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Forming Benzylic Iodides via a Nickel Catalyzed Diastereoselective Dearomative Carboiodination Reaction of Indoles

Austin D. Marchese, Florian Lind[†], Áine E. Mahon[†], Hyung Yoon and Mark Lautens*

Abstract: A diastereoselective dearomative carboiodination reaction is reported. We report a novel metal-catalyzed approach to install reactive secondary benzylic iodides. Utilizing the unique reactivity of nickel, we have expanded the carboiodination reaction onto non-activated aromatic double bonds forming a previously unattainable class of iodides. We also report a broadly applicable method to avoid the use of a metallic reducing agent by utilizing an alkyl phosphite as the ligand. The reaction is thought to proceed through a *syn* intramolecular carbonickelation onto a 2-substituted indole followed by a diastereoretentive reductive elimination of the carbon–iodine bond. The complex iodinated indolines generated in the reaction were obtained in moderate to good yields and good to excellent diastereoselectivity. The products were easily functionalized via a variety of synthetic methods.

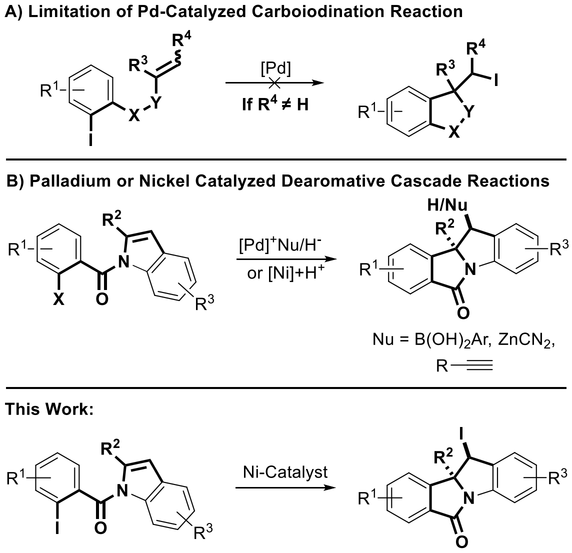
Since our first report of catalytic reversible oxidative addition into C–X bonds in 2010,[1] we have been exploring the utility of carbohalogenation as a strategy in synthesis.[2] A significant limitation to the carboiodoination cyclization methodology is the requirement of a terminal activated alkene (Scheme 1A). All efforts to expand the scope have been met with failure. These challenges associated with using an internal alkene in a carboiodination reaction include the difficulty of the reductive elimination as well as additional potential decomposition pathways (e.g. β-elimination).

We and others have explored dearomative functionalization reactions and have been successful at C–H and various C–C bond formations (Scheme 1B).[3] However, the corresponding C–X termination step has failed with all palladium catalysts examined to date. Perhaps this is not surprising due to the limited range of ligands in the Pd-carboiodination reaction and the sensitive nature of the resulting benzylic iodides,[4] as well as the added difficulty of the final reductive elimination step to turn over the catalytic cycle.

Our recent discovery of a nickel catalyzed carboiodination[5a] and the potential for an alternative mechanism[6] opened the door to exploring the creation of highly sensitive benzylic iodides. To the best of our knowledge, there is only one example of nickel catalyzed dearomative functionalization,[7] leaving this concept largely unexplored. Nickel is known to catalyze the reductive elimination of a Csp^2–X bond[8] however, the formation of a Csp^3–X bond is rare.[5]

Herein we report the diastereoselective dearomative carboiodination reaction using our nickel-phosphite caboiodination catalyst, yielding reactive secondary benzylic iodides in moderate to good yield and good to excellent diastereoselectivity. To demonstrate the synthetic versatility of these benzylic iodides, the products were subjected to a wide variety of transformations including, oxidation/reduction, nucleophilic displacements, decarboxylative elimination and radical cross-coupling reactions. These derivatized products were isolated in moderate to excellent yields with high chemo- and stereoselectivity.

Aside from the reduction of the C–I bond, there are no literature known procedures to generate these derivatized compounds via a 1-pot bisfunctionalization, making these benzylic iodides a useful intermediate to a broad-scope of elusive 1,2-bisfunctionalized indolines.



