Truce-Smiles rearrangement of substituted phenyl ethers

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID:	OB-ART-04-2015-000812.R1
Article Type:	Paper
Date Submitted by the Author:	15-May-2015
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Equation 4.cdx	

Truce-Smiles rearrangement of substituted phenyl ethers

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Abstract:

The requirement of aryl ring activation by strong-electron withdrawing substituents in substrates for the intramolecular nucleophilic aromatic substitution reaction known as the Truce-Smiles rearrangement was examined. Preliminary mechanistic experiments support the S_NAr mechanism, including ^{1}H and ^{13}C NMR spectra of a Meisenheimer intermediate formed *in situ*. The rearrangement was generally observed to be successful for substrates with strong electron withdrawing substituents, such as nitro-, cyano-, and benzoyl-functional groups, but also for those with multiple, weakly electron withdrawing substituents, such as chloro- and bromo- functional groups. These results lend further clarification to the effect of aryl substituents in this type of S_NAr reaction. Additionally, the survey revealed several tandem cyclization and/or elimination reactions accessed by certain substrates.

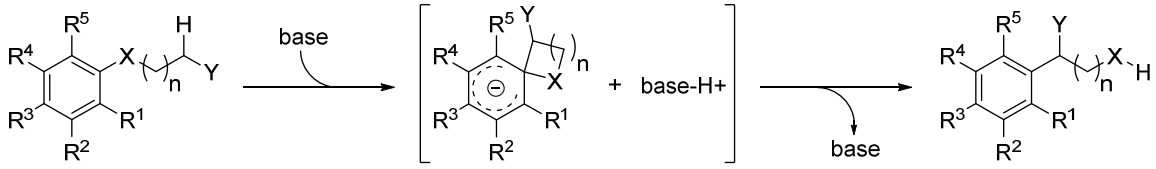
Introduction

The Truce-Smiles rearrangement is a relatively unknown and unexploited intramolecular nucleophilic aromatic substitution reaction that forms an aryl-sp^3 C-C bond concomitant with breaking a C-heteroatom bond. The reaction can therefore be seen as a perfectly atom economical method for replacing an easily-formed chemical bond with one that is of greater synthetic value and which, despite its interesting mechanism and great synthetic potential, remains quite unstudied and possibly misunderstood. The eponymous Truce-Smiles rearrangement (Equation 1) was first reported by Truce in the 1950s,[1] with a related reaction having been reported by Dohmori previously.[2] The reaction has received scattered attention in the literature since that time, with increased interest[3-11] within recent years.

Interestingly, the definition of the Truce-Smiles rearrangement has evolved from Truce's original classification to become more inclusive with respect to activating substituents on the migrating aromatic ring of the substrate, although more restrictive with respect to mechanism.[12] This more inclusive description defines the reaction as a variation of the Smiles rearrangement, with the Truce variant distinguished by a carbanion nucleophile. The carbanion is typically generated by deprotonation, necessitating the inclusion of a functional group to lower the pK_a of the adjacent protons (shown as "Y" in Equation 1), unless the tether fulfills this function.

In the evolved definition of the reaction, the Truce-Smiles rearrangement is more restrictively proposed to proceed through a bicyclic reaction intermediate, shown in Equation 1, as is the accepted hypothesis for other examples of Smiles reactions. The

reaction intermediate is a delocalized anionic cyclohexadienyl σ-adduct, known as a Meisenheimer adduct, and is typical of the S_NAr mechanism.



Equation 1: General reaction for the Truce-Smiles rearrangement

With respect to the migrating aryl ring, many reports have focused upon substrates that would produce stabilized proposed Meisenheimer intermediates, such as nitro-substituted phenyl rings[3,4,7,8,11] and pyridines.[6,9,10] However, activation with strong electron-withdrawing substituents is not a requirement, as indicated by most of Truce's pioneering work.[13,14] The discrepancy likely arises as a result of some of the traditional Truce-Smiles rearrangements occurring via radical pathways.[15,16] The reported incidents of the Truce-Smiles rearrangement are neither methodical nor thorough, and frequently lack mechanistic investigation, resulting in interesting potential substrates that remain to be explored. Therefore, we herein report our assay of the scope of substrates with substituted phenyl groups as migrating aryl rings in the rearrangement reaction.

Results and Discussion

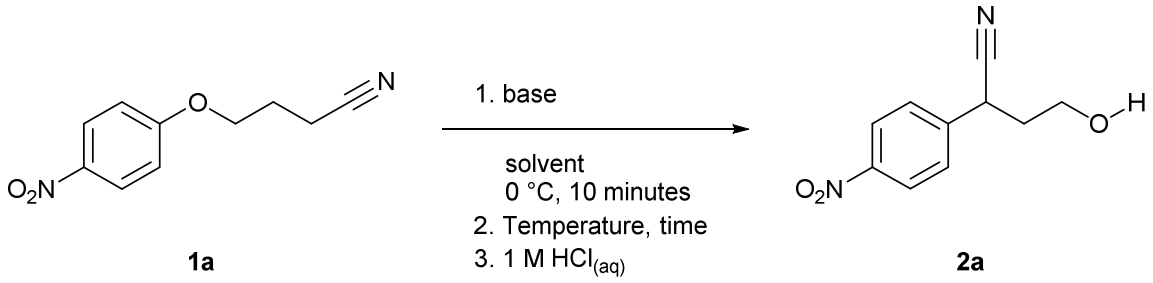
Our initial foray into the wide range of unexplored substrate structures viable for Truce-Smiles rearrangement focuses upon aryl ethers of 4-butanenitrile in which the aryl

group is a phenyl ring substituted with various neutral, aprotic, electron withdrawing functional groups. The use of aryl ethers facilitated the synthesis of a variety of substrates that were easily modified at key points of elaboration in substrate design. The substrates incorporate a nitrile functional group to lend resonance stabilization to the proposed α-carbanion nucleophile, which is disposed appropriately to the ring such as to proceed through a five-membered ring spirocyclic Meisenheimer intermediate, favoured by Smiles rearrangements. Generally, a modular approach was realized through alkylation of an array of available substituted phenols allowing for examination of substituent effects while maintaining a consistent distance between the carbanion nucleophile and the electrophilic ring atom.

Compound **1a** typifies the structure of the substrates examined herein - a phenyl ring para-substituted with a nitro functional group is the epitome of a nucleophilic aromatic substitution substrate. Consequently, **1a** was used to perform the process of determining optimized conditions for the Truce-Smiles rearrangement. Table 1 shows the outcome of optimization experiments. The reaction was found to be strongly influenced by solvent. Of the various polar aprotic solvents investigated, DMF provided the optimal outcome (compare entry 1 to entries 2-5).

Despite reports in the literature suggesting the enhancement of intramolecular nucleophilic aromatic substitution reaction rates by the inclusion of additives to coordinate the countercation of the base,[17] addition of 10% (v/v) hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), or 1,3-dimethyl-2-imidazolidinone (DMI) did not improve the yield (compare entries 1 to 6, 7, and 8, respectively). The reaction was observed to have

reached completion after reacting for four hours at 20º C (ambient lab temperature) or for 30 minutes at 40º C (compare entries 1 and 9). A hydrogen α-to the nitrile functional group is predicted to have the highest acidity in the molecule with a pK_a of ~33.[18] Although all three non-nucleophilic bases examined were found to be suitable (compare entry 1 to entries 10, 11, and 12), further reactions were performed using sodium hydride due to the short duration of the reaction. A moderate excess of base was employed, as the excess 0.5 equivalents had no apparent effect upon reaction outcome (compare entries 1 and 13). The reaction is concentration dependent, favoring dilute reaction conditions (compare entries 1 and 14), as is the expected observation for promotion of the intramolecular reaction of a highly reactive species. Optimization reactions were performed using 0.5 mmol of substrate **1a**; entry 15 demonstrates that the reaction maintains a consistent yield when scaled-up conducted using 2.5 mmol of **1a**.



1a **2a**

Table 1: Optimization study of Truce-Smiles rearrangement reaction conditions

entry	base	equivalents of base	solvent	[1a] (mM)	Temp. (º C)	time (h)	% yield 2a

1	NaH	1.5	DMF	50	20	4	86
2	NaH	1.5	DMSO	50	20[a]	4	75
3	NaH	1.5	dioxane	50	20	4	38
4	NaH	1.5	THF	50	20	4	-
5	NaH	1.5	acetonitrile	50	20	4	-
6	NaH	1.5	9:1 DMF:HMPA	50	20	4	72
7	NaH	1.5	9:1 DMF:DMPU	50	20	4	79
8	NaH	1.5	9:1 DMF:DMI	50	20	4	78
9	NaH	1.5	DMF	50	40	0.5	74
10	*t*-BuOK	1.5	DMF	50	20	4	80
11	LiHMDS	1.5	DMF	50	20	4	79
12	LiHMDS	1.5	THF	50	20	4	43
13	NaH	1.0	DMF	50	20	4	85

14	NaH	1.5	DMF	250	20	4	65
15	NaH	1.5	DMF	50[b]	20	4	92

[a] NaH addition performed at 20 º C

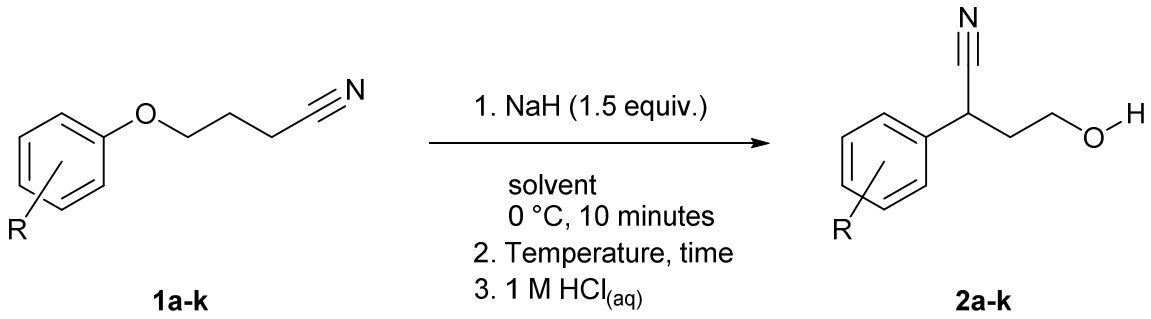
[b] Reaction performed at 5-times larger scale

