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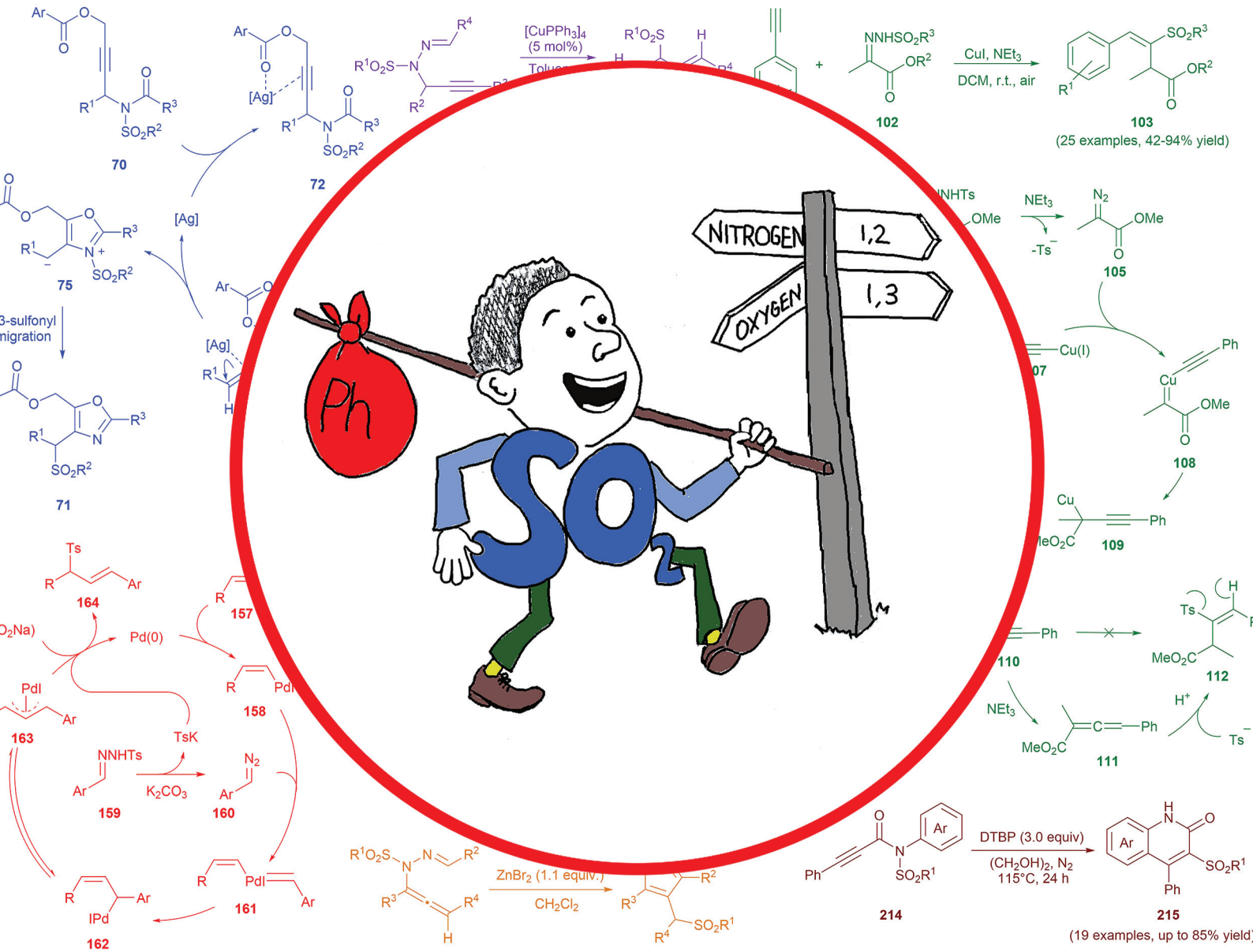

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REVIEW ARTICLE
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Synthetic and mechanistic aspects of sulfonyl migrations

Aaran J. Flynn,[a] Alan Ford[b] and Anita R. Maguire *[c]

