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Engaging Nonaromatic, Heterocyclic Tosylates in Reductive Cross-Coupling with Aryl and Heteroaryl Bromides

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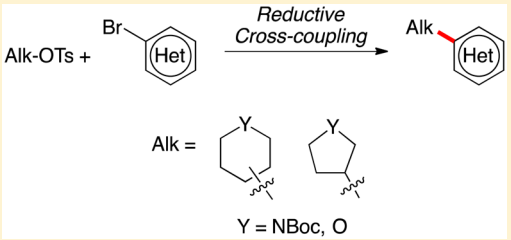
Supporting Information

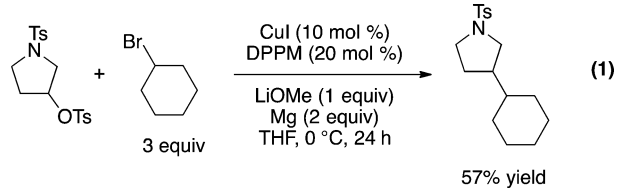
ABSTRACT: A method has been developed for the introduction of nonaromatic heterocyclic structures onto aryl and heteroaryl bromides using alkyl tosylates in a reductive cross-coupling manifold. This protocol offers an improvement over previous methods by utilizing alkyl tosylate coupling partners that are bench-stable, crystalline solids that can be prepared from inexpensive, commercially available alcohols.



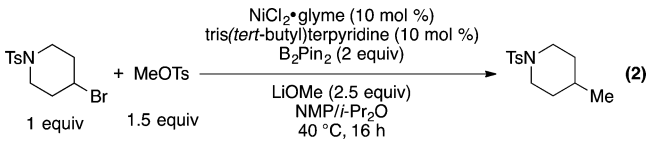
Recently, reductive cross-coupling protocols have garnered a significant amount of attention as a means of forming C−C bonds without the necessity for generation of an organometallic reagent.[1] Although several methods have been developed for the introduction of nonaromatic heterocycles onto arenes,[2] a particularly attractive route involves the direct reductive coupling between nonaromatic heterocyclic halides and (hetero)aryl halides that forges the sp^3−sp^2 linkage.[3] Unlike earlier methods, these reductive protocols allow the desired transformation to be carried out in a single step and tolerate a variety of functional groups (Scheme 1). As one example of the importance of such efforts, medicinal chemistry programs continue to struggle to incorporate nonaromatic heterocycles during SAR investigations, and new methods that enable more complex functional group arrays will extend the scope of matter in attractive physical property space.

Although the previously reported methods of Gong et al.[3c] (Scheme 1A) and Molander et al.[3d] (Scheme 1B) increase the efficiency in the installation of nonaromatic heterocycles onto arenes by eliminating the need for a low-yielding metalation step, the cost and availability of the nonaromatic, heterocyclic halides may still be prohibitive in some cases. An improvement of this protocol was envisioned in which less expensive alkyl coupling partners could be used to effect the desired transformation. Notably, the alcohols of nitrogen- and oxygen-containing nonaromatic heterocycles are significantly less expensive than the corresponding bromides and iodides.[4] The alcohols can be easily converted to the nonaromatic heterocyclic tosylates,[5] which are stable, colorless, crystalline solids at room temperature, compared to the corresponding bromides, many of which were liquids or gummy solids that became discolored after a few weeks even when refrigerated.[6]

A similar approach was developed by Liu et al., who developed a Cu-catalyzed cross-coupling of unactivated alkyl tosylates with aryl and alkyl bromides.[7] An example was illustrated in which a nonaromatic heterocyclic tosylate was coupled with cyclohexyl bromide in good yield (eq 1).



Recent work by Gong et al. demonstrated the Ni-catalyzed reductive methylation of alkyl halides with methyl tosylate.[8] Among the substrates were select *N*-containing nonaromatic heterocyclic bromides (eq 2).



A general, functional group-tolerant method was therefore pursued that would allow the reductive cross-coupling of a variety of nonaromatic heterocyclic tosylates with aryl and heteroaryl halides. A protocol was envisioned for this transformation based on previous work in the area of Ni-catalyzed reductive cross-coupling of saturated heterocyclic substructures.[3d]

Optimization of the targeted transformation was initiated on the cross-coupling of *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate with *N*-Boc-5-bromoindole (eq 3).

