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PII: S0040-4020(19)30599-X

DOI: https://doi.org/10.1016/j.tet.2019.05.047

Reference: TET 30368

To appear in: *Tetrahedron*

Received Date: 4 March 2019

Revised Date: 21 May 2019

Accepted Date: 22 May 2019

Please cite this article as: Tercenio QD, Alexanian EJ, Nickel-catalyzed, ring-forming aromatic C–H alkylations with unactivated alkyl halides, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.05.047.

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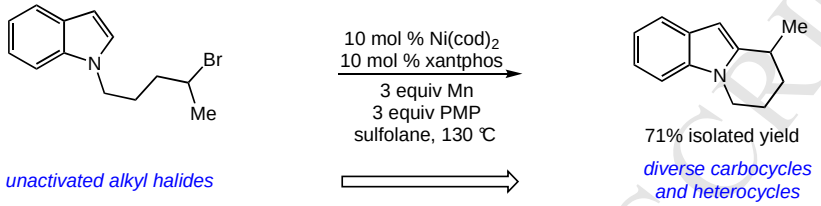

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Nickel catalysis
C−H alkylation
Unactivated halides
carbocyclization

ABSTRACT

The development of a nickel-catalyzed C−H alkylation of aromatic substrates with unactivated alkyl halides is described. This carbocyclization facilitates the synthesis of diverse fused ring systems from simple aromatic substrates and is an attractive alternative to traditional polar or radical-mediated ring formations. The present system uses unactivated primary and secondary alkyl bromides and chlorides, while avoiding the use of precious palladium catalysts and more reactive alkyl halides commonly used in related C–H alkylations.

1. Introduction

Carbocyclizations of arenes and heteroarenes with alkyl halides are fundamental transformations for the syntheses of polycyclic aromatic compounds [1]. Synthetic methods achieving this goal include the classical Friedel-Crafts reaction [2] and radical-mediated homolytic aromatic substitutions (HAS) [3]; however, their applications are largely limited to either electron-rich or electron-poor aromatic substrates, respectively. Undesired reductive dehalogenation is also frequently observed in HAS reactions, and while the use of alkyl xanthates (dithiocarbonates) can mitigate this problem, these reactions require additional synthetic effort [4].

Metal-catalyzed aromatic C−H alkylations constitute mild, attractive alternatives to these processes; however, existing methods use either activated alkyl halides (e.g., α-halocarbonyls) [5,6], substrate directing groups [7], or require the use of precious palladium catalysts [8]. For example, we have previously reported a palladium-catalyzed, ring-forming C−H alkylation of aromatic substrates using unactivated alkyl iodides and bromides [8a]. While this work offered an attractive approach to catalytic C–H alkylation, the required use of palladium catalysts and relatively unstable alkyl iodides is a drawback to the system.

Recent studies have demonstrated the broad utility of nickel catalysts in activating alkyl halides for diverse C−C bond constructions [9]. For instance, we have recently reported a general approach to nickel-catalyzed Mizoroki-Heck-type carbocyclizations proceeding via a hybrid organometallic-radical pathway [9h]. We hypothesized that this reactivity in nickel catalysis could unlock a general, intramolecular ring-forming aromatic C–H alkylation using more attractive alkyl bromides and chlorides as substrates. Herein, we report the development of such a nickel-catalyzed C−H alkylation, applicable to a diverse range of aromatic substrates using primary and secondary unactivated alkyl bromides and chlorides as coupling partners (Fig. 1).

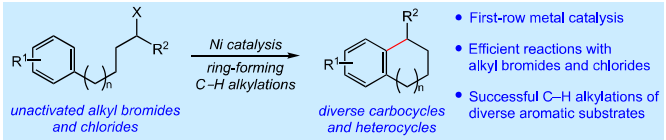

Fig 1. Nickel-catalyzed C–H alkylations of aromatic substrates.

2. Results and discussion

Our studies commenced with the carbocyclization of secondary alkyl bromide **1** (Table 1). We determined that a catalytic system comprised of 5 mol % $Ni(cod)_2$ and 5 mol % 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) was capable of catalyzing the C–H alkylation of substrate **1**, producing indoline **2** in good yield (61%). Our previously reported protocol using 10 mol % $Pd(PPh_3)_4$ was slightly less

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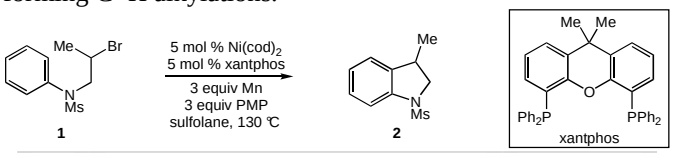
effective in this case (entry 2, 55%) [8a]. Substituting $NiBr_2$·glyme as the nickel precatalyst also led to decreased yield (entry 3) [10]. The use of xantphos as ligand was critical to the reaction; substituting either 10 mol % PPh_3 as ligand (entry 4) or 5 mol % BINAP (entry 5) led to poor reactivity. Decreasing the reaction temperature from 130 °C to 80 °C significantly lowered efficiency (entry 6). Substituting the inorganic base Cs_2CO_3 for PMP, or Zn for Mn as reductant also significantly decreased yield (entries 7 and 8). The use of Ph*t*Bu as solvent–as with the palladium-catalyzed system–led to a decreased yield (entry 9) [8a], as did omitting Mn from the reaction (entry 10). No reaction occurred in the absence of $Ni(cod)_2$ (entry 11).

