rich2/ccj-cjc/ccj-cjc/ccj99914/ccj0808d14z | xppws | S=3 | 2/18/17 | 5:01 | Art: cjc-2016-0594 | Input-1st disk, 2nd ??
Pagination not final (cite DOI) / Pagination provisoire (citer le DOI)

NRC Research Press

INVITED REVIEW

The Truce–Smiles rearrangement and related reactions: a review

Fn1 Anna R.P. Henderson, Joel R. Kosowan, and Tabitha E. Wood

Abstract: The Truce–Smiles rearrangement is an X → C aryl migration reaction that is achieved by an intramolecular nucleophilic aromatic substitution pathway. The reaction exhibits a wide substrate scope with respect to a migrating aryl ring and leaving group, appearing in many different tandem reaction sequences, to achieve a wide variety of product outcomes. We present an extensive survey of reported examples of the Truce–Smiles rearrangement from the chemistry literature (1950s until present) organized by various substrate design variables or aspects of the reaction method. Present deficiencies in our understanding of the reaction are identified with recommendations for future research directions and useful developments in the application of the reaction are celebrated.

Key words: organic chemistry, named organic reactions, rearrangement reaction, aryl migration reaction, reaction methodology.

Résumé : Le réarrangement de Truce–Smiles est une réaction de migration X → C du groupe aryle qui se produit par un mécanisme de substitution nucléophile aromatique intramoléculaire. La réaction s'applique à une vaste gamme de substrats – dont le groupement migrateur aryle et le groupe partant sont variables – que l'on retrouve dans plusieurs différentes séquences de réactions en tandem, et permet d'obtenir une grande variété de produits de réaction. Nous avons recensé de manière approfondie les exemples du réarrangement de Truce–Smiles publiés dans la littérature chimique (des années 1950 jusqu'à aujourd'hui) et les avons organisés selon les divers types de structure des substrats ou les divers aspects de la méthode de réaction. Nous avons relevé les lacunes actuelles limitant notre compréhension de la réaction et proposons des recommandations pour orienter les recherches futures. Nous saluons également les progrès réalisés dans l'application de la réaction. [Traduit par la Rédaction]

Mots-clés : chimie organique, appellations de réactions organiques, réaction de réarrangement, réaction de migration d'aryle, méthodologie de réaction.

Table of contents

1. Introduction

Rearrangement reactions are arguably some of the most efficient and elegant chemical reactions known. They not only potentially benefit from the enhanced reactivity and selectivity provided by intramolecularity, but also achieve significant structural alterations of substrate molecules with little waste. The Truce–Smiles rearrangement is an intramolecular nucleophilic aromatic substitution reaction featuring a carbanion nucleophile. It has been known for several decades, however thorough and systematic investigations of its mechanism and application have not yet been completed. The Truce–Smiles rearrangement is potentially of great practical interest to synthetic organic chemists due to its perfect atom economy and its resultant formation of a new carbon–carbon bond in the product. The reaction is also of great theoretical interest due to the unknown influence of the numerous conceivable design variables of Truce–Smiles rearrangement substrates.

The Truce–Smiles rearrangement is so-named because William Truce recognized it as a variation of the Smiles rearrangement when he published his first report on the reaction in 1958.[1] Truce and his colleagues at the Department of Chemistry, Purdue University, published a series of journal articles about the reaction as

Received 10 November 2016. Accepted 9 January 2017.

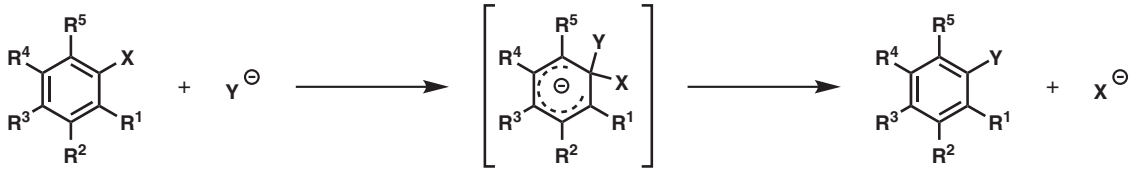
A.R.P. Henderson,* J.R. Kosowan,* and T.E. Wood. Department of Chemistry, The University of Winnipeg, 515 Portage Avenue, Winnipeg, MB R3B 2E9, Canada.

Corresponding author: Tabitha E. Wood (email: te.wood@uwinnipeg.ca).

*Both authors contributed equally to this work.

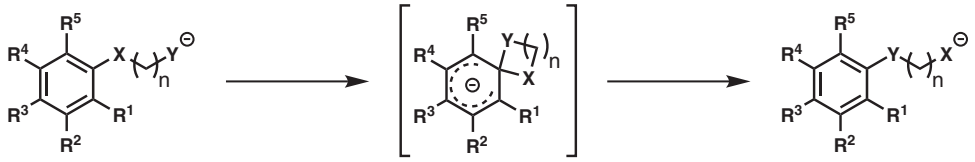
Copyright remains with the author(s) or their institution(s). Permission for reuse (free in most cases) can be obtained from RightsLink.

Scheme 1. General scheme for S_NAr mechanism.



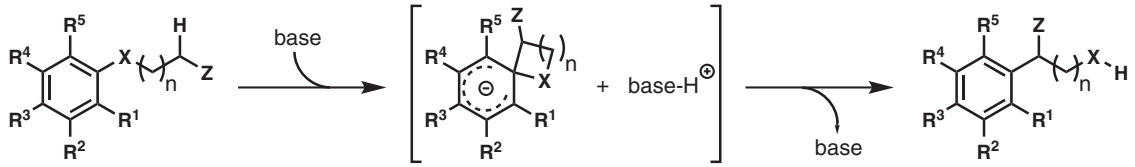
1

Scheme 2. General scheme of a Smiles rearrangement.



2

Scheme 3. General scheme of a base-catalyzed Truce–Smiles rearrangement.



3

it related to the base-promoted rearrangement of aryl sulfones.[1–7] However, it could be argued that the first report of Truce–Smiles reactivity can be attributed to Renzo Dohmori who, over a decade beginning in 1954, published a series of journal articles[8–15] with his colleagues about the base-promoted rearrangement of aryl sulfonamides as part of their work at the Central Research Laboratory of Daiichi Seiyaku Company, Ltd. The work of Dohmori may have escaped comparison with Truce's work because the rearrangement of sulfonamides was reported as part of a tandem sequence of reactions. The definition and etymology of the reaction will be discussed in more detail later in sections 2 and 5.

Since the initial reports by Truce and Dohmori, the reaction has received attention from other research groups, notably Victor Drozd and colleagues,[16,17] but has largely languished in obscurity, with only sporadic reports in the chemistry literature. However, the reaction has recently begun to receive a more systematic investigation by researchers such as Takashi Hirota[18–28] and Timothy Snape.[29–31] Despite our awareness of the Truce–Smiles rearrangement for 60 years, there remain many unanswered questions about the scope and limitations of this reaction. In this review, we seek to summarize the current state of our understanding of the reaction and hope to inspire continued progress.

2. Mechanistic considerations

2.1. Nucleophilic aromatic substitution

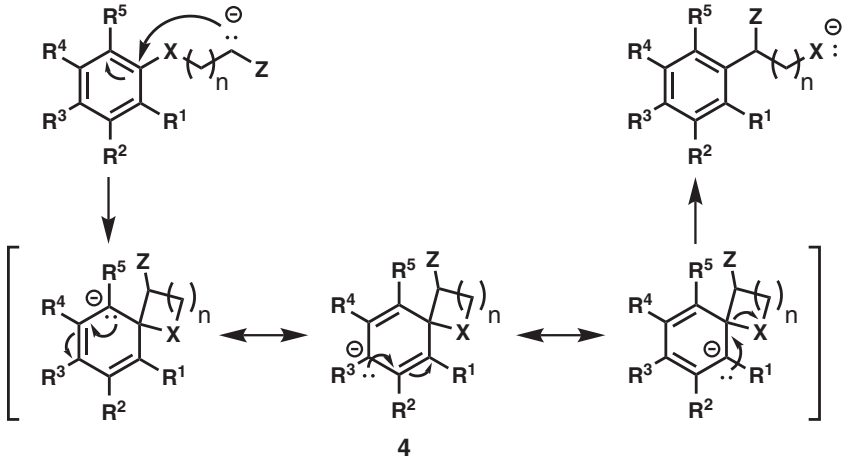
Observations of the nature of the Truce–Smiles rearrangement are generally consistent with the mechanism of a nucleophilic S1 aromatic substitution reaction, S_NAr (Scheme 1). This reaction can be stepwise with a stable cyclohexadienyl anion intermediate sigma-adduct (**1**), commonly known as a Meisenheimer adduct/complex, or it can be concerted with a transition state Meisen- S2 heimer adduct.[32] The Smiles rearrangement (Scheme 2) is the reaction named for chemist Samuel Smiles[33] that describes an intramolecular nucleophilic aromatic substitution wherein the nucleophile is a heteroatom, i.e., Y is a heteroatom in the reaction shown in Scheme 2. The intramolecular nature of the nucleophile results in a spirocyclic Meisenheimer adduct (**2**). The Truce–Smiles rearrangement involves a carbanion nucleophile, which differentiates it from the Smiles rearrangement, and the general scheme shown in Scheme 3 depicts the Truce–Smiles rearrangement spe- S3 cifically when the carbanion nucleophile is prepared by deprotonation. Generation of the nucleophile will be discussed further in section 4.4, but deprotonation through use of a base is the most commonly employed method.

The proposed mechanism of the Truce–Smiles rearrangement such as the one implied in Scheme 3 and shown in Scheme 4 S4 consists of the typical addition–elimination sequence prescribed by S_NAr and is very similar to the mechanism proposed for the Smiles rearrangement. Because the reaction is intramolecular, the typical S_NAr Meisenheimer adduct is a spirocycle (**3** or **4**), with the spirocyclic center bonded to the nucleophile and the atom (X in Scheme 3 or 4) that serves both to link the nucleophile to the aromatic ring and as the leaving group during the elimination step. Stabilization of the Meisenheimer adduct is essential to promoting nucleophilic aromatic substitution. This is generally achieved by including strongly electron–withdrawing substituents at positions ortho and (or) para to the leaving group or linking substituent, directing nucleophilic attack to the ipso carbon on the migrating aryl ring of the substrate. The role of substituents on the migrating aryl ring in the rearrangement reaction is further discussed in section 4.1.

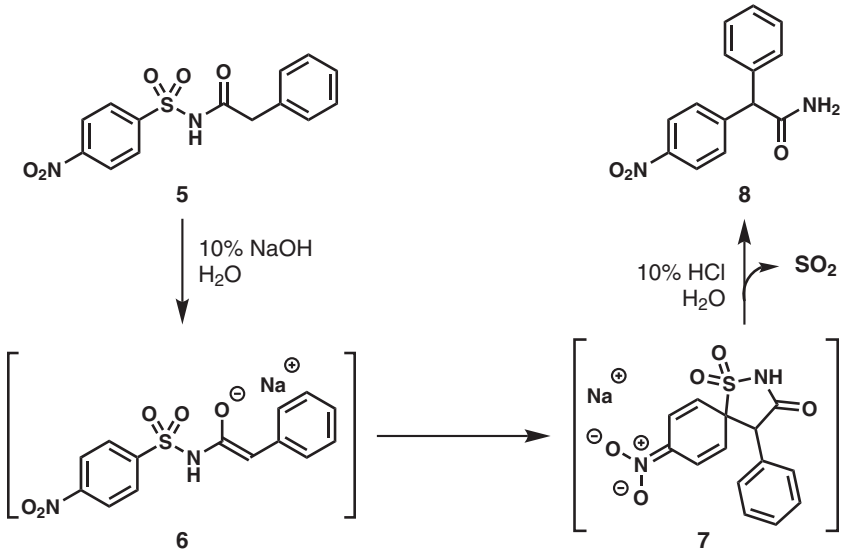
2.1.1. Tandem reactions

Many of the reported examples of the Truce–Smiles rearrangement appear as part of tandem reaction sequences. A popular combination is the tandem Truce–Smiles rearrangement – sulfur dioxide extrusion sequence. The reactions studied by Dohmori and colleagues fit this category, a typical example of which is shown in Scheme 5. Many of their reported reactions combined S5 multiple additional subsequent tandem reactions such as hydrolysis, decarboxylation, or deacetylation.[9] Gravimetric analysis of the extruded sulfur dioxide, via the formation of $BaSO_4$, was exploited

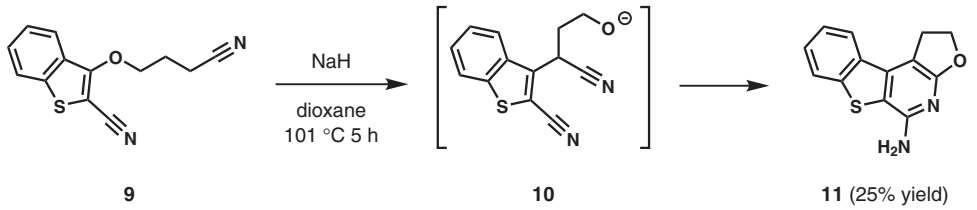
Scheme 4. Proposed S_NAr mechanism of the Truce–Smiles rearrangement.



Scheme 5. Typical tandem Truce–Smiles rearrangement – sulfur dioxide extrusion reaction studied by Naito and colleagues.[9]



Scheme 6. Example of tandem Truce–Smiles rearrangement – heterocyclic ring closing reaction investigated by Okuda and colleagues.[28]



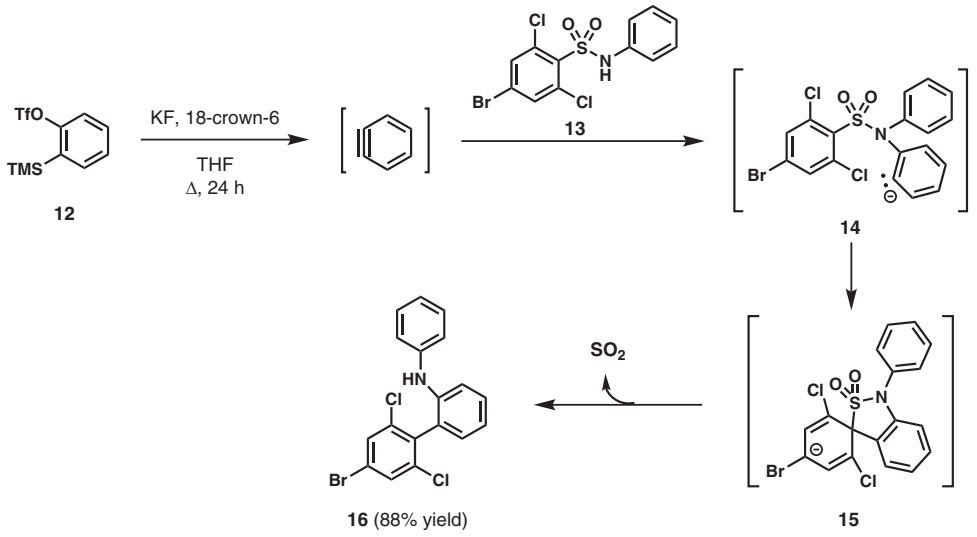
as a convenient method for measuring reaction rates in kinetic studies of these reactions.[15]

The tandem Truce–Smiles rearrangement – sulfur dioxide extrusion[34–43] sequence is likely a common combination, because the sulfonyl group is a useful substituent on the migrating aryl ring that can serve as both an activating group for stabilizing the Meisenheimer adduct by withdrawing electron density through an inductive effect and as a competent leaving group. This is discussed further in section 4.1.

