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Complete List of Authors:	Liu, Zheng-Fen; Yunnan University, Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology Li, Minyan; University of Pennsylvania, Department of Chemistry Wang, Bijun; Yunnan University, Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology Deng, Guogang; Yunnan University, Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology Chen, Wen; Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education, Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education Kim, Byeong-Seon; University of Pennsylvania, Department of Chemistry Zhang, Hongbin; Key Laboratory of Medicinal Chemistry for Natural Resource, School of Chemical Science and Technology Yang, Xiao-Dong; Yunnan University, Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology Walsh, Patrick; University of Pennsylvania, Department of Chemistry

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RESEARCH ARTICLE

Chemoselective synthesis of aryl(pyridinyl)methanol derivatives through Ni-NIXANTPHOS catalyzed α-arylation and tandem arylation/rearrangement of pyridylmethyl ethers†

Zhengfen Liu,[a] Minyan Li,[b] Bijun Wang,[a] Guogang Deng,[a] Wen Chen,[a] Byeong-Seon Kim,[b] Hongbin Zhang,[a] Xiaodong Yang,*[a] and Patrick J. Walsh*[b]

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An efficient synthesis of aryl(pyridyl)-methanol derivatives using a nickel-NIXANTPHOS catalyst is described. Combinations of Ni-NIXANTPHOS catalyst, solvent, and reaction temperature achieved chemoselective arylation and tandem arylation/rearrangement of pyridylmethyl ethers. A large variety of aryl halides were tolerated (55 examples, up to 96% yield). The scalability of the reaction is demonstrated. The order of the tandem arylation and [1,2]-Wittig rearrangement was probed by comparative studies.

Introduction

Nitrogen containing compounds are of great interest to synthetic organic chemists due to their widespread existence in natural products and bioactive agents.[1] Among such compounds, bioactive molecules bearing aryl(pyridinyl)methanol cores (free alcohols or ethers) are frequently found in pharmaceuticals such as histamine H1 antagonists,[2] HIV-1 NNRT inhibitor,[3] aldosterone synthase inhibitor,[4] and LTA4H inhibitor (Fig. 1).[5]

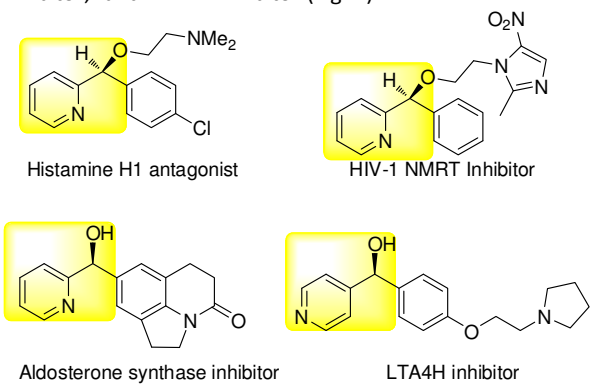

Fig. 1 Representative bioactive compounds with aryl(pyridinyl)methanol cores.

Regarding the synthesis of aryl(pyridinyl)methanol derivatives, transition metal catalysed hydrogenation of ketones has been widely employed (Scheme 1a).[6] In some cases, hydrogenation proceeded sluggishly due to coordination of the pyridine moiety.[7] Another popular approach to aryl(pyridinyl)methanol cores is Wittig rearrangement (Scheme 1b).[8] The need to first synthesize the functionalized ethers and then employ excess stoichiometric organolithium reagents limit the scope and functional group tolerance of this approach.[8g] Considering the value of aryl(pyridinyl)methanol derivatives, our group strived to accomplish the synthesis of these compounds through a tandem reaction that can form up to two C–C bonds. Beginning with pyridylmethyl ethers, aryl or vinyl bromides and a Pd-NIXANTPHOS catalyst,[9] direct arylation of pyridylmethyl ethers,[9a,10] alkenylation of pyridylmethyl ethers (Scheme 1c-i),[11] and bis-arylation of 4-pyridylmethyl ethers (Scheme 1c-ii)[12] were successfully developed. The reactions exhibit good selectivity and tolerance of functionalized aryl bromides. Moreover, we observed that a subsequent [1,2]-Wittig rearrangement could occur after the α-arylation, providing one-pot access to diverse aryl(pyridyl)methanols in good yields (Scheme 1c-iii).[13]

