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Cobalt-Catalyzed C-H Nitration of Indoles Employing a Removable Directing Group

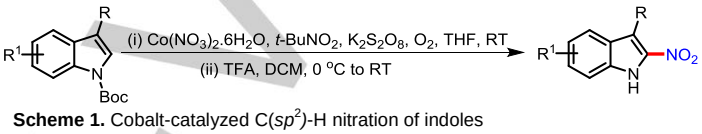
Paridhi Saxena and Manmohan Kapur*

Abstract: A mild and efficient C(sp^2)-H nitration of 3-substituted indoles, using the economical and non-toxic cobalt nitrate hexahydrate [$Co(NO_3)_2.6H_2O$] as catalyst and *tert*-butyl nitrite (TBN) as the nitro source, is being reported. This approach provides a unique methodology involving a site-selective C-N bond formation for preparation of C-2 substituted nitro indoles. Utilization of the ^{t}Boc as the removable directing group enhances the synthetic utility of the method.

Introduction

The transition metal catalyzed functionalization of C-H bonds is a unique synthetic strategy for regioselective C-C or C-X bond construction.[1] A variety of directing groups have been utilized for the directed C-H functionalization which has been recognized as a straightforward and efficient method for enabling quick access to an array of structurally diversified molecules. Nitrogen heterocycles such as indoles are biologically interesting scaffolds owing to their prevalence in bioactive natural products.[2] Introduction of an amine functional group at the C-2 position of indoles is a challenging task. One method of introducing the amino group is *via* nitration and subsequent functionalization.[3] The traditional nitration methods possess limitations such as poor functional group compatibility, use of harsh reaction conditions and possible overnitration.[4] Thus, to overcome these issues, several approaches have been developed for regioselective nitration.[5,6] Over the past few years significant progress in C(sp^2)-H nitration using *ortho*-metallation strategy has been achieved. Majority of the reports predominantly employ complexes of Pd, Rh and Cu as catalysts.[7] Our group recently reported a palladium-catalyzed, heteroatom-directed strategy for *ortho*-nitration of anilines employing a removable pyrimidine directing group.[7l] Recently, Ribas[8a] and co-workers described the first example of a cobalt-catalyzed remote C-H functionalization of 8-aminoquinoline based on a single electron transfer (SET) mechanism. Das and co-workers demonstrated a cobalt-catalyzed, proton-coupled electron transfer (PCET) mediated regioselective *ortho*-specific nitration of aromatic C(sp^2)-H bonds using 2-aminopyridine as directing group.[8c]

In recent times, considerable interest has been shown towards first-row transition metal catalysts as they are cost-efficient and naturally more abundant.[9,10] Guo and co-workers recently developed a regioselective nickel-catalyzed remote C-H nitration of 2-aryloxazoline amides using *tert*-butyl nitrite as a nitro source.[10f] To the best of our knowledge, the transition metal-catalyzed C-2 nitration of indoles has not yet been explored and still remains a great challenge as it suffers from poor regioselectivity. Therefore, development of an efficient catalytic approach for the C(sp^2)-H nitration of indoles is greatly desired. In this context we report herein, a cobalt-catalyzed C(sp^2)-H nitration of 3-substituted indoles under mild reaction conditions and involving the use of *tert*-butyl carboxylate (^{t}Boc) as a removable directing group (Scheme 1).



Scheme 1. Cobalt-catalyzed C(sp^2)-H nitration of indoles

Results and Discussion

We commenced our investigations by screening several catalysts with a various nitro sources and solvents. With a variety of directing groups at the nitrogen, the reaction resulted mostly in complex mixtures when the C-3 position was unsubstituted. We then proceeded with *N*-Boc-3-methyl indole as a model substrate to screen the reaction conditions (Table 1, see supporting information for complete optimization). Our initial efforts were directed towards Pd-catalysis but in this case the reaction failed to give desired product and minor amount of indolon-2-one was obtained (Entry 3, Table 1).[11] The cobalt catalyst to be initially screened was $Co(NO_3)_2.6H_2O$ in the presence of *t*-$BuNO_2$ as the nitro source and $K_2S_2O_8$ as a oxidant in TFE at room temperature (Entry 9, Table 1). The corresponding product was obtained with 51% yield. The reaction showed inferior results with other cobalt catalyst such as $CoBr_2$, $Co(OAc)_2$, $Co(acac)_2$ and we also found that $Co(NO_3)_2.6H_2O$ in absence of the nitro source does not lead to desired product. Several other nitro sources were examined and we observed that *t*-$BuNO_2$ gave the best results. In an attempt to improve the yield, many oxidants (eg. Oxone, PIFA), were screened and $K_2S_2O_8$ was found to give the best yield. Next, the effect of solvent was also investigated. We found that reaction proceeded in TFE with moderate yield with a considerably shorter reaction time. Unlike in TFE, the reaction was comparatively slower in THF but resulted in better yield and a cleaner conversion. The reaction showed low efficiency when molecular oxygen was not used. On increasing the catalyst loading to beyond 40 mol%, the product yield was dramatically reduced.

The best condition was found to be $Co(NO_3)_2.6H_2O$ (10 mol%)/ *t*-$BuNO_2$ (2.0 equiv)/ $K_2S_2O_8$ (2.0 equiv)/ O_2 (balloon) in THF at room temperature (Entry 11, Table 1). We next investigated several other directing groups[7h] to check their compatibility with the nitration protocol. However, under the optimized reaction

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conditions, only traces of the expected product was obtained in case of the 2-pyridyl group whereas no product formation was observed with 2-pyrimidyl as a directing group. When acetyl was employed as the directing group, the expected product was not obtained.