Scheme 1. Limitation of the Pd-carbiodination reaction and Pd– and Ni–catalyzed dearomative cascade reactions.

We began the investigation employing NiI_2 (10 mol%), $P(Oipr)_3$ (20 mol%), Mn (60 mol%), in toluene (0.2 M) at 100 °C for 24 hours and obtained the product in 15% yield with 20% recovered starting material. Increasing the ligand load to 40%, gave **2a** in 26% yield with complete consumption of starting material. We hypothesized that the product might be unstable under the reaction conditions and showed that the reaction was complete in only 2 hours, affording **2a** in 67% yield with 10:1 d.r (Entry 2). Changing the ligand:metal ratio did not positively alter the yield (Entries 3-5). The reaction did not proceed in the absence of ligand or nickel; however, removing Mn did not impact the formation of **2a**.[9]

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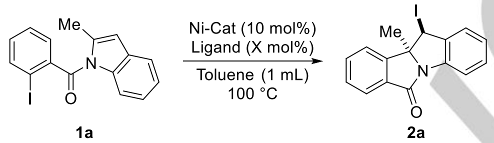
The use of phosphites to reduce Ni(II) precatalysts represents a simpler protocol.[10] Our previously reported carboiodination reaction of N-(2-iodophenyl)-*N*-methyl phenylacrylamide gave the 3,3-disubstituted oxindole in a comparable yield of 84%, using a phosphite as the ligand and the reducing agent.[11] This discovery adds value to the previously reported methodology, as the removal of Mn-powder reduces the amount of waste generated, need for an aqueous workup, as well as allowing for the opportunity to perform in-situ NMR monitoring experiments.



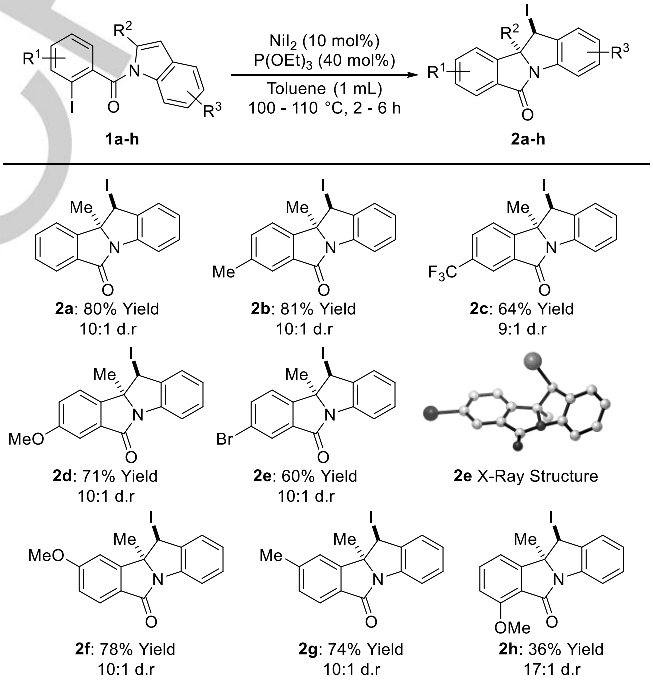
Entry	Ni–Cat	Ligand (mol %)	Time(h)	Yield (%)	d.r
1[a]	NiI_2	$P(Oipr)_3$ (40)	1	35	10:1
2[a]	NiI_2	$P(Oipr)_3$ (40)	2	67	10:1
3[a]	NiI_2	$P(Oipr)_3$ (40)	3	54	10:1
4	NiI_2	$P(Oipr)_3$ (30)	2	61	9:1
5	NiI_2	$P(Oipr)_3$ (50)	2	28	N.R
6	**NiI_2**	**$P(OEt)_3$ (40)**	**2**	**81(80)**	**10:1**
7	$Ni^0[P(OEt)_3]_4$	N/A	3	10	N.R
8[b]	NiI_2	$P(OEt)_3$ (40)	3	29	10:1

Table 1. Optimization of the Ni–catalyzed dearomative carboiodination Reaction. Yields determined by 1H NMR using 1,3,5–trimethoxybenzene. a. reactions were run with Mn present. Yields in bracket is isolated. a. 60 mol% of Mn was added. b. Reaction was run using the aryl bromide starting material with 2 eqv KI at 110 °C.