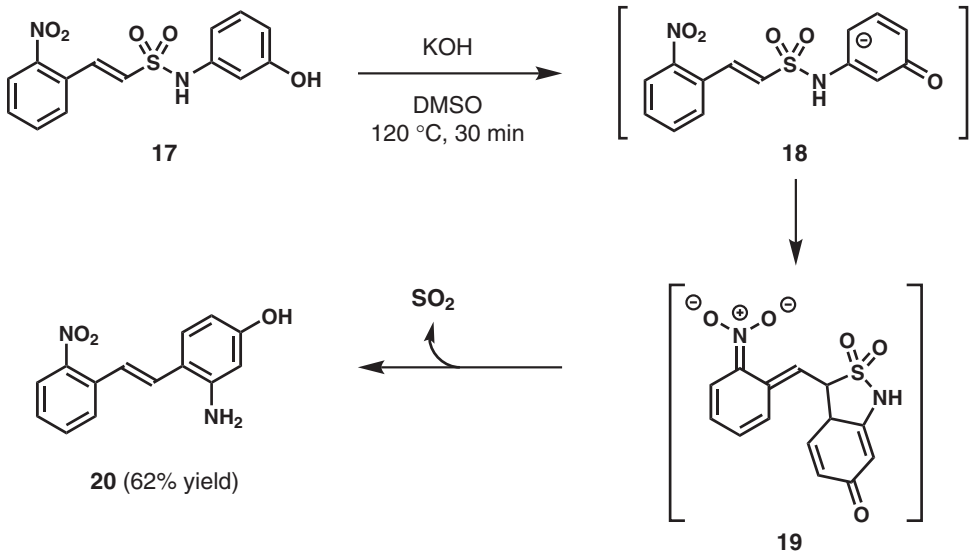
Another example of a tandem sequence that has been well explored is the use of the anionic leaving group from the Truce–Smiles rearrangement as a nucleophile in a subsequent reaction. Hirota and colleagues have investigated the use of anionic oxygen or sulfur leaving groups post-Truce–Smiles rearrangement in the formation of dihydrofuran- or thiodihydrofuran-fused amino pyridines by trapping with nitrile electrophiles.[18,19,21–23,25,28] A typical example of this tandem process is shown in Scheme 6. The cyano substituent on the alkyl tether of substrate **9** serves during the rearrangement as a functional group (Z in Schemes 3 and 4) to stabilize the carbanion, lowering the pK_a of the associated precursory C–H bond. The product of the rearrangement, **10** in Scheme 6, undergoes a tandem cyclization by attack of the oxyanion on the Z group cyano substituent to form a furan ring and a nitrogen anion. The nitrogen anion further reacts with a cyano substituent on the migrating aryl ring, which has also served as an activating

S6

Scheme 7. Example of tandem benzyne – Truce–Smiles rearrangement – sulfur dioxide extrusion reaction.[43]



Scheme 8. Example of vinylogous Truce–Smiles rearrangement.[35]



group to nucleophilic aromatic substitution by stabilizing the Meisenheimer adduct, to form the tetracyclic product **11**.

The tandem combination of a reaction that prepares the substrate in situ with the Truce–Smiles rearrangement is another commonly used sequence. Researchers have typically chosen to prepare an aryl ether substrate by Williamson ether synthesis[30,31,44–46] or an aniline substrate,[47,48] with judicious choice of a base that can subsequently form the carbanion intermediate to instigate the Truce–Smiles rearrangement. In one unusual example[43] (Scheme 7), a benzyne intermediate is used to form the sulfonamide bond linking the nucleophilic and electrophilic portions of the substrate **14** with concurrent production of the carbanion nucleophile. The tandem benzyne – Truce–Smiles rearrangement example also features a subsequent tandem sulfur dioxide extrusion before arriving at the final product, diarylamine **16**.[43]

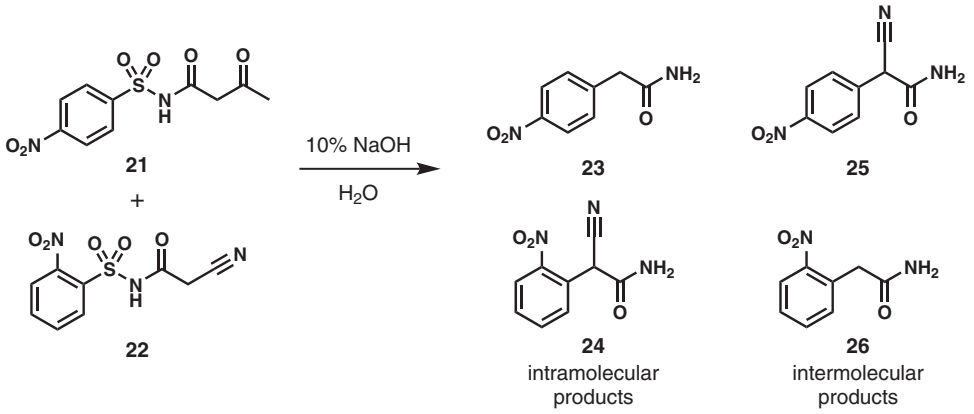
2.1.2. Vinylogous reactions

An interesting extension of the S_NAr mechanism for the Truce–Smiles rearrangement has been the reported[35] vinylogous version of the reaction. An example of this reaction is shown in Scheme 8. The account, which features the unique use of a phenolate carbanion nucleophile such as **18**, reports a series of three nitrostyrene substrates that successfully produce rearranged stilbene products.[35] The report also provides an account of the rearrangement of numerous non-vinylogous substrates. The apparent preference of the carbanion nucleophile to attack in a vinylogous manner as opposed to at the conventional S_NAr ipso carbon electrophile may be influenced by the apparent preference of Truce–Smiles rearrangement reactions to proceed via 5-membered spirocyclic Meisenheimer adducts as opposed to the alternative 7-membered adduct. This preference will be discussed in more detail in section 4.3.

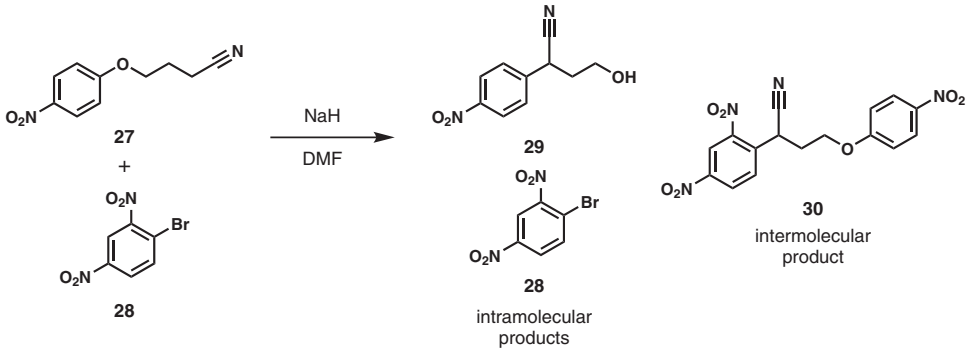
2.1.3. Experimental evidence for mechanism

Some experiments have been conducted to provide support for a S_NAr mechanism for the Truce–Smiles rearrangement. The intramolecular nature of the nucleophilic attack, as opposed to intermolecular, has been supported by two sets of competition experiments,[10,49] as shown in Schemes 9 and 10. The experiment conducted by Dohmori's research group (Scheme 9) relied on the assumption that the two sulfonamide substrates have the same

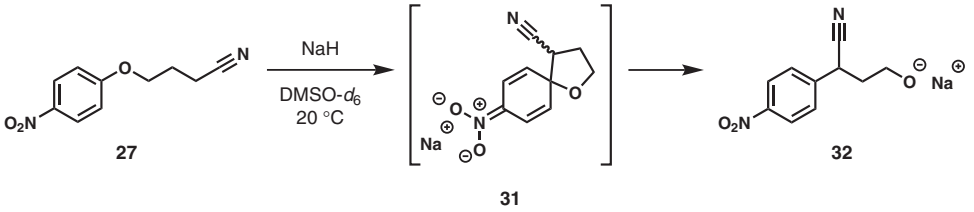
Scheme 9. Experiment demonstrating intramolecular mechanism.[10]



Scheme 10. Experiment demonstrating intramolecular mechanism.[49]



Scheme 11. Truce–Smiles rearrangement studied by ^{1}H and ^{13}C NMR spectroscopy.[49]



reaction rate, an assumption that was later verified.[15] The experiment conducted by our research group (Scheme 10) relied upon the assumption that 2,4-dinitrobromobenzene is at least equal in reactivity, with respect to nucleophilic aromatic substitution, to the aryl ether substrate. This was deemed a safe assumption based on both the inclusion of bromide, an excellent leaving group, and two strongly activating nitro groups at the ortho- and para-positions, relative to the leaving group. Intramolecular products (**23** and **24** in Scheme 9 and **29** in Scheme 10) were formed exclusively in both experiments[10,49] with no indication of intermolecular products (**25**, **26**, or **30**) supporting the mechanism as an intramolecular nucleophilic aromatic substitution.

In addition to the competition experiments, we also performed a brief examination of the effect of substrate concentration upon the yield of the Truce–Smiles rearrangement.[49] This experiment resulted in complete consumption of the rearrangement substrate at high and low substrate concentrations but resulted in higher yields of the rearrangement product at lower concentrations of the substrate. This observation suggests competing side-reactions, possibly intermolecular nucleophilic aromatic substitution at higher concentrations, an observation that supports the hypothesis that the Truce–Smiles rearrangement features an intramolecular reaction.

Fig. 1. Isomers arising from addition of nucleophile during intramolecular nucleophilic aromatic substitution.

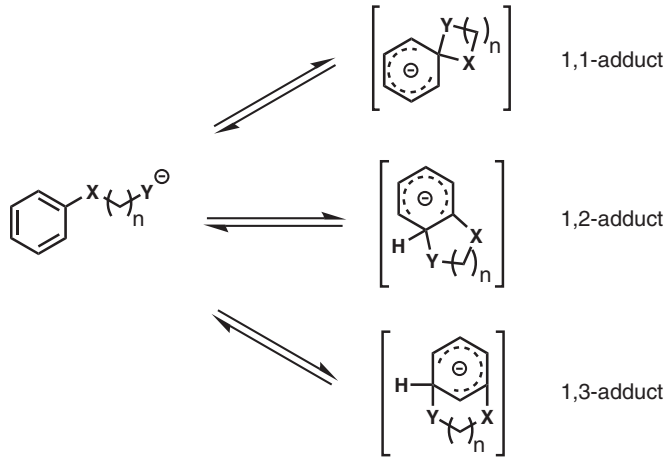
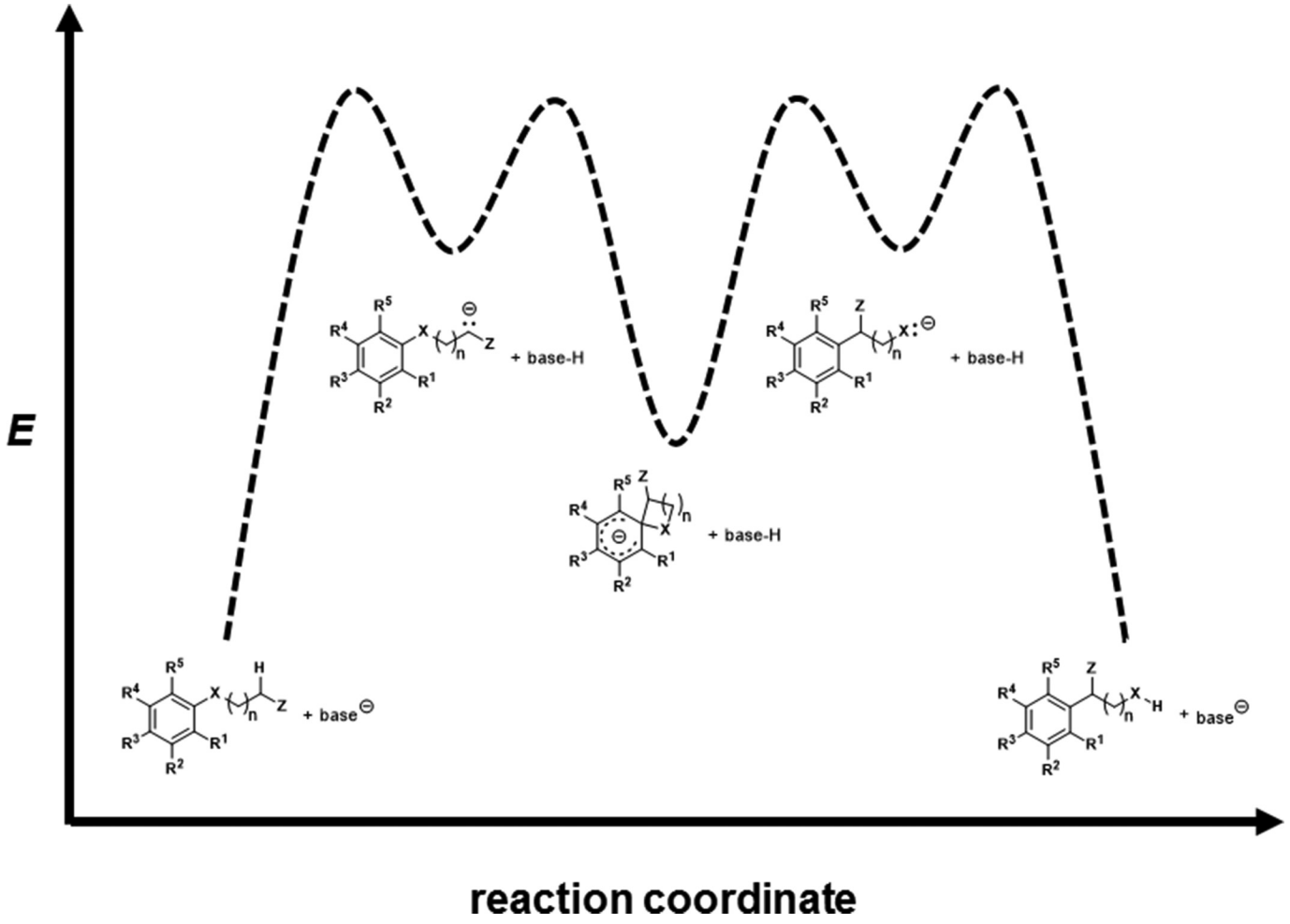


Fig. 2. Expected energy diagram for typical Truce–Smiles rearrangement assuming S_NAr mechanism.



Experimental evidence of the formation of a Meisenheimer adduct during the Truce–Smiles rearrangement has been provided by a report from our lab.[49] The experiment involved the in situ formation and observation of a stable Meisenheimer adduct **31**, as shown in Scheme 11. The chemical shifts of the signals attributable to the adduct observed by ^{1}H and ^{13}C NMR were consistent with other reported examples[50,51] from intermolecular nucleophilic aromatic substitution reactions and Smiles rearrangements. Particularly compelling was the observed inequivalency of the diastereotopic carbon and hydrogen atoms in the cyclohexadienyl ring due to the unsymmetric influence of the newly formed chiral furan ring in the spirocycle.[49]

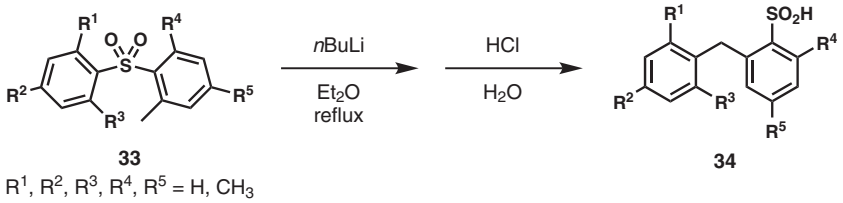
Typically, nitro-substituted Meisenheimer adducts are relatively stable intermediates that have been isolated in crystalline form and studied by X-ray crystallography.[51] They have also been extensively studied using absorbance spectroscopy due to their characteristic strong absorbance in the visible wavelength range.[51] The equilibrium established by in situ mixtures of regioisomeric species (Fig. 1) complicates the use of absorbance spectroscopy in studying Meisenheimer adducts. Spirocyclic Meisenheimer adducts are more stable than their corresponding non-spirocyclic equivalents arising from analogous intermolecular nucleophilic aromatic substitution reactions, making X-ray crystallographic studies of the solid-state structures of Meisenheimer adducts arising from Truce–Smiles rearrangements a particularly promising avenue of investigation.

2.1.4. Thermodynamic and kinetic studies of mechanism

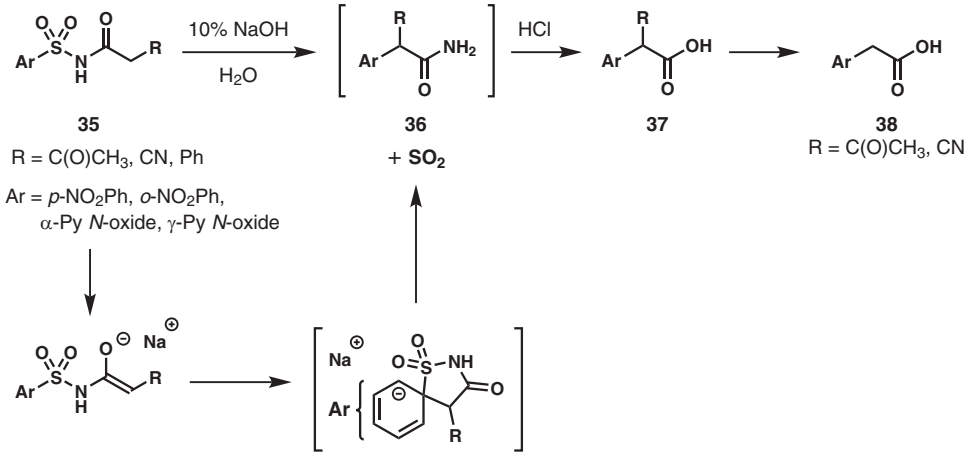
There have been a few studies reporting kinetic information from the Truce–Smiles rearrangement. The specific examples reported in these studies exhibit a wide variety of reaction conditions and include tandem reaction sequences, which makes it difficult to extend any general conclusions from comparing their results. However, the studies reveal interesting information about each particular example of the Truce–Smiles rearrangement, and each study is consistent with a S_NAr mechanism for the reaction.

