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Reductive Cross-Coupling of Nonaromatic, Heterocyclic Bromides with Aryl and Heteroaryl Bromides

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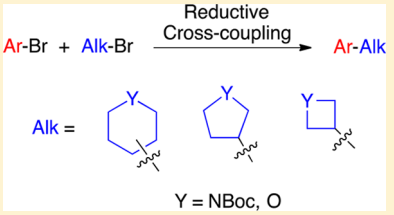
Supporting Information

ABSTRACT: Reductive cross-coupling allows the direct C−C bond formation between two organic halides without the need for preformation of an organometallic reagent. A method has been developed for the reductive cross-coupling of nonaromatic, heterocyclic bromides with aryl or heteroaryl bromides. The developed conditions use an air-stable Ni(II) source in the presence of a diamine ligand and a metal reductant to allow late-stage incorporation of saturated heterocyclic rings onto aryl halides in a functional-group tolerant manner.



INTRODUCTION

There is a clear need in organic chemistry for versatile synthetic methods that can couple an array of shelf-stable, nonaromatic heterocycles in a high throughput fashion with certain templates from medicinal chemistry programs. Because of the dramatic advances in sp^2−sp^2 couplings over the past decade, drug target molecules have shown increasing trends toward flat, planar structures.[1] Incorporation of saturated, heteroatom-containing ring systems onto complex structures is desirable, as it allows a larger amount of three-dimensional space to be occupied in comparison to planar aromatic heterocycles, potentially permitting greater selectivity toward a druggable target while maintaining acceptable physical properties for good absorption and selectivity. Although methods exist to prepare saturated heteroaromatic structures, many are multistep processes that require cyclization[2] or hydrogenation[3] reactions to access the target structures (Scheme 1).

A great deal of interest has recently emerged, therefore, in the formation of sp^3−sp^2 bonds involving nonaromatic heterocyclic structures. Interestingly, while sp^3−sp^2 coupling methods are known, many of the existing methods are either ineffective or extremely low-yielding on secondary alkyl substrates containing heteroatoms, e.g., piperidines, pyrrolidines, azetidines, tetrahydropyrans, tetrahydrofurans, or oxetanes.[1b] Several C−H arylation methods exist to access aryl- and heteroaryl-substituted nonaromatic heterocycles,[4] but these methods are limited by their lack of applicability to the entire class of desired structures.

One current approach to this desired sp^3−sp^2 bond formation includes the cross-coupling of an arylmetallic species (M = Mg, Si, Zn, B) with a nonaromatic, heterocyclic halide (Scheme 2, route 1).[5] The coupling of arylboronic acids with nonaromatic heterocycles can also be achieved using coupling partners other than the corresponding halides. Recently, a cross-coupling of saturated heterocyclic sulfonylhydrazones with boronic acids has allowed functionalization of four-, five-, and six-membered saturated heterocycles.[1b] Although such methods have shown success, they have not been thus far adapted to parallel medicinal chemistry strategies.

A second approach to the desired sp^3−sp^2 cross-coupling involves the formation of an alkylmetallic reagent that can be coupled with an aryl halide (Scheme 2, route 2). This pathway allows addition of the saturated heterocyclic structures directly onto larger structures containing an aryl halide. However, existing methods pose additional limitations. Many of the alkylmetallic materials are not stable and must be formed either immediately prior to or during the reaction.[6] One valuable method makes use of air-stable alkylstannanes to achieve similar transformations,[7] but the necessity of a large protecting group on tin makes this method less than ideal for large scale synthesis.

Our initial efforts toward developing a method that would allow direct C−C bond formation between a nonaromatic heterocycle and an aryl halide focused on creating an atom-economical, air-stable, alkylmetallic species capable of such a transformation. We directed our attention toward the cross-coupling of nonaromatic heterocyclic alkyltrifluoroborate salts (Scheme 3), which were prepared through a nickel-catalyzed borylation of the corresponding halides.[8] High throughput experimentation was utilized to determine conditions that would allow the desired transformations to take place, but thus far extensive screening of Pd-, Ni,- and Cu-catalyzed conditions has failed to lead to a generally applicable, high-yielding process.

A method for late-stage incorporation of nonaromatic heterocycles onto an aryl ring without having to metalate either of the partners would clearly be more efficient and versatile (Scheme 2, route 3). Therefore, direct coupling of a nonaromatic heterocycle with an aryl halide under conditions

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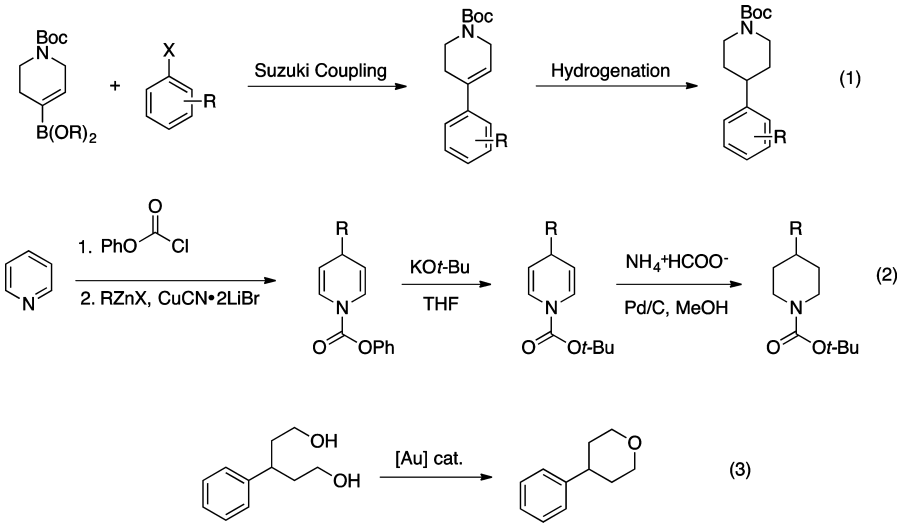
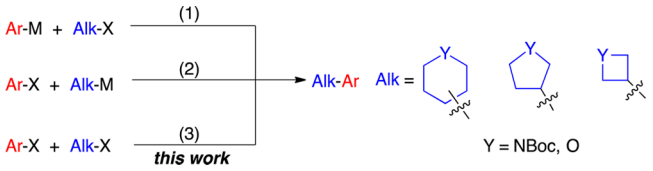
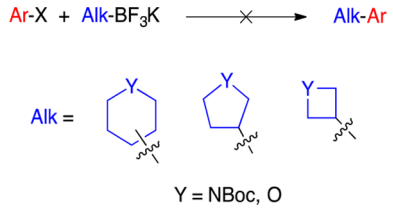
Scheme 1. Methods for Preparation of Saturated Heteroaromatic Structures



Scheme 2. Methods for sp^3–sp^2 Cross-Coupling Involving Saturated Heterocyclic Structures

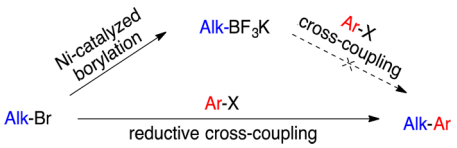


Scheme 3. Cross-Coupling of Nonaromatic Heterocyclic Trifluoroborate Salts with Aryl Halides



that possessed general functional group tolerance was sought. Inspired by the extensive work that has been carried out in the field of reductive cross-coupling within the past decade,[9] we considered a reductive pathway for the cross-coupling of aryl halides with nonaromatic heterocyclic halides. A number of notable reductive cross-coupling examples have been demonstrated by Weix et al. in the reactions of primary and secondary alkyl bromides and iodides with aryl iodides, bromides, and chlorides under conditions that are remarkably functional-group tolerant.[9a−d] Application of a similar method was envisioned that would allow the saturated heterocyclic alkyl bromides to be employed directly in the cross-coupling, without a separate metalation step (Scheme 4). Gong et al.

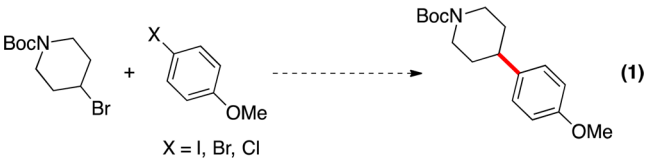
Scheme 4. Reductive Coupling Approach[9] Compared to Trifluoroborate Preparation[10] and Coupling



has succeeded at developing methods that allow the reductive cross-coupling of *N*-tosyl-4-bromopiperidine with alkyl and aryl bromides and iodides.[9e−g] These methods, however, have not been extended to other nonaromatic heterocyclic systems, and only limited examples of heteroaryl bromide coupling partners were demonstrated. A reductive cross-coupling pathway was therefore pursued as a general method that would allow the direct installation of a variety of commercially available, saturated heterocyclic halides with aryl halides in a manner that improves atom economy, cost, and efficiency compared to traditional cross-coupling approaches.