As further evidence to support the proposed mechanism of this reaction, a series of additional experiments were performed. Using the determined optimal conditions, the reaction was performed in the presence of a competing intermolecular S_NAr substrate, 1-bromo-2,4-dinitrobenzene, with the overall concentration of substrates maintained at 50 mM. The absence of substituted 2,4-dinitrophenyl products supports the proposed intramolecular nature of the reaction. To support the hypothesis of the reaction proceeding via a classical polar S_NAr mechanism, the reaction was performed in the presence of a radical scavenger, either TEMPO or 1,1-diphenylethylene. The yield of the rearranged product, **2a**, was unaffected by the presence of radical scavengers, supporting the absence of a radical intermediate. The regioselectivity of the reaction, as indicated by the exclusive formation of products with substitution patterns conserved from the substrate, supports a S_NAr mechanism, over involving the participation of a benzyne intermediate. An intense purple colour is observed upon the addition of base to a colourless solution of substrate **1a**, that is dissipated upon the addition of aqueous acid. This observation suggests the formation of a para-nitrophenyl derived Meisenheimer intermediate, which typically exhibit strong absorption at appropriate visible wavelengths.[19] Further, ^1H and ^{13}C NMR spectra of the reaction mixture in $(CD_3)_2SO$ showed formation of an intermediate with spectral properties consistent with the

proposed anionic Meisenheimer intermediate.[20] The spectra show that C2 and C6 are not equivalent, and similarly C3 and C5, due to the unsymmetrical substitution of the cyclic ether ring. Consequently, H2 and H6 display a coupling constant J = 2.4 Hz, which is equal to that shared by H3 and H5, and is consistent with other reported unsymmetric nitro-substituted anionic intermediates.[21]

A series of substrates **1b**-**z** were prepared to examine the effect of substituents on the aromatic ring upon the outcome of the attempted Truce-Smiles rearrangement. The majority of the aryl ether substrates were successfully prepared in high yield following the Williamson ether synthesis procedure that was successful for the preparation of **1a**. However, the 2,4-dinitrophenyl substrate (**1d**) was synthesized using aqueous phase-transfer conditions modified from literature,[22] and the 2,4-di(trifluoromethyl)phenyl substrate (**1i**) was prepared using an Ullmann reaction procedure modified from literature.[23]

The ability of substrates **1b**-**z** to undergo Truce-Smiles rearrangement was examined using the conditions optimized for prototypical substrate **1a**. Substrates that yielded mixtures of products were subjected to lower temperatures or shorter reaction times, while those that failed to yield product were subjected to higher reaction temperatures, to a maximum of 60 ºC. The first series of substrates include strong inductive and resonance electron withdrawing substituents (Table 2). As hypothesized, substrates substituted with a nitro group at the para- (**1a**,**d**) or ortho- (**1c**,**d**) position made suitable substrates for nucleophilic aromatic substitution, while meta- (**1b**) substitution did not. The cyano group situated in a para- (**1e**) or ortho- (**1f**) position was sufficient to activate the phenyl ring to nucleophilic aromatic substitution.



1a-k **2a-k**

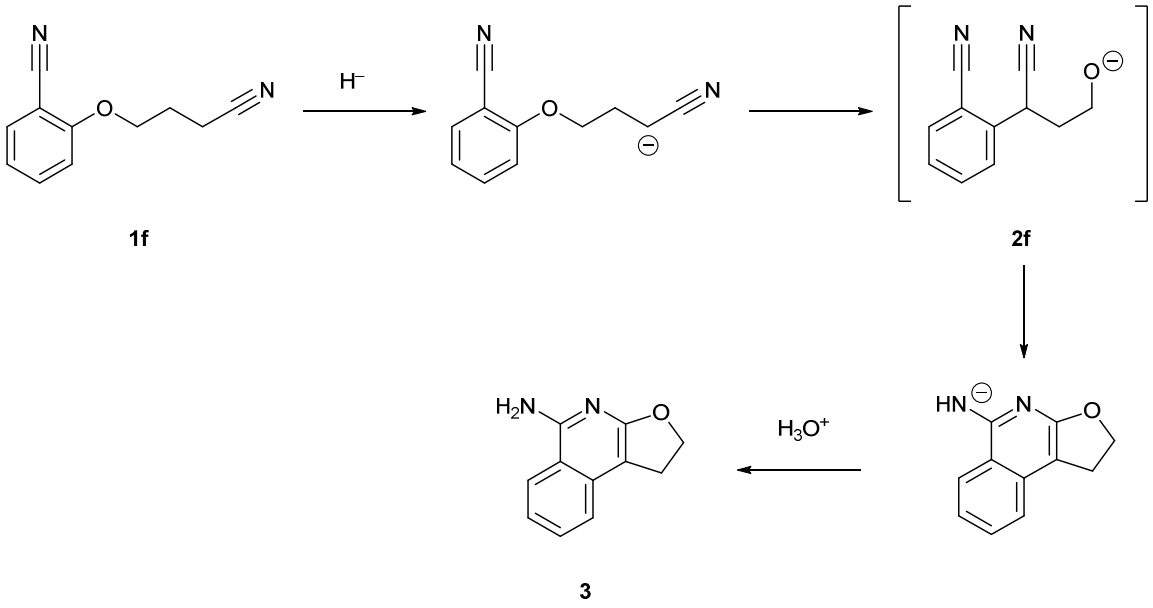
Table 2: Scope of Truce-Smiles rearrangement with strong electron withdrawing group substituted aryl substrates

entry	1	–R	solvent	Temperature (° C)	time (h)	% yield 2
1	**a**	4–NO_2	DMF	20	4	86
2	**b**	3–NO_2	DMF	60	20	-
3	**c**	2–NO_2	DMF	0	1.5	94
4	**d**	2,4–di NO_2	DMF	0	1.5	22
5	**e**	4–C≡N	DMF	40	20	58
6	**f**	2–C≡N	DMF	20	20	17 (**3**)
7	**f**	2–C≡N	DMSO	20[a]	20	44

						31 (**3**)
8	**g**	6–C≡N–2–naphthyl	DMF	40	20	64
9	**h**	4–CF_3	DMF	60	20	-
10	**i**	2,4–di CF_3	DMF	60	20	-
11	**j**	4–C(O)Ph	DMF	40	20	70
12	**k**	2–C(O)Ph	DMF	20	20	81 (**4**)
13	**k**	2–C(O)Ph	DMSO	20[a]	20	85 (**4**)

[a] NaH addition performed at 20 º C

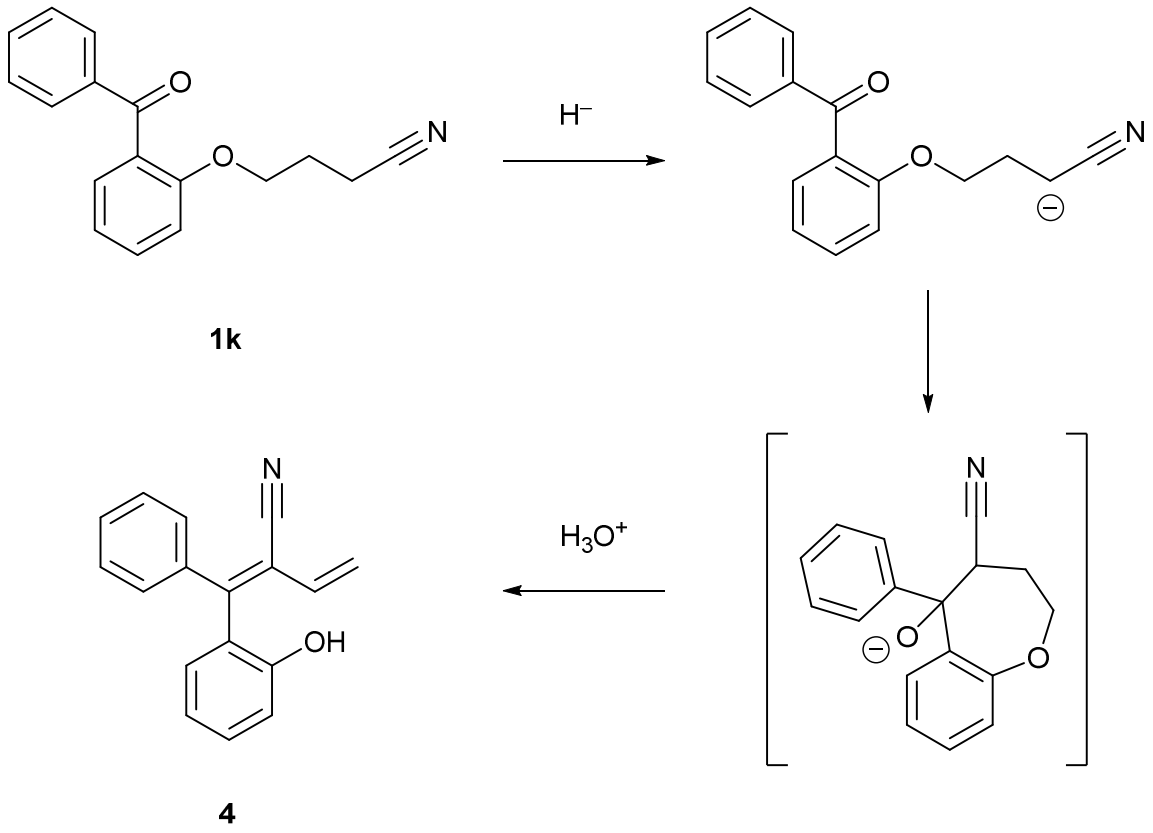
Interestingly, the ortho-cyano group (**1f**) allowed for tandem cyclization (Equation 2) to form the tricyclic product (**3**),[24] although the yield of the Truce-Smiles rearrangement product (**2f**) could be increased by changing the medium of the reaction to a DMSO solution (entry 7). The 6-cyano-2-naphthol derivative (**1g**) underwent the rearrangement reaction in high yield, in keeping with the observation that extended aromatic systems are prone to S_NAr.[25] Surprisingly, the trifluoromethyl group provided insufficient activation for substrates (**1h, i**), even at the highest reaction temperatures examined. These results suggest the importance of resonance stabilization relative to inductive stabilization of the anionic Meisenheimer intermediate proposed for these reactions.