A generic energy diagram that would be consistent with a typical base-catalyzed intramolecular S_NAr mechanism involving an anionic nucleophile for a Truce–Smiles rearrangement is shown in Fig. 2. This potential energy profile assumes that the Meisenheimer adduct is more stable relative to the carbanion nucleophile, as would be expected for a substrate featuring activating substituents on the migrating aryl ring. The relative energy of the rearranged X anion species is arbitrarily shown as equal to the carbanion, but this depends on the nature of the leaving group X atom. The relative energies of the neutral substrate and the neutral rearranged product following reprotonation by the conjugate acid of the base used in the reaction are also arbitrarily set. This potential energy profile suggests that deprotonation of the substrate to form the carbanion nucleophile or the decomposition of the Meisenheimer adduct are likely candidates for the rate-determining step of the overall reaction. It is consistent with our observation,[49] discussed in the previous section, that the Meisenheimer adduct acts as a stable resting species for the Truce–Smiles

Scheme 12. Truce–Smiles rearrangement reaction that was the focus of kinetic experiments.[3]



Scheme 13. Tandem Truce–Smiles rearrangement reactions that were the focus of kinetic experiments.[15]



rearrangement until an acidic work-up provides an excess source of H^+ electrophile to drive the rearrangement to completion.

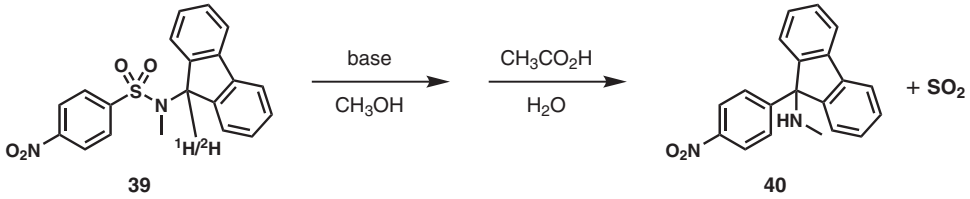
A kinetic study by Truce and Ray[3] examined the rearrangement of diarylsulfone substrates through benzylic anions prepared by deprotonation of *ortho*-methyl groups using *n*-butyllithium (Scheme 12). The stoichiometry of the diarylsulfone relative to the base was examined as a variable in addition to the methyl substitution patterns indicated in Scheme 12. The reaction rates were measured by back titration of the residual iron(III) ions following standard addition of $FeCl_3$ to aliquots of the reaction mixture and removal by filtration of the rearranged product **34** as insoluble iron(III) sulfinate salts. The reaction rates showed[3] that deprotonation is not the rate-determining step and that the rearrangement followed first-order kinetics for the overall rearrangement, consistent with the intramolecular S_NAr mechanism. This study also revealed the reaction rate-enhancing influence of a second ortho-substituent on the ring bearing the nucleophilic *ortho*-methyl group. The origin of the rate enhancement is proposed to be a steric effect that increases the probability of the substrate adopting a more reactive conformation.[3] This effect is discussed further in section 4.1.2.

A kinetic study by Dohmori[15] examined a tandem Truce–Smiles rearrangement – extrusion of sulfur dioxide – hydrolysis sequence for a series of *N*-acyl arylsulfonamides, **35** (Scheme 13). For the substrates bearing an acetyl or a cyano Z-substituent (Scheme 3) at the nucleophilic carbon, the rearrangement–extrusion–hydrolysis sequence was also concomitant with the loss of this acetyl or cyano functional group to yield final product **38**. An incomplete series of 10 analog substrates with structural variations in migrating aryl ring and substituents adjacent to the nucleophilic carbon (Scheme 13) were compared in the study. Reaction rates were measured examining temperature as another variable. As mentioned previously, the production of sulfur dioxide provided a convenient method of measuring the reaction rate through gravimetric analysis of $BaSO_4$ produced from the sulfur dioxide.[15] The reaction rate constants provided a means of calculating free energy of activation ($\Delta G^‡$), enthalpy of activation ($\Delta H^‡$), and entropy of activation ($\Delta S^‡$) values. Comparison of these values revealed the anticipated reactivity trends associated with activation of the migrating aryl ring, i.e., the pyridine *N*-oxide substrates have higher reaction rates than their nitrophenyl analogs, discussed further in section 4.1. The comparison also revealed a correlation between $\Delta S^‡$ values and the nature of the nucleophilic carbon substituent variable. The entropy data suggests that the transition states for the rate-determining step of the reaction of the *N*-phenylacetyl substrates (R = Ph in Scheme 13) are more sterically crowded than for the acetoacetyl and cyanoacetyl substrates (R = $C(O)CH_3$ and CN in Scheme 13, respectively). This suggests that the rate-determining step of the reaction involves the S_NAr Meisenheimer adduct.[15]

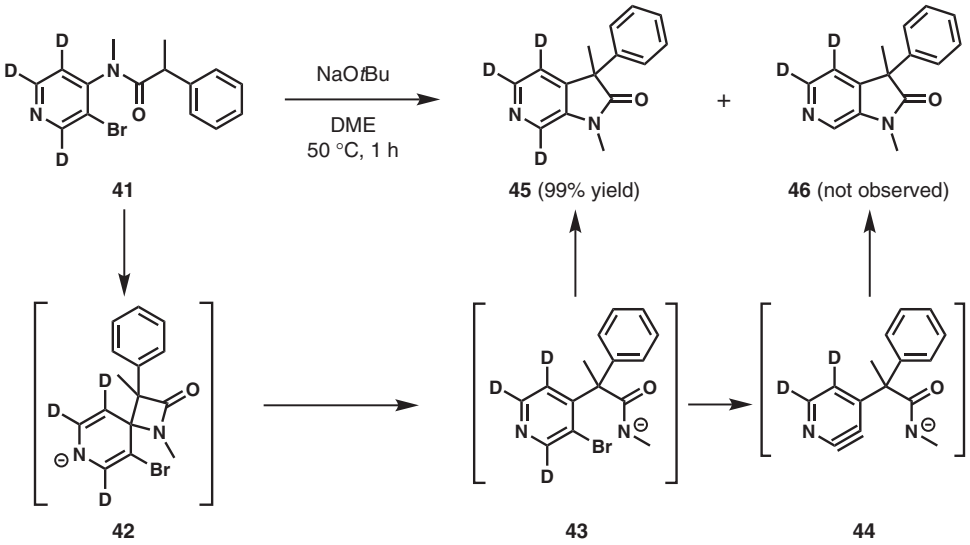
A kinetic study by Meng and Thibblin[38] of imine-forming elimination reactions featured an isolated example of a tandem Truce–Smiles rearrangement – sulfur dioxide extrusion sequence that had occurred unexpectedly. The report examines the rearrangement of the aryl sulfonate substrate **39** (Scheme 14) and its analog that is deuterated at the 9-position of the fluorene ring. The reaction rates were determined by quenching aliquots of the reaction mixture and quantifying concentrations of the residual unreacted substrate by HPLC analysis. Their interpretation of the rate data, the observed large kinetic isotope effect (k_H/k_D = 5.8 ± 0.3 when sodium methoxide is used as a base), and the large Brønsted parameter calculated with data from reactions performed using different bases (β = 0.50 when quinuclidine and DABCO are used as bases) concluded that the transition state of the rate-limiting step involved deprotonation at the 9-position. The authors opined that the most likely mechanism was deprotonation of **39** at the 9-position, followed by stepwise formation of a stable Meisenheimer adduct intermediate and subsequent elimination of sulfur dioxide concurrent with reprotonation at the nitrogen and ring opening to yield the final rearranged product, **40**. More concerted mechanisms were also discussed as less likely possibilities in the report.[38]

The observation that products of the Truce–Smiles rearrangement exhibit a conserved substitution pattern on the migrating

Scheme 14. Tandem Truce–Smiles rearrangement reaction that was the focus of kinetic experiments.[38]



Scheme 15. Tandem Truce–Smiles rearrangement experiment to support S_NAr mechanism.[52]

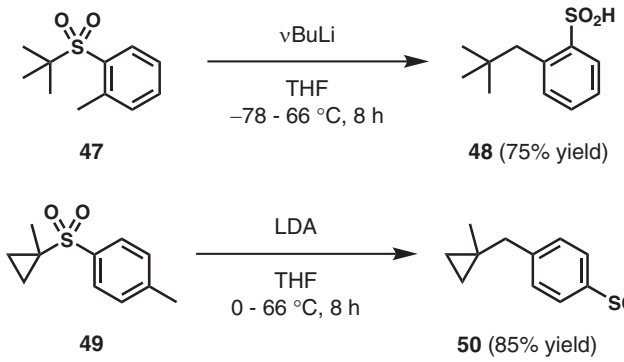


aryl ring, suggesting nucleophile attack exclusively at the ipso carbon, is used as experimental evidence to discount a benzyne mechanism for the reaction, as this alternate mechanism would instead yield a mixture of regioisomers. However, the intramolecular nature of the reaction might influence regioselectivity in the case of a benzyne mechanism leading it to appear regiospecific when it is instead just highly regioselective. In the study of a tandem Truce–Smiles rearrangement synthesis of aza-oxindoles,[52] Dey and colleagues provided further evidence to discount the benzyne mechanism through the use of a pyridine substrate, **41**, bearing deuterium substituents on the migrating aryl ring. As shown in Scheme 15, the experiment showed exclusive formation of the S_NAr product, **45**, with no observation of any of the product **46** expected for the alternative benzyne mechanism. This report also provides the only published computational reaction modelling experiments for the Truce–Smiles rearrangement. Density functional theory modelling of the reaction potential energy surface supports the hypothesis of a tandem two S_NAr reaction mechanism (Scheme 15): first, the Truce–Smiles rearrangement featuring a stable Meisenheimer adduct intermediate, **42**, and second, a subsequent substitution to close the product lactam ring. The rate-determining step was predicted by the calculated model to be the C–N bond-breaking decomposition of the Meisenheimer adduct, seen as the transformation of intermediate **42** to **43** in Scheme 15.[52]

2.2. Alternate mechanisms

It is not the intention of this review to provide analysis of Truce–Smiles rearrangements for which there is strong evidence that the reaction mechanism follows one alternative to S_NAr. However, it is worthy of mention that the mechanism of many of the reactions presented in our discussion have little evidence supporting their mechanism and alternative mechanisms for similar transformations have been reported in the literature.

Scheme 16. Radical rearrangement reactions studied by Snyder and Truce[7] and Madaj et al.[53]

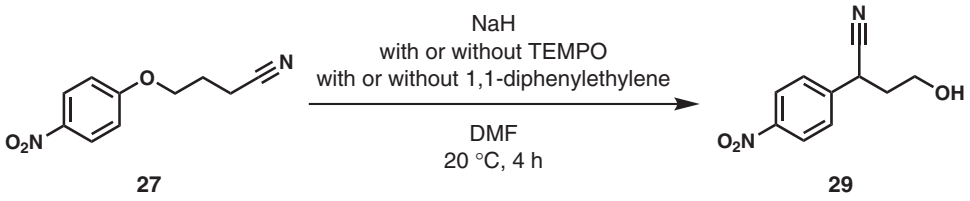


2.2.1. *Radical mechanisms*

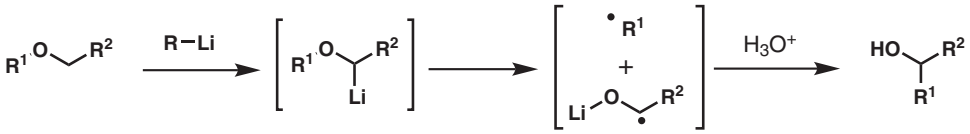
The existence of radical intermediates in some of the reactions reported as Truce–Smiles rearrangements is almost certain. Other sources can provide the reader with a more thorough discussion of the role of single electron transfer mechanisms in aromatic substitution reactions.[32]

The reactions studied by Truce exhibited reactivity that cannot be explained by the standard ionic S_NAr mechanism and are attributable to radical reaction mechanisms instead.[7,53] Two examples of such reactions are shown in Scheme 16. These reactions were included in Truce's definition of the Truce–Smiles rearrangement,[54,55] which made his definition inconsistent with the scope of the reaction as defined in standard references on named organic reactions. This inconsistent nomenclature will be discussed further in section 5.

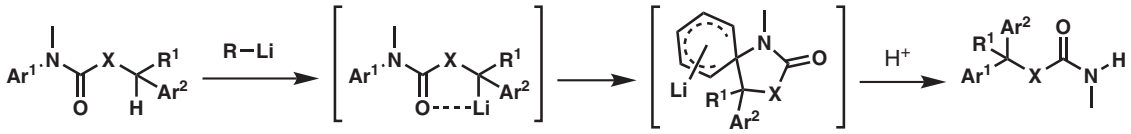
Scheme 17. Experiment probing existence of radical intermediates in Truce–Smiles rearrangement.[49]



Scheme 18. General scheme for the [1,2]-Wittig rearrangement.



Scheme 19. General scheme for the Clayden rearrangement.



Our report of experiments involving the Truce–Smiles rearrangement provided some experimental observations supporting a standard ionic S_NAr mechanism for those reactions and discounting a radical mechanism.[49] These experiments involved comparing the yield of rearranged product **29** for the Truce–Smiles rearrangement (Scheme 17) when the reaction was conducted in the presence and absence of radical scavengers. The yield of this particular reaction was found to be unaffected by the presence of radical scavengers, which suggested the absence of a radical intermediate.[49]

The [1,2]-Wittig rearrangement is capable of achieving the same aryl migration process as the Truce–Smiles rearrangement (Scheme 18). The mechanism of the [1,2]-Wittig rearrangement involves radicals and is narrower in scope with respect to its focus on ethers but is wider in scope with respect to the variety of carbon fragments that can migrate. The reaction shown in Scheme 18 could be considered a radical mechanism for the Truce–Smiles rearrangement when R^1 is an aryl ring; there are a limited number of examples from the literature wherein R^1 is an aryl ring.[56–60] These reported reactions are presumed to proceed via a [1,2]-Wittig rearrangement radical mechanism; however, a very similar reaction reported by Dudley and colleagues[58,61] is proposed to proceed via an anionic mechanism, and so the possibility that some reported [1,2]-Wittig rearrangements might correspond better with the definition of a Truce–Smiles rearrangements remains a possibility.

Another reaction that exhibits some parallels to the Truce–Smiles rearrangement is the so-called[62] "Clayden rearrangement" (Scheme 19), a 1,4-aryl migration reaction[63,64] that could be viewed as proceeding through an intermediate that is highly related to a 5-membered spirocyclic Meisenheimer adduct, a hypothesis supported[65,66] by mechanistic studies.

Other examples of aryl migration reactions that are able to achieve similar resultant chemical transformations as the Truce–Smiles rearrangement but have been suggested to proceed through a radical mechanism are dominated by substrates featuring organosulfur linkages to the migrating aryl ring such as sulfonates,[67,68] sulfonamides,[67,69–72] sulfones,[73] sulfoxides,[73] sulfonium salts,[74] and thioethers.[73,75–77] Additionally, examples of silyl ethers,[78] hydroxamate esters,[79] amides,[80–82] and ethers[83,84] have been reported. There is also a series of isolated reports of aryl migrations to carbon believed to proceed by photochemical processes.[73,82,85]

3. Reaction conditions

Reaction conditions have not been a focus of the experiments described in reports of the Truce–Smiles rearrangement. A survey of reported reaction conditions shows great variety with respect to time and temperature but reveals reactions generally conducted using a stoichiometric amount of a strong base in a polar solvent. The base is typically strong because the pK_a of C–H bonds tend to be relatively high. It is typically used in a stoichiometric amount even though the Truce–Smiles rearrangement appears catalytic with respect to base, as a stable Meisenheimer adduct will represent a thermodynamic local minimum for the reaction, as discussed in section 2.1.4. The nature of the chosen base typically determines whether the solvent is protic or aprotic. Polar aprotic solvents such as DMSO, DMF, and acetonitrile should theoretically be excellent choices as solvents to promote the rearrangement reaction through enhancing the reactivity of small, hard carbanion nucleophiles, stabilizing the Meisenheimer complex, and stabilizing soft, polarizable anionic leaving groups.