Table 1
Catalyst system development for nickel-catalyzed ring-forming C−H alkylations.

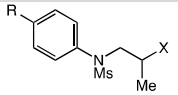
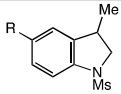
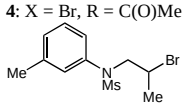
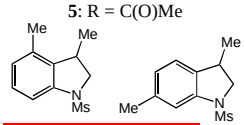
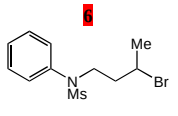
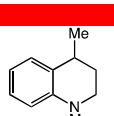


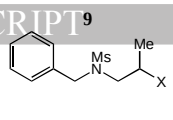
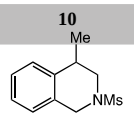
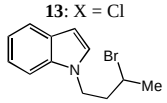
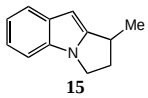
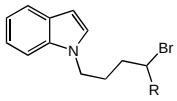
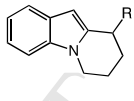
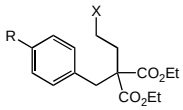
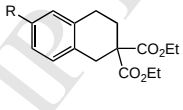
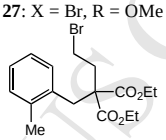
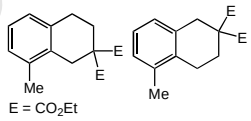
entry	variation from standard conditions above	yield (%)[a]
1	None	61
2	10 mol % $Pd(PPh_3)_4$, 2 equiv PMP, Ph*t*Bu,130 °C	55
3	5 mol % $NiBr_2$•glyme instead of $Ni(cod)_2$	51
4	10 mol % PPh_3 instead of 5 mol % xantphos	0
5	5 mol % BINAP instead of 5 mol % xantphos	24
6	80 °C instead of 130 °C	19
7	Cs_2CO_3 instead of PMP	0
8	Zn instead of Mn	19
9	Ph*t*Bu instead of sulfolane	50
10	no Mn	38
11	no $Ni(cod)_2$	0

Reactions were performed with $[\mathbf{1}]_0$ = 0.15 M. [a]Yields determined by ^{1}H NMR spectroscopy of crude reaction mixture using an internal standard.

With a suitable catalytic system in hand, we investigated the carbocyclization using a diverse range of substrates (Table 2). The synthesis of indoline product **2** was successful using either the unactivated alkyl bromide **1** or the alkyl chloride **3**, albeit in reduced yield (entries 1 and 2). Transformation of an aromatic ketone derivative **4** was also successful (entry 3). Carbocyclization of a *meta*-substituted substrate **6** led to a mixture of regioisomers (entry 4). Extension of the alkyl tether in substrate **9** enabled access to the tetrahydroquinoline ring system in good yield (58%, entry 5). We were also able to access the tetrahydroisoquinoline framework in the cyclizations of alkyl bromide substrate **11** and chloride **13**, providing product **12** in 50% and 58% yield, respectively.

Table 2.
Scope of nickel-catalyzed carbocyclization of unactivated alkyl bromides and chlorides.

entry	substrate	product	yield (%)[a]
			
1[b]	**1**: X = Br, R = H	**2**: R = H	61
2[c]	**3**: X = Cl, R = H		45
3	**4**: X = Br, R = C(O)Me	**5**: R = C(O)Me	52
4	 **6**	 **7** **8**	52 1.9:1 **7:8**
5			58

	 **9**	 **10**	
6	**11**: X = Br	**12**	50
7	**13**: X = Cl		58
8	 **14**	 **15**	56
			
9	**16**: R = H	**17**: R = H	47
10	**18**: R = Me	**19**: R = Me	71
			
11[b,d]	**20**: X = Br, R = H	**21**: R = H	80
12[e]	**22**: X = Cl, R = H		51
13[b,d]	**23**: X = Br, R = Cl	**24**: R = Cl	67
14[b,d]	**25**: X = Br, R = CF_3	**26**: R = CF_3	63
15[b,d]	**27**: X = Br, R = OMe	**28**: R = OMe	58
16[b,d]	 **29**	 **30** **31**	69 4:1 **30:31**

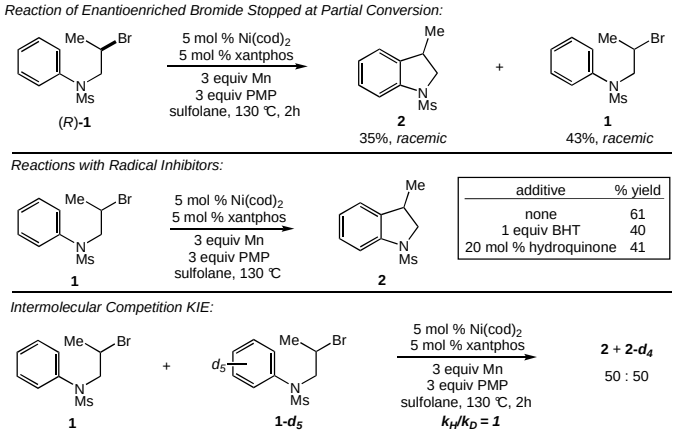
Reactions were performed with $[\text{substrate}]_0$ = 0.15 M in sulfolane at 130 °C with 10 mol% $Ni(cod)_2$, 10 mol % xantphos, 3 equiv Mn, and 3 equiv PMP (1,2,2,6,6-pentamethylpiperidine) as base. [a]Isolated yields. [b]Reactions performed with 5 mol% $Ni(cod)_2$ and 5 mol% xantphos. [c]Reaction performed at 150 °C. [d]Reaction performed at 60 °C in DMSO with Et_3N as the base. [e]Reaction performed in Ph*t*Bu.