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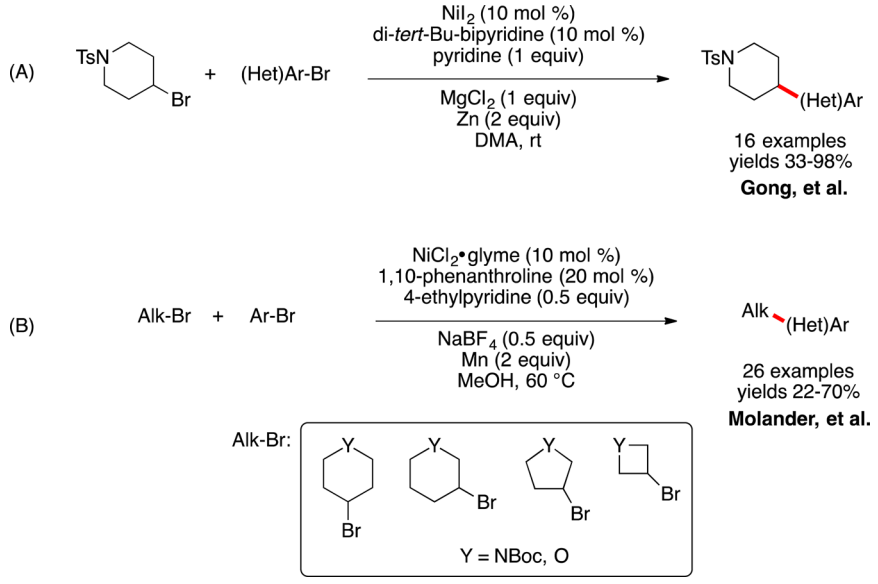
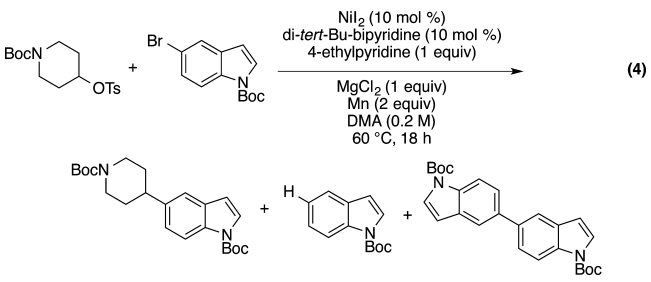
Scheme 1. Reductive Methods for sp^3–sp^2 Cross-Coupling Involving Saturated Heterocyclic Structures

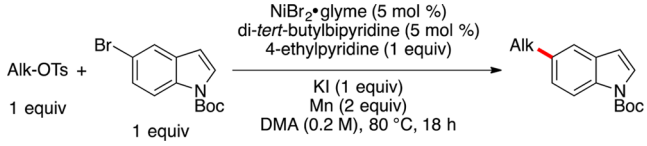


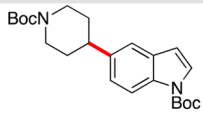
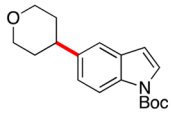
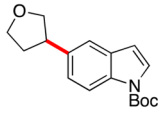
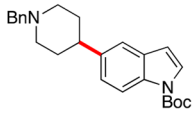
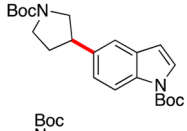
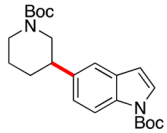
Under previously developed conditions, 1-Boc-4-bromopiperidine had been successfully cross-coupled with *N*-Boc-5-bromoindole in the presence of catalytic NiI_2 and $MgCl_2$ as an additive. Under this protocol, the reaction of *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate with *N*-Boc-5-bromoindole led to the formation of the desired cross-coupled product in addition to nearly equal amounts of biaryl homocoupling and protodehalogenation of the indole substrate (eq 4). Unreacted alkyl tosylate remained, but no Boc-cleavage was observed on any of the reaction components. Upon application of these conditions to several aryl and heteroaryl bromides, these major side products were formed to a significant extent in every case.