On the basis of our previous success in synthesis of aryl(pyridyl)methanol derivatives, we sought to broaden our approach from the following aspects: (1) study the possibility of using Earth abundant nickel/NIXANTPHOS-based catalyst in place of the precious metal palladium/NIXANTPHOS catalyst; (2) expand the scope of aryl halide coupling partners to include more economical and abundant aryl chlorides and; (3) study the chemoselectivity of arylation *versus* tandem arylation/Wittig rearrangement with a nickel catalyst. In this article, we report a versatile and highly selective method for the synthesis of aryl(pyridinyl)methanol derivatives (Scheme 1d). Under two distinct combinations of nickel catalyst, base,

[a] *Key Laboratory of Medicinal Chemistry for Natural Resources, Ministry of Education and Yunnan Province, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China. E-mail: xdyang@ynu.edu.cn*

[b] *Department of Chemistry, Roy and Diana Vagelos Laboratories, Penn/Merck Laboratory for High-Throughput Experimentation, University of Pennsylvania, Philadelphia, PA 19104-6323, United States. E-mail: pwalsh@sas.upenn.edu*

† Electronic supplementary information (ESI) available. CCDC 1569085. For ESI and crystallographic data in CIF or other electronic format see
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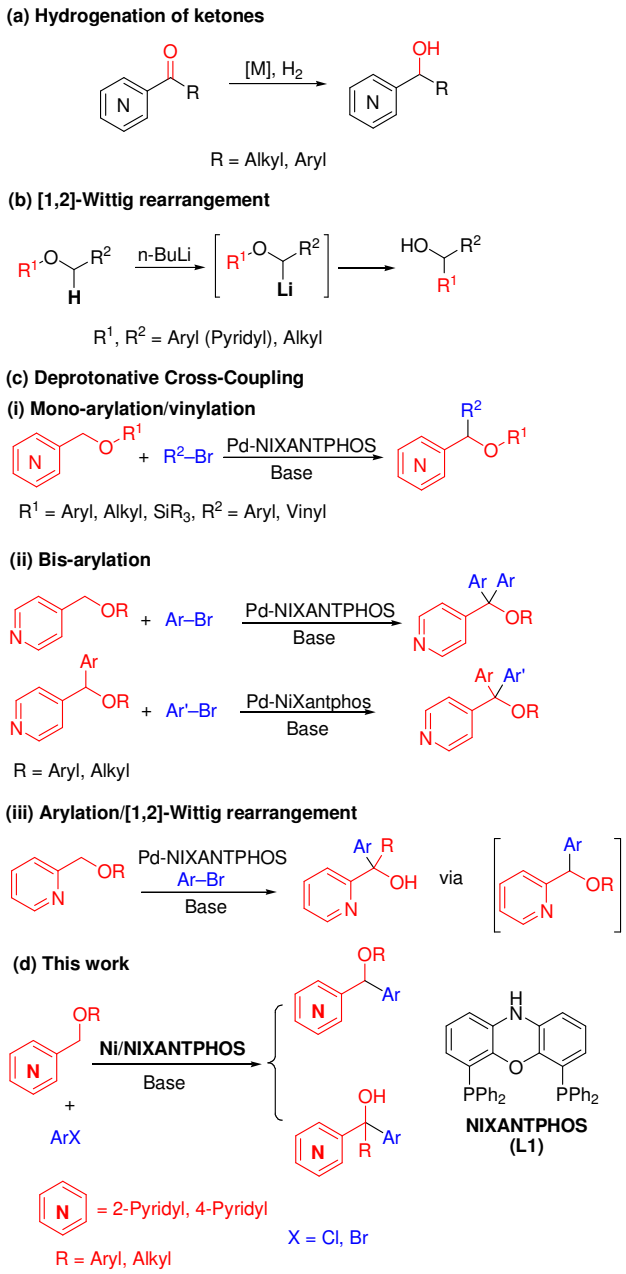


Scheme 1 Synthesis of aryl(pyridinyl)methanol derivatives.

