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Diastereoselective Palladium-Catalyzed Arylcyanation/Heteroarylcyanation of Enantioenriched *N*-Allylcarboxamides

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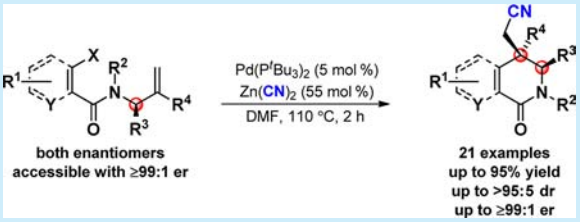
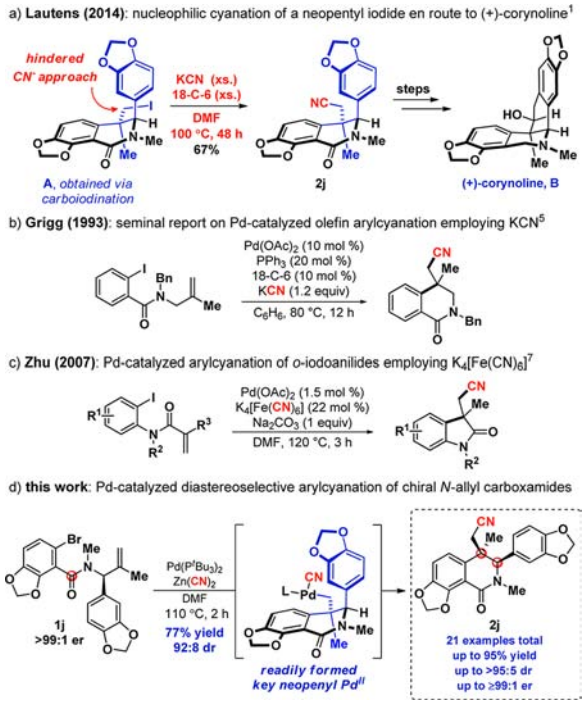
Supporting Information

ABSTRACT: A diastereoselective Pd-catalyzed arylcyanation/heteroarylcyanation of chiral *N*-allylcarboxamides using $Zn(CN)_2$ as the cyanide source is reported. Nitrile-containing dihydroisoquinolinone products are obtained in good to excellent yields with up to >95:5 dr and with full preseveration of enantioenrichment. By circumventing a difficult nucleophilic cyanation of a hindered neopentyl iodide, this approach represents an improvement to the previously reported formal synthesis of (+)-corynoline.



We recently reported the development of a highly diastereoselective Pd-catalyzed carboiodination of enantioenriched *N*-allylcarboxamides to access substituted dihydroisoquinolinones.[1] The synthetic utility of this reaction was highlighted by its use in the key C−C bond-forming step in the formal synthesis of (+)-corynoline[2] **B** (Scheme 1a). Our synthetic design relied on a challenging nucleophilic cyanation of hindered neopentyl iodide **A** containing a flanking aromatic group to obtain nitrile **2j**, which possessed all the carbon atoms found in the natural product. This transformation proceeded, albeit under forcing conditions (100 °C, 48 h), using excess KCN and 18-C-6 in DMF. With the goal of increasing the efficiency of this sequence, we envisioned employing a Pd-catalyzed arylcyanation of an enantioenriched *N*-allylcarboxamide as a means to incorporate this key functional groups while at the same time circumventing the need for an otherwise challenging two step process.

Scheme 1. Hindered Alkyl Nitrile Synthesis via Nucleophilic Cyanation and Pd-Catalyzed Arylcyanation



A survey of the chemical literature revealed reports of Pd-catalyzed arylcyanation to be scarce. Nonetheless, evidence to suggest the feasibility of this process existed. Inspired by the pioneering work of Larock[3] and Torri,[4] Grigg first demonstrated Pd-catalyzed intramolecular alkene arylcyanation via anion capture[5] using KCN in the presence of 18-C-6 (Scheme 1b).[6] Subsequently, Zhu reported improved conditions for the intramolecular alkene arylcyanation of *o*-iodoanilides using $K_4[Fe(CN)_6]$ en route to racemic 3,3-disubstituted oxindole derivatives (Scheme 1c).[7] The authors also included preliminary data concerning an enantioselective variant, which employed chiral bisphosphine ligands. Other major contributions[8] to the field of metal-catalyzed cyanation have been both direct cyanation of aryl halides using palladium[9] and carbocyanation proceeding via C−C bond cleavage using nickel.[10,11]

Despite these advances there exist no reports of Pd-catalyzed diastereoselective alkene arylcyanation using enantioenriched aryl bromides and no reports of heteroarylcyanation.