The use of $NiBr_2$·glyme in place of NiI_2 and the elimination of $MgCl_2$ significantly reduced the formation of both the protodehalogenated and homocoupled side products. Further optimization revealed that addition of 1 equiv of KI significantly improved conversion to the cross-coupled product, as did an increase in reaction temperature from 60 to 80 °C. The amount of Ni and ligand could be reduced from 10 to 5 mol % without a decrease in yield. With these modifications to the original reaction conditions, the cross-coupling of *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate with *N*-Boc-5-bromoindole proceeded in 73% yield (Table 1, entry 1).

Table 1. Cross-Coupling of Nonaromatic, Heterocyclic Tosylates with *N*-Boc-5-Bromoindole



Entry	Product		Yield (%)
1		**1a**	73, 51[a]
2		**1b**	69
3		**1c**	36, 28[a]
4		**1d**	66
5		**1e**	52
6		**1f**	24

[a]From the corresponding alkyl mesylate.

The developed conditions were applied to the reductive cross-coupling of a variety of nonaromatic, heterocyclic tosylates with *N*-Boc-5-bromoindole (Table 1). The method was extended to other six-membered ring systems, including a benzyl-protected piperidine system, tetrahydropyran, and

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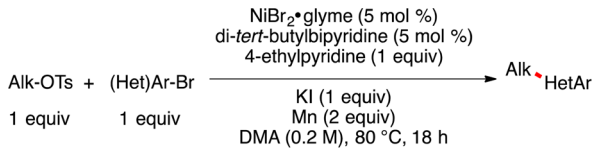
tert-butyl 3-(tosyloxy)piperidine-1-carboxylate. Both pyrrolidinyl and tetrahydrofuranyl tosylate systems participated in the cross-coupling. It was observed that the corresponding mesylates of the tetrahydrofuranyl and piperidinyl systems reacted under the standard conditions, albeit in lower yields (Table 1, entries 1 and 3). Unfortunately, both azetidine and oxetane substrates were unreactive under the standard protocol, and the use of aryl chlorides instead of aryl bromides led to minimal product formation. Interestingly, under the conditions developed for nonaromatic, heterocyclic systems, cyclohexyl tosylate was unreactive.

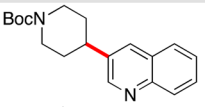
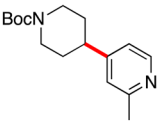
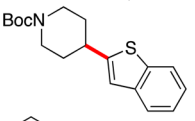
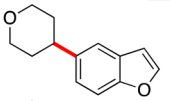
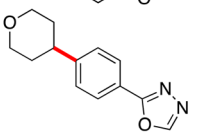
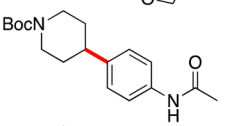
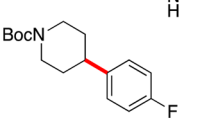
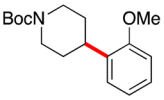
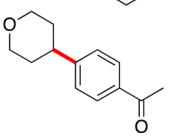
A variety of heteroaryl bromide substrates, including quinoline, pyridine, benzothiophene, and benzofuran substrates, provided the desired cross-coupling products in moderate to good yields. Additionally, aryl bromides reacted under the same conditions, and the reaction tolerated amide and ketone functional groups in addition to *ortho*-substitution. The scalable nature of the method was demonstrated by the ability to carry out a gram-scale reaction without a decrease in the yield (Table 2, entry 1).

Although the mechanism of this reaction has not been investigated, it is possible that KI serves to generate an alkyl iodide *in situ* from the corresponding alkyl tosylate. Notably, other metal halides, e.g. CsI, LiI, and KBr, served as suitable additives for the given transformation, albeit leading to lower product conversion. Based on a previously proposed mechanistic pathway for reductive cross-coupling reactions,[1c] once formed, the nonaromatic, heterocyclic halide could serve as a source of alkyl radicals, which would then combine with an Ar–$Ni^{(II)}$–Br complex generated from the oxidative addition of the aryl bromide to $Ni^{(0)}$. Reductive elimination from the newly generated diorgano-$Ni^{(III)}$ species would provide the cross-coupled product and a $Ni^{(I)}$ species that would be reduced to $Ni^{(0)}$ by Mn.