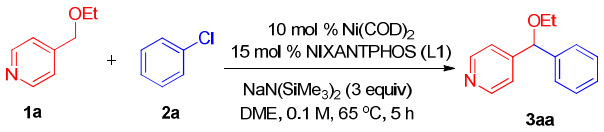
solvent and reaction temperatures, direct α-arylation and tandem arylation/[1,2]-Wittig rearrangement of pyridyl methyl ethers were achieved in high yields. A wide variety of aryl bromides, aryl chlorides and pyridylmethyl ethers were suitable coupling partners (55 examples). The scalability of the reaction is demonstrated and the sequence of the arylation/rearrangement was probed.

Results and discussion

Based on our initial work in the functionalization of pyridyl methyl ethers[10,11,13] and development of Ni-NIXANTPHOS-based catalysts,[14] we first studied the coupling between 4-pyridylmethyl ethyl ether **1a** and chlorobenzene **2a** using 10 mol % $Ni(COD)_2$ as nickel source, 15 mol % of van Leeuwen's NIXANTPHOS (**L1**, Scheme 1),[14a] and $NaN(SiMe_3)_2$ as base in DME at 65 °C for 5 h. Under these conditions, direct arylation product **3aa** was obtained in 70% assay yield (AY, determined by ^{1}H NMR analysis, Table 1, entry 1). In sharp contrast to the NIXANTPHOS-based catalyst, the analogous Xantphos-based catalyst led to a significant drop in AY (14%, entry 1 vs. 2). This result is consistent with our hypothesis that the N–H deprotonated NIXANTPHOS-bound ligand imparts enhanced reactivity to transition metal catalysts.[14c,15]

We continued testing other phosphine ligands for the purpose of comparison to NIXANTPHOS (**L1**). Unfortunately, no reaction was observed with DavePhos (**L3**), DPEphos (**L4**), Pxy_3 (**L5**), DCEphos (**L6**), SPhos (**L7**), XPhos (**L8**), RuPhos (**L9**), DPPE (**L10**), P(*o*-Tol)$_3$ (**L11**) (see supplementary Table S1), despite the known ability of such ligands to efficiently promote a variety of coupling reactions. As listed in entries 3–6 (Table 1), other nickel sources, such as $Ni(acac)_2$, $NiCl_2$•glyme, $Ni(OAc)_2$ and $NiBr_2$, afforded lower AY's (19–41%) with NIXANTPHOS than $Ni(COD)_2$ (70% yield, entry 1). Exploring the impact of different bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, Li*O*t*B*u, Na*O*t*B*u, and K*O*t*B*u] with the $Ni(COD)_2$/NIXANTPHOS catalyst, we observed that the AY increased to 76% (entry 7) when $LiN(SiMe_3)_2$ was used (see supplementary Table S1 for detail). Lowering the reaction temperature to room temperature (23 °C) led to an increase in AY to 81% (79% isolated yield, entry 8). Further reducing the catalyst loading to 5 and 2.5 mol % caused the AY to drop to 71 and 60%, respectively (see supplementary Table S1 for detail). Interestingly, $LiN(SiMe_3)_2$ outperformed $NaN(SiMe_3)_2$ which

