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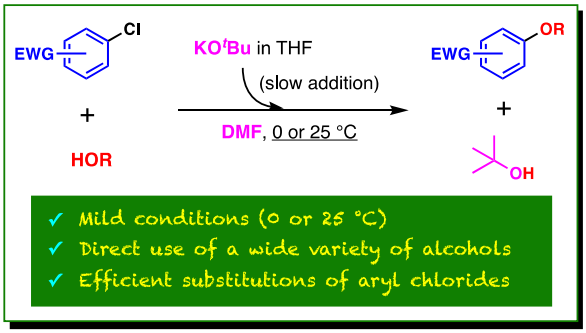
Aryl ether syntheses via aromatic substitution proceeding under mild conditions

Shin Ando,* Marina Tsuzaki, and Tadao Ishizuka*

Faculty of Life Sciences, Kumamoto University, 5-1 Oe-honmachi Chuo-ku, Kumamoto 862-0973, Japan

ando@gpo.kumamoto-u.ac.jp (S.A), tstone@gpo.kumamoto-u.ac.jp (T.I.)



Abstract

In this study, mild conditions for aromatic substitutions during the syntheses of aryl ethers were developed. In the reaction conditions, the choices of solvent, base, and the sequence for the addition of the reagents proved important. A wide variety of alcohols were used directly as nucleophiles and smoothly reacted with aryl chlorides that possessed either a nitro or a cyano group at either the *o*- or *p*-position. Controlled experiments we performed suggested that the reaction underwent a charge transfer process mediated by a combination of DMF and *tert*-BuOK.

Introduction

Aryl ether is one of the most fundamental functional groups and is ubiquitous in biologically active compounds such as pharmaceuticals and agrochemicals. Therefore, chemical transformations to reconstruct this functionality are continuously studied, and many effective methodologies have been reported to date. The transition metal catalyzed cross-coupling reactions between alcohols and aryl halides are representative and powerful methodologies. This type of transformation is widely used and includes a copper mediated/catalyzed reaction that is widely known as Ullman-type coupling[1] and a palladium-catalyzed version that is referred to as Buchwald-Hartwig type coupling.[2] Under these metal-catalyzed processes, the reactivity trends usually depend on a leaving group of aryl halides, I > Br > Cl > F, and aryl bromides are the most commonly used. These catalytic processes are applicable to a wide variety of substrates, but the requirement of a metal catalyst, which is often expensive and toxic, is a drawback. For an alternative to these metal-catalyzed processes, aromatic nucleophilic substitution reactions such as S_NAr are used for the aryl ether syntheses from aryl halides (Figure 1).[3] Under these traditional catalyst-free reaction conditions, an inverted order of reactivities, compared with the metal-catalyzed reactions, is usually observed depending on the order of the leaving groups: F > Cl >

Br > I. Although some relevant studies in this decade have introduced the possibility of other concerted mechanisms among the reactions that occur in this class,[4] the S_NAr has commonly been recognized as the reaction that will form "Meisenheimer complexes".[5] This reaction is useful in the synthesis of aryl ethers from aryl fluorides or chlorides, but heating under high temperature in the presence of either sodium or potassium alkoxide, which serves as both a nucleophile and a strong base, is a typical reaction condition. In addition to these harsh conditions, a necessity for the electronic activation of aryl halides with EWGs such as nitro, cyano, and acyl groups is a general limitation. In particular, for the S_NAr reactions of aryl chlorides, only highly activated aryl substrates with plural EWGs are applicable. Here, we report the development of aromatic substitutions for aryl ether syntheses, which can be performed either at 0 or 25 °C. Under the conditions we developed, aryl chlorides activated by a nitro or a cyano group can be coupled with a wide variety of alcohols.

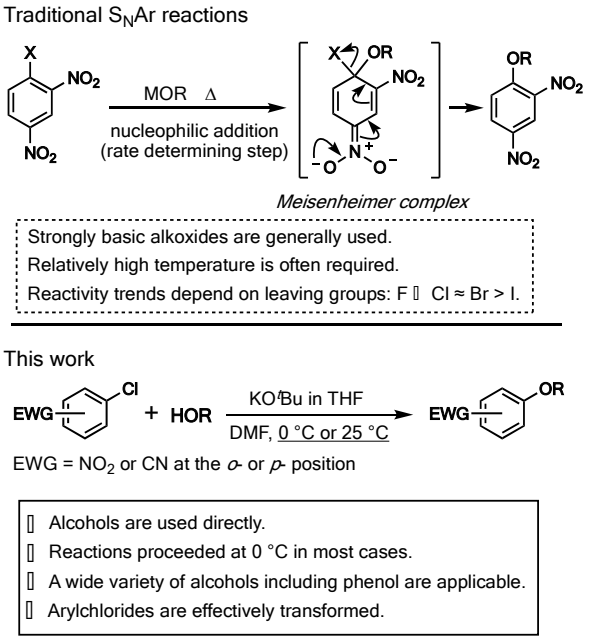
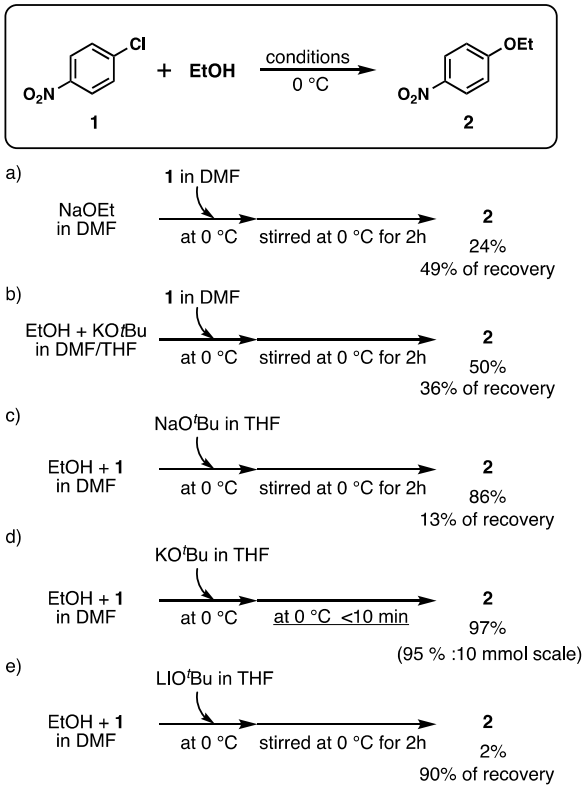


Figure 1. Representative features of traditional S_NAr reactions and the reaction reported in this study.

Results and Discussion

During the course of our study to develop a mild and useful method for the syntheses of aryl ethers, we serendipitously found that the sequence used for the addition of reagents drastically changed the reactivities (Scheme 1). In the first trial, the ethoxylation of 1-chloro-4-nitrobenzene **1** with the use of sodium ethoxide in DMF was attempted at 0 °C, and 1-ethoxy-4-nitrobenzene **2** was isolated in a 24% yield after 2h with a 49% recovery of starting material **1** (Scheme 1a).[6] When we mixed *tert*-BuOK with ethanol to form KOEt *in situ* prior to an addition of 1-chloro-4-nitrobenzene **1**, we isolated1-ethoxy-4-nitrobenzene **2** in a 50% yield with a 36% recovery (Scheme 1b). In contrast to

these results, a dropwise addition of *tert*-BuONa solution in THF over 5 min to a solution of 1-chloro-4-nitrobenzene **1** and EtOH in DMF resulted in a much higher yield of 1-ethoxy-4-nitrobenzene **2** (Scheme 1c; 86% yield with 13% recovery). As we added *tert*-BuOK instead of *tert*-BuONa, a complete conversion was observed in 10 min and 1-ethoxy-4-nitrobenzene **2** was isolated in a 97% yield (Scheme 1d), whereas the use of *tert*-BuOLi resulted in a poor yield (Scheme 1e). When etherification with *tert*-BuOK was attempted on a 10 mmol scale, 1.60 g of 1-ethoxy-4-nitrobenzene **2** was obtained (95%). Based on these preliminary results, we decided to investigate these unique phenomena more carefully to gain insight into the nature of this transformation.