Many other ligands were screened, with phosphites emerging as the only viable option.[12] Triethyl phosphite was found to be the optimal ligand, giving the product in an 81% yield and 10:1 d.r (Entry 6). It is noteworthy that $Ni^0[(POEt)_3]_4$ gave **2a** in only 10% yield, supporting our previous study with added phosphite. Other solvents and temperatures were screened but gave no improvement.[13]

Use of the aryl bromide with 2 equiv of exogenous iodide, gave **2a** in a 29% yield (Entry 8). The same diastereomer, was formed. Although the yield was considerably lower, the result demonstrates the ability of the catalyst to insert into the aryl bromide bond and perform a bromide to iodide exchange.

We explored the scope of the reaction, starting with modifying electronic effects on the aryl iodide.[14] Electron donating groups at the 4 and 5 position (**2b, 2d**–**2g**) were tolerated giving good yields and d.r of the corresponding products. Introducing an electron withdrawing $–CF_3$ group para to the iodide gave a slightly reduced yield and d.r. (**2c**). An *o*-methoxy group (**2h**) was tolerated, albeit in lower yields, but with a 17:1 d.r. Chemoselectivity was observed when the 4–bromo–indoline **2e** was formed in a 60% yield with a 10:1 d.r. A crystal structure was obtained confirming the stereochemical assignment. The X-ray structure of **2e** revealed the relationship between the iodine and the aryl group is *syn*, which is consistent with a syn carboiodination-reductive elimination mechanism[15]. The tolerance of a bromide is noteworthy, as it suggests a selective oxidative addition into the aryl iodide.



Scheme 2. Ni–catalyzed dearomative carboiodination reaction scope. All yields refer to isolated products. D.r. values were determined by ^1H NMR analysis of the crude reaction mixture. Reactions were run on a 0.2mmol scale. *2f was run on a 0.166mmol scale.

Both electron withdrawing and donating groups were compatible at the 5–position of the indole. An indole bearing the electron withdrawing fluorine gave a more stable product than the corresponding 5-methoxy indole, though **2i** was obtained in lower d.r than **2j**. With increasing steric bulk at the 2 position of the indole, the reactivity of the substrate decreased, but the d.r improved with the higher congeners (**2a**,**2j**,**2k**). This result supports the hypothesis of a steric influence affecting the diastereoselectivity. We saw a significant improvement in the diastereoselectivity of the reaction when an electron withdrawing ester was placed at the 2 position of the indole, as products **2m** and **2n** were obtained as a single diastereomer. The increased diastereoselectivity could be a combination of the increased steric bulk on the indole as well as change in electronic bias of the system. When an aromatic group was placed at the 2–position the reaction was sluggish, which might be attributed to added π–conjugation. Both **2o** and **2p** required the catalyst load to be doubled, and a higher temperature of 120 °C in the case of **2p.** Although the yields were lower, the d.r. remained ≥ 20:1. Substitution of the aryl iodide with a heteroaromatic iodide was tolerated giving the thiophene-fused product **2q** in a 54% yield and 12:1 d.r.

To test the scalability of the reaction we employed substrate **1n** at 1mmol to give **2n** in a somewhat reduced 63% yield, but with the same diastereoselectivity (>20:1) (Scheme 4). The