Herein, we report the development of a Pd-catalyzed diastereoselective arylcyanation/heteroarylcyanation of chiral *N*-allylcarboxamides using a substoichiometric amount of $Zn(CN)_2$ en route to complex and enantioenriched nitrile-containing dihydroiosqinolinones possessing vicinal tertiary and quaternary stereocenters (Scheme 1d).

After examining a series of reaction parameters for the arylcyanation of carboxamide **1a** (>99:1 er),[12] we found

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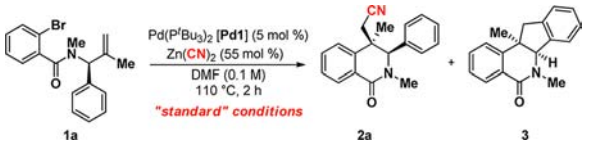
$Pd(P^tBu_3)_2$ (5 mol %) in the presence of $Zn(CN)_2$ (55 mol %) in DMF at 110 °C for 2 h to be optimal in terms of yield and selectivity, in addition to being most tolerant to less costly aryl bromides. Under these conditions, **2a** could be obtained in 90% yield with a 95:5 dr and >99:1 er.[13] The absolute stereochemistry of the major diastereomer was unambiguously determined to be *syn* by an X-ray diffraction study. These conditions were found to completely inhibit the formation of inseparable byproduct **3**, presumably arising from a domino carbopalladation/C−H functionalization sequence,[14] as well as the product of direct aryl halide cyanation.[9] Table 1 highlights the effect various reaction parameters have on the reaction in terms of yield, diastereoselectivity, and byproduct formation.

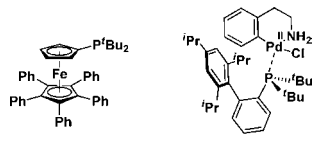
Table 1. Pd-Catalyzed Diastereoselective Arylcyanation Reaction of Chiral *N*-Allylcarboxamides: Effect of Reaction Parameters[a]



1a 2a 3

entry	variation from the "standard" conditions	dr[a]	yield of **2a**[b–d] (%)	yield **3**[b] (%)
1	**none**	**95:5**	**86 (90)**[e]	**0**
2	Zn dust (5 mol %)	93:7	89	0
3	$Pd(QPhos)_2$ instead of [**Pd1**]	90:10	69	0
4	[**Pd2**] instead of [**Pd1**]	94:6	4	0
5	dioxane instead of DMF	75:25	11	0
6	PhMe instead of DMF		0	0
7[f]	$K_4[Fe(CN)_6]$ instead of $Zn(CN)_2$		0	32
8	ArI instead of ArBr	93:7	55	0
9[g]	ArI instead of ArBr	88:12	77	0
10	ArCl instead of ArBr	94:6	57	0
11	90 °C	96:4	73	0

[a]Reactions run on 0.3 mmol scale. See the Supporting Information for full details of optimization. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. [c]Yield of both diastereomers. [d]Values in parentheses represent isolated yields. [de] [e]Average value over three experiments. [f]Run in the presence of Na_2CO_3 (1 equiv). [g]Reaction run in the presence of Zn dust (10 mol %).