RESULTS AND DISCUSSION

Optimization was initially approached using high throughput experimentation (~200 reactions), which allowed quick screening of many combinations of nickel sources, ligands, additives, and solvents on a small scale (10 μmol). The reactions of 1-Boc-4-bromopiperidine with 4-chloro-, 4-bromo-, and 4-iodoanisole were screened (eq 1), and the bromide coupling partner proved preferable for the desired transformation.



Initial screening was conducted to examine the nickel source and ligands in the presence of Zn dust, pyridine, NaI, and DMF based on conditions developed by Weix et al.[9a−d] In the presence of $Ni(cod)_2$, numerous ligands were tested,[11] and while several bipyridine and phenanthroline derivatives led to the formation of the desired product, 1,10-phenanthroline was determined to be the most suitable ligand for the reaction. It was confirmed empirically that both a pyridine derivative as well as an inorganic salt additive were necessary for the success of the reaction. Screening of further nickel sources[12] led to the discovery that $NiCl_2$·glyme, an air-stable Ni(II) source, could be used to promote the cross-coupling. Various pyridine derivatives[13] were tested for activity as additives in the reaction system (Table 1), and the use of 50 mol % of 4-ethylpyridine

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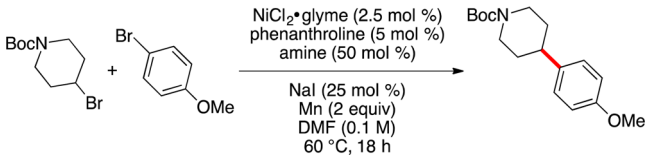
led to a lower amounts of protodehalogenation of the alkyl bromide (Alk-H) and elimination of biaryl homocoupling (Ar–Ar).

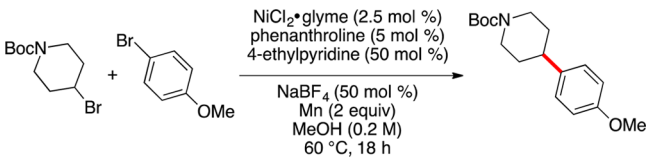
Table 1. Optimization of Pyridine Additive in the Reaction of 1-Boc-4-Bromopiperidine with 4-Bromoanisole



entry	amine	product/Alk-H/Ar–Ar
1	pyridine	1:1.14:0.09
2	3,5-lutidine	1:1.70:0.04
3	4-*N*,*N*-dimethylaminopyridine	1:2.76:0.04
4	4-ethylpyridine	1:0.84:0
5	4-benzylpyridine	1:2.20:0.04

Other polar solvents[14] were explored, leading to improved conditions using MeOH as a reaction solvent. Some of the continued optimization results are shown in Table 2, with

Table 2. Optimization of the Reaction of 1-Boc-4-Bromopiperidine with 4-Bromoanisole



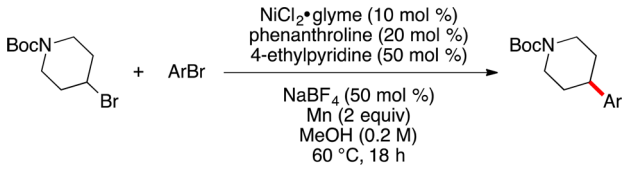
entry	variation to conditions	product/Alk-H/Ar–Ar
1	none	1:0.10:0.12
2	CsI instead of $NaBF_4$	1:0.12:0.09
3	KBF_4 instead of $NaBF_4$	1:0.10:0.13
4	3 equiv of Mn	1:0.37:0.07
5	reaction run under air	no product formation
6	temp = rt	1:0.29:0.06
7	M^0 = Zn instead of Mn	1:0.74:0.32

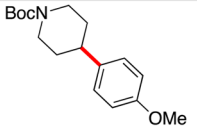
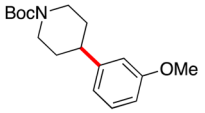
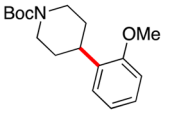
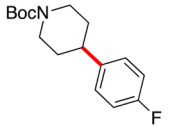
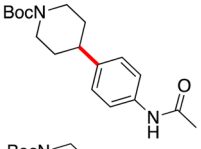
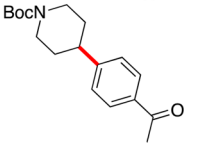
product formation shown relative to the amounts of protodehalogenated alkyl bromide (Alk-H) and biaryl homocoupling (Ar–Ar), which were the two major side products observed in the reaction. The use of Mn powder instead of Zn dust not only led to less protodehalogenated material but also did not require activation prior to use.[15] Numerous inorganic salts[16] were tested as additives in the cross-coupling, and 1 equiv of $NaBF_4$ was found to improve conversion to the desired product compared to the iodide additives tested. The beneficial effect of $NaBF_4$ on the cross-coupling was somewhat surprising, given that one of the presumed roles of the NaI additive under established reductive coupling conditions was alkyl iodide formation from the corresponding alkyl bromide.[9b] Other proposed mechanistic roles for the halide additives often found necessary in reductive coupling protocols include aiding reductive elimination from the Ni center or acting as bridging ligands,[17] neither of which would appear to apply to a noncoordinating ligand such as BF_4^-.

A 2:1 ratio of 1,10-phenanthroline to $NiCl_2$·glyme was determined to be ideal, and the use of anhydrous and/or degassed MeOH was unnecessary, as it did not improve the reaction. It was noted that neither *N*-Ts-4-bromopiperidine nor *N*-Cbz-4-bromopiperidine reacted with 4-bromoanisole under the developed conditions; likewise, under conditions reported by Gong et al. for the reductive coupling of *N*-Ts-4-bromopiperidine,[9g] the desired coupling with 1-Boc-4-bromopiperidine did not proceed.

With satisfactory conditions in hand for the cross-coupling of 1-Boc-4-bromopiperidine with 4-bromoanisole, the substrate scope was explored with various aryl bromides (Table 3). The

Table 3. Cross-Coupling of 1-Boc-4-Bromopiperidine with Aryl Bromides



entry	product		yield (%)
1		**1a**	65, 68[a]
2		**1b**	64
3		**1c**	58
4		**1d**	70
5		**1e**	53
6		**1f**	62

[a]6.0 mmol scale, modification to general conditions: 5 mol % $NiCl_2$·glyme, 10 mol % phenanthroline.

reaction conditions tolerated *ortho*-substitution (entry 3), as well as amide (entry 5) and ketone (entry 6) functional groups. The scalable nature of the reaction was demonstrated by the application of the optimized method to a 6.0 mmol reaction (entry 1), in which the catalyst loading could be reduced to 5 mol % (from 10 mol %) without diminished yield.

The cross-coupling of 1-Boc-4-bromopiperidine was next explored with heteroaryl bromides under the same conditions (Table 4). Although limitations on the substrate scope were noted, the method could be extended to 5-bromobenzofuran (entry 1) as well as a variety of pyridyl bromides. The cross-coupling was successfully achieved at the 2-, 3-, and 4-positions of pyridine systems and proceeded even in the presence of *ortho*-substitution (entry 3). In all cases of cross-couplings of

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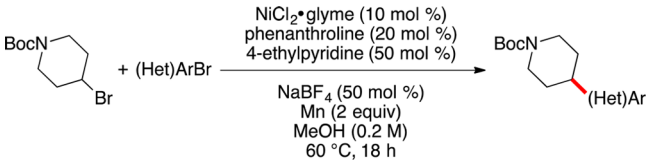
Table 4. Cross-coupling of 1-Boc-4-Bromopiperidine with Heteroaryl Bromides



