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Recent Advances in The Smiles Rearrangement: New Opportunities for Arylation

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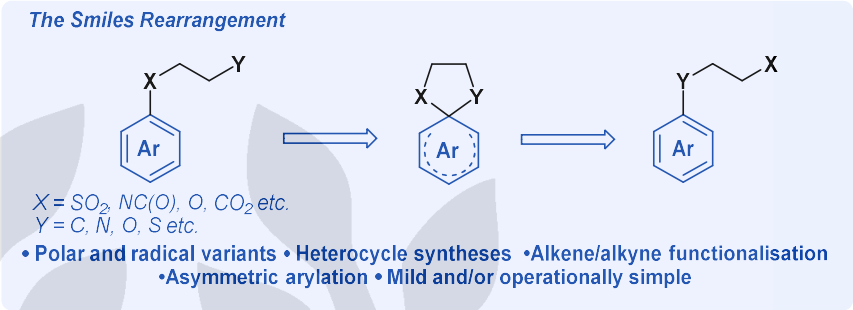

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Contents

1)Introduction
2)Polar Smiles Rearrangements
3)Radical Smiles: Alkene and Alkyne Functionalisation
4)Radical Smiles: C-X bond cleavage
5) Miscellaneous Radical Smiles Rearrangements
6) Conclusions

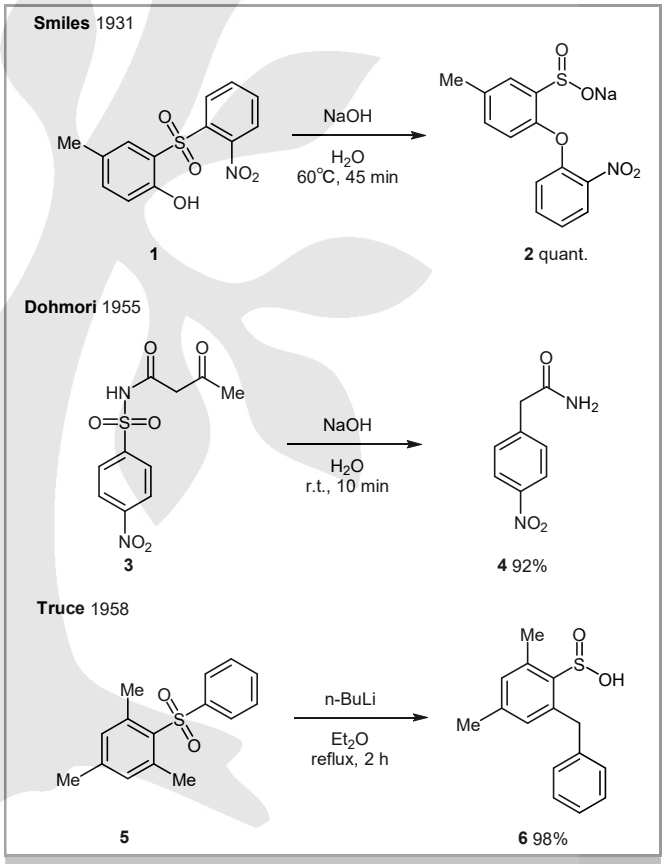
Key words rearrangements, arylation, radicals, Smiles

Introduction

The Smiles rearrangement is an intramolecular nucleophilic aromatic *ipso*-substitution reaction, enabling aryl migration to take place.[1-6] The original incarnation of the reaction used anionic heteroatomic species as the incoming nucleophile (Scheme 1, conversion of **1** to **2**), until Dohmori and Truce demonstrated the reaction's applicability to carbon-centred nucleophiles (Scheme 1, **3** to **4** and **5** to **6** respectively).[7-11] This key advancement led to Smiles chemistry being utilized for C-C bond formation in decades to come, with pivotal contributions from Speckamp and Motherwell demonstrating that the reaction can also operate via a radical pathway.[12-17]

Performing an arylation using *ipso*-substitution is highly appealing; it negates the need for a cross-coupling organometallic and precious metal catalyst, converts simple and easy to prepare starting materials into difficult-to-arylate products, and is very amenable to cascade processes, where the key Smiles arylation is set up *in situ* through another bond-forming step, enhancing efficiency.

Previous reviews on the topic[1-6] have detailed the key advances in the field, such as the rearrangement's applicability to biaryl syntheses,[18-20] the use of the rearrangement in heterocyclic syntheses and also the use of the reaction as a tandem bond-forming process.[21-23] This Short Review will aim to recount the key advances that have been made since 2017.



Scheme 1 Smiles, Dohmori and Truce's seminal contributions to the field of aryl migration

Polar Smiles Rearrangements

The anionic Smiles rearrangement is characterized by operational simplicity, frequently just simple base treatment, with no requirement for elaborate transition metal catalyst systems, and is often used to access difficult-to-synthesize tertiary and quaternary benzylic stereocenters.

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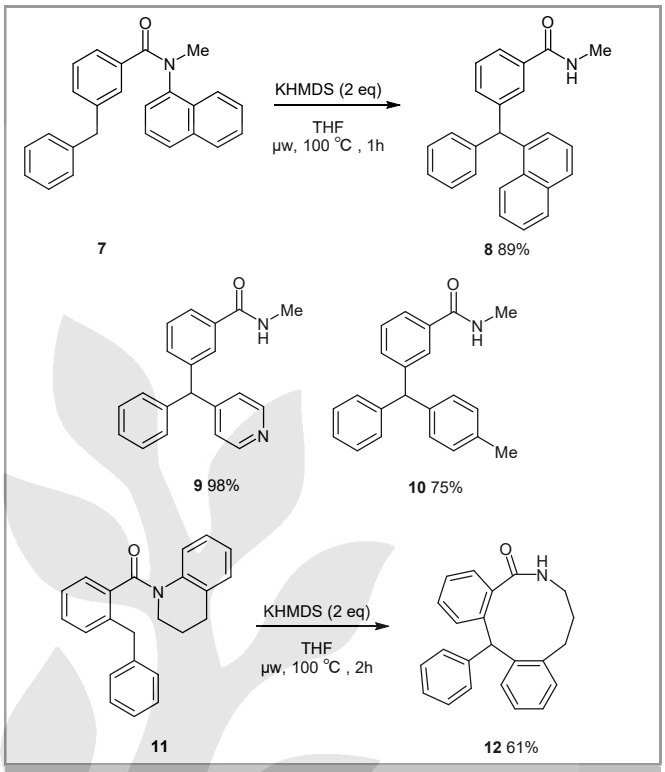
The work of the Clayden group has demonstrated the utility of aryl-ureas and aryl-amides as excellent Smiles substrates, capable of undergoing rearrangement under basic conditions. Features of the Clayden rearrangement include a remarkably broad scope of migrating ring, often requiring no activation from electron withdrawing groups. Classical Smiles chemistry, by contrast, usually requires electron poor or heteroaromatic arene rings to facilitate the S_NAr reaction. Additionally, the system has been exemplified in a number of asymmetric contexts, using chiral organolithium methods for enantio-controlled construction of sp^3 aryls. [24-26]

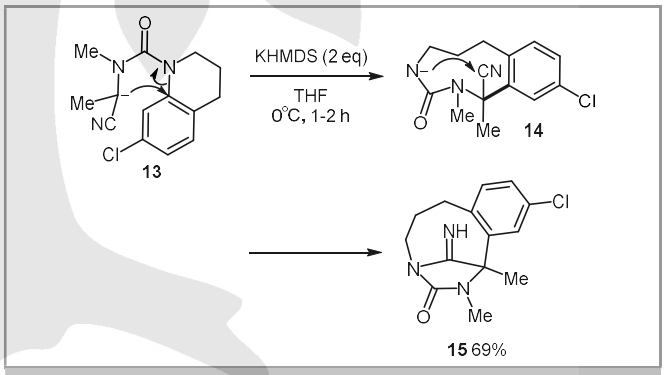
Recent examples include a benzylic arylation reaction (see Scheme 2) whereby a benzanilide-based starting material **7** was deprotonated using a strong base, allowing for an intramolecular nucleophilic aromatic substitution reaction to occur, giving the triarylmethane product **8** in excellent yield with short reaction times. Heterocycles such as pyridine and substituted phenyl rings could be migrated efficiently (**9** and **10**). Furthermore, by tethering the *N*-substituent to the migrating arene (*e.g.* **11**), the reaction gave products containing medium sized lactam rings (**12**), negating the need for a more traditional entropically disfavored cyclisation reaction.[27] The efficiency of the reaction was attributed to the conformational preference of the starting materials. The authors commented that amide **7** prefers to adopt an *E*-conformation whereby the *N*-aryl substituent lies opposite to the carbonyl, allowing for spatial proximity to the nucleophilic benzylic position.[28]

A related reaction by the same group built on this idea of ring expansion via aryl migration, showing that metalated nitriles tethered to a urea linkage can undergo a Smiles rearrangement, giving a medium sized ring (see Scheme 3).[29] After deprotonation via a strong base, the α-nitrile carbanion **13** can undergo *ipso*-substitution on to the neighboring aromatic ring, giving a ring expansion.



