

Palladium-Catalyzed Synthesis of 2-Cyanoindoles from 2-gem-Dihalovinylanilines

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Supporting Information

ABSTRACT: An efficient Pd(0)-catalyzed synthesis of 2cyanoindoles from 2-gem-dihalovinylanilines is reported. Few methods have aimed to synthesize these scaffolds, which are found in many natural products and have high bioactivity. This protocol features a robust catalyst system utilizing $Zn(TFA)_2$ to prolong the catalytic activity. Additionally, the amount of cyanide in the reaction phase is minimized by taking advantage of the solubility of $Zn(CN)_2$ in a two-solvent mixture.



M etal-catalyzed cyanation of aromatic and heteroaromatic compounds has been an important research objective, as nitriles serve as versatile synthetic handles for functional group manipulation.¹⁻³ Derivatives of 2-cyanoindoles exhibit high bioactivity and can be identified in many natural products and pharmaceutical agents (Scheme 1).^{4,5}

Scheme 1. Examples of Biologically Relevant Compounds Featuring 2-Cyanoindole-Derived Cores



Recent protocols have utilized Rh,^{6,7} Pd,⁸ Cu,⁹ Co,¹⁰ or Mn/ Zn¹¹ as catalysts to activate the C–H bond at the 2-position of indoles for cvanation (Scheme 2a). These methods allow functionalization of indoles without prefunctionalization of the starting material. However, the use of specific directing groups, which are removed under harsh conditions, limits the scope of the free indole products. Our group $^{12-17}$ and others $^{18-20}$ have developed protocols for the synthesis of functionalized heterocycles from vinylic gem-dihalide substrates (Scheme 2b). The reaction involves two orthogonal coupling reactions: a Buchwald-Hartwig-type coupling to form the core heterocycle and a second coupling reaction such as a Suzuki, Heck, or Sonogashira coupling. Seminal reports by Hartwig²¹ ²³ of the reversibility of oxidative addition with a bulky palladium catalyst into aryl-halogen bonds led our group to develop a catalytic synthesis of 2-bromoindoles in the absence of a coupling partner.²⁴ Herein we report a protocol for the palladium-catalyzed synthesis of 2-cyanoindoles from 2-gemdihalovinylanilines and an external source of cyanide to terminate the coupling sequence (Scheme 2c).

Scheme 2. Metal-Catalyzed Syntheses of 2-Substituted Indoles









We began our studies with conditions similar to those previously reported²⁴ and the use of $Zn(CN)_2$ as the cyanide source. After screening reaction parameters, we found $Pd(t-Bu_3P)_2$ (5 mol %), $Zn(CN)_2$ (0.55 equiv), $Zn(TFA)_2$ (10 mol %), and K_3PO_4 (2 equiv) in PhMe–DMA (3:1) at 110 °C for 18 h on a 0.5 mmol scale to be our optimal conditions for **2a** in 74% yield (Table 1, entry 1). The reaction was run on a 1 mmol scale with no change in yield (Table 1, entry 2). The use of the *gem*-dichloride is possible, delivering the product in comparable yield (Table 1, entry 3).

When no additive was used, the reaction was irreproducible and failed to fully consume all of the starting material (Table 1,

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Table 1. Optimized Conditions



^{*a*}Average of three runs. ^{*b*}Yield determined by ¹H NMR analysis of the crude mixture using 1,3,5-trimethoxybenzene as an internal standard. ^{*c*}Large amounts of **3** were isolated (42%).

entry 4). Grushin and Macgregor have recently described the modes of Pd catalyst deactivation during cyanations by the presence of air, water, amines, and excess cyanide.²⁵ Limited reports on the use of Zn(0) and $Zn(OAc)_2$ to improve catalytic turnover are available.^{26,27} When Zn(0) was used, improved conversion was observed, but the reaction remained irreproducible with variance in the yield of up to 30% in parallel studies (Table 1, entry 5). The use of $Zn(OAc)_2$ was detrimental to the reaction, and large amounts of bromoalkyne 3 were produced (Table 1, entry 6). The trifluoro variant was used to reduce the basicity of the acetate counterion in order to prevent the elimination from occurring. $Zn(TFA)_2$ led to full consumption of the starting material and the highest yield consistently. Although the role of the additive is unclear, it may facilitate transmetalation.

The solvent ratio was carefully selected to accommodate the opposing polarity requirements for cyclization^{12-17,24} and cvanation,³ as they necessitate the use of nonpolar and polar conditions, respectively. In the absence of DMA as a cosolvent, full consumption of the starting material, is achieved and 2a' is the major product (Table 1, entry 7). The bromoindole is a likely intermediate in the reaction (vide infra), suggesting that the cyanation is slower. We reasoned that the lower reactivity was the result of the poor solubility of $Zn(CN)_2$ in PhMe.²⁵ In contrast, poor conversions were observed in a 1:1 solvent ratio (Table 1, entry 8). Only 2a was observed, suggesting that cyanation of 2a' occurred rapidly but with poor catalytic turnover. A 3:1 solvent ratio was found to be ideal for a consecutive cyclization/cyanation. We believe that this may also moderate the amount of $Zn(CN)_2$ present in solution throughout the reaction, hence slowing the formation of catalytically inert, coordinatively saturated palladium complexes. DMA proved to be better than other polar solvents such as THF and MeCN because of its high boiling point. Reactions with DMF yielded greater amounts of 3 as a byproduct, presumably by solvent decomposition at high temperatures.28