Equation 2: Proposed reaction to form **3** from **1f** via tandem cyclization of **2f**

Benzophenone derivatives **1j** and **1k** were prepared as substrates to assess the substituent effects of an acyl functional group without introducing acidic hydrogen atoms that might interfere with the formation of the α-cyano carbanion nucleophile. The benzoyl functional group activates the substrate to rearrangement when situated at the para- (**1j**) position. However, when situated at the ortho- position (**1k**), it blocked reactivity. Subjecting substrate (**1k**) to reaction conditions in an attempt to promote a Truce-Smiles rearrangement yielded only the highly-unsaturated diene product (**4**), the result of an intramolecular attack at the electrophilic ketone carbonyl carbon atom by the carbanion formed *in situ*, followed by subsequent elimination of the phenol ring and a molecule of water (Equation 3). This suggests the approach of the nucleophile toward the intended electrophilic aryl *ipso*-carbon may have been blocked by the position of the benzoyl functional group. Indeed, the ^{1}H NMR spectrum of **1k** shows a marked shielding

188 ($\Delta\delta$ ~0.7 ppm) of the hydrogen atoms α- to the nitrile functional group of the
189 butanenitrile moiety, relative to the corresponding *para*-substituted substrate (**1j**). This
190 shielding of the ^{1}H NMR signal suggests that **1k** assumes a stable conformation in which
191 the phenyl ring of the benzoyl functional group is in close proximity to the nucleophilic
192 site.
193

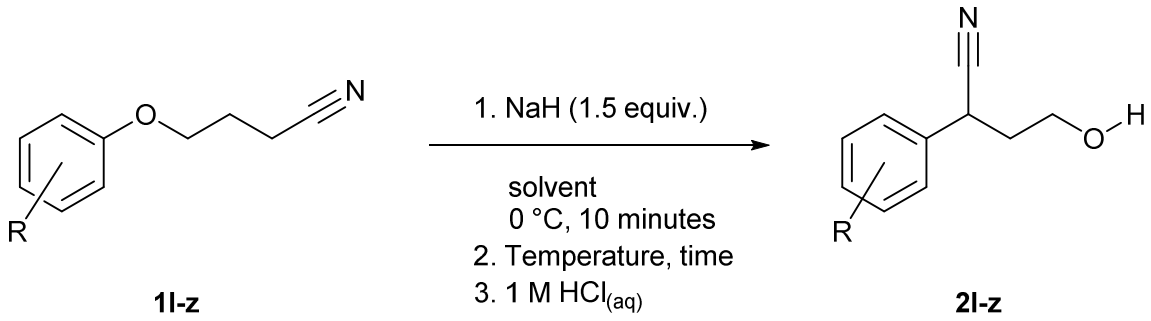


194

195 **Equation 3:** Proposed reaction to form **4** from **1k**
196

197 A second series of substrates was prepared to examine the effect of halogen
198 substituents upon the reactivity of substrates toward Truce-Smiles rearrangement (Table
199 3). The halogens are an interesting group of substituents to examine based upon their
200 varying degrees of contrasting resonance electron donating and inductive electron

withdrawing effects, in addition to varying steric effects. Fluoro (**2l-p**) substituents proved insufficient to activate the ring to Truce-Smiles rearrangement. This suggests that the destabilizing resonance effect of fluoro substituents upon the anionic Meisenheimer intermediate when positioned ortho- and para- is dominant to the stabilizing inductive effect.[26] The mono-chloro substituted substrate (**1q**) did not undergo rearrangement under the conditions examined, however appropriate di- (**1r,s**) and tri-chloro substitution (**1t**) provided effective activation. The decreased resonance effect of chloro substituents, and therefore the decreased destabilization of the resulting Meisenheimer intermediate relative to the fluoro-substituted substrates, likely explains some of the increased reactivity observed for the chloro-substituted substrates. Additionally, the higher yield for the di-ortho-substituted (**2s**) product over the ortho, para-disubstituted (**2r**) product suggests that a steric effect attributable to the sterically-demanding ortho-chloro substituents may also be ascribed a role in increasing reactivity. This increased reactivity may be accomplished by favouring a more reactive conformation of the intermediate anion due to steric strain, which leads to an increase in the rate of reaction of substrates **1s** and **1t** relative to **1r** or to the ortho-fluoro substituted substrates. A similar steric effect phenomenon has been proposed for Truce-Smiles reactions involving benzyl carbanions of ortho-substituted diarylsulfones.[27] Evidence of restricted rotation around the newly formed aryl-sp^3C bond can be seen in the ^{13}C NMR spectra of **2s** and **2t**, but is not apparent in the spectrum of **2r**.



1l-z **2l-z**

Table 3: Scope of Truce-Smiles rearrangement with halogenated aryl substrates

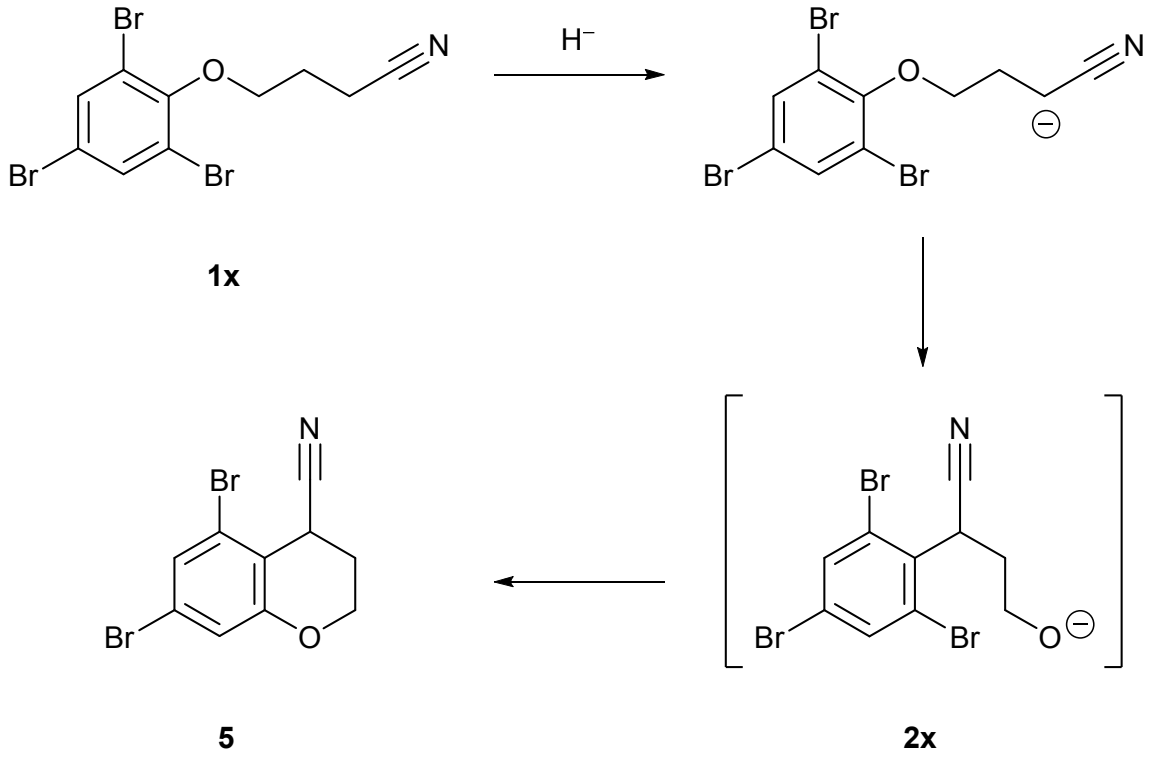
entry	1	–R	solvent	Temperature (º C)	time (h)	% yield 2
1	**l**	4–F	DMF	60	20	-
2	**m**	2,4–di F	DMF	60	20	-
3	**n**	2,6–di F	DMF	60	20	-
4	**o**	2,4,6–tri F	DMF	60	20	-
5	**p**	2,3,4,5,6– penta F	DMF	60	20	-
6	**q**	4–Cl	DMF	60	20	-
7	**r**	2,4–di Cl	DMSO	20[a]	20	42
8	**s**	2,6–di Cl	DMSO	20[a]	20	56
9	**t**	2,4,6–tri Cl	DMF	40	20	25

10	**t**	2,4,6–tri Cl	DMSO	20[a]	20	34
11	**u**	4–Br	DMF	60	20	-
12	**v**	2,4–di Br	DMF	60	20	-
13	**w**	2,6–di Br	DMF	60	20	30
14	**x**	2,4,6–tri Br	DMF	40	20	40 (**5**)
15	**x**	2,4,6–tri Br	DMSO	20[a]	20	69 (**1v**)
16	**y**	4–I	DMF	60	20	-
17	**z**	2,4,6–tri I	DMF	60	20	-

[a] NaH addition performed at 20 º C

The reactivity of the bromo-substituted substrates follows a similar trend to their chloro-substituted analogues, showing no apparent reactivity for the mono-bromo substrate (**1p**) and the ortho, para-dibromo substrate (**1q**) and increased reactivity in di-ortho substituted substrates **1w** and **1x**. Interestingly, the tri-bromo-substituted substrate (**1x**) undergoes a tandem nucleophilic aromatic substitution of an ortho-bromo substituent by the intermediate alkoxide of rearrangement product **2x** to form the bicyclic chromene compound **5** (Equation 4). Compound **1v** is formed by debromination of **1x** when the rearrangement is attempted in DMSO. The iodo-substituted substrates (**1y,z**) failed to show reactivity under the reaction conditions examined. These compounds may represent

the limit at which electronic effects, although iodo substituents provide decreased resonance destabilization of the Meisenheimer intermediate relative to fluoro substituents, come to dominate any pre-organizing steric effects of the halogen substituents.



Equation 4: Proposed reaction to form **5** from **1x**

Conclusion

This study has filled its intended goal of beginning a systematic survey of the substrate scope of the Truce-Smiles rearrangement. The results support the previously established requirement for a strong-electron withdrawing substituent in the ortho- or para- positions of the substrate aryl ring. However, the indispensability of a nitro group as that strong

electron withdrawing group has been challenged, revealing that the cyano group or an aprotic acyl group may act as a replacement. Further, di- and tri-substitution with chloro and bromo substituents, particularly in ortho-positions activates the substrate ring sufficiently for Truce-Smiles rearrangement. The delicate balance of activation and deactivation by steric effects of ortho-substituents has also been illustrated. Additionally, the study has illuminated several interesting tandem reactions that involve the Truce-Smiles rearrangement as the first chemical step toward the preparation of bicyclic and tricyclic products.