The concept of *in situ* sulfonate/halogen exchange has been proposed in the Ni-catalyzed reductive methylation of alkyl halides with methyl tosylate[8] and in Ni-catalyzed dimerizations of alkyl pseudohalides.[9] Although the latter contribution employs NaI as an additive, the former (eq 2) uses no obvious source of nucleophilic halide and there is no speculation on the proposed pathway for alkyl halide formation. It has been suggested that in instances where reactive alkyl halides undergo rapid dimerization in the presence of Ni catalysts, their slow formation from a less reactive species, i.e., alkyl mesylate or tosylate, may be advantageous.[8,10] In our hands, *N*-Boc-4-iodopiperidine was never observed in the analytical sampling of the crude reaction mixture. Additionally, under the developed reductive coupling conditions, *N*-Boc-4-iodopiperidine in place of the corresponding tosylate was unreactive with or without the KI additive.[11] If the alkyl iodide is, in fact, only a capable coupling partner when formed in low concentration and rapidly consumed, these observations can be rationalized. However, the use of alkyl iodides did not lead to formation of an alkyl–alkyl dimer or radical disproportionation products, which would be predicted if rapid radical formation were problematic. Furthermore, the reaction also proceeds to some extent in the absence of KI.[12] These observations bring to question the possibility of alkyl iodide formation as the sole function of KI within the process and suggest that perhaps the iodide additive plays a more complex role,[1b,13] possibly in stabilization of a transient nickel complex that facilitates reductive elimination in the catalytic cycle or as a bridging ligand that facilitates electron transfer.

Table 2. Cross-Coupling of Nonaromatic, Heterocyclic Tosylates with Heteroaryl Bromides



Entry	Product		Yield (%)
1		**2a**	74, 81[a]
2		**2b**	60
3		**2c**	42
4		**2d**	49
5		**2e**	62
6		**2f**	38
7		**2g**	65
8		**2h**	60
9		**2i**	72

[a]Reaction carried out on 3.0 mmol scale.

In conclusion, a method has been developed for the reductive cross-coupling of nonaromatic, heterocyclic tosylates with aryl and heteroaryl bromides. Notably, low catalyst loadings are used for these transformations, and stoichiometric ratios of the coupling partners are also employed.[1b] This method provides an extension to previously reported reductive cross-coupling protocols between nonaromatic, heterocyclic bromides and (hetero)aryl bromides by allowing use of pseudohalide alkyl partners that can easily be accessed from less expensive, commercially available alcohols.

EXPERIMENTAL SECTION

General Considerations. DMA 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 vacuum. Solids were weighed out in air and were stored on a laboratory bench without special considerations. ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125.8 MHz, respectively. Melting points (°C)

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were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. HRMS data were obtained on a TOF mass spectrometer using ESI.

Experimental Procedure. An oven-dried Biotage 10 mL microwave vial equipped with a magnetic stirbar was charged with alkyl tosylate (0.5 mmol), $NiBr_2$·glyme (0.025 mmol, 7.7 mg), 4,4′-di-*tert*-butyl-2,2′-bipyridine (0.025 mmol, 6.7 mg), KI (0.5 mmol, 83.0 mg), and Mn powder (1.0 mmol, 55.0 mg). The vial was sealed with a disposable Teflon septum cap and was evacuated and purged with Ar three times. Dimethylacetamide (2.5 mL) and 4-ethylpyridine (0.5 mmol, 54 mg) were added via syringe, followed by the (hetero)aryl bromide (0.5 mmol). In cases where the (hetero)aryl bromide was a solid, it was added to the vial along with the other solids. The reaction was stirred under Ar at 80 °C for 18 h, after which the solution was cooled and diluted with 5 mL of MeCN. The resulting mixture was filtered through a pad of Celite, which was rinsed with MeCN (∼10 mL), and the solution was concentrated. The resulting residue was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL), and the combined organic portions were washed with H_2O (2 × 10 mL) and brine (10 mL). 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 to 60% EtOAc).

