Monatshefte für Chemie - Chemical Monthly
https://doi.org/10.1007/s00706-018-2324-6

ORIGINAL PAPER

Novel cobalt-valine catalyzed O-arylation of phenols with electron deficient aryl iodides

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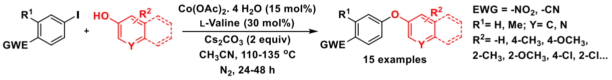
Received: 26 July 2018 / Accepted: 15 October 2018

Abstract

A Novel cobalt-catalyzed O-arylation of phenols with electron deficient aryl iodides is described. The reaction employs cheap and easy-to-handle cobalt acetate tetrahydrate as the catalyst precursor and naturally occurring L-valine as the ligand without the use of any transmetallating or reducing agents. The new protocol offers a wide scope for a variety of phenols towards O-arylation with moderate to excellent yields with electron deficient aryl iodides.

Graphical abstract



Keywords Cobalt catalysis · C–O coupling · Etherification · Valine · Reducing agent

Introduction

Exploration of transition metal catalyzed methodologies for the development of carbon–heteroatom single bonds, especially carbon–oxygen bonds, has been a persistent effort in synthetic organic chemistry for the past few decades [1]. The natural abundance and biological potencies of many pharmaceutical derivatives containing ether cores easily substantiate their importance in synthetic organic chemistry [2].

After being first reported in 1904 through a stoichiometric amount of copper-mediated coupling between aryl halides with phenols [3], the advances made in the field had been very fascinating [4]. Along with the development of catalytic versions of the pioneering copper salt mediated C–O coupling protocols, use of alternate metals like palladium [5], iron [6], or nickel [7] was also interesting and sometimes more inventive. Another break through was the Chan–Lam coupling, which couples boronic acids with phenols, has also witnessed decent development [8]. In order to improve the efficiency of catalytic reactions, chemists in catalysis always showed urge in finding alternative metals or ligands in spite of the efficacy of the prevailing protocols which always led to the development of new catalysts and protocols. Cobalt-catalyzed cross-coupling chemistry is also a well-developed area having a history of more than 70 years with the initial report of homo-coupling of aromatic magnesium reagents by Kharash [9]. Although initial focus of this area was mainly on the development of carbon–carbon bonds, worthy developments also ensued in carbon–sulfur [10] and carbon–nitrogen [11] coupling reactions. However, cobalt-catalyzed carbon–oxygen coupling reactions are sparsely reported in literature and to the best of our knowledge the only report available is by Kundu et al. in 2015 [12]. The protocol was highly efficient for the coupling between phenols and aryl/styrenyl halides; but required equal amounts of copper iodide as the transmetallating agent along with cobalt catalyst making the catalytic system more complex and expensive (Scheme 1). As the catalytic activity of the cobalt in other carbon–heteroatom bond forming reactions

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00706-018-2324-6) contains supplementary material, which is available to authorized users.

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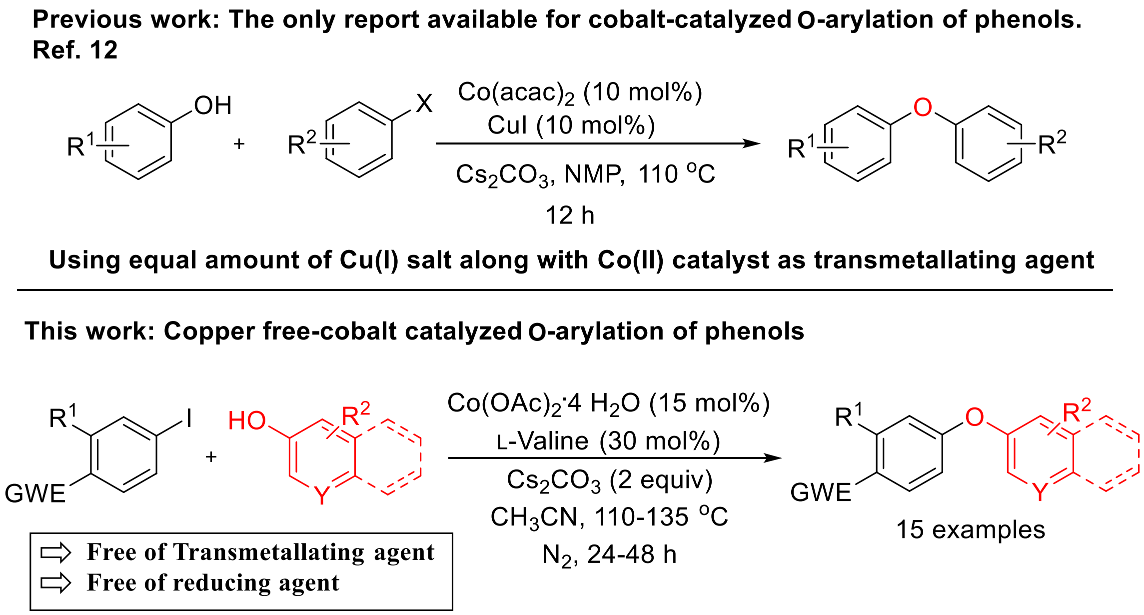
Scheme 1



