18 h with constant nitrogen sparging (entry 7), providing further evidence for a base mediated process. Since this argument could not be applied to explain the observed epimerization in dioxane, we tested for the ability of reaction components to mediate epimerization in

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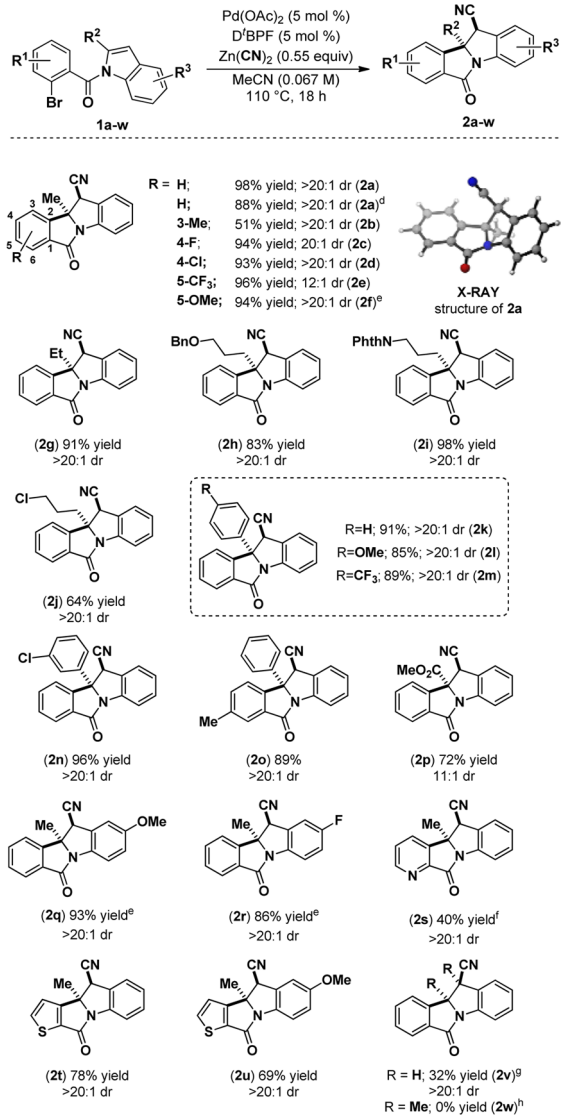
dioxane. Although neither $Zn(CN)_2$ nor $ZnBr_2$ (0.55 equiv) caused epimerization, when **2a** was reacted with $Pd(OAc)_2$ and D^{t}BPF with or without $Zn(CN)_2$ in dioxane, 1.2:1 and 1:3 mixtures of **2a** and **2a′** were obtained in 91% and 93% yields, respectively (entries 8 and 9). Even $Pd(OAc)_2$ alone was found to epimerize **2a** in dioxane to some extent (dr = 4.7:1, entry 10). To date, the exact origin for epimerization in dioxane remains unclear. Another possibility may involve donation of the amide nitrogen electron pair into the adjacent aryl group, causing expulsion of $^-$CN, which could then be reincorporated via a 1,4-attack of the resulting *N*-benzoyl iminium species leading to the observed stereochemical inversion.[17]

Next, the conditions optimized for **1a** were tested on a series of indole substrates possessing sterically and electronically diverse *o*-bromobenzoyl groups (Scheme 3). Indoline **2b** could be obtained in 51% yield as a single diastereomer, suggesting that the reaction is sensitive to steric hindrance in close proximity to the C−Br bond. F- and CF_3-containing indolines **2c** and **2e** were obtained in 94% and 96% yields with 20:1 and 12:1 dr. Furthermore, Cl-containing **2d** was obtained in 93% yield with >20:1 dr. Electron-rich substrates were also well tolerated, and **2f** bearing an OMe moiety was afforded in 94% yield with >20:1 dr.

Ethyl groups (**2g**, 91%), benzylated alkyl alcohols (**2h**, 83%), amines protected as phthalimides (**2i**, 98%), and alkyl chlorides (**2j**, 64%) could be incorporated into the final products, which were obtained with >20:1 dr. Various aromatic groups could easily be incorporated at this position, and it was found that electron-neutral, -rich, and -poor substrates were all converted to the desired products **2k**−**2o** with excellent yields and selectivities. A methyl-indole-2-carboxylate substrate was also reactive and was converted to the corresponding indoline **2p** in 72% yield with 11:1 dr. To test the local electronic effects of the indole component of **1**, substrates **1q** and **1r** were synthesized and subjected to the standard conditions. Electron-rich indoline **2q** was obtained in 93% yield in >20:1 dr. Electron-deficient F-containing **2r** was obtained in 86% in >20:1 dr after only 5 h. In an effort to incorporate heteroaromatic groups into the product landscape, pyridine-containing **1s** and thiophene-containing **1t** and **1u** were tested. They were found to provide the desired products **2s**−**2u** in 40%, 78%, and 69% yield, respectively, all in >20:1 dr. The initial substrates lacked a suitable *β*-H so C−CN reductive elimination was the only option, but a substrate was tested to determine the efficiency of C−CN bond formation vs epimerization/*β*-H elimination or competing cyclization via C−H functionalization.[18] In practice, **2v** can be obtained in 32% yield in >20:1 dr, where the majority of the remaining mass balance was recovered **1v**. Substrate **1w** possessing a 2,3-dimethylindole motif was also tested, which would allow vicinal tetrasubstituted C atoms to be forged in a single reaction. Unfortunately, this reaction failed to produce any of the desired indoline **2w**, while only a catalytic amount of the product arising from carbopalladation/*β*-H elimination was observed.[9]