Experimental Section

General Methods. All glassware used for Truce-Smile rearrangement reactions was flame-dried under a vacuum and reactions were run under an inert atmosphere of nitrogen. All reagents and solvents were commercial grade. All organic layers collected from extractions were dried using anhydrous $MgSO_4$. Thin layer chromatography (TLC) was performed using aluminum-backed silica gel plates (250 μm) plates, and flash column chromatography used 230-400 mesh silica. Compounds were visualized using UV light (λ = 254 nm) and either phosphomolybdic acid or vanillin solutions. Melting points were determined using a capillary melting point apparatus and are reported uncorrected. FTIR spectra were recorded of samples as a thin film on a KBr plate (transmission). ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were acquired on a 400 MHz instrument. $^{13}C\{^{19}F\}$ and ^{19}F NMR spectra were acquired on a 500 MHz instrument. Chemical shifts are reported relative to tetramethylsilane (TMS) as an internal standard set to δ 0.00 ppm

for ^{1}H, relative to the $CDCl_3$ solvent residual as an internal standard set to δ 77.16 ppm for ^{13}C, and relative to the $CFCl_3$ as an external standard set to δ 0 ppm for ^{19}F. Multiplicities are reported as apparent (app), broad (br), singlet (s), doublet (d), triplet (t), quartet (q) and combinations thereof, or multiplet (m). NMR data were processed by using ACD/Labs SpecManager software, product version 12.00. HRMS data was obtained by electrospray (ESI) using an ion trap.

Preparation of 4-Butanenitrile Aryl Ether Substrates 1a-z

General Procedure A

To a round-bottom flask fitted with a reflux condenser was added the substituted phenol (1.1 mmol, 1.1 equiv), anhydrous potassium carbonate (0.138 g, 1.0 mmol, 1.0 equiv.), 4-bromobuytronitrile (0.10 mL, 1.0 mmol), and acetone (10 mL). The reaction mixture was heated with stirring to the boiling point of acetone using a heating block and reflux was maintained for 20 hours. The solution was concentrated, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with 1 M $NaOH_{(aq)}$ (2 × 15 mL). The organic layer from the extraction was dried, filtered, and concentrated.

4-(4-Nitrophenoxy)butanenitrile (1a).

General procedure A: The product was obtained from the extraction as a light yellow crystalline solid (0.204 g, 99%). CAS: 99072-20-5; mp 48-49 °C (lit.[28] mp 50-52 °C, lit.[29] mp 53-54 °C); TLC R_f (40% ethyl acetate, 60% hexanes): 0.44; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3086, 2948, 2248, 1593, 1513, 1344, 1263, 1045, 846; ^{1}H NMR (400 MHz,

$CDCl_3$) δ(ppm): 8.17 (2H, d, *J* = 9.3 Hz), 6.98 (2H, d, *J* = 9.3 Hz), 4.20 (2H, t, *J* = 5.8 Hz), 2.66 (2H, t, *J* = 7.2 Hz), 2.22 (2H, app pentet, *J* = 6.5 Hz); ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ(ppm): 8.22 (2H, d, *J* = 9.3 Hz), 7.17 (2H, d, *J* = 9.3 Hz), 4.22 (2H, t, *J* = 6.0 Hz), 2.72 (2H, t, *J* = 7.2 Hz), 2.11 (2H, app pentet, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 163.3, 141.5, 125.7, 119.0, 114.3, 66.1, 24.9, 13.9; ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ(ppm): 163.5, 141.0, 125.8, 120.1, 114.9, 66.9, 24.5, 13.3; LRMS (ESI) *m/z* (relative intensity): 229.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}N_2O_3$: 229.0584, found: 229.0586.

4-(3-Nitrophenoxy)butanenitrile (1b).

General procedure A: The product was obtained from the extraction as a light yellow crystalline solid (0.197 g, 95 %). CAS: 19157-86-9; mp 53-54 °C (lit.[30] mp 50-54 °C); TLC R_f (50 % ethyl acetate, 50 % hexanes): 0.54; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3098, 2941, 2248, 1530, 1352, 1248, 1048, 816; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.83 (1H, dd, *J* = 8.2 Hz, *J* = 1.9 Hz), 7.72 (1H, app t, *J* = 2.3 Hz), 7.45 (1H, app t, *J* = 8.3 Hz), 7.24 (1H, dd, *J* = 8.3 Hz, *J* = 2.5 Hz), 4.18 (2H, t, *J* = 5.8 Hz), 2.64 (2H, t, *J* = 7.1 Hz), 2.20 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 158.9, 149.2, 130.2, 121.5, 119.0, 116.2, 108.9, 66.1, 25.2, 14.2; LRMS (ESI) *m/z* (relative intensity): 229.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}N_2O_3$: 229.0584, found: 229.0594.

4-(2-Nitrophenoxy)butanenitrile (1c).

General procedure A: The product was obtained from the extraction as a light yellow amorphous solid (0.197 g, 96 %). CAS: 1184140-43-9; mp 44-46 °C; TLC R_f (50 % ethyl acetate, 50 % hexanes): 0.34; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3056, 2957, 2250, 1522, 1359, 854; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.87 (1H, dd, *J* = 8.3 Hz, *J* = 1.6 Hz), 7.55 (1H, app td, *J* = 8.0 Hz, *J* = 1.7 Hz), 7.09-7.05 (2H, m), 4.24 (2H, t, *J* = 5.5 Hz), 2.69 (2H, t, *J* = 7.0 Hz), 2.20 (2H, app pentet, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 151.3, 139.3, 134.1, 125.7, 120.5, 118.9, 114.3, 66.5, 24.8, 13.5; LRMS (ESI) *m/z* (relative intensity): 229.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}N_2O_3$: 229.0584, found: 229.0589.

4-(2,4-Dinitrophenoxy)butanenitrile (1d).

To a round-bottom flask fitted with a reflux condenser was added 2,4-dinitrophenol (moistened with ~20% water, 0.460 g, 2.0 mmol), sodium hydroxide (0.184 g, 4.6 mmol, 2.3 equiv.), tetra-*n*-butylammonium iodide (0.0004 g, 1.2 μmol, 0.0006 equiv.), 4-bromobuytronitrile (0.40 mL, 4.0 mmol, 2.0 equiv.), and water (4 mL). The reaction mixture was heated with stirring to the boiling point of water using a heating block and reflux was maintained for 20 hours. The solution was extracted with ethyl acetate (40 mL) and washed with 1 M $NaOH_{(aq)}$ (2 × 30 mL). The organic layer from the extraction was dried, filtered, and concentrated. Flash column chromatography (100 % dichloromethane) yielded the product as a light yellow amorphous solid (0.061 g, 12 %). mp 49-51 °C; TLC R_f (100 % dichloromethane): 0.53; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3117, 3089, 2951, 2892, 2249, 1537, 1346, 1032; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.80 (1H, d, *J* = 2.7 Hz), 8.47 (1H, dd, *J* = 9.3 Hz, *J* = 2.7 Hz), 7.23 (1H, d, *J* = 9.3 Hz),

4.39 (2H, t, *J* = 5.7 Hz), 2.71 (2H, t, *J* = 6.9 Hz), 2.27 (2H, app pentet, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 156.2, 140.8, 139.0, 129.4, 122.3, 118.6, 114.5, 67.9, 25.1, 14.1; LRMS (ESI) *m/z* (relative intensity): 274.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9N_3O_5$: 274.0434, found: 274.0431.

4-(4-Cyanophenoxy)butanenitrile (1e).

General procedure A: The product was obtained from the extraction as a colourless amorphous solid (0.182 g, 98 %). CAS: 1016732-57-2; mp 52-53 °C; TLC R_f (60 % ethyl acetate, 40 % hexanes): 0.62; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3059, 2955, 2248, 2225, 1606, 1257, 839; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.60 (2H, d, *J* = 9.1 Hz), 6.96 (2H, d, *J* = 9.1 Hz), 4.14 (2H, t, *J* = 5.7 Hz), 2.61 (2H, t, *J* = 7.0 Hz), 2.18 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 161.7, 134.2, 119.1, 118.9, 115.3, 104.7, 65.8, 25.3, 14.3; LRMS (ESI) *m/z* (relative intensity): 209.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O$ + Na: 209.0685, found: 209.0691.

4-(2-Cyanophenoxy)butanenitrile (1f).

General procedure A: Flash column chromatography (40 % ethyl acetate, 60 % hexanes) yielded the product as a colourless amorphous solid (0.176 g, 94 %). CAS: 194724-60-2; mp 48-50 °C (lit.[24] mp 48-49 °C); TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.41; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2949, 2889, 2228, 1599, 1260, 1045 (consistent with lit.[24]); ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.59-7.53 (2H, m), 7.05 (1H, t, *J* = 7.6 Hz), 6.98 (1H, d, *J* = 8.5 Hz), 4.21 (2H, t, *J* = 5.7 Hz), 2.70 (2H, t, *J* = 7.1 Hz), 2.22 (2H, app pentet, *J* = 6.4 Hz) (consistent with lit.[24]); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 159.9,

134.5, 133.8, 121.5, 118.9, 116.2, 112.4, 102.2, 66.2, 25.2, 14.1; LRMS (ESI) *m/z* (relative intensity): 209.1 (100%), 395.2 (18%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O$: 209.0685, found: 209.0692.

4-[(6-Cyanonaphthalen-2-yl)oxy]butanenitrile (1g).

General procedure A: The product was obtained from the extraction as a light brown crystalline solid (0.192 g, 81 %). mp 104-105 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.44; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2223, 1267; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.07 (1H, d, *J* = 1.0 Hz), 7.75-7.72 (2H, m), 7.52 (1H, dd, *J* = 8.5 Hz, *J* = 1.5 Hz), 7.22 (1H, dd, *J* = 9.1 Hz, *J* = 2.5 Hz), 7.14 (1H, d, *J* = 2.5 Hz), 4.22 (2H, t, *J* = 5.8 Hz), 2.64 (2H, t, *J* = 7.0 Hz), 2.22 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 158.7, 136.2, 133.7, 130.1, 127.8, 127.1, 120.5, 119.5, 119.1, 106.9, 106.8, 65.6, 25.2, 14.2; LRMS (ESI) *m/z* (relative intensity): 259.1 (43%), 495.2 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{12}N_2O$: 259.0842, found: 259.0838.