Over the past 20 years reports of sulfonyl migrations have appeared, frequently described as 'unusual' and 'unexpected'. This comprehensive review compiles, for the first time, sulfonyl migrations reported over the last 20 years including formal 1,2-, 1,3-, 1,4-, 1,5-, 1,6- and 1,7-sulfonyl shifts, occurring through either radical or polar processes, either inter- or intramolecularly. Discussion of the sulfonyl migrations is structured according to reaction type, *i.e.* nitrogen–carbon, nitrogen–oxygen, nitrogen–nitrogen, oxygen–carbon (including anionic and non-anionic thia-Fries rearrangements), oxygen–oxygen and carbon–carbon migrations. Discussion of the underlying mechanisms for the migrations is included, with particular attention afforded to the principal techniques utilised for their elucidation, namely isotopic-labelling, crossover experiments, density functional theory calculations and electron paramagnetic resonance spectroscopy amongst others.

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1. Introduction

Retrosynthetic analysis, formalised by E. J. Corey in the 1989 book *The Logic of Chemical Synthesis* revolutionised the art of total synthesis of complex organic molecules,[1] and coupled with an ever increasing number of efficient and selective synthetic methodologies with predictable outcomes across a diverse substrate range, has delivered elegant total syntheses. Critical to success is the ability to accurately anticipate the

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Aaran J. Flynn was born in London, England, in 1992. He obtained his B.Sc. in Chemistry of Pharmaceutical Compounds from University College Cork in 2015. He was awarded a Ph.D scholarship from the Synthesis and Solid State Pharmaceutical Centre and commenced his studies under the direction of Prof. Anita Maguire later that year. Under her guidance he has conducted research in a variety of areas, including copper-catalysed asymmetric sulfur oxidation, [3 + 2]-dipolar cycloadditions of electron deficient diazo compounds, and the synthesis of acyclic α-carboxynucleoside phosphonates.

Alan Ford

Dr Alan Ford was born in Gateshead, England, in 1972. He studied at the University of Hull, England, and received a B.Sc. in chemistry in 1993 and a Ph.D. in 1996. He has held postdoctoral positions in the Selective Synthesis Group, University of Hull, from 1997 to 1998, in the Department of Metal-Mediated Organic Synthesis, Debye Institute, University of Utrecht, The Netherlands, from 1998 to 2000, and in the Organic and Pharmaceutical Synthesis Research Team, Department of Chemistry, University College Cork, Ireland, from 2000 to the present. His main research interests include development of novel rhodium catalysts for asymmetric carbene chemistry and the synthesis of nucleoside analogues as potential antiviral agents.

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reactivity of molecules under different conditions, which requires an excellent understanding of functional group chemistry including identification of trends in reactivity that are both predictable and readily rationalisable.

Numerous reports observing 'unusual', 'unprecedented', 'unexpected' and 'novel' sulfonyl migrations attracted our attention, following observation of an unanticipated sulfonyl migration in our work.[2] What became clear from a survey of the literature is that sulfonyl migrations remain only partially understood despite their potential synthetic utility. Sulfones[3–14] and related species[15–17] are widely used as activating groups and/or protecting groups and offer substantial synthetic versatility. Accordingly, sulfonyl migrations are potentially valuable from a synthetic perspective, provided they are sufficiently understood to enable their use in a predictive manner.

While most sulfonyl migrations prior to the beginning of the 21st century were originally discovered as side reactions, and regularly as isolated cases, the last 20 years has seen a significant increase in the number of reports focusing on the utility of incorporating a sulfonyl molecular handle capable of migration. As such, attempts to understand the mechanisms of these often 'unexpected' reactions have garnered significant recent attention; however, the ability to observe formal 1,2-, 1,3-, 1,4-, 1,5-, 1,6- or 1,7-sulfonyl migrations, in an inter- or intramolecular fashion, occurring through either radical or polar processes, highlights the difficulty in accurately predicting the outcome of such reactions. Bearing this complexity in mind, it is not surprising that the current knowledge in this field is not sufficiently developed to enable incorporation of sulfonyl migration into a retrosynthetic plan.

In this review, sulfonyl migrations reported over the last two decades (up to early 2019) are compiled, and their synthetic and mechanistic development is described; the sulfonyl migrations are classified based on the migration type, namely nitrogen–carbon, nitrogen–oxygen, nitrogen–nitrogen, oxygen–carbon (including anionic and non-anionic thia-Fries rearrangements), oxygen–oxygen and carbon–carbon. Particular emphasis is afforded to the efforts made to elucidate the mechanistic pathway for the migrations.