4. Substrate scope

Early reports of the Truce–Smiles rearrangement are dominated by the use of benzylic carbanions, usually generated by lithiation of diarylsulfones. However, a complete survey of the over 60 years of literature shows a chemically diverse range of viable rearrangement substrates, which suggests that the reaction is very general. There are scattered reports of successful substrates including aryl sulfones, sulfonamides, sulfonates, thioethers, ethers, anilines, anilides, phosphines, and ketones. There are several aspects of the substrate structural design that can serve as variables in the Truce–Smiles rearrangement, including the migrating aryl ring, the linker atom that also serves as the leaving group (X in Scheme 20), the molecular tether that attaches the migrating aryl ring to the nucleophile, and the nucleophile that typically features an attached functional group (Z in Scheme 20) to stabilize the nucleophilic carbanion and lower the pK_a of the precursor C–H bond. The reported incidents of the Truce–Smiles rearrangement are neither methodical nor thorough, and there are many interesting potential substrates that remain to be explored. Each of the four iden-

Scheme 20. Structural design variables of a Truce–Smiles rearrangement substrate.

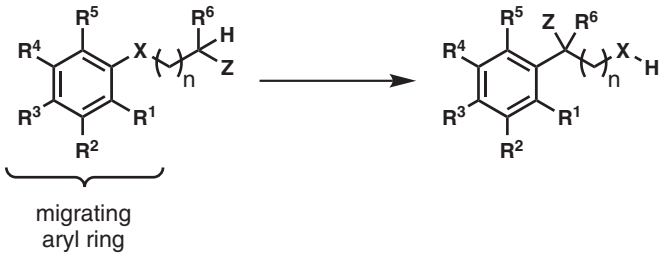
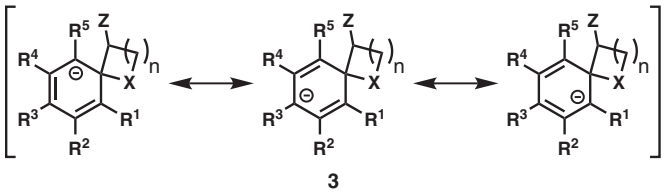


Fig. 3. Resonance contributors to Truce–Smiles rearrangement Meisenheimer adduct.



3

tified substrate structural variables is discussed in the following sections.

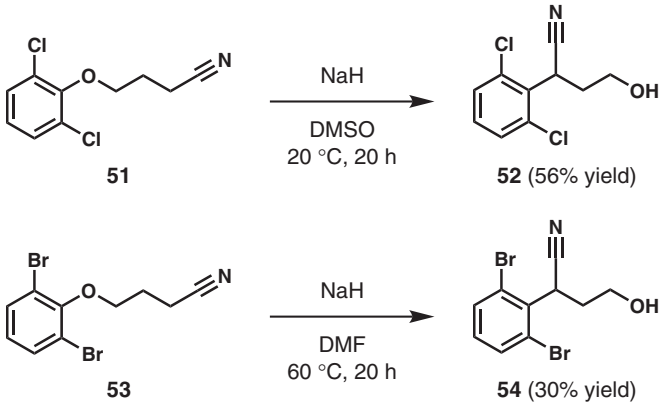
4.1. Activated aromatic system

An electron deficient aromatic ring is activated toward nucleophilic aromatic substitution not only due to the decreased repulsion between the π-electron system and the nucleophile, but also because of the relative stabilization of the cyclohexadienyl anion on sp^3 rehybridization of the electrophilic carbon and loss of aromaticity. The resonance structures that make major contributions to the Meisenheimer adduct are shown in Fig. 3. These resonance contributors underpin the theory behind what constitutes activation of an aromatic system to nucleophilic substitution and provide an explanation of the observed trends in structure and reactivity.

4.1.1. Substituted benzene derivatives and related arenes

Substituted phenyl rings comprise the migrating aryl ring in the vast majority of reported examples of the Truce–Smiles rearrangement. Considering the major resonance contributors to the cyclohexadienyl anion Meisenheimer complex (Fig. 3), it can be predicted that functional groups exerting a strong mesomeric electron-withdrawing effect substituted at the ortho- and para-positions relative to the leaving group will activate the aryl ring to nucleophilic aromatic substitution. This aids in explaining why functional groups such as $–NO_2$, –CN, –C(O)R, and $–SO_2R$ are commonly featured ortho- and para-substituents on the migrating aryl ring of successful Truce–Smiles rearrangement substrates, as well as many other S_NAr reactions. Substitution of the migrating aryl ring with these functional groups at meta-positions has also been shown to stabilize the Meisenheimer adduct, but the trend in stabilization energies has been shown[86] to follow: meta ≪ ortho < para. Similarly, extended aromatic systems such as naphthyl rings are known to be activated to nucleophilic aromatic substitution due to the increased amount of potential delocalization of the anionic charge.[87] Conversely, ortho- or para-substitution of the migrating aryl ring with functional groups exerting a strong mesomeric electron-donating effect should theoretically destabilize a migrating aryl ring to Truce–Smiles rearrangement. Consequently, substrates that are known to successfully undergo Truce–Smiles rearrangement featuring functional groups such as –OR in the ortho- and para-positions are rare[4] in the absence of an activating group.

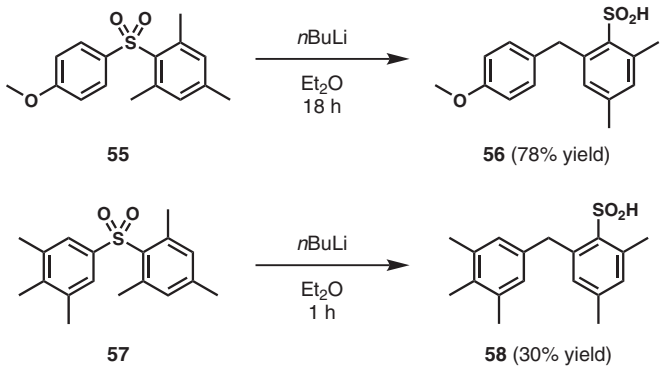
Scheme 21. Experiments demonstrating successful rearrangement of substrates bearing inductively withdrawing substituents.[49]



51 **52** (56% yield)

53 **54** (30% yield)

Scheme 22. Example of substrates bearing deactivating functional groups on the migrating ring.[4]



55 **56** (78% yield)

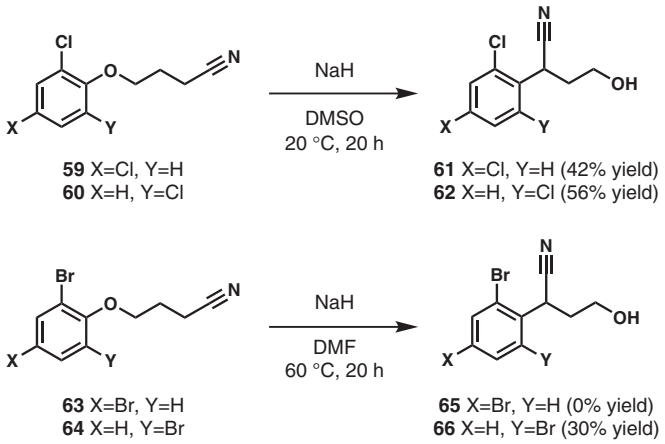
57 **58** (30% yield)

It has been shown for other nucleophilic aromatic substitution reactions that functional groups exerting a strong inductive electron-withdrawing effect can function as activating groups, especially when substituted at the ipso-position. This may explain some of the observed trends in reactivity for different linker atoms and molecular tethers, discussed further in section 4.2, and the successful rearrangement of seemingly "unactivated" substrates employed by Truce's research group, discussed later in this section. Experiments from our own research group demonstrated[49] that multiple inductively electron-withdrawing substituents were sufficient to activate a substrate to Truce–Smiles rearrangement. Some examples of these experiments are shown in Scheme 21.

Truce stated[54,55] that a defining feature of the Truce–Smiles rearrangement was that substrates did not require the activating strong electron-withdrawing groups on the migrating ring that are typically required by S_NAr substrates. He demonstrated that the migrating ring of a Truce–Smiles rearrangement substrate could even be substituted with deactivating groups, some examples of which are shown in Scheme 22.[4] These results are further supported by studies conducted by Drozd.[16] These studies also revealed that intramolecular nucleophilic aromatic substitution reactions of these substrates often formed mixtures of isomeric cyclohexadienyl anion intermediates (Fig. 1), a result that is discussed further in section 5.

Undoubtedly, the intramolecular nature of the Truce–Smiles rearrangement allows for enhanced reaction rates for substrates relative to analogous intermolecular nucleophilic aromatic substitutions, thus permitting the reaction of aryl rings that would be insufficiently activated for intermolecular S_NAr. However, Truce's description of these substrates as lacking activating substituents does not take into consideration the sulfonyl functional group

Scheme 23. Apparent ortho-substituent effect for migrating aryl ring.[49]



featured in all of the diarylsulfone substrates he studied. This sulfonyl group activates the ring as it has been shown that substituents exerting a strong electron-withdrawing inductive effect, as would be seen here due to the polarized C–S bond, can provide substantial stabilization of the cyclohexadienyl anion Meisenheimer adduct when bonded at the ipso-position.[86] There is precedent for nucleophilic aromatic substitution reactions, both intermolecular[88] and intramolecular,[89] wherein a sulfonyl group acts as the only activating group for a benzene substrate and concurrently as the leaving group. The vast majority of published reports and subsequent systematic studies of the effect of activating groups on the migrating aryl ring have revealed that strong resonance electron-withdrawing substituents in ortho- and para-positions activate the ring, which is in keeping with the anticipated trends of a S_NAr reaction.[49]

4.1.2. *Effect of ortho substituents*

Experiments from our lab have shown a possible influence from ortho-substituents on the migrating aryl ring on the successful rearrangement of Truce–Smiles substrates.[49] The yields of rearranged products isolated for the series of four dihalo-substituted substrates shown in Scheme 23 show that the 2,6-dihalo-substrates, **60** and **64**, more readily underwent rearrangement than their corresponding 2,4-dihalo-analogs, **59** and **63**. This may be due to decreased destabilization of the Meisenheimer adduct by the mesomeric electron-donating chloro- and bromo-substituents when they are in the ortho- versus para-position analogous to the observed trends for fluoro-substituents.[86] Alternatively, steric strain between the two ortho-halo substituents and the tether atoms of the 2,6-disubstituted substrates may lead these substrates to preferentially adopt a conformation that favours the rearrangement reaction. Conventionally, ortho-substituents on the migrating aryl ring are thought of as acting to destabilize Meisenheimer adducts of intramolecular nucleophilic aromatic substitution reactions through both steric and electronic effects.[90,91] However, these experiments exclusively employ nitro substituents whose mesomeric electron-withdrawing effect alter the predicted effect on the rate of the rearrangement reaction with respect to the halo-substituents employed in our experiment. Without a greater number of comparable experiments, it is difficult to assess how general this trend may be, but it seems to be an aspect of substrate design worthy of further investigation.

A different type of ortho-substituent effect for the Truce–Smiles rearrangement was observed in the foundational experiments, conducted by the research groups of Truce and Drozd on the rearrangement of diarylsulfones. As described previously, these studies involved substrates that bore an *ortho*-tolyl ring from which the nucleophilic benzylic carbanion lithium metallated

Fig. 4. Conformational isomerism for ortho-substituted diarylsulfone substrates.[3]

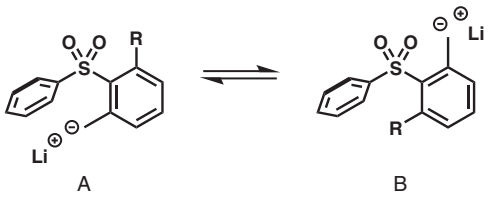
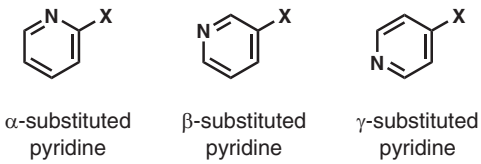


Fig. 5. Substituted pyridine nomenclature.



species was formed. Kinetic measurements showed that substrates bearing 2,6-xylyl or mesityl aryl rings exhibited higher Truce–Smiles rearrangement reaction rates than their corresponding *ortho*-tolyl analogs.[3] The importance of the second ortho-substituent was argued as an entropic advantage that favoured a more reactive conformational isomer, as seen in Fig. 4. The substrate is predicted to occupy the conformation appropriate for intramolecular S_NAr attack of the nucleophilic benzyllithium (A in Fig. 4) to a higher extent when the second ortho-substituent is more similar in steric demand to the lithiated methyl substituent, e.g., when R is a methyl group as opposed to a hydrogen atom.

4.1.3. *Pyridine and related aza-aromatics*

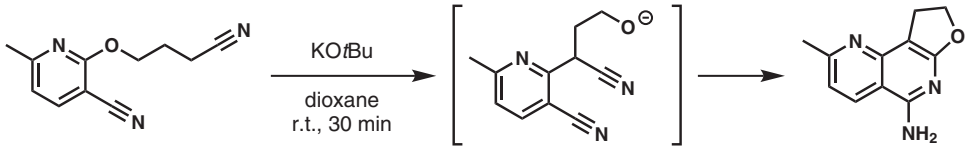
Fully aromatic 6-membered ring N-heterocycles are π-deficient, and therefore, aza group substitution in a benzene ring should activate the ring toward S_NAr by providing stabilization of the Meisenheimer adduct, as the nitrogen atoms have the potential to withdraw electron density by both inductive and mesomeric effects. Considering the major resonance contributors to the cyclohexadienyl anion Meisenheimer adduct (Fig. 3), this corresponds with studies showing the relative rates of nucleophilic aromatic substitution of 2-, 3-, 4-substituted halopyridines (Fig. 5) are much more reactive for 2- and 4-substituted substrates than for 3-substituted substrates. These observations can be attributed to greater mesomeric effect stabilization when the negative charge resides largely on the more electronegative nitrogen atoms in the ring. The S_NAr activating effect of an aza group replacing the ring carbon atoms at the 2- or 4-position is near[92] that of $–NO_2$ substituted in the 2- or 4-position on a phenyl ring. Diazines, wherein a halogen leaving group is 2- and 4-substituted with respect to nitrogen, are even more reactive than the corresponding pyridines.[93]

Consequently, there are a large number of pyridine and diazine substrates reported in the literature as Truce–Smiles rearrangement substrates. Though the literature lacks any systematic comparison examining the effects of substrate structural design on the Truce–Smiles rearrangement, there are some conclusions that can be gleaned from an overview of the known work.

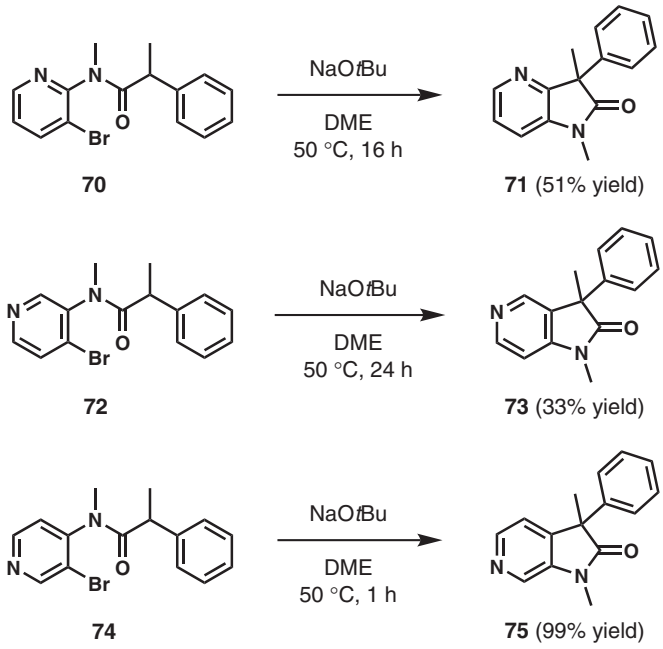
By far the most common pyridine isomer reported for examples of substrates that undergo the Truce–Smiles rearrangement are 2-substituted pyridine substrates.[18,19,21,46,52,58,61,94] As an example of one of these substrates, Scheme 24 shows the successful rearrangement and tandem cyclization of a 2-substituted pyridine substrate, **67**, that is also activated by the presence of a cyano substituent at an ortho-position relative to the leaving group.[21] Similarly, there are numerous examples of successful rearrangements of 4-substituted pyridine substrates in the literature.[23,46,48,52,95]

In keeping with theory, examples of the successful rearrangement of 3-substituted pyridine substrates[22,52] are the rarest for

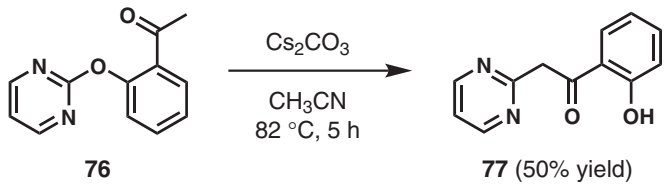
Scheme 24. Example of successful rearrangement of 2-substituted pyridine substrate.[21]



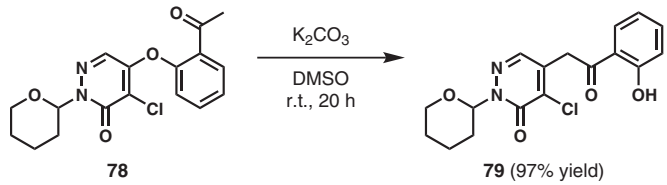
Scheme 25. Example of successful rearrangement of 3-substituted pyridyl substrate and comparison with 2- and 4-substituted analogs.[52]



Scheme 26. Example of successful rearrangement of 2-pyrimidyl substrate.[46]



Scheme 27. Example of successful rearrangement of 4-pyridazinyl substrate.[46]



the pyridine series. One example of the successful rearrangement of a 3-substituted pyridine from the literature[52] lends itself to comparison with the corresponding 2- and 4-substituted pyridine analog substrates regarding reactivity. For the substrates studied by Dey's research group, the 4-substituted pyridine substrate, **74**, appears to be the superior rearrangement substrate as evidenced by a high yield of product and a brief reaction time, followed by 2-substituted pyridine substrate, **70**, with the 3-substituted pyridine, **72**, as the poorest substrate (Scheme 25). The comparison of these three analogous substrates is complicated by the tandem nature of the reaction, with the activating effects of the second nucleophilic aromatic substitution reaction predicted to be the opposite of the first substitution (Truce–Smiles rearrangement) in the sequence.[52]

Reports of diazines as substrates of the Truce–Smiles rearrangement are rare, despite the theoretical prediction that they should provide excellent substrates. Scheme 26 shows an example of a successful rearrangement of a 2-pyrimidyl substrate, **76**.[46] A 2-pyrimidyl substrate is activated to nucleophilic aromatic substitution with the leaving group 2-substituted to two aza units. There are two reported examples in the literature.[46,94] Unfortunately, it is difficult to compare the reactivity of these two 2-pyrimidyl substrate examples, as neither study provides a systematic analysis of substrate design relative to a quantitative measure such as product yield.