is well established without the use of any co-catalyst [10, 11] we decided to develop a protocol for carbon–oxygen coupling between aryl halides and phenols using cobalt as the sole catalyst based on our experience in transition metal catalyzed cross-coupling reactions [13].

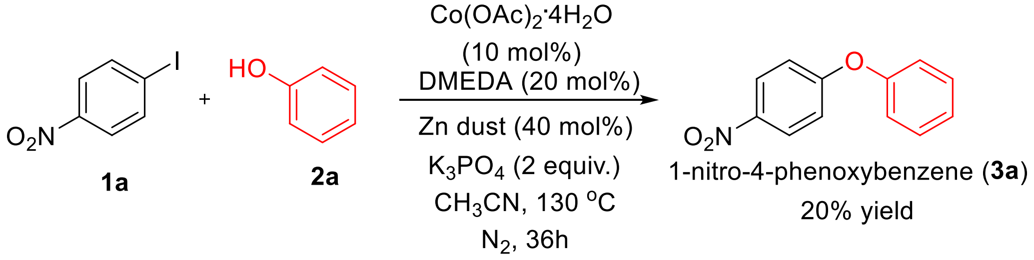
Herein, we report a copper-free cobalt-catalyzed coupling between electron-deficient aryl halides and phenols using the naturally occurring amino acid L-valine as the ligand in the absence of any reducing agent.

Results and discussion

Initially, commercially available 4-iodonitrobenzene (**1a**) and phenol (**2a**) were chosen as the model substrates to develop an optimum condition. Expecting a Co^{I}/Co^{II} catalytic process to cause the desired coupling, we also decided to include a reducing agent. As we are interested to develop an economic and eco-friendly protocol, cheap and non-toxic zinc dust was chosen as a suitable reducing agent. Our previous experience in similar transformations with other metals helped us to add a ligand and a base to the formulation. Choosing $Co(OAc)_2{\cdot}4H_2O$ (10 mol%) as the catalyst precursor, we performed the preliminary reaction between **1a** (1 equiv.) and **2a** (1.2 equiv.) in the presence of DMEDA (20 mol%), Zn dust (40 mol%), and 2 equiv. of K_3PO_4 in acetonitrile at 130 °C under nitrogen atmosphere (Scheme 2). The progress of the reaction was monitored by TLC. The reaction was quenched after 36 h and an appropriate work up procedure was carried out followed by purification of the crude reaction mixture by column chromatography using silica gel (1% hexane–EtOAc) to afford the desired product **3a** in 20% yield.

The product **3a** was characterized using ^{1}H NMR, ^{13}C NMR, and HRMS studies. Duplication of the reaction at 110 °C by using 2 equiv. of KOH instead of K_3PO_4 maintaining all other parameters the same resulted in the enhancement of yield to 42%. Hence we decided to continue further optimization studies at 110 °C using KOH as the base.