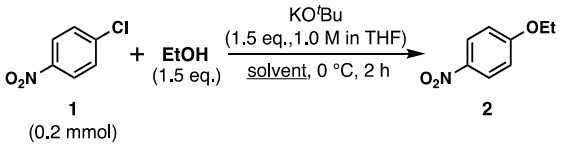


Scheme 1. Drastic change in reactivity during an ethoxylation of 1-chloro-4-nitrobenzene **1**

Results from the experiments to test the effects of reaction solvents are summarized in Table 1. With the use of a commercially available *tert*-BuOK solution in THF as a base, we screened aprotic polar solvents because of the polar characteristics of the reaction (entries 1 to 6). In addition to DMF, DMAc (entry 3), DMPU (entry 4), and DMSO (entry 6) were found to be usable solvents; DMF and DMSO were particularly effective and converted 1-chloro-4-nitrobenzene **1** completely. The reaction in DMSO included some intractable side products and the yield of the substituted product **2** (74%) was somewhat lower than in DMF. The use of ethanol as a solvent, which also serves as a nucleophile, was

fruitless (entry 7), and the reaction in THF gave us only a trace amount (<5%) of 1-ethoxy-4-nitrobenzene **2** (entry 8). The ratio of DMF to THF also affected the reactivity (entries 1, 9, and 10), and the reactivity was lowered when we used less than 50 v/v% of DMF as a solvent. Based on the results of these experiments, we selected DMF as a solvent for further investigations.

Table 1. Effects of reaction solvents



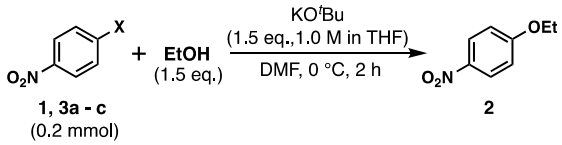
entry	solvent	yield (%)	recovery of **1** (%)
1	DMF/THF (1.0 mL/0.3 mL)	97[a]	0
2	DMI/THF (1.0 mL/0.3 mL)	0	76
3	DMAc/THF (1.0 mL/0.3 mL)	33	53
4	DMPU/THF (1.0 mL/0.3 mL)	19	34
5	NMP/THF (1.0 mL/0.3 mL)	0	53
6	DMSO/THF (1.0 mL/0.3 mL)	74	0
7	EtOH/THF (1.0 mL/0.3 mL)	0	77
8	THF (1.3 mL)	trace	88
9	DMF/THF (0.65 mL/0.65 mL)	86	11
10	DMF/THF (0.25 mL/0.75 mL)	41	59

[a] Data from Scheme 1d.

We next tested a form of reactivity that depended on a leaving group of 4-nitrohalobenzenes (Table 2), and a trend in reactivity that was the same as that of the general S_NAr reaction. Although the

reactivities of 1-bromo-4-nitrobenzene **3b** and 1-iodo-4-nitrobenzene **3c** under these mild conditions were somewhat higher than our expectations based on literature searches, some undesired side products were observed during the reaction using these substrates. These results indicated that the rate-determining step would not be a cleavage of the C–X bond.

Table 2. Effects of leaving groups



1, 3a - c (0.2 mmol) **2**

entry	substrate	yield (%)	recovery of S.M. (%)
1	**3a** (X = F)	quant.	0
2	**1** (X = Cl)	97[a]	0
3	**3b** (X = Br)	68	16
4	**3c** (X = I)	42	26

[a] Data from Scheme 1d.

To investigate the scope of the aromatic components, chlorobenzene derivatives with an EWG at the *p*- or *o*- position and some *N*-heterocycles were applied to the ethoxylation conditions we found (Figure 2). Regardless of the requirement of the reaction at 25 °C in the case of cyano-substituted chlorobenzene, nitro- and cyano-substituted aryl chlorides were effectively ethoxylated (**4a** – **4c**). A trifluoromethyl group at the ortho position was ineffective for activating the aryl chlorides. Acyl groups

such as benzoyl and pivaloyl showed less reactivity and resulted in the recovery of large amount of the starting materials (**4e** and **4f**), but the reaction of benzophenone with a fluoride leaving group at 0 °C resulted in an excellent yield. It should be emphasized that two similar *N*-heterocycles, pyridine and quinoline, showed contrasting results. Although the alkoxylation of 2-chloropyridine is aptly known to be a practical reaction under the typical S_NAr conditions, ethoxylation under the presented method at 25 °C gave no pyridyl ether (**4g**). On the other hand, ethoxylation at the 2- or 4- position of quinoline smoothly proceeded at 0 °C and produced ethyl ethers in excellent yields (**4h** and **4i**). An important intermediate to a bidentate ligand, 4,7-dichloro-1,10-phenanthroline, was applicable to access a novel diethoxy derivative **4j** in a quantitative yield.

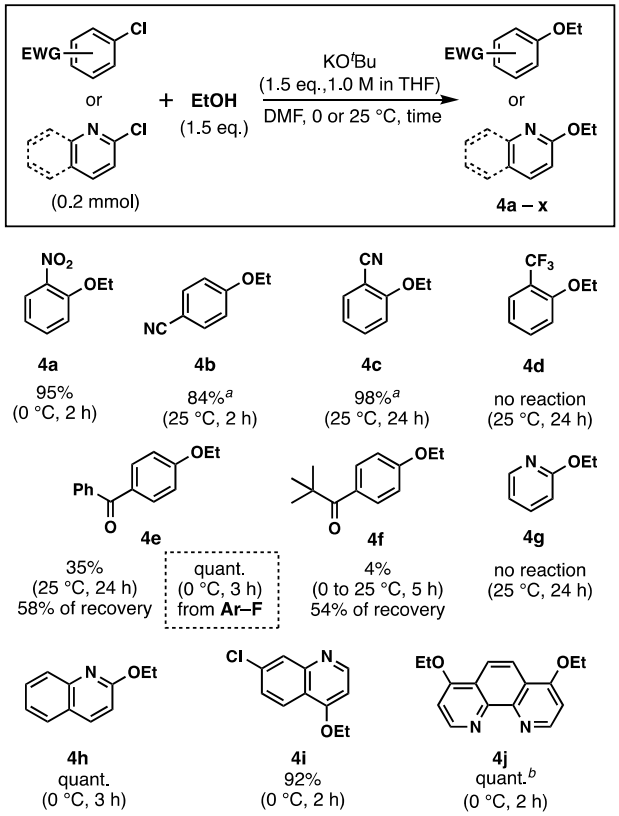


Figure 2. Ethoxylation of aryl chlorides; [a] 2.0 eq. of EtOH and 2.0 eq. of KO^{t}Bu were used. [b] 3.0 eq. of EtOH and 3.0 eq. of KO^{t}Bu were used.