We next applied the catalytic C−H alkylation to the synthesis of indole derivatives (entries 8-10). Our system serves as an efficient alternative to related carbocyclizations of indoles that necessitated the use of stoichiometric metals or peroxides [3,4]. Catalytic cyclization of indole **14** successfully provided dihydro-1H-pyrrolo[1,2-*a*]indole **15** in 56% yield (entry 8). Addition of a methylene unit to the tether enables the preparation of tetrahydropyrido[1,2-*a*]indoles from primary or secondary alkyl bromides in 47% and 71% yield, respectively (entries 9 and 10).

The C–H alkylation is also applicable to the preparation of tetrahydronapthalenes, as demonstrated in entries 11-16. Both electron-rich and electron-poor substrates provided the desired products in moderate yield using both alkyl bromide and alkyl chloride substrates. Interestingly, the reaction of ortho-substituted aromatic substrate **29** delivered a 4:1 mixture of product **30** and **31**–which was also previously observed using palladium catalysis–consistent with an alkyl shift during the course of the reaction [8a,11].

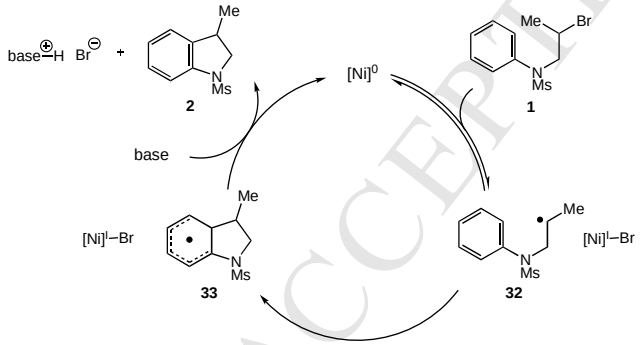
Several experiments were conducted to probe the reaction mechanism and draw comparisons to our prior work involving palladium catalysis (Scheme 2). The reaction of enantioenriched substrate (*R*)-**1** under standard conditions led to racemic indoline **2**, which is consistent with a single-electron pathway involving stereoablation. Moreover, when the reaction was stopped at partial conversion, racemization of the recovered starting material was observed, consistent with a reversible single-electron activation of the alkyl halide substrate. Reactions performed in the presence of radical inhibitors BHT and hydroquinone proceeded with somewhat decreased yields (40% and 41%, respectively) as compared to the standard reaction

(61%). These results support the formation of caged radical intermediates rather than dissociated radical species [5d]. Finally, deuterated **1**-d_5 was prepared and subjected to an intermolecular competition KIE experiment. The lack of a kinetic isotope effect (k_H/k_D = 1) indicates that C−H bond cleavage does not occurs during the rate-determining step of the alkylation.



Scheme 1. Mechanistic studies of the C–H alkylation.

A plausible mechanism consistent with our current studies is depicted in Scheme 2. The nickel catalyst promotes reversible atom abstraction of the alkyl halide substrate to generate carbon-centered radical **32**. The subsequent carbon-centered radical cyclizes on to the aromatic ring to form the cyclohexadienyl radical **33**. Rearomatization then delivers the product, which we hypothesize proceeds via single-electron oxidation to a cyclohexadienyl cation and deprotonation. This mechanism is therefore analogous to that of our previously reported palladium-based system [8a]. The current system is clearly more effective in atom abstraction however, as evidenced by the successful reactions of alkyl chlorides–which are not possible using palladium catalysis.



Scheme 2. Plausible catalytic cycle for the nickel-catalyzed ring-forming C−H alkylation.

3. Conclusions

In conclusion, we have developed a ring-forming C−H alkylation of aromatic compounds using unactivated alkyl halides and an inexpensive, first-row metal catalyst system. These reactions provide access to an array of valuable polycyclic carbocycles and heterocycles, without the requirements of electronic activation common to alternative polar or radical-mediated C–H alkylations. This work also extends the scope of catalytic, ring-forming C–H alkylations to include the use of attractive unactivated alkyl chlorides.

4. Experimental section

4.1 General information

Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were obtained using a Bruker model AVANCE III 400 or 600 (^{1}H NMR at 400 MHz or 600 MHz and ^{13}C NMR at 100 MHz or 151 MHz) spectrometer with solvent resonance as internal reference (^{1}H NMR: $CDCl_3$ at 7.28 ppm, ^{13}C NMR: $CDCl_3$ at 77.00 ppm). 1H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using a ThermoScientificQ Exactive HF-Xmass spectrometer with electrospray introduction or atmospheric pressure chemical ionization in positive mode. These samples were prepared in methanol.

HPLC analysis was performed on a Shimadzu SPD-M20A photodiode array (PDA) system equipped with Daicel Chiralpak IE, IF, IG, and OJ-H columns using a flow rate of 1 mL per minute. The solvent system used for HPLC resolution of enantiomers was hexanes and isopropanol. Flash Chromatography was performed using SiliaFlash P60 silica gel (40-63μm) purchased from Silicycle. Visualization was achieved using a short wave UV light (254 nm), or aqueous basic potassium permanganate solution, or aqueous acidic ceric ammonium molybdate solution followed by heating. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), toluene, acetonitrile (MeCN), and dimethylformamide (DMF) were dried by passage through a column of neutral alumina under nitrogen prior to use. *tert*-Butylbenzene and dimethylsulfoxide (DMSO) was dried over 3 Å molecular sieves and degassed with argon prior to use. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

4.2 Substrate preparation

General procedure A: Bromination of secondary alcohols.