Scheme 2



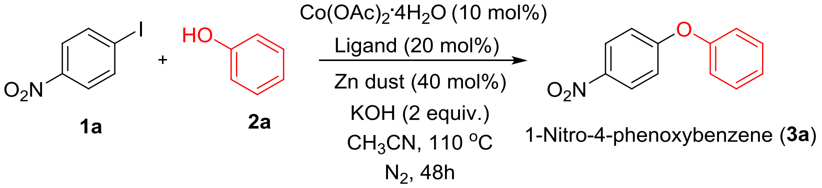
Since ligands hold a prominent role in metal catalyzed coupling reactions by either stabilization of the active oxidation state or that of possible organometallic intermediates and thereby affecting the desired conversion, we decided to perform ligand optimization studies first. We have chosen **L1**–**L10** which includes N–N, N–O and O–O class of ligands as well as a phosphine ligand (Table 1). The N–N ligands such as **L1** and **L4** gave lower yields of 42% and 38%, respectively. Yields for both phosphine (**L3**) and O–O ligands (**L10**) were in the range of 49–53%. The N–O ligands were more promising as the picolinic acid (**L2**) gave 76% yield of the product. In order to make the ligand selection more environmentally friendly, amino acids were also monitored. Proline (**L5**) and alanine (**L6**) gave identical yields of 50% and 47%, respectively. We were pleased to observe that L-valine (**L7**) gave a favourable yield of 75%. But structurally resembling isoleucine (**L9**) afforded only 52% of the product while its structural isomer L-leucine (**L8**) gave 68% yield. Although ligands **L2** and **L7** gave similar yields, we decided to proceed further with the more environmentally benign and cheap L-valine. The inevitability of maintaining a 1:2 ratio of metal: ligand was clearly visible from the lowering of yields in the case of **L8** as ligand at a lower concentration of 15 mol% (Table 1, entries 8 and 9).

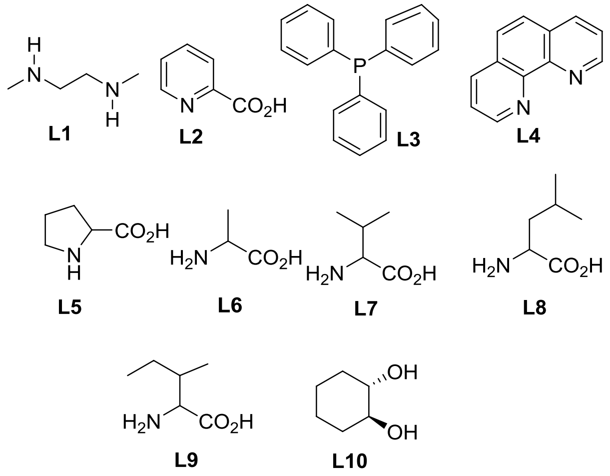
Although the ligand optimization studies gave a good yield of 75% with **L7** as the ligand, quest for a quantitative yield made us look for the possibility of a more fitting solvent and base (Table 2). We performed a range of reactions by altering the solvent/base while maintaining all the other parameters intact with **L7** as the ligand.

Apart from acetonitrile, all the remaining solvents failed to give any promising yield. Both toluene and DME did not afford any detectable conversion. The protic solvent ethanol also showed a poor conversion. Therefore, further base optimization studies were done choosing acetonitrile as the solvent. Thus the activity of hydroxide, carbonate, butoxide, bicarbonate, as well as phosphate-containing bases, was monitored. Sodium bicarbonate, sodium carbonate, and potassium carbonate only afforded traces of the desired product. K_3PO_4 gave a yield of 39% while NaOH afforded 46%. KO*t*Bu and NaO*t*Bu gave moderate yields of 63% and 58%, respectively, while Cs_2CO_3 afforded, to our delight, a good yield of 80%. We then decided to proceed further with Cs_2CO_3 as the base despite the fact that almost similar yield was given by KOH (75%). After finding a successful ligand, solvent and base, we decided to study the effect of the catalyst loading and reaction time in the reaction in order to make the protocol more efficient (Table 3).

From Table 3, we came to the conclusion that the reaction is complete by 24 h using a loading of 15 mol% of $Co(OAc)_2{\cdot}4H_2O$ and 30 mol% of valine affording 95% of the coupling product. It is surprising that the reaction

Table 1 Ligand optimization studies for cobalt-catalyzed O-arylation of phenol with 4-nitroiodobenzene





Entry	Ligand	Yield[a,b] /%	Entry	Ligand	Yield /%
1	**L1**	42	7	**L7**	75
2	**L2**	76	8	**L8**	68
3	**L3**	49	9	**L8**	53 [c]
4	**L4**	38	10	**L9**	52
5	**L5**	50	11	**L10**	53
6	**L6**	47			

[a] Reaction conditions: 4-nitroiodobenzene (0.65 mmol), phenol (0.78 mmol), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), ligand (20 mol%), Zn dust (40 mol%), KOH (2 equiv.), 2.5 cm^3 CH_3CN, 110 °C, 48 h, N_2 atm; [b] Isolated yield; [c] ligand 15 mol%.