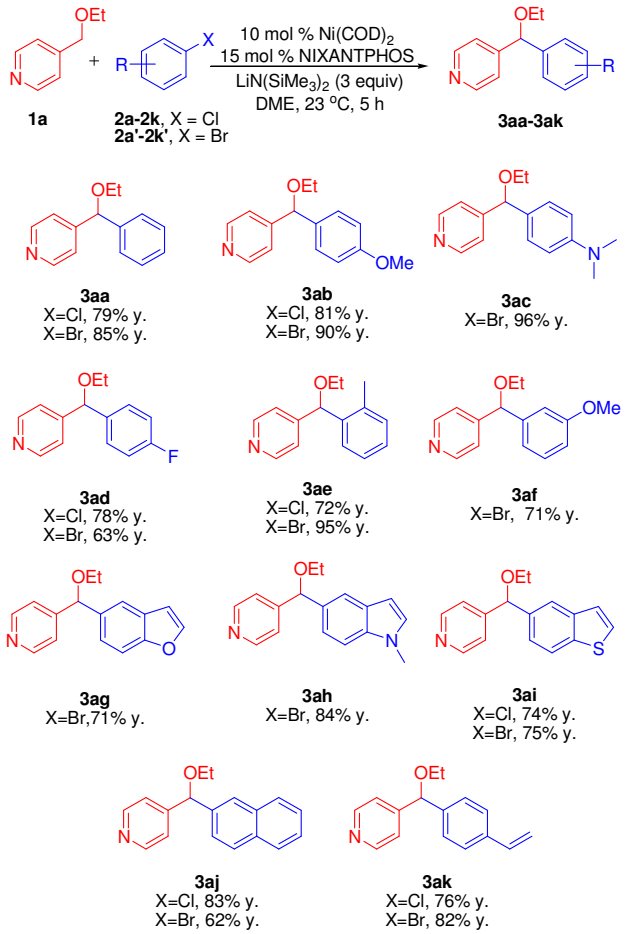
Table 1 Optimization of arylation of 4-pyridylmethyl ethyl ether **1a** with chlorobenzene **2a**[a, b]



Entry	Ligand	Base	AY (%)
1	L1	$NaN(SiMe_3)_2$	70
2	Xantphos (L2)	$NaN(SiMe_3)_2$	14
3[c]	L1	$NaN(SiMe_3)_2$	20
4[d]	L1	$NaN(SiMe_3)_2$	19
5[e]	L1	$NaN(SiMe_3)_2$	41
6[f]	L1	$NaN(SiMe_3)_2$	23
7	L1	$LiN(SiMe_3)_2$	76
8[g]	L1	$LiN(SiMe_3)_2$	81 (79)[c]

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a**, and 1.5 equiv of **2a**. [b] Assay yield determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] $Ni(acac)_2$. [d] $NiCl_2$•gly. [e] $Ni(OAc)_2$. [f] $NiBr_2$. [g] 23 °C.

Table 2 Scope of aryl halides in α-arylation of 4-pyridylmethyl ethyl ether **1a**[a]