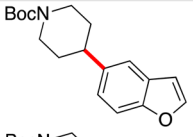
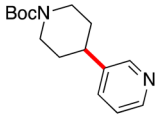
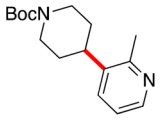
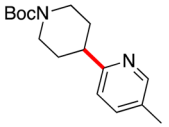
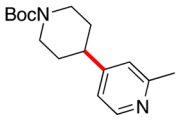
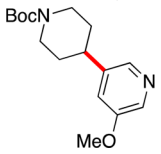
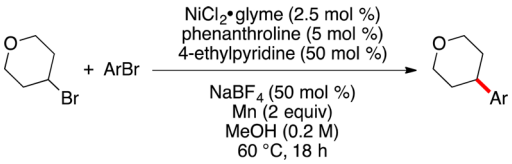
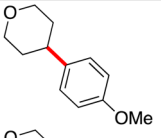
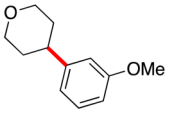
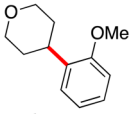
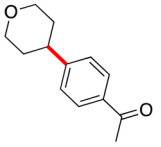
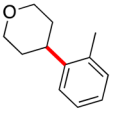
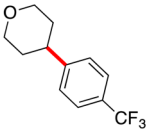
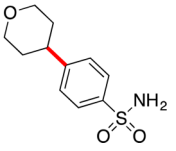
entry	product		yield (%)
1		**2a**	58
2		**2b**	43
3		**2c**	24
4		**2d**	22
5		**2e**	40
6		**2f**	35

Table 5. Cross-Coupling of 4-Bromotetrahydropyran with Aryl Bromides



entry	product		yield (%)
1		**3a**	62
2		**3b**	59
3		**3c**	58
4		**3d**	50
5		**3e**	43
6		**3f**	53
7		**3g**	41

pyridine substructures, significant amounts of protodehalogenated alkyl bromide were observed.

The cross-coupling conditions were next applied to 4-bromotetrahydropyran (Table 5), and although the optimized conditions led to significant product formation, the reactions actually proceeded to a greater extent with reduced amounts of Ni and 1,10-phenanthroline. Lowering the catalyst loading to 2.5 mol % (from 10 mol %) and the ligand to 5 mol % (from 20 mol %) allowed the successful cross-coupling of 4-bromotetrahydropyran with a variety of aryl bromides. Comparable yields of couplings with 2-, 3-, and 4-bromoanisole were achieved with both 4-bromotetrahydropyran and 1-Boc-4-bromopiperidine, suggesting that comparable reactivity between the systems can be expected. The method was shown to tolerate the presence of a ketone (entry 4), a trifluoromethyl group (entry 6), as well as an aryl sulfonamide (entry 7).

With conditions in place for the cross-coupling of aryl bromides with both 1-Boc-4-bromopiperidine and 4-bromotetrahydropyran, we sought to expand the scope of nonaromatic heterocyclic bromides under the developed conditions (Table 6). A variety of saturated heterocyclic bromides were successfully cross-coupled with 4-bromoanisole, and we were delighted to see the robustness of the process upon application to four-, five-, and six-membered ring systems. As with the 4-bromotetrahydropyran couplings, the oxygen-containing alkyl bromides could be coupled with reduced catalyst loading of 2.5 mol % (compared to 10 mol % needed to cross-couple the *N*-Boc substrates).

The 3-bromotetrahydrofuran system showed isomerization to the 2-substituted product in a ratio of approximately 8:1 (2-substituted product/3-substituted product) when coupled under the developed conditions. However, increasing the catalyst loading with this substrate (from 2.5 mol % to 20 mol % Ni) allowed the desired 3-substituted product to be isolated as the major isomer (entry 7). The observation that increased catalyst loading leads to a lower level of isomerized product is difficult to reconcile with the mechanism of this process, by which isomerization presumably occurs by a β-hydride elimination/hydrometalation process that would not appear to be dependent on catalyst concentration.

Interestingly, the reductive cross-coupling of 3-bromotetrahydrofuran with 4-bromoacetophenone resulted in minimal (<5%) isomerization under the standard conditions (eq 2). Increasing the catalyst loading in this case did not further reduce the observed isomerization. Furthermore, isomerization was not observed with any other alkyl bromide under the developed reductive coupling conditions.

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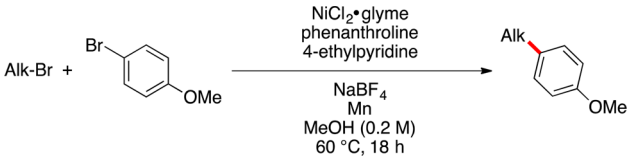
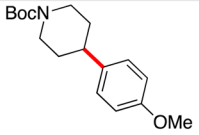
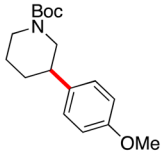
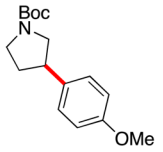
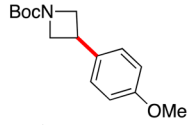
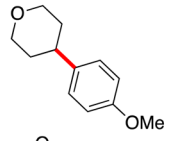
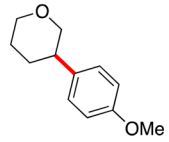
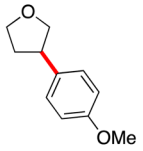
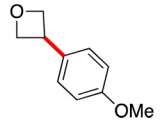
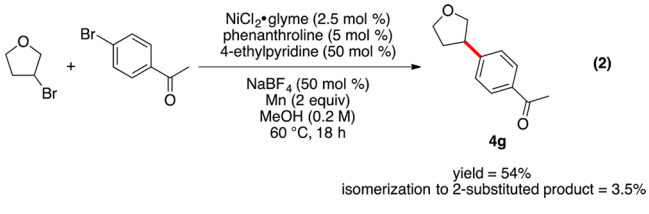
Table 6. Cross-Coupling of 4-Bromoanisole with Various Non-Aromatic, Heterocyclic Bromides[a]



entry	product		yield (%)
1		**1a**	65
2		**4a**	50
3		**4b**	40
4		**4c**	48
5		**3a**	62
6		**4d**	43
7		**4e**	41[b]
8		**4f**	43

[a]General conditions: Entries 1–4: $NiCl_2$·glyme (10 mol %), phenanthroline (20 mol %), 4-ethylpyridine (50 mol %), $NaBF_4$ (50 mol %), Mn (2 equiv), MeOH (0.2 M), 60 °C, 18 h; Entries 5–8: $NiCl_2$·glyme (2.5 mol %), phenanthroline (5 mol %), 4-ethylpyridine (50 mol %), $NaBF_4$ (50 mol %), Mn (2 equiv), MeOH (0.2 M), 60 °C, 18 h. [b]20 mol % $NiCl_2$·glyme and 10 mol % phenanthroline was used; product was isolated as an 8:1 mixture of isomers (3-substituted product/2-substituted product).



As limitations had been recognized upon extension of the developed method to heteroaryl bromides beyond pyridyl systems, we sought to develop a set of conditions to allow cross-coupling of desired saturated heterocyclic bromides with a wide array of heteroaryl bromides. The reaction of 1-Boc-4-bromopiperidine with 3-bromoquinoline was chosen as a model system for establishment of a new set of reaction conditions. Various nickel sources were tested, along with numerous amine-based ligands in the presence of various solvents and additives. The use of NiI_2 in the presence of DMA as a reaction solvent allowed formation of the desired product. Further improvements to reaction conditions were achieved through the use of 4,4′-di-*tert*-butyl-2,2′-bipyridine as a ligand and the use of $MgCl_2$ as an additive, as had previously been reported by Gong et al. for a similar reductive coupling.[9g] With these changes to the previously described conditions, the cross-coupling of 1-Boc-4-bromopiperidine with 3-bromoquinoline was achieved in 60% yield (Table 7, entry 1). These conditions were next applied to a variety of heteroaryl bromides, including both free and protected indoles (Table 7, entry 2 and Table 8). The scope was further extended to include 4-bromotetrahydropyran as a coupling partner under the developed set of conditions (Table 7, entries 7–9).

The applicability of this method to other alkyl bromides of interest was demonstrated by carrying out the cross-coupling of *N*-Boc-5-bromoindole with other nonaromatic, heterocyclic bromides of interest (Table 8). Isomerization was not observed with any of the alkyl bromides under the conditions employed.

In conclusion, by applying modifications to existing methods for reductive cross-coupling protocols, two methods have been developed for the direct coupling of saturated heterocyclic bromides to aryl and heteroaryl bromides. These methods allow the direct installation of nonaromatic heterocyclic structures to molecules bearing an aryl bromide under conditions that employ air-stable components and are functional group tolerant.