4-[4-(Trifluoromethyl)phenoxy]butanenitrile (1h).

General procedure A: Flash column chromatography (20 % ethyl acetate, 80 % hexanes) yielded the product as a colourless oil (0.195 g, 85 %). CAS: 1092292-41-5; mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.28; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2943, 2250, 1332, 1312, 837; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.56 (2H, d, *J* = 8.5 Hz), 6.96 (2H, d, *J* = 8.5 Hz), 4.13 (2H, t, *J* = 5.7 Hz), 2.60 (2H, t, *J* = 7.1 Hz), 2.17 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 160.9, 127.1 (q, *J* = 4 Hz), 124.5 (q, *J* = 271 Hz), 123.6 (q, *J* = 33 Hz), 119.0, 114.6, 65.6, 25.4, 14.3; LRMS (ESI)

m/z (relative intensity): 252.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}F_3NO$: 252.0607, found: 252.0598.

4-[2,4-Di(trifluoromethyl)phenoxy]butanenitrile (1i).

To a 4 mL glass vial was added 1-bromo-2,4-di(trifluoromethyl)benzene (0.34 mL, 2.0 mmol), 4-hydroxybuytronitrile[31,32] (0.75 mL, 8.8 mmol, 4.4 equiv.), anhydrous cesium carbonate (0.879 g, 3.0 mmol, 1.5 equiv.), copper(I) iodide (0.038 g, 0.2 mmol, 0.1 equiv.), 1,10-phenanthroline (0.072 g, 0.4 mmol, 0.2 equiv.), and toluene (1 mL). The vial was sealed with a poly(tetrafluoroethylene)-lined screw-cap lid and the reaction mixture was heated with stirring to 150 °C using a heating block for 20 hours. The solution was diluted with toluene (5 mL) and filtered through a pad of silica. The silica was rinsed with ethyl acetate (3 x 5 mL) and the filtrate was concentrated. Flash column chromatography (20 % ethyl acetate, 80 % hexanes) yielded the product as a colourless oil (0.092 g, 16 %). mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.29; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2954, 2890, 2251, 1597, 1515, 1266, 1129; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.85 (1H, s), 7.79 (1H, dd, *J* = 8.7 Hz, *J* = 1.7 Hz), 7.09 (1H, d, *J* = 8.7 Hz), 4.25 (2H, t, *J* = 5.6 Hz), 2.64 (2H, t, *J* = 7.1 Hz), 2.22 (2H, app pentet, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 158.7, 130.9, 125.1, 123.7 (q, *J* = 269 Hz), 123.4 (q, *J* = 34 Hz), 123.0 (q, *J* = 273 Hz), 119.6 (q, *J* = 32 Hz), 118.8, 112.9, 66.4, 25.3, 14.0; LRMS (ESI) *m/z* (relative intensity): 222.1 (100%), 320.0 (97%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_9F_6NO$: 320.0481, found: 320.0474.

4-[4-(Benzoyl)phenoxy]butanenitrile (1j).

General procedure A: The product was obtained from the extraction as a colourless crystalline solid (0.245 g, 92 %). CAS: 143804-25-5; mp 65-68 °C; TLC R_f (50 % ethyl acetate, 50 % hexanes): 0.49; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3060, 2946, 2248, 1652, 1256, 1049, 845; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.83 (2H, d, *J* = 8.9 Hz), 7.75 (2H, d, *J* = 6.8 Hz), 7.57 (1H, app t, *J* = 8.2 Hz), 7.47 (2H, app t, *J* = 7.5 Hz), 6.96 (2H, d, *J* = 8.9 Hz), 4.17 (2H, t, *J* = 5.8 Hz), 2.62 (2H, t, *J* = 7.2 Hz), 2.19 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 195.4, 161.9, 138.1, 132.5, 132.0, 130.6, 129.7, 128.2, 119.0, 114.0, 65.6, 25.3, 14.1; LRMS (ESI) *m/z* (relative intensity): 288.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2$: 288.0995, found: 288.0997.

4-[2-(Benzoyl)phenoxy]butanenitrile (1k).

General procedure A: Flash column chromatography (40 % ethyl acetate, 60 % hexanes) yielded the product as a colourless crystalline solid (0.232 g, 88 %). mp 79-81 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.50; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2246, 1647; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.79-7.76 (2H, m), 7.60-7.55 (1H, m), 7.50-7.44 (4H, m), 7.10 (1H, td, *J* = 7.6 Hz, *J* = 0.8 Hz), 6.95 (1H, d, *J* = 8.3 Hz), 4.00 (2H, t, *J* = 5.4 Hz), 1.89 (2H, t, *J* = 7.5 Hz), 1.84-1.77 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 196.1, 155.8, 138.2, 132.6, 132.1, 129.5, 128.9, 128.6, 128.2, 120.9, 118.8, 111.8, 65.1, 24.8, 13.0; LRMS (ESI) *m/z* (relative intensity): 288.1 (100%), 553.2 (88%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2$: 288.0995, found: 288.0986.

4-(4-Fluorophenoxy)butanenitrile (1l).

General procedure A: Flash column chromatography (30 % ethyl acetate, 70 % hexanes) yielded the product as a colourless oil (0.175 g, 97 %). CAS: 24115-22-8; mp <25 °C (lit.[33] mp <25 °C); TLC R_f (30 % ethyl acetate, 70 % hexanes): 0.43; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3076, 2926, 2249, 1505, 1249, 1208, 1056, 829; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 6.98 (2H, dd, *J* = 9.3 Hz, *J* = 8.3 Hz), 6.83 (2H, dd, *J* = 9.3 Hz, *J* = 4.3 Hz), 4.04 (2H, t, *J* = 5.7 Hz), 2.59 (2H, t, *J* = 7.1 Hz), 2.13 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.6 (d, *J* = 239 Hz), 154.6, 119.2, 116.0 (d, *J* = 24 Hz), 115.7 (d, *J* = 8 Hz), 66.1, 25.6, 14.3; LRMS (ESI) *m/z* (relative intensity): 202.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}FNO$: 202.0639, found: 202.0638.

4-(2,4-Difluorophenoxy)butanenitrile (1m).

General procedure A: Flash column chromatography (20 % ethyl acetate, 80 % hexanes) yielded the product as a colourless oil (0.190 g, 96 %). CAS: 1016737-82-8; mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.37; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2959, 2885, 2250, 1260, 1211, 1042; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 6.94 (1H, td, *J* = 9.1 Hz, *J* = 5.3 Hz), 6.87 (1H, ddd, *J* = 11.0 Hz, *J* = 8.3 Hz, *J* = 3.0 Hz), 6.82-6.77 (1H, m), 4.11 (2H, t, *J* = 5.8 Hz), 2.63 (2H, t, *J* = 7.2 Hz), 2.15 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.1 (dd, *J* = 242 Hz, *J* = 11 Hz), 152.9 (dd, *J* = 249 Hz, *J* = 12 Hz), 143.0 (dd, *J* = 11 Hz, *J* = 4 Hz), 116.6 (d, *J* = 10 Hz), 110.7 (dd, *J* = 23 Hz, *J* = 4 Hz), 105.1 (dd, *J* = 27 Hz, *J* = 22 Hz), 68.1, 25.7, 14.1; LRMS (ESI) *m/z* (relative intensity): 220.0 (100%), 360.3 (32%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9F_2NO$: 220.0544, found: 220.0554.

4-(2,6-Difluorophenoxy)butanenitrile (1n).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless oil (0.187 g, 95 %). CAS: 1378344-87-6; mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.44; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2961, 2895, 2250, 1595, 1292, 1239, 1037; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.02-6.86 (3H, m), 4.23 (2H, t, *J* = 5.7 Hz), 2.67 (2H, t, *J* = 7.2 Hz), 2.11 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 156.2 (dd, *J* = 248 Hz, *J* = 6 Hz), 135.3 (t, *J* = 14 Hz), 123.5 (t, *J* = 9 Hz), 112.3 (dd, *J* = 17 Hz, *J* = 7 Hz), 72.0 (t, *J* = 3 Hz), 26.3, 13.9; LRMS (ESI) *m/z* (relative intensity): 220.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9F_2NO$: 220.0544, found: 220.0546.

4-(2,4,6-Trifluorophenoxy)butanenitrile (1o).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless oil (0.202 g, 94 %). mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.40; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2968, 2891, 2250, 1238; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 6.70 (2H, app t, *J* = 8.4 Hz), 4.17 (2H, t, *J* = 5.7 Hz), 2.66 (2H, t, *J* = 7.2 Hz), 2.10 (2H, app pentet, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.5 (dt, *J* = 246 Hz, *J* = 14 Hz), 156.1 (ddd, *J* = 250 Hz, *J* = 15 Hz, *J* = 8 Hz), 132.1 (td, *J* = 15 Hz, *J* = 6 Hz), 101.0 (app t, *J* = 27 Hz), 72.4, 26.2, 13.9; LRMS (ESI) *m/z* (relative intensity): 238.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_8F_3NO$: 238.0450, found: 238.0460.

4-(2,3,4,5,6-Pentafluorophenoxy)butanenitrile (1p).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless oil (0.198 g, 79 %). CAS: 1155103-22-2; mp < 25 °C; TLC R_f (10 % ethyl acetate, 90 % hexanes): 0.22; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2969, 2897, 2252, 1161; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 4.28 (2H, t, *J* = 5.7 Hz), 2.66 (2H, t, *J* = 7.1 Hz), 2.16 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 141.8 (dm, *J* = 248 Hz), 138.0 (dm, *J* = 246 Hz), 137.7 (dm), 133.2 (t, *J* = 13 Hz) 118.8, 73.1, 26.1, 13.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ(ppm): –157 (dm, *J* = 24 Hz), –163 (tm, *J* = 21 Hz), –164 (tm, *J* = 22 Hz); LRMS (APCI) *m/z* (relative intensity): 252.0 (100%); HRMS (APCI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_6F_5NO$: 252.0442, found: 252.0431.

4-(4-Chlorophenoxy)butanenitrile (1q).