Scheme 2 Triarylmethane synthesis via a Truce-Smiles rearrangement using benzanilides

The urea anion **14** can then undergo nucleophilic attack of the nitrile, giving the unusual hydantoin-bridged medium ring scaffold **15**. As with their previous work, the migrating ring is unactivated, allowing for a variety of electronically diverse phenyl rings to be migrated. The reaction can also tolerate heteroatomic substitution on the tethering ring of **13**, with X-ray crystallography elucidating these complex structures throughout the work.



Scheme 3 Hydantoin-bridged medium ring scaffolds via Truce-Smiles rearrangements from Clayden and co-workers

Prior studies from the group include the application of the Truce-Smiles rearrangement to the preparation of α-arylated amino acids in an asymmetric fashion. Using a similar *N*-aryl urea-based system in the starting material linked to an amino acid derived imidazolidinone derivative (**16**), deprotonation triggers the rearrangement to give the α-arylated product **17** in high enantiomeric excess (see Scheme 4). The system incorporates a large range of electronically diverse arene/heteroarene rings, and can be applied to a plethora of amino acids, with routes to

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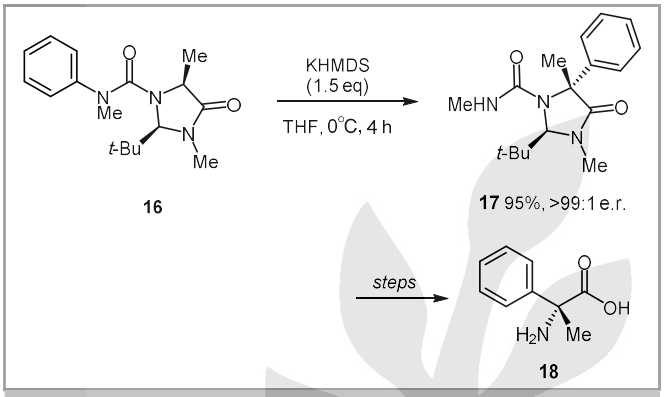
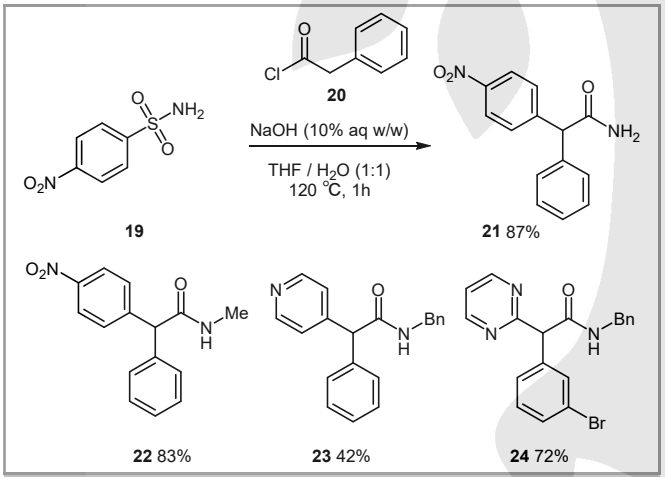
both the *R* and *S* enantiomers of **18**. Whilst there have been a variety of methods for the α-alkylation of amino acids, arylation had remained challenging.[30] This solution to the problem paved the way to asymmetric arylated amino acids in multigram quantities without the need for transition metal catalysis.[31]



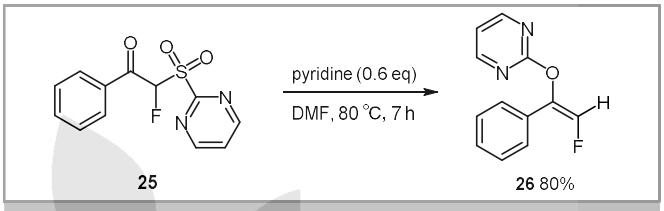
Scheme 4 Production of α-arylated amino acids via Truce-Smiles rearrangement

Greaney and co-workers have shown how arylsulfonamides (*e.g.* **19**) can be used in an S_N2 reaction/Smiles rearrangement tandem reaction to yield valuable benzhydryl derivatives **21** (see Scheme 5).[32] The sulfonamide acts as a discrete arylating agent, with the SO_2 moiety providing a traceless linker that is extruded out of the reaction as a thermodynamic driving force for the reaction.[33] The product scope encompassed nitroarene (**22**), pyridine, and pyrimidine migrating species (**24**), and was tolerant of a range of *N*-substituents on the sulfonamide. The group also noted that when *o*-nosylamides are employed in place of **19**, indazole products are isolated owing to further reaction at the nitro group.



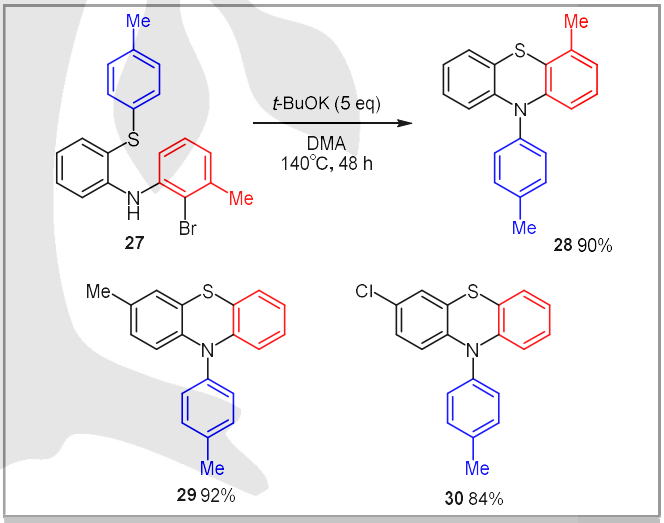
Scheme 5 Truce-Smiles rearrangement via a ketene intermediate by Greaney and co-workers

Jiang and co-workers have also utilized enolate chemistry in the polar Smiles rearrangement, showing how the reaction can occur through oxygen instead of carbon. With catalytic amounts of pyridine at elevated temperatures, an α-fluoro-β-keto-2-pyrimidinylsulfone starting material, **25**, underwent the Smiles rearrangement smoothly to give (*E*)-monofluorovinyl ether product **26** via a desulfonylative pathway (see Scheme 6). The reaction was capable of efficiently migrating pyrimidine and benzothioazole systems, with a broad scope of aliphatic and aromatic ketone substituents. The group then showed how the products of the reaction could be diversified in Heck reactions to give bulky, tetrasubstituted enol ethers.[34]



Scheme 6 Jiang and co-workers' desulfonylative Smiles rearrangement

A further example of the polar Smiles rearrangement mediated by anionic heteroatoms is exemplified by Yoshida who showed that by using *o*-sulfanylanilines (**27**) under basic conditions, a nitrogen-based Smiles rearrangement could be achieved, followed by a subsequent S_NAr reaction to give the N-arylphenothiazine product **28** (scheme 7).[35, 36] The researchers noted that owing to the lack of activation of either of the participating aromatic rings, both processes operate through a concerted mechanism. Groups such as naphthalene, *p*-chlorobenzene and benzofuran underwent the rearrangement smoothly, with the products representing a valuable scaffold with applications as photoredox catalysts, components in organic semiconductors and fluorescent compounds. Moreover, the starting materials can be easily constructed using metal-free benzyne chemistry, whereby an aryne precursor is treated with an *S*-aryl-*S*-(*o*-bromoaryl)sulfilimine in the presence of potassium fluoride and 18-crown-6.