To a solution of secondary alcohol (1 equiv) in Et_2O (0.5 M) was added phosphorus tribromide (0.5 equiv) dropwise. The reaction mixture was stirred at room temperature for 1 hour and was then quenched with H_2O. The aqueous layer was back extracted three times with Et_2O and the combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

General procedure B: Appel bromination of secondary alcohols.

To a solution of secondary alcohol (1 equiv) and 2,6-lutidine (0.25 equiv) in THF (0.3 M) were added triphenylphosphine (1.2 equiv) and tetrabromomethane (1.2 equiv). The reaction mixture was stirred for 16 hours at room temperature. The reaction mixture was then diluted with hexane (50 mL) and filtered. The filter cake was washed with hexane/ether (1:1) (50 mL). The filtrate was concentrated under reduced pressure and purified by flash chromatography.

General procedure C: Tosylation of secondary alcohols.

To a solution of 4-methylbenzenesulfonyl chloride (1.5 equiv) and trimethylamine hydrochloride (0.1 equiv) in DCM (0.3 M) at 0 °C was added triethylamine (2.5 equiv) dropwise. The alcohol (1 equiv) was then added in DCM, and the reaction mixture was stirred at room temperature for 16 hours. To the reaction mixture

was added *N*,*N*-dimethylpropane-1,3-diamine (2 equiv) and stirred for 15 minutes before being quenched with H_2O. The aqueous layer was extracted three times with DCM and the combined organic layers were washed sequentially with 1 M HCl solution, saturated $NaHCO_3$, and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

General procedure D: Chlorination of secondary tosylate.

To a solution of lithium chloride (3 equiv) in DMF (0.5 M) was added the alkyl tosylate (1 equiv). The reaction mixture was heated to 90°C and stirred for 20 hours. The reaction mixture was cooled to room temperature and diluted with Et_2O and washed with 1 M HCl solution (2x). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography.

***N*-(2-bromopropyl)-*N*-phenylmethanesulfonamide (1)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-(2-hydroxypropyl)-*N*-(phenyl-d_5)methanesulfonamide (SI-1)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-(2-bromopropyl)-*N*-(phenyl-d_5)methanesulfonamide (1-d_5)**. Secondary alcohol **SI-1** (1.5 g, 1 equiv, 6.4 mmol) was brominated with phosphorus tribromide (0.30 mL, 0.5 equiv, 3.2 mmol) in DCM (18.7 mL, 1 M) following General procedure A. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide **1-d_5** as a white solid (571 mg, 30% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.11 – 4.05 (m, 1H), 4.01 (dt, *J* = 13.4, 6.6 Hz, 1H), 3.90 (dd, *J* = 13.4, 7.0 Hz, 1H), 2.96 (s, 3H), 1.73 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 77.34, 77.02, 76.70, 58.72, 46.07, 37.79, 22.95. **HRMS (APCI)** Exact mass calculated for $C_{10}H_{10}D_5BrNO_2S$ $[M+H]^+$, 297.0321. Found 297.0313.

***N*-(2-hydroxypropyl)-*N*-phenylmethanesulfonamide (SI-2)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

1-(*N*-phenylmethylsulfonamido)propan-2-yl 4-methylbenzenesulfonate (SI-3). Secondary alcohol **SI-2** (2.0 g, 1 equiv, 9.0 mmol) was tosylated with 4-methylbenzenesulfonyl chloride (2.57 g, 1.5 equiv, 13.5 mmol), trimethylamine hydrochloride (86 mg, 0.1 equiv, 0.9 mmol), and triethylamine (3.1 mL, 2.5 equiv, 22.5 mmol) in DCM (20 mL, 0.3 M) following General procedure C. The crude product was purified by flash chromatography using 30% ethyl acetate in hexanes to provide secondary tosylate **SI-3** as a colorless oil (2.5 g, 73% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.35 (m, 3H), 7.35 – 7.29 (m, 4H), 4.73 – 4.66 (m, 1H), 3.92 (dd, *J* = 14.5, 6.8 Hz, 1H), 3.75 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.94 (s, 3H), 2.47 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.87, 139.48, 133.88, 129.87, 129.72, 128.62, 128.47, 128.35, 127.75, 77.46, 77.28, 77.06, 76.85, 55.36, 38.01, 21.70, 18.18. **HRMS (APCI)** Exact mass calculated for $C_{17}H_{22}NO_5S_2$ $[M+H]^+$, 384.0939. Found 384.0934.

1-(*N*-phenylmethylsulfonamido)propan-2-yl 4-methylbenzenesulfonate (3). Secondary tosylate **SI-3** (2.21 g, 1 equiv, 5.76 mmol) was chlorinated with lithium chloride (0.733 g, 3 equiv, 17.3 mmol) in DMF (11 mL, 0.5 M). The crude product was purified by flash chromatography in 20% ethyl acetate in hexanes to provide secondary chloride **3** as a white solid (856 mg, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.42 – 7.37 (m, 3H), 4.03 – 3.95 (m, 2H), 3.85 – 3.78 (m, 1H), 2.97 (s, 3H), 1.56 – 1.50 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.16, 129.80, 128.80, 128.64, 77.30, 77.09, 76.87, 58.38, 54.83, 37.96, 22.13. **HRMS (APCI)** Exact mass calculated for $C_{10}H_{15}ClNO_2S$ $[M+H]^+$, 248.0512. Found 248.0507.