General procedure A: Flash column chromatography (30 % ethyl acetate, 70 % hexanes) yielded the product as a colourless crystalline solid (0.166 g, 85 %). CAS: 501941-41-9; mp 43-44 °C (lit.[34] mp 44.5-45.3 °C); TLC R_f (30 % ethyl acetate, 70 % hexanes): 0.45; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3097, 2953, 2248, 1244, 1090, 822; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.24 (2H, d, *J* = 8.7 Hz), 6.82 (2H, d, *J* = 8.7 Hz), 4.04 (2H, t, *J* = 5.8 Hz), 2.58 (2H, t, *J* = 7.1 Hz), 2.13 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.1, 129.5, 126.2, 119.1, 115.9, 65.7, 25.5, 14.2; LRMS (ESI) *m/z* (relative intensity): 218.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}ClNO$: 218.0343, found: 218.0338.

4-(2,4-Dichlorophenoxy)butanenitrile (1r).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless crystalline solid (0.228 g, 99 %). CAS: 63867-25-4; mp 45-47 °C (lit.[34] mp 46-48 °C, lit.[35] mp 46-50 °C); TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.44; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3100, 2946, 2885, 2249, 1266, 1064; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.38 (1H, d, *J* = 2.5 Hz), 7.19 (1H, dd, *J* = 8.8 Hz, *J* = 2.5 Hz), 6.85 (1H, d, *J* = 8.8 Hz), 4.12 (2H, t, *J* = 5.7 Hz), 2.66 (2H, t, *J* = 7.0 Hz), 2.19 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 152.8, 130.1, 127.7, 126.5, 124.0, 119.1, 114.5, 66.8, 25.5, 14.1; LRMS (ESI) *m/z* (relative intensity): 252.0 (100%), 254.0 (30%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9Cl_2NO$: 251.9953, found: 251.9962.

4-(2,6-Dichlorophenoxy)butanenitrile (1s).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless oil (0.185 g, 80 %). CAS: 40324-60-5; mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.48; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3080, 2954, 2884, 2249, 1250, 1036; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.30 (2H, d, *J* = 8.3 Hz), 7.01 (1H, t, *J* = 8.3 Hz), 4.13 (2H, t, *J* = 5.7 Hz), 2.75 (2H, t, *J* = 7.2 Hz), 2.19 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 150.9, 129.5, 129.1, 125.5, 119.4, 70.6, 26.4, 14.2; LRMS (ESI) *m/z* (relative intensity): 252.0 (100%), 254.0 (45%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9Cl_2NO$: 251.9953, found: 251.9947.

4-(2,4,6-Trichlorophenoxy)butanenitrile (1t).

General procedure A: Flash column chromatography (10 % ethyl acetate, 90 % hexanes) yielded the product as a colourless crystalline solid (0.258 g, 98 %). CAS: 1039893-81-6; mp 37-39 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.63; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3078, 2955, 2885, 2449, 1257, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.32 (2H, s), 4.11 (2H, t, *J* = 5.7 Hz), 2.73 (2H, t, *J* = 7.2 Hz), 2.18 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 149.8, 130.0, 128.9, 119.2, 70.8, 26.3, 14.1; LRMS (ESI) *m/z* (relative intensity): 286.0 (100%), 288.0 (95%), 290.0 (8%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_8Cl_3NO$: 285.9564, found: 285.9561.

4-(4-Bromophenoxy)butanenitrile (1u).

General procedure A: The product was obtained from the extraction as a colourless amorphous solid (0.181 g, 75 %). CAS: 439798-58-0; mp 38-40 °C (lit.[36] mp 62 °C, lit.[37] mp <25 °C); TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.40; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2930, 2249, 1489, 1244, 1052; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.38 (2H, d, *J* = 9.0 Hz), 6.78 (2H, d, *J* = 9.0 Hz), 4.05 (2H, t, *J* = 5.7 Hz), 2.58 (2H, t, *J* = 7.2 Hz), 2.14 (2H, app pentet, *J* = 6.4 Hz) (consistent with lit.[36,37]); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.5, 132.3, 119.1, 116.3, 113.2, 65.6, 25.3, 14.1 (consistent with lit.[37]); LRMS (ESI) *m/z* (relative intensity): 262.0 (97%), 264.0 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}BrNO$: 261.9838, found: 261.9845.

4-(2,4-Dibromophenoxy)butanenitrile (1v).

General procedure A: Flash column chromatography (30 % ethyl acetate, 70 % hexanes) yielded the product as a colourless crystalline solid (0.209 g, 65 %). CAS: 1340260-50-5;

mp 56-58 °C; TLC R_f (30 % ethyl acetate, 70 % hexanes): 0.22; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2950, 2878, 2249, 1556, 1245, 1069, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.68 (1H, d, *J* = 2.4 Hz), 7.37 (1H, dd, *J* = 8.7 Hz, *J* = 2.4 Hz), 6.77 (1H, d, *J* = 8.7 Hz), 4.11 (2H, t, *J* = 5.6 Hz), 2.67 (2H, t, *J* = 7.1 Hz), 2.19 (2H, app pentet, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 153.9, 135.4, 131.3, 119.0, 114.5, 113.5, 113.1, 66.6, 25.3, 14.0; LRMS (APCI) *m/z* (relative intensity): 317.9 (17%), 319.9 (100%), 321.9 (18%); HRMS (APCI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9Br_2NO$: 317.9124, found: 317.9124.

4-(2,6-Dibromophenoxy)butanenitrile (1w).

General procedure A: The product was obtained from the extraction as a colourless oil (0.147 g, 46 %). CAS: 1016834-03-9; mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.42; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3074, 2950, 2878, 2249, 1556, 1245, 1069, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.50 (2H, d, *J* = 8.0 Hz), 6.88 (1H, t, *J* = 8.1 Hz), 4.12 (2H, t, *J* = 5.5 Hz), 2.75 (2H, t, *J* = 7.3 Hz), 2.21 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 152.6, 132.9, 126.8, 119.5, 118.4, 70.3, 26.5, 14.3; LRMS (APCI) *m/z* (relative intensity): 317.9 (20%), 319.9 (100%), 321.9 (18%); HRMS (APCI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_9Br_2NO$: 317.9124, found: 317.9114.

4-(2,4,6-Tribromophenoxy)butanenitrile (1x).

General procedure A: The product was obtained from the extraction as a colourless crystalline solid (0.118 g, 30 %). CAS: 1039943-44-6; mp 87-88 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.42; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3105, 3064, 2953, 2898, 2253, 1562, 1247, 1032; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.65 (2H, s), 4.10 (2H, t, *J*

= 5.7 Hz), 2.73 (2H, t, *J* = 7.0 Hz), 2.20 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 152.2, 135.3, 119.4, 119.0, 118.0, 70.5, 26.4, 14.3; LRMS (APCI) *m/z* (relative intensity): 395.8 (5%), 397.8 (100%), 399.8 (93%), 401.8 (5%); HRMS (APCI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_8Br_3NO$: 395.8229, found: 395.8244.

4-(4-Iodophenoxy)butanenitrile (1y).

General procedure A: The product was obtained from the extraction as a colourless crystalline solid (0.217 g, 75 %). CAS: 79887-21-1; mp 59-60 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.37; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3087, 3070, 2971, 2944, 2250, 1586, 1244, 1042, 511; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.56 (2H, d, *J* = 8.9 Hz), 6.67 (2H, d, *J* = 8.9 Hz), 4.03 (2H, t, *J* = 5.8 Hz), 2.57 (2H, t, *J* = 7.0 Hz), 2.12 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 158.4, 138.4, 119.1, 117.0, 83.5, 65.5, 25.5, 14.3; LRMS (ESI) *m/z* (relative intensity): 309.9 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}INO$: 309.9699, found: 309.9697.

4-(2,4,6-Triiodophenoxy)butanenitrile (1z).

General procedure A: The product was obtained from the extraction as a colourless crystalline solid (0.143 g, 27 %). CAS: 1038977-67-1; mp 137-138 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.42; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2947, 2359, 1237, 1031, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.05 (2H, s), 4.06 (2H, t, *J* = 5.6 Hz), 2.75 (2H, t, *J* = 7.2 Hz), 2.25 (2H, app pentet, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 157.4, 147.5, 119.5, 91.9, 89.8, 70.3, 26.5, 14.5; LRMS (APCI) *m/z* (relative

intensity): 412.9 (100%), 539.8 (5%); HRMS (APCI) *m/z*: $[M + H]^+$ calcd for $C_{10}H_8I_3NO$: 539.7813, found: 539.7790.

Preparation of Rearrangement Products 2a, 2c-g, 2j, 2r-t, 2w, and Products 3, 4 and 5

General Procedure B

To a round-bottom flask was added the rearrangement substrate (**1**) (0.5 mmol) and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMF (10 mL) was added and the solution was cooled with stirring using an ice water cooling bath. Sodium hydride (60% dispersion in oil) (0.030 g, 0.75 mmol, 1.5 equiv.) was added and low temperature was maintained for 10 minutes. The reaction mixture was removed from the cooling bath and brought to a temperature for an amount of time as described in **Table 2** and **Table 3**. The solution was neutralized at room temperature with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2×20 mL). The organic layer from the extraction was dried, filtered, and concentrated.

