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Nickel-Catalyzed Enantioselective Carbamoyl Iodination: A Surrogate for Carbamoyl Iodides

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Supporting Information Placeholder

ABSTRACT: This work reports the enantioselective formal transfer of a carbamoyl iodide across a 1,1-disubstituted styrene using Ni-catalysis. Employing an air-stable Ni(II) precatalyst and a commercially available chiral ligand ((*S*)-*t*BuPHOX), enantioenriched 3,3-disubstituted iodooxindoles were obtained in up to 90% yield and up to 97:3 e.r. This methodology was applied to the total synthesis of (–)-esermethole and (–)-phenserine. *Keywords*: Nickel, Enantioselective, Carbamoyl-Iodination Reaction, Oxindoles

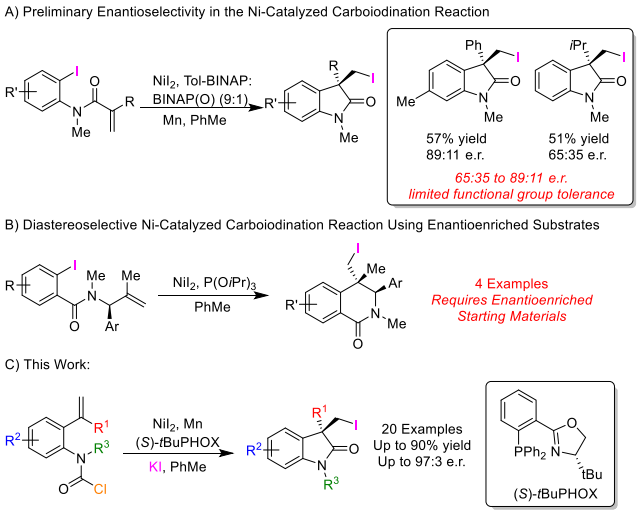
Carbon–halogen bonds are useful synthetic handles in organic chemistry. Metal-catalyzed carbohalogenation reactions have emerged as a valuable synthetic tool that allows access to a variety of heterocyclic scaffolds containing a C–X bond.[1] Despite significant advances, two glaring limitations exist: the reliance on aryl halides as the initial electrophile for these transformations and a lack of enantioselective variants.[1a] In the case of nickel, no highly enantioselective carbohalogenation reaction has been reported.

Nickel catalysis has emerged as a powerful synthetic tool over the last two decades. In addition to performing related palladium−catalyzed cross-coupling reactions, it also offers a unique set of reactivity that diverges from its 4d counterpart.[2] Nickel is known to incorporate a breadth of different electrophiles in cross-coupling reactions, however the use of carbamoyl chlorides remains very limited. During the submission of this manuscript, an asymmetric cooperative Ni/photoredox acyl-carbamoylation employing styrene-tethered carbamoyl chlorides was reported.[2a]

Pd-[3] and Ni-[4]catalyzed carbohalogenation reactions typically generate C(sp^3)–I bonds through initiating the reaction on a pre-existing aryl halide precursor. Recently, we demonstrated carbamoyl chlorides as terminal electrophiles in copper and palladium−catalyzed cyclizations.[5] We envisioned performing an enantioselective Ni-catalyzed acyl-halogen transfer across a π-system to afford the carbohalogenated products using carbamoyl chlorides as the entry into the catalytic cycle.

In 2018, we reported the Ni-catalyzed carboiodination reaction (Scheme 1a)[4d] and subsequently expanded the scope of the reaction to generate benzylic C–I bonds *via* a diastereoselective-dearomative cyclization on indoles.[4b] We identified a diastereoselective variant, affording dihydroisoquinolones and tetrahydroquinolines (Scheme 1b).[4a] Preliminary enantioselective results were described employing a Ni-catalyst with a dual ligand system of Tol-BINAP and BINAP(O) (Scheme 1a). Efforts to improve the enantioselectivity or expand the scope were unsuccessful. We hypothesized that by employing the *ortho*-styryl carbamoyl chlorides, an enantioselective carboiodination reaction yielding 3,3-disubstituted iodo-oxindoles could be achieved (Scheme 1c).