Table 1. Optimization Studies[a]

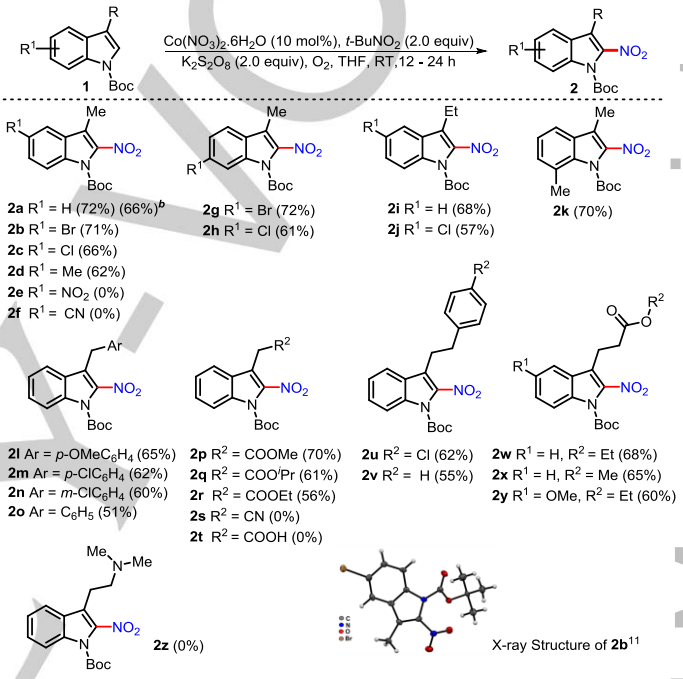
Entry	Conditions	Yield (%)[b] of **2a**
1	HNO_3/AcOH	<5[c]
2	$Pd(OAc)_2$/ $AgNO_2$/ $K_2S_2O_8$/ DCE	NR
3	$Pd(OAc)_2$/ $AgNO_2$/ $K_2S_2O_8$/ AcOH/DCE	
4	$Pd(OAc)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ DCE	10[c]
5	$[Ru(p\text{-cym})Cl_2]_2$/ $AgNO_2$/ $K_2S_2O_8$/ $AgSbF_6$/ DCE	<5[c]
6	$CuCl_2.2H_2O$/ $Fe(NO_3)_3.9H_2O$/ DCE	Complex mixture
7	$Cu(OAc)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ TFE	NR[c]
8	$Fe(NO_3)_3.9H_2O$/ DCE	NR
9	$Co(NO_3)_2.6H_2O$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	51
10	$Co(NO_3)_2.6H_2O$/ $AgNO_2$/ $K_2S_2O_8$/ O_2/ TFE	26
11	**$Co(NO_3)_2.6H_2O$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ THF**	**71**
12	$Co(NO_3)_2.6H_2O$/ $K_2S_2O_8$/ O_2/ THF	NR
13	$Co(NO_3)_2.6H_2O$/ *t*-$BuNO_2$/ O_2/ TFE	12
14	$CoBr_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	Complex mixture
15	$Co(OAc)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	42[c]
16	$Co(acac)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	<5[c]
17	$Mn(OAc)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	NR
18	$Sc(OTf)_2$/ *t*-$BuNO_2$/ $K_2S_2O_8$/ O_2/ TFE	10[c]

[a]Reaction conditions: Unless otherwise mentioned, all the reactions performed with **1a** (0.15 mmol), catalyst (10 mol%), nitro source (2.0 equiv), oxidant (2.0 equiv) and additive (2.0 equiv) in 1 mL of solvent. [b]Isolated yield. [c]Complex mixture was obtained. NR = No Reaction. Boc = *tert*-butyl carboxylate, DCE = 1,2-dichloroethane, TFE = 2,2,2 trifluoroethanol.

With the optimized reaction conditions established, we explored the scope and generality of this Co-catalyzed C-2 nitration of 3-substituted indoles. A wide range of 3-substituted *N*-Boc indoles reacted smoothly resulting in the corresponding product in moderate to good yield (Scheme 2). The reaction worked well with substituents at the C-5, C-6 as well as C-7 positions (**2a**-**2k**, Scheme 2),[11] with a few exceptions (**2e**, **2f**, Scheme 2). The results also showed that the reaction had excellent regioselectivity and compatibility with alkyl, methoxy, halo and other functional groups. However some electron withdrawing groups (-NO_2, -CN, -COR, -CHO) were not tolerated at C-3. The benzyl group on 3-position of the indole (**2l-2o**, Scheme 2) also showed good regioselectivity to nitration protocol. In addition, a wide range of long alkyl chain substituted indoles performed well and furnished the corresponding products (**2p-2y**, Scheme 2). The reaction was scalable to gram scale (Compound **2a**, Scheme 2). Surprisingly, tryptamine derived substrate when subjected to the reaction conditions did not give the desired product (**2z**, Scheme 2). Acyl functional groups as well as phenyl group at C3 were also not tolerated and no transformation was observed in those cases (See Scheme S1 of Supporting Information for details).

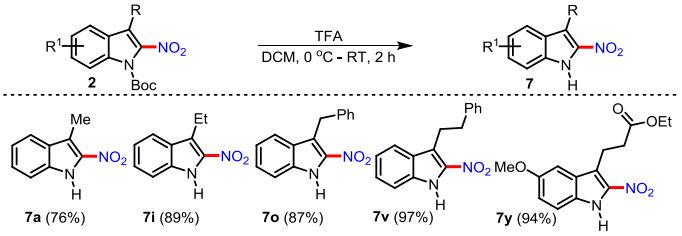
To emphasize the synthetic potential of this methodology, we attempted the deprotection using TFA in DCM. The reaction resulted in the corresponding 2-nitroindole derivatives in fairly good yields (Scheme 3).

To explore the reaction pathway, control experiments were carried out. The experiment with 1.0 equiv of the metal catalyst did not result in any conversion to product, indicative that the nitrate from the catalyst was not acting as the nitro source (Scheme 4A). It is noteworthy to report when nitration reaction was performed using Pd-catalysis it did not give the corresponding product **2a** and instead several side products were formed. Interestingly, the Pd-catalysis when attempted with 2.0 equiv $AgNO_2$ yielded 3-acetoxy indolin-2-ones (**3a**, Scheme 4B) in 34% yield.[11]



[a] All yields are isolated yields. [b] carried out on 1 g scale.