***tert*-Butyl 5-(1-(*tert*-Butoxycarbonyl)piperidin-4-yl)-1*H*-indole-1-carboxylate (1a).** The spectral data are in accordance with those published.[3d] The title compound was obtained as a colorless oil in 73% yield (146 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (br, 1H), 7.58−7.57 (m, 1H), 7.39 (s, 1H), 7.18−7.16 (m, 1H), 6.53−6.52 (d, J = 3.6 Hz, 1H), 4.27 (br, 2H), 2.86−2.82 (m, 2H), 2.76−2.71 (m, 1H), 1.87−1.85 (m, 2H), 1.69−1.67 (m, 11H), 1.50 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.0, 149.8, 140.5, 134.0, 130.9, 126.2, 123.6, 118.7, 115.3, 107.4, 83.6, 79.4, 44.3 (br), 42.8, 33.8, 28.7, 28.3

***tert*-Butyl 5-(Tetrahydro-2*H*-pyran-4-yl)-1*H*-indole-1-carboxylate (1b).** The title compound was obtained as a white solid in 69% yield (104 mg). The spectral data are in accordance with those published.[3d] Mp: 82−84 °C (lit. 86−87 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.06 (m, 1H), 7.58−7.57 (m, 1H), 7.40 (s, 1H), 7.20−7.18 (m, 1H), 6.53−6.52 (d, J = 3.7 Hz, 1H), 4.11−4.08 (m, 2H), 3.58−3.53 (m, 2H), 2.86−2.83 (m, 1H), 1.92−1.79 (m, 4H), 1.66 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 149.9, 140.6, 134.0, 131.0, 126.3, 123.5, 118.7, 115.3, 107.4, 83.7, 68.7, 41.7, 34.6, 28.3.

***tert*-Butyl 5-(Tetrahydrofuran-3-yl)-1*H*-indole-1-carboxylate (1c).** The title compound was obtained as a colorless oil in 36% yield (52 mg). From the corresponding mesylate, the compound was isolated in 28% yield (40 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.06 (m, 1H), 7.59−7.58 (m, 1H), 7.44 (s, 1H), 7.22−7.20 (d, J = 8.6 Hz, 1H), 6.53−6.52 (d, J = 3.6 Hz, 1H), 4.20−4.17 (m, 1H), 4.13−4.08 (m, 1H), 3.97−3.92 (m, 1H), 3.79−3.76 (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, 137.1, 134.1, 131.0, 126.4, 123.8, 119.3, 115.4, 107.3, 83.8, 75.1, 68.7, 45.0, 35.1, 28.3.

***tert*-Butyl 5-(1-Benzylpiperidin-4-yl)-1*H*-indole-1-carboxylate (1d).** The title compound was obtained as a colorless oil in 66% yield (129 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09−8.07 (m, 1H), 7.60−7.59 (d, J = 3.4 Hz, 1H), 7.42−7.38 (m, 5H), 7.36−7.34 (m, 1H), 7.18−7.16 (m, 1H), 6.54−6.53 (d, J = 3.7 Hz, 1H), 5.19 (s, 2H), 4.37 (br, 2H), 2.94−2.93 (m, 2H), 2.80−2.75 (m, 1H), 1.91−1.89 (m, 2H), 1.71−1.67 (m, 11H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.3, 149.7, 140.0, 136.9, 130.7, 128.4, 127.9, 127.8, 126.1, 123.3, 118.5, 115.0, 107.1, 83.5, 67.0, 44.7, 42.5, 33.5 (br), 28.1; FT-IR (neat): 1732, 1698, 1366, 1223 cm^{-1}; HRMS (ES+) m/z calcd for $C_{25}H_{31}N_2O_2$ $(M + H)^+$ 391.2386, found 391.2379.