Scheme 1. Generating Enantioenriched Compounds with the Ni-Catalyzed Carboiodination Reaction



Use of carbamoyl chlorides as the electrophile presents a unique challenge arising from the difficulty of generating a C(sp^3)−Cl bond via a reductive elimination. We needed a surrogate for an unstable "carbamoyl iodide". Adding a nucleophilic source of iodide (KI), provided an effective *in situ* halogen exchange protocol leading to the desired iodinated products.[3e,3k,4d]

In 2014, Tong reported a single example of a Pd-catalyzed carbamoyl iodination reaction generating a racemic 3,3-disubstituted oxindole in 55% yield , with the remaining 45% attributed to the 6-endo Heck-type quinolone product.[3e] Recently, Li and Zhang reported an enantioselective carboiodination using $Pd_2(dba)_3$ (10 mol%) and XuPhos (20 mol%) as a ligand, starting from the aryl iodide precursor, yielding iodoindolines and dihydrobenzofurans.[3a] There is no report describing the highly enantioselective synthesis of 3,3-disubstituted iodo-oxindoles with either Pd- or Ni-catalysis.

Herein, we report an enantioselective Ni-catalyzed carboiodination reaction generating 3,3-disubstitiuted iodo-oxindoles by employing a simple Ni(II) precatalyst and the commercially available (*S*)-

*t*BuPHOX ligand (Scheme 1c). 3,3-Disubstituted oxindoles are an important class of molecules, as they are known intermediates of multiple pharmaceuticals and bioactive compounds; specifically potent acetylcholine esterase inhibitors such as physostigmine and phenserine.[6] To demonstrate the applicability of our work, we undertook the total syntheses of (−)-esermethole and (–)-phenserine.

To explore the viability of this process, we first employed our previously optimized catalytic system with the addition of two equivalents of KI. Triisopropyl phosphite failed to promote the reaction but employing triphenylphosphine as the ligand in the presence of Mn^0 **2a** in 80% yield. The reaction did not proceed in the absence of Mn^0 as the reducing agent or without NiI_2, supporting the proposal the catalytic cycle is initiated by a reduced Ni species (see SI for full optimization).

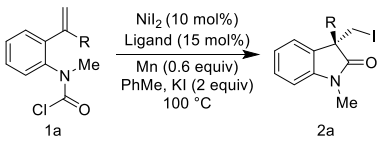
Tol-BINAP (**L1**) as the ligand gave moderate conversion and 65:35 e.r. (Table 1). Monodentate ligands such as Monophos (**L2**) afforded the product in 28% yield with low enantioselectivity. Utilization of a modified Trost-ligand (**L3**) impeded the reaction. Employing bidentate phosphines such as (**L4**) and Josiphos (**L5**) gave the product in low to moderate yields and enantioselectivities. PHOX ligands proved to be the better choice. Ligands containing *sec*-butyl (**L6**) and benzyl (**L8**) substituents on the oxazoline backbone afforded the product in moderate yields but poor enantioselectivity, however using *t*BuPHOX as a ligand afforded the product in 83% yield and 83:17 e.r.

Changing the *α*-substituent of the styrene had a dramatic effect on the enantioselectivity of the reaction, as R = *i*Pr gave the product in 91% yield and 92:8 e.r. Reducing the temperature to 85 °C improved the e.r. to 95:5 with minimal impact on yield. Unfortunately, further changes to the temperature or adjusting the metal-ligand ratio did not positively affect the reaction. Reproducibility was possible employing a pre-stirred solution of NiI_2, Mn, (*S*)-*t*BuPHOX, and KI in freshly distilled toluene. Under this protocol, **2a** was obtained in an average NMR yield of 91% (87% isolated) and 95:5 e.r.