***N*-(2-hydroxypropyl)-*N*-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methanesulfonamide (SI-4)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-(2-bromopropyl)-*N*-(4-(2-methyl-1,3-dioxolan-2-yl)phenyl)methanesulfonamide (SI-5)**. Secondary alcohol **SI-4** (0.833 g, 1 equiv, 2.80 mmol) was brominated with 2,6-lutidine (82.0 µL, 0.25 equiv, 0.7 mmol), triphenylphosphine (0.918 g, 1.2 equiv, 3.50 mmol), and tetrabromomethane (1.11 g, 1.2 equiv, 3.36 mmol) in THF (10 mL, 0.3 M) following General procedure B. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide **SI-5** as a white solid (212 mg, 20% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.11 – 4.04 (m, 3H), 4.01 (dt, *J* = 13.4, 6.7 Hz, 1H), 3.89 (dd, *J* = 13.4, 6.9 Hz, 1H), 3.85 – 3.77 (m, 2H), 2.97 (s, 3H), 1.73 (d, *J* = 6.5 Hz, 3H), 1.67 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.07, 138.55, 128.46, 126.83, 108.45, 77.26, 77.05, 76.83, 64.64, 64.63, 58.72, 46.03, 37.83, 27.62, 22.92. **HRMS (APCI)** Exact mass calculated for $C_{14}H_{21}BrNO_4S$ $[M+H]^+$, 378.0374. Found 378.0365.

***N*-(4-acetylphenyl)-*N*-(2-bromopropyl) methane sulfonamide (4)**. To a solution of acetal **SI-5** (0.210 g, 1 equiv, 0.555 mmol) in acetonitrile (11 mL, 0.05 M) was added copper (II) chloride dihydrate (0.189 g, 2 equiv, 1.11 mmol). The reaction solution was stirred for 3 hours at room temperature before being quenched with water. The aqueous layer was extracted three times with Et_2O, and the combined aqueous layer was washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using 40% ethyl acetate in hexanes to provide secondary bromide **4** as a white solid (148 mg, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 – 8.00 (m, 2H), 7.56 – 7.50 (m, 2H), 4.10 (dd, *J* = 12.9, 6.5 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.96 (dd, *J* = 12.8, 6.1 Hz, 1H), 2.98 (s, 3H), 2.64 (s, 3H), 1.72 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 196.88, 143.41, 136.56, 129.84, 128.23, 77.26, 77.05, 76.84, 58.39, 45.96, 38.12, 26.74, 22.99. **HRMS (APCI)** Exact mass calculated for $C_{12}H_{17}BrNO_3S$ $[M+H]^+$, 334.0113. Found 334.0104.

***N*-(2-hydroxypropyl)-*N*-(*m*-tolyl)methanesulfonamide (SI-6)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-(2-bromopropyl)-*N*-(*m*-tolyl)methanesulfonamide (6)**. Secondary alcohol **SI-6** (1.92 g, 1 equiv, 7.89 mmol) was brominated with phosphorus tribromide (372 µL, 0.5 equiv, 3.95 mmol) in DCM (10 mL, 1 M) following General procedure A. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide **6** as a white solid (450 mg, 25% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 11.1, 4.8 Hz, 1H), 7.24 – 7.15 (m, 3H), 4.09 – 3.97 (m, 2H), 3.93 – 3.83 (m, 1H), 2.97 (s, 3H), 2.41 (s, 3H), 1.77 – 1.70 (m, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.95, 138.92, 129.54, 129.51, 129.41, 125.45, 77.26, 77.05, 76.84, 58.74, 46.13, 37.84, 22.96, 21.39. **HRMS (APCI)** Exact mass calculated for $C_{11}H_{17}BrNO_2S$ $[M+H]^+$, 306.0163. Found 306.0159.

***N*-(3-hydroxybutyl)-*N*-phenylmethanesulfonamide (SI-7)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-(3-bromobutyl)-*N*-phenylmethanesulfonamide (9)**. Secondary alcohol **SI-7** (1.43 g, 1 equiv, 5.88 mmol) was brominated with phosphorus tribromide (0.277 mL, 0.5 equiv, 2.94 mmol) in DCM (10 mL, 0.5 M) following General procedure A. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide **6** as a white solid (450 mg, 25% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.40 – 7.35 (m, 3H), 4.21 – 4.14 (m, 1H), 3.94 – 3.83 (m, 2H), 2.91 (s, 3H), 2.04 – 1.98 (m, 2H), 1.71 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 139.08, 129.67, 128.33, 128.32, 77.30, 77.08, 76.87, 49.45, 47.47, 40.00, 36.80, 26.43. **HRMS (APCI)** Exact mass calculated for $C_{11}H_{17}BrNO_2S$ $[M+H]^+$, 306.0163. Found 306.0158.