Scheme 7 Smiles rearrangement to yield *N*-arylphenothiazines from Yoshida and co-workers

Organocatalysis has also played a role in polar Smiles chemistry, whereby transition-metal free conditions are employed to provide new arylated products of high value. *N*-heterocyclic carbenes (NHC) represent an important class of organocatalyst, allowing for the unmasking of umpolung reactivity of typically electrophilic substrates.[37] Glorius and co-workers used NHC catalysis to trigger Smiles rearrangements on the salicylaldehyde derivatives shown in Scheme 8. Using the highly nucleophilic

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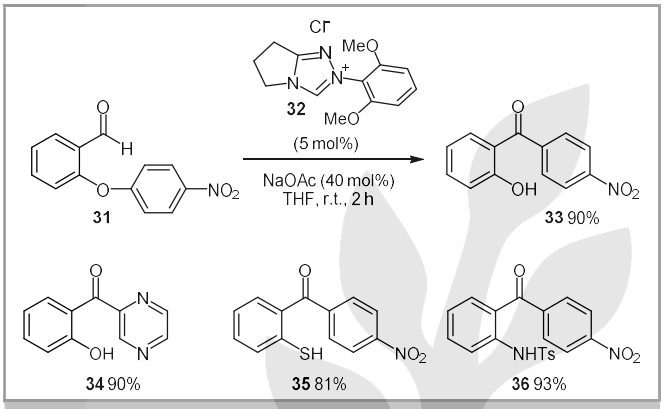
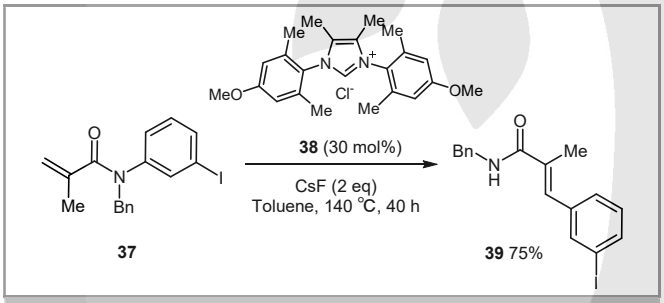
triazolium NHC **32** as catalyst, 2-hydroxybenzophenones **33** could be accessed in high yield with excellent scope for the migrating ring. The reaction was extended to both thioether (**35**) and amino (**36**) substrates, with DFT calculations supported the expected mechanism of Breslow intermediate formation and intramolecular SNAr reaction.[38]



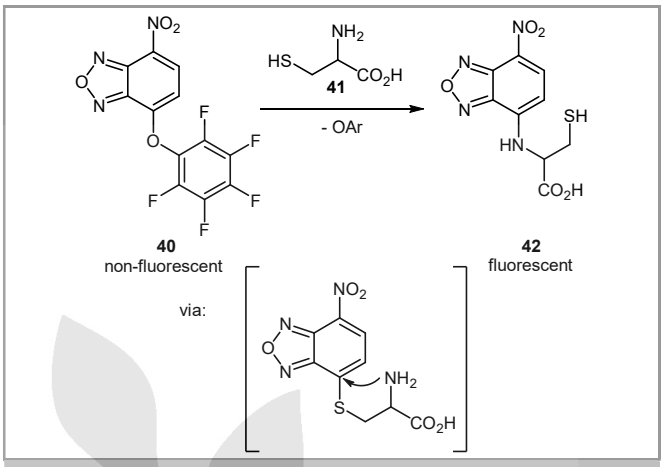
Scheme 8 NHC catalyzed Smiles rearrangement from Glorius and co-workers

Tobisu and co-workers showed how *N*-arylacrylamide starting material **37** could be treated with an NHC catalyst (**38**) to yield rearranged, arylated products (Scheme 9).[39] After formation of the deoxy-Breslow intermediate via Michael addition, a Meisenheimer complex can be formed between the terminal alkenyl carbon of the starting material and the *ipso* position of the migrating ring, mediating the rearrangement and giving product **39**. Subsequent elimination completes the catalytic cycle, returning the active NHC catalyst. The scope of migrating aryl ring was notably broad, encompassing a variety of aryl and heteroaryl species including anisoles and halogenated phenyl rings.



Scheme 9 NHC-catalyzed Smiles rearrangement via deoxy-Breslow intermediate from Tobisu and co-workers

The polar Smiles rearrangement has also sought application in chemical biology, whereby the Kim laboratory have shown that cysteine can be used as a nucleophilic component of the Smiles rearrangement, migrating a heterocycle to constitute a fluorescent probe (Scheme 10).[40] Compound **40** can undergo S_NAr via the thiol side-chain of cysteine (**41**), followed by an *S*-to-*N* Smiles rearrangement to give fluorescent compound **42**. Given that cysteine levels in biopsy samples have been recognized as a biomarker for the disease glioblastoma, this Smiles based probe can provide a significant fluorescence output with no short or long term toxicity or immune response.[41]

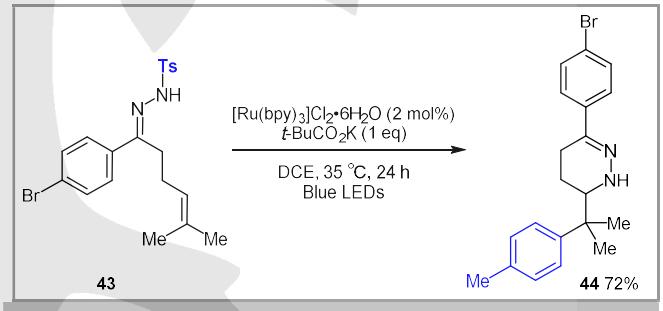


Scheme 10 Kim and co-workers' use of the Smiles Rearrangement for the synthesis of a fluorescent probe

Radical Smiles: Alkene and Alkyne Functionalisation

In the radical manifold, the ability for electrophilic, open-shell species to undergo intra-and intermolecular bond formation with unsaturated systems can enable expedient access to radical Smiles intermediates.[4-6] The resulting products allow for sp^3-sp^3 and sp^2-sp^3 bonds to be forged in a single step. Exploiting photoredox catalysis for generation of the initial single-electron species allows for exceptional operational mildness in comparison to alternative strategies for sp^3-aryl formation.[42]

A recent example from the Liu group highlighted how arylsulfonylhydrazones such as **43** can act as nitrogen-centred radical precursors, capable of undergoing a *6-exo-trig* cyclisation reaction to yield an alkyl radical (Scheme 11).[43] Subsequent Smiles rearrangement the affords the aminoarylated product **44**. Inspired by earlier work from Belmont and Xiao,[22, 44] the hydrazonyl radical is generated via a single electron transfer (SET) event between the excited ruthenium photocatalyst and the deprotonated starting material.



Scheme 11 Liu and co-workers' intramolecular aminoarylation of unactivated alkenes

The rearrangement was capable of migrating electron rich and electron poor arene systems, giving substituted tetrahydropyridazines products, a valuable motif for medicinal chemistry applications.