EXPERIMENTAL SECTION

General Considerations. MeOH was used as received and was neither dried nor degassed prior to use. Mn powder (~325 mesh) was purchased and used directly. 4-Ethylpyridine was distilled under a vacuum. Solids were weighed out in air and were stored on a laboratory bench without special considerations. ^1H and ^{13}C NMR spectra were recorded at 500 and 125.8 MHz, respectively. Melting points (°C) were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. HRMS data were obtained using a TOF mass spectrometer using ESI or CI, as specified.

Method A: Procedure for the Reductive Cross-Coupling of Nonaromatic Heterocyclic Bromides with Aryl Bromides. An oven-dried Biotage 10 mL microwave vial equipped with a magnetic stirbar was charged with alkyl bromide (1.0 mmol), $NiCl_2$·glyme (0.1 mmol, 22.0 mg), 1,10-phenanthroline (0.2 mmol, 36.0 mg), $NaBF_4$ (0.5 mmol, 54.9 mg), and Mn powder (2.0 mmol, 109.9 mg). The vial was sealed with a disposable Teflon septum cap and was evacuated and purged with Ar three times. MeOH (5 mL) and 4-ethylpyridine (0.5 mmol, 54 mg) were added via syringe, followed by the aryl bromide (1.0 mmol). In cases where the aryl bromide was a solid, it was added to the vial along with the other solids. The reaction was stirred under Ar with conventional heating at 60 °C for 18 h, after which the solution was cooled and diluted with 5 mL of EtOAc. The resulting mixture was filtered through Celite, which was rinsed with EtOAc (~10 mL). The solution was concentrated, and the product was isolated by column chromatography, eluting with a gradient of EtOAc in hexanes (0 to 20% EtOAc). Note: For tetrahydropyranyl, tetrahydrofuranyl, and oxetanyl substrates, the amount of $NiCl_2$·

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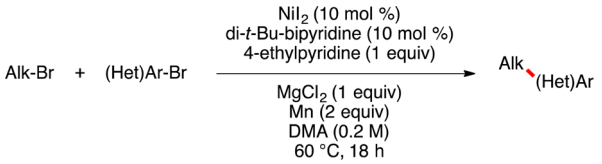
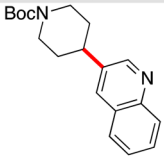
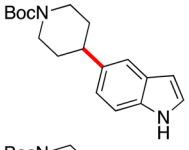
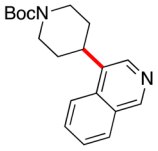
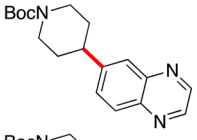
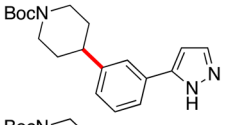
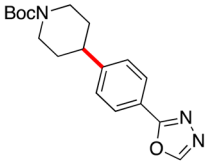
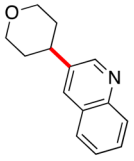
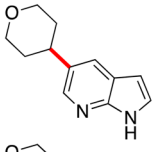
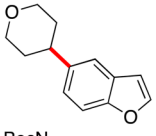
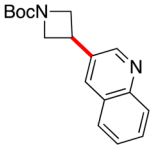
Table 7. Cross-Coupling of Bromoheteroaromatics with Various Non-Aromatic, Heterocyclic Bromides

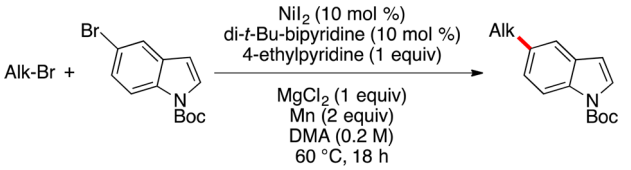


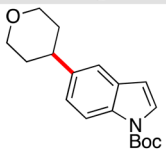
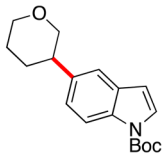
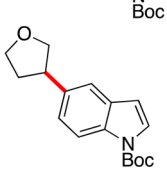
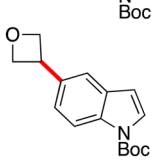
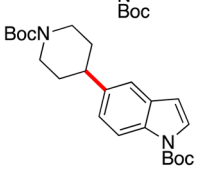
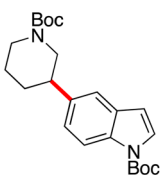
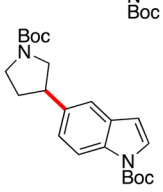
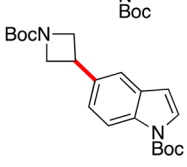
entry	product		yield (%)
1		**5a**	60
2		**5b**	27
3		**5c**	38
4		**5d**	29
5		**5e**	65
6		**5f**	32
7		**5g**	41
8		**5h**	45
9		**5i**	49
10		**5j**	30

glyme was reduced to 0.025 mmol (5.5 mg), and the amount of 1,10-phenanthroline was reduced to 0.05 mmol (9.0 mg).

Method B: Procedure for the Reductive Cross-Coupling of Nonaromatic Heterocyclic Bromides with Heteroaryl Bromides. An oven-dried Biotage 10 mL microwave vial equipped with a magnetic stirbar was charged with the alkyl bromide (1.0 mmol), NiI_2 (0.1 mmol, 31.3 mg), 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.1 mmol, 26.8 mg), $MgCl_2$ (1 mmol, 95.2 mg), and Mn powder (2.0 mmol, 109.9 mg). The vial was sealed with a disposable Teflon septum cap and was evacuated and purged with Ar three times. Dimethylacetamide (5 mL) and 4-ethylpyridine (1.0 mmol, 108 mg) were added via syringe, followed by the heteroaryl bromide (1.1 mmol). In cases where the aryl bromide was a solid, it was added to the vial along with the other solids. The reaction was stirred under Ar with conventional heating at 60 °C for 18 h, after which the solution was cooled and diluted with 25 mL of distilled H_2O. The resulting mixture was

Table 8. Cross-Coupling of *N*-Boc-5-Bromoindole with Various Non-Aromatic, Heterocyclic Bromides



entry	product		yield (%)
1		**6a**	73
2		**6b**	37
3		**6c**	44
4		**6d**	70
5		**6e**	51
6		**6f**	48
7		**6g**	38
8		**6h**	36

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extracted (3 × 10 mL) with EtOAc, and the combined organic portions were washed (2 × 10 mL) with H_2O. The organic layer was dried ($NaSO_4$), after which it was filtered and concentrated. The product was isolated by column chromatography eluting with a gradient of EtOAc in hexanes (10−60% EtOAc).

*tert-Butyl 4-(4-Methoxyphenyl)piperidine-1-carboxylate (**1a**).*[6c] The title compound was obtained as a colorless oil in 65% yield (189 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13−7.11 (m, 2H), 6.86−6.84 (m, 2H), 4.23 (br, 2H), 3.79 (s, 3H), 2.80−2.77 (m, 2H), 2.59 (tt, J = 12.2, 3.5 Hz, 1H), 1.81−1.78 (m, 2H), 1.60−1.57 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.2, 155.0, 138.1, 127.8, 114.0, 79.5, 55.4, 44.8 (br), 42.0, 33.6, 28.6.

*tert-Butyl 4-(3-Methoxyphenyl)piperidine-1-carboxylate (**1b**).* The title compound was obtained as a colorless oil in 64% yield (186 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25−7.21 (m, 1H), 6.81−6.75 (m, 3H), 4.24 (br, 2H), 3.80 (s, 3H), 2.81−2.74 (m, 2H), 2.64−2.59 (m, 1H), 1.83−1.81 (m, 2H), 1.63−1.61 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.9, 155.0, 147.7, 129.6, 119.3, 112.9, 111.5, 79.6, 55.3, 44.2 (br), 42.9, 33.3, 28.6; FT-IR (neat): 2974, 1690, 1423, 1166 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{17}H_{25}NO_3Na$ (M + Na)$^+$ 314.1732, found 314.1737.

*tert-Butyl 4-(2-Methoxyphenyl)piperidine-1-carboxylate (**1c**).*[3c] The title compound was obtained as a white solid in 58% yield (169 mg) according to method A. mp: 63−65 °C; Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.12 (m, 2H), 6.92−6.89 (m, 1H), 6.85−6.83 (m, 1H), 4.21 (br, 2H), 3.81 (s, 3H), 3.09−3.04 (m, 1H), 2.81−2.80 (m, 2H), 1.77−1.75 (m, 2H), 1.58−1.54 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 156.9, 155.1, 134.0, 127.2, 126.6, 120.1, 110.5, 79.4, 55.4, 45.2 (br), 35.5, 32.0, 28.7.