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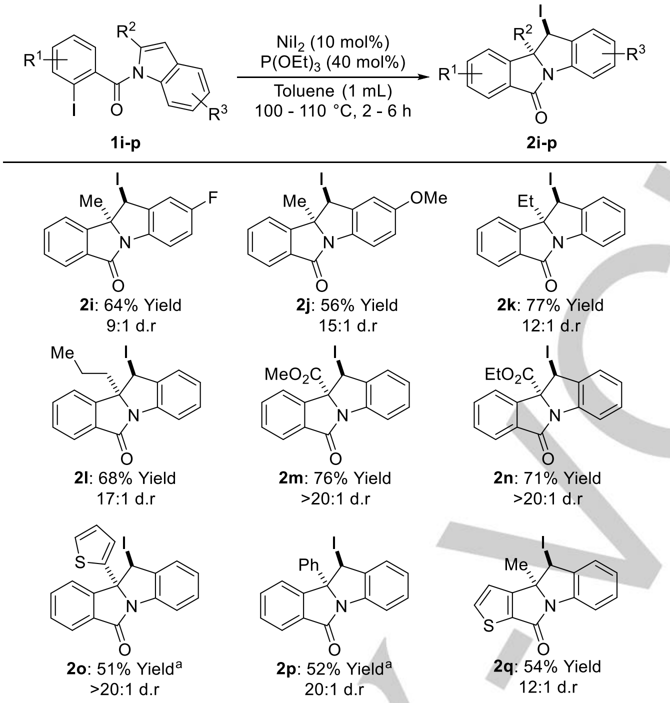


Scheme 3. Ni–catalyzed dearomative carboiodination reaction scope. 0.2 mmol scale. All yields refer to isolated products. d.r. values were determined by ^{1}H NMR analysis of the crude reaction mixture. All reactions were run on a 0.2mmol scale. a. 20 mol% of NiI_2 and 80 mol% of $P(OEt)_3$ was used.

reaction was best run at 105 ºC for 4.75h in a more concentrated solution (0.25 M).

To showcase the reactivity of the product iodides we sought to derivatize the C–I bond via simple synthetic methods (Scheme 4). Until recently, Pd-catalyzed dearomative-trapping methods in the literature have been primarily limited to the formation of C–C and C–H bonds,[16] rendering the incorporation of heteroatoms or other halides difficult.

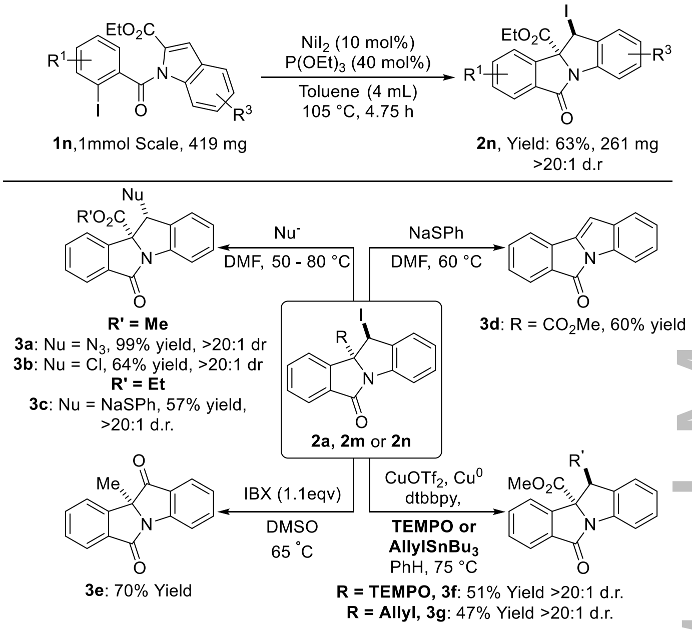
Reactive nucleophiles gave selective displacement of the benzylic iodide. Azide and chloride react to give **3a** and **3b** in moderate to excellent yields. The nucleophilic displacement occurred via an S_N2 process, giving the anti-diastereomer, which is not possible to achieve by other metal-catalyzed methodologies.

When a soft nucleophile was employed, the identity of the ester plays a key role. With R=CO_2Me we obtained exclusively a Krapcho–type decarboxylation-elimination to form the substituted indole scaffold (**3d**). When R=CO_2Et, the decarboxylation is disfavoured and we obtained the displacement product containing thiophenolate in 57% yield (**3c**). Although the eliminated product was not the intended pathway, we note an interesting control based on the identity of the R group. The formation of this product is also noteworthy as attempts to form the Heck type product on the 2-H indole substrate lead to no reaction (see SI for more details).