Truce-Smiles rearrangements via *inter*molecular addition to alkenes represent especially powerful systems for generating skeletal diversity, encompassing a variety of incoming electrophiles and alkenyl starting materials. The Stephenson group reported an innovative approach to alkene aminoarylation, via sulfonamide addition to electron rich alkenes

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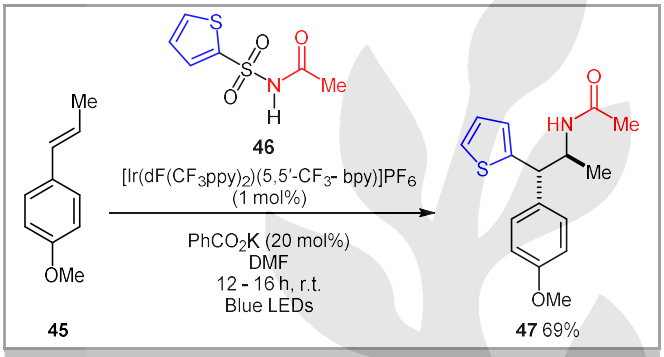
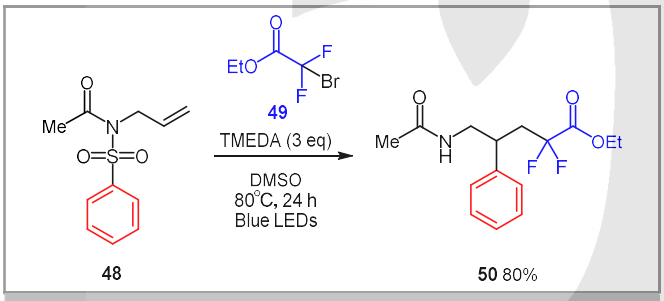
45 under photoredox conditions (Scheme 12). Using an iridium photocatalyst, the olefin starting material was oxidized via SET to a radical-cation, which could then be attacked by an arylsulfonylacetamide (*e.g.* **46**) to forge a C-N bond via nucleophilic addition in an anti-Markovnikov fashion. The resulting benzylic radical could then undergo the Truce-Smiles rearrangement to give the arylethylamine product **47**. A variety of heteroarene and naphthalene based arene systems could be migrated with good to excellent efficiency in a diastereoselective fashion.[45]



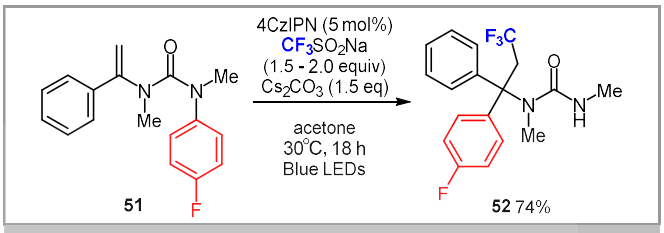
Scheme 12 Intermolecular aminoarylation of anethole alkenes via Truce-Smiles rearrangement

The Greaney group have reported that intermolecular addition to unactivated alkenes can be used to yield Truce-Smiles products under metal-free conditions (Scheme 13). They showed that stoichiometric TMEDA base could form an electron donor-acceptor complex with **49**, allowing for a reactive difluoroalkyl radical to be generated from upon irradiation. Subsequent intermolecular addition to an allylamine based starting material **48**, triggering the Truce-Smiles rearrangement with extrusion of sulfur dioxide. Electronically diverse arene rings could be migrated, giving arylethylamine products such as **50**.[46]



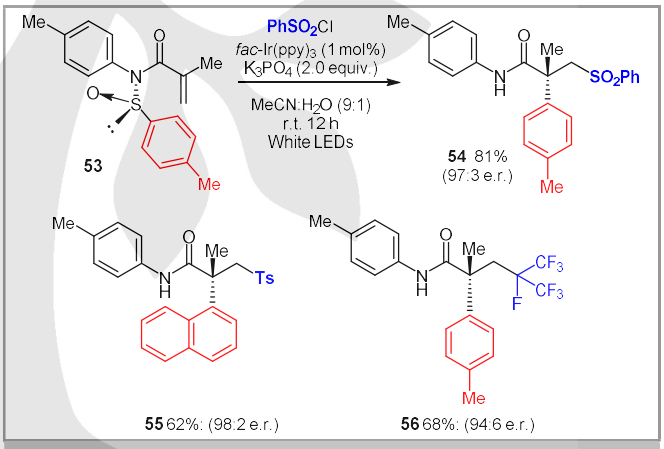
Scheme 13 Carboarylation of unactivated alkenes via radical Truce-Smiles rearrangement

The Clayden group showed that their urea-based Truce-Smiles rearrangement could be triggered by radical addition to a vinyl urea via a radical-polar crossover reaction (Scheme 14). Using an organic photocatalyst for SET oxidation of sodium trifluoromethylsulfinate, trifluoromethyl radicals could undergo addition to a vinyl-urea starting material (**51**). The photocatalytic cycle could then be closed upon reduction of the resulting carbon centred radical to the respective anion, capable of mediating the aryl migration as described previously, giving product **52**. Overall, the reaction constructs a quaternary center through the carboarylation of an alkene.[47]



Scheme 14 Truce-Smiles rearrangement via a radical-polar crossover reaction

The Nevado group have pioneered intermolecular addition to acrylamide Michael acceptor alkenes to trigger Truce-Smiles rearrangements from sulfonamides.[48-52] They recently reported the first asymmetric variant of this rearrangement in the radical manifold, exploiting chiral sulfinamide substrates.[53] Using an iridium photocatalyst at room temperature, species such as sulfonyl chlorides and alkyl halides could be reduced to open shell species, capable of undergoing intermolecular addition to sulfinamide **53** (Scheme 15). A Truce-Smiles rearrangement can then occur, yielding an all-carbon quaternary center with a transfer of chirality from the sulfinamide to the newly formed stereocenter (**54**). Similar to desulfonylative Smiles rearrangements, the sulfinamide acts as a traceless linker with a formal unit of sulfur monoxide being lost during the reaction. The scope was generally very broad, encompassing a variety of incoming radical species and migrating rings in good to excellent yield and enantiomeric ratio. Computational studies by the group revealed that the rearrangement does not proceed via a discrete Meisenheimer intermediate, instead proceeding via concerted aromatic substitution.



Scheme 15 Asymmetric Truce-Smiles rearrangement using chiral sulfonamides from Nevado and co-workers

Zeng and co-workers have also shown an example of the Truce-Smiles rearrangement using arylsulfonyl radicals as an initiating species. Arylsulfonyl azides were used as radical precursors, giving the reactive open-shell species upon reduction by the iridium photocatalyst under visible light irradiation. Radical addition to the vinylsilane component of **57**, followed by subsequent *5-exo-dig* cyclisation, desulfonylative Smiles rearrangement and aromatic addition/aromatization led to fused heterocycle **58** (Scheme 16). The reaction scope was capable of varying substituents on each phenyl ring involved in the cascade as producing unusual bridged structures upon changing the vinylsilane to an allylsilane group.[54]

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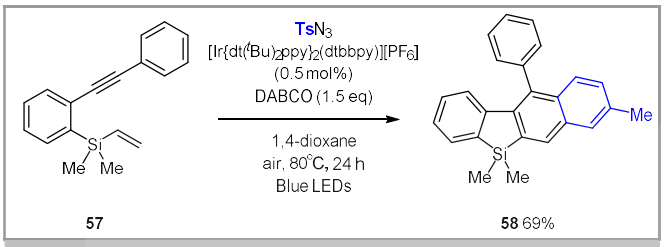


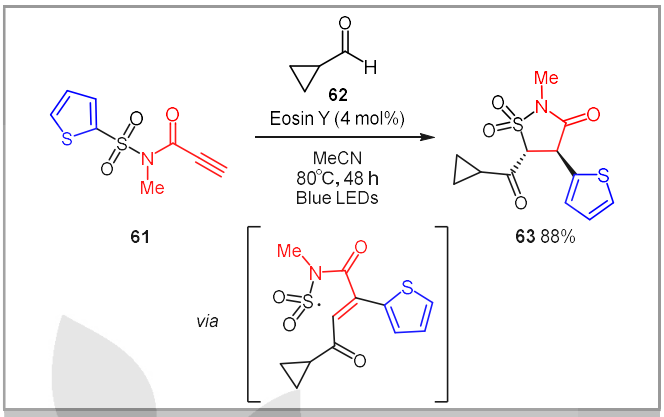
Scheme 16 Radical Smiles cascade producing silicon-based heterocyclic scaffolds

Alkyne functionalisation via Truce-Smiles rearrangement has also been explored in recent literature reports. The Ye group designed a starting material that was capable of functionalizing an ynamide in an intramolecular fashion (Scheme 17). The benzophenone unit in **59** could be reduced to a ketyl radical in the presence of a strongly reducing photoredox catalyst and a Hantzsch ester which could undergo *5-exo-dig* cyclisation, followed by a Truce-Smiles rearrangement. Following this, the catalytic cycle is closed via oxidizing the post-Smiles radical intermediate, allowing it to aromatize into substituted indole **60**. The reaction boasts short reaction times and mild conditions, giving heterocyclic products in excellent yields. They also showed how isoquinoline products could be yielded by modifying the starting material to a benzylic ynamide.[55]