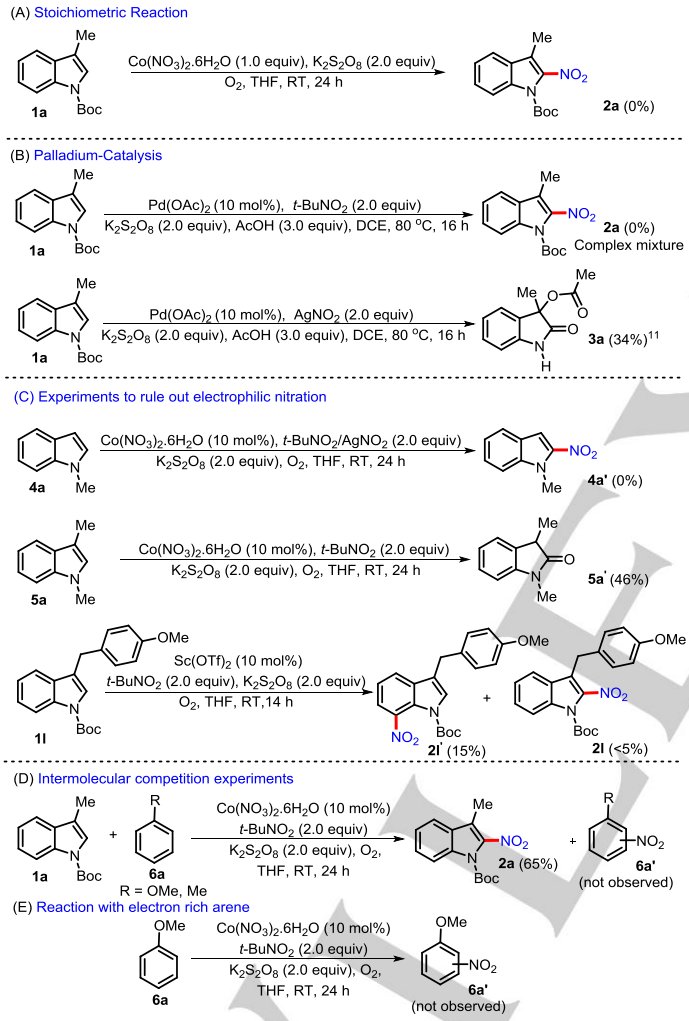
Scheme 2. Substrate Scope[a]



Scheme 3. Removal of the Directing Group

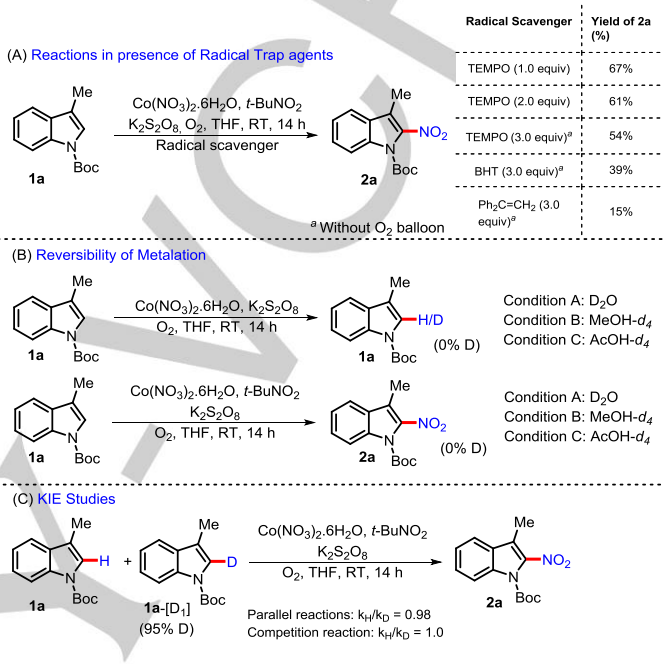
To rule out the possibility of electrophilic metalation, we performed the optimized nitration reaction on *N*-methyl indole (Scheme 4C). The substrate did not result in the nitration product under standard conditions. Subsequently we tried the reaction with *N*-methyl-3-methyl indole **5a**, which afforded 1,3-

dimethyl indolin-2-one **5a'** as the only product with 46% conversion. We also performed control experiments to check possibility of electrophilic reaction with Lewis acid $Sc(OTf)_2$.[13] This reaction condition afforded **2l'** with 15% conversion and less than 5% C-2 product (**2l**) was isolated. Next, we performed competition reactions with electron rich arenes (Scheme 4D), this exclusively give **2a** as the only product and no nitration was observed on the electron-rich arenes. Similarly no nitration was observed when electron-rich arenes were subjected to standard condition. These experimental evidences clearly exclude the possibility of electrophilic substitution being involved in this nitration reaction.



Scheme 4. Control Experiments

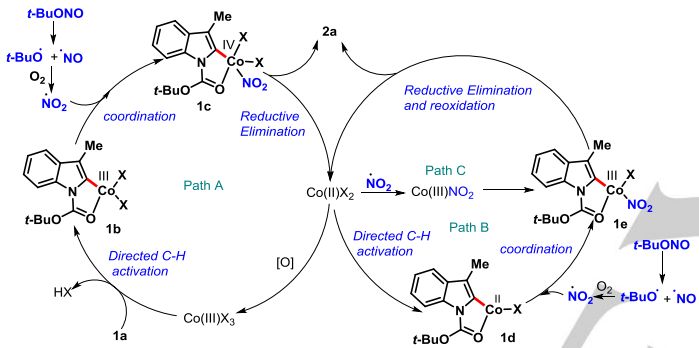
To obtain mechanistic insights into this Co-catalyzed C-H nitration, a series of experiments were carried out (Scheme 5).[14] To check the possibility of single electron transfer pathway, radical trapping experiments were undertaken. Initially 1 equivalent of TEMPO was used as a radical scavenger, which gave 67% of **2a** (Scheme 5A). The radical trap did not inhibit the reaction which initially led us to believe that the pathway may not involve a radical process. However, considerable reduction in the yield was observed when 3 equivalents of the spin trap agent 1,1-diphenyl ethylene was used. In this case, we were also able to isolate the adduct nitro-diphenyl ethylene (see the Supporting Information), clearly indicating that a nitro radical was involved in the reaction.