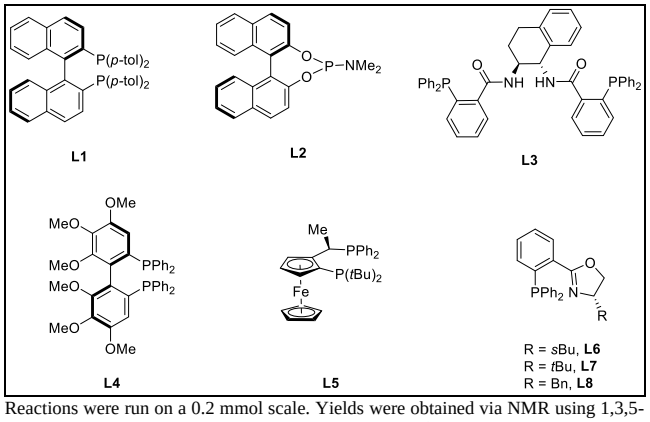
We explored the scope of the reaction, starting with the pendant group on the *α*-position of the styrene (Scheme 2). Changing the isopropyl group to a methyl group gave the product in a reduced yield of 72% but an increased e.r. of 97:3. This observation supports our hypothesis that the difference in hybridization of the pendant substituent is playing a key role in controlling the enantioselectivity, beyond purely steric reasons. Both *n*-butyl (**2c**) and benzyl (**2d**) groups at the α-position of the styrene were equally effective. Having a cyclopropyl moiety at the same position had a slight negative effect on the reaction, giving product **2e** in 57% yield and 94.5:5.5 e.r, with only 65% conversion. No ring opening of the cyclopropane was observed. Unfortunately, having a Ph moiety at the α-position required a reaction temperature of 95 °C, giving compound **2f** in 74% yield and 84:16 e.r. Next, we explored electronic and steric effects of substituents on the aromatic backbone (Scheme 2). Both electron withdrawing and donating groups were well tolerated at the 3- and 4-positions of the aryl backbone (**2g-k**). The capacity to prepare oxindoles substituted at the 3- position is noteworthy, as *ortho*-substituted oxindoles have proven to be difficult to synthesize via the traditional aryl halide route. A difficult oxidative addition into di-*ortho* substituted C–X bonds is likely responsible. Substrates bearing a CF_3 group (**2l**) or halogens (**2m,n**) at the 5-position were successful, albeit in lower yields. In the case of product **2l**, significant amounts of the decarbonylated starting material was observed. Having a 4,5-dimethoxy (**2o**) substitution pattern or 6-fluoro moiety showed a decrease in enantioselectivity of the reaction (Scheme 3). As the size of the *N*-protecting group increases from methyl to allyl (**2r**) to PMB (**2r**) we observed a steady decrease in enantioselectivity but maintain good reactivity.

Chemoselectivity was demonstrated by reacting a substrate with a second site for oxidative addition (**1n**), or a second alkene moiety as in **1r** and **1s**. All gave products in high yield and e.r.

Table 1. Optimization of Enantioselective Reaction



Entry	R =	Ligand/Variation	Yield (%)	e.r.
1	Ph	Tol-BINAP (**L1**)	64	65:35
2	Ph	Monophos (**L2**)	28	55:45
3	Ph	Trost-ligand (**L3**)	0	-
4	Ph	**L4**	46	75:25
5	Ph	Josiphos (**L5**)	20	50:50
6	Ph	*s*BuPHOX (**L6**)	65	60:40
7	Ph	*t*BuPHOX(**L7**)	83	83:17
8	Ph	BnPHOX (**L8**)	71	50:50
9	*i*Pr	**L7**	92	92:8
10	***i*Pr**	**L7, 85 °C instead of 100 °C**	**91[a] (87)[b]**	**95:5**
12	*i*Pr	**L7**, 80 °C instead of 100 °C	25	95.5:4.5
13	*i*Pr	**L7**, 11 mol% ligand	65	95:5