We then tested the scope of an alcoholic nucleophile for this transformation (Figure 3). For an aromatic substrate, 1-chloro-4-nitrobenzene **1** was tested first (**5a**–**t**). Primary alcohols such as methanol, *n*-butanol, and allyl alcohols smoothly reacted and gave the corresponding ethers in excellent yields (**5a**–**d**). The reaction with isopropanol, a secondary alcohol, required warming to 25 °C and resulted in a slightly decreased yield (**5e**; 76%). Benzyl and *p*-methoxybenzyl protected ethers were

obtained in good yields (**5f**; 80% and **5g**; quantitative yield), and a cyclopropane ring was installed with no problem (**5h**; 95%). Regardless of the requirement of a longer reaction time at 25 °C, diaryl ether (**5i**) was also accessible in an efficient manner (86%). At 25 °C, 2,2,2-trifluoroethanol gave us trifluoroethyl ether **5j** in good yield, whereas heptafluorobutanol was only mildly reactive (**5k**, 29% after stirring for 24 h at 25 °C). Linear alkyl structures with unsaturated bond(s) were also applicable, and geraniol and (-)-β-citronellol showed good reactivity at 0 °C (**5l** in 84% and **5m** in 86%, respectively). Some secondary alcohols with chiral centers were used for etherification. (-)-Menthol and diacetone-D-glucose were highly reactive under the presented conditions at 0 °C (**5n** in 83% and **5o** in 90%, respectively), but cholesterol diminished the reactivity and resulted in a decreased yield (**5p** in a 65% yield). In some cases, we noticed that nitrophenol **7** was generated as a side product. During a session of *tert*-butoxylation, nitrophenol was obtained as a major product (35% yield) with *tert*-butylether **5q** (23%) and 1-chloro-4-nitrobenzene was recovered (30%). The reaction with homoallyl alcohols such as 3-buten-1-ol and *cis*-3-hexen-1-ol gave nitrophenol **7** and yields of coupled ethers **5r** and **5s** were moderate (54% and 65%, respectively), which was also the case for the reaction with 2-butyn-1-ol (**5t** in 37% with 33% of nitrophenol **7**). The isolated homoallyl ether **5s** was treated

under the reaction conditions to examine pathways leading to nitrophenol, and we isolated nitrophenol **7** in a 69% yield (Scheme 2a). The use of H_2O instead of alcohols would not produce nitrophenol **7** at all, however, which suggested that the cleavages of the alkyl groups to generate nitrophenol **7** occurred after the substitution reactions. We then found that the etherification of 4-chlorobenzonitrile was amenable to reaction with secondary alcohols and 2,2,2-trifluoroethanol to afford the ethers in moderate to good yields (**6a**, **6c**–**f**) at 25 °C. Unfortunately, a diaryl ether **6b** was not formed via the reaction with phenol at 25 °C. Additionally, a chiral secondary alcohol at the benzylic position was reacted with 1-chloro-4-nitrobenzene to examine the possibility of racemization, and this resulted in a good yield with a complete retention of the chirality (Scheme 2b). To demonstrate the arylation of an alcohol, we reacted 0.2 mmol of (-)-menthol **10** with 1.5 eq. of 1-chloro-4-nitrobenzene **1**via the slow addition of 1.5 eq. of *tert*-BuOK solution in THF at 0 °C (Scheme 2c). The coupled product **5n** was obtained in a quantitative yield based on (-)-menthol, which indicated that the presented conditions could be useful for the arylations of alcohols.

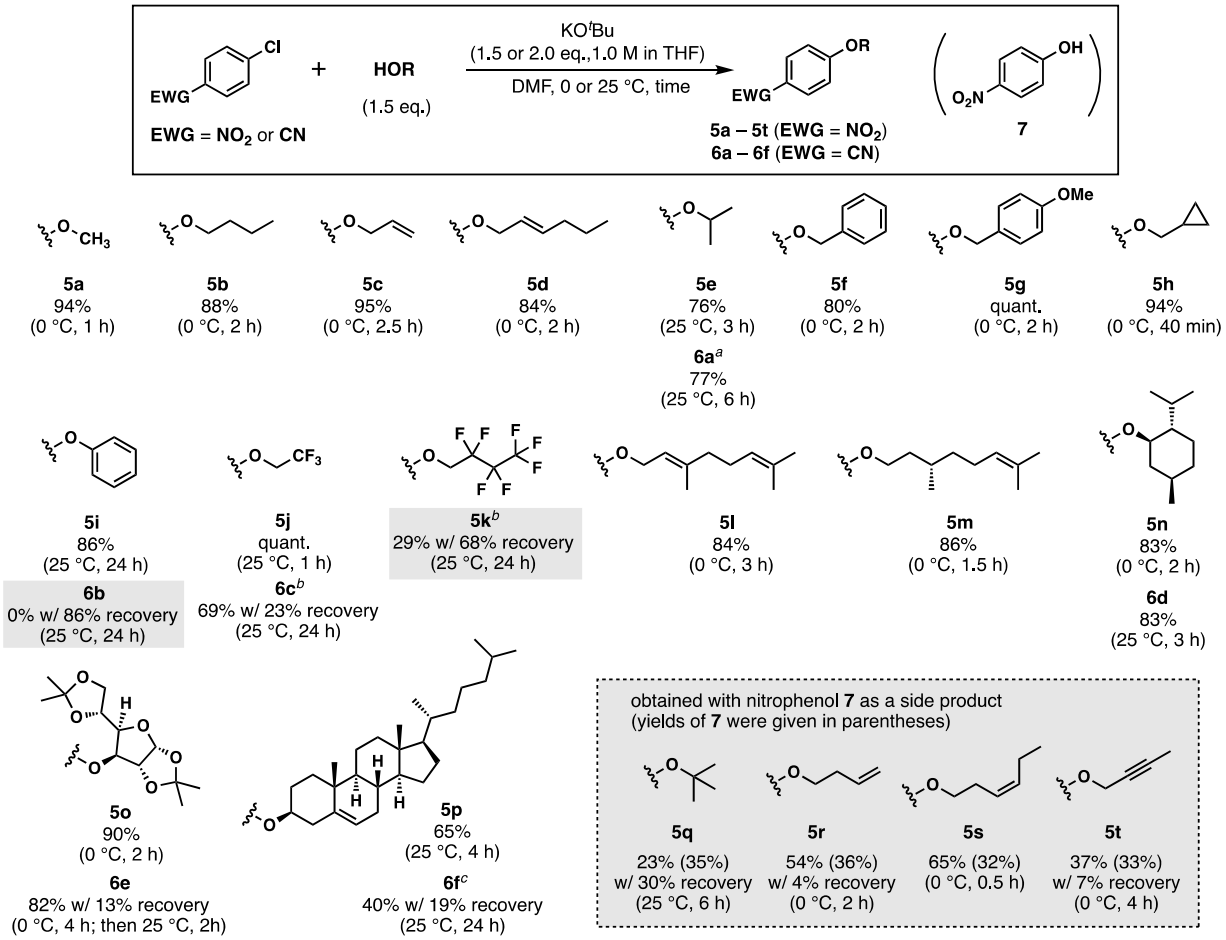
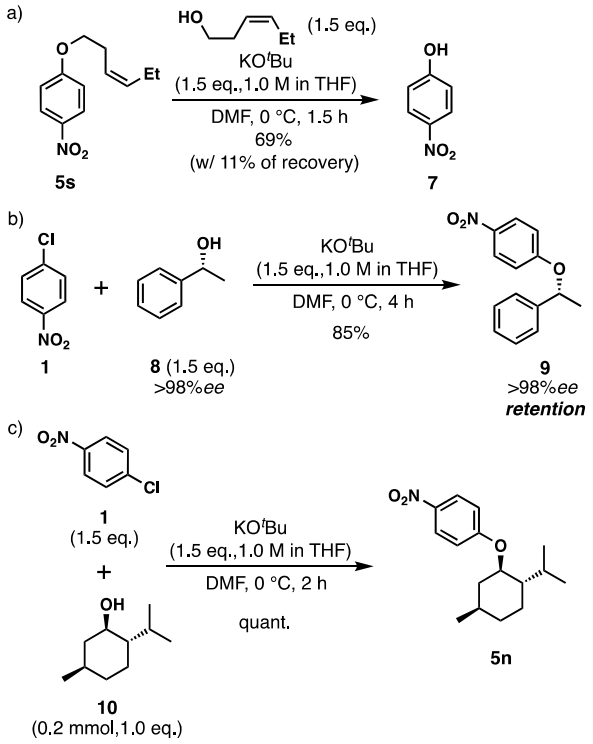