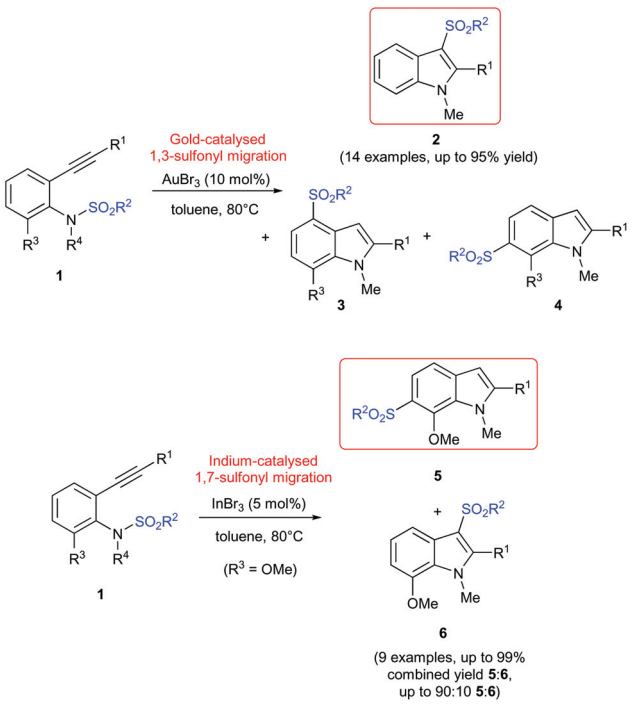
Anita R. Maguire

Professor Anita R. Maguire was born in 1964 in Cork. She undertook undergraduate and postgraduate studies at University College Cork (B. Sc., 1985; Ph.D., 1989), focusing during her studies on asymmetric catalysis in reactions of α-diazoketones. Following postdoctoral research in the Facultes Universitaires, Namur, Belgium, and subsequently at the University of Exeter, she returned to UCC in 1991 initially as a Lecturer in Organic Chemistry, then as Associate Professor of Organic Chemistry in 2002, and then as the first Professor of Pharmaceutical Chemistry in 2004. In 2011 she was appointed as Vice President for Research and Innovation at University College Cork. She was an Adjunct Professor at the University of Bergen from 2011–2016. Her research interests include asymmetric synthesis, including biocatalysis and transition-metal catalysis, the development of novel synthetic methodology employing α-diazocarbonyl compounds, organosulfur chemistry, and continuous flow chemistry, and the design and synthesis of bioactive compounds with potential pharmaceutical applications and she is a Co-PI in the SSPC. She is the inaugural Chair of the National Forum on Research Integrity and was elected a Member of the Royal Irish Academy in 2014.

2. Nitrogen to carbon sulfonyl migration

2.1. Transition-metal catalysed reactions

2.1.1. Gold-catalysed sulfonyl migration. Nakamura *et al.* reported the gold- and indium-catalysed synthesis of 3- and 6-sulfonylindoles from *ortho*-alkynyl-*N*-sulfonylanilines **1** (Scheme 1).[18,19] In the presence of catalytic $AuBr_3$, a 1,3-sulfonyl migration was observed, to afford 3-sulfonylindoles **2** in good to high yields (up to 95%), with minor amounts of the regioisomers **3** and **4** also observed. Interestingly, using $InBr_3$ as catalyst the major products are 6-sulfonylindoles **5** which



Scheme 1 Gold- and indium-catalysed synthesis of 3- and 6-sulfonylindoles from *ortho*-alkynyl-*N*-sulfonylanilines, *via* 1,3- and 1,7-sulfonyl migration.