Table 2 Solvent and base optimization studies for cobalt-catalyzed O-arylation of phenol with 4-nitroiodobenzene

Entry	Solvent	Base	Yield/%[a, b]
1	CH_3CN	KOH	75
2[c]	CH_3CN	KOH	50
3	Ethanol	KOH	23
4	Toluene	KOH	nd
5	DME	KOH	Traces
6	CH_3CN	K_3PO_4	39
7	CH_3CN	$Na_2CO_3{\cdot}H_2O$	Traces
8	CH_3CN	K_2CO_3	Traces
9	CH_3CN	NaOH	46
10	CH_3CN	$NaHCO_3$	Traces
11	CH_3CN	KO*t*Bu	63
12	CH_3CN	NaO*t*Bu	58
13	CH_3CN	Cs_2CO_3	80

nd not detected

[a] Reaction conditions: 4-nitroiodobenzene (0.65 mmol), phenol (0.78 mmol), $Co(OAc)_2{\cdot}4H_2O$ (10 mol%), L-valine (20 mol%), Zn dust (40 mol%), base (2 equiv.), 2.5 cm^3 solvent, 110 °C, 48 h, N_2 atm

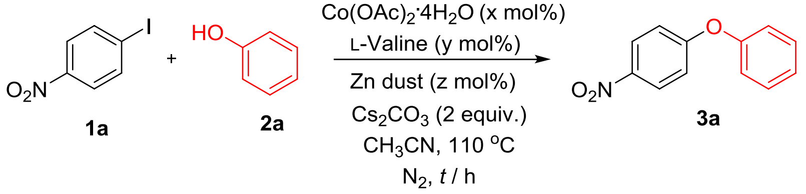
[b] Isolated yield

[c] $Co(OAc)_2{\cdot}4H_2O$ (15 mol%), L-valine (30 mol%), Zinc dust (60 mol%)

worked without a reducing agent which prompted us a different mechanistic proposal for the reaction as the reaction gave 96% yield of the product in the absence of zinc dust (Table 3, entry 5). When the reaction was performed in the absence of cobalt catalyst and ligand the yield of the product was decreased to 28% attesting the inevitable role of the catalytic system developed (Table 3, entry 6) in the desired conversion. Thus having an optimized reaction condition ($Co(OAc)_2{\cdot}4H_2O$ (15 mol%), L-Valine(30 mol%), Cs_2CO_3 (2 equiv.), 2.5 cm^3 CH_3CN, 110 °C, 24 h, N_2 atm) affording excellent yield in hand, we decided to investigate the scope of the reaction on a variety of aryl halides and phenols.

When the optimized reaction conditions were attempted in the case of neutral or electron rich aryl iodides towards the coupling with phenols, the results were disappointing as the desired coupling did not occur. We then decided to continue with aryl iodides bearing electron withdrawing groups. In the case of 4-nitroiodobenzene moderate to excellent yields were observed except with 2-naphthol (Table 4). Here, the yields were found to be decreasing with the increase of electron density in the phenolic partner (entries **3a**, **3b**, and **3c**); Steric factors in the phenols are also found to have remarkable effect as yields were decreased for 2-substituted phenols compared to their 4-substituted analogues. Among chlorophenols 4-substituted analogue gave 90% of yield while it was reduced to 71% with 2-chlorophenol. Similarly, yields were 81% and 71%, respectively, for 4-cresol and 2-cresol. The lower yield for the reaction of 2-naphthol was surprising despite having any remarkable electronic or steric features. The reaction was also applicable in the case of heterocyclic phenol as 3-pyridinol gave **3h** in a yield of 40%. The reactivities of 4-bromo and 4-chloronitrobenzene were also examined which furnished **3a** in lower yields of 42% and 18%, respectively, in contrast to normal S_NAr reactions.