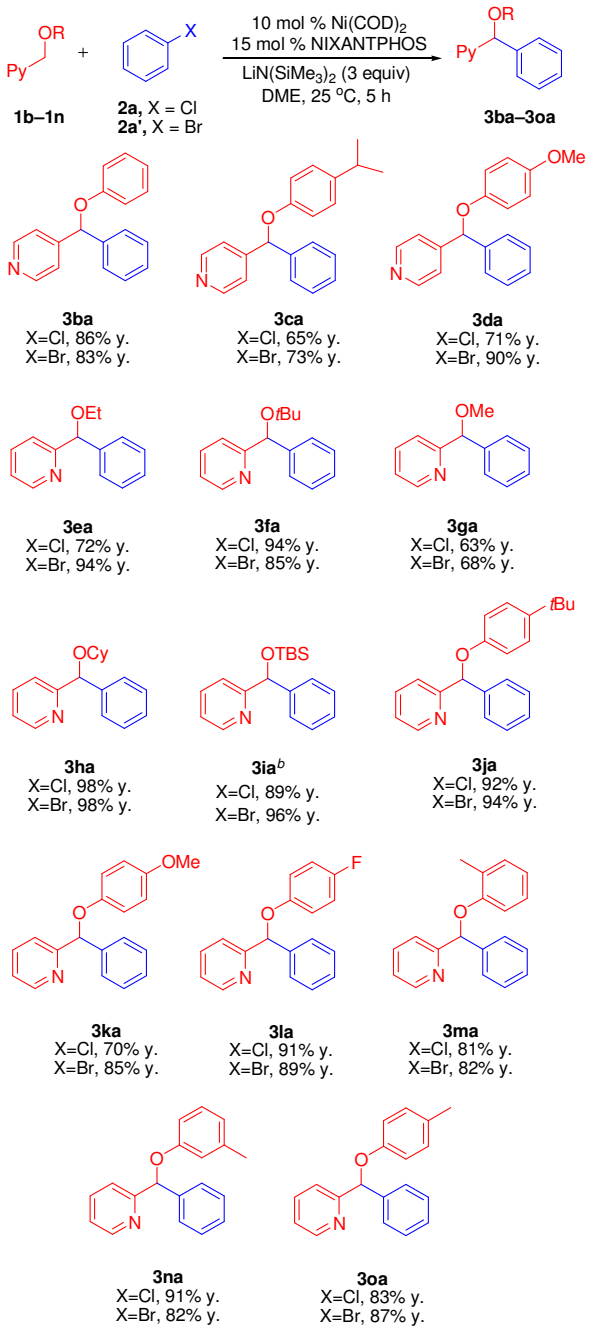


[a] Reactions conducted on 0.2 mmol scale using 1 equiv of **1a**, and 1.5 equiv of aryl halides **2**. Isolated yield after chromatographic purification.

was the best base for arylation using aryl bromide substratess using the Pd/NIXANTPHOS-based catalyst.[13]

Under our optimal conditions (Table 1, entry 8), an array of aryl halides were employed in the arylation of 4-pyridylmethyl ethyl ether **1a** (Table 2). Overall, aryl halides bearing electronically diverse substituents at the *para*-, *meta*- and *ortho*-positions all coupled with **1a** in good to excellent yields (62–96%). Product **3aa** was obtained in 79 and 85% yield with chlorobenzene **2a** and bromobenzene **2a'** as coupling partners, respectively. Aryl halides bearing electron-donating groups 4-OMe resulted in products **3ab** in 81 (X = Cl) and 90% (X = Br) yield while the aryl bromide **2c'** possessing 4-NMe_2 provided **3ac** in 94% yield. Coupling between **1a** and 4-fluoro substituted aryl halides afforded product **3ad** in 78 (X = Cl) and 63% (X = Br) yields. Sterically hindered 2-chlorotoluene **2e** and 2-bromotoluene **2e'** coupled with **1a** to give **3ae** in 72 and 95% yields, respectively. 3-Bromoanisole (**2f'**) coupled with **1a** to give **3af** in 82% yield. Additionally, **1a** readily coupled with

Table 3 Scope of pyridylmethyl ethers in α-arylation with aryl halides **2a** and **2a'**[a]



[a] Reactions conducted on a 0.2 mmol scale using 1 equiv of pyridylmethyl ethers **1**, and 1.5 equiv. of halobenzene **2**. Isolated yield after chromatographic purification. [b] 65 °C reaction temperature, 12 h reaction time.

heterocyclic aryl halides 5-bromobenzofuran **2g'** (71% yield), *N*-methyl-5-bromoindole **2h'** (84% yield), 5-bromobenzothiophene **2i'** (75% yield) and 5-chlorobenzothiophene **2i** (74% yield). 2-Chloronaphthalene **2j** and 2-bromonaphthalene **2j'** coupled with **1a** in 83 and 62%

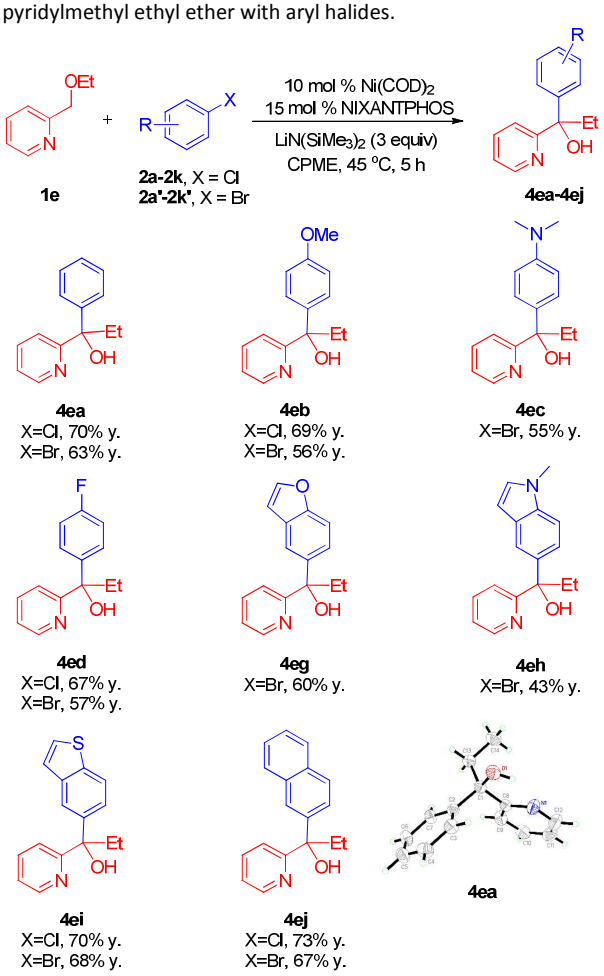
yields, respectively. Finally, 1-chloro-4-vinylbenzene **2k** and 1-bromo-4-vinylbenzene **2k'** successfully coupled with **1a** affording product **3ak** in 76 and 82% yields. This latter reaction occurred with high chemoselectivity–no Heck-type arylation products were observed.