Scheme 17 Smiles rearrangement triggered by ketyl radical addition to an ynamide

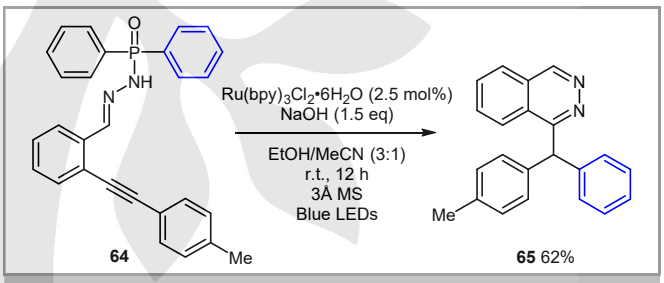
The Zhang group also showed that alkynes could also be functionalized in a similar fashion using α-bromo-*N*-benzyl-alkylamides under blue LED irradiation to give fused heterocyclic products.[56]

Intermolecular alkyne functionalisation under metal-free conditions was achieved by the Wu group who showed that electrophilic radical species could undergo addition to *N*-(hetero)arylsulfonyl propiolamides (**61**) to trigger a Truce-Smiles rearrangement to give isothiazolidin-3-one 1,1-dioxide species (*e.g.* **62**) (Scheme 18). The necessary initiating radical species, such as acyl radicals, could be generated using Eosin Y as a HAT catalyst, under visible light irradiation. The transformation consists of a radical addition to the pendant alkyne, setting up a typical 5-*exo* Truce-Smiles rearrangement. Unusually, SO_2 is retained in the product through sulfur-carbon bond formation with the putative alkene. The catalytic cycle is closed by a reverse-HAT process, giving the closed-shell product **63**. The process was shown to be capable of incorporating a diverse range of aliphatic and aromatic aldehydes as well as phosphine oxides as suitable starting materials. Migrating species included electron rich and poor phenyl rings, pyridyl rings and thiophene all in modest to excellent yield.[57]



Scheme 18 Truce-Smiles rearrangement promoted by hydrogen atom transfer

Whilst many studies employ arylsulfonamides as arene precursors, Brachet demonstrated that an arylphosphoramidate-based starting material **64** can also be used, with the phosphorous-containing group acting as both a traceless linker and aryl precursor (Scheme 19). Building on the previously published synthesis of **65** via a desulfonylative rearrangement, the group showed that starting material **64** can be deprotonated using a strong base, and the resulting anion oxidized by a ruthenium photocatalyst to give a nitrogen-centred radical. This electrophilic species can then undergo a cyclisation reaction,[58] giving an alkenyl radical, capable of undergoing the Truce-Smiles rearrangement. Reduction of the resulting phosphorous-based radical and cleavage of the N-P bond by ethanolysis gives **65** as the product.[59]



Scheme 19 Phospho-Smiles rearrangement from Brachet and co-workers

Radical Smiles: Rearrangements via C-X Bond Cleavage

SET reduction of C-heteroatom bonds to offers a direct approach to Truce-Smiles rearrangement, with the widespread development of photoredox catalysis being key to many recent advances in this area. The Stephenson group showed that an alkyl bromide containing starting material could be engaged in an *in-situ* Finkelstein reaction to give the corresponding alkyl iodide, followed by SET reduction to the reactive primary alkyl radical species. Despite the presence of a sulfonamide in starting material **66**, the alkyl radical instead migrated the thiophene ring, forming a new C(sp^2)-C(sp^3) bond in product **67** (Scheme 20). Along with many thiophene containing examples, it was shown that non-aromatic electron poor cycloalkene derivatives could also be migrated efficiently. The products given in the reaction act as useful precursors to tetrahydrothienoazepinones, an important pharmaceutical scaffold.[60]

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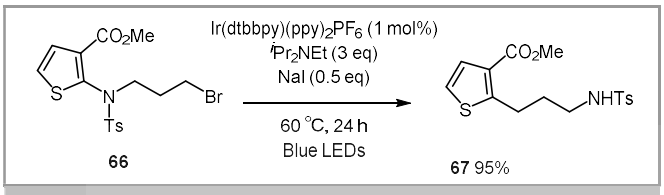
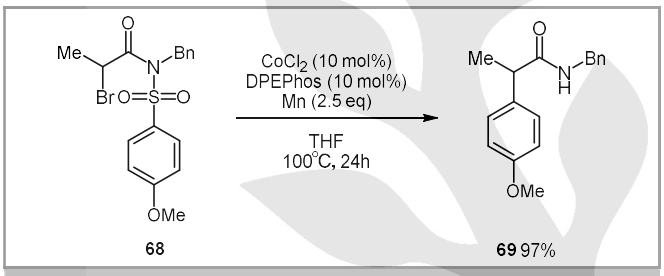


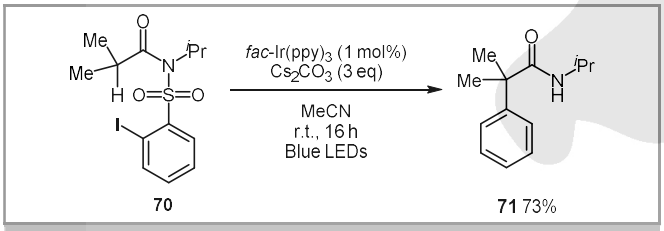
Scheme 20 Truce-Smiles rearrangement via C-N bond cleavage

The concept of converting alkyl halides to sp^3-aryls via a Truce-Smiles rearrangement was further explored by the Cossy group, whereby a cobalt catalyst was used to reduce an α-bromo *N*-sulfonyl amide **68** to the corresponding alkyl radical, which was then capable of undergoing aryl migration to yield product **69** in high yield (Scheme 21). During the reaction, the cobalt (II) catalyst is reduced to a cobalt (I) catalyst by elemental manganese. This active cobalt (I) species is then capable of reducing **68** to the corresponding alkyl radical for the Truce-Smiles rearrangement.[61]



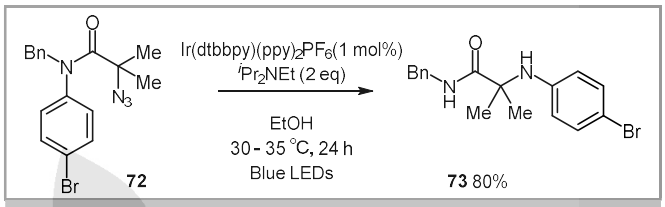
Scheme 21 Cossy and co-workers' use of cobalt catalysis for a Truce-Smiles rearrangement

Building on their previous successes of using hydrogen atom transfer for sulfonate-based Smiles rearrangements, the Studer group showed that an analogous rearrangement could be applied to sulfonamide-based starting materials.[62] Using a strongly reducing iridium photocatalyst, aryl iodide **70** could be reduced to the respective aryl radical, capable of performing a 1,5-hydrogen atom transfer reaction on a neighboring tertiary center (Scheme 22). A Truce-Smiles rearrangement can then be performed giving a new all-carbon quaternary center in product **71**. The rearrangement was capable of migrating *para*/*meta*-substituted phenyl rings as well as incorporating a variety of amide scaffolds. The group has also demonstrated that the transformation can be carried out under UV-irradiation, negating the need for an iridium photocatalyst.[63]



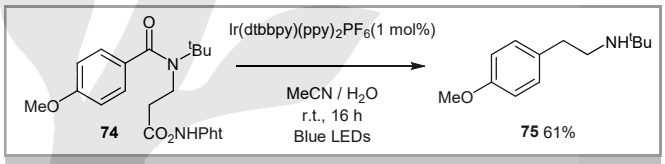
Scheme 22 HAT mediated Truce-Smiles rearrangement

Another species that has been identified as a suitable candidate for Smiles chemistry is the α-azido amide. Using a similar catalytic cycle to Stephenson, the Yu group showed that the pendant azide group in **72** could be reduced to an aminyl radical by the iridium photocatalyst with loss of nitrogen gas (Scheme 23). This nitrogen centred radical can then migrate the neighboring arene ring in an *N* to *N* process, giving **73**. This constitutes the only known literature example of such a reaction.[64]