Scheme 5. Mechanistic Studies

In order to examine the reversibility of the C-H activation step, we performed the reactions with isotopically labelled solvents (D_2O, MeOH-d_4, AcOH-d_4) (Scheme 5B). In case of D_2O and MeOH-d_4, no deuterium incorporation was observed at the C-2 position of the recovered starting material in either of the case. Similar results were observed with AcOH-d_4 when no nitro reagent present. These experiments rule out the possibility of C-H metalation being the reversible step in the nitration reaction. Surprisingly, with the nitro-source, in case of AcOH-d_4, instead of deuterium incorporation in the starting material, the C-2 nitration product (31%) along with C-6 nitration product (16%) was observed (see the Supporting Information). This indicated that in protic media, there was a possibility of generation of the NO_2 cation which led to the electrophilic nitration product at C6 in this case. To further analyze the mechanism of this C(sp^2)-H nitration, the kinetic isotope effect was also determined. The KIE measured by competitive nitration between 1:1 mixture of **1a** and **1a**-[D1] such that ^{1}H NMR analysis of the starting material showed k_H/k_D value of 1.0 whereas a value of 0.98 was obtained for parallel experiments. This suggested that the cleavage of C-H bond was not involved in the rate-determining step. This also seemed to indicate that the C-H bond cleavage may not be via a concerted-metallation-deprotonation (CMD) pathway.

A plausible mechanism can be proposed on the basis of the previous reports.[8,12] We can propose three possible pathways, as depicted in Scheme 6. In path A, the Co(II) catalyst is oxidized to give Co(III) species which reacts with **1a** via directed, chelation-assisted C-H activation. The cyclometalated intermediate **1b** undergoes nitro-coordination to generate Co(IV) intermediate **1c** which upon reductive elimination, leads to the desired nitration product. Path B involves generation of Co(II) intermediate **1d** followed by nitro-coordination to form the cobaltacycle **1e**. Subsequent reductive elimination affords the desired product and re-oxidation in the presence of oxidant regenerates the Co(II) species. It may also be possible that the Co(II) catalyst, upon reaction with NO_2 radical is converted to Co(III) species (Path C, Scheme 6), followed by formation of **1e**. Path C may be the most likely pathway for this transformation, since it involves a Co(III)-Co(I) pathway which is most widely accepted catalytic cycle for Cobalt-catalyzed C-H functionalizations.



Scheme 6. Plausible Mechanism

Conclusions

In summary, we have developed a simple and efficient method involving cobalt catalysis for the C-2 selective C-H nitration of 3-substituted indoles under mild reaction conditions. Reaction proceeds at room temperature and has good functional group tolerance and afforded the formation of a variety of C-2 nitrated indole derivatives with moderate to good yield. The removal of the directing group enhances the synthetic utility of the C-H functionalization approach. This method is expected to be a unique approach to access C-2 aminated indoles.

Experimental Section

General Methods: All commercially available compounds (Acros, Sigma-Aldrich, Alfa-Aesar, Merck etc.,) were used without purification. Unless otherwise noted, all reactions were performed in oven-dried glassware. All reactions were run under nitrogen atmosphere (or oxygen, where specified). All solvents used in the reactions were purified before use. Tetrahydrofuran was distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, dioxane, toluene and dichloroethane were distilled from CaH_2. Petroleum ether with a boiling range of 40–60 °C was used. Melting points are uncorrected. ^{1}H, and ^{13}C NMR: Recorded on Bruker Avance III 400 MHz NMR Spectrometer, Bruker Avance III 500 MHz NMR Spectrometer; spectra were recorded at 295 K in $CDCl_3$; chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (^{1}H δ 7.25; ^{13}C δ 77.0). HRMS: Bruker Daltonics MicroTOF-Q-II with electron spray ionization (ESI) or Atmospheric pressure chemical ionization (APCI). GC-HRMS: Performed on Agilent 7200 GC-QToF (with Electron Impact (EI), 70eV) with 7890A GC using DB-5 column. GC-LRMS: Performed on Agilent 7890A GC with Agilent 5975C MS (EI 70 eV) using DB-5 column. IR: Perkin Elmer Spectrum BX FTIR, Shimadzu IR Affinity-1 FTIR and were recorded as thin films between KBr plates.

The substituted 3-methyl-1*H*-indoles and 3-benzyl-1*H*-indoles were prepared according to procedures reported in literature.[15],[20],[21] Similarly substituted- 2-(1*H*-indol-3-yl)acetate and 3-vinylindoles were also prepared according to literature procedures.[22],[23] 3-vinylindoles were further reduced according to procedures reported in literature for preparation of corresponding indoles.

General procedure for Boc protection of the synthesised indoles:[15],[16],[17]

To a solution of the indole (1.70 mmol) in dry CH_2Cl_2 (4 mL) were added pyridine (2.21 mmol), $(Boc)_2O$ (2.21 mmol) and DMAP (0.17 mmol) at 0 °C. The reaction mixture was stirred at room temperature until completion of the reaction (TLC). The mixture was then extracted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (19:1 Petroleum ether: EtOAc).

***tert*-butyl 3-ethyl-1*H*-indole-1-carboxylate (1i):**

Prepared according to the general procedure and the title compound was isolated as a colorless gel Yield 82% (0.35 g); TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.38 (s, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 2.74 (q, *J* = 7.5 Hz, 2H), 1.70 (s, 9H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.9, 130.7, 124.2, 123.1, 122.2, 121.6, 118.9, 115.2, 83.2, 28.3, 18.1, 13.5; ESI-HRMS: Calculated for $C_{15}H_{19}NNaO_2$ $[M+Na]^+$ 268.1308, found 268.1313.

***tert*-butyl 5-chloro-3-ethyl-1*H*-indole-1-carboxylate (1j):**

Prepared according to the general procedure and the title compound was isolated as a colorless gel Yield 75% (0.43 g); TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.38 (s, 1H), 7.29 – 7.26 (m, 1H), 2.69 (dq, *J* = 7.5, 1.3 Hz, 2H), 1.69 (s, 9H), 1.34 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 133.7, 129.7, 129.4, 126.8, 125.3, 120.8, 116.3, 86.5, 27.6, 17.6, 14.2; ESI-HRMS: Calculated for $C_{15}H_{18}ClNNaO_2$ $[M+Na]^+$ 302.0918, found 302.0939.

***tert*-butyl 3-(2-isopropoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (1q):**

Prepared according to the general procedure and the title compound was isolated as a colorless gel Yield 86% (0.47 g); TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.1 Hz, 1H), 7.60 (s, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 5.08 (q, *J* = 6.4 Hz, 1H), 3.70 (d, *J* = 2.0 Hz, 2H), 1.69 (s, 9H), 1.32 – 1.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 149.6, 135.4, 130.1, 124.4, 124.3, 122.5, 119.1, 115.2, 113.4, 83.5, 68.4,

31.5, 28.2, 21.8; ESI-HRMS: Calculated for $C_{18}H_{23}NNaO_4$ $[M+Na]^+$ 340.1519, found 340.1517.