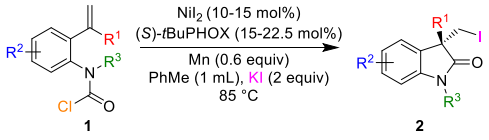


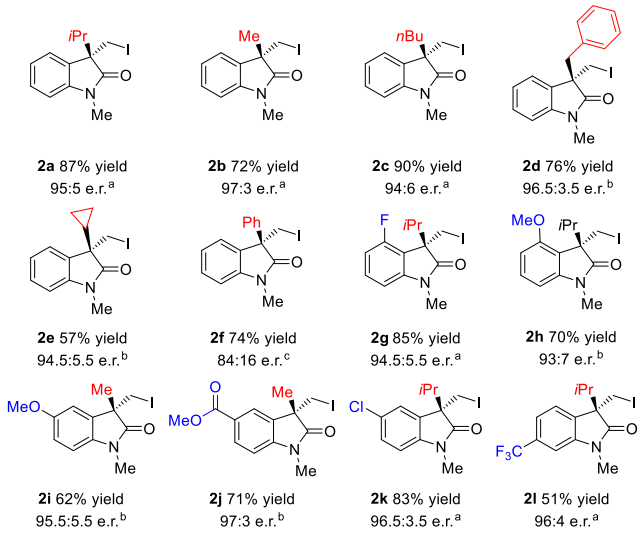
Reactions were run on a 0.2 mmol scale. Yields were obtained via NMR using 1,3,5-trimethoxybenzene as an internal standard. [a]Average of 3 reactions employing a 30 min pre-stir of NiI_2, Mn, (*S*)-*t*BuPHOX and KI. [b]Number in parenthesis is an isolated yield.

Removing the aryl backbone in favor of linear *N*-Ph protected carbamoyl chlorides, in analogy to the work of Tong,[4e] furnished *γ*-lactam **2t** in 58% combined yield with a d.r. of 1.5:1. Although the diastereoselectivity is low, this example demonstrates that further optimization will allow Ni-catalysis in diastereoselective carbamoyl iodination, generating iodo-*γ*-lactams. We also explored how increasing the scale would impact the reaction and found that at 1 mmol, **2i** could be isolated in 60% yield in a 94:6 e.r. accompanied by 30% recovered starting material.

To demonstrate the utility of the methodology in total synthesis, we successfully prepared (–)-esermethole and (–)-phenserine

Scheme 2. Scope of the Ni-Catalyzed Carbamoyl Iodination Reaction



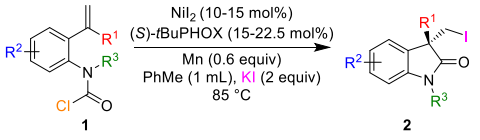


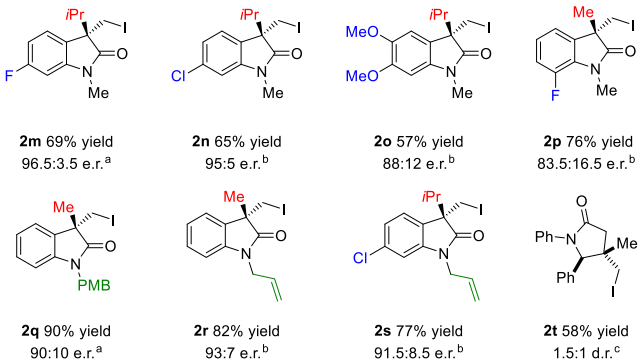
[a] Reaction was run with 10 mol% catalyst and 15 mol% (*S*)-*t*BuPHOX for 24 h. [b]Reaction was run with 15 mol% catalyst and 22.5 mol% (*S*)-*t*BuPHOX for 36 h. [c]Reaction was run at 95 °C with 10 mol% catalyst and 15 mol% (*S*)-*t*BuPHOX for 24 h.