General Procedure C

To a round-bottom flask was added the rearrangement substrate (**1**) (0.5 mmol) and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMSO (10 mL) was added followed by sodium hydride (60% dispersion in oil) (0.030 g, 0.75 mmol, 1.5 equiv.) and the reaction mixture was stirred for 20 hours. The solution was neutralized

614 with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL),
615 and washed with water (2 × 20 mL). The organic layer from the extraction was dried,
616 filtered, and concentrated.
617
618 **4-Hydroxy-2-(4-nitrophenyl)butanenitrile (2a).**
619 General Procedure B: Flash column chromatography (40 % ethyl acetate, 60 % hexanes)
620 yielded the product as a yellow oil (0.088 g, 86 %). mp <25 °C; TLC R_f (40 % ethyl
621 acetate, 60 % hexanes): 0.26; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3413, 3081, 2937, 2245,
622 1524, 1348, 1049, 852; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.27 (2H, d, *J* = 8.8 Hz),
623 7.59 (2H, d, *J* = 8.8 Hz), 4.29 (1H, dd, *J* = 9.0 Hz, *J* = 6.5 Hz), 3.93-3.88 (1H, m), 3.77-
624 3.72 (1H, m), 2.26-2.08 (2H, m), 1.85 (1H, br s); ^{1}H NMR (400 MHz, $(CD_3)_2SO$)
625 δ(ppm): 8.28 (2H, d, *J* = 8.8 Hz), 7.71 (2H, d, *J* = 8.8 Hz), 4.87 (1H, t, *J* = 5.0 Hz), 4.51
626 (1H, dd, *J* = 8.9 Hz, *J* = 6.5 Hz), 3.57-3.35 (2H, m), 2.10 (1H, ddt, *J* = 14.0 Hz, *J* = 8.5
627 Hz, *J* = 5.5 Hz), 2.03-1.95 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 147.8, 142.8,
628 128.6, 124.4, 119.8, 58.6, 37.9, 33.5; ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ(ppm): 147.1,
629 143.7, 129.0, 124.1, 120.5, 57.5, 37.2, 32.6; LRMS (ESI) *m/z* (relative intensity): 229.1
630 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{10}N_2O_3$: 229.0584, found: 229.0577.
631
632 **4-Hydroxy-2-(2-nitrophenyl)butanenitrile (2c).**
633 General Procedure B: Flash column chromatography (50 % ethyl acetate, 50 % hexanes)
634 yielded the product as a light yellow oil (0.097 g, 94 %). mp <25 °C; TLC R_f (50 % ethyl
635 acetate, 50 % hexanes): 0.29; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3346, 3110, 2886, 2244,
636 1529, 1350, 1055, 849; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.04 (1H, dd, *J* = 8.3 Hz, *J*

637 = 1.3 Hz), 7.80 (1H, dd, *J* = 7.7 Hz, *J* = 1.5 Hz), 7.72 (1H, app td, *J* = 7.6 Hz, *J* = 1.3
638 Hz), 7.54 (1H, app td, *J* = 7.8 Hz, *J* = 1.5 Hz), 4.94 (1H, dd, *J* = 9.3 Hz, *J* = 5.3 Hz),
639 3.91-3.84 (2H, m), 2.27-2.16 (2H, m), 1.84 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$)
640 δ(ppm): 148.0, 134.3, 130.9, 130.5, 129.6, 125.8, 119.9, 59.6, 37.9, 30.6; LRMS (ESI)
641 *m/z* (relative intensity): 229.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for
642 $C_{10}H_{10}N_2O_3$: 229.0584, found: 229.0591.
643
644 **4-Hydroxy-2-(2,4-dinitrophenyl)butanenitrile (2d).**
645 General Procedure B: Flash column chromatography (50 % ethyl acetate, 50 % hexanes)
646 yielded the product as a light yellow oil (0.025 g, 22 %) and 2,4-dinitrophenol (0.008 g, 9
647 %). mp <25 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.19; IR (KBr, thin film)
648 $\bar{\nu}_{max}$ (cm^{-1}): 3112, 2924, 2888, 2248, 1537, 1349, 1059; ^{1}H NMR (400 MHz, $CDCl_3$)
649 δ(ppm): 8.90 (1H, d, *J* = 2.5 Hz), 8.55 (1H, dd, *J* = 8.7 Hz, *J* = 2.5 Hz), 8.07 (1H, d, *J* =
650 8.8 Hz), 5.07 (1H, dd, *J* = 9.3 Hz, *J* = 5.3 Hz), 3.94-3.89 (2H, m), 2.30-2.16 (2H, m), 1.57
651 (1H, t, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 148.1, 147.9, 137.5, 132.2,
652 128.2, 121.1, 118.7, 59.4, 37.6, 31.0; LRMS (ESI) *m/z* (relative intensity): 274.0 (100%);
653 HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9N_3O_5$: 274.0434, found: 274.0442.
654
655 **4-Hydroxy-2-(4-cyanophenyl)butanenitrile (2e).**
656 General Procedure B: Flash column chromatography (2 % methanol, 98 %
657 dichloromethane) yielded the product as a light yellow oil (0.054 g, 58 %) and recovered
658 reactant **1e** (0.013 g, 14 %). mp <25 °C; TLC R_f (60 % ethyl acetate, 40 % hexanes):
659 0.22; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3512, 3096, 2936, 2232, 1049, 833; ^{1}H NMR (400

MHz, $CDCl_3$) δ(ppm): 7.71 (2H, d, *J* = 8.4 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 4.22 (1H, dd, *J* = 9.0 Hz, *J* = 6.5 Hz), 3.92-3.85 (1H, m), 3.76-3.70 (1H, m), 2.23-2.05 (2H, m), 1.65 (1H, t, *J* = 4.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 140.9, 133.1, 128.5, 119.7, 118.2, 112.6, 58.8, 38.0, 33.8; LRMS (ESI) *m/z* (relative intensity): 209.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O$: 209.0685, found: 209.0684.

4-Hydroxy-2-(2-cyanophenyl)butanenitrile (2f).

General Procedure C: Flash column chromatography (40 % ethyl acetate, 60 % hexanes) yielded the product as a colourless oil (0.042 g, 44 %) and **3** (0.029 g, 31 %). mp <25 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.23; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3446, 2934, 2886, 2227, 1053; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.73-7.67 (3H, m), 7.50-7.46 (1H, m), 4.54 (1H, dd, *J* = 8.4 Hz, *J* = 6.6 Hz), 3.92-3.80 (2H, m), 2.26-2.18 (2H, m), 1.66 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 139.5, 134.0, 133.7, 129.0, 128.7, 119.3, 116.8, 111.9, 59.3, 38.0, 32.7; LRMS (ESI) *m/z* (relative intensity): 209.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O$: 209.0685, found: 209.0691.

4-Hydroxy-2-(6-cyanonaphthalen-2-yl)butanenitrile (2g).

General Procedure B: Flash column chromatography (50 % ethyl acetate, 50 % hexanes) yielded the product as a colourless crystalline solid (0.073 g, 64 %). mp 77-78 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.11; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3060, 2959, 2934, 2886, 2229, 1050, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 8.24 (1H, s), 7.96-7.93 (3H, m), 7.66 (1H, d, *J* = 8.6 Hz), 7.59 (1H, d, *J* = 8.6 Hz), 4.35 (1H, t, *J* = 7.6 Hz), 3.95-3.89 (1H, m), 3.79-3.74 (1H, m), 2.30-2.17 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$)

δ(ppm): 136.5, 134.8, 134.0, 131.8, 129.8, 129.3, 127.4, 126.9, 126.8, 120.4, 119.0, 110.2, 59.0, 38.1, 33.9; LRMS (ESI) *m/z* (relative intensity): 259.1 (100%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{15}H_{12}N_2O$: 259.0842, found: 259.0837.

4-Hydroxy-2-[4-(benzoyl)nitrophenyl]butanenitrile (2j).

General Procedure B: Flash column chromatography (50 % ethyl acetate, 50 % hexanes) yielded the product as a light yellow oil (0.093 g, 70 %) and recovered reactant **1j** (0.016 g, 12 %). mp <25 °C; TLC R_f (50 % ethyl acetate, 50 % hexanes): 0.20; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3482, 3060, 2933, 2243, 1652, 1281, 1049, 849; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.84-7.78 (4H, m), 7.61 (1H, app t, *J* = 7.4 Hz), 7.52-7.48 (4H, m), 4.23 (1H, dd, *J* = 9.0 Hz, *J* = 6.6 Hz), 3.92-3.86 (1H, m), 3.78-3.72 (1H, m), 2.26-2.09 (2H, m), 2.05 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 196.2, 140.1, 137.6, 137.3, 132.9, 131.0, 130.1, 128.5, 127.6, 120.3, 58.9, 38.1, 33.6; LRMS (ESI) *m/z* (relative intensity): 288.1 (95%), 553.2 (100%), 818.3 (35%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{15}NO_2$: 288.0995, found: 288.1002.

4-Hydroxy-2-(2,4-dichlorophenyl)butanenitrile (2r).

General Procedure C: Flash column chromatography (20 % ethyl acetate, 80 % hexanes) yielded the product as a colourless oil (0.048 g, 42 %) and recovered reactant **1r** (0.026 g, 23 %). mp <25 °C; TLC R_f (20 % ethyl acetate, 80 % hexanes): 0.17; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3446, 2885, 2245, 1475, 1045; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.51 (1H, d, *J* = 8.4 Hz), 7.44 (1H, d, *J* = 2.2 Hz), 7.33 (1H, dd, *J* = 8.4 Hz, *J* = 2.2 Hz), 4.53 (1H, dd, *J* = 9.5 Hz, *J* = 5.6 Hz), 3.90-3.81 (2H, m), 2.20-2.05 (2H, m), 1.53 (1H, br s);

^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 135.2, 133.7, 132.2, 130.2, 130.1, 128.2, 119.8, 59.5, 36.6, 31.1; LRMS (ESI) *m/z* (relative intensity): 252.0 (100%) 254.0 (61%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9Cl_2NO$: 251.9953, found: 251.9950.

4-Hydroxy-2-(2,6-dichlorophenyl)butanenitrile (2s).

General Procedure C: Flash column chromatography (40 % ethyl acetate, 60 % hexanes) yielded the product as a colourless oil (0.065 g, 56 %). mp <25 °C; TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.30; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3444, 2941, 2884, 2244, 1436, 1057, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.37 (2H, d, *J* = 8.1 Hz), 7.23 (1H, dd, *J* = 8.7 Hz, *J* = 7.5 Hz), 5.06 (1H, dd, *J* = 9.0 Hz, *J* = 6.6 Hz), 3.93-3.85 (1H, m), 3.81-3.75 (1H, m), 2.52-2.44 (1H, m), 2.17-2.08 (1H, m), 1.62 (1H, br t, *J* = 4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm):135.3, 130.8, 130.1, 129.4 (br), 118.4, 59.3, 33.7, 29.4; LRMS (ESI) *m/z* (relative intensity): 252.0 (100%), 483.0 (37%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9Cl_2NO$: 251.9953, found: 251.9950.

4-Hydroxy-2-(2,4,6-trichlorophenyl)butanenitrile (2t).

General Procedure B: Flash column chromatography (35 % ethyl acetate, 65 % hexanes) yielded the product as a colourless crystalline solid (0.033 g, 25 %) and recovered reactant **1t** (0.065 g, 49 %).