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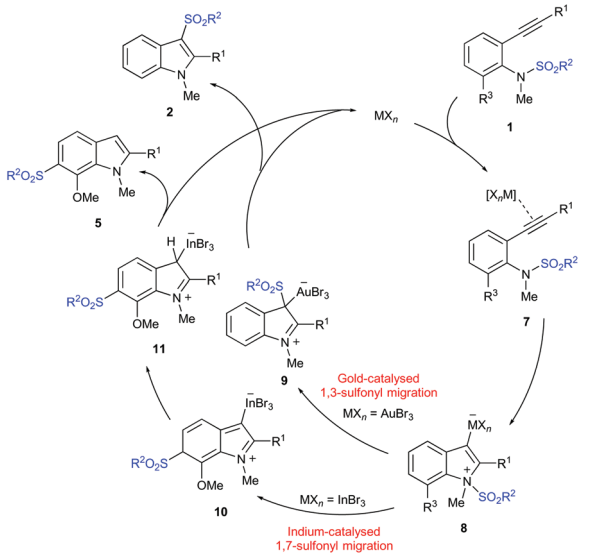
were isolated in up to 99% yield, indicating that an unprecedented 1,7-sulfonyl migration has occurred. The presence of a methoxy group at the 6-position of the *ortho*-alkynyl-*N*-sulfonylanilines proved crucial in yielding the 1,7-sulfonyl migration products.

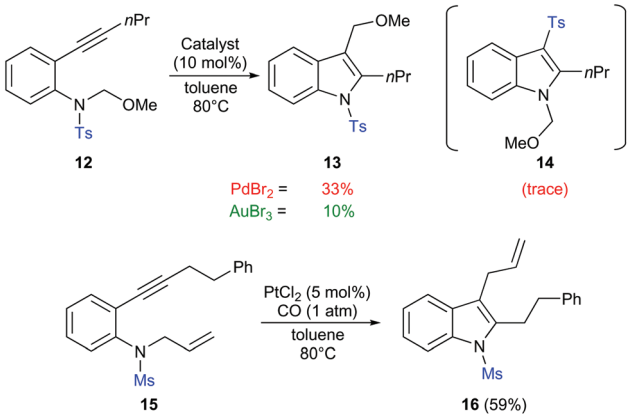
In order to probe the mechanism of the sulfonyl migration, crossover experiments were performed which determined that both the gold- and indium-catalysed reactions were intramolecular processes. Interconversion of the reaction products was eliminated as a possibility by stirring a mixture of the 3-,4- and 6-sulfonylindole products in the presence of catalyst for a further two hours – no change in product distribution was observed.

The following mechanism was postulated in accordance with the observed results (Scheme 2). Coordination of the Lewis-acidic transition metal to the alkyne of **1** forms the intermediate π-complex **7**. Nucleophilic addition of the nitrogen to the electron-deficient alkynyl moiety leads to the cyclised intermediate **8**, which can undergo two diverging pathways depending on the metal catalyst employed. For the gold-catalysed process, intramolecular 1,3-sulfonyl migration occurs followed by elimination of $AuBr_3$ to afford the 3-sulfonylindole products **2**. Alternatively, for the indium-catalysed process, a consecutive 1,7-sulfonyl migration and 1,5-proton shift occurs. Elimination of $InBr_3$ yields the 6-sulfonylindole products **5**. Notably, the formation of indole **2** is the first example of sulfodemetalation, in which the vinyl–Au intermediate is captured intramolecularly by the sulfonyl group (Scheme 2, **8** to **2**).

In an earlier communication the authors described the reaction of *N*-methoxymethyl-2-(1-pentynyl)-*N*-tosylaniline **12** in the presence of catalytic $PdBr_2$, to give the indole **13** in 33% yield, with only trace amounts of the tosyl migration product **14** observed (Scheme 3).[20] Interestingly, repeating this reaction using the optimised $AuBr_3$ catalyst afforded exclusively **13**



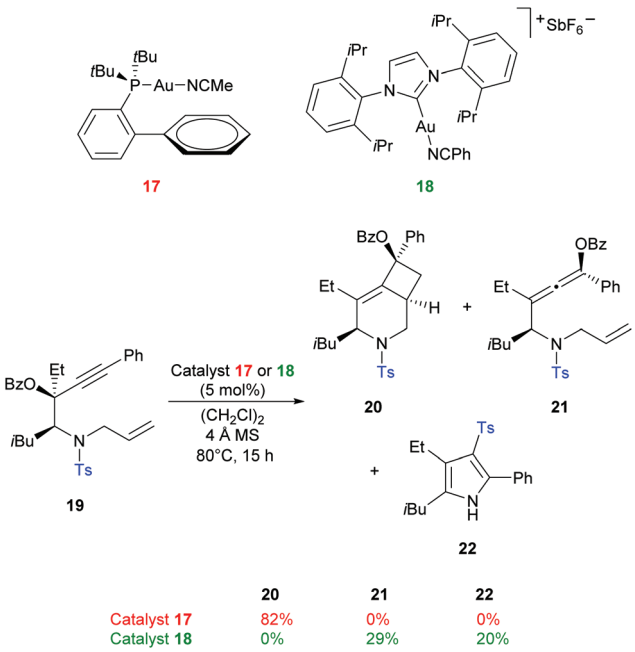
Scheme 2 Proposed mechanistic cycle for the gold- and indium-catalysed synthesis of 3-and 6-sulfonylindoles.