Figure 3. The aromatic substitution with varied alcoholic nucleophiles. [a]3.0 eq. of alcohol was used. [b]2.0 eq. of alcohol was used. [c]Twice the amount of DMF was used.

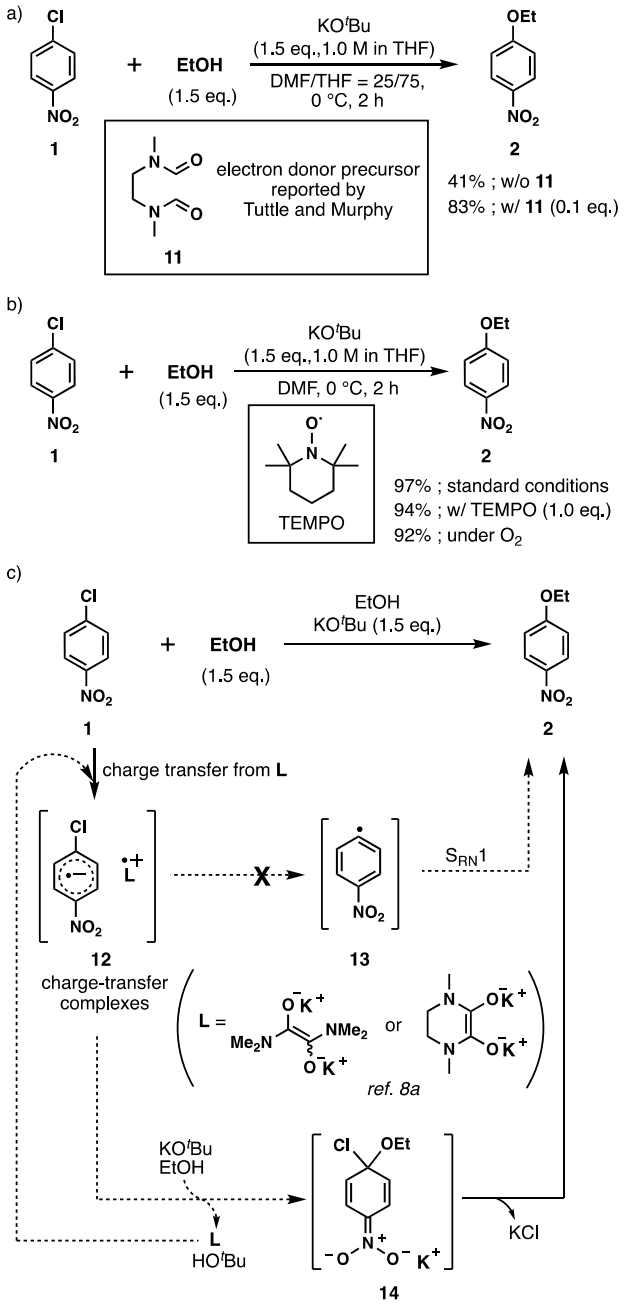


Scheme 2. a) Cleavage of a homoallyl group under the presented conditions. b) An aromatic substitution with a chiral secondary alcohol at a benzylic position. c) An arylation of (-)-menthol with the use of an excess amount of 1-chloro-4-nitrobenzene **1**.

Since the high reactivity under the presented conditions deviated from the typical reactivity of the S_NAr reaction, we decided to conduct some controlled experiments (Scheme 3a and 3b). Under the presented conditions, some reactions seemed to deviate from the typical reactivity of the S_NAr reaction: 1) low reaction temperature, 2) inferior yields using premixed ethanol and KO^{t}Bu (see Scheme 1b), 3) unsatisfactory reactivity toward acylated aryl chlorides, and, 4) extreme differences in

the reactivities between 2-chloropyridine and 2-chloroquinoline. Based on these observations, the reagents we used, and discussions found in the literature concerning the mechanisms of S_NAr reactions,[7] we hypothesized that the substitutions under the presented conditions would include a charge transfer process via a combination of DMF and KO^{t}Bu.[8] To test this hypothesis, we added compound **11**, which had been reported as an electron donor precursor by Tuttle and Murphy,[8a,9] to the conditions shown in entry 10 of Table 1. In contrast to the moderate yield without **11**, the yield was significantly increased in the presence of 10 mol% of compound **11** (83%, Scheme 3a), which supports the involvement of a charge transfer process. We then performed the reaction in the presence of 1.0 eq. of TEMPO as a radical scavenger (Scheme 3b), but the yield of the product was unaffected. The reaction under an oxygen atmosphere was also attempted, but the yield was the same level as that under an argon atmosphere. Although dissociation of C–X bond after the formation of "charge-transfer complex" **12** would generate an aryl radical **13**, based on the above observations, the $S_{RN}1$ pathway[10] seemed unreasonable (Scheme 3c). A trend wherein reactivity depended on the halogen leaving groups (see Table 2) would also support this explanation.[11] With respect to the inferior yield when using premixed ethanol and KO^{t}Bu (Scheme 1b), the premixing would have generated potassium ethoxide

and *tert*-butanol *in situ*, which would result in an inefficient SET process. In a similar manner, when the reaction was performed using a larger amount of an alcohol than *tert*-BuOK, it would not proceed, which was likely due to changes in the equilibrium between alcohols and *tert*-BuOK. Single-electron captures by the carbonyl moieties of acylated aryl chlorides **4e** and **4f** would have caused the low yields. Since the reduction potential of pyridine is lower than that of quinoline,[12] the SET to 2-chloropyridine was expected to be less effective than that to 2-chloroquinoline, which caused the significant difference in their reactivities. Ultimately, we became convinced that the charge-transfer complex **12** generated by a combination of DMF and KO^{t}Bu played a key role in the formation of the Meisenheimer complex **14** at low temperature,[7a,13] although more detailed mechanistic studies are required to understand the mechanisms of all processes. During the formation of the Meisenheimer complex **14**, the electron donors **L** would regenerate and could work as a catalyst.