***tert*-butyl 3-(2-ethoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (1r):**

Prepared according to the general procedure and the title compound was isolated as a colorless gel Yield 91% (0.39 g); TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.73 (s, 2H), 1.69 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 152.1, 149.6, 130.1, 124.5, 124.3, 122.5, 119.0, 115.2, 113.2, 83.6, 81.0, 61.0, 31.2, 28.2, 14.2; ESI-HRMS: Calculated for $C_{17}H_{21}NNaO_4$ $[M+Na]^+$ 326.1363, found 326.1370.

***tert*-butyl 3-(4-chlorophenethyl)-1*H*-indole-1-carboxylate (1u):**

Prepared according to the general procedure and the title compound was isolated as a colorless gel Yield 79% (0.40 g); TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.39 – 7.30 (m, 2H), 7.30-7.23 (m, 3H), 7.22 – 7.11 (m, 2H), 3.00 (s, 4H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.8, 140.2, 131.7, 130.5, 129.7, 128.4, 124.3, 122.5, 122.3, 120.1, 118.8, 115.3, 83.4, 34.9, 28.2, 26.8; ESI-HRMS: Calculated for $C_{21}H_{22}ClNNaO_2$ $[M+Na]^+$ 378.1231, found 378.1253.

***tert*-butyl-3-(3-ethoxy-3-oxopropyl)-5-methoxy-1*H*-indole-1-carboxylate (1y):**

Prepared according to the general procedure and the title compound was isolated as a white solid Yield 72% (0.36 g), M. p. 100-101 ^{o}C, TLC R_f 0.40 (19:1, Petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.37 (s, 1H), 6.99 (s, 1H), 6.94 (dt, J = 9.0, 2.0 Hz, 1H), 4.19 (q, J = 7.3, 2H), 3.89 (d, J = 1.6 Hz, 3H), 3.01 (t, J = 7.7 Hz, 2H), 2.77 – 2.68 (m, 2H), 1.67 (s, 9H), 1.28 (t, J = 7.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 155.7, 131.1, 123.1, 119.2, 116.0, 112.9, 101.6, 83.2, 60.5, 55.7, 33.8, 28.2, 20.3, 14.2; ESI-HRMS: Calculated for $C_{19}H_{25}NNaO_5$ $[M+Na]^+$ 370.1625, found 370.1625.

***tert*-butyl 3-(2-(dimethylamino)ethyl)-1*H*-indole-1-carboxylate (1z):**

Prepared according to the general procedure and the title compound was isolated as a white solid Yield 86% (0.47 g), M. p. 97-99 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.1 Hz, 1H), 7.52 (dt, J = 7.7, 1.0 Hz, 1H), 7.39 (s, 1H), 7.33 – 7.26 (m, 1H), 7.24 – 7.18 (m, 1H), 2.92 – 2.81 (m, 2H), 2.66 (dd, J = 9.2, 6.7 Hz, 2H), 2.35 (s, 6H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7, 130.6, 124.3, 122.6, 122.3, 118.8, 118.7, 115.3, 83.3, 59.2, 45.4, 28.2, 23.3. ESI-HRMS: Calculated for $C_{17}H_{24}N_2NaO_2$ $[M+Na]^+$ 311.1730, found 311.1718.

General procedure for the Co-catalyzed C-H nitration reaction:

In a Schlenk tube equipped with a stir bar, the substrate (0.129 mmol) was dissolved in dry THF (1.0 mL). Oxygen was bubbled into the reaction mixture for 10 min followed by the addition of $Co(NO_3)_2.6H_2O$ (10 mol%), *t*-$BuNO_2$ (2.0 equiv) and $K_2S_2O_8$ (2.0 equiv). The tube was fitted with a Teflon screw cap under an oxygen flow. The reaction mixture was allowed to stir at room temperature for 12-24 h and then diluted with EtOAc and filtered through a pad of Celite. The filtrate was extracted with EtOAc and washed with $NaHCO_3$ solution. The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by a silica gel flash column chromatography to result in the desired product.

***tert*-butyl 3-methyl-2-nitro-1*H*-indole-1-carboxylate (2a):**

Yield: 72% (56 mg), Physical appearance: Yellow solid, M. p. 81-83 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 2.51 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 135.6, 129.4, 126.6, 124.0, 121.6, 121.5, 114.7, 85.9, 27.6, 9.6; IR (KBr, cm^{-1}): 2984, 2925, 1748, 1519, 1451, 1311, 1155, 1114, 914, 860, 747; ESI-HRMS: Calculated for $C_{14}H_{16}N_2NaO_4$ $[M+Na]^+$ 299.1002, found 299.0998.

***tert*-butyl 5-bromo-3-methyl-2-nitro-1*H*-indole-1-carboxylate (2b):**

Yield: 71% (64 mg), Physical appearance: Yellow solid, M. p. 73-75 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 1.9 Hz, 1H), 7.60 (dd, J = 9.0, 2.0 Hz, 1H), 2.45 (s, 3H), 1.57 (s, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 134.0, 132.2, 128.1, 127.0, 124.1, 119.9, 117.2, 116.5, 86.5, 27.6, 9.4; IR (KBr, cm^{-1}): 2915, 2909, 2350, 1739, 1517, 1448, 1378, 1270, 1124, 1055, 866, 811; ESI-HRMS: Calculated for $C_{14}H_{15}BrN_2NaO_4$ $[M+Na]^+$ 377.0107 and 379.0088, found 377.0134 and 379.0114.

***tert*-butyl 5-chloro-3-methyl-2-nitro-1*H*-indole-1-carboxylate (2c):**

Yield: 66% (56 mg), Physical appearance: Yellow solid, M. p. 88-90 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.47 (dd, J = 8.9, 2.1 Hz, 1H), 2.46 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 133.6, 129.8, 129.6, 127.7, 124.3, 120.9, 120.0, 116.2, 86.5, 27.6, 9.4; IR (KBr, cm^{-1}): 2981, 2931, 1754, 1524, 1450, 1347, 1270, 1227, 1127, 920, 840, 760, 681; ESI-HRMS: Calculated for $C_{14}H_{15}ClN_2NaO_4$ $[M+Na]^+$ 333.0613, found 333.0592.