(Scheme 4). The Ni-catalyzed acyliodination reaction has an advantage over the traditional Pd-catalyzed nucleophilic trapping methodologies. By employing simple S_N2 chemistry the products can be quickly and easily functionalized into a broad array of medicinally relevant 3,3- disubstituted oxindoles without the need to develop new methodologies and catalysts for each unique desired functional group. By way of a S_N2 displacement of the iodide with KCN furnished the cyano-oxindole **3a** in 81% yield and 95:5 e.r. Employing a modified protocol from a previous report from Hiyama and co-workers, the nitrile of the cyano-oxindole **3a** was reduced with $LiAlH_4$ to form a primary amine, which subsequently performs a reductive amination on C-2 of the oxindole affording compound **3b**.[6a] Compound **3b** was subsequently methylated via reductive amination with an aqueous solution of formaldehyde using $NaBH(OAc)_3$ as the reducing agent. (–)-Esermethole was obtained in 73% yield and 95:5 e.r., in just 4 steps of over 70% yield each from the carboiodinated oxindole. (–)-Esermethole was then demethylated using BBr_3, and the crude (–)-eseroline (51% yield) was subsequently converted to(–)-phenserine(20% yield, $[\alpha]_D$ = –59.1 (c = 0.027)) using Na-metal to generate the corresponding phenoxide, followed by the addition of PhNCO.[7a] Alternatively, using methyl isocyanate would have yielded (–)-physostigmine,[6b,7a] another acetylcholine esterase inhibitor. The opposite enantiomer, (+)-phenserine (Posiphen), is also an interesting compound which is currently in clinical trials as a selective inhibitor of amyloid precursor proteins.[8] Our method could conceivably be used in the synthesis of this compound, as the (*R*)-*t*BuPHOX ligand is also readily available.

There are three plausible reaction mechanisms for the Ni-catalyzed carbamoyl iodination reaction (Scheme 5). The first two follow an oxidative addition - migratory insertion - reductive elimination pathway. Within this pathway, either a Ni(0)-Ni(II) cycle (Mechanism A) or Ni(I)-Ni(III) (Mechanism B) cycle are possible.

Scheme 3. Scope of the Ni-Catalyzed Carbamoyl Iodination Reaction

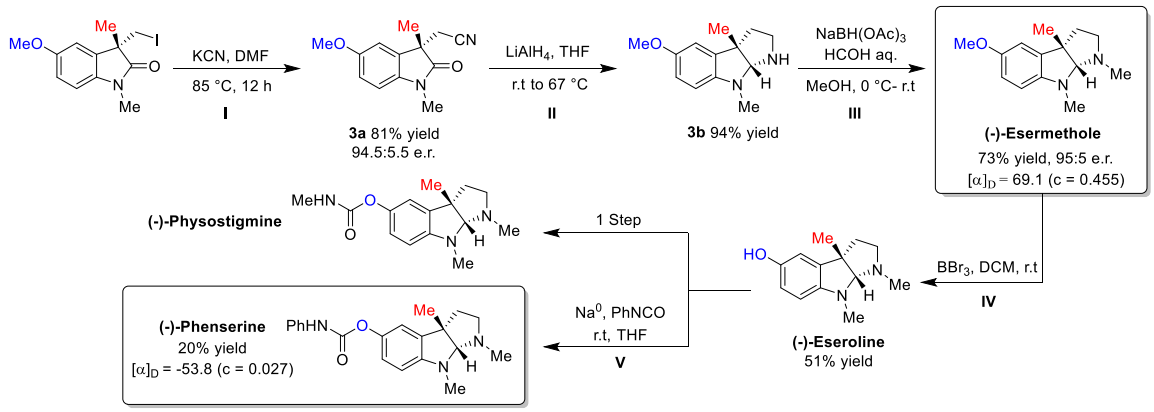




[a]Reaction was run with 10 mol% catalyst and 15 mol% (*S*)-*t*BuPHOX for 24 h. [b]Reaction was run with 15 mol% catalyst and 22.5 mol% (*S*)-*t*BuPHOX for 36 h. [c]Reaction was run with 20 mol% catalyst and 20 mol% PPh_3 for 24 h.