***N*-benzyl-*N*-(2-hydroxypropyl)methanesulfonamide (SI-8)** was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

***N*-benzyl-*N*-(2-bromopropyl)methanesulfonamide (11)**. Secondary alcohol **SI-8** (1.30 g, 1 equiv, 5.34 mmol) was brominated with phosphorus tribromide (0.25 mL, 0.5 equiv, 2.67 mmol) in DCM (10 mL, 0.5 M) following General procedure A. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide **11** as a white solid (408 mg, 25% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 (t, *J* = 5.7 Hz, 4H), 7.38 – 7.34 (m, 1H), 4.63 (d, *J* = 15.1 Hz, 1H), 4.41 (d, *J* = 15.1 Hz, 1H), 4.14 (h, *J* = 6.8 Hz, 1H), 3.52 – 3.46 (m, 2H), 2.94 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl3) δ 135.41, 128.93, 128.65, 128.36, 77.27, 77.06, 76.85, 55.38, 52.52, 46.76, 39.76, 23.23. **HRMS (APCI)** Exact mass calculated for $C_{11}H_{17}BrNO_2S$ $[M+H]^+$, 306.0163. Found 306.0156.

1-(*N*-benzylmethylsulfonamido)propan-2-yl 4-methylbenzenesulfonate (SI-9). Secondary alcohol **SI-8** (1.74 g, 1 equiv, 7.15 mmol) was tosylated with 4-methylbenzenesulfonyl chloride (2.04 g, 1.5 equiv, 10.7 mmol), trimethylamine hydrochloride (68.3 mg, 0.1 equiv, 0.715 mmol), and triethylamine (2.49 mL, 2.5 equiv, 17.9 mmol) in DCM (80 mL, 0.3 M) following General Procedure C. The crude product was purified by flash chromatography using 30% ethyl acetate in hexanes to provide secondary tosylate **SI-9** as a colorless oil (1.65 g, 58% yield). **^{1}H NMR** (600 MHz, CDCl3) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.31 (m, 7H), 4.78 – 4.70 (m, 1H), 4.58 (d, *J* = 15.2 Hz, 1H), 4.33 (d, *J* = 15.2 Hz, 1H), 3.44 (dd, *J* = 15.4, 8.2 Hz, 1H), 3.22 (dd, *J* = 15.4, 4.3 Hz, 1H), 2.92 (s, 3H), 2.48 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 145.12, 135.19, 133.88, 129.98, 128.88, 128.73, 128.23, 127.75, 77.28, 77.07, 76.99, 76.86, 51.54, 50.72, 40.00, 21.72, 18.04. **HRMS (ESI)** Exact mass calculated for $C_{18}H_{23}NO_5S_2Na$ [M+Na], 420.0915. Found 420.0907.

***N*-benzyl-*N*-(2-chloropropyl)methanesulfonamide (13)**. Secondary tosylate **SI-9** (1.64 g, 1 equiv, 4.13 mmol) was chlorinated with lithium chloride (0.525 g, 3 equiv, 12.4 mmol) in DMF (8 mL, 0.5 M). The crude product was purified by flash chromatography in 20% ethyl acetate in hexanes to provide secondary chloride **13** as a white solid (648 mg, 60% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 4H), 7.35 (qd, *J* = 7.7, 3.5 Hz, 1H), 4.63 (d, *J* = 15.1 Hz, 1H), 4.43 (d, *J* = 15.2 Hz, 1H), 4.14 (h, *J* = 6.7 Hz, 1H), 3.40 (d, *J* = 7.0 Hz, 2H), 2.95 (s, 3H), 1.43 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** (151 MHz, CDCl3) δ 135.45, 128.90, 128.59, 128.29, 77.31, 77.10, 76.89, 55.31, 54.63, 52.27, 39.86, 22.40. **HRMS (APCI)** Exact mass calculated for $C_{11}H_{17}ClNO_2S$ $[M+H]^+$, 262.0669. Found 262.0663.

1-(3-bromobutyl)-1H-indole (14). To a suspended solution of sodium hydride (0.48 g, 60% dispersion in mineral oil, 1.2 equiv, 12 mmol) in THF (30 mL, 0.25 M), a solution of indole (1.2 g, 1 equiv, 10 mmol) in THF (10 mL) was added dropwise and stirred for 30 minutes. To the reaction mixture was added 1,3-dibromobutane (2.4 mL, 2 equiv, 20 mmol) was added dropwise and stirred for 20 hours at room temperature. The reaction mixture was quenched with saturated NH_4Cl and washed three times with Et_2O, dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using a gradient of 2.5-5% ethyl acetate in hexanes to provide secondary bromide 14 as a yellow oil (1.08 g, 43% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.28 (q, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 3.1 Hz, 1H), 7.16 (dd, *J* = 16.9, 9.3 Hz, 1H), 6.55 (d, *J* = 3.0 Hz, 1H), 4.43 (ddd, *J* = 14.5, 6.8, 4.4 Hz, 1H), 4.38 (ddd, *J* = 14.7, 8.8, 6.2 Hz, 1H), 4.01 – 3.94 (m, 1H), 2.38 – 2.32 (m, 1H), 2.27 – 2.19 (m, 1H), 1.74 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 135.77, 128.73, 128.07, 121.65, 121.11, 119.51, 109.36, 101.46, 77.29, 77.08, 76.87, 48.36, 44.72, 41.11, 26.66. **HRMS (APCI)** Exact mass calculated for $C_{12}H_{15}BrN$ $[M+H]^+$, 252.0388. Found 252.0382.

1-(4-bromobutyl)-1H-indole (16) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [12].

1-(4-bromopentyl)-1H-indole (18) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [12].