***tert*-butyl 3,5-dimethyl-2-nitro-1*H*-indole-1-carboxylate (2d):**

Yield: 62% (60 mg), Physical appearance: Yellow solid, M. p. 80-82 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 8.5 Hz, 1H), 7.39 (s, 1H), 7.35 (d, J = 8.6 Hz, 1H), 2.48 (s, 3H), 2.45 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 133.9, 133.7, 131.0, 126.7, 121.6, 121.1, 114.5, 85.7, 77.3, 77.2, 77.0, 76.6, 27.6, 21.3, 9.6; IR (KBr, cm^{-1}): 2980, 2927, 1746,1516, 1455, 1372, 1271, 1157, 926, 843, 797, 758,716; ESI-HRMS: Calculated for $C_{15}H_{18}N_2NaO_4$ $[M+Na]^+$ 313.1159, found 313.1178.

***tert*-butyl 6-bromo-3-methyl-2-nitro-1*H*-indole-1-carboxylate (2g):**

Yield: 72% (65 mg), Physical appearance: Yellow solid, M. p. 73-75 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 1.5 Hz, 1H), 7.55 – 7.40 (m, 2H), 2.48 (s, 3H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 135.9, 127.6, 125.4, 123.3, 122.6, 121.1, 118.0, 86.6, 27.6, 9.5; IR (KBr, cm^{-1}): 2914, 2851, 1745, 1650, 1517, 1448, 1310, 1156, 1018, 856, 745; ESI-HRMS: Calculated for $C_{14}H_{15}BrN_2NaO_4$ $[M+Na]^+$ 377.0107 and 379.0088, found 377.0110 and 379.0086.

***tert*-butyl 6-chloro-3-methyl-2-nitro-1*H*-indole-1-carboxylate (2h):**

Yield: 61% (50 mg), Physical appearance: Yellow solid, M. p. 91-93 ^{o}C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$):

δ 8.13 (d, *J* = 1.9 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.52 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 135.7, 135.4, 125.0, 124.9, 122.5, 121.1, 115.0, 86.5, 27.6, 9.5. IR (KBr, cm^{-1}): 3362, 2927, 2369, 1750, 1653, 1559, 1458, 1370, 1270, 1156, 1125, 820; ESI-HRMS: Calculated for $C_{14}H_{15}ClN_2NaO_4$ $[M+Na]^+$ 333.0614, found 333.0613.

***tert*-butyl 3-ethyl-2-nitro-1*H*-indole-1-carboxylate (2i):**

Yield: 68% (69 mg), Physical appearance: Yellow solid, M. p. 96-97 °C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.48 (m, 1H), 7.38 – 7.29 (m, 1H), 2.93 (q, *J* = 7.6 Hz, 2H), 1.58 (s, 9H), 1.33 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 135.6, 129.2, 126.9, 125.7, 124.0, 121.4, 114.9, 85.9, 27.6, 17.7, 14.2; IR (KBr, cm^{-1}): 3645, 3372, 2968, 1739, 1514, 1454, 1253, 1154, 761; ESI-HRMS: Calculated for $C_{15}H_{18}N_2NaO_4$ $[M+Na]^+$ 313.1159, found 313.1183 .

***tert*-butyl 5-chloro-3-ethyl-2-nitro-1*H*-indole-1-carboxylate (2j):**

Yield: 57% (58 mg), Physical appearance: Yellow gel, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 7.51 (dd, *J* = 8.9, 2.1 Hz, 1H), 2.90 (q, *J* = 7.6 Hz, 2H), 1.61 (s, 9H), 1.37 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 133.7, 129.7, 129.3, 126.8, 125.3, 120.8, 116.3, 86.5, 27.6, 17.6, 14.2; IR (KBr, cm^{-1}): 2920, 2845, 2398, 1729, 1554, 1455, 1275, 1158, 1063, 1018, 861. ESI-HRMS: Calculated for $C_{15}H_{17}ClN_2NaO_4$ $[M+Na]^+$ 347.0769, found 347.0759.

***tert*-butyl 3,7-dimethyl-2-nitro-1*H*-indole-1-carboxylate (2k):**

Yield: 70% (68 mg), Physical appearance: Yellow solid, M. p. 104-106 °C, TLC R_f 0.50 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 2.61 (s, 3H), 2.57 (s, 3H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 134.2, 131.9, 127.0, 123.6, 123.0, 120.5, 119.7, 86.5, 27.3, 19.6, 10.3; IR (KBr, cm^{-1}): 2914, 2393, 1765, 1644, 1505, 1372, 1254,1230, 1097, 841, 731; ESI-HRMS: Calculated for $C_{15}H_{18}N_2NaO_4$ $[M+Na]^+$ 313.1159, found 313.1135.

***tert*-butyl 3-(4-methoxybenzyl)-2-nitro-1*H*-indole-1-carboxylate (2l):**

Yield: 65% (61 mg), Physical appearance: Pale yellow gel, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.30 – 7.25 (m, 1H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.80 (t, *J* = 8.7 Hz, 2H), 4.20 (s, 2H), 3.75 (s, 3H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 147.8, 135.5, 129.5, 129.1, 125.9, 124.1, 123.1, 122.0, 114.9, 114.1, 86.1, 55.2, 29.2, 27.6; IR (KBr, cm^{-1}): 2941, 2850, 1671, 1540, 1450, 1161, 1055, 815, 728; ESI-HRMS: Calculated for $C_{21}H_{22}N_2NaO_5$ $[M+Na]^+$ 405.1421, found 405.1449.

***tert*-butyl 3-(4-chlorobenzyl)-2-nitro-1*H*-indole-1-carboxylate (2m):**

Yield: 62% (68 mg), Physical appearance: Pale yellow gel, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 8.3, 5.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.25 – 7.19 (m, 4H), 4.23 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 136.0, 135.4, 132.6, 129.8, 129.3, 128.8, 127.8, 125.6, 124.3, 121.8, 114.9, 86.4, 29.4, 27.6; IR (KBr, cm^{-1}): 2981, 2932, 2827, 2316, 1792, 1655, 1510, 1452, 1300, 1241, 1201, 1042, 807, 725; ESI-HRMS: Calculated for $C_{20}H_{19}ClN_2NaO_4$ $[M+Na]^+$ 409.0926, found 409.0938.