Conversely, there is precedence for a nucleophilic metal-X addition across the unsaturation followed by a C–C bond forming reaction with the carbamoyl chloride electrophile (Mechanism C).[5b,c] To gain insight into the reaction pathway, we performed a series of mechanistic studies (Scheme 6). When manganese was removed from the reaction, <5% yield of the desired oxindole was obtained, suggesting the catalytic cycle is not initiated by a Ni(II) catalyst. Using 20 mol% $Ni(PPh_3)_4$ resulted in a single turnover of the catalytic cycle, giving product **2a** in 19% yield. We hypothesized that the low yield of the reaction may be due to either saturation of the Ni-catalyst by ligand, the importance of Mn or its salts to turn over the catalytic cycle, or the possibility that a Ni(0) catalyst was not the active catalyst under our reaction conditions. Under identical reaction conditions with the addition of 0.6 equivalents of Mn only one turnover was observed, suggesting the Mn^0 is not playing a role in turning over the catalytic cycle. To probe the potential saturation of the Ni(0) catalyst we employed the Ni(COD)(DQ) (10 mol%) developed by the Engle group[9], in the presence of 20 mol% PPh_3. This reaction yielded only a small amount **2a** (10% yield) and the 6-endo trig Heck-type product (46% yield). In line with the previous experiments, this suggests a Ni(0) catalyst can perform the oxidative addition and migratory insertion steps, but is not necessarily a competent catalyst in this reaction. We postulate that the lack of selectivity of the reaction is due to the DQ and COD ligands in solution. Finally, adding TEMPO (1 equiv and 2 equiv) completely hindered the reaction, showing no conversion of starting material. Based on the need for a reducing agent, it is unlikely a Ni(II) promoted iodonickelation occurs (Mechanism C). Furthermore, we never observed products stemming from a Ni–I migratory insertion and subsequent β-hydride elimination, or in the case of **2e**, the ring-opening of the cyclopropane, which would be expected by-products under this mechanism. Based on the results of the control experiments employing the Ni(0) precatalysts, the lack of reactivity when introducing TEMPO, and literature precedence, namely the recent report by Wang[2g] which employed an analogous Ni-catalyst, the most likely pathway proceeds via a Ni(I)-Ni(III) cycle (Mechanism B). However, Mechanism A cannot be completely ruled out and

Scheme 4. Total Synthesis of (–)-Esermethole and (–)-Phenserine

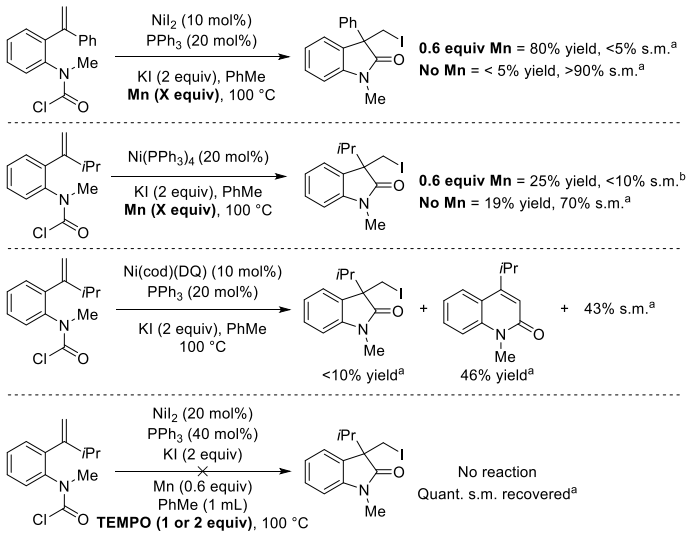


I) KCN (5 equiv), DMF (0.05M), 85 °C, 12 h. II)$LiAlH_4$ (4 equiv, 4.0 M), THF (0.03M) r.t., 60 min then reflux (67 °C), 30 min. III) HCHO (aq) (5.0 equiv), $NaBH(OAc)_3$ (5.0 equiv), MeOH, 0 °C–r.t., 1.5 h. IV) BBr_3 (4.7 equiv), DCM (0.1 M), r.t, 2h. V) Na^0-metal, Et_2O (0.03M) 2 min then PhNCO (1.03 equiv), 40 min.

may be occurring simultaneously during the reaction, albeit as the minor-pathway.