Scheme 3 Migratory aptitude of tosyl and mesyl groups relative to methoxymethyl and allyl groups respectively.

albeit in 10% yield.[19] Therefore, regardless of the catalyst species, the migratory aptitude of the migrating group appears to be crucial to the outcome. Specifically, in this instance, the methoxymethyl group has a greater ability to migrate than the tosyl group. Similarly, in a separate report, Fürstner and Davies observed that an allyl group preferentially migrated in the presence of a mesyl group for the platinum-catalysed transformation of **15** to **16** (Scheme 3).[21]

In 2011, the Chan group described the gold-catalysed tandem 1,3-migration/[2 + 2]-cycloaddition of 1,7-enyne benzoates **19** to azabicyclo[4.2.0]oct-5-enes **20** (Scheme 4, catalyst **17**).[22] Interestingly, during optimisation studies, the gold(I)



Scheme 4 Gold-catalysed tandem 1,3-migration/[2 + 2]-cycloaddition of 1,7-enyne benzoates to azabicyclo[4.2.0]oct-5-enes; observation of a potential deaurative 1,3-sulfonyl migration.

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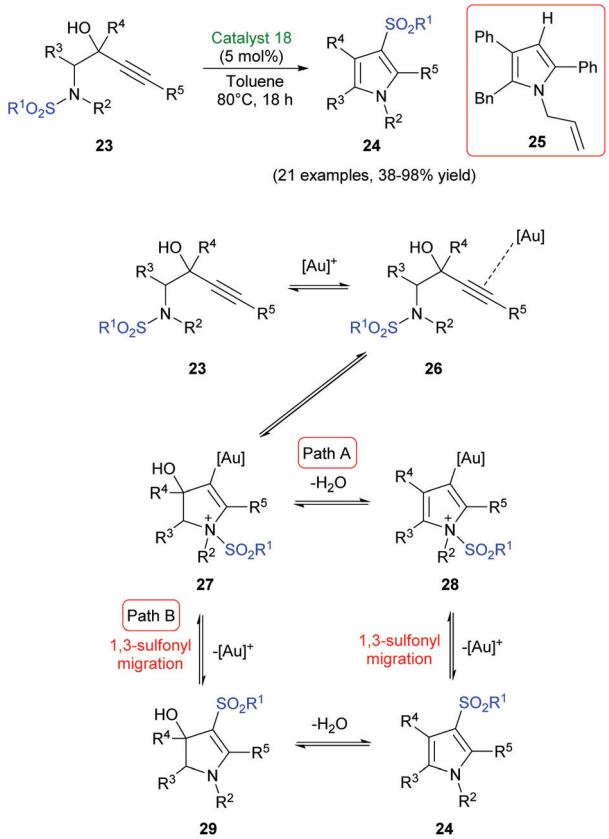
carbene complex **18** catalysed the cycloisomerisation of 1,7-enyne ester **19** to afford the 3-sulfonyl-1*H*-pyrrole **22** in 20% yield (Scheme 3, catalyst **14**). Inspired by this fortuitous result, and recognising that the reaction pathway may have involved a deaurative 1,3-sulfonyl migration, the authors set out to investigate the rearrangement process.