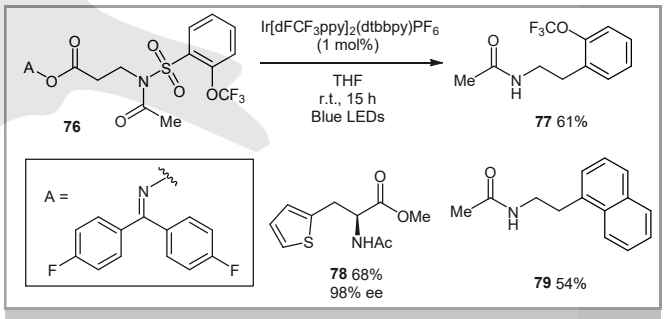
Scheme 23 *N* to *N* aryl migration reaction via the reduction of alkyl azides

In 2017, Reiser showed that visible-light mediated decarboxylation could be used as a driving force for a Truce-Smiles rearrangement. Using an iridium photosensitizer, a ω-aryl-*N*-(acyloxy) phthalimide (**74**) could be decarboxylated and a variety of substituted phenyl rings could be migrated, giving phenylethylamines such as **75** (Scheme 24). The procedure also allowed for the retention of stereocentres on the ethyl linker, and was used for the synthesis of an N-protected precursor to the ADHD treatment amphetamine in high enantiomeric excess.[65]



Scheme 24 Decarboxylative Smiles rearrangement

Greaney and co-workers showed that the tandem use of decarboxylation and desulfonylation could be used in a Truce-Smiles rearrangement under mild conditions.[66] Firstly, benzophenone oxime ester **76** is photosensitized by the iridium catalyst, resulting in decarboxylation and generation of a reactive primary alkyl radical (Scheme 25). This carbon-centred radical could then undergo aryl migration via *ipso*-substitution with the concurrent loss of sulfur dioxide. The scope of the transformation incorporated substituted phenyl rings and thiophene-containing species. When an aspartate derived starting material was employed, unnatural α-amino acid **74** could be synthesized in high enantiomeric excess and good yield.



Scheme 25 Decarboxylative, desulfonylative Truce-Smiles rearrangement

Radical Smiles: Miscellaneous Rearrangements

Manipulation of carbonyl compounds via single electron redox processes is a valuable tool for arylation chemistry, with anthranilate and salicylate derivatives being particularly well

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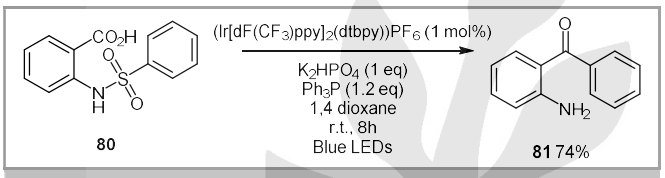
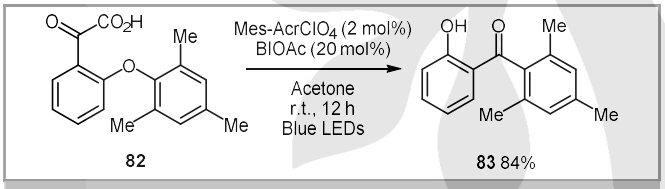
exemplified as Smiles substrates. Zhu and co-workers showed that a combination of stoichiometric phosphine and an iridium photoredox catalyst could be used for the deoxygenation of the anthranilic acid derivative **80** (Scheme 26).[67] Following on from initial findings from Motherwell,[68] the group were able to generate 2-aminobenzophenones in excellent yield (**81**). The scope of both migrating arene species and anthranilate scaffolds demonstrated in the reaction was impressively vast, with examples applied to two short natural product syntheses and various downstream heterocyclic assemblies. The rearrangement was also applicable to salicylate starting materials, giving a range of 2-hydroxylbenzophenone products.



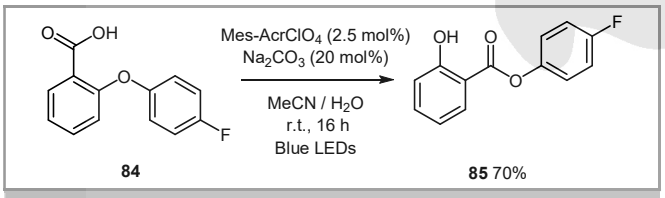
Scheme 26 Deoxygenative acyl radical mediated-Smiles rearrangement

An alternative strategy to generate analogous products from salicylates was devised by the Chen group whereby the combination of a hypervalent iodine catalyst (acetoxybenziodoxole, BIOAc) and an organocatalyst were used to decarboxylate α-ketoacids such as **82** (Scheme 27).[69] The resulting acyl radical could then undergo a Smiles rearrangement with the neighboring biaryl ether, giving the benzophenone product **83**. It was also noted that the transformation can also be carried out in pH neutral aqueous media, possibly paving the way for future involvement in biological studies.



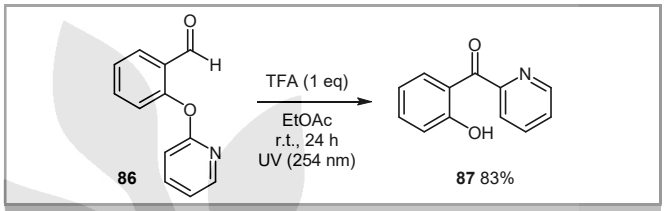
Scheme 27 Chen and co-workers' metal-free approach to 2-hydroxybenzophenone synthesis

Gonzalez-Gomez has demonstrated the transformation of 2-aryloxybenzoic acids **84** into aryl salicylates **85** using an acridinium photocatalyst (Scheme 28). The reaction was amenable to flow chemistry, reducing the reaction times to only one hour.[70] In a related study, Song and co-workers have described the synthesis of the same product class but starting from salicylaldehydes, using NHC / acridinium co-catalysis.[71]



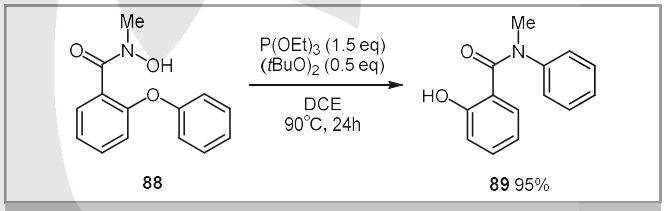
Scheme 28 Aryl salicylate synthesis via Smiles rearrangement

Zeng and co-workers have described a salicylaldehyde Smiles rearrangement, but using UV light to yield 2-hydroxybenzophenone derivatives via the direct excitation of the aldehyde **86** (Scheme 29).[72] The use of a Brønsted acid for protonation of the migrating pyridine ring allows for Minisci-type *ipso*-substitution, forming a new C-C bond (**87**). The reaction scope embraced numerous examples of pyridyl rings as the migrating species, along with benzothiazoles, pyrazines, and a handful of phenyl rings that underwent rearrangement in moderate yield.



Scheme 29 Zeng's aryl migration reaction under UV irradiation

Biaryl ethers have further proven themselves to be effective starting materials for radical Smiles rearrangements in work by Schmidt and co-workers.[73] Hydroxamic acid **88** was treated with triethyl phosphite and a peroxide under thermal conditions to yield amide **89**, which upon hydrolysis will yield an aniline product (Scheme 30). The group have also shown how a variety of phenols can be incorporated in the procedure, including electron rich, electron poor, hindered and heterocyclic species. The Smiles rearrangement in this instance has applicability in the conversion of biomass derived products into higher value chemical commodities. The reaction begins with the peroxide providing radical initiation via hydrogen atom transfer of the starting material **88**, giving an oxygen centred radical which could then undergo oxygen atom transfer with the phosphite reagent. The resulting amidyl radical is then responsible for mediating the *ipso* substitution, forming the new C-N bond. A further HAT process propagates the chain and gives closed shell product **89**.



Scheme 30 Schmidt's deoxygenative *N*-centred radical substitution reaction

Another example of *O* to *N* migration was demonstrated by the Murphy group, who showed that *O*-aryl ethanolamine substrates (such as **90**) can be oxidized by a photoredox catalyst to yield the respective radical cation intermediates, which can then be intercepted by the pendant amine group in an *ipso* substitution to give *N*-arylated product **91** (Scheme 31).[74] This Smiles rearrangement is entirely redox neutral and able to proceed at near-ambient temperatures under metal-free conditions. When the substrate contained an *ortho*-methoxy substituent and a propyl tether, the reaction yielded tetrahydroquinolines in modest to excellent yields, via an *ortho*-substitution reaction on the respective radical cation intermediate.