The scope of 4- and 2-pyridylmethyl ethers, with different O–R substituents, was examined in the direct arylation with chlorobenzene (**2a**) and bromobenzene (**2a'**) (Table 3). 4-Pyridylmethyl aryl ethers **1b** (R=Ph), **1c** (R=4-C_6H_4-*i*Pr) and **1d** (4-C_6H_4-OMe) coupled with chlorobenzene **2a** in 86, 65 and 71% yields, respectively. Similar yields were observed with bromobenzene **2a'** (73–90%). As for 2-pyridylmethyl alkyl ethers [R = ethyl (**1e**), *t*-butyl (**1f**), methyl (**1g**), cyclohexyl (**1h**)] and *tert*-butyldimethylsilyl ethers (**1i**) were coupled with **2a** in 72, 94, 63, 98 and 89% yield, respectively. When bromobenzene (**2a'**) was used with these 2-pyridylmethyl ethers, products **3ea**, **3fa**, **3ga**, **3ha** and **3ia** were formed in 94, 85, 68, 98 and 96% yields, respectively. We also studied a series of 2-pyridylmethyl aryl ethers in their coupling with chloro- and bromobenzene. Aryl groups included 4-*t*Bu (**1j**), 4-OMe (**1k**), 4-F (**1l**) as well as 2-Me (**1m**), 3-Me (**1n**), and 4-Me (**1o**). Coupling of **1j**, **1k**, **1l**, **1m**, **1n**, **1o** with chlorobenzene **2a** afforded products in 92, 70, 91, 81, 91 and 83% yields, respectively. When bromobenzene **2a'** was used, products **3ja**–**3oa** were obtained in 82–94% yields.

Next, we studied the tandem arylation/[1,2]-Wittig rearrangement. According to our previous results, the [1,2]-Wittig rearrangement occurred in the absence of metal catalysts and could be controlled by base, solvent and reaction temperature.[13] Hence, we selected 2-pyridylmethyl ethyl ether (**1e**) and chlorobenzene (**2a**) as coupling partners and studied the base $MN(SiMe_3)_2$ (M = Li, Na, K), solvent (CPME, DME, toluene, THF) and temperature (65, 45 and 23 °C, see supplementary Table S2 for full reaction optimization). We were delighted to find that a combination of $LiN(SiMe_3)_2$, CPME and 45 °C afforded arylation/[1,2]-Wittig rearrangement product **4ea** in 70% isolated yield as shown in Table 4. Moreover, compound **4ea** was characterized by X-ray crystallography, confirming its structure (CCDC 1569085).[16] Under these reaction conditions, only tandem arylation/[1,2]-Wittig rearrangement was observed with no remaining ether intermediates (determined by analysis of TLC and/or ^{1}H NMR of the unpurified reaction mixtures).