***tert*-Butyl 5-(1-(*tert*-Butoxycarbonyl)pyrrolidin-3-yl)-1*H*-indole-1-carboxylate (1e).** The title compound was obtained as a colorless oil in 52% yield (100 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08−8.07 (m, 1H), 7.59−7.58 (m, 1H), 7.42 (s, 1H), 7.20−7.19 (m, 1H), 6.54−6.53 (d, J = 3.5 Hz, 1H), 3.89−3.80 (m, 1H), 3.67−3.58 (m, 1H), 3.44−3.30 (m, 3H), 2.29−2.28 (m, 1H), 2.06−2.02 (m, 1H), 1.67 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, CD_3OD): δ 155.0, 149.7, 135.7, 134.2, 131.0, 125.9, 123.3, 118.9, 114.9, 107.1, 83.5, 79.5, 52.8 and 52.3, 46.0 and 45.6, 44.0 and 43.3, 33.2 and 32.4, 27.7, 27.2.

***tert*-Butyl 5-(1-(*tert*-Butoxycarbonyl)piperidin-3-yl)-1*H*-indole-1-carboxylate (1f).** The title compound was obtained as a colorless oil in 24% yield (48 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−8.06 (m, 1H), 7.59−7.58 (m, 1H), 7.42 (s, 1H), 7.21−7.19 (m, 1H), 6.54−6.53 (d, J = 3.6 Hz 1H), 4.18 (br, 2H), 2.77−2.76 (m, 3H), 2.09−2.05 (m, 1H), 1.80−1.77 (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, 32.4, 28.6, 28.3, 25.7.

***tert*-Butyl 4-(Quinolin-3-yl)piperidine-1-carboxylate (2a).** The title compound was obtained as a yellow oil in 74% yield (116 mg). On a 3.0 mmol scale, the product was isolated in 81% yield (759 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.80−8.79 (d, J = 2.2 Hz 1H), 8.07−8.06 (d, J = 8.5 Hz, 1H), 7.90 (s, 1H), 7.77−7.75 (d, J = 8.3 Hz, 1H), 7.67−7.64 (m, 1H), 7.53−7.50 (m, 1H), 4.30 (br, 2H), 2.88−2.83 (m, 3H), 1.94−1.91 (m, 2H), 1.74−1.71 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.9, 151.0, 147.2, 138.3, 132.7, 129.2, 129.0, 128.2, 127.7, 126.8, 79.7, 44.6 (br), 40.3, 33.0, 28.6.

***tert*-Butyl 4-(2-Methylpyridin-4-yl)piperidine-1-carboxylate (2b).** The title compound was obtained as a yellow oil in 60% yield (83 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39−8.38 (d, J = 5.1 Hz, 1H), 6.97 (s, 1H), 6.92−6.91 (d, J = 5.2 Hz, 1H), 4.24 (br, 2H), 2.78−2.76 (m, 2H), 2.60−2.58 (m, 1H), 2.51 (s, 3H), 1.81−1.77 (m, 2H), 1.62−1.55 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.7, 154.9, 154.8, 149.4, 121.9, 119.5, 79.8, 44.3 (br), 42.1, 32.4, 28.6, 24.6.

***tert*-Butyl 4-(Benzo[*b*]thiophen-2-yl)piperidine-1-carboxylate (2c).** The title compound was obtained as a white solid in 42% yield (67 mg). Mp: 83−84 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.32−7.26 (m, 2H), 7.03 (s, 1H), 4.23 (br, 2H), 3.03−3.00 (m, 1H), 2.88−2.82 (m, 2H), 2.07−2.04 (m, 2H), 1.72−1.66 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.9, 150.6, 140.0, 138.8, 124.3, 123.8, 123.1, 122.4, 119.0, 79.7, 44.3 (br), 38.4, 33.8, 28.6; FT-IR (neat): 1681, 1428, 1156 cm^{-1}; HRMS (ES+) m/z calcd for $C_{18}H_{23}NO_2SNa$ $(M + Na)^+$ 340.1347, found 340.1346.

5-(Tetrahydro-2*H*-pyran-4-yl)benzofuran (2d). The title compound was obtained as a colorless oil in 49% yield (50 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62−7.61 (m, 1H), 7.47−7.45 (m, 2H), 7.19−7.17 (d, J = 8.6 Hz, 1H), 6.75−6.74 (m, 1H), 4.13−4.10 (m, 2H), 3.59−3.54 (m, 2H), 2.88−2.83 (m, 1H), 1.92−1.80 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 153.9, 145.4, 140.8, 127.7, 123.6, 118.9, 111.4, 106.7, 68.7, 41.7, 34.7.