Zinc has been commonly employed in metal-catalyzed cyanations as a cocatalyst[15] which reduces any Pd(II) species to catalytically active Pd(0) species,[16] and it has been reported to act as a cyanide scavenger to prevent catalyst poisoning.[9,17] However, its addition to the reaction of aryl bromides showed no significant improvement to the reaction outcome (Table 1, entry 2). The use of other Pd precatalysts containing bulky ligands, such as $Pd(QPhos)_2$ and Buchwald's ^{t}BuXPhos Pd G1 [**Pd2**], produced inferior yields and selectivities (Table 1, entries 3 and 4). Other solvents such as 1,4-dioxane or PhMe led to greatly attenuated reactivity and yields (Table 1, entries 5 and 6).[15] When the reaction was run using the conditions reported by Zhu, formation of **2a** did not occur. Instead, arylation product **3** was observed in 32% yield (Table 1, entry 7), a result which may be explained by the slower rate of cyanide transfer to the Pd catalyst with respect to that of $Zn(CN)_2$,[18] as well as the presence of carbonate base. $Zn(CN)_2$ appears to have the optimal reactivity profile, as both cyanide equivalents are transferred over the course of the reaction. Its highly covalent nature leads to a decreased amount of free cyanide in solution, which deters catalyst deactivation.[19] Both aryl iodide and chloride derivatives of **1a** led to inferior results (Table 1, entries 8 and 10). However, the reactivity of the ArI derivative could be restored by adding a catalytic amount of Zn dust to the reaction (Table 1, entry 9).[19,20] The decreased yields of ArI substrates under the standard conditions may be a result of trace dimerization of the starting material, consequently generating Pd(II). In this reaction, zinc may act to maintain appropriate concentration levels of the active catalyst.[21,22] Finally, lowering the reaction temperature to 90 °C led to sluggish conversion of **1a**, while no improvement in diastereoselectivity was observed (Table 1, entry 11).

Having found suitable conditions, the scope of the arylcyanation was explored using a variety of aryl, vinyl, and heteroaromatic bromides (Schemes 1 and 2). It should be noted that in all cases the desired products (**2a−s**) were obtained with essentially no erosion of er (98:2 to >99:1). In addition, either enantiomer of the product could be accessed with nearly complete enantioenrichment. *o*-Me substituted **1b** was reacted under the standard reaction conditions, yielding the desired product **2b** in 89% with a >95:5 dr. Dihalogenated carboxamide **1c** was efficiently cyclized to afford the desired chlorodihydroisoquinolinone product **2c** in 89% yield with a 94:6 dr. By converting the *N*-protecting group from methyl to benzyl (**1d**), product **2d** could be obtained in 85% yield with 91:9 dr. Chloro- and trifluoromethyl-substituted aryl bromides **1e** and **1f** afforded the desired products in 70% and 78% yields with 91:9 and 89:11 dr, respectively. Substitution on the allylic aromatic group (**1g−i**) shows no deleterious effects and the corresponding products (**2g−i**) were obtained in high yields with good to excellent levels of selectivity. (+)-Corynoline precursor **2j** could be obtained in 77% yield with 92:8 dr under the standard conditions. The reaction could be run on gram scale (4.75 mmol) to obtain **2j** in 79% yield with >95:5 dr using a decreased catalyst loading (2.5 mol % [Pd]). We were able to increase the efficiency of the previously reported route to from 56% over two steps (Pd-catalyzed carboiodination followed by nucleophilic cyanation using KCN)[1] to 79% in a single Pd-catalyzed transformation.

Alkyl PMB ether **1k** was transformed to the desired product **2k** in 66% yield with almost no diastereoselectivity (53:47 dr). This finding can be rationalized by the decreased steric demand of the alkyl group compared to the Ar group, and is consistent with previous models suggesting that diastereoselectivity is governed by $A^{1,2}$ strain[23] in this class of substrates.[24] Other alkyl groups (R^4) such as Et (**1l**) and an alkyl PMB ether (**1m**) were tolerated leading to the desired products **2l** and **2m** in 73% and 77% yield and 95:5 and 92:8 dr, respectively. Product **2n** was obtained in 67% yield with an 87:13 dr from the corresponding vinyl bromide **1n** with the aid of the amine base PMP.[25] In this example, trace amounts of cyclopropanation products were observed, which are thought to arise from cyclopropanative carbopalladation of the activated olefin by the neopentyl Pd(II) intermediate.[24]