Diethyl 2-benzyl-2-(2-bromoethyl)malonate (20) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

Diethyl 2-benzyl-2-(2-chloroethyl)malonate (22). To a suspended solution of sodium hydride (1.06 g, 60% dispersion in mineral oil, 1.3 equiv, 26.5 mmol) in THF (6.8 mL, 0.3 M) was added benzyl malonate (5.1 g, 1 equiv, 20.4 mmol). The reaction mixture was stirred for 30 minutes at room temperature and then 1-bromo-2-chloroethane (17.0 mL, 10 equiv, 204 mmol) was added. The reaction mixture was heated to reflux and stirred for 24 hours. The reaction was quenched with H_2O and extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a gradient of 5-10% ethyl acetate in hexanes to give a colorless oil (2.4 g, 38% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 3H), 7.15 – 7.09 (m, 2H), 3.63 – 3.56 (m, 2H), 3.29 (s, 2H), 2.34 – 2.19 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.41, 135.37, 129.90, 128.48, 127.25, 77.27, 77.06, 76.85, 61.67, 57.89, 40.09, 39.35, 35.73, 14.02. **HRMS (APCI)** Exact mass calculated for $C_{16}H_{22}ClO_4$ $[M+H]^+$, 313.1207. Found 313.1191.

Diethyl 2-(2-bromoethyl)-2-(4-chlorobenzyl)malonate (23) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

Diethyl 2-(2-bromoethyl)-2-(4-(trifluoromethyl)benzyl) malonate (25) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

Diethyl 2-(2-bromoethyl)-2-(4-methoxybenzyl)malonate (27) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

Diethyl 2-(2-bromoethyl)-2-(2-methylbenzyl)malonate (29) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

4.3 Nickel-catalyzed reactions

C-H alkylation procedure A:

To a one-dram vial equipped with a magnetic stir bar in a glove box under argon atmosphere was added $Ni(cod)_2$ (3.4 mg, 10 mol %, 0.0125 mmol), xantphos (7.2 mg, 10 mol %, 0.0125 mmol), Mn (20.6 mg, 3 equiv, 0.375 mmol), 1,2,2,6,6-pentamethylpiperidine (67.9 µL, 3 equiv, 0.375 mmol), primary or secondary bromide or chloride (0.125 mmol, 1 equiv) and dissolved in sulfolane (1.046 g, 0.15 M). The reaction vial was removed from the glove box and heated to 130 °C, stirring for 8-24 hours. The reaction was allowed to cool to ambient temperature, was diluted with Et_2O, and was quenched with 1 M HCl solution. The organic layer was washed twice with H_2O, dried over a $MgSO_4$, filtered, concentrated under reduced pressure. The crude product was purified by flash chromatography or preparatory TLC using ethyl acetate and hexanes as the eluent. Any modifications to procedures are noted in **Table 2**.

C-H alkylation procedure B:

To a one-dram vial equipped with a magnetic stir bar in a glove box under argon atmosphere was added $Ni(cod)_2$ (1.7 mg, 5 mol %, 0.00625 mmol), xantphos (3.6 mg, 5 mol %, 0.00625 mmol), Mn (20.6 mg, 3 equiv, 0.375 mmol), triethylamine (52.3 µL, 3 equiv, 0.375 mmol), primary bromide (0.125 mmol, 1 equiv) and dissolved in DMSO (0.83 mL, 0.15 M). The reaction vial was removed from the glove box and heated to 60 °C, stirring for 8-24 hours. The reaction was allowed to cool to ambient temperature, was diluted with Et_2O, and was quenched with 1 M HCl solution. The organic layer was washed twice with H_2O, dried over a $MgSO_4$, filtered, concentrated under reduced pressure. The crude product was purified by flash chromatography or preparatory TLC using ethyl acetate and hexanes as the eluent.

3-methyl-1-(methylsulfonyl)indoline (2) was synthesized using $Ni(cod)_2$ (1.7 mg, 5 mol %, 0.00625 mmol) and xantphos (3.6 mg, 5 mol %, 0.00625 mmol) according to C-H alkylation procedure A using secondary bromide **1** (36.5 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **2** as a light orange solid (16.1 mg, 61% yield). Physical and spectral data were in accordance with literature data [8a].

3-methyl-1-(methylsulfonyl)indoline (2) was synthesized according to C-H alkylation procedure A using secondary chloride **2** (30.9 mg, 0.125 mmol) was heated to 150 °C. The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **2** as a light orange solid (11.9 mg, 45% yield). Physical and spectral data were in accordance with literature data [8a].

1-(3-methyl-1-(methylsulfonyl)indolin-5-yl)ethan-1-one (5) was synthesized according to C-H alkylation procedure A using secondary bromide **4** (41.8 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **5** as a light orange solid (16.5 mg, 52% yield). Physical and spectral data were in accordance with literature data [8a].

Mixture of 3,7-dimethyl-1-(methylsulfonyl)indoline and 3,6-dimethyl-1-(methylsulfonyl)indoline (7 and 8) was synthesized according to C-H alkylation procedure A using secondary bromide **6** (38.3 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 15% ethyl acetate in hexanes to provide to provide a 1.9:1 ratio of **7** and **8** as a colorless oil (14.6 mg, 52% yield). Physical and spectral data were in accordance with literature data [8a].