*tert-Butyl 4-(4-Fluorophenyl)piperidine-1-carboxylate (**1d**).*[3c] The title compound was obtained as a colorless oil in 70% yield (195 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15−7.12 (m, 2H), 6.99−6.96 (m, 2H), 4.23 (br, 2H), 2.82−2.74 (m, 2H), 2.64−2.59 (m, 1H), 1.80−1.77 (m, 2H), 1.59−1.55 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.5 (d, J = 244.1 Hz), 154.9, 141.6 (d, J = 3.7 Hz), 128.2 (d, J = 7.8 Hz), 115.3 (d, J = 21.0 Hz), 79.6, 44.1 (br), 42.1, 33.5, 28.6.

*tert-Butyl 4-(4-Acetamidophenyl)piperidine-1-carboxylate (**1e**).* The title compound was obtained as a white solid in 53% yield (169 mg) according to method A. mp: 165−168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (br, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.11−7.10 (m, 2H), 4.20 (br, 2H), 2.80−2.72 (m, 2H), 2.60−2.55 (m, 1H), 2.12 (s, 3H), 1.77−1.74 (m, 2H), 1.58−1.53 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.9, 155.1, 141.8, 136.5, 127.3, 120.4, 79.7, 44.4 (br), 42.2, 33.4, 28.6, 24.5; FT-IR (neat): 3312, 1700, 1661, 1427, 1170 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{26}N_2O_3Na$ (M + Na)$^+$ 341.1841, found 341.1851.

*tert-Butyl 4-(4-Acetylphenyl)piperidine-1-carboxylate (**1f**).* The title compound was obtained as a yellow solid in 62% yield (188 mg) according to method A. mp: 81−82 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 4.24 (br, 2H), 2.79−2.72 (m, 2H), 2.69−2.67 (m, 1H), 2.56 (s, 3H), 1.80 (d, J = 12.8 Hz, 2H), 1.63−1.60 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.8, 154.9, 151.4, 135.7, 128.8, 127.2, 79.7, 44.3 (br), 42.9, 33.0, 28.6, 26.7; FT-IR (neat): 2980, 1678, 1425, 1173 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{25}NO_3Na$ (M + Na)$^+$ 326.1732, found 326.1729.

*tert-Butyl 4-(Benzofuran-5-yl)piperidine-1-carboxylate (**2a**).* The title compound was obtained as a white solid in 58% yield (175 mg) according to method A. mp: 104−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60−7.59 (m, 1H), 7.44−7.42 (m, 2H), 7.14−7.13 (m, 1H), 6.72 (s, 1H), 4.26 (br, 2H), 2.82−2.76 (m, 2H), 2.75−2.71 (m, 1H), 1.86−1.84 (m, 2H), 1.68−1.65 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.0, 153.9, 145.4, 140.6, 127.7, 123.6, 118.9, 111.4, 106.6, 79.6, 44.5 (br), 42.9, 33.9, 28.7; FT-IR (neat): 2974, 1678, 1428, 1164 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{23}NO_3Na$ (M + Na)$^+$ 324.1576, found 324.1588.

*tert-Butyl 4-(Pyridin-3-yl)piperidine-1-carboxylate (**2b**).*[1b] The title compound was obtained as an orange oil in 43% yield (113 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48−8.47 (m, 2H), 7.50−7.48 (m, 1H), 7.25−7.22 (m, 1H), 4.25 (br, 2H), 2.82−2.78 (m, 2H), 2.68−2.66 (m, 1H), 1.83−1.80 (m, 2H), 1.65−1.60 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.9, 148.9, 148.0, 140.9, 134.2, 123.6, 79.7, 44.2 (br), 40.3, 33.0, 28.6.

*tert-Butyl 4-(2-Methylpyridin-3-yl)piperidine-1-carboxylate (**2c**).* The title compound was obtained as an orange oil in 24% yield (66 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34−8.33 (m, 1H), 7.45−7.43 (m, 1H), 7.11−7.09 (m, 1H), 4.27 (br, 2H), 2.85−2.80 (m, 3H), 2.58 (s, 3H), 1.77−1.74 (m, 2H), 1.60−1.55 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.9, 154.9, 146.7, 138.8, 133.4, 121.7, 79.7, 44.4 (br), 38.2, 32.2, 28.6, 22.2; FT-IR (neat): 2975, 1690, 1422, 1161 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{16}H_{25}N_2O_2$ (M+H)$^+$ 277.1916, found 277.1920.

*tert-Butyl 4-(5-Methylpyridin-2-yl)piperidine-1-carboxylate (**2d**).* The title compound was obtained as a red-orange oil in 22% yield (61 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.43−7.41 (m, 1H), 7.03−7.02 (m, 1H), 4.24 (br, 2H), 2.82−2.79 (m, 3H), 2.29 (s, 3H), 1.89−1.87 (m, 2H), 1.69−1.66 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.6, 154.9, 149.6, 137.3, 130.9, 120.4, 79.4, 44.2, 44.1 (br), 31.9, 28.6, 18.1; FT-IR (neat): 2973, 1690, 1422, 1167 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{16}H_{25}N_2O_2$ (M+H)$^+$ 277.1916, found 277.1915.

*tert-Butyl 4-(2-Methylpyridin-4-yl)piperidine-1-carboxylate (**2e**).* The title compound was obtained as a yellow oil in 40% yield (111 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40−8.39 (m, 1H), 6.97 (s, 1H), 6.91−6.90 (m, 1H), 4.24 (br, 2H), 2.80−2.76 (m, 2H), 2.61−2.58 (m, 1H), 2.55 (s, 3H), 1.81−1.78 (m, 2H), 1.62−1.57 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.6, 154.8, 154.8, 149.4, 121.8, 119.4, 79.7, 44.3 (br), 42.1, 32.4, 28.6, 24.5; FT-IR (neat): 1690, 1422, 1165 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{16}H_{25}N_2O_2$ (M + H)$^+$ 277.1916, found 277.1917.

*tert-Butyl 4-(5-Methoxypyridin-3-yl)piperidine-1-carboxylate (**2f**).* The title compound was obtained as a yellow solid in 35% yield (102 mg) according to method A. mp: 79−80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (m, 2H), 6.99 (s, 1H), 4.25 (br, 2H), 3.84 (s, 3H), 2.85−2.74 (m, 2H), 2.69−2.65 (m, 1H), 1.83−1.80 (m, 2H), 1.62−1.60 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, CD_3OD): δ 156.6, 155.2, 142.9, 139.9, 134.6, 119.8, 79.8, 55.0, 44.0 (br), 39.9, 32.6, 27.5; FT-IR (neat): 1681, 1421, 1166 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{16}H_{25}N_2O_3$ (M + H)$^+$ 293.1865, found 293.1866.

*4-(4-Methoxyphenyl)tetrahydro-2H-pyran (**3a**).*[1b] The title compound was obtained as a colorless oil in 62% yield (119 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.2 Hz, 2H), 4.06 (dd, J = 10.6, 3.3 Hz, 2H), 3.79 (s, 3H), 3.51(td, J = 11.3, 2.8 Hz, 2H), 2.73−2.66 (m, 1H), 1.82−1.72 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.2, 138.3, 127.7, 114.0, 68.6, 55.4, 40.9, 34.6.

*4-(3-Methoxyphenyl)tetrahydro-2H-pyran (**3b**).* The title compound was obtained as a colorless oil in 59% yield (113 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26−7.23 (m, 1H), 6.84−6.76 (m, 3H), 4.09−4.07 (m, 2H), 3.81 (s, 3H), 3.55−3.50 (m, 2H), 2.75−2.71 (m, 1H), 1.84−1.76 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 159.9, 147.7, 129.6, 119.3, 113.0, 111.4, 68.5, 55.3, 41.8, 34.0; FT-IR (neat): 2980, 1601, 1270, 1130 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{12}H_{17}O_2$ (M + H)$^+$ 193.1229, found 193.1221.

*4-(2-Methoxyphenyl)tetrahydro-2H-pyran (**3c**).* The title compound was obtained as a white solid in 58% yield (111 mg) according to method A. mp: 79−80 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18−7.17 (m, 2H), 6.94−6.93 (m, 1H), 6.86−6.85 (m, 1H), 4.05 (d, J = 11.3 Hz, 2H), 3.81 (s, 3H), 3.56 (t, J = 11.6 Hz, 2H), 3.22−3.17 (m, 1H), 1.80−1.71 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 157.0, 134.1, 127.2, 126.7, 120.8, 110.5, 68.8, 55.4, 34.6, 32.8; FT-IR (neat): 2940, 1494, 1234 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{12}H_{17}O_2$ (M + H)$^+$ 193.1229, found 193.1233.