Heteroaromatic halides were also explored under the optimized conditions (Scheme 3). 3-Bromopicolinic acid derivative **1o** and thiophene **1p** were transformed to the corresponding products **2o** and **2p** in 70% and 87% yield,

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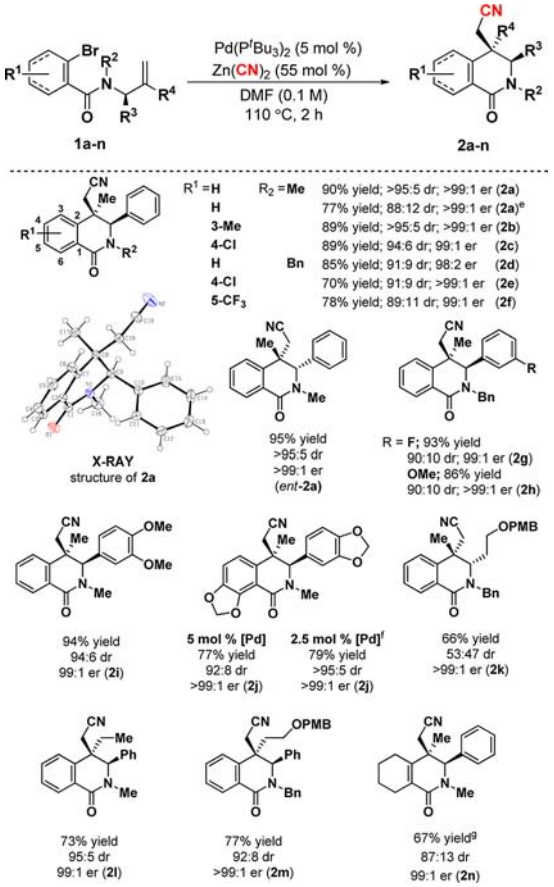
Scheme 2. Pd-Catalyzed Diastereoselective Arylcyanation Reaction of Chiral *N*-Allylcarboxamides: Aryl and Vinyl Bromide Scope[a]

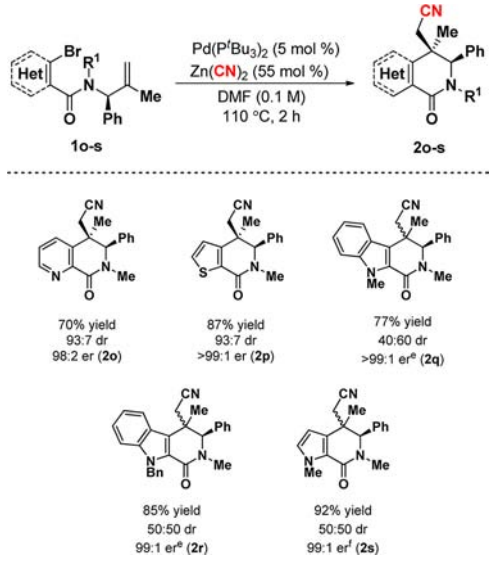


[a]Reactions were run on a 0.3 mmol scale unless otherwise stated. [b]All yields shown are combined isolated yields of the diastereomers. [c]dr's were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]er's were determined by HPLC using a chiral stationary phase. [e]Reaction was run using the ArI derivative of **1a** in the presense of 10 mol % Zn dust. [f]Reaction was run on a 4.75 mmol scale. [g]Reaction run in the presence of 50 mol % of PMP. PMP = 1,2,2,6,6-pentamethylpiperidine.

respectively, with 93:7 dr in both cases. Notably, 3-bromoindoles **1q** and **1r** successfully underwent heteroarylcyanation, affording **2q** and **2r** in 77% and 85% yield, albeit with almost no diastereoselectivity. In the case of *N*-Me indole **1q**, a switch in stereochemistry of the major diastereomer was observed, and the *anti* product was found to be in slight excess. Pyrrole **1s** also underwent efficient conversion to product in 92% yield also with no diastereoselectivity. This finding echoes the results of **2p**–**r**, which suggests that the extended aromatic structure of the indole substrates is not causing the observed decrease in selectivity. Instead, the electron rich nature of such hetereoaryl Pd(II) intermediates resulting from carbon–halogen oxidative addition with respect to the aryl analogs is thought to cause this effect. Nevertheless, examples **2o**–**s** represent the first Pd-catalyzed heteroarylcyanation reactions, to the best of our knowledge.