One of these reports also includes the successful rearrangement of a 4-pyridazinyl substrate (Scheme 27).[46] This substrate should theoretically be activated to nucleophilic aromatic substitution with the leaving group 3-substituted to one aza unit and 2-substituted to the other aza unit, with these effects enhanced by the presence of an activating oxo substituent at the 3-position on the ring, relative to the leaving group. The combination of these structural design features provides a migrating aryl ring that is highly activated and, therefore, an excellent substrate for the Truce–Smiles rearrangement.[46]

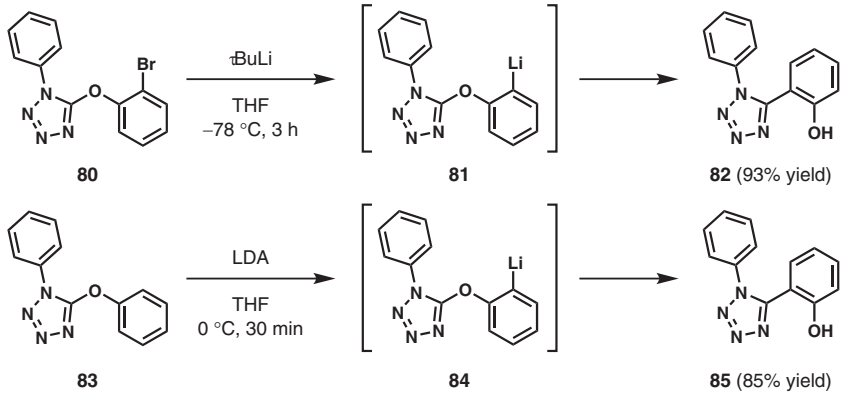
There is an isolated report of the use of a series of tetrazole aryl ethers such as **80** and **83** as excellent substrates for the Truce– Smiles rearrangement.[96] Theoretically, the corresponding Meisenheimer adduct should be well stabilized by the nitrogen atoms in the tetrazole ring and the electrophilic ring carbon should be very activated to nucleophilic attack. The report also features an interesting method for generating the nucleophilic carbanion, which the authors showed could be successfully prepared by lithium–halogen exchange of bromophenyl ether substrates such as **80** or directed ortho-metalation of phenyl ether substrates such as **83** (Scheme 28).[96]

Following from the idea that the aza group of N-heteroaromatics acts to stabilize the Meisenheimer adduct, the presence of a formal positive charge on nitrogen has a further activating effect such as in N-heteroaromatic *N*-oxides. This is seen in studies of other S_NAr reactions and is supported by observations made in Dohmori's studies of the Truce–Smiles rearrangement.[11–15] These studies reported successful rearrangement of 2-pyridyl *N*-oxide, 4-pyridyl *N*-oxide, and 4-quinolinyl *N*-oxide substrates.[11] An interesting comparison can be made from these reports between the reactivity of a 2-pyridyl substrate, **89**, relative to its *N*-oxide analog, **86**, in that the oxide derivative successfully undergoes the rearrangement while the pyridine derivative does not and becomes subject to a hydrolysis side reaction, suggesting that the rate of the rearrangement reaction is much slower for this substrate (Scheme 29).

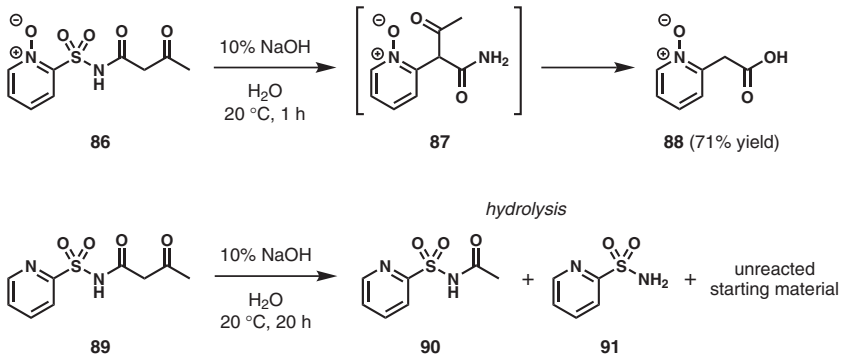
Beyond N-heterocycles, the scope of the Truce–Smiles rearrangement has successfully been expanded to include substrates that feature sulfur-containing N-heterocycles as the migrating aryl ring such as benzothiazole,[35] thienopyridine,[97] and benzothiophene.[23] Examples of each of these substrates (**92**, **94**, and **97**, respectively) are shown in Scheme 30.

The Truce research group reported[98] an attempted rearrangement of a thiophene substrate, which resulted in a product sug-

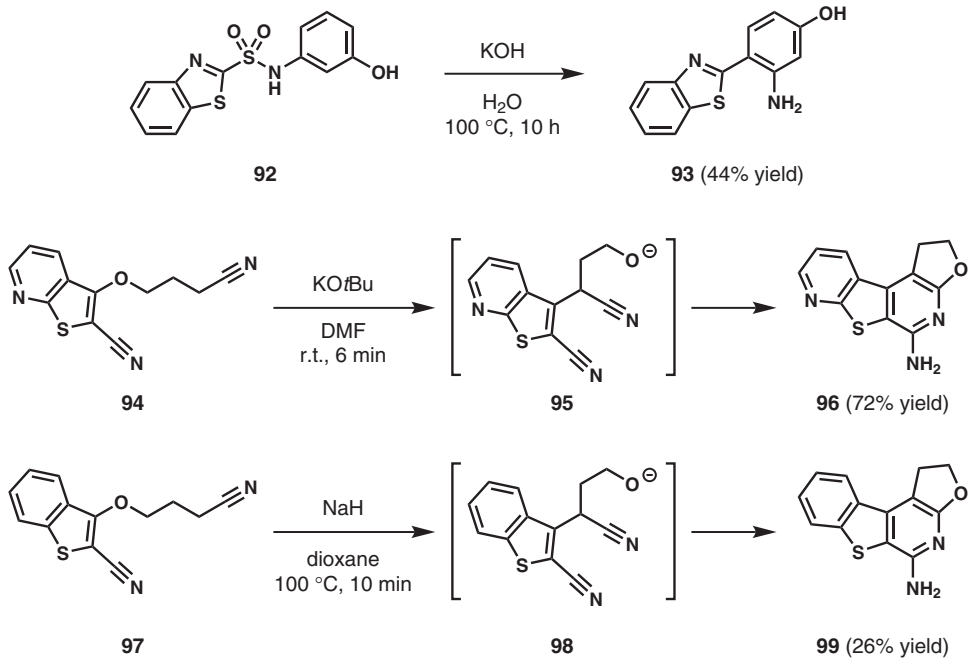
Scheme 28. Examples of successful rearrangement of tetrazole substrates.[96]



Scheme 29. Example of successful rearrangement of a 2-pyridyl *N*-oxide substrate relative to its 2-pyridyl analog.[13,14]

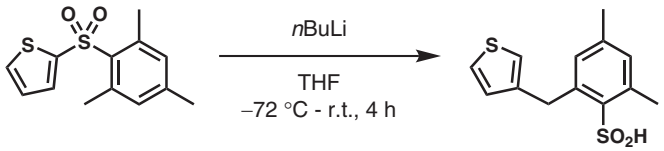


Scheme 30. Example of successful rearrangement of benzothiazole,[35] thienopyridine,[97] and benzothiophene[23] substrates.



gesting nucleophilic aromatic substitution at the ortho-position rather than the ipso-position of the migrating aryl ring. The product resulted from formation of the 1,2-adduct isomer (Fig. 1) rather than the 1,1-adduct and, therefore, represented a side reaction rather than the Truce–Smiles rearrangement. The reaction and its resulting alternate rearrangement product, **101**, are shown in Scheme 31. This observation suggests that perhaps the thiophenyl sulfone substrate, **100**, experiences a slower reaction rate via the Truce–Smiles rearrangement than the corresponding diarylsulfones that were typically the subject of research by Truce and colleagues. S31

Scheme 31. Failed rearrangement of thiophenyl substrate.[98]



100 **101** (88% yield)

This section of the review has illustrated the scattered and adventitious nature of the literature pertaining to the Truce–Smiles rearrangement of heterocyclic substrates. Hopefully, the practical utility of heterocycles, especially in the areas of materials chemistry and medicinal chemistry, will encourage a more thorough investigation into the use of these compounds as substrates.

4.2. Linker group

The linker group that attaches the nucleophilic portion of the Truce–Smiles rearrangement substrate to the electrophilic aryl portion can influence the rate of the rearrangement in several ways. First, an electron-withdrawing linker group can serve to activate the aromatic ring by enhancing the electrophilicity of the ipso carbon and through stabilization of the Meisenheimer adduct. Second, the linker group plays a role in the substitution reaction as the leaving group. Working under the assumption that most Truce–Smiles rearrangements follow a reaction progression featuring a stable Meisenheimer intermediate (Fig. 2), the linker group will influence the rate of all reaction steps beyond initial formation of the carbanion nucleophile. To our knowledge, there has been no systematic study of the effect of the linker group on Truce–Smiles rearrangement reactivity.

4.2.1. Influence of leaving group

Promotion of the elimination reaction to decompose the Meisenheimer adduct and form the desired S_NAr product is facilitated by a nucleophile that is a worse leaving group than the intended leaving group (i.e., X linking group). As well, the rate of the reverse reaction is suppressed when the leaving group is less nucleophilic than the intended nucleophile. With this in mind, the nucleophile of the Truce–Smiles rearrangement is always some carbanion species, typically a strong nucleophile and a poor leaving group. A survey of the literature for trends in leaving groups does suggest some significant influence of this variable over the success of the reaction. The Truce–Smiles rearrangement is a C–C bond-forming reaction that can be classified as an X → C aryl migration. The definition of the reaction is inclusive of a variety of linker X atoms.

4.2.2. C → C rearrangements

Reported examples of Truce–Smiles rearrangements featuring the migration of an aryl group from carbon are rare. The one report[99] that we are aware of describes a series of aryl alkyl ketones such as **102** that successfully undergo the rearrangement followed by a series of tandem chemical steps to yield 3-hydroxyquinoline products such as **104** (Scheme 32). S32

4.2.3. N → C rearrangements

A more common linker atom for Truce–Smiles rearrangement substrates is nitrogen. Substrates featuring X = N may be anilides,[48,100] isolated as the less substituted amide or trapped by an electrophile,[52] or alternatively anilines,[47] isolated as the amine. One unusual example[101] of a substrate was a *N*-arylated pyrrole, **105**, that yielded the *N*-unsubstituted pyrrole, **107**, on rearrangement (Scheme 33). S33

4.2.4. P → C rearrangements

There are a series of scattered reports of Truce–Smiles rearrangements featuring phosphorous as the linking X atom. These reactions appear to involve substrates wherein the migrating aryl ring is tethered to the nucleophilic carbanion by a phosphonium[102–104] functional group, and the rearranged product is isolated as the neutral phosphine or the rearrangement of a phosphine substrate to yield the phosphide anion.[105] Scheme 34 shows an example of the rearrangement of such a phosphine substrate, **108**, to yield a phosphide anion, isolated as the lithium salt, co-crystallized with two equivalents of THF solvent molecules, **109**. S34

4.2.5. O → C rearrangements

The aryl ether linkage is a common choice for Truce–Smiles substrates featuring an oxygen linking atom. Many of the numerous substrates[21–23,25,26,28,97] studied by the Hirota's research group have been alkyl aryl ethers and the substrates studied by Snape's research group are diaryl ethers.[30,31] The studies that we have published thus far from the Wood research group have exclusively been alkyl aryl ethers.[49] Typically, an acidic aqueous work-up provides the products from these rearrangement products as the appropriate alcohol[58,61] or phenol,[44–46,95,96] unless the rearranged alkoxide anion intermediate has been trapped by a tandem reaction, typically cyclization to form a cyclic ether-containing compound[49] or lactone.[94] The reaction shown in Scheme 35 represents a typical rearrangement of a diarylether, **110**, formed in situ, with tandem Truce–Smiles rearrangement to yield a phenol product, **111**.[44] S35

4.2.6. S → C rearrangements

By far, the most common linker groups for reported examples of the Truce–Smiles rearrangement have been sulfur based. These reports include the numerous original studies of diarylsulfones performed by the research groups of Truce[1–5] and Drozd,[17,106–109] as well as the original studies of *N*-acyl sulfonamides performed by Dohmori.[8–15] In the rearrangement of sulfones, the rearranged product is typically isolated in the form of a sulfinic acid such as **113** (Scheme 36) or sulfinate salt;[110] however, some[34,41] sulfone rearrangements feature a tandem loss of sulfur dioxide. S36

In the rearrangement of sulfonamides, the rearranged product is typically isolated as an amine following tandem extrusion of sulfur dioxide[35,38–40,42,43] or, in the case of sulfonate, as an alcohol.[36,37] This type of reaction sequence was discussed in section 2.1.1., with an illustrating example shown in Scheme 7.

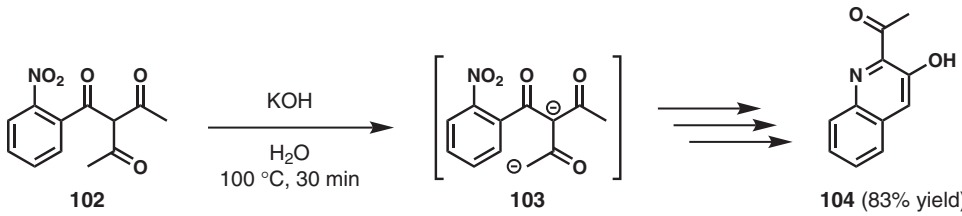
Many of the numerous substrates[18,19,23] studied by the Hirota's research group have been alkyl aryl thioethers. In the rearrangement of thioethers, there are no reported examples of isolating the thiol rearranged product. Instead, the intermediate sulfur anion is intercepted by an electrophile such as an alkylating agent[111] or, in Hirota's examples, by a tandem cyclization reaction to form a cyclic thioether-containing product.

4.3. Tether length

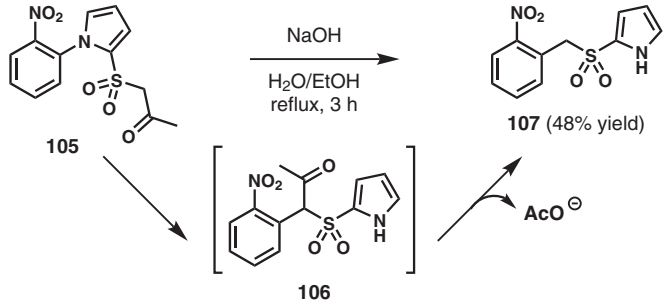
A review of the literature reveals Truce–Smiles rearrangements with substrates, wherein the nucleophilic carbon is located two, three, four, and five atoms removed from the aromatic ring. Thus, the reaction can supposedly proceed through 3-, 4-, 5-, and 6-membered ring spirocyclic Meisenheimer adducts. There have been no reported systematic studies of the effect of tether length; however, a review of the incomplete data reveals that substrates providing a 5-membered ring intermediate constitute the largest portion of the successful rearrangement reactions. Ring size has been identified as a very important variable in intramolecular nucleophilic aromatic substitution reactions, including the Smiles rearrangement,[90,91] and therefore, it is reasonable to hypothesize that this is true of the Truce–Smiles rearrangement as well.