With our optimized conditions in hand, we proceeded to investigate the scope of the transformation (Scheme 3). The

Scheme 3. Scope of the Pd(0)-Catalyzed Synthesis of 2-Cyanoindoles from gem-Dibromides⁴



"Reactions were run on a 0.5 mmol scale. ${}^{b}Pd(t-Bu_{3}P)_{2}$ (7.5 mol %), Zn(TFA)₂ (15 mol %), 120 °C. "From 4-bromo-2-(2,2-dibromovinyl)aniline using Zn(CN)₂ (2.2 equiv).

synthesis of 1a-q was realized from the nitroaldehydes by olefination using CBr₄ and reduction as we previously reported (see the Supporting Information). Extending the aromatic system to the naphthyl ring delivered product 2b with no loss in yield (74%). Alkyl substitution adjacent to the aniline or the vinyl dibromide delivered products 2c and 2d in 71% and 69% vield, respectively. Alkyl and benzyl groups on the aniline nitrogen provided the N-capped indoles with no loss in yield (2e-g, 72%, 72%, 77%), even when a sterically demanding isopropyl group was used. Placing an electron-donating OMe at the para position relative to the aniline gave an improved yield (2h, 77%), presumably by increasing the nucleophilicity of the nitrogen. In contrast, an electron-withdrawing substituent para to the aniline, as in 2i and 2j bearing CO2Me and F, necessitated slightly higher catalyst loading and higher temperature to achieve full consumption (48%, 67%). A Clcontaining aniline was well-tolerated and delivered product 2k with minimal loss in yield (70%). An opposite trend was found for the electronic effect of the position para to the olefin. While the methoxy substitution required forcing conditions to deliver product 2l in 68% yield, the methyl ester-containing scaffold reacted smoothly to afford product 2m in 75% yield. Fluorine substitution led to product 2n, albeit in reduced yield (61%). Having similar electronic properties to 1h, 1o reacted smoothly to afford 20 in slightly improved yield (77%). Interestingly, the highly electron-rich nature of the scaffold bearing the dioxolane ring was more challenging, providing 2p in reduced yield (53%). Upon treatment under the standard conditions, Brcontaining scaffold 1q led to a complex mixture, possibly because of competing cyanation of the aryl ring. Increasing the $Zn(CN)_2$ loading to 2.2 equiv afforded **2q** in satisfactory yield (61%).

To further evaluate the mechanism of the transformation and gain insight into the roles of the observed species, 2a' and 3 were synthesized. Subjecting 2a' to the standard conditions delivered the desired product in 93% yield (eq 1):This result



supports the proposal that the reaction proceeds via the formation of 2a'. In contrast, when 3 was subjected to the same conditions, 60% of the material was recovered unreacted with no other compounds identified (eq 2):This result suggests that 3 is part of a nonproductive decomposition pathway leading to loss in mass balance under these conditions.



We sought to investigate the order of events, i.e., the possibility that cyanation occurs prior to cyclization. Although we have never observed these products in reactions carried out to partial conversions, this sequence remains a plausible pathway since oxidative addition of a catalyst across the C–(E)-Br bond would give the kinetically favored product. Selective coupling of the C–(E)-Br with boronic acids is known,¹⁴ but any attempts²⁹ to cyanate by selective cross-coupling led to full recovery of unreacted starting material. The difficulty of this cyanation by metal-catalyzed methods raises doubt about cyanation occurring prior to cyclization.

A plausible mechanism for the reaction is shown in Scheme 4. Oxidative addition into the C–Br bond of 1a provides the stabilized palladacycle. Deprotonation of the aniline and reductive elimination provides 2a'. Oxidative addition into the C2–Br bond occurs reversibly. Transmetalation from a zinc species and reductive elimination delivers 2a and regenerates the catalyst.

Scheme 4. Proposed Mechanism



To show the synthetic versatility of these products, a one-pot derivatization was performed (Scheme 5). Upon completion of the Pd step, NaN_3 and NH_4Cl were added to the vial, and upon heating for 14 h, 4 was isolated in 65% yield.

Scheme 5. One-Pot Derivatization To Afford the Corresponding Tetrazole



In conclusion, we have developed a convenient method for the synthesis of 2-cyanoindoles from easily accessible aniline precursors. This reaction utilizes an additive that maintains the catalytic activity and a solvent mixture that limits the cyanide concentration in the reaction phase to prevent catalyst poisoning. Finally, the versatility of the products was demonstrated by extending the protocol to a one-pot transformation of the nitrile to the tetrazole.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b02244.

Procedures, characterization data, and $^1\mathrm{H}/^{13}\mathrm{C}$ NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(29) Catalysts such as Pd, Ni, and Cu were used with varying ligands and $Zn(CN)_2$ or KCN as the cyanide source. Along with 1a, gem-vinyl dihalides with *o*-nitro functionality and dimethyl-protected aniline were used. All of these reactions led to recovery of the starting material.