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*1-(4-(Tetrahydro-2H-pyran-4-yl)phenyl)ethan-1-one (**3d**).* The title compound was obtained as a white solid in 50% yield (102 mg) according to method A. mp: 75−76 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.10−4.07 (m, 2H), 3.56−3.51 (m, 2H), 2.85−2.84 (m, 1H), 2.58 (s, 3H), 1.84−1.75 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.9, 151.5, 135.6, 128.9, 127.1, 68.3, 41.8, 33.7, 26.7; FT-IR (neat): 2940, 1681, 1268, 1118 cm^{-1}; HRMS (CI+) m/z calcd. for $C_{13}H_{16}O_2$ $(M)^+$ 204.1150, found 204.1144.

*4-(o-Tolyl)tetrahydro-2H-pyran (**3e**).* The title compound was obtained as a colorless oil in 43% yield (76 mg) according to method A. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24−7.17 (m, 4H), 4.14−4.11 (m, 2H), 3.61−3.58 (m, 2H), 3.07−2.99 (m, 1H), 2.40 (s, 3H), 1.93−1.82 (m, 2H), 1.75−1.68 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 143.6, 135.0, 130.0, 126.3, 125.9, 125.4, 68.6, 37.3, 33.1, 19.2; FT-IR (neat): 2951, 1386, 1133, 1122 cm^{-1}; HRMS (CI+) m/z calcd. for $C_{12}H_{16}O$ $(M)^+$ 176.1201, found 176.1209.

*4-(4-(Trifluoromethyl)phenyl)tetrahydro-2H-pyran (**3f**).*[1b] The title compound was obtained as a white solid in 53% yield (122 mg) according to method A. mp: 30−31 °C. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.11−4.08 (m, 2H), 3.57−3.51 (m, 2H), 2.83−2.81 (m, 1H), 1.84−1.76 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.9, 128.8 (q, J = 32 Hz), 127.3, 125.6 (q, J = 4 Hz), 125.5 (q, J = 272 Hz), 68.3, 41.6, 33.8.

*4-(Tetrahydro-2H-pyran-4-yl)benzenesulfonamide (**3g**).* The title compound was obtained as a white solid in 41% yield (99 mg) according to method A. mp: 186−188 °C. ^{1}H NMR (500 MHz, acetone-d6): δ 7.82 (d, J = 8.1 Hz, 2H), 7.44 (d, J = 8.2 Hz, 2H), 6.51 (s, 2H), 3.97 (d, J = 11.1 Hz, 2H), 3.50−3.45 (m, 2H), 2.91−2.88 (m, 1H), 1.74−1.72 (m, 4H); ^{13}C NMR (125.8 MHz, acetone-d_6): δ 150.7, 142.3, 127.4, 126.4, 67.7, 41.4, 33.7; FT-IR (neat): 3306, 1339, 1156 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{11}H_{14}NO_3S$ $(M - H)^-$ 240.0694, found 240.0702.

*tert-Butyl 3-(4-Methoxyphenyl)piperidine-1-carboxylate (**4a**).*[1b] The title compound was obtained as a colorless oil in 50% yield (146 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.15 (br, 2H), 3.77 (s, 3H), 2.71−2.63 (m, 3H), 1.99−1.97 (m, 1H), 1.81−1.72 (m, 1H), 1.59−1.57 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.4, 155.0, 135.8, 128.1, 114.0, 79.5, 55.3, 51.4 (br), 43.9 (br), 41.9, 32.1, 28.6, 25.7.

*tert-Butyl 3-(4-Methoxyphenyl)pyrrolidine-1-carboxylate (**4b**).*[1b] The title compound was obtained as a colorless oil in 40% yield (111 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 3.82−3.73 (m, 4H), 3.65−3.52 (m, 1H), 3.40−3.19 (m, 3H), 2.22−2.21 (m, 1H), 1.98−1.92 (m, 1H), 1.47 (s, 9H) ; ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.5, 154.7, 133.6, 128.1, 114.1, 79.3, 55.4, 52.9 and 52.1, 46.1 and 45.8, 43.7 and 42.8, 33.7 and 32.8, 28.7

*tert-Butyl 3-(4-Methoxyphenyl)azetidine-1-carboxylate (**4c**).*[1b] The title compound was obtained as a colorless oil in 48% yield (126 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, J = 6.9 Hz, 2H), 6.88 (d, J = 7.2 Hz, 2H), 4.31−4.28 (m, 2H), 3.93−3.92 (m, 2H), 3.80 (s, 3H), 3.69−3.68 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.7, 156.6, 134.5, 127.9, 114.2, 79.6, 57.0 (br), 55.4, 33.0, 28.6.

*3-(4-Methoxyphenyl)tetrahydro-2H-pyran (**4d**).* The title compound was obtained as a light yellow solid in 43% yield (83 mg) according to method A. mp: 38−39 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.4 Hz, 2H), 4.00−3.94 (m, 2H), 3.79 (s, 3H), 3.46−3.42 (m, 1H), 3.36−3.31 (m, 1H), 2.81−2.80 (m, 1H), 2.03−2.01 (m, 1H), 1.79−1.69 (m, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.4, 134.9, 128.4, 114.0, 74.2, 68.3, 55.4, 42.3, 30.7, 26.4; FT-IR (neat): 2932, 1513, 1247, 1084 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{12}H_{16}O_2$ $(M)^+$ 192.1150, found 192.1147.

*3-(4-Methoxyphenyl)tetrahydrofuran (**4e**).*[1b] The title compound was obtained as a colorless oil in 41% yield (39 mg) according to method A. Compound was isolated as a mixture of isomers (approximately 17% 2-(4-methoxyphenyl)tetrahydrofuran[4a]). Spectral data were in accordance with those published for the major isomer. ^{1}H NMR (500 MHz, $CDCl_3$): 7.18−7.16 (m, 2H), 6.88−6.85 (m, 2H), 4.13−4.10 (m, 1H), 4.08−4.03 (m, 1H), 3.93−3.89 (m, 1H), 3.80 (s, 3H), 3.70−3.66 (m, 1H), 3.37−3.34 (m, 1H), 2.35−2.32 (m, 1H), 2.01−1.95 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.4, 134.7, 128.3, 114.1, 74.9, 68.6, 55.4, 44.4, 34.9.

*3-(4-Methoxyphenyl)oxetane (**4f**).*[1b] The title compound was obtained as a colorless oil in 43% yield (71 mg) according to method A. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 5.05 (t, J = 7.2 Hz, 2H), 4.74 (t, J = 6.4 Hz, 2H), 4.20−4.17 (m, 1H), 3.81 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.8, 133.8, 128.0, 114.3, 79.4, 55.4, 39.8.

*1-(4-(Tetrahydrofuran-3-yl)phenyl)ethan-1-one (**4g**).* The title compound was obtained as a colorless oil in 54% yield (102 mg) according to method A. Compound was isolated as a mixture of isomers (approximately 3.5% 1-(4-(tetrahydrofuran-2-yl)phenyl)-ethan-1-one). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 4.15−4.06 (m, 2H), 3.94−3.90 (m, 1H), 3.77−3.74 (m, 1H), 3.49−3.44 (m, 1H), 2.58 (s, 3H), 2.43−2.38 (m, 1H), 2.04−1.99 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.7, 148.9, 135.8, 128.9, 127.6, 74.5, 68.6, 45.1, 34.7, 26.7; FT-IR (neat): 2925, 1681, 1606, 1269 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{12}H_{15}O_2$ $(M + H)^+$ 191.1072, found 191.1066.

*tert-Butyl 4-(Quinolin-3-yl)piperidine-1-carboxylate (**5a**).* The title compound was obtained as a yellow oil in 60% yield (187 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81−8.80 (m, 1H), 8.08−8.06 (m, 1H), 7.91−7.90 (m, 1H), 7.77−7.76 (m, 1H), 7.68−7.64 (m, 1H), 7.53−7.50 (m, 1H), 4.30 (br, 2H), 2.89−2.84 (m, 3H), 1.94−1.92 (m, 2H), 1.74−1.72 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.9, 151.0, 147.2, 138.3, 132.6, 129.2, 129.0, 128.2, 127.6, 126.8, 79.7, 44.5 (br), 40.3, 33.0, 28.6; FT-IR (neat): 1687, 1424, 1233, 1167 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{19}H_{25}N_2O_2$ $(M + H)^+$ 313.1916, found 313.1914.