Scheme 3. The reaction in the presence of a) compound **11** as an electron donor precursor and b) TEMPO or O_2 as a free radical scavenger. c) A possible reaction pathway.

Conclusion

In conclusion, we developed mild conditions for the etherification of aryl chlorides activated with either a nitro or a cyano group. The addition of a solution of KO^{t}Bu in THF into a solution of aryl chloride and an alcoholic nucleophile in DMF enabled ether formations with the use of a wide variety of alcohols that included chiral secondary alcohols. With this method, the pre-formation of either potassium or sodium alkoxide, which is generally highly exothermic, was not required, and the reaction proceeded at either 0 or 25 °C. Additionally, the use of a commercial solution of KO^{t}Bu in THF avoided the need to handle the hygroscopic and air- and moisture-sensitive KO^{t}Bu powder, which made the process more user-friendly.[14] Preliminary controlled experiments indicated that this ether formation involves a charge-transfer complex generated by a combination of DMF and KO^{t}Bu. Investigations are underway in our laboratory to further explain the mechanisms involved and to develop more useful aromatic substitution methods.

Experimental Section

General Information. CAUTION. Although we did not notice any exothermic phenomena, explosion hazards of strong base in DMSO or in DMF had been reported.[14] A safety evaluation must be conducted prior to a large scale synthesis. All reactions were carried out under an argon atmosphere with freshly distilled

solvents under anhydrous conditions, unless otherwise noted. Anhydrous DMSO and THF were purchased and used without further distillation. Ethanol and methanol were distilled from either sodium ethoxide or methoxide. Other reagents were used without further purification. Compound **11** was prepared according to the literature.[8a] Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded at 600 and 151 MHz, respectively. Chemical shifts are reported in δ ppm and reference either an internal tetramethylsilane or solvent peaks. The following abbreviations are used to indicate the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; qt = quintet; sex = sextet; sept = septet dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; dt = doublet of triplets; app = apparent; m = multiplet; br = broad. Melting points were uncorrected. High-resolution mass spectra were recorded on a double-focusing magnetic-sector mass analyzer operating in a fast atomic bombardment (FAB) mode.

Typical experimental procedures and data of ether compounds obtained in this study. A two-neck round-bottom flask was charged with an aryl/heteroaryl chloride (0.2 mmol) and a magnetic stir bar. The flask was evacuated and backfilled with argon (three times), and DMF (0.8 mL) was added using a syringe. An

alcohol in DMF (0.3 mmol in 0.2 mL) was added to the resultant flask, then the flask was cooled to 0 °C in an ice bath. 1.0 M *tert*-BuOK solution in THF (0.3 mL) was added dropwise over 5 min by a syringe with stirring at 0 °C. After stirring at 0 °C or 25 °C until TLC monitoring indicated the completion of the reaction, the reaction was quenched by an addition of sat. NH_4Cl aq. at 0 °C. The mixture was then transferred to a separatory funnel and extracted with Et_2O or CH_2Cl_2 (×3), and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by a column chromatography on silica gel (amino-functionalized silica gel was used for compound **4j**) to afford the desired product.

1-ethoxy-4-nitrobenzene (**2**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 32.3 mg (97%), 1.60 g (95% on a 10 mmol scale); State of the product: pale yellow solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S3) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S4) δ = 164.0, 141.4, 125.9, 114.4, 64.4, 14.5 ppm. Other spectroscopic properties were identical to those previously reported.

1-ethoxy-2-nitrobenzene (**4a**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 31.9 mg (95%); State of the product: yellow liquid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S5) δ = ^{1}H-NMR ($CDCl_3$)

7.81 (dd, *J* = 1.8, 7.8 Hz, 1H), 7.51 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.07 (dd, *J* = 1.2, 8.4 Hz, 1H), 7.01 (ddd, *J* = 1.2, 7.2, 7.8 Hz, 1H), 4.19 (q, *J*.=.6.6 Hz, 2H), 1.48 (t, *J* = 6.6 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S6) δ = 152.3, 140.2, 133.9, 125.5, 120.1, 114.5, 65.4, 14.5 ppm. Other spectroscopic properties were identical to those previously reported.

4-ethoxybenzonitrile (**4b**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 24.8 mg (84%); State of the product: colorless solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S7) δ = 7.58 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S8) δ = 162.3, 134.0, 119.3, 115.2, 103.7, 63.9, 14.5 ppm. Other spectroscopic properties were identical to those previously reported.

2-ethoxybenzonitrile (**4c**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 28.8 mg (98%); State of the product: colorless solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S9) δ = 7.56 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.51 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 6.99 (ddd, *J* = 0.6, 7.2, 7.2 Hz, 1H), 6.95 (dd, *J* = 0.6, 8.4 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S10) δ = 160.6, 134.2, 133.8, 120.5, 116.5, 112.2, 102.1, 64.6, 14.5 ppm. Other spectroscopic properties were identical to those previously reported.

(4-ethoxyphenyl)(phenyl)methanone (**4e**).[15] Eluent for column chromatography: 10–30% CH_2Cl_2/*n*-hexane; Yield: 44.9 mg (99% from Ar-F); State of the product: pale yellow oil; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S11) δ = 7.83 (d, *J* = 9.0 Hz, 2H), 7.76 (dd, *J* = 1.2, 8.4 Hz, 2H), 7.57 (dddd, *J* = 1.2, 1.2, 7.2, 7.2 Hz, 1H), 7.48 (dd, *J* = 7.2, 7.2 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S12) δ = 195.5, 162.6, 138.3, 132.5, 131.8, 129.9, 129.6, 128.1, 114.0, 63.7, 14.6 ppm. . Other spectroscopic properties were identical to those previously reported.

1-(4-ethoxyphenyl)-2,2-dimethylpropan-1-one (**4f**).[15] Eluent for column chromatography: 1–5% EtOAc/*n*-hexane; Yield: 1.6 mg (4%); State of the product: pale brown liquid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S13) δ = 7.85 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.38 (s, 9H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S14) δ = 206.2, 161.4, 130.9, 129.9, 113.7, 63.6, 43.8, 28.4, 14.7 ppm.. Other spectroscopic properties were identical to those previously reported.

2-ethoxyquinoline (**4h**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 34.8 mg (quant.); State of the product: pale yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S15) δ = 7.98 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.62 (ddd, *J* = 1.2, 7.2, 8.4 Hz, 1H), 7.37 (ddd, *J* =

1.2, 7.2, 8.4 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.55 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S16) δ = 162.1, 146.7, 138.5, 129.4, 127.4, 127.2, 125.0, 123.8, 113.3, 61.6, 14.6 ppm.. Other spectroscopic properties were identical to those previously reported.

7-chloro-4-ethoxyquinoline (**4i**).[15] Eluent for column chromatography: 10–30% EtOAc/*n*-hexane; Yield: 38.3 mg (92%); State of the product: colorless solid ; ^1H NMR (600 MHz, 300 K, DMSO-d_3, Figure S17) δ = 8.87 (d, J = 5.4 Hz, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H), 7.70 (dd, J = 1.8, 9.0 Hz, 1H), 7.17 (d, J = 5.4 Hz, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.60 (3H, t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S18) δ = 161.5, 152.5, 149.7, 135.6, 127.8, 126.3, 123.5, 119.9, 100.8, 64.3, 14.4 ppm.. Other spectroscopic properties were identical to those previously reported.