2-(4-(Tetrahydro-2*H*-pyran-4-yl)phenyl)-1,3,4-oxadiazole (2e). The title compound was obtained as a white solid in 62% yield (77 mg). Mp: 110−112 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 4.10−4.07 (m, 2H), 3.55−3.50 (m, 2H), 2.85−2.79 (m, 1H), 1.87−1.76 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 164.8, 152.7, 150.3, 127.7, 127.5, 121.7, 68.3, 41.7, 33.7; FT-IR (neat): 1615, 1493, 1086 cm^{-1}; HRMS (ES+) m/z calcd for $C_{13}H_{15}N_2O_2$ $(M + H)^+$ 231.1134, found 231.1134.

***tert*-Butyl 4-(4-Acetamidophenyl)piperidine-1-carboxylate (2f).** The title compound was obtained as a white solid in 38% yield (61 mg). The spectral data are in accordance with those published.[3d] Mp: 171−172 °C (lit. 165−168 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (br, 1H), 7.40 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.1 Hz, 2H), 4.21 (br, 2H), 2.79−2.74 (m, 2H), 2.61−2.56 (m, 1H), 2.14 (s, 3H), 1.78−1.75 (m, 2H), 1.57−1.53 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.6, 155.0, 141.9, 136.4, 127.3, 120.4, 79.7, 44.4 (br), 42.2, 33.4, 28.6, 24.6.

***tert*-Butyl 4-(4-Fluorophenyl)piperidine-1-carboxylate (2g).** The title compound was obtained as a colorless oil in 65% yield (91 mg). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15−7.13 (m, 2H), 7.00−6.97 (m, 2H),

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4.24 (br, 2H), 2.81−2.74 (m, 2H), 2.64−2.59 (m, 1H), 1.81−1.78 (m, 2H), 1.62−1.55 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.5 (d, J = 244.1 Hz), 155.0, 141.6 (d, J = 3.4 Hz), 128.2 (d, J = 7.7 Hz), 115.3 (d, J = 20.9 Hz), 79.6, 44.4 (br), 42.1, 33.5, 28.6.

***tert*-Butyl 4-(2-Methoxyphenyl)piperidine-1-carboxylate (2h).** The title compound was obtained as a white solid in 60% yield (87 mg). Mp: 65−66 °C (lit: 63−65 °C). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20−7.14 (m, 2H), 6.95−6.93 (m, 1H), 6.88−6.86 (m, 1H), 4.24 (br, 2H), 3.83 (s, 3H), 3.12−3.07 (m, 1H), 2.84−2.81 (m, 2H), 1.82−1.78 (m, 2H), 1.61−1.57 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 156.9, 155.1, 134.0, 127.2, 126.6, 120.8, 110.5, 79.4, 55.4, 44.4 (br), 35.5, 32.0, 28.7.

1-(4-(Tetrahydro-2*H*-pyran-4-yl)phenyl)ethan-1-one (2i). The title compound was obtained as a white solid in 72% yield (74 mg). Mp: 71−73 °C (lit: 75−76 °C). The spectral data are in accordance with those published.[3d] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.08−4.05 (m, 2H), 3.54−3.49 (m, 2H), 2.83−2.78 (m, 1H), 2.56 (s, 3H), 1.85−1.73 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.9, 151.5, 135.6, 128.9, 127.1, 68.3, 41.7, 33.7, 26.7.

■ 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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■ REFERENCES

(1) For examples of reductive couplings, see: (a) Everson, D. A.; Shrestha, R.; Weix, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 920. (b) Everson, D. A.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 16192. (d) Everson, D. A.; Buonomo, J. A.; Weix, D. J. *Synlett* **2014**, *25*, 233. (e) Gomes, P.; Gosmini, C.; Perichon. *J. Org. Lett.* **2013**, *5*, 1043. (f) Gosmini, C.; Bassene-Ernst, C.; Durandetti, M. *Tetrahedron* **2009**, *65*, 6141. (g) Durandetti, M.; Nedelec, J.-Y.; Perichon, J. *J. Org. Chem.* **1996**, *61*, 1748. (h) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 7442. (i) Leon, T.; Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1221. (j) Yan, C.-S.; Peng, Y.; Xu, X.-B.; Wang, Y.-W. *Chem.—Eur. J.* **2012**, *18*, 6039. (k) Durandetti, M.; Gosmini, C.; Perichon, J. *Tetrahedron* **2007**, *63*, 1146. (l) Everson, D. A.; Weix, D. J. *J. Org. Chem.* **2014**, *79*, 4793.