Under the optimal conditions, a variety of aryl halides underwent the tandem arylation/rearrangement with 2-pyridylmethyl ethyl ether (**1e**). Beginning with electron rich 4-chloro- and 4-bromoanisole, aryl(2-pyridyl)methanol product **4eb** was obtained in 69 and 56% yield, respectively. Similarly, 4-bromo-*N*,*N*-dimethylaniline **2c'** and 1-bromo-4-fluorobenzene **2d'** coupled with 2-pyridylmethyl ethyl ether (**1e**) in 55 (**4ac**) and 57% (**4ad**) yield, respectively. The yield of **4ad** increased to 67% when 1-chloro-4-fluorobenzene **2d** was employed. Heterocyclic aryl halides were also good substrates under the arylation/rearrangement conditions, affording 5-bromobenzofuran, *N*-methyl-5-bromoindole, and 5-bromo-

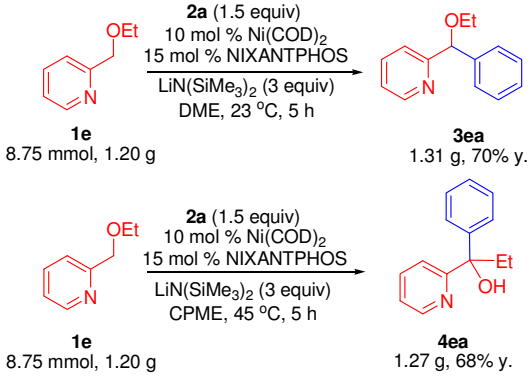
Table 4 Tandem arylation/[1,2]-Wittig rearrangement of 2-pyridylmethyl ethyl ether with aryl halides.



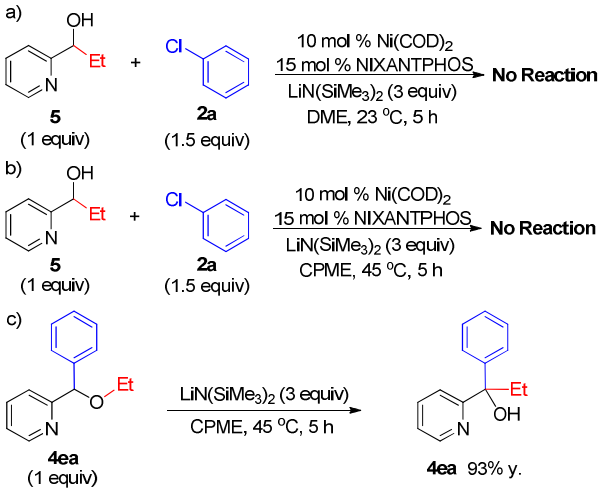
[a] Reactions conducted on 0.2 mmol scale using 1 equiv of **1e**, and 1.5 equiv of aryl halides **2**. Isolated yield after chromatographic purification.

benzothiophene products **4eg**, **4eh**, **4ei** in 60 (X = Br), 43 (X = Br) and 68% (X = Br, 70% yield when X = Cl) yield, respectively. 2-Naphthyl halides (X = Cl, Br) furnished product **4ej** in 73 and 67% yields, respectively.

To investigate the scalability of our method, we conducted the coupling of 2-pyridylmethyl ethyl ether (**1e**) and with chlorobenzene (**2a**) on gram scale under the optimal conditions of the direct arylation and the arylation/rearrangement (Scheme 2). The desired products **3ea** and **4ea** were isolated in 1.31 g (70% yield) and 1.27 g (68% yield), respectively.



Scheme 2 Gram scale synthesis.



Scheme 3 Probing the order of the tandem arylation/[1,2]-Wittig rearrangement.

We next probed the order of the arylation and rearrangements steps with the Ni-catalyst. Under optimal conditions for both the arylation and the arylation/rearrangement, no coupling product was observed between 1-(pyridin-2-yl)propan-1-ol **5** and chlorobenzene **2a** (Scheme 3a-b). In contrast, in the absence of the Ni-NIXANTPHOS catalyst, ether **4ea** underwent [1,2]-Wittig rearrangement upon exposure to $LiN(SiMe_3)_2$ in 93% yield (Scheme 3c). These results are consistent with 1) arylation occurring before the [1,2]-Wittig rearrangement and 2) no catalyst is required for the rearrangement.