Reported examples of Truce–Smiles rearrangements occurring through the formation of 3-membered ring spirocyclic Meisenheimer adducts are rare.[47,58,61] Some examples of these proposed structures are shown in Fig. 6. It could be argued that the ring F6

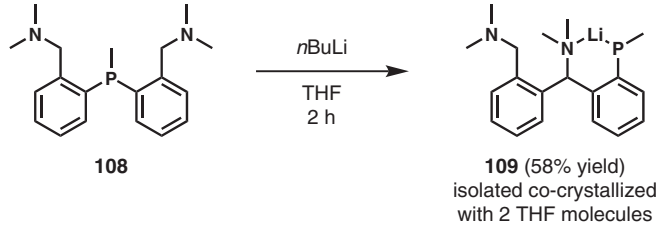
Scheme 32. Example of rearrangement of an aryl ketone and tandem cyclization yielding a quinolone.[99]



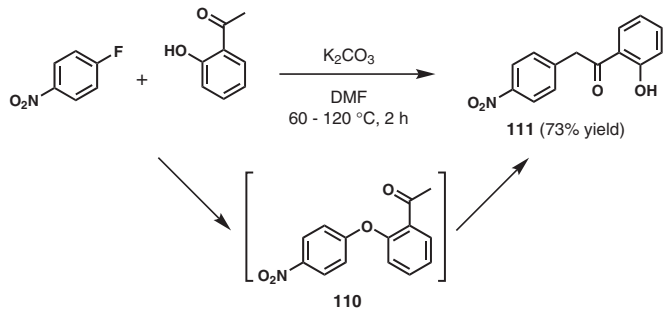
Scheme 33. Example of rearrangement of an *N*-arylated pyrrole yielding an *N*-unsubstituted pyrrole.[101]



Scheme 34. Example of rearrangement of a phosphine yielding a phosphide anion.[105]



Scheme 35. Example of rearrangement of a diaryl ether yielding a phenol.[44]



contraction reactions observed as part of the tandem Ugi–Smiles – Truce–Smiles reactions reported by El Kaim and colleagues are specially favoured by stable conformations accessible to the bicylic substrate, formed in situ, that are not easily accessed by typical acylic substrates.[47] Dudley and colleagues favour a hypothesis involving the intermediacy of an ionic benzyllithium species for their reported 1,2-aryl migration of 2-benzyloxypyridines, in keeping with the intramolecular S_NAr mechanism of the Truce–Smiles rearrangement. However, they also concede that a radical mechanism, in keeping with the [1,2]-Wittig reaction, cannot be entirely ruled out.[58,61]

Examples of Truce–Smiles rearrangements occurring through the formation of 4-membered ring spirocyclic Meisenheimer adducts are also relatively uncommon.[36,39,48,52,95] Each of the examples shown in Fig. 7 arise from isolated, seemingly adventitious, F7

Scheme 36. Example of rearrangement of a diarylsulfone yielding a sulfinic acid.[1]

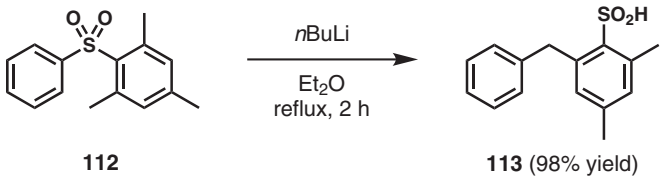
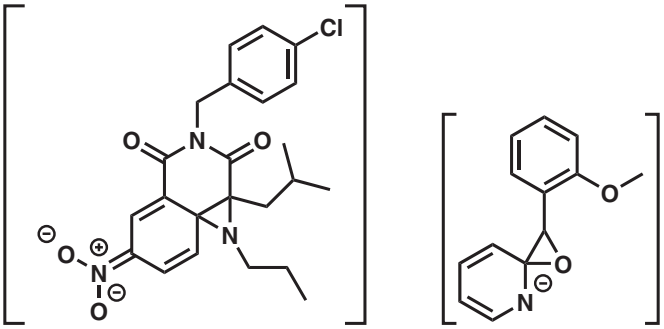


Fig. 6. Putative reported 3-membered ring spirocyclic Meisenheimer adducts.[47,61]

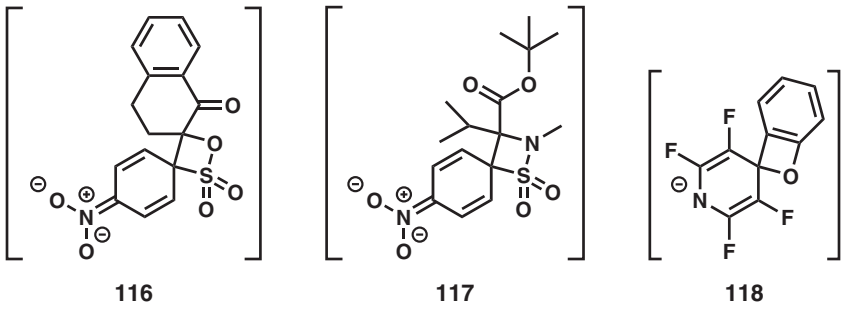


observations from a variety of research groups, making it difficult to draw conclusions from these non-systematic, inconsistent examples. The nucleophilic carbanions tend to be more substituted in these examples than in substrates that favour 5- or 6-membered ring spirocyclic Meisenheimer adducts, which supports a hypothesis that steric crowding of the nucleophile may promote the substrate to adopt a more reactive conformation. However, in at least one of these examples, increased substitution at the nucleophilic carbon position was observed to decrease reactivity.[48] In the absence of evidence of the existence of these putative intermediate structures, it remains difficult to draw clear conclusions.

Examples of Truce–Smiles rearrangements occurring through the formation of 5-membered ring spirocyclic Meisenheimer adducts are most common in the literature, including the reactions reported by Dohmori and colleagues,[8–15] the research groups of Truce,[1–4] Drozd,[16,17] Hirota,[18,19,21–23,25,27,97] Snape,[31] and Wood,[49] as well as with many other isolated[34,35,41,43,94,99–101,103–105,110,112] reactions reported (Fig. 8). This is in agreement with trends showing greatest reactivity for other intramolecular substitution reactions involving 5-membered ring intermediates and (or) transition states.[113] It is hypothesized that the 5-membered ring represents a minimum in activation energy relative to larger or smaller sized ring analogs due to a favourable combination of ring strain, minimized electrostatic interactions, and proximity between the nucleophile and electrophile for achieving the appropriate conformation to react. F8

Examples of Truce–Smiles rearrangements occurring through the formation of 6-membered ring spirocyclic Meisenheimer adducts are relatively uncommon in comparison with reported

Fig. 7. Putative reported 4-membered ring spirocyclic Meisenheimer adducts.[36,39,48,52,95]



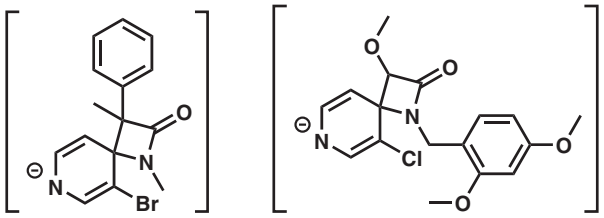
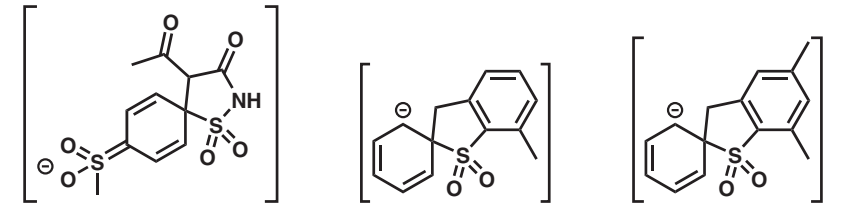
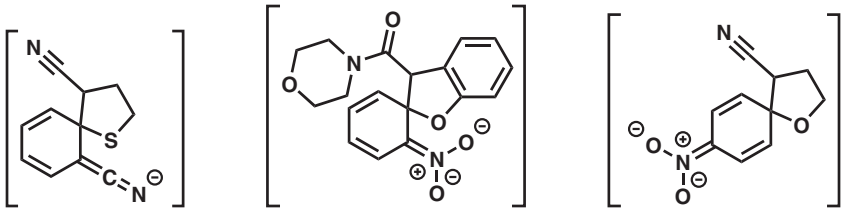


Fig. 8. Some examples of putative reported 5-membered ring spirocyclic Meisenheimer adducts.[2,13,17,31,49,114]





5-membered ring examples.[5,30,44–46,102] Generally, the linker connecting the electrophilic aryl ring to the nucleophilic carbanion center in the examples shown in Fig. 9 tend to be more unsaturated than in substrates that favour smaller ring spirocyclic Meisenheimer adducts, possibly suggesting that the fewer degrees of rotational freedom of the atoms in the linker promotes the formation of these less common, larger intermediate rings. F9

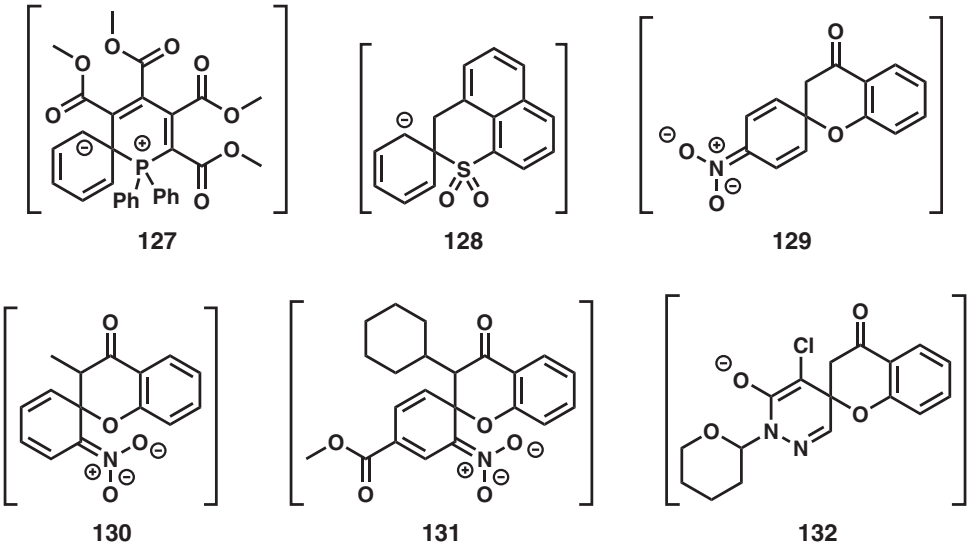
To our knowledge, there are no reported examples of Truce–Smiles rearrangement reactions that have been proposed to proceed through a spirocyclic Meisenheimer adduct with greater than six atoms in one ring. A thorough examination of the factors that influence reaction rates for the Truce–Smiles rearrangement logically includes studies of the effect of tether length, and therefore spirocyclic Meisenheimer adduct ring size, as one of the fundamentally important substrate design features.

4.4. Nucleophile design

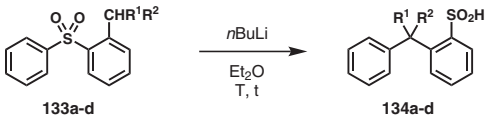
Of all the various methods for generating carbanions, relatively few have been successfully employed for generating the nucleophile in the Truce–Smiles rearrangement. A survey of the Truce–Smiles rearrangement literature reveals that the most common method for generating the carbanion nucleophile is the use of a base to deprotonate the substrate. Typically, this requires activation of the C–H bond to lower the pK_a into a range that is compatible with synthetically useful bases. This activation may be achieved by the inclusion of a functional group (Z in Scheme 20) that will stabilize the carbanion by withdrawing electron density, most often carbonyls or nitriles.

Most of the early Truce–Smiles rearrangement research focused on the use of a benzyllithium species as the carbanion nucleophile.[16,55] The benzyllithium nucleophile was typically generated from an *ortho*-tolyl methyl group, but variations in substitution of the methyl group have been reported (Scheme 37). The reaction S37 has been observed to be slower when the nucleophilic carbon is substituted with electron-donating substituents that should act to both raise the nucleophilicity of the formed benzyllithium from an electronic perspective, while lowering it from a steric perspective,

Fig. 9. Putative reported 6-membered ring spirocyclic Meisenheimer adducts.[5,30,44–46,102]



Scheme 37. Tolerated variations in substitution of benzylic carbanion nucleophiles.[2,107–110]



	R^1	R^2	T (°C)	t (h)	yield (%)	ref
a	H	H	34	4	65-70	2
b	H	CH_3	r.t.	48	62	108
c	H	$(CH_2)_2Ph$	34	4	60	107
d	Ph	Ph	r.t.	24	90	110

raising the pK_a of the attached hydrogen atom.[2,107–110] However, even the very delocalized and sterically demanding benzyldiphenyl anion derived from substrate **133d** undergoes the rearrangement in excellent yield.

Alternative methods for generating the carbanion nucleophile, which has seen some popular use in the Truce–Smiles rearrangement, have been directed-ortho metalation,[58,61,96,100,111] or lithium–halogen exchange.[95,96] As well, the use of benzyne[43,112] or alkyne[102] intermediates in the generation of aryl anions has been employed in several reports and, in one example, the use of a phenolate anion.[35]

5. Competing reactions

The most common side products reported for Truce–Smiles rearrangements are different S_NAr regioisomers. Because the reaction is intramolecular, typically, the most common side products are those arising from attack of the nucleophile at ortho-positions on the migrating ring forming a 1,2-isomer of the Meisenheimer adduct (Fig. 1), as opposed to the desired ipso-position forming the 1,1-isomer. Truce and Drozd extensively investigated the regioselectivity of the rearrangement of their diarylsulfone benzyllithium substrates.[16,54] An example of these alternative reaction pathways
S38 is shown in Scheme 38.

Drozd and colleagues successfully developed reactions for trapping the Meisenheimer 1,2-adduct regioisomers as dihydrothioxanthene 10,10-dioxides that could be further derivatized. One example of the reactions used to trap the ortho-substituted intermediate,
S39 **143**, is shown in Scheme 39.

The definition of the Truce–Smiles rearrangement is inconsistent, in part based on the competing rearrangement that produces these 1,2-adduct regioisomers and in part based on Truce–Smiles reactions that proceed through radical mechanisms. In a reflective review[55] written as a Professor Emeritus of Chemistry at Purdue University in 1990, Truce defined the Truce–Smiles rearrangement as inclusive of both of these types of reactivity in addition to the more conventional reactions that achieve ipso-substitution by a typical ionic S_NAr route. This is a definition that he had been consistent in presenting in his publications about his eponymous rearrangement reaction.[54,117] Despite this, perhaps in an effort to draw closer parallels to the Smiles rearrangement mechanism or for simplicity, the Truce–Smiles rearrangement has come to be defined more exclusively as it has been presented in this review, as only the reactions that achieve ipso-substitution by a typical ionic S_NAr route.[29,118,119] We have willingly adopted this change in definition and have excluded the competing rearrangement products such as 1,2-adduct regioisomers and the Truce–Smiles reactions that proceed through radical mechanisms.

6. Applications

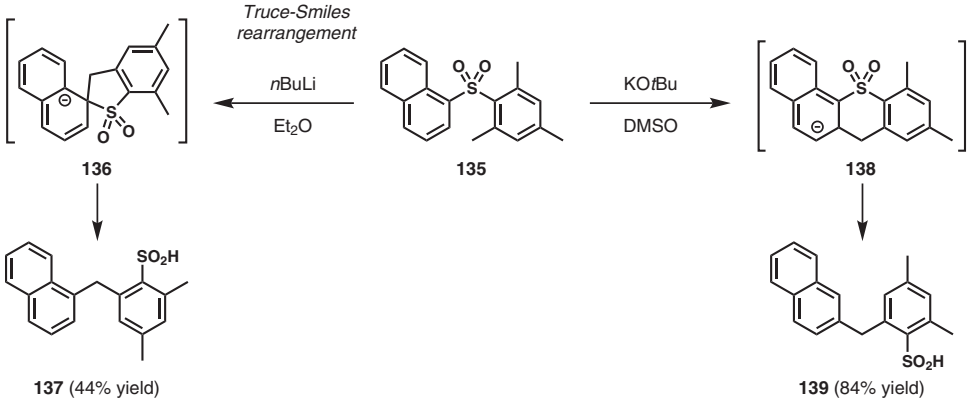
One of the earliest demonstrations of the practical usefulness of the Truce–Smiles rearrangement was its use in the synthesis of the central nervous system stimulant drug methyl phenyl(piperidin-2-yl) acetate, or Ritalin (Scheme 40).[12] Dohmori and colleagues illus- S40
trated that the tandem Truce–Smiles – sulfur extrusion – hydrolysis sequences that typified the reactions that were the focus of their studies could provide an efficient method for the formation of a C–C bond that would ultimately attach the piperidinyl moiety to the phenyl acetate moiety in **151**.