***tert*-butyl 3-(3-chlorobenzyl)-2-nitro-1*H*-indole-1-carboxylate (2n):**

Yield: 60% (65 mg), Physical appearance: Pale yellow gel, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.25 (m, 2H), 7.23 – 7.13 (m, 3H), 4.24 (s, 2H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 139.5, 135.4, 134.5, 129.9, 129.3, 128.6, 127.0, 126.7, 125.6, 124.3, 121.8, 121.6, 114.9, 86.4, 29.7, 27.6; IR (KBr, cm^{-1}): 3056, 2923, 2852, 2316, 1747, 1647, 1520, 1452, 1305, 1261, 1230, 1112, 849, 764; ESI-HRMS: Calculated for $C_{20}H_{19}ClN_2NaO_4$ $[M+Na]^+$ 409.0926, found 409.0937.

***tert*-butyl 3-(2-methoxy-2-oxoethyl)-2-nitro-1*H*-indole-1-carboxylate (2p):**

Yield: 70% (70 mg), Physical appearance: Yellow solid, M. p. 70-72 °C, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.00 (s, 2H), 3.71 (s, 3H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 147.6, 135.3, 129.5, 125.6, 124.4, 121.4, 116.7, 114.8, 86.4, 52.5, 29.9, 27.6; IR (KBr, cm^{-1}): 2991, 2918, 2800, 1751, 1520, 1454, 1300, 1270, 1141, 839, 741; ESI-HRMS: Calculated for $C_{16}H_{18}N_2NaO_6$ $[M+Na]^+$ 357.1057, found 357.1075.

***tert*-butyl 3-(2-isopropoxy-2-oxoethyl)-2-nitro-1*H*-indole-1-carboxylate (2q):**

Yield: 61% (72 mg), Physical appearance: Yellow solid, M. p. 56-58 °C, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.39 – 7.30 (m, 1H), 5.01 (q, *J* = 6.30 Hz, 1H), 3.96 (s, 2H), 1.58 (s, 9H), 1.20 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 135.3, 129.4, 125.7, 124.3, 121.4, 117.1, 114.8, 99.9, 86.3, 77.3, 69.3, 30.4, 27.6, 21.7; IR (KBr, cm^{-1}): 2978, 2922, 2852, 1741, 1524, 1454, 1311, 1270, 1155, 841, 750; ESI-HRMS: Calculated for $C_{18}H_{22}N_2NaO_6$ $[M+Na]^+$ 385.1370, found 385.1347.

***tert*-butyl 3-(2-ethoxy-2-oxoethyl)-2-nitro-1*H*-indole-1-carboxylate (2r):**

Yield: 56% (60 mg), Physical appearance: Yellow solid, M. p. 65-67 °C, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58 – 7.49 (m, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.99 (s, 2H), 1.58 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 139.4, 132.6, 126.9, 124.7, 121.4, 121.4, 112.3, 85.0, 62.9, 13.9; IR (KBr, cm^{-1}): 3289, 2914, 1683, 1504, 1366, 1259, 1231, 1150, 1009, 824, 747; ESI-HRMS: Calculated for $C_{17}H_{20}N_2NaO_6$ $[M+K]^+$ 387.0953, found 387.0953.

***tert*-butyl 3-(4-chlorophenethyl)-2-nitro-1*H*-indole-1-carboxylate (2u):**

Yield: 62% (68 mg), Physical appearance: Yellow gel, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.31, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.17 (m, 2H), 2.97 (m, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 139.0, 135.5, 132.2, 129.7, 129.3, 128.6, 125.7, 124.2, 124.1, 121.3, 114.9, 86.1, 35.2, 27.6, 26.5; IR (KBr, cm^{-1}): 2973, 2930, 1749, 1519, 1446, 1353, 1311, 1258, 1154,1114,1013, 839, 763; ESI-HRMS: Calculated for $C_{21}H_{21}ClN_2NaO_4$ $[M+Na]^+$ 423.1082, found 423.1107.

***tert*-butyl 2-nitro-3-phenethyl-1*H*-indole-1-carboxylate (2v):**

Yield: 55% (51 mg), Physical appearance: Pale yellow gel, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.34 – 7.25 (m, 3H), 7.23 – 7.16 (m, 3H), 3.24 – 3.15 (m, 2H), 2.99 (m, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 140.6, 135.5, 129.2, 128.5, 128.4, 126.4, 125.9, 124.7, 124.0, 121.4, 114.8, 86.0, 35.9, 29.7, 27.6, 26.6; IR (KBr, cm^{-1}): 2973, 2395, 2350, 1740, 1641, 1519, 1371, 1156, 1042, 755; ESI-HRMS: Calculated for $C_{21}H_{22}N_2NaO_4$ $[M+Na]^+$ 389.1472, found 389.1493.

tert-butyl 3-(3-ethoxy-3-oxopropyl)-2-nitro-1*H*-indole-1-carboxylate (2w):

Yield: 68% (66 mg), Physical appearance: Yellow solid, M. p. 101-103 ^{o}C, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.58 – 7.48 (m, 1H), 7.39 – 7.31 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 1.58 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 147.8, 135.5, 129.4, 125.6, 124.2, 123.5, 121.6, 114.8, 86.2, 60.8, 33.9, 27.6, 19.7, 14.1; IR (KBr, cm^{-1}): 2978, 2930, 1741, 1642, 1520, 1370, 1267, 1227, 1114, 1039, 840, 747; ESI-HRMS: Calculated for $C_{18}H_{22}N_2NaO_6$ $[M+Na]^+$ 385.1370, found 385.1393.

tert-butyl 3-(3-methoxy-3-oxopropyl)-2-nitro-1*H*-indole-1-carboxylate (2x):

Yield: 65% (63 mg), Physical appearance: Yellow solid, M. p. 90-92 ^{o}C, TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 3.65 (s, 3H), 3.23 (t, J = 7.6 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 147.8, 135.5, 129.4, 125.5, 124.2, 123.4, 121.5, 114.8, 86.2, 51.8, 33.7, 27.6, 19.7; IR (KBr, cm^{-1}): 2920, 2845, 1742, 1520, 1450, 1304,1251, 1113, 1042, 835, 747; ESI-HRMS: Calculated for $C_{17}H_{20}N_2NaO_6$ $[M+Na]^+$ 317.1214, found 317.1223.