*tert-Butyl 4-(1H-Indol-5-yl)piperidine-1-carboxylate (**5b**).* The title compound was obtained as a yellow oil in 27% yield (81 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (br, 1H), 7.46 (s, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.19−7.18 (m, 1H), 7.05 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 6.51−6.50 (m, 1H), 4.26 (br, 2H), 2.84−2.82 (m, 2H), 2.76−2.70 (m, 1H), 1.88−1.86 (m, 2H), 1.73−1.68 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.2, 137.4, 134.9, 128.2, 124.8, 121.5, 118.2, 111.2, 102.4, 79.6, 44.8 (br), 43.0, 34.1, 28.7; FT-IR (neat): 1669, 1428, 1166 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{24}N_2O_2Na$ $(M + Na)^+$ 323.1735, found 323.1738.

*tert-Butyl 4-(Isoquinolin-4-yl)piperidine-1-carboxylate (**5c**).*[1b] The title compound was obtained as a yellow oil in 38% yield (204 mg) according to method B. Spectral data were in accordance with those published. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (s, 1H), 8.41−8.40 (m, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.75−7.71 (m, 1H), 7.61−7.58 (m, 1H), 4.33 (br, 2H), 3.40−3.35 (m, 1H), 2.94−2.92 (m, 2H), 2.00−1.97 (m, 2H), 1.85−1.80 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.0, 151.6, 140.2, 134.2, 134.0, 130.5, 128.8, 128.5, 126.9, 122.1, 79.8, 44.8 (br), 36.5, 32.6, 28.6.

*tert-Butyl 4-(Quinoxalin-6-yl)piperidine-1-carboxylate (**5d**).* The title compound was obtained as a yellow solid in 29% yield (91 mg) according to method B. mp: 108−110 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.82−8.81 (m, 2H), 8.07−8.05 (m, 1H), 7.91 (s, 1H), 7.68−7.66 (m, 1H), 4.31 (br, 2H), 2.93−2.88 (m, 3H), 1.97−1.94 (m, 2H), 1.79−1.73 (m, 2H), 1.50 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.9, 148.2, 145.2, 144.6, 143.3, 142.1, 130.2, 129.6, 126.4, 79.7, 44.7 (br), 42.9, 33.0, 28.6; FT-IR (neat): 1689, 1423, 1164 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{23}N_3O_2Na$ $(M + Na)^+$ 336.1688, found 336.1686.

*tert-Butyl 4-(3-(1H-Pyrazol-5-yl)phenyl)piperidine-1-carboxylate (**5e**).* The title compound was obtained as a colorless oil in 65%

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yield (214 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.17 (br, 1H), 7.61−7.58 (m, 3H), 7.35−7.32 (m, 1H), 7.17−7.13 (m, 1H), 6.78−6.61 (m, 1H), 4.25 (br, 2H), 2.83−2.77 (m, 2H), 2.68−2.64 (m, 1H), 1.83−1.81 (m, 2H), 1.65−1.63 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.1, 148.9, 146.4, 133.4, 132.5, 129.0, 126.4, 124.5, 124.1, 102.6, 79.7, 44.4 (br), 42.8, 33.2, 28.7; FT-IR (neat): 2930, 1687, 1427, 1169 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{19}H_{26}N_3O_2$ $(M + H)^+$ 328.2025, found 328.2016.

*tert-Butyl 4-(4-(1,3,4-Oxadiazol-2-yl)phenyl)piperidine-1-carboxylate (**5f**).* The title compound was obtained as a white solid in 32% yield (105 mg) according to method B. mp: 146−147 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.00 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 7.4 Hz, 2H), 4.26 (br, 2H), 2.81−2.74 (m, 2H), 2.72−2.69 (m, 1H), 1.85−1.82 (m, 2H), 1.65−1.62 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 164.7, 154.8, 152.7, 150.2, 127.7, 127.4, 121.7, 79.6, 44.7 (br), 42.8, 33.0, 28.6; FT-IR (neat): 2924, 1670, 1428, 1167 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{23}N_3O_3Na$ $(M + Na)^+$ 352.1637, found 352.1637.

*3-(Tetrahydro-2H-pyran-4-yl)quinoline (**5g**).* The title compound was obtained as an orange solid in 41% yield (87 mg) according to method B. mp: 97−99 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.93 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.68−7.65 (m, 1H), 7.54−7.51 (m, 1H), 4.14−4.12 (m, 2H), 3.61−3.57 (m, 2H), 3.00−2.95 (m, 1H), 1.96−1.86 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 151.1, 147.3, 138.3, 132.5, 129.3, 129.0, 128.2, 127.7, 126.8, 68.3, 39.2, 33.7; FT-IR (neat): 2951, 2851, 1494, 1120 cm^{-1}; HRMS (CI+) m/z calcd. for $C_{14}H_{16}NO$ $(M + H)^+$ 214.1232, found 214.1237.

*5-(Tetrahydro-2H-pyran-4-yl)-1H-pyrrolo[2,3-b]pyridine (**5h**).* The title compound was obtained as a white solid in 45% yield (91 mg) according to method B. mp: 165−167 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.12 (br, 1H), 8.26−8.25 (m, 1H), 7.83−7.82 (m, 1H), 7.38−7.37 (m, 1H), 6.48−6.47 (m, 1H), 4.12 (dt, J = 11.8, 6.2 Hz, 2H), 3.60−3.56 (m, 2H), 2.93−2.88 (m, 1H), 1.95−1.82 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 148.2, 142.0, 133.2, 126.9, 126.1, 120.7, 100.3, 68.6, 39.5, 34.7; FT-IR (neat): 2954, 1587, 1354, 1086 cm^{-1}; HRMS (CI+) m/z calcd. for $C_{12}H_{14}N_2O$ $(M)^+$ 202.1106, found 202.1110.

*5-(Tetrahydro-2H-pyran-4-yl)benzofuran (**5i**).* The title compound was obtained as a colorless oil in 49% yield (99 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.61 (m, 1H), 7.47−7.45 (m, 2H), 7.19−7.17 (m, 1H), 6.75−6.74 (m, 1H), 4.13−4.10 (m, 2H), 3.60−3.55 (m, 2H), 2.89−2.84 (m, 1H), 1.90−1.81 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 153.9, 145.4, 140.8, 127.8, 123.6, 118.9, 111.4, 106.7, 68.7, 41.7, 34.7; FT-IR (neat): 2936, 2360, 1469, 1128 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{13}H_{14}O_2$ $(M)^+$ 202.0994, found 202.0995.

*tert-Butyl 3-(Quinolin-3-yl)azetidine-1-carboxylate (**5j**).* The title compound was obtained as a yellow oil in 30% yield (85 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.10−8.08 (m, 2H), 7.80 (d, J = 8.2 Hz, 1H), 7.70−7.67 (m, 1H), 7.56−7.53 (m, 1H), 4.45−4.42 (m, 2H), 4.09−4.06 (m, 2H), 3.95−3.90 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 156.5, 150.3, 147.5, 135.0, 133.1, 129.4, 129.4, 128.0, 127.7, 127.1, 80.0, 56.7 (br), 31.4, 28.5; FT-IR (neat): 2972, 1698, 1400, 1140 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{17}H_{21}N_2O_2$ $(M + H)^+$ 285.1603, found 285.1613.

*tert-Butyl 5-(Tetrahydro-2H-pyran-4-yl)-1H-indole-1-carboxylate (**6a**).* The title compound was obtained as a white solid in 73% yield (220 mg) according to method B. mp: 86−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06−8.05 (m, 1H), 7.58−7.57 (m, 1H), 7.40 (s, 1H), 7.20−7.18 (m, 1H), 6.54−6.53 (m, 1H), 4.11−4.08 (m, 2H), 3.58−3.53 (m, 2H), 2.87−2.82 (m, 1H), 1.89−1.79 (m, 4H), 1.67 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.9, 140.6, 134.1, 131.0, 126.3, 123.6, 118.7, 115.3, 107.4, 83.6, 68.6, 41.6, 34.6, 28.3; FT-IR (neat): 2951, 1724, 1364, 1132 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{24}NO_3$ $(M + H)^+$ 302.1756, found 302.1755.