4,7-diethoxy-1,10-phenanthroline (**4j**). Eluent for column chromatography (amino functionalized silica gel): 1–3% MeOH/CH_2Cl_2; Yield: 53.7 mg (quant.); State of the product: colorless solid; mp 184–186 °C; ^1H NMR (600 MHz, 300 K, $CDCl_3$, Figure S19) δ = 8.97 (d, J = 5.2 Hz, 2H), 8.18 (s, 2H), 6.95 (d, J = 5.2 Hz, 2H), 4.31 (q, J = 7.0 Hz, 4H), 1.60 (t, J = 7.0 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S20) δ = 161.5, 151.0, 146.9, 120.9, 118.8, 103.2, 64.2, 14.4 ppm; HRMS(FAB+) *m/z* calcd for $C_{16}H_{16}O_2N_2$ $[M + H]^+$: 269.1290; found: 269.1306.

1-methoxy-4-nitrobenzene (**5a**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 28.8 mg (94%); State of the product: pale yellow solid ;^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S21) δ = 8.22 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S22) δ = 164.6, 141.6, 125.9, 114.0, 55.9 ppm.. Other spectroscopic properties were identical to those previously reported.

1-butoxy-4-nitrobenzene (**5b**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 34.3 mg (88%); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S23) δ = 8.20 (d, *J* = 9.2 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 4.06 (t, *J* = 6.5 Hz, 2H), 1.82 (tt, *J* = 6.5, 7.2 Hz, 2H), 1.52 (tq, *J* = 7.2, 7.2 Hz, 2H), 1.00 (t, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S24) δ = 164.2, 141.3, 125.9, 114.4, 68.6, 31.0, 19.1, 13.7 ppm.. Other spectroscopic properties were identical to those previously reported.

1-(prop-2-enoxy)-4-nitrobenzene (**5c**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 34.9 mg (95%); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S25) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.05 (tdd, *J* = 5.3, 10.2, 17.4 Hz, 1H), 5.44 (tdd, *J* = 1.2, 1.2, 17.4 Hz, 1H), 5.36 (tdd, *J* = 1.2, 1.2, 10.2 Hz, 1H), 4.64 (ddd, *J* = 1.2, 1.2, 5.4 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S26) δ = 163.6, 141.6, 131.9, 125.9, 118.6, 114.7, 69.4 ppm.. Other spectroscopic

properties were identical to those previously reported.

(*E*)-1-(hex-2-enoxy)-4-nitrobenzene (**5d**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 37.7 mg (84%); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S27) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.88 (dt, *J* = 7.2, 15.6 Hz, 1H), 5.69 (ttd, J=1.2, 6.0, 15.6 Hz, 1H), 4.58 (d, *J* = 6.0 Hz, 2H), 2.10 (td, *J* = 7.2, 7.2 Hz, 2H), 1.45 (tq, *J* = 7.2, 7.2 Hz, 2H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S28) δ = 163.8, 141.4, 136.7, 125.8, 123.6, 114.7, 69.5, 34.3, 22.0, 13.6 ppm.. Other spectroscopic properties were identical to those previously reported.

1-(1-methylethoxy)-4-nitrobenzene (**5e**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 27.7 mg (76%); State of the product: yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S29) δ = 8.19 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.67 (sep, *J* = 6.0 Hz, 1H), 1.39 (d, *J* = 6.0 Hz, 6H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S30) δ = 163.2, 141.0, 125.9, 115.2, 70.9, 21.7 ppm. Other spectroscopic properties were identical to those previously reported.

1-benzyloxy-4-nitrobenzene (**5f**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 36.5 mg (80%); State of the product: pale yellow solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S31) δ = 8.22 (d, *J* = 9.0 Hz, 2H), 7.46–7.40 (m, 4H), 7.39–7.37 (m, 1H), 7.04 (2H, d, *J* = 9.0 Hz, 2H), 5.18 (s, 2H) ppm; ^{13}C{^{1}H}

NMR(151 MHz, 300 K, $CDCl_3$, Figure S32) δ = 163.7, 141.7, 135.5, 128.8, 128.5, 127.5, 125.9, 114.9, 70.7 ppm. Other spectroscopic properties were identical to those previously reported.

1-methoxy-4-(4-nitrophenoxymethyl)benzene (**5g**).[15] Eluent for column chromatography: 5–10% EtOAc/*n*-hexane; Yield: 51.9 mg (quant.); State of the product: yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S33) δ = 8.21 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.10 (s, 2H), 3.84 (s, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S34) δ = 163.8, 159.9, 141.6, 129.3, 127.5, 125.9, 114.8, 114.2, 70.5, 55.3 ppm. Other spectroscopic properties were identical to those previously reported.

1-{(cyclopropyl)methoxy}-4-nitrobenzene (**5h**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 36.2 mg (94%); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S35) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 3.91 (d, *J* = 7.2 Hz, 2H), 1.34-1.27 (m, 1H), 0.72-0.69 (m, 2H), 0.41–0.38 (m, 2H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S36) δ = 164.1, 141.4, 125.9, 114.4, 73.5, 9.9, 3.3 ppm. Other spectroscopic properties were identical to those previously reported.

1-nitro-4-phenoxybenzene (**5i**).[15] Eluent for column chromatography: 1–5% EtOAc/*n*-hexane; Yield: 37.1 mg (86%); State of the product: pale yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S37) δ = 8.21 (d, *J* =

9.0 Hz, 2H), 7.45 (dd, *J* = 7.2, 9.0 Hz, 2H), 7.27 (ddd, *J* = 1.2, 1.2, 7.2 Hz, 1H), 7.10 (dd, *J* = 1.2, 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H)ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S38) δ = 163.3, 154.7, 142.6, 130.3, 125.9, 125.4, 120.5, 117.1 ppm. Other spectroscopic properties were identical to those previously reported.

1-nitro-4-(2,2,2-trifluoroethoxy)benzene (**5j**).[15] Eluent for column chromatography: 1–5% EtOAc/*n*-hexane; Yield: 43.6 mg (quant.); State of the product: pale yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S39) δ = 8.25 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 4.47 (q, *J* = 7.8 Hz, 2H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S40) δ = 161.8, 142.9, 126.0, 122.8 (q, *J* = 277.6 Hz), 114.9, 65.8 (q, *J* = 36.2 Hz) ppm. Other spectroscopic properties were identical to those previously reported.

1-(2,2,3,3,4,4,4-heptafluorobutoxy)-4-nitrobenzene (**5k**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 18.6 mg (29 %); State of the product: pale yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S41) δ = 8.27 (d, *J* = 9.27 Hz, 2H), 7.06 (2H, d, *J* = 9.0 Hz, 2H), 4.57 (t, *J* = 12.0 Hz, 2H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S42) δ = 161.8, 143.0, 126.0, 114.9, 65.1 (t, *J* = 27.9 Hz) ppm. Other spectroscopic properties were identical to those previously reported.

(E)-1-(3,7-dimethylocta-2,6-dienoxy)-4-nitrobenzene (**5l**).[15] Eluent for column chromatography: 1–3%

EtOAc/*n*-hexane; Yield: 46.3 mg (84 %); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S43) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 5.47 (qt, *J* = 1.2, 6.6 Hz, 1H), 5.08 (tt, *J* = 1.2, 6.6 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 2H), 2.14–2.09 (m, 4H), 1.76 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H)ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S44) δ = 164.0, 142.5, 141.3, 131.9, 125.8, 123.5, 118.2, 114.6, 65.7, 39.4, 26.2, 25.6, 17.6, 16.7 ppm. Other spectroscopic properties were identical to those previously reported.