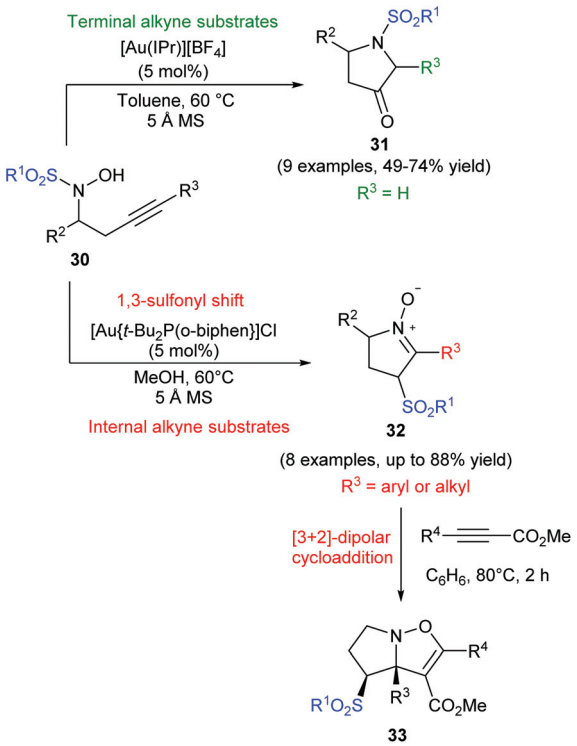
In their continuation of these studies, the authors reasoned that the chemical yield of the process could be enhanced by use of the corresponding 1,7-enyne alcohols **23** as substrates (Scheme 5), presumably due to ease of water elimination. The NHC–gold(I) complex **18** was determined to be the optimal catalyst, with moderate to excellent yields of the rearranged pyrroles **24** obtained.[23] An intramolecular 1,3-sulfonyl migration was postulated based on the results of crossover experiments, and the fact that pyrrole **25** was recovered unchanged after exposure to *p*-toluenesulfonyl chloride under the optimised reaction conditions. The reaction mechanism was postulated to proceed *via* activation of the propargylic alcohol **23** through coordination of the gold catalyst with the alkyne moiety to give the Au(I)-intermediate **26**. An intramolecular aminocyclisation is triggered involving *anti* addition of the *N*,*N*-disubstituted amino moiety to the triple bond affording the vinyl gold complex **27**. Dehydration of this species leads to the formation of the cationic pyrrole–gold adduct **28**, which subsequently undergoes an intramolecular 1,3-sulfonyl migration resulting in deauration and generation of the pyrrole product **24** (Scheme 5, path A). Alternatively, the vinyl gold complex **27** undergoes the deaurative 1,3-sulfonyl migration first to afford the 2,3-dihydro-1*H*-pyrrol-3-ol adduct **29** that upon dehydrative aromatisation affords the pyrrole **24** (Scheme 5, path B).

The Shin group reported the gold-catalysed synthesis of 3-pyrrolidinones **31** and nitrones **32** from *N*-sulfonyl hydroxylamines **30** *via* oxygen-transfer redox and 1,3-sulfonyl migration (Scheme 6).[24] In the case of terminal alkynes, a gold-catalysed 5-*exo-dig* addition of the hydroxylamine moiety to the alkyne occurs through the oxygen (Scheme 7). Cleavage of the N–O bond is rate limiting, and the presence of the electron-withdrawing sulfonyl moiety facilitates the overall reaction process to afford 3-pyrolidinones **31** in moderate to good yields.

However, to the surprise of the authors, when internal alkynes are utilised a different mechanistic pathway occurs, resulting in the formation of 3-sulfonylnitrones **32**. In this instance, the nitrogen of the hydroxylamine moiety is the preferred nucleophile, which allows for a 5-*endo-dig* cyclisation to occur giving **36** (Scheme 7). Subsequent 1,3-sulfonyl migration leads to **37**. Loss of the gold catalyst and tautomerisation of the resulting vinyl hydroxylamine leads to the nitrone **32**. The identity of the nitrone products **32** were confirmed by trapping with dipolarophiles *via* [3 + 2]-dipolar cycloaddition (Scheme 6).



Scheme 5 Gold-catalysed domino aminocyclisation/1,3-sulfonyl migration of *N*-substituted *N*-sulfonyl-aminobut-3-yn-2-ols to 1-substituted 3-sulfonyl-1*H*-pyrroles.



Scheme 6 Gold-catalysed synthesis of 3-pyrrolidinones and nitrones from *N*-sulfonyl hydroxylamines *via* oxygen-transfer redox and 1,3-sulfonyl migration.