*tert-Butyl 5-(Tetrahydro-2H-pyran-3-yl)-1H-indole-1-carboxylate (**6b**).* The title compound was obtained as a colorless oil in 37% yield (112 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.05 (m, 1H), 7.58−7.57 (m, 1H), 7.41 (s, 1H), 7.19−7.17 (m, 1H), 6.53−6.52 (m, 1H), 4.03−4.01 (m, 2H), 3.50−3.41 (m, 2H), 2.97−2.93 (m, 1H), 2.10−2.09 (m, 1H), 1.82−1.79 (m, 3H), 1.67 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.9, 137.2, 134.2, 131.0, 126.3, 124.0, 119.4, 115.2, 107.3, 83.7, 74.4, 68.4, 43.0, 31.0, 28.3, 26.5; FT-IR (neat): 2933, 1732, 1368, 1084 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{18}H_{23}NO_3Na$ $(M + Na)^+$ 324.1576, found 324.1582.

*tert-Butyl 5-(Tetrahydrofuran-3-yl)-1H-indole-1-carboxylate (**6c**).* The title compound was obtained as a colorless oil in 44% yield (126 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−8.07 (m, 1H), 7.59−7.58 (m, 1H), 7.44 (s, 1H), 7.22−7.21 (m, 1H), 6.53−6.52 (m, 1H), 4.20−4.16 (m, 1H), 4.12−4.08 (m, 1H), 3.97−3.94 (m, 1H), 3.80−3.76 (m, 1H), 3.52−3.49 (m, 1H), 2.42−2.39 (m, 1H), 2.08−2.04 (m, 1H), 1.67 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.9, 137.2, 134.1, 131.0, 126.4, 123.8, 119.3, 115.3, 107.3, 83.8, 75.1, 68.7, 45.1, 35.1, 28.1; FT-IR (neat): 2979, 1731, 1471, 1134 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{17}H_{20}NO_3$ $(M - H)^-$ 286.1443, found 286.1444.

*tert-Butyl 5-(Oxetan-3-yl)-1H-indole-1-carboxylate (**6d**).* The title compound was obtained as a yellow oil in 70% yield (191 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14−8.13 (m, 1H), 7.61−7.60 (m, 1H), 7.57 (s, 1H), 7.37−7.35 (m, 1H), 6.56−6.55 (m, 1H), 5.13−5.10 (m, 2H), 4.84−4.82 (m, 2H), 4.33−4.30 (m, 1H), 1.68 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.8, 136.1, 134.5, 131.1, 126.6, 123.2, 119.0, 115.6, 107.3, 83.8, 79.4, 40.5, 28.3; FT-IR (neat): 2973, 1731, 1368, 1162 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{16}H_{18}NO_3$ $(M - H)^-$ 272.1287, found 272.1280.

*tert-Butyl 5-(1-(tert-Butoxycarbonyl)piperidin-4-yl)-1H-indole-1-carboxylate (**6e**).* The title compound was obtained as a colorless oil in 51% yield (204 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (br, 1H), 7.58−7.57 (m, 1H), 7.38 (s, 1H), 7.17−7.16 (m, 1H), 6.53−6.52 (m, 1H), 4.21 (br, 2H), 2.87−2.82 (m, 2H), 2.76−2.71 (m, 1H), 1.87−1.85 (m, 2H), 1.67 (s, 9H), 1.50 (s, 9H), 1.49−1.46 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.0, 149.9, 140.5, 134.0, 130.9, 126.3, 123.5, 118.7, 115.2, 107.4, 83.7, 79.5, 44.4 (br), 42.8, 33.8, 28.6, 28.3; FT-IR (neat): 1733, 1691, 1365, 1163 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{23}H_{32}N_2O_4Na$ $(M + Na)^+$ 423.2260, found 423.2257.

*tert-Butyl 5-(1-(tert-Butoxycarbonyl)piperidin-3-yl)-1H-indole-1-carboxylate (**6f**).* The title compound was obtained as a colorless oil in 48% yield (192 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.06 (m, 1H), 7.58−7.57 (m, 1H), 7.41 (s, 1H), 7.20−7.18 (m, 1H), 6.53−6.52 (m, 1H), 4.17 (br, 2H), 2.78−2.76 (m, 3H), 2.07−2.04 (m, 1H), 1.79−1.77 (m, 1H), 1.70−1.59 (m, 11H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.0, 149.9, 138.2, 134.2, 130.9, 126.3, 123.8, 119.1, 115.2, 107.3, 83.7, 79.5, 51.2 (br), 44.3 (br), 42.7, 32.3, 28.6, 28.3, 25.8; FT-IR (neat): 2977, 1733, 1689, 1367 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{23}H_{32}N_2O_4Na$ $(M + Na)^+$ 423.2260, found 423.2256.

*tert-Butyl 5-(1-(tert-Butoxycarbonyl)pyrrolidin-3-yl)-1H-indole-1-carboxylate (**6g**).* The title compound was obtained as a colorless oil in 38% yield (147 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−8.06 (m, 1H), 7.58−7.57 (m, 1H), 7.42 (s, 1H), 7.20−7.18 (m, 1H), 6.53−6.52 (m, 1H), 3.89−3.80 (m, 1H), 3.67−3.57 (m, 1H), 3.43−3.30 (m, 3H), 2.29−2.28 (m, 1H), 2.04−2.01 (m, 1H), 1.67 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, CD_3OD): δ 155.1, 149.7, 135.8, 134.3, 131.0, 125.9, 123.2, 118.8, 114.8, 107.1, 83.6, 79.6, 52.8 and 52.3, 46.0 and 45.5, 44.0 and 43.3, 33.2 and 32.4, 27.6, 27.2; FT-IR (neat): 2976, 1732, 1693, 1367 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{22}H_{30}N_2O_4Na$ $(M + Na)^+$ 409.2103, found 409.2106.

*tert-Butyl 5-(1-(tert-Butoxycarbonyl)azetidin-3-yl)-1H-indole-1-carboxylate (**6h**).* The title compound was obtained as a colorless oil in 36% yield (134 mg) according to method B. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11−8.10 (m, 1H), 7.60−7.59 (m, 1H), 7.49 (s, 1H), 7.27−7.26 (m, 1H), 6.54−6.53 (m, 1H), 4.38−4.35 (m, 2H), 4.03−4.00 (m, 2H), 3.83−3.82 (m, 1H), 1.67 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.6, 149.7, 136.8, 134.4, 131.0, 126.6, 123.1, 119.0, 115.5, 107.2, 83.8, 79.5, 57.2 (br), 33.7, 28.6, 28.3; FT-IR (neat): 2676, 1733, 1699, 1368 cm^{-1}; HRMS (ES+) m/z calcd. for $C_{21}H_{28}N_2O_4Na$ $(M + Na)^+$ 395.1947, found 395.1938.

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■ ASSOCIATED CONTENT

Supporting Information

Figures of ^{1}H and ^{13}C NMR spectra. 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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(11) 4,4′-Dimethoxy-2,2′-bipyridine, 4,4′-di-*tert*-butyl-2,2′-bipyridine, 4,4′-dimethyl-2,2′-bipyridine, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline, 2,9-dimethyl-1,10-phenanthroline, 2,2′-biquinoline, terpyridine, 1,3-diphenylurea, picolinic acid, 1,3-di-*i*-Pr-imidazolium chloride

(12) NiI_2, $NiI_2{\cdot}H_2O$, $NiBr_2$, $NiBr_2{\cdot}$glyme, $NiCl_2{\cdot}$glyme, Ni(II) phthalocyanine, $Ni(OTf)_2$, $NiCl_2{\cdot}$hexaamine, $Ni(acac)_2$, NiCl·dppe, Ni(II) dimethylglyoxime.

(13) Pyridine, 2,3-dimethylpyridine, 2,6-dimethylpyridine, 4-ethylpyridine, 2-dimethylaminopyridine, 4-dimethylaminopyridine, 4-benzylpyridine.

(14) DMF, DMSO, sulfolane, THF, *i*-PrOH, MeOH, EtOH, *t*-BuOH, *s*-BuOH, TFE, H_2O, CH_3CN, DMPU, NMP, DMA.

(15) In our hands, Zn dust required activation with aqueous HCl prior to use, as has also been demonstrated by Weix, et al. (ref 9b); different lengths and methods of storage led to inconsistent results with Zn.

(16) NaI, KI, n-Bu_4NI, NaBr, LiBr, LiCl, MnI_2, CuI, MgI_2, ZnI_2, LiI, CaI_2, CsI, FeI_3, $NaBF_4$, KBF_4, $LiBF_4$, $MgCl_2$, $ZnCl_2$, $ZnBr_2$, $FeCl_3$.

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