4-methyl-1-(methylsulfonyl)-1,2,3,4-tetrahydroquinoline (10) was synthesized according to C-H alkylation procedure A using secondary bromide **9** (38.3 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **10** as a light orange solid (16.3 mg, 58% yield). Physical and spectral data were in accordance with literature data [8a].

4-methyl-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (12) was synthesized according to C-H alkylation procedure A using secondary bromide **11** (38.3 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **12** as a light orange solid (14.1 mg, 50% yield). Physical and spectral data were in accordance with literature data [8a].

4-methyl-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (12) was synthesized according to C-H alkylation procedure A using secondary chloride **13** (32.7 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 10% ethyl acetate in hexanes to provide **12** as a light orange solid (16.3 mg, 58% yield). Physical and spectral data were in accordance with literature data [8a].

1-methyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole (15) was synthesized according to C-H alkylation procedure A using secondary bromide **14** (31.5 mg, 0.125 mmol). The crude product was purified by preparatory TLC using 2.5% ethyl acetate in hexanes to provide **15** as a pale-yellow oil (12.0 mg, 56% yield). Physical and spectral data were in accordance with literature data [13].

6,7,8,9-tetrahydropyrido[1,2-a]indole (17) was synthesized according to C-H alkylation procedure A using primary bromide **16** (31.5 mg, 0.125 mmol). The crude product was purified by preparatory TLC using 2.5% ethyl acetate in hexanes to provide **17** as a pale-yellow oil (10.1 mg, 47% yield). Physical and spectral data were in accordance with literature data [14].

9-methyl-6,7,8,9-tetrahydropyrido[1,2-a]indole (19) was synthesized according to C-H alkylation procedure A using secondary bromide **18** (33.3 mg, 0.125 mmol). The crude product was purified by preparatory TLC using 2.5% ethyl acetate in hexanes to provide **19** as a pale-yellow oil (16.4 mg, 71% yield). Physical and spectral data were in accordance with literature data [13].

Diethyl 3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (21) was synthesized according to C-H alkylation procedure B using primary bromide **20** (44.7 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide **21** as a colorless oil (27.6 mg, 80% yield). Physical and spectral data were in accordance with literature data [8a].

Diethyl 3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (21) was synthesized according to C-H alkylation procedure A using primary chloride **22** (39.1 mg, 0.125 mmol) in *tert*-butylbenzene (0.83 mL, 0.15 M). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide **18** as a colorless oil (17.6 mg, 51% yield).

Physical and spectral data were in accordance with literature data. Supplementary data to this article can be found online at [8a].

Diethyl 6-chloro-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (24) was synthesized according to C-H alkylation procedure B using primary bromide **23** (49.0 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide **24** as a colorless oil (26.0 mg, 67% yield). Physical and spectral data were in accordance with literature data [8a].

Diethyl 6-(trifluoromethyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (26) was synthesized according to C-H alkylation procedure B using primary bromide **25** (53.2 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide **26** as a colorless oil (27.1 mg, 63% yield). Physical and spectral data were in accordance with literature data [8a].

Diethyl 6-methoxy-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (28) was synthesized according to C-H alkylation procedure B using primary bromide **24** (48.4 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide **28** as a colorless oil (27.6 mg, 80% yield). Physical and spectral data were in accordance with literature data [8a].

Mixture of diethyl 8-methyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate and diethyl 5-methyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (30 and 31) was synthesized according to C-H alkylation procedure B using primary bromide **26** (46.4 mg, 0.125 mmol). The crude product was purified by flash column chromatography using 5% ethyl acetate in hexanes to provide a 4:1 ratio of **30** and **31** as a colorless oil (25.0 mg, 69% yield). Physical and spectral data were in accordance with literature data [8a].

4.3 Stereochemical experiments

(*S*)-N-(2-hydroxypropyl)-N-phenylmethanesulfonamide ((*S*)-SI-2) was prepared according to a literature procedure, and spectral data were in accordance with the literature values [8a].

(*R*)-N-(2-bromopropyl)-N-phenylmethanesulfonamide ((*R*)-1). Secondary alcohol **(*S*)-SI-2** (1.5 g, 1 equiv, 6.5 mmol) was brominated with 2,6-lutidine (0.18 g, 0.19 mL, 0.25 equiv, 1.6 mmol), triphenylphosphine (2.1 g, 1.2 equiv, 8.2 mmol), and tetrabromomethane (2.6 g, 1.2 equiv, 7.9 mmol) in THF (20 mL, 0.3 M) following General Procedure B. The crude product was purified by flash chromatography using 20% ethyl acetate in hexanes to provide secondary bromide SI-5 as a white solid (0.693 g, 36% yield).

(*R*)-N-(2-bromopropyl)-N-phenylmethanesulfonamide **((*R*)-1)** was subjected to $Ni(cod)_2$ (1.7 mg, 5 mol %, 0.00625 mmol) and xantphos (3.6 mg, 5 mol %, 0.00625 mmol) following C-H alkylation procedure A and was stopped after 2 hours. The crude reaction mixture was purified by flash chromatography using 10% ethyl acetates in hexanes to provide the product **2** and unreacted starting material. The enantiomeric excess of **2** was determined to be 0% and the recovered starting material **(*R*)-1** was determined to have racemized by chiral HPLC analysis using 99:1 hexanes:isopropanol mobile phase and column IF [15].

Acknowledgments

Financial support was provided by Award R01 GM 107204 from the National Institute of General Medical Sciences.

Appendix A. Supplementary data

References and notes

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