Conclusions

In this paper, we successfully employed an earth abundant nickel catalyst based on NIXANTPHOS in the synthesis of aryl(2-pyridyl)methanol derivatives. The chemoselective direct arylation and tandem arylation/[1,2]-Wittig rearrangement of pyridyl methyl ethers can be effectively controlled by variation of the reaction conditions. A wide variety of aryl halides were tolerated under the reaction conditions. Gram scale reactions were also used to demonstrate the scalability. We anticipate that this approach broadens the utility and scope of the pyridyl methyl ether arylation developed by our team.

Experimental

General Methods

All air- and moisture-sensitive solutions and chemicals were handled under nitrogen or in a nitrogen filled glovebox and solutions were transferred via syringe. Anhydrous CPME (cyclopentyl methyl ether), DME (dimethoxyethane), toluene and THF (tetrahydrofuran) were purchased from Sigma-Aldrich and used without further purification. Unless otherwise stated, all reagents were commercially available and used as received without further purification. Chemicals were obtained from Sigma-Aldrich, Acros, TCI and Alfa-Aesar. TLC was performed with Merck TLC Silica gel 60 F254 plates with detection under UV light at 254 nm. Silica gel (200-300 mesh, Qingdao) was used for flash chromatography. Proton nuclear magnetic resonance (1H-NMR) spectra were recorded on a Bruker DRX 400 spectrometer at 400 MHz. Carbon-13 nuclear magnetic resonance (13C-NMR) was recorded on Bruker DRX 400 spectrometer at 100 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 100 Series FTIR spectrometer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte.

General procedure for the Ni-catalyzed chemoselective α-arylation of pyridylmethyl ethers

An oven-dried 8 mL reaction vial equipped with a stir bar was charged with pyridylmethyl ether **1a** (0.2 mmol, 1.0 equiv), chlorobenzene **2a** (0.3 mmol, 1.5 equiv) in a glove box under a nitrogen atmosphere at room temperature. A solution (from a stock solution) of $Ni(COD)_2$ (5.5 mg, 0.02 mmol, 10 mol %) and NIXANTPHOS (16.6 mg, 0.03 mmol, 15 mol %) in 1 mL of dry DME was taken up by syringe and added to the reaction vial. A solution of $LiN(SiMe_3)_2$ (100.4 mg, 0.6 mmol, 3.0 equiv) in 1 mL of dry DME was added by syringe to the reaction mixture. Total volume of the reaction is 2 mL. The vial was capped, removed from the glove box, and stirred for 5 h in total at 25 °C. The reaction mixture was quenched with 3 drops of H_2O, diluted with 2 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with an additional 6 mL of ethyl acetate (3 x 2 mL) and the solution was concentrated in vacuo. The crude material was loaded onto a silica gel column and purified by flash chromatography.

General procedure for the Ni-catalyzed chemoselective tandem arylation/[1,2]-Wittig rearrangement reaction of 2-pyridylmethyl ethers

An oven-dried 8 mL reaction vial equipped with a stir bar was charged with 2-pyridylmethyl ethyl ether **1e** (0.20 mmol, 1.0

equiv) and chlorobenzene **2a** (0.3 mmol, 1.5 equiv) in a glove box under a nitrogen atmosphere at room temperature. A solution (from a stock solution) of $Ni(COD)_2$ (5.5 mg, 0.02 mmol, 10 mol %) and NIXANTPHOS (16.6 mg, 0.03 mmol, 15 mol %) in 1 mL of dry CPME was taken up by syringe and added to the reaction vial. A solution of $LiN(SiMe_3)_2$ (100.4 mg, 0.6 mmol, 3.0 equiv) in 1 mL of dry CPME was added by syringe to the reaction mixture. Total volume of the reaction is 2 mL. The vial was capped, removed from the glove box, and stirred for 5 h in total at 45 °C. The reaction mixture was quenched with 3 drops of H_2O, diluted with 2 mL of ethyl acetate, and filtered over a pad of $MgSO_4$ and silica. The pad was rinsed with an additional 6 mL of ethyl acetate (3 x 2 mL) and the solution was concentrated in vacuo. The crude material was loaded onto a deactivated silica gel column and purified by flash chromatography.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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16 CCDC 1569085 contains the supplementary crystallographic data for compound **4ea**. The data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.