Table 3 Catalyst loading studies for Cobalt-catalyzed O-etherification



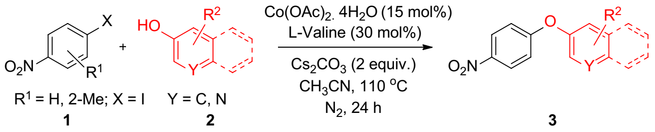
Entry	$Co(OAc)_2{\cdot}4H_2O$ (x mol%)	L-Valine (y mol%)	Zinc dust (z mol%)	Time/h	Yield/%[a, b]
1	5	10	20	48	67
2	10	20	40	24	78
3	10	20	40	48	80
4	15	30	40	24	95
5	15	30	No zinc	24	96
6	–	–	–	24	28
7[c]	15	30	–	24	77

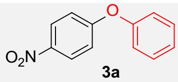
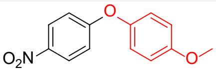
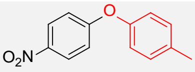
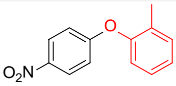
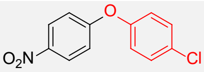
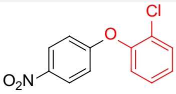
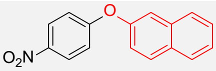
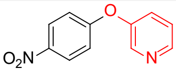
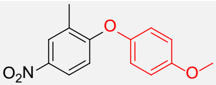
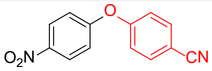
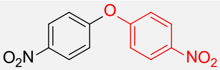
[a] Reaction conditions: 4-nitroiodobenzene (0.65 mmol), phenol (0.78 mmol), Cs_2CO_3 (2 equiv.), 2.5 cm^3 CH_3CN, 110 °C, N_2 atm

[b] Isolated yield

[c] TEMPO (4 equiv.)

Table 4 Cobalt-catalyzed O-arylation of phenols using 4-halonitrobenzene



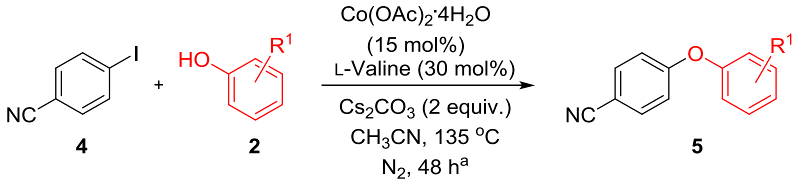
Entry	Product	Yield (%) [a, b]	MP °C
1	 **3a**	95 X = Br; 42 X = Cl; 18	MP: 58-60 °C (lit.[15] 58-59 °C)
2	 **3b**	60	MP: 110-112 °C; (lit.[16] 110-111 °C)
3	 **3c**	81	MP: 69-71 °C
4	 **3d**	71	
5	 **3e**	90	MP: 76-78 °C (lit.[17] 75-78 °C)
6	 **3f**	76	MP: 76-78 °C (lit.[18] 76.8-77 °C)
7	 **3g**	24	MP: 138-139 °C (lit.[17] 137-139 °C)
8	 **3h**	40	110-112 °C (lit.[19] 106-108 °C).
9	 **3i**	17	
10	 **3j**	traces	
11	 **3k**	nd[c]	

nd not detected

[a]Reaction conditions: 4-iodobenzonitrile (0.65 mmol), phenol (0.78 mmol), $Co(OAc)_2 \cdot 4H_2O$ (15 mol%), L-valine (30 mol%), Cs_2CO_3 (2 equiv.), 2.5 cm^3 CH_3CN, 135 °C, 48 h, N_2 atm

[b]Isolated yield

Table 5 Cobalt-catalyzed O-arylation of phenols



Entry	Product	Yield/%[a, b]	M.p./°C Ref.
1	**5a**, $R^1 = 4\text{-OMe}$	55	109–111 (109–110 [19])
2	**5b**, $R^1 = 4\text{-Me}$	45	72–73
3	**5c**, $R^1 = 2\text{-Me}$	43	
4	**5d**, $R^1 = H$	36	
5	**5e**, $R^1 = 4\text{-Cl}$	35	80–82 (80–83 [19])
6	**5f**, $R^1 = 2\text{-Cl}$	31	

nd not detected

[a] Reaction conditions: 4-iodobenzonitrile (0.65 mmol), phenol (0.78 mmol), $Co(OAc)_2{\cdot}4H_2O$ (15 mol%), L-valine (30 mol%), Cs_2CO_3 (2 equiv.), 2.5 cm^3 CH_3CN, 135 °C, 48 h, N_2 atm

[b] Isolated yield

The reaction failed in the case of 4-cyano- and 4-nitrophenols as only traces of the product was formed in the former while the latter did not afford the product at all.