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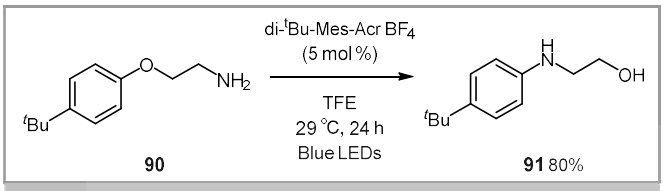
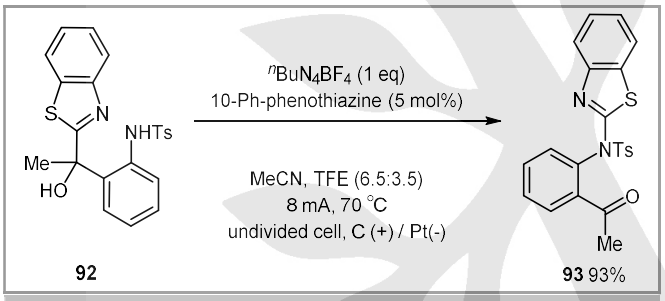


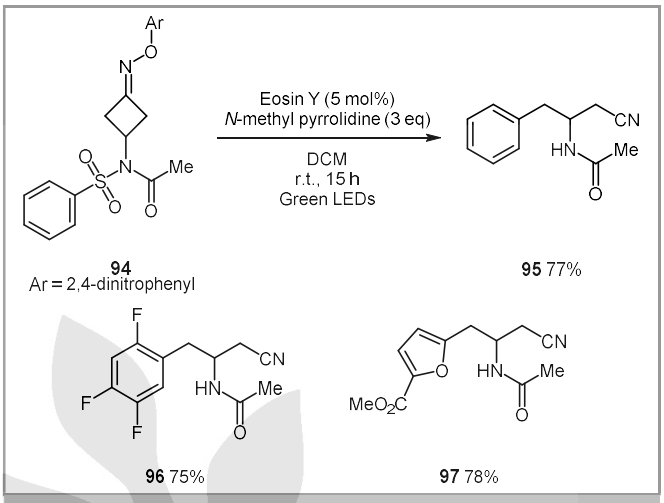
Scheme 31 Murphy's *O* to *N* Smiles rearrangement via a radical cation intermediate

Whilst photoredox catalysis has been regularly employed as a means of accessing reactive radical intermediates under mild conditions, Smiles chemistry has also benefited from the recent renaissance of organic electrochemistry. C. Guo and co-workers initially demonstrated that *C* to *N* aryl migration was possible for salicylamide derivatives via electrochemical reduction.[75] Subsequently, K. Guo and co-workers reported the electrochemical Smiles system shown in Scheme 32, for the synthesis of trisubstituted anilines **93**.[76] Mechanistically, the reaction proceeds via production of trifluoroethoxide at the cathode, which can then deprotonate the sulfonamide starting material **92**. After single electron oxidation to the respective *N*-aryl sulfonaminyl radical, *C* to *N* aryl migration can then take place. Anodic oxidation to the ketone furnishes the product **93**.



Scheme 32 Electrochemical *C* to *N* Smiles rearrangement

Recently, the Greaney group have demonstrated the possibility of using the ring opening of a strained 3-aminocyclobutanone system to trigger a Truce-Smiles rearrangement.[77] The reaction used an organic dye in a photoredox cycle to generate an iminyl radical from starting material **94** (Scheme 33). From there, the cyclobutanone ring could open in a β-cleavage reaction to give a primary alkyl radical, suitably positioned to carry out the aryl migration. The reaction could be carried out at room temperature, migrating a range of substituted phenyl rings and heterocycles such as benzothiophene, furan and benzothiadiazole in good to excellent yield. The β-aminonitrile products (**95** - **97**) could serve as divergent precursors to 1,3-diamines or unnatural β-amino acids.



Scheme 33 Truce-Smiles rearrangement by strain release

Conclusions

The arylation reactions described in this review showcase the facility of Smiles chemistry to operate across polar and radical manifolds, a significant versatility that creates rich possibilities for innovative synthesis. The former provides operational simplicity and efficiency, and the latter allows for mild reaction conditions and very broad substrate scope. Critically, both approaches are amenable to incorporating new catalysis (e.g. photoredox, HAT, NHC) and synthesis technologies (e.g. electrochemistry) to create novel arylation transformations. These reaction systems will continue to grow as synthesis evolves to embrace new catalysis modes, enabling future applications in diverse areas such as asymmetric arylation, the large-scale synthesis of arylated fine chemicals, chemical biology protocols, and production of polyarene organic materials.

References

(1) Snape, T. J. *Chem. Soc. Rev.* **2008**, *37*, 2452.
(2) Holden, C. M.; Greaney, M. F. *Chem. Eur. J.* **2017**, *23*, 8992.
(3) Henderson, A. R. P.; Kosowan, J. R.; Wood, T. E. *Can. J. Chem.* **2017**, *95*, 483.
(4) Allart-Simon, I.; Gérard, S.; Sapi, J. *Molecules* **2016**, *21*, 878
(5) Allen, A. R.; Noten, E. A.; Stephenson, C. R. J. *Chem. Rev.* **2021**. ASAP, doi.org/10.1021/acs.chemrev.1c00388
(6) Huynh, M.; De Abreu, M.; Belmont, P.; Brachet, E. *Chem. Eur. J.* **2021**, *27*, 3581.
(7) Warren, A. L.; Smiles, S. *J. Chem. Soc.* **1931**, 914.
(8) Levy, A. A.; Rains, H. C.; Smiles, S. *J. Chem. Soc.* **1931**, 3264.
(9) Naito, T.; Dohmori, R.; Nagase, O. *J. Pharm. Soc. Jpn.* **1954**, *74*, 593.
(10) Naito, T.; Dohmori, R.; Shimoda, M. *Pharm. Bull.* **1955**, *3*, 34.
(11) Truce, W. E.; Ray, W. J.; Norman, O. L.; Eickemeyer, D. B. *J. Am. Chem. Soc.* **1958**, *80*, 3625.
(12) Loven, R.; Speckamp, W. N. *Tetrahedron Lett.* **1972**, *13*, 1567.
(13) Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 631.
(14) Motherwell, W. B.; Pennell, A. M. K. *J. Chem. Soc. Chem. Commun.* **1991**, 877.
(15) Da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137.
(16) Da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 141.
(17) Bonfand, E.; Forslund, L.; Motherwell, W. B.; Vázquez, S. *Synlett* **2000**, 475.
(18) Waldau, E.; Pütter, R. *Angew. Chem., Int. Ed.*, **1972**, *11*, 826-828;