One of the most practical applications of the Truce–Smiles rearrangement has been its reported combination in a synthetic sequence for the large-scale (25 kg) production of an indole intermediate by Merck & Co., Inc., process chemists.[45] The key step in this high-yielding synthesis, which featured a 55% overall yield in seven chemical transformations, was a Truce–Smiles rearrangement inspired by a report from Snape.[30] The last two steps in the synthesis are shown in Scheme 41. The Truce–Smiles rearrangement S41
is used to convert the easily installed aryl ether bond of substrate **152** into a new C–C bond that will ultimately constitute the C3–C3a bond in the indole product, **155**, following ring closure.

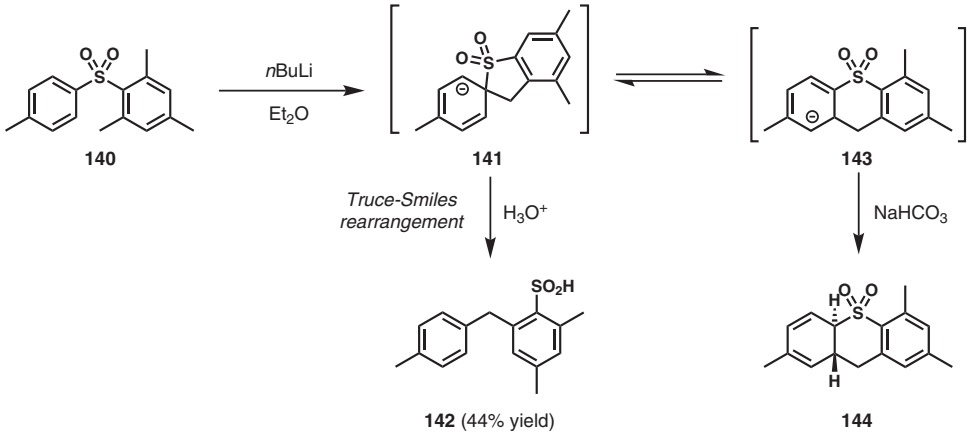
6.1. Stereoselective reactions

The development of conditions for the Truce–Smiles rearrangement that would provide predictable and controllable stereochemical outcomes represents a highly valuable and useful route

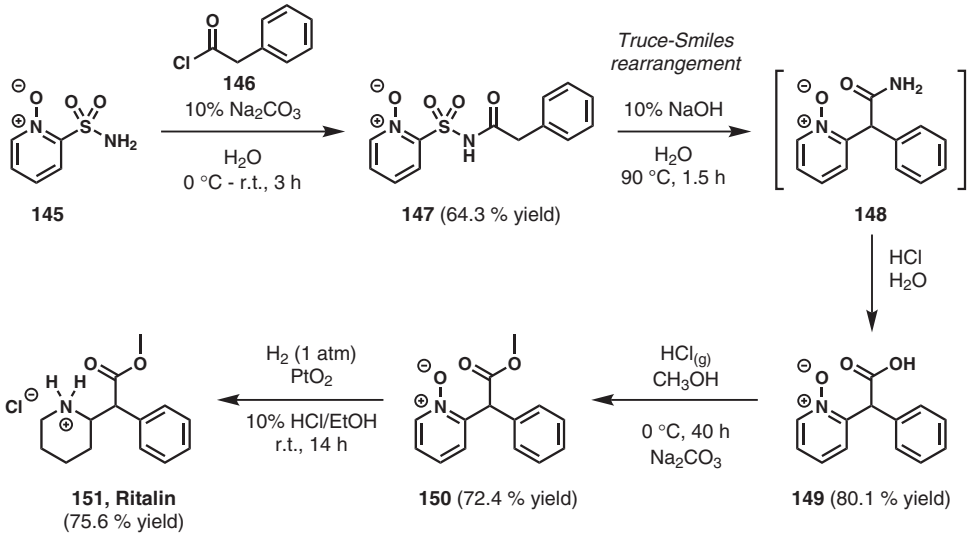
Scheme 38. Example of regioselective nucleophilic aromatic substitution reactions studied by Truce and colleagues.[6,115]



Scheme 39. Example of regioselective nucleophilic aromatic substitution reactions studied by Drozd and Trifonova.[116]



Scheme 40. Synthesis of Ritalin using Truce–Smiles rearrangement.[12]

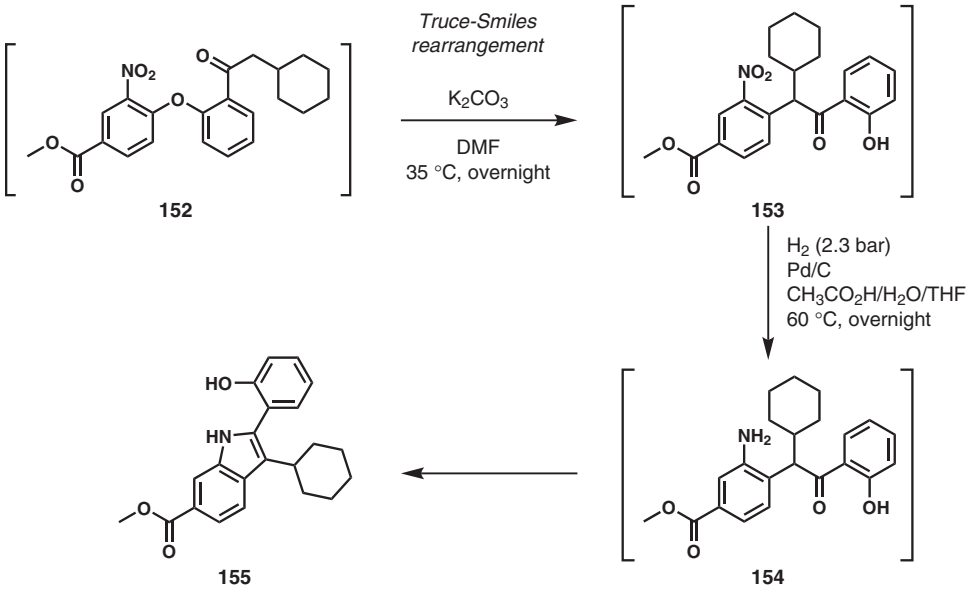


of investigation. Some Truce–Smiles rearrangements using enantiomerically pure substrates have been shown to result in racemic rearranged products.[39] However, reports have started to appear more frequently in the recent literature of stereoselective Truce–Smiles rearrangements.[31,37,40]

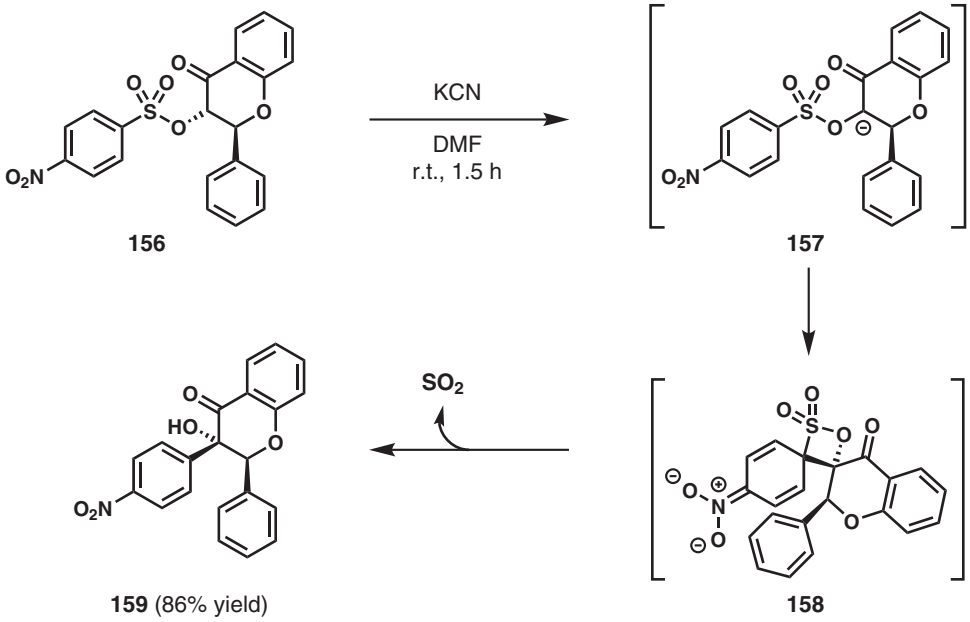
Patonay and colleagues reported a highly stereoselective reaction that provided a high yield of a rearranged arylsulfonate as a diastereomerically pure alcohol, **159** (Scheme 42).[37] The authors chose not to propose a hypothesis to explain the high degree of observed stereoselectivity; however, it seems likely that the existing chiral center on the dihydropyrone ring exerts an influence on the stereochemistry of the sterically crowded 4-membered ring spirocyclic Meisenheimer adduct, **158**, formed in the course of the reaction. This proposal relies on the favoured formation of the Meisenheimer adduct diastereomer according to the assumed S_NAr mechanism shown in Scheme 42.

S42

Scheme 41. Large-scale synthetic process involving Truce–Smiles rearrangement.[45]



Scheme 42. Diastereoselective Truce–Smiles rearrangement.[37]



Lupi and colleagues[40,42] reported highly diastereoselective Truce–Smiles rearrangements on a series of chiral sulfonamides that were prepared with defined absolute configuration at the chirality center alpha to nitrogen. The favoured diastereomer of the Meisenheimer adduct **162** (Scheme 43) is selectively formed by *Re* face attack by the stable enolate intermediate, **161**, as described in their detailed discussion of the aryl migration stereochemical outcome.

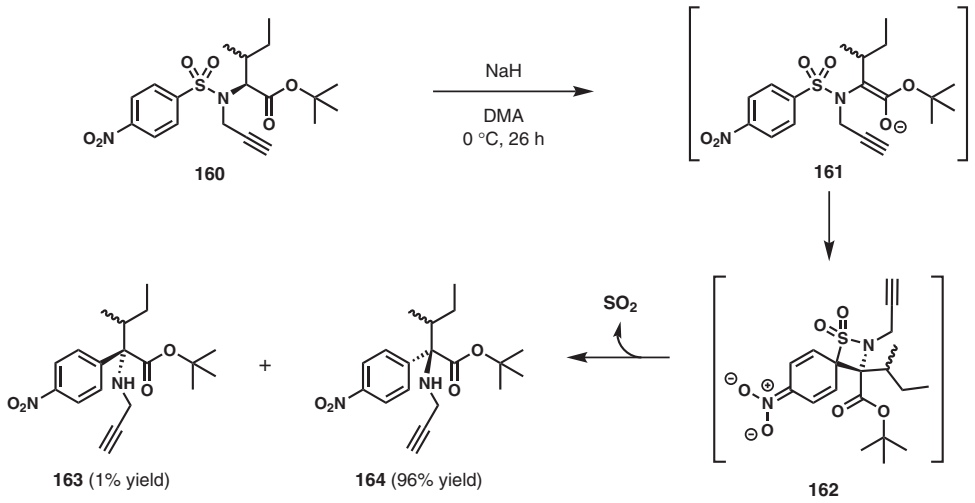
Using enantiomerically pure (2*S*, 5*S*)-bis(methoxymethyl)pyrrolidine as a chiral auxiliary in the in situ prepared substrate diarylethers, a diastereomeric ratio of 1:1.6 was observed by Ameen and Snape for the rearranged product phenols **169** and **170** shown in Scheme 44.[31] A mechanistic model was proposed in which attack from the *Si* face of the enolate is blocked by one of the methoxymethyl groups of the chiral auxiliary leading to the diastereoselective formation of a chiral Meisenheimer adduct (**168**).[31]

7. Conclusion and future outlook

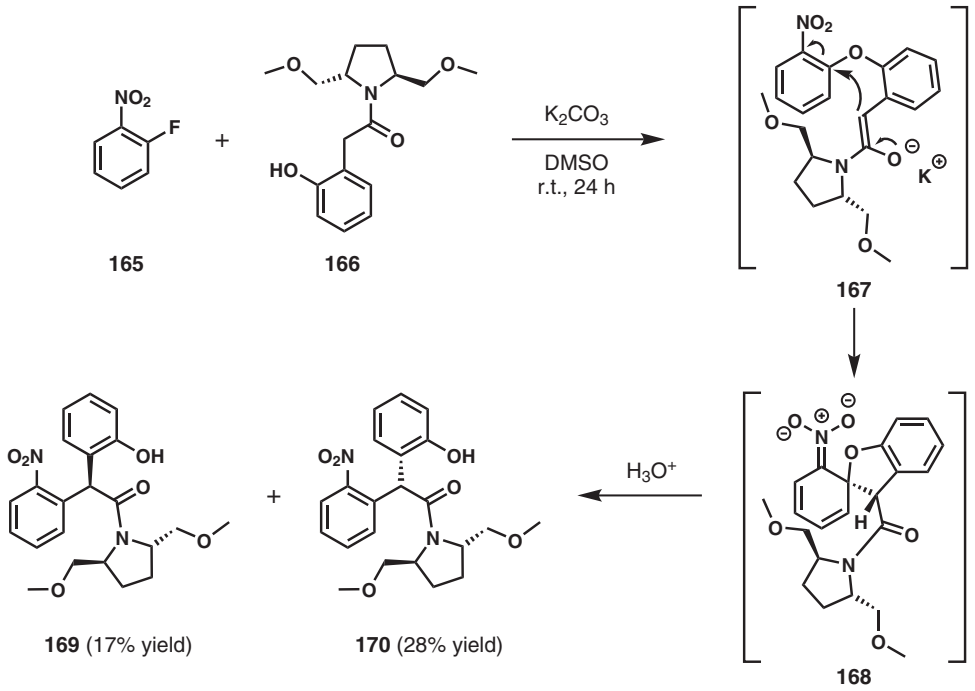
The intention of this review is to shed some light on the Truce–Smiles rearrangement. We find it to be an under-utilized and under-explored transformation that has been demonstrated to be useful in practical synthetic organic applications, but whose potential has yet to be realized. By including various tandem reaction sequences and permitting an inclusive definition of the methods used for the preparation of the carbanion nucleophile, we discovered many diverse examples of successful reaction substrates reported in the literature. However, the reports are frequently isolated studies of the reaction that appear to have been discovered as adventitious outcomes, sometimes as just one molecule in a paper of unrelated reactions.

The research groups who have made the investment to study the reaction in an organized systematic manner have contributed greatly to laying the foundation for our understanding of the

Scheme 43. Diastereoselective Truce–Smiles rearrangement.[40]



Scheme 44. Diastereoselective Truce–Smiles rearrangement.[31]



mechanism and the influence of substrate design on the success of the rearrangement. We sought to celebrate their research achievements by summarizing them herein and have hopefully outlined some of the research areas that we view as most urgently in need of attention from current researchers in moving the Truce–Smiles rearrangement forward in the future.

Acknowledgements

Financial support for this work was provided by the Natural Sciences and Engineering Research Council (NSERC) of Canada and the University of Winnipeg.

References

(1) Truce, W. E.; Ray, W. J.; Norman, O. L.; Eickemeyer, D. B. *J. Am. Chem. Soc.* **1958**, *80*, 3625. doi:10.1021/ja01547a038.
(2) Truce, W. E.; Ray, W. J. *J. Am. Chem. Soc.* **1959**, *81*, 481. doi:10.1021/ja01511a054.
(3) Truce, W. E.; Ray, W. J. *J. Am. Chem. Soc.* **1959**, *81*, 484. doi:10.1021/ja01511a055.
(4) Truce, W. E.; Guy, M. M. *J. Org. Chem.* **1961**, *26*, 4331. doi:10.1021/jo01069a036.
(5) Truce, W. E.; Hampton, D. C. *J. Org. Chem.* **1963**, *28*, 2276. doi:10.1021/jo01044a029.
(6) Truce, W. E.; Robbins, C. R.; Kreider, E. M. *J. Am. Chem. Soc.* **1966**, *88*, 4027. doi:10.1021/ja00969a024.
(7) Snyder, D. M.; Truce, W. E. *J. Am. Chem. Soc.* **1979**, *101*, 5432. doi:10.1021/ja00512a063.
(8) Naito, T.; Dohmori, R.; Nagase, O. *Yakugaku Zasshi* **1954**, *74*, 593.
(9) Naito, T.; Dohmori, R.; Sano, M. *Yakugaku Zasshi* **1954**, *74*, 596.
(10) Naito, T.; Dohmori, R.; Shimoda, M. *Pharm. Bull.* **1955**, *3*, 34. doi:10.1248/cpb1953.3.34.
(11) Naito, T.; Dohmori, R. *Pharm. Bull.* **1955**, *3*, 38. doi:10.1248/cpb1953.3.38.
(12) Naito, T.; Dohmori, R.; Kotake, T. *Chem. Pharm. Bull.* **1964**, *12*, 588. doi:10.1248/cpb.12.588.
(13) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 591. doi:10.1248/cpb.12.591.
(14) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 595. doi:10.1248/cpb.12.595.
(15) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 601. doi:10.1248/cpb.12.601.
(16) Drozd, V. N. *Int. J. Sulfur Chem.* **1973**, *8*, 443.
(17) Drozd, V. N. *Dokl. Akad. Nauk SSSR* **1966**, *169*, 107.
(18) Sasaki, K.; Shamsur, R. A. S.; Kashino, S.; Hirota, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1767. doi:10.1039/C39940001767.