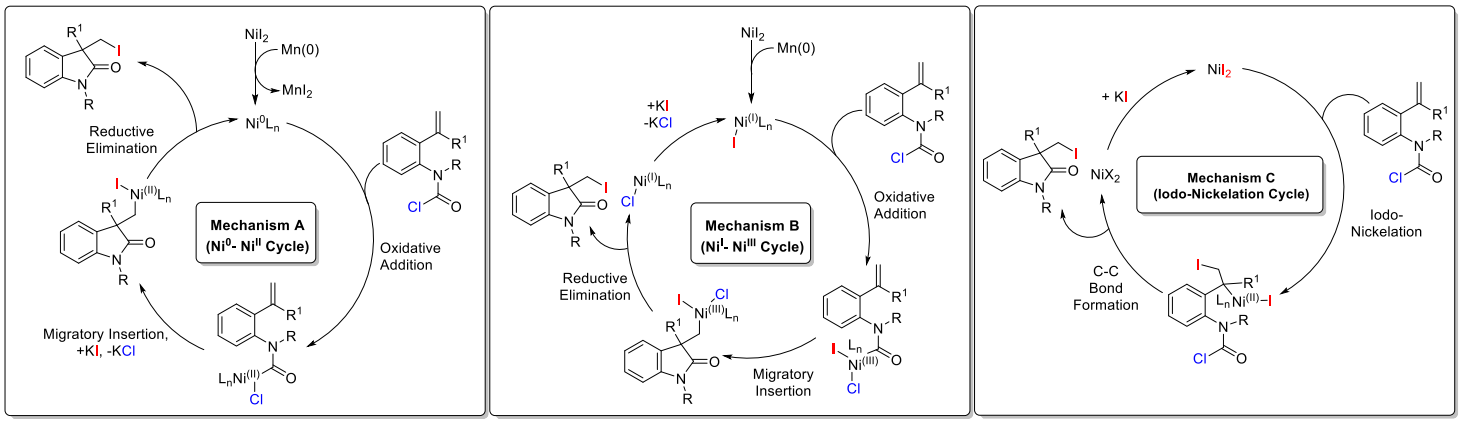
The carboiodination reaction has proven to be a powerful tool to synthesize a wide array of medicinally important scaffolds with a functional C–I handle. This work addresses the major limitations of metal-catalyzed carboiodination methodologies, namely the insufficient diversity of electrophilic coupling partners, and lack of enantioselective reports. This is the first highly enantioselective example using nickel to build 3,3-disubstituted iodo-oxindoles. Exemplifying the applicability of the carboiodination methodology, we achieved the total synthesis of (–)-esermethole and (–)-phenserine. Future works are ongoing, including developing additional enantioselective Ni-catalyzed carboiodination reactions to access other privileged heterocycles as well as DFT studies to better understand the reaction mechanism.

Scheme 6. Mechanistic Control Studies



a) Yield was determined via NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. b) Isolated yield.

Scheme 5. Plausible Mechanisms



ASSOCIATED CONTENT

Supporting Information

Instrumentation and chemicals, optimization of reaction condition, experimental procedure and characterization data for products, NMR spectra and Chiral HPLC conditions, total synthesis procedure and characterization.

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Notes

The authors declare no competing financial interests.

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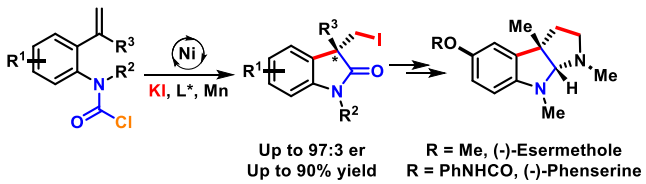
R1
R3
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Cl
Ni
KI, L*, Mn
R3
I
R1
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RO
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N
Me
H
N
Me
Up to 97:3 er
Up to 90% yield
R = Me, (-)-Esermethole
R = PhNHCO, (-)-Phenserine