We employed an oxidizing agent that is selective for benzylic alcohols and halide moieties, namely IBX. The desired dicarbonyl product **3e** was isolated in 70% yield, which was somewhat higher than expected as oxidation reactions of crowded alkyl halides typically give poor yields.[17]

Employing a copper catalyzed cross-coupling protocol, we were able to obtain the products using two different radical coupling partners in moderate yields. When TEMPO was employed, we obtained the product in a 51% yield as a single diastereomer (**3f**). This yield is comparable to the secondary benzylic halides reported in the literature.[18] We also used allyltributyltin under the same conditions and obtained the allylated product **3g** in a 47% yield as a single diastereomer.

We were also able to obtain selective reduction of the C–I bond of **2m** using Zn/AcOH[19], giving the indoline scaffold **3h** in 65% yield (see SI for more details). We attempted radical benzylic iodination of **3h**, but all efforts proved unsuccessful. The inability to instal the iodine via conventional iodination methods supports the value of the dearomative carboiodination reaction(see SI for more details).



Scheme 4. Scalability test and derivatization studies concerning the benzylic iodide.

In conclusion, we have identified a method to generate reactive secondary benzylic halides via a diastereoselective dearomative carboiodination reaction, using an air stable nickel precatalyst. We have successfully expanded and diversified the carboiodination reaction to include secondary benzylic carbon–iodine bond formation. A wide variety of functional groups and substitution patterns were tolerated giving moderate to good yields and good to excellent diastereoselectivity.

We have demonstrated subsequent carbon–iodine bond transformations via nucleophilic attack, elimination, oxidation, reduction and copper catalyzed cross coupling. This method further illustrates the utility of nickel catalysis and represents significant advance in the carboiodination reaction and dearomative 1,2-difunctionalization reaction in the synthesis of iodoindoline scaffolds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information
Experimental procedures, optimization, characterization and X-Ray data (PDF)

X-ray data for **2e** (CIF)

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Notes
The authors declare no competing financial interests.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbohalogenation Diastereoselective Catalysis Dearomative Nickel

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[9] Reaction with NiI$_2$ 40% P(O*i*pr)$_3$, in 1mL toluene in the absence of Mn (entry 2 without Mn) yielded 65% product with a 10:1 d.r.
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[11] Reaction was run with 0.2mmol of *N*-(2-iodophenyl)-*N*-Methyl-phenylacrylamide, NiI$_2$ (10 mol%) and P(O*i*pr)$_3$ (40 mol%) for 10 hours in toluene (1mL). The yield was determined by H^1 NMR using 1,3,5-trimethoxybenzene as an internal standard.
[12] The use of PPh$_3$, P(OPh)$_3$, BINAP/BINAPO, and various BOX, PhOX, PyOX, and PyBOX as ligands, all failed to yield any reactivity. Mn was added in these reactions as a reducing agent.
[13] Dioxane was the only other successful solvent, giving the product in a 73% yield. Lowering the reaction temperature to 90ºC required 6 hours for full conversion, yielding 75% of the product. Increasing the reaction temperature to 110 ºC gave **2A** in 75% yield with a 10:1 d.r.

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[14] All yields are of the isolated major diastereomer[14]) Due to the different reactivities of the aryl iodides and stabilities of the products, reactions were run between 2–6 hours at 100–120ºC.

[15] Mechanistic investigations are underway to determine the oxidation state of the nickel during this reaction. Typical reductive elimination of halides proceeds through a Ni(III) species, however this usually requires oxidative conditions.

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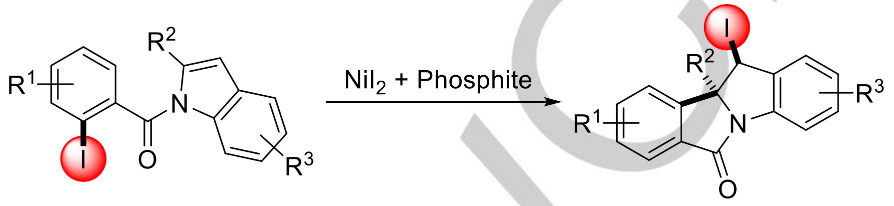

Novel approach to benzylic iodides
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