(19) Sasaki, K.; Rouf, A. S. S.; Kashino, S.; Hirota, T. *Heterocycles* **1995**, *41*, 1307. doi:10.3987/COM-95-7064.
(20) Kingsford-Adaboh, R.; Kashino, S.; Sasaki, K.; Rouf, A. S. S.; Hirota, T. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1996**, *C52*, 372. doi:10.1107/S0108270195013035.
(21) Sasaki, K.; Rouf, A. S. S.; Hirota, T. *J. Heterocycl. Chem.* **1996**, *33*, 49. doi:10.1002/jhet.5570330109.
(22) Hirota, T.; Matsushita, T.; Sasaki, K.; Kashino, S. *Heterocycles* **1995**, *41*, 2565. doi:10.3987/COM-95-7212.
(23) Hirota, T.; Tomita, K.-I.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* **2001**, *55*, 741. doi:10.3987/COM-01-9168.
(24) Okuda, K.; Watanabe, N.; Hirota, T.; Sasaki, K. *Tetrahedron Lett.* **2010**, *51*, 903. doi:10.1016/j.tetlet.2009.12.010.
(25) Okuda, K.; Yoshida, M.; Hirota, T.; Sasaki, K. *Chem. Pharm. Bull.* **2010**, *58*, 363. doi:10.1248/cpb.58.363.
(26) Okuda, K.; Deguchi, H.; Kashino, S.; Hirota, T.; Sasaki, K. *Chem. Pharm. Bull.* **2010**, *58*, 685. doi:10.1248/cpb.58.685.
(27) Okuda, K.; Yoshida, M.; Hirota, T.; Sasaki, K. *J. Heterocycl. Chem.* **2013**, *50*, E9. doi:10.1002/jhet.1016.
(28) Okuda, K.; Nikaido, T.; Hirota, T.; Sasaki, K. *Synth. Commun.* **2013**, *43*, 1619. doi:10.1080/00397911.2012.656295.
(29) Snape, T. J. *Chem. Soc. Rev.* **2008**, *37*, 2452. doi:10.1039/b808960d.
(30) Snape, T. J. *Synlett* **2008**, *2008*, 2689. doi:10.1055/s-0028-1083523.
(31) Ameen, D.; Snape, T. J. *Eur. J. Org. Chem.* **2014**, *2014*, 1925. doi:10.1002/ejoc.201301716.
(32) Terrier, F. *Modern Nucleophilic Aromatic Substitution*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2013. doi:10.1002/9783527656141.
(33) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1931**, 914. doi:10.1039/JR9310000914.
(34) Drews, H.; Fields, E. K.; Meyerson, S. *Chem. Ind. (London)* **1961**, 1403.
(35) Waldau, E.; Pütter, R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 826. doi:10.1002/anie.197208261.
(36) Hoffman, R. V.; Jankowski, B. C.; Carr, C. S.; Duesler, E. N. *J. Org. Chem.* **1986**, *51*, 130. doi:10.1021/jo00352a002.
(37) Patonay, T.; Hegedüs, L.; Patonay-Péli, E. *J. Heterocycl. Chem.* **1993**, *30*, 145. doi:10.1002/jhet.5570300126.
(38) Meng, Q.; Thibblin, A. *J. Am. Chem. Soc.* **1997**, *119*, 1224. doi:10.1021/ja9624681.
(39) Wilson, M. W.; Ault-Justus, S. E.; Hodges, J. C.; Rubin, J. R. *Tetrahedron* **1999**, *55*, 1647. doi:10.1016/S0040-4020(98)01209-5.
(40) Lupi, V.; Penso, M.; Foschi, F.; Gassa, F.; Mihali, V.; Tagliabue, A. *Chem. Commun.* **2009**, 5012. doi:10.1039/B910326K.
(41) El Rayes, S.; Linden, A.; Abou-Hadeed, K.; Hansen, H.-J. *Helv. Chim. Acta* **2010**, *93*, 1894. doi:10.1002/hlca.201000191.
(42) Foschi, F.; Landini, D.; Lupi, V.; Mihali, V.; Penso, M.; Pilati, T.; Tagliabue, A. *Chem. - Eur. J.* **2010**, *16*, 10667. doi:10.1002/chem.201000989.
(43) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2016**, *55*, 2450. doi:10.1002/anie.201510236.
(44) Mitchell, L. H.; Barvian, N. C. *Tetrahedron Lett.* **2004**, *45*, 5669. doi:10.1016/j.tetlet.2004.05.111.
(45) Alorati, A. D.; Gibb, A. D.; Mullens, P. R.; Stewart, G. W. *Org. Process Res. Dev.* **2012**, *16*, 1947. doi:10.1021/op300303p.
(46) Liu, Y.; Zhang, X.; Ma, Y.; Ma, C. *Tetrahedron Lett.* **2013**, *54*, 402. doi:10.1016/j.tetlet.2012.11.024.
(47) El Kaim, L.; Grimaud, L.; Le Goff, X. F.; Schiltz, A. *Org. Lett.* **2011**, *13*, 534. doi:10.1021/ol1028817.
(48) Getlik, M.; Wilson, B. J.; Morshed, M. M.; Watson, I. D. G.; Tang, D.; Subramanian, P.; Al-awar, R. *J. Org. Chem.* **2013**, *78*, 5705. doi:10.1021/jo4003773.
(49) Kosowan, J. R.; W'Giorgis, Z.; Grewal, R.; Wood, T. E. *Org. Biomol. Chem.* **2015**, *13*, 6754. doi:10.1039/C5OB00812C.
(50) Ah-kow, G.; Terrier, F.; Pouet, M.-J.; Simonnin, M.-P. *J. Org. Chem.* **1980**, *45*, 4399. doi:10.1021/jo01310a027.
(51) Strauss, M. J. *Chem. Rev.* **1970**, *70*, 667. doi:10.1021/cr60268a003.
(52) Dey, C.; Katayev, D.; Ylijoki, K. E. O.; Kündig, E. P. *Chem. Commun.* **2012**, *48*, 10957. doi:10.1039/c2cc36068c.
(53) Madaj, E. J., Jr.; Snyder, D. M.; Truce, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3466. doi:10.1021/ja00272a049.
(54) Truce, W. E.; Madaj, E. J., Jr. *Sulfur Rep.* **1983**, *3*, 259. doi:10.1080/01961778308082458.
(55) Truce, W. E. *Sulfur Rep.* **1990**, *9*, 351. doi:10.1080/01961779008048733.
(56) Tomooka, K.; Yamamoto, H.; Nakai, T. *J. Am. Chem. Soc.* **1996**, *118*, 3317. doi:10.1021/ja953933h.
(57) Stéphan, E.; Dousset, M.; Foy, N.; Jaouen, G. *J. Chem. Res.* **2002**, 506. doi:10.3184/030823402103170547.
(58) Yang, J.; Dudley, G. B. *J. Org. Chem.* **2009**, *74*, 7998. doi:10.1021/jo901707x.
(59) Gao, G.; Gu, F.-L.; Jiang, J.-X.; Jiang, K.; Sheng, C.-Q.; Lai, G.-Q.; Xu, L.-W. *Chem. Eur. J.* **2011**, *17*, 2698. doi:10.1002/chem.201003111.
(60) Zheng, L.-S.; Jiang, K.-Z.; Deng, Y.; Bai, X.-F.; Gao, G.; Gu, F.-L.; Xu, L.-W. *Eur. J. Org. Chem.* **2013**, *2013*, 748. doi:10.1002/ejoc.201201301.
(61) Yang, J.; Wangweerawong, A.; Dudley, G. B. *Heterocycles* **2012**, *85*, 1603. doi:10.3987/COM-12-12492.
(62) Tomohara, K.; Yoshimura, T.; Hyakutake, R.; Yang, P.; Kawabata, T. *J. Am. Chem. Soc.* **2013**, *135*, 13294. doi:10.1021/ja406653n.
(63) Clayden, J.; Dufour, J.; Grainger, D. M.; Helliwell, M. *J. Am. Chem. Soc.* **2007**, *129*, 7488. doi:10.1021/ja071523a.
(64) Clayden, J. In *Lithium Compounds in Organic Synthesis*; Luisi, R., Capriati, V., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2014; p. 375. doi:10.1002/9783527667512.ch13.
(65) Grainger, D. M.; Campbell Smith, A.; Vincent, M. A.; Hillier, I. H.; Wheatley, A. E. H.; Clayden, J. *Eur. J. Org. Chem.* **2012**, *2012*, 731. doi:10.1002/ejoc.201101475.
(66) Vincent, M. A.; Maury, J.; Hillier, I. H.; Clayden, J. *Eur. J. Org. Chem.* **2015**, *2015*, 953. doi:10.1002/ejoc.201403572.
(67) Tada, M.; Shijima, H.; Nakamura, M. *Org. Biomol. Chem.* **2003**, *1*, 2499. doi:10.1039/b303728b.
(68) Motherwell, W. B.; Vázquez, S. *Tetrahedron Lett.* **2000**, *41*, 9667. doi:10.1016/S0040-4039(00)01746-9.
(69) Pudlo, M.; Allart-Simon, I.; Tinant, B.; Gérard, S.; Sapi, J. *Chem. Commun.* **2012**, *48*, 2442. doi:10.1039/c2cc15670a.
(70) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480. doi:10.1021/ja403954g.
(71) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 13086. doi:10.1002/anie.201307377.
(72) Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504. doi:10.1021/ol403391v.
(73) Winkler, J. D.; Lee, E. C. Y. *J. Am. Chem. Soc.* **2006**, *128*, 9040. doi:10.1021/ja060962r.
(74) Kitamura, T.; Zhang, B.-X.; Fujiwara, Y. *Tetrahedron Lett.* **2002**, *43*, 2239. doi:10.1016/S0040-4039(02)00216-2.
(75) Jo, H.; Fitzgerald, M. E.; Winkler, J. D. *Org. Lett.* **2009**, *11*, 1685. doi:10.1021/ol900186y.
(76) Akiba, K.; Ohara, Y.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2976. doi:10.1246/bcsj.55.2976.
(77) Jones, R. C. F.; Nichols, J. R. *Tetrahedron* **2013**, *69*, 4114. doi:10.1016/j.tet.2013.03.040.
(78) Studer, A.; Bossart, M.; Vasella, T. *Org. Lett.* **2000**, *2*, 985. doi:10.1021/ol005661f.
(79) Quiclet-Sire, B.; Tran, N. D. M.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5514. doi:10.1021/ol3026044.
(80) Rey, V.; Pierini, A. B.; Peñéñory, A. B. *J. Org. Chem.* **2009**, *74*, 1223. doi:10.1021/jo801892c.
(81) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817. doi:10.1021/ol0515681.
(82) Nishio, T.; Koyama, H.; Sasaki, D.; Sakamoto, M. *Helv. Chim. Acta* **2005**, *88*, 996. doi:10.1002/hlca.200590095.
(83) Black, M.; Cadogan, J. I. G.; Leardini, R.; McNab, H.; McDougald, G.; Nanni, D.; Reed, D.; Zompatori, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1825. doi:10.1039/A800884A.
(84) Factor, A.; Finkbeiner, H.; Jerussi, R. A.; White, D. M. *J. Org. Chem.* **1970**, *35*, 57. doi:10.1021/jo00826a014.
(85) Hoffmann, N.; Pete, J.-P. *J. Org. Chem.* **1997**, *62*, 6952. doi:10.1021/jo970554t.
(86) Birch, A. J.; Hinde, A. L.; Radom, L. *J. Am. Chem. Soc.* **1980**, *102*, 6430. doi:10.1021/ja00541a009.
(87) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273. doi:10.1021/cr60153a002.
(88) Nitzschke, H.-J.; Budha, H. *Chem. Ber.* **1955**, *88*, 264. doi:10.1002/cber.19550880216.
(89) Hellwinkel, D.; Lenz, R. *Chem. Ber.* **1985**, *118*, 66. doi:10.1002/cber.19851180108.
(90) Crampton, M. R.; Willison, M. J. *J. Chem. Soc., Perkin Trans. 2* **1976**, 155. doi:10.1039/P29760000155.
(91) Bernasconi, C. F.; Gandler, J. R. *J. Org. Chem.* **1977**, *42*, 3387. doi:10.1021/jo00441a014.
(92) Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* **1983**, *34*, 305. doi:10.1016/S0065-2725(08)60823-5.
(93) Chambers, R. D.; Martin, P. A.; Waterhouse, J. S.; Williams, D. L. H.; Anderson, B. *J. Fluorine Chem.* **1982**, *20*, 507. doi:10.1016/S0022-1139(00)82276-9.
(94) Erickson, W. R.; McKennon, M. J. *Tetrahedron Lett.* **2000**, *41*, 4541. doi:10.1016/S0040-4039(00)00701-2.
(95) Ponce González, J.; Edgar, M.; Elsegood, M. R. J.; Weaver, G. W. *Org. Biomol. Chem.* **2011**, *9*, 2294. doi:10.1039/c0ob00790k.
(96) Dankwardt, J. W. *J. Org. Chem.* **1998**, *63*, 3753. doi:10.1021/jo9718410.
(97) Okuda, K.; Takechi, H.; Hirota, T.; Sasaki, K. *Heterocycles* **2011**, *83*, 1315. doi:10.3987/COM-11-12187.
(98) Truce, W. E.; VanGemert, B.; Brand, W. W. *J. Org. Chem.* **1978**, *43*, 101. doi:10.1021/jo00395a024.
(99) Bayne, D. W.; Nicol, A. J.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1975**, 782. doi:10.1039/C39750000782.
(100) Fukazawa, Y.; Kato, N.; Itô, S. *Tetrahedron Lett.* **1982**, *23*, 437. doi:10.1016/S0040-4039(00)86853-7.
(101) Kimbaris, A.; Cobb, J.; Tsakonas, G.; Varvounis, G. *Tetrahedron* **2004**, *60*, 8807. doi:10.1016/j.tet.2004.07.036.
(102) Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 2126. doi:10.1039/JR9610002126.
(103) Zbiral, E. *Monatsh. Chem. Verw. Tl.* **1964**, *95*, 1759. doi:10.1007/BF00901736.
(104) Schmidbaur, H.; Schnatterer, S. *Chem. Ber.* **1983**, *116*, 1947. doi:10.1002/cber.19831160522.
(105) Izod, K.; O'Shaughnessy, P.; Clegg, W. *Organometallics* **2002**, *21*, 641. doi:10.1021/om010856s.

(106) Drozd, V. N.; Sheichenko, V. I. *Zh. Org. Khim.* **1967**, *3*, 554.
(107) Drozd, V. N.; Nikonova, L. A. *Zh. Org. Khim.* **1968**, *4*, 1060.
(108) Drozd, V. N.; Nikonova, L. A. *Zh. Org. Khim.* **1969**, *5*, 1453.
(109) Drozd, V. N.; Nikonova, L. A. *Zh. Org. Khim.* **1969**, *5*, 325.
(110) Crowther, G. P.; Hauser, C. R. *J. Org. Chem.* **1968**, *33*, 2228. doi:10.1021/jo01270a013.
(111) Chenard, B. L. *J. Org. Chem.* **1983**, *48*, 2610. doi:10.1021/jo00163a041.
(112) Zbiral, E. *Tetrahedron Lett.* **1964**, *5*, 3963. doi:10.1016/S0040-4039(01)89349-7.
(113) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183. doi:10.1016/S0065-3160(08)60129-X.
(114) Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* **2001**, *55*, 741. doi:10.3987/COM-01-9168.
(115) Truce, W. E.; Brand, W. W. *J. Org. Chem.* **1970**, *35*, 1828. doi:10.1021/jo00831a025.
(116) Drozd, V. N.; Trifonova, O. I. *Zh. Org. Khim.* **1971**, *7*, 1926.
(117) Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React.* **1970**, *18*, 99.
(118) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163. PMID: 23605513.
(119) Kumar, R. R.; Perumal, S. In *Smiles rearrangement*; John Wiley & Sons: Hoboken, N.J., 2009; pp. 489–515.