(S)-1-(3,7-dimethyloct-6-enoxy)-4-nitrobenzene (**5m**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 47.8 mg (86 %); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S45) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.11 (qdt, *J* = 1.2, 1.2, 7.2 Hz, 1H), 4.06–4.13 (m, 2H), 2.05 (tdd, *J* = 7.2, 7.2, 14.4 Hz, 1H), 2.00 (tdd, *J* = 7.2, 7.2, 14.4 Hz, 1H), 1.88 (qt, *J* = 4.8, 6.6 1H), 1.73–1.67 (m, 1H), 1.69 (d, *J* = 1.2 Hz, 3H), 1.68–1.63 (m, 1H), 1.62 (s, 3H), 1.40 (tdd, *J* = 6.0, 7.8, 9.6 Hz, 1H), 1.25 (ddd, *J* = 6.0, 7.8, 9.6 Hz, 1H), 0.97 (d, *J* = 6.6 Hz, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S46) δ = 164.2, 141.3, 131.4, 125.8, 124.4, 114.4, 67.2, 37.0, 35.8, 29.4, 25.7, 25.4, 19.5, 17.6 ppm.. Other spectroscopic properties were identical to those previously reported.

1-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexoxy)-4-nitrobenzene (**5n**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 46.0 mg (83 %); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K,

$CDCl_3$, Figure S47) δ = 8.19 (d, *J* = 9.6 Hz, 2H), 6.94 (d, *J* = 9.6 Hz, 2H), 4.17 (dt, *J* = 4.2, 10.6 Hz, 1H), 2.16–2.09 (m, 2H), 1.77–1.74 (m, 2H), 1.60–1.49 (m, 2H), 1.15–1.05 (m, 2H), 1.10–0.92 (m, 1H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S48) δ = 163.7, 141.0, 126.0, 115.0, 78.4, 47.8, 39.8, 34.3, 31.4, 26.2, 23.8, 22.0, 20.6, 16.6 ppm.. Other spectroscopic properties were identical to those previously reported.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-(4-nitrophenoxy)tetrahydrofuro[2,3-*d*][1,3]dioxole (**5o**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 68.8 mg (90 %); State of the product: pale yellow solid ; ^1H NMR (600 MHz, 300 K, $CDCl_3$, Figure S49) δ = 8.24 (d, *J* = 9.6 Hz, 2H), 7.08 (2H, d, *J* = 9.6 Hz, 2H) 5.96 (d, *J* = 3.6 Hz, 1H), 4.83 (d, *J* = 3.0 Hz, 1H), 4.58 (d, *J* = 3.6 Hz, 1H), 4.42 (ddd, *J* = 4.8, 6.0, 8.4 Hz, 1H), 4.30 (dd, *J* = 3.0, 8.4 Hz, 1H), 4.16 (dd, *J* = 6.0, 8.4 Hz, 1H), 4.10 (dd, *J* = 5.4, 9.0 Hz, 1H), 1.57 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S50) δ = 161.9, 142.2, 125.9, 115.4, 112.4, 109.4, 105.2, 82.2, 80.6, 80.3, 71.9, 67.2, 26.8, 26.6, 26.2, 25.1 ppm.. Other spectroscopic properties were identical to those previously reported.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-3-(4-nitrophenoxy)-2,3,4,7,8,9,10,1

1,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthrene (**5p**). Eluent for column chromatography: 10–30% CH_2Cl_2/*n*-hexane; Yield: 66.2 mg (65 %); State of the product: pale yellow solid ; mp 183–185°C; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S51) δ = 8.18 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.43 (ddd, *J* = 3.0, 3.0, 5.4 Hz, 1H), 4.24 (dddd, *J* = 4.8, 4.8, 10.8, 10.8 Hz, 1H), 2.42–2.5 (m, 2H), 2.05–1.99 (m, 3H), 1.96 (ddd, *J* = 3.6, 3.6, 13.2 Hz, 1H), 1.85 (dtd, *J* = 6.0, 9.6, 13.2 Hz, 1H), 1.77–1.69 (m, 1H), 1.62–1.47 (m, 6H), 1.40-1.25 (m, 4H), 1.22-1.05 (m, 7H), 1.07 (s, 3H), 1.05–0.96 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 2.4 Hz, 3H), 0.87 (d, *J* = 2.4 Hz, 3H), 0.70 (s, 3H) ppm; ^{13}C{^{1}H} NMR (151 MHz, 300 K, $CDCl_3$, Figure S52) δ = 163.0, 141.0, 139.4, 125.9, 123.0, 115.1, 77.8, 56.6, 56.1, 50.1, 42.2, 39.6, 39.4, 38.2, 36.9, 36.7, 36.1, 35.7, 31.83, 31.78, 28.1, 27.90, 27.86, 24.2, 23.7, 22.7. 22.5, 21.0, 19.3, 18.6, 11.8 ppm; HRMS(FAB+) *m/z* calcd for $C_{33}H_{49}O_3NNa$ $[M + Na]^+$: 530.3610; found: 530.3616.

1-(1,1-dimethylethoxy)-4-nitrobenzene (**5q**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 9.1 mg (23 %); State of the product: yellow oil; ^{1}H NMR (600 MHz, 298 K, $CDCl_3$, Figure S53) δ = 8.17 (d, *J* = 9.24 Hz, 2H), 7.06 (d, *J* = 9.24 Hz, 2H), 1.47 (s, 9H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S54) δ = 161.9, 142.4, 125.1, 121.6, 80.5, 28.8 ppm. Other spectroscopic properties were identical to those previously reported.

1-(but-3-enoxy)-4-nitrobenzene (**5r**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 20.9 mg (54 %); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S55) δ = 8.21 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 5.90 (tdd, *J* = 6.6, 10.2, 17.4 Hz, 1H), 5.20 (tdd, *J* = 1.2, 1.2, 17.4 Hz, 1H), 5.16 (tdd, *J* = 1.2, 1.2, 10.2 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.60 (tdt, *J* = 1.2, 6.6, 6.6 Hz, 2H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S56) δ = 163.9, 141.5, 133.6, 125.9, 117.6, 114.4, 68.0, 33.3 ppm. Other spectroscopic properties were identical to those previously reported.

(*Z*)-1-(hex-3-enoxy)-4-nitrobenzene (**5s**). Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 28.8 mg (65 %); State of the product: yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S57) δ = 8.20 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 5.58 (ttd, *J* = 1.2, 7.2, 10.8 Hz, 1H), 5.42 (ttd, *J* = 1.2, 7.2, 10.8 Hz, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.58 (td, *J* = 6.6, 6.6 Hz, 2H), 2.11 (qd, *J* = 7.2, 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S58) δ = 163.9, 141.4, 134.9, 125.8, 123.1, 114.3, 68.3, 27.0, 20.6, 14.1 ppm; HRMS(FAB+) *m/z* calcd for $C_{12}H_{16}O_3N[M + H]^+$: 222.1130; found: 222.1139.