Finally, a series of derivitization experiments were carried out to examine the synthetic utility of these indolines products (Scheme 4). We reasoned that trapping of an *α*-cyano anion[19] with the Davis oxaziridine[20] would generate the cyanohydrin alkoxide, which could spontaneously eliminate cyanide under the reaction conditions to yield **3**. This reaction proceeded using NaHMDS as the base followed by the (±)-Davis oxaziridine to generate ketone **3** in 74% yield. It was found that **2a** could be alkylated in >20:1 dr with NaH and either *tert*-butyl bromoacetate or bromoacetaldehyde dimethyl acetal to generate ester-containing **4** or aldehyde precursor **5** in 76% and 77% yields, respectively. Indoline **2j** was primed to undergo intramolecular alkylation from the convex side to generate the *cis*-angularly fused carbocycle-containing **6**.

Scheme 3. Dearomative Indole Bisfunctionalization via Pd-Catalyzed Arylcyanation: Reaction Scope[a−c]



[a]Reactions were run on a 0.2 mmol scale unless otherwise stated. [b]All yields shown are combined isolated yields of the diastereomers. [c]dr's were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]Reaction was run on a 1 g (3.17 mmol) scale. [e]Reaction was run for 5 h. [f]$Pd(P^tBu_3)_2$ (10 mol %). [g]Majority of the remaining mass balance was **1v**. [h]Only Heck product was observed. Phth = Phthalimide.

In summary, we have developed a Pd-catalyzed dearomative bisfunctionalization of indoles that proceeds via an intramolecular arylcyanation mechanism. This also represents the first cyanation reaction proceeding via a transmetalation to a 2° benzylic Pd(II) intermediate. By using a $Pd(OAc)_2$/D^{t}BPF catalyst system and $Zn(CN)_2$, complex indolines bearing vicinal tertiary and tetrasubstituted tertiary carbon stereocenters can be obtained in excellent yields and dr from simple indoles. These scalable conditions tolerate a broad variety of functional groups, and by judiciously choosing MeCN, epimerization of the products under the reaction conditions is largely inhibited. Studies toward the application of this method and the

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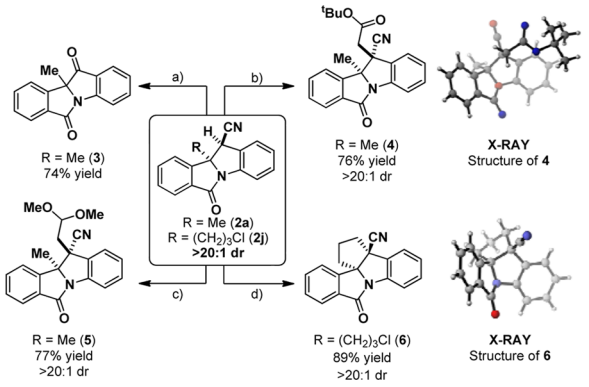
Scheme 4. Derivatization of Products[a]



[a]Reaction conditions: (a) NaHMDS; then (±)-Davis oxaziridine, THF, −78 °C to rt; (b) NaH; then TBAI, $BrCH_2CO_2{}^tBu$, DMF, 0 °C to rt; (c) NaH; then TBAI, $BrCH_2CH(OMe)_2$, DMF, 0 to 60 °C; (d) NaH, TBAB, THF, 65 °C. NaHMDS = sodium hexamethyldisilazide; TBAI = tetra-*n*-butylammonium iodide; DMF = *N*,*N*-dimethylformamide; TBAB = tetra-*n*-butylammonium bromide; THF = tetrahydrofuran.

development of an enantioselective variant are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02403.

All characterization data; ^1H and ^{13}C spectra (PDF)
Crystallographic data for **2a** (CIF)
Crystallographic data for **4** (CIF)
Crystallographic data for **5** (CIF)
Crystallographic data for **6** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) For details, see the Supporting Information.

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(17) This pathway was suggested by a referee during the review process. Attempts to trap the proposed intermediate with PhSH failed, and only a mixture of **2a** and **2a′** was obtained in 64% yield.

(18) Trace cyclized product resulting from C2−H functionalization was detected; see: Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317.

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