The reaction also worked in the case of cyano substituted iodobenzene **4** but required some elevated temperature and increased reaction span (Table 5). In the case of **4** more electron-rich phenols were found to give the highest yields. Moreover, steric factors have not found much impact. Even under this elevated reaction temperature, other aryl iodides including 4-iodoanisole, iodobenzene, methyl-4-iodobenzoate, etc. did not give any conversion while 4-iodoacetophenone and 3-(trifluoromethyl)iodobenzene furnished traces of the products.

A plausible mechanism (Scheme 3) can involve an initial complexation of the phenol with the Co(II)-metal ion forming a complex **A**. Complex **A** then reacts with iodoarene leading to a four-membered transition state **B**. The etherification can involve an intermolecular halogen exchange at this stage (**C**) releasing catalytically active Co(II) species. The involvement of radical species at any stage in this process was ruled out as the yield remained good even after performing the reaction in the presence of four equivalents of TEMPO as the radical scavenger (Table 3, entry 7). Although this kind of halogen exchange mechanism has been theoretically proposed for copper-catalyzed etherification reactions [14] the feasibly of this in the current cobalt-catalyzed protocol needed further studies including computational calculations which are still going on in our laboratories.

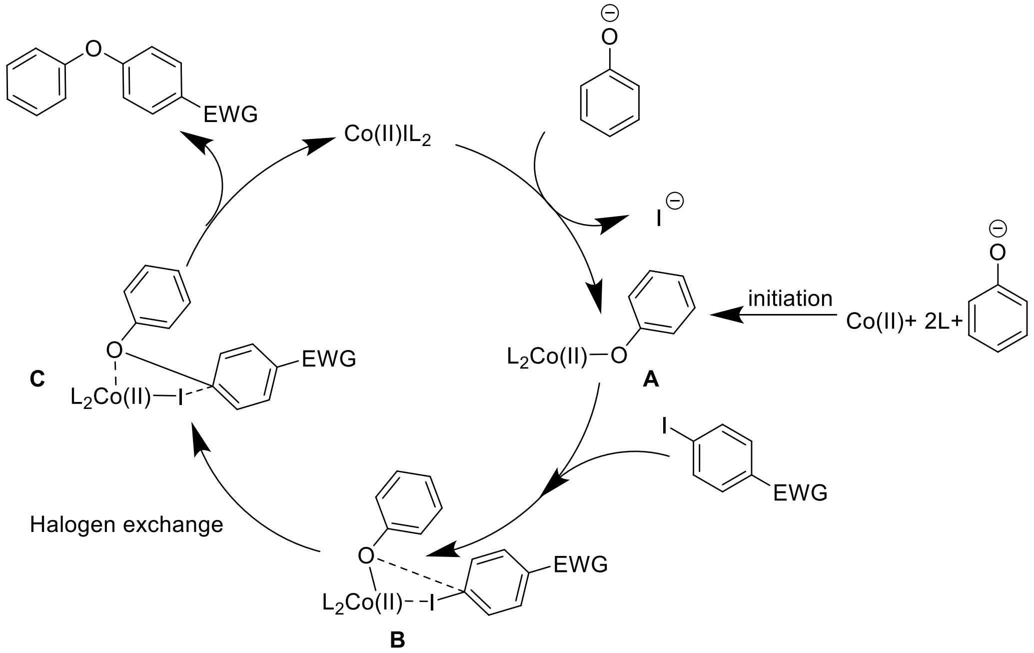
Conclusions

In summary, we have developed a novel cobalt-valine catalyzed O-arylation of phenols using electron deficient aryl iodides without the use of any transmetallating or reducing agents. The methodology uses cheap and easy-to-handle $Co(OAc)_2{\cdot}4H_2O$ as the catalyst and naturally occurring L-valine as the ligand. The reaction provided excellent yields in the case of 4-nitroiodobenzene and also worked well in the case of 4-iodobenzonitrile, but the latter case required a slightly elevated temperature and slightly more reaction time. At this stage the protocol is only limited to electron-deficient aryl halides. But efforts are still going on in our laboratories to include electron-rich aryl halides and to widen the substrate scope with more phenols and more electron-deficient aryl iodides. A plausible mechanism was proposed which involves a halogen atom transfer step and needs further studies to ascertain.