General Procedure C: Flash column chromatography (35 % ethyl acetate, 65 % hexanes) yielded the product as a colourless crystalline solid (0.045 g, 34.3 %) and recovered reactant **1t** (0.027 g, 20.1 %). mp 74-76 °C; TLC R_f (35 % ethyl acetate, 65 % hexanes): 0.42; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3078, 2939, 2886, 2246, 1168, 1055; ^{1}H NMR (400

MHz, $CDCl_3$) δ(ppm): 7.40 (2H, s), 5.02 (1H, dd, *J* = 9.1 Hz, *J* = 6.6 Hz), 3.92-3.86 (1H, m), 3.80-3.75 (1H, m), 2.46 (1H, dddd, *J* = 14.2 Hz, *J* = 9.3 Hz, *J* = 5.6 Hz, *J* = 4.3 Hz), 8.09 (1H, dddd, *J* = 14.2 Hz, *J* = 8.5 Hz, *J* = 6.3 Hz, *J* = 4.8 Hz), 1.57 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 135.9, 135.3, 129.6, 129.4 (br), 118.0, 59.2, 33.6, 29.2; LRMS (ESI) *m/z* (relative intensity): 286.0 (100%), 288.0 (91%), 290.0 (6%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_8Cl_3NO$: 285.9564, found: 285.9555.

4-Hydroxy-2-(2,6-dibromophenyl)butanenitrile (2w).

General Procedure C: Flash column chromatography (30 % ethyl acetate, 70 % hexanes) yielded the product as a colourless oil (0.037 g, 30 %), recovered reactant **1w** (0.037 g, 30 %), and 2,6-dibromophenol (0.040 g, 41 %). mp <25 °C; TLC R_f (30 % ethyl acetate, 70 % hexanes): 0.22; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3443, 2934, 2883, 2242, 1576, 1430, 1058; ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.60 (2H, d, *J* = 8.1 Hz), 7.06 (1H, t, *J* = 8.1 Hz), 5.15 (1H, dd, *J* = 9.3 Hz, *J* = 6.3 Hz), 3.94-3.87 (1H, m), 3.85-3.78 (1H, m), 2.53 (1H, qd, *J* = 9.4 Hz, *J* = 4.7 Hz), 2.14 (1H, dddd, *J* = 13.9 Hz, *J* = 8.6 Hz, *J* = 6.3 Hz, *J* = 5.1 Hz), 1.55 (1H, br t, *J* = 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 134.5 (br), 133.4, 133.0 (br), 130.9, 125.7 (br), 124.1 (br), 118.3, 59.4, 34.5, 33.7; LRMS (ESI) *m/z* (relative intensity): 339.9 (48%), 341.9 (100%), 343.9 (45%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_9Br_2NO$: 339.8943, found: 339.8927.

1,2-Dihydrofuro[2,3-*c*]isoquinolin-5-amine (3).

To a round-bottom flask was added the rearrangement substrate (**1f**) (0.093 g, 0.5 mmol) and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMF

(10 mL) was added and the solution was cooled with stirring using an ice water cooling bath. Sodium hydride (60% dispersion in oil) (0.030 g, 0.75 mmol, 1.5 equiv.) was added and low temperature was maintained for 10 minutes. The reaction mixture was removed from the cooling bath and brought to 60 °C for 20 hours. The solution was neutralized at room temperature with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2 × 20 mL). The organic layer from the extraction was dried, filtered, and concentrated. Flash column chromatography (50 % ethyl acetate, 50 % hexanes) yielded the product as an orange crystalline solid (0.015 g, 17 %). CAS: 194724-61-3; mp 188 °C (dec.) (lit.[24] 109-192 °C); TLC R_f (40 % ethyl acetate, 60 % hexanes): 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.71 (1H, d, *J* = 8.5 Hz), 7.55 (1H, t, *J* = 7.5 Hz), 7.43 (1H, d, *J* = 8.3 Hz), 7.22 (1H, t, *J* = 7.7 Hz), 5.14 (2H, br s), 4.71 (2H, t, *J* = 8.7 Hz), 3.33 (2H, t, *J* = 8.7 Hz) (consistent with lit.[24]); LRMS (ESI) *m/z* (relative intensity): 187.1(100%); HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{11}H_{10}N_2O$: 187.0866, found: 187.0860.

(2*E*)-2-[(2-Hydroxyphenyl)(phenyl)methylidene]but-3-enenitrile (4).

To a round-bottom flask was added the rearrangement substrate (**1k**) (0.133 g, 0.5 mmol) and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMSO (10 mL) was added followed by sodium hydride (60% dispersion in oil) (0.030 g, 0.75 mmol, 1.5 equiv.) and the reaction mixture was stirred for 20 hours. The solution was neutralized with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2 × 20 mL). The organic layer from the extraction was dried, filtered, and concentrated. Flash column chromatography (50 % ethyl acetate, 50 %

hexanes) yielded the product as a colourless crystalline solid (0.106 g, 85 %). mp 111-113 °C; TLC R_f (30 % ethyl acetate, 70 % hexanes): 0.50; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 3061, 2220, 1643, 1603, 1263; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.49-7.47 (2H, m), 7.42-7.36 (3H, m), 7.31 (1H, ddd, *J* = 8.2 Hz, *J* = 7.2 Hz, *J* = 1.9 Hz), 7.02 (1H, dd, *J* = 7.7 Hz, *J* = 2.0 Hz), 6.97 (1H, td, *J* = 7.2 Hz, *J* = 1.0 Hz), 6.91 (1H, dd, *J* = 8.3 Hz, *J* = 0.8 Hz), 6.32 (1H, dd, *J* = 17.1 Hz, *J* = 10.5 Hz), 5.89 (1H, d, *J* = 17.0 Hz), 5.44 (1H, d, *J* = 10.5 Hz), 4.86 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 153.0, 152.2, 138.3, 131.4, 131.3, 131.2, 130.4, 129.5, 128.8, 124.9, 121.0, 120.8, 116.9, 116.9, 113.1; LRMS (ESI) *m/z* (relative intensity): 270.1 (100%), 517.2 (37%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{13}NO$: 270.0889, found: 270.0889.

5,7-Dibromo-3,4-dihydro-2*H*-chromene-4-carbonitrile (5).

To a round-bottom flask was added the rearrangement substrate (**1x**) (0.199 g, 0.5 mmol) and the flask was evacuated and backfilled with nitrogen three times. Anhydrous DMF (10 mL) was added and the solution was cooled with stirring using an ice water cooling bath. Sodium hydride (60% dispersion in oil) (0.030 g, 0.75 mmol, 1.5 equiv.) was added and low temperature was maintained for 10 minutes. The reaction mixture was removed from the cooling bath and brought to 40 °C for 20 hours. The solution was neutralized at room temperature with 1 M $HCl_{(aq)}$, diluted with ethyl acetate (20 mL), washed with 1 M $HCl_{(aq)}$ (15 mL), and washed with water (2 × 20 mL). The organic layer from the extraction was dried, filtered, and concentrated. Flash column chromatography (20 % ethyl acetate, 80 % hexanes) yielded the product as a colourless crystalline solid (0.064 g, 40 %) recovered reactant **1x** (0.046 g, 23 %). mp 132-133 °C; TLC R_f (20 % ethyl

acetate, 80 % hexanes): 0.49; IR (KBr, thin film) $\bar{\nu}_{max}$ (cm^{-1}): 2929, 2887, 2237, 1228, 1077, 1059; ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.37 (1H, d, *J* = 2.0 Hz), 7.05 (1H, d, *J* = 2.0 Hz), 4.45 (1H, ddt, *J* = 11.6 Hz, *J* = 3.8 Hz, *J* = 2.0 Hz), 4.26 (1H, td, *J* = 12.2 Hz, *J* = 2.0 Hz), 4.04 (1H, dt, *J* = 5.4 Hz, *J* = 1.8 Hz), 2.39 (1H, dq, *J* = 14.3 Hz, *J* = 2.2 Hz), 2.22 (1H, dddd, *J* = 14.3 Hz, *J* = 12.5 Hz, *J* = 5.5 Hz, *J* = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm): 156.1, 127.8, 125.7, 123.6, 120.6, 118.9, 114.8, 63.2, 27.8, 25.8; LRMS (ESI) *m/z* (relative intensity): 337.9 (49%), 339.9 (100%), 341.9 (46%); HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_7Br_2NO$: 337.8787, found: 337.8782.

***In situ* Preparation of Meisenheimer intermediate**

[(4-Cyano-1-oxaspiro[4.5]deca-6,9-dien-8-ylidene)(oxido)-l5-azanyl]oxidanide.

To a 5 mm NMR tube was added the rearrangement substrate (**1a**) (0.010g, 0.05 mmol) dissolved in $(CD_3)_2SO$ (99.5 atom% ^{2}H,+ 0.1 v/v TMS) (1 mL). Sodium hydride (60% dispersion in oil) (0.002 g, 0.05 mmol, 1 equiv.) was added and the reaction mixture was vortexed repeatedly over 16 hours. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ(ppm): 7.38 (1H, dd, *J* = 9.5 Hz, *J* = 2.4 Hz), 7.34 (1H, dd, *J* = 9.5 Hz, *J* = 2.4 Hz), 6.38 (1H, dd, *J* = 9.5 Hz, *J* = 2.4 Hz), 6.22 (1H, dd, *J* = 9.5 Hz, *J* = 2.4 Hz), 4.61 (1H, br s), 3.42-3.33 (2H, m), 2.28 (2H, m); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ(ppm): 148.4, 127.6, 125.7, 125.2, 124.5, 117.1, 113.2, 74.0, 60.0, 59.9, 32.2, 32.1.

Associated Content

Copies of ^{1}H and ^{13}C NMR spectra of compounds **1a**–**z**, **2a**, **2c**–**g**, **2j**, **2r**–**t**, **2w**, **3**, **4**, and **5**.

Acknowledgements

Financial support for this work was provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada, the University of Winnipeg, and the Government of Manitoba Career Focus Program. Dr. K. Marat (University of Manitoba) is gratefully acknowledged for obtaining the $^{13}C\{^{19}F\}$ NMR spectrum. We also would like to thank Mr. Xiao Feng (Dalhousie University Maritime Mass Spectrometry Laboratories) for obtaining the mass spectra of all synthesized compounds.

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