1-(but-2-ynoxy)-4-nitrobenzene (**5t**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 14.0 mg (37 %); State of the product: pale yellow solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S59) δ = 8.22 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 4.76 (q, *J* = 2.4 Hz, 2H), 1.88 (t, *J* = 2.4 Hz, 3H) ppm; ^{13}C{^{1}H}

NMR(151 MHz, 300 K, $CDCl_3$, Figure S60) δ = 162.7, 141.9, 125.8, 115.0, 85.1, 72.7, 57.0, 3.6 ppm. Other spectroscopic properties were identical to those previously reported.

4-(1-methylethoxy)benzonitrile (**6a**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 24.7 mg (77 %); State of the product: pale yellow oil ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S61) δ = 7.57 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 4.62 (sep, *J* = 6.0 Hz, 1H), 1.37 (d, *J* = 6.0 Hz, 6H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S62) δ = 161.3, 134.0, 119.3, 116.0, 103.4, 70.4, 21.8 ppm. Other spectroscopic properties were identical to those previously reported.

4-(2,2,2-trifluoroethoxy)benzonitrile (**6c**).[15] Eluent for column chromatography: 2–5% EtOAc/*n*-hexane; Yield: 27.8 mg (69 %); State of the product: colorless solid ; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S63) δ = 7.65 (d, *J* = 9.0 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 4.42 (q, *J* = 7.8 Hz, 2H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S64) δ = 160.2, 134.2, 122.9 (q, *J* = 277.6 Hz), 118.5, 115.5, 106.2, 65.6 (q, *J* = 36.2 Hz) ppm. Other spectroscopic properties were identical to those previously reported.

4-((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexoxy)benzonitrile (**6d**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 42.7 mg (83 %); State of the product: colorless solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S65) δ = 7.56 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.11 (dt, *J* = 4.2, 10.8 Hz, 1H),

2.14–2.08 (m, 2H), 1.72-1.76–1.72 (m, 2H), 1.57–1.46 (m, 2H), 1.11 (dddd, *J* =3.0, 9.4, 12.6, 12.6 Hz, 1H), 1.05 (ddd, *J* =10.8, 12.6, 12.6 Hz, 1H), 0.94-0.99 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 7.2 Hz, 3H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S66) δ = 161.8, 134.0, 119.3, 115.9, 103.2, 77.8, 47.8, 39.8, 34.3, 31.3, 26.2, 23.7, 22.0, 20.5, 16.6 ppm. Other spectroscopic properties were identical to those previously reported.

4-(((3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl) oxy)benzonitrile (**6e**).[15] Eluent for column chromatography: 3–10% EtOAc/*n*-hexane; Yield: 59.6 mg (82 %); State of the product: colorless solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S67) δ = 7.63 (2H, d, *J* = 9.0 Hz), 7.06 (d, *J* = 9.0 Hz, 2H), 5.94 (d, *J* = 3.6 Hz, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 4.56 (d, *J* = 3.6 Hz, 1H), 4.41 (ddd, *J* = 4.8, 6.0, 8.6 Hz, 1H), 4.29 (dd, *J* = 3.0, 8.4 Hz, 1H), 4.15 (dd, *J* = 6.0, 9.0 Hz, 1H), 4.09 (dd, *J* = 4.8, 8.6 Hz, 1H), 1.57 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.30 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR(151 MHz, 300 K, $CDCl_3$, Figure S68) δ = 160.2, 134.1, 118.8, 116.1, 112.4, 109.4, 105.2 (overlapped), 82.2, 80.31, 80.26, 71.9, 67.2, 26.9, 26.6, 26.2, 25.2 ppm. Other spectroscopic properties were identical to those previously reported.

4-(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)benzonitrile (**6f**).[15] Eluent for column

chromatography: 10–30% CH_2Cl_2/*n*-hexane; Yield: 39.0mg (40 %); State of the product: colorless solid; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S69) δ = 7.56 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 5.42 (ddd, *J* = 1.8, 1.8, 4.8 Hz, 1H), 4.19 (dddd, *J* = 4.2, 4.2, 10.8, 10.8 Hz, 1H), 2.49–2.38 (m, 2H), 2.06–2.00 (m, 3H), 1.95 (ddd, *J* = 3.6, 13.2 Hz, 1H), 1.85 (dtd, *J* = 6.0, 9.6, 13.2 Hz, 1H), 1.75–1.68 (m, 1H), 1.61–1.46 (m, 6H), 1.42–1.25 (m, 4H), 1.21–1.06 (m, 7H), 1.07 (s, 3H), 1.06–0.96 (m, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 3.0 Hz, 3H), 0.87 (d, *J* = 3.0 Hz, 3H), 0.70 (s, 3H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S70) δ = 161.3, 139.6, 134.0, 122.9, 119.3, 116.1, 103.5, 77.4, 56.7, 56.2, 50.2, 42.3, 39.7, 39.5, 38.3, 37.0, 36.8, 36.2, 35.8, 31.92, 31.87, 28.2, 27.99, 27.95, 24.3, 23.8, 22.8, 22.5, 21.1, 19.4, 18.7, 11.9 ppm. Other spectroscopic properties were identical to those previously reported.

(*R*)-1-nitro-4-(1-phenylethoxy)benzene (**9**).[15] Eluent for column chromatography: 1–3% EtOAc/*n*-hexane; Yield: 41.8 mg (85 %); State of the product: yellow oil; ^{1}H NMR (600 MHz, 300 K, $CDCl_3$, Figure S71) δ = 8.11 (d, *J* = 9.0 Hz, 2H), 7.38–7.34 (m, 4H), 7.29 (dddd, *J* = 1.8, 1.8, 6.6, 6.6 Hz, 1H), 5.41 (q, *J* = 6.6 Hz, 1H), 1.69 (d, *J* = 6.6 Hz, 3H), 6.91 (d, *J* = 9.0 Hz, 2H) ppm; ^{13}C{^{1}H} NMR(151 MHz, 300 K, $CDCl_3$, Figure S72) δ = 163.0, 141.7, 141.3, 128.9, 128.0, 125.7, 125.4, 115.7, 77.0, 24.3 ppm. Other spectroscopic properties were identical to those previously reported.

Procedure for the reaction on 10 mmol scale. A two-necked round bottom flask was charged with 1-chloro-4-nitrobenzene (1.58 g, 10 mmol) and a magnetic stir bar. One neck was capped with a rubber septum and the other was connected to a vacuum line. The flask was then evacuated and backfilled with argon (this process was repeated three times). DMF (50 mL) was added by a syringe through the septum followed by EtOH (0.88 mL, 15 mmol). The resultant solution was cooled in an ice bath, and a commercial *tert*-BuOK solution in THF (1.0 M, 15 mL) was added over 5 min by a syringe. After stirring for 1h at the same temperature, the reaction was quenched with sat. NH_4Cl aq. (50 mL). The mixture was transferred to a separatory funnel and extracted with Et_2O (30 mL ×3), and the combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. H_2O was added to the residue to precipitate the insoluble solid, which was filtered and washed with H_2O. After drying under reduced pressure, the resultant solid was purified by column chromatography (1–3 % EtOAc/*n*-hexane) on silica gel to afford 1-ethoxy-4-nitrobenzene (1.60 g, 95%) as a pale yellow solid.

Supporting Information. The list of the incompatible substrates. HPLC data of compound **9**. Copies of the ^{1}H and ^{13}C NMR spectra of all ether compounds.

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