Experimental

$Co(OAc)_2{\cdot}4H_2O$ was purchased from Merck Specialities Pvt. Ltd, India. Ligands such as DMEDA, *trans*-cyclohexane-1,2-diol, picolinic acid, triphenyl phosphine, and phenanthroline were purchased from Sigma-Aldrich, USA. Amino acids including L-alanine, L-valine, L-leucine, and L-isoleucine as well as zinc dust were purchased from SRL, India. The bases used were

Scheme 3



potassium phosphate (Alfa Aesar), cesium carbonate, KO*t*Bu, NaO*t*Bu (Spectrochem, India), KOH, NaOH (Merck), $NaHCO_3$, and K_2CO_3 (Nice Chemicals, India). Aryl iodides and phenols were purchased from Alfa Aesar and Sigma-Aldrich. All the solvents used for the purification of the products were purchased from Nice Chemicals and distilled prior to use. NMR spectra were recorded on 500 (^{1}H) and 125 (^{13}C) MHz, respectively, on a Bruker-500 MHz NMR spectrometer instrument. The chemical shift values were reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as internal standards. Coupling constants (*J*) were stated in Hertz (Hz). The HRMS were recorded on XEVO G2 Q-TOF (Waters) mass spectrometer. Column chromatography was performed using silica gel 100–200 mesh purchased from Merck Specialities Pvt. Ltd. India and mixtures of hexane–ethylacetate were used for elution. TLC was carried out using Merck SilicaGel 60/UV254 either by UV fluorescence or by iodine chamber.

General procedure for O-arylation of phenol

An oven-dried sealed tube equipped with a magnetic stirring bar was charged with aryl iodide (0.65 mmol), $Co(OAc)_2\cdot 4H_2O$ (15 mol%), L-valine (30 mol%), cesium carbonate (2 equiv.), and phenol (0.78 mmol). Acetonitrile solvent (2.5 cm^3) was added and the sealed tube was evacuated using a vacuum pump, filled with nitrogen, and tightly sealed. It was then stirred in a pre-heated oil bath for 24–48 h. After the completion of the reaction, the reaction mixture was extracted with 15 cm^3 of EtOAc and the EtOAc layer was separated and washed with water. The aqueous layer was collected and further extracted two more times with EtOAc (2×15 cm^3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated using a rotatory evaporator. The residue was later purified by column chromatography (silica 100–200 mesh) using hexane–EtOAc mixture as the eluent.

1-(4-Methoxyphenoxy)-2-methyl-4-nitrobenzene (3i, $C_{14}H_{13}NO_4$) Pale yellow liquid; yield: 29 mg (17%); $R_f = 0.70$ (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.13$ (s, 1H), 7.96 (dd, $J = 9.0$, 3.5 Hz, 1H), 6.99 (d, $J = 9.0$ Hz, 2H), 6.94 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 9.0$ Hz, 1H), 3.83 (s, 3H), 2.96 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 162.29$, 156.92, 148.38, 142.10, 128.66, 126.64, 123.15, 121.51, 115.26, 55.69, 16.36 ppm; HRMS (QToF): *m/z* calculated for $C_{14}H_{13}NO_4$ ($[M+H]^+$) 260.0923, found 260.0931.

Acknowledgements SMU thanks the University Grants Commission (UGC-New Delhi), India for a research fellowship. SS and NAH thank the Council of Scientific and Industrial Research (CSIR-New Delhi), India for their research fellowships. GA thanks the Kerala State Council for Science Technology and Environment (KSCSTE), Trivandrum, India for a research grant (Order no. 341/2013/KSCSTE dated 15.03.2013). We greatly acknowledge the support from Department of Science and Technology (DST-New Delhi) under the DST-PURSE programme.

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