(2) (a) Liu, D.; Liu, C.; Li, H.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 4453. (b) Gartia, Y.; Ramidi, P.; Jones, D. E.; Pulla, S.; Ghosh, A. *Catal. Lett.* **2014**, *144*, 507. (c) Millet, A.; Larini, P.; Clot, E.; Baudoin, O. *Chem. Sci.* **2013**, *4*, 2241. (d) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (e) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 9756. (f) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, *11*, 1794. (g) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3556. (h) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G. *Org. Lett.* **2008**, *10*, 3259. (i) Pompeo, M.; Froese, R. D. J.; Hadei, N.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 11354. (j) Han, C.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 7532. (k) Corley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120. (l) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592. (m) Duplais, C.; Krasovskiy, A.; Lipshutz, B. H. *Organometallics* **2011**, *30*, 6090. (n) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529. (o) Li, L.; Wang, C.-Y.; Huang, R.; Biscoe, M. R. *Nat. Chem.* **2013**, *5*, 607.

(3) (a) Yu, X.; Yang, T.; Wang, S.; Xu, H.; Gong, H. *Org. Lett.* **2011**, *13*, 2138. (b) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.* **2013**, *4*, 4022. (c) Wang, S.; Qian, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3352. (d) Molander, G. A.; Traister, K. M.; O'Neill, B. T. *J. Org. Chem.* **2014**, *79*, 5771.

(4) Based on price comparison of an online supplier.

(5) Katz, J. D.; Jewell, P.; Guerin, D. J.; Lim, J.; Dinsmore, C. J.; Deshmukh, S. V.; Pan, B.-S.; Marshall, C. G.; Lu, W.; Altman, M. D.; Dahlberg, W. K.; Davis, L.; Falcone, D.; Gabarda, A. E.; Hang, G.; Hatch, H.; Holmes, R.; Kunii, K.; Lumb, K. J.; Lutterbach, B.; Mathvink, R.; Nazef, N.; Patel, S. B.; Qu, X.; Reilly, J. F.; Rickert, K. W.; Rosenstein, C.; Soisson, S. M.; Spencer, K. B.; Szewczak, A. A.; Walker, D.; Wang, W.; Young, J.; Zeng, Q. *J. Med. Chem.* **2011**, *54*, 4092.

(6) Several vendors recommend storage of nonaromatic, heterocyclic bromides at <7 °C.

(7) Liu, J.-H.; Yang, C.-T.; Lu, X.-Y.; Zhang, Z.-Q.; Xu, L.; Cui, M.; Lu, X.; Xioa, B.; Fu, Y.; Liu, L. *Chem.—Eur. J.* **2014**, *20*, 15334.

(8) Liang, Z.; Xue, W.; Lin, K.; Gong, H. *Org. Lett.* **2014**, *16*, 5620.

(9) (a) Xu, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H. *Chem. Sci.* **2013**, *4*, 4022. (b) Prinsell, M. R.; Everson, D. A.; Weix, D. J. *Chem. Commun.* **2010**, *46*, 5743.

(10) Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.

(11) When *N*-Boc-4-bromopiperidine was used under the standard conditions, product was isolated in 24% yield (0.5 mmol scale).

(12) With the use of $NaBF_4$ as an additive in place of KI under the standard conditions, the reaction of *tert*-butyl 4-(tosyloxy)piperidine-1-carboxylate with *N*-Boc-5-bromoindole proceeded in 13% yield on a 1.0 mmol scale.

(13) For possible roles of halide additives in Ni catalyzed reactions see: (a) Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627. (b) Zembayashi, M.; Yoshida, J.; Kumada, M. *Tetrahedron Lett.* **1977**, *18*, 4089. (c) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645.

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