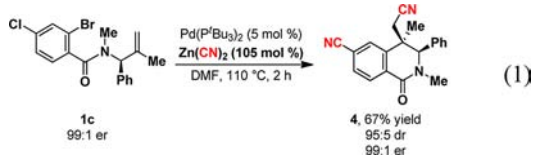
A tandem arylcyanation/direct cyanation could be achieved yielding bis nitrile **4** in 67% yield with a 95:5 dr using dihalogenated carboxamide **1c** when the Zn(CN)$_2$ loading was increased to 105 mol % (eq 1).[26] Notably, no direct aryl bromide

Scheme 3. Pd-Catalyzed Diastereoselective Arylcyanation Reaction of Chiral *N*-Allylcarboxamides: Scope of Heteroaryl Bromides[a]



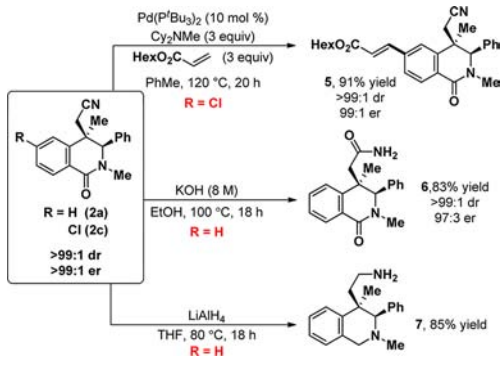
[a]Reactions were run on a 0.3 mmol scale unless otherwise stated. [b]All yields shown are combined isolated yields of the diastereomers. [c]dr's were determined by ^{1}H NMR analysis of the crude reaction mixture. [d]dr's were determined by HPLC using a chiral stationary phase. [e]Both diastereomers were found to possess this er. [f]er value for the *syn* diastereomer.

cyanation products were observed in this case, signifying that carbopalladation of the olefin is a faster process.



Finally, product derivitization studies were undertaken to assess the synthetic utility of the enantioenriched dihydroisoquinolinones. Pure diastereomers of products **2a** and **2c** were chosen to elicit the reactivity of the key functional groups (Scheme 4). A Mizoroki–Heck reaction of aryl chloride **2c** was accomplished using a variation to Fu's conditions[27] which furnished the *trans* alkene product **5** in 91% yield. Primary amide **6** could be obtained in 83% yield via nitrile hydrolysis of **2a** under basic conditions. Finally, global reduction of cyclized product **2a**

Scheme 4. Derivitization of Alkyl Nitrile Products



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using excess $LiAlH_4$ in refluxing THF, produced diamine **7** in 85% yield.

In conclusion, we have developed a diastereoselective Pd-catalyzed arylcyanation of enantioenriched carboxamides which yields neopentyl nitrile-containing dihydroisoquinolinones with full preseveration of enantioenrichment and with yields and dr's up to 95% and >95:5, respectively. The reaction conditions were shown to tolerate various functionality and substrate classes, notably vinyl and heteroaromatic bromide substrates. The latter series represents the first examples of a Pd-catalyzed hetero-arylcyanation reaction. This method represents a marked improvement to our previous work concerning the synthesis of the alkaloid natural product (+)-corynoline, specifically the incorporation of the key hindered nitrile function group.

■ ASSOCIATED CONTENT

Supporting Information

All characterization data, including spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) PMP acts to regenerate Pd(0) from HPd(II)X, which arises from a cycloproopanation/β-hydride elimination sequence. See ref 24 for examples. Without the amine incomplete conversion is observed, and C−H functionalization of the allyl aromatic group is observed as the major product when Cs_2CO_3 is used.

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