tert-butyl 3-(3-ethoxy-3-oxopropyl)-5-methoxy-2-nitro-1*H*-indole-1-carboxylate (2y):

Yield: 60% (71mg), Physical appearance: Yellow solid, M. p. 100-102 ^{o}C TLC R_f 0.40 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 9.3 Hz, 1H), 7.42 (s, 1H), 7.01 (d, J = 9.2 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.82 (t, J = 7.3 Hz, 2H), 2.57 (t, J = 7.2 Hz, 2H), 1.63 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 149.0, 146.9, 133.1, 131.0, 126.6, 122.2, 117.9, 116.6, 109.6, 84.4, 60.5, 57.3, 33.9, 28.1, 20.0, 14.2; IR (KBr, cm^{-1}): 2980, 2369, 1735, 1588, 1531, 1435, 1373, 1276, 1221, 1158, 1075, 853, 765; ESI-HRMS: Calculated for $C_{19}H_{24}N_2NaO_7$ $[M+Na]^+$ 415.1476, found 415.1486.

General procedure for Boc-deprotection:

To a solution of 2-nitro-*N*-Boc indole (0.3 mmol) in CH_2Cl_2 (3 mL), was added TFA (0.1 mmol) dropwise at 0 °C under argon atmosphere, following which the cooling bath was removed and the mixture was stirred at room temperature for 1-2 h. Upon completion of the reaction, the reagent and the solvent were removed under reduced pressure and the residue was diluted with CH_2Cl_2. The organic layer was washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography (9:1 Petroleum ether: EtOAc).

3-methyl-2-nitro-1*H*-indole (7a):

Yield: 76% (62 mg), Physical appearance: Yellow solid, M. p. 105-107 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 2.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 128.6, 127.2, 122.1, 121.6, 118.3, 117.2, 112.1, 10.2; IR (KBr, cm^{-1}): 3269, 3058, 2919, 2398, 1617, 1447, 1288, 1152, 1047, 735, 592; ESI-HRMS: Calculated for $C_9H_8N_2NaO_2$ $[M+Na]^+$ 199.0472, found 199.0478.

3-ethyl-2-nitro-1*H*-indole (7i):

Yield: 89% (75 mg), Physical appearance: Yellow solid, M. p. 89-91 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (s, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.26 (t, J = 7.7Hz, 1H), 3.24 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.8, 128.5, 126.4, 123.4, 122.0, 121.6, 112.1, 18.0, 14.0; IR (KBr, cm^{-1}): 3239, 2963, 2855, 1618, 1549, 1457, 1335, 1291, 1150, 1082, 765; ESI-HRMS: Calculated for $C_{10}H_{10}N_2NaO_2$ $[M+Na]^+$ 213.0641, found 213.0634.

3-benzyl-2-nitro-1*H*-indole (7o):

Yield: 87% (81 mg), Physical appearance: Yellow solid, M. p. 85-87 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.17 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.49 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.33 (d, J = 7.7 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.25 – 7.18 (m, 2H), 4.61 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 133.7, 128.6, 128.6, 128.5, 126.8, 126.4, 122.5, 122.0, 119.3, 112.2, 30.3; IR (KBr, cm^{-1}): 3358, 3114, 2919, 2851, 2320, 1643, 1536, 1120, 1047, 756; ESI-HRMS: Calculated for $C_{15}H_{12}N_2NaO_2$ $[M+Na]^+$ 275.0800, found 275.0791.

Ethyl 3-(5-methoxy-2-nitro-1*H*-indol-3-yl)propanoate (7y):

Yield: 94% (85 mg), Physical appearance: Yellow solid, M. p. 93-95 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.43 (dd, J = 8.9, 1.8 Hz, 1H), 7.17 (bs, 1H), 6.98 (d, J = 8.8 Hz, 1H), 4.12 (q, J = 8.0 Hz, 2H), 3.96 (s, 3H), 2.94 (t, J = 8.0 Hz, 2H), 2.60 (t, J = 8.0 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 145.6, 132.7, 126.1, 124.2, 114.0, 113.1, 108.8, 60.3, 58.0, 34.8, 20.3, 14.1; IR (KBr, cm^{-1}): 3216, 3094, 2919, 1472, 1302, 1204, 1075, 1029, 862, 795; ESI-HRMS: Calculated for $C_{14}H_{16}N_2O_5$ $[M+H]^+$ 293.1127, found 293.1126.

2-nitro-3-phenethyl-1*H*-indole (7v):

Yield: 97% (73 mg), Physical appearance: Yellow solid, M. p. 110-112 ^{o}C, TLC R_f 0.30 (19:1, Petroleum ether: EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.25 – 7.16 (m, 2H), 3.55 – 3.44 (m, 2H), 3.02 (dd, J = 9.3, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 133.6, 128.6, 128.5, 128.4, 126.6, 126.2, 122.0, 121.7, 120.8, 112.1, 35.8, 27.0; ESI-HRMS: Calculated for $C_{16}H_{14}N_2O_2$ $[M+H]^+$ 267.1133, found 267.1124.

The deuterated substrate **1a**[D_1] was prepared according to the procedure reported in literature.[25]

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Keywords: Indoles • Weak coordinating groups • C(sp^2)-H nitration • Removable directing group • Cobalt catalysis.

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FULL PAPER

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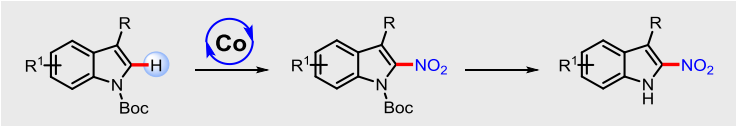
Cobalt-Catalyzed C-H Nitration of Indoles Employing a Removable Directing Group



A mild and efficient C(sp^2)-H nitration of 3-substituted indoles, using the economical and non-toxic cobalt nitrate hexahydrate [$Co(NO_3)_2.6H_2O$] as catalyst and *tert*-butyl nitrite (TBN) as the nitro source, is being reported. This approach provides a unique methodology involving a site-selective C-N bond formation for preparation of C-2 substituted nitro indoles. Utilization of the ^{t}Boc as the removable directing group enhances the synthetic utility of the method.