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(19) Rasheed, O. K.; Hardcastle, I. R.; Raftery, J.; Quayle, P. *Org. Biomol. Chem.* **2015**, *13*, 8048.
(20) Holden, C. M.; Sohel, S. M. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 2450.
(21) Dey, C.; Katayev, D.; Ylijoki, K. E. O.; Kündig, E. P. *Chem. Commun.* **2012**, *48*, 10957.
(22) Brachet, E.; Marzo, L.; Selkti, M.; König, B.; Belmont, P. *Chem. Sci.* **2016**, *7*, 5002.
(23) Pudlo, M.; Allart-Simon, I.; Tinant, B.; Gérard, S.; Sapi, J. *Chem. Commun.* **2012**, *48*, 2442.
(24) Clayden, J.; Farnaby, W.; Grainger, D. M.; Hennecke, U.; Mancinelli, M.; Tetlow, D. J.; Hillier, I. H.; Vincent, M. A. *J. Am. Chem. Soc.* **2009**, *131*, 3410.
(25) Clayden, J.; Donnard, M.; Lefranc, J.; Minassi, A.; Tetlow, D. J. *J. Am. Chem. Soc.* **2010**, *132*, 6624.
(26) Atkinson, R. C.; Fernández-Nieto, F.; Mas Rosellõ, J.; Clayden, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 8961.
(27) Abrams, R.; Jesani, M. H.; Browning, A.; Clayden, J. *Angew. Chem. Int. Ed.* **2021**, *60*, 11272.
(28) Costil, R.; Lefebvre, Q.; Clayden, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 14602.
(29) Millward, M. J.; Ellis, E.; Ward, J. W.; Clayden, J. *Chem. Sci.* **2021**, *12*, 2091.
(30) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron Asymmetry* **2007**, *18*, 569.
(31) Leonard, D. J.; Ward, J. W.; Clayden, J. *Nature* **2018**, *562*, 105.
(32) Barlow, H. L.; Rabet, P. T. G.; Durie, A.; Evans, T.; Greaney, M. F. *Org. Lett.* **2019**, *21*, 9033.
(33) Chu, X.-Q.; Ge, D.; Cui, Y.-Y.; Shen, Z.-L.; Li, C.-J. *Chem. Rev.* **2021**, *121*, 12548.
(34) Kang, L.; Wang, F.; Zhang, J.; Yang, H.; Xia, C.; Qian, J.; Jiang, G. *Org. Lett.* **2021**, *23*, 1669.
(35) Matsuzawa, T.; Hosoya, T.; Yoshida, S. *Org. Lett.* **2021**, *23*, 2347.
(36) Pluta, K.; Jeleń, M.; Morak-Młodawska, B. *J. Mol. Struct.* **2020**, 1204.
(37) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307.
(38) Janssen-Müller, D.; Singha, S.; Lied, F.; Gottschalk, K.; Glorius, F. *Angew. Chemie, Int. Ed.* **2017**, *56*, 6276.
(39) Yasui, K.; Kamitani, M.; Fujimoto, H.; Tobisu, M. *Org. Lett.* **2021**, *23*, 1572.
(40) An, J. M.; Kang, S.; Huh, E.; Kim, Y.; Lee, D.; Jo, H.; Joung, J. F.; Kim, V. J.; Lee, J. Y.; Dho, Y. S.; Jung, Y.; Hur, J. K.; Park, C.; Jung, J.; Huh, Y.; Ku, J. L.; Kim, S.; Chowdhury, T.; Park, S.; Kang, J. S.; Oh, M. S.; Park, C. K.; Kim, D. *Chem. Sci.* **2020**, *11*, 5658.
(41) Weller, M.; Wick, W.; Aldape, K.; Brada, M.; Berger, M.; Pfister, S. M.; Nishikawa, R.; Rosenthal, M.; Wen, P. Y.; Stupp, R.; Reifenberger, G. *Nat. Rev. Dis. Prim.* **2015**, 1.
(42) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(43) Tu, J.-L.; Tang, W.; Liu, F. *Org. Chem. Front.* **2021**, *8*, 3712.
(44) Hu, X. Q.; Chen, J. R.; Wei, Q.; Liu, F. L.; Deng, Q. H.; Beauchemin, A. M.; Xiao, W. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 12163.
(45) Monos, T. M.; McAtee, R. C.; Stephenson, C. R. J. *Science* **2018**, *361*, 1369.
(46) Whalley, D. M.; Duong, H. A.; Greaney, M. F. *Chem. Eur. J.* **2019**, *25*, 1927.
(47) Abrams, R.; Clayden, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 11600.
(48) Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. J. *Am. Chem. Soc.* **2013**, *135*, 14480.
(49) Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 13086.
(50) Kong, W.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5078.
(51) Kong, W.; Fuentes, N.; García-Domínguez, A.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 2487.
(52) Fuentes, N.; Kong, W.; Fernández-Sánchez, L.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 964.
(53) Hervieu, C.; Kirillova, M. S.; Suárez, T.; Müller, M.; Merino, E.; Nevado, C. *Nat. Chem.* **2021**, *13*, 327.
(54) Chen, F.; Shao, Y.; Li, M.; Yang, C.; Su, S. J.; Jiang, H.; Ke, Z.; Zeng, W. *Nat. Commun.* **2021**, *12*, 1.
(55) Wang, Z. S.; Chen, Y. B.; Zhang, H. W.; Sun, Z.; Zhu, C.; Ye, L. W. *J. Am. Chem. Soc.* **2020**, *142*, 3636.
(56) Gao, X.; Li, C.; Yuan, Y.; Xie, X.; Zhang, Z. *Org. Biomol. Chem.* **2020**, *18*, 263.
(57) Yan, J.; Cheo, H. W.; Teo, W. K.; Shi, X.; Wu, H.; Idres, S. B.; Deng, L. W.; Wu, J. *J. Am. Chem. Soc.* **2020**, *142*, 11357.
(58) Fuss, D.; Wu, Y. Q.; Grossi, M. R.; Hollett, J. W.; Wood, T. E. *J. Phys. Org. Chem.* **2018**, *31*, e3742.
(59) De Abreu, M.; Belmont, P.; Brachet, E. *J. Org. Chem.* **2021**, *86*, 3758.
(60) Alpers, D.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 12167.
(61) Gillaizeau-Simonian, N.; Barde, E.; Guérinot, A.; Cossy, J. *Chem. Eur. J.* **2021**, *27*, 4004.
(62) Friese, F. W.; Mück-Lichtenfeld, C.; Studer, A. *Nat. Commun.* **2018**, *9*, 1.
(63) Radhoff, N.; Studer, A. *Angew. Chem. Int. Ed.* **2021**, *60*, 3561.
(64) Liang, S.; Wei, K.; Lin, Y.; Liu, T.; Wei, D.; Han, B.; Yu, W. *Org. Lett.* **2021**, *23*, 4527.
(65) Faderl, C.; Budde, S.; Kachkovskyi, G.; Rackl, D.; Reiser, O. *J. Org. Chem.* **2018**, *83*, 12192.
(66) Johnson, S.; Kovács, E.; Greaney, M. F. *Chem. Commun.* **2020**, *56*, 3222.
(67) Ruzi, R.; Ma, J.; Yuan, X. A.; Wang, W.; Wang, S.; Zhang, M.; Dai, J.; Xie, J.; Zhu, C. *Chem. Eur. J.* **2019**, *25*, 12724.
(68) Motherwell, W. B.; Vazquez, S. *Tetrahedron Lett.* **2000**, *41*, 9667.
(69) Li, J.; Liu, Z.; Wu, S.; Chen, Y. *Org. Lett.* **2019**, *21*, 2077.
(70) Gonzalez-Gomez, J. C.; Ramirez, N. P.; Lana-Villarreal, T.; Bonete, P. *Org. Biomol. Chem.* **2017**, *15*, 9680.
(71) Xia, Z. H.; Dai, L.; Gao, Z. H.; Ye, S. *Chem. Commun.* **2020**, *56*, 1525.
(72) Dou, Q.; Li, C. J.; Zeng, H. *Chem. Sci.* **2020**, *11*, 5740.
(73) Lardy, S. W.; Luong, K. C.; Schmidt, V. A. *Chem. Eur. J.* **2019**, *25*, 15267.
(74) Lawson, C. A.; Dominey, A. P.; Williams, G. D.; Murphy, J. A. *Chem. Commun.* **2020**, *56*, 11445.
(75) Chang, X.; Zhang, Q.; Guo, C. *Org. Lett.* **2019**, *21*, 4915.
(76) Liu, C.; Jiang, Q.; Lin, Y.; Fang, Z.; Guo, K. *Org. Lett.* **2020**, *22*, 795.
(77) Whalley, D. M.; Seayad, J.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2021**, *60*, 22219.

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Biosketches

	David Whalley, originally from Northamptonshire, England began his studies in Chemistry at the University of Nottingham with a Year Abroad at the National University of Singapore. He undertook his Masters project studying natural product synthesis with Professor Christopher Moody. For his PhD, he is studying organic radical rearrangements for new arylation strategies with Professor Michael Greaney at the University of Manchester, as well as a two year attachment, again in Singapore, at the Agency for Science, Technology And Research (A*STAR) under Dr Jayasree Seayad and Dr Hung Duong.
	Michael Greaney received his MChem degree from Oxford in 1996, and carried out PhD work with William Motherwell at UCL, completing his thesis in the area of new fluorinating agents in 1999. Following postdoctoral work with Jeffrey Winkler at the University of Pennsylvania, working on natural product synthesis, he returned to the UK in 2002 to begin independent research at the University of Edinburgh. He moved to his current position as Professor of Organic Chemistry at the University of Manchester in 2011. Research in Michael's group focusses on new synthesis and catalysis methods, with emphasis on C-H activation, photoredox catalysis, and metal-free approaches to arylation.

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