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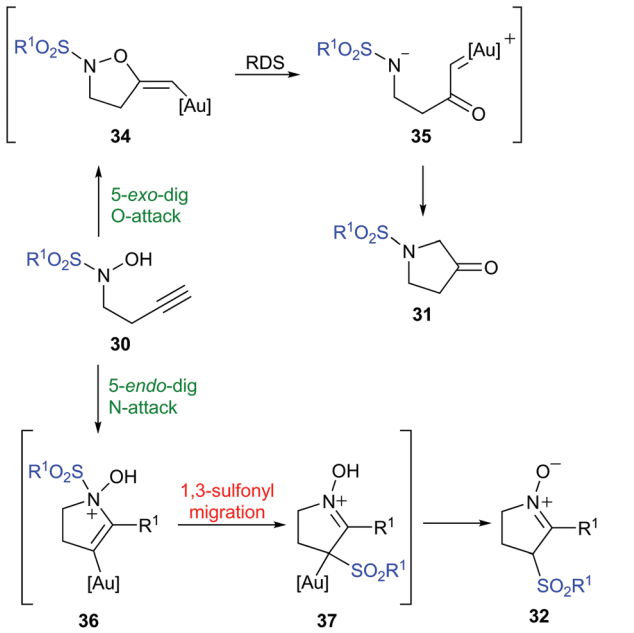
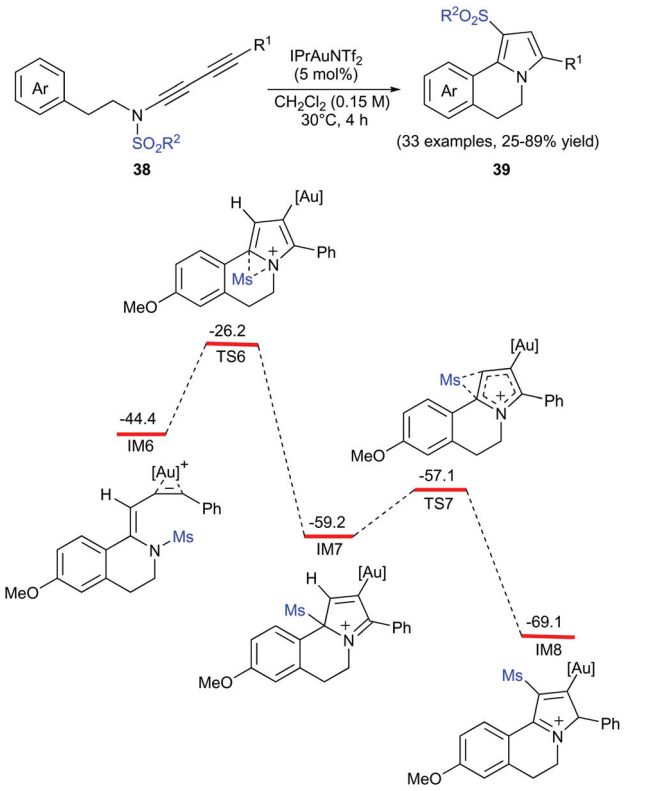


Scheme 7 Access to 3-pyrrolidinones and nitrones *via* *N*-sulfonylhydroxylamines.



Scheme 8 Cascade reaction of diynamides and relevant section of the DFT reaction coordinate for sulfonyl migration.

Liu *et al.* recently developed a gold-catalysed cascade reaction of diynamides **38** to generate a series of sulfone containing pyrrolo[2,l-*a*]isoquinolines **39** featuring the core structural motif of the lemellarin alkaloids (Scheme 8).[25] Notably, all three functional moieties on the nitrogen of the ynamide participate in the cascade transformation, with a formal 1,4-sulfonyl migration a key mechanistic step. A crossover experiment, with two different sulfonyl diynamides, did not lead to crossover products, indicating that the migration of the sulfonyl group occurs in an intramolecular fashion. DFT studies suggested that the formal 1,4-sulfonyl migration is in fact two sequential 1,2-sulfonyl shifts (Scheme 8). The alternative 1,3-sulfonyl shift was considered to be an unlikely mechanistic route as the transition states for both the suprafacial and antarafacial 1,3-sulfonyl shifts are 24.0 and 22.6 kcal mol^{-1} higher in energy than that for **TS6** (Scheme 8).

The Sahoo group recently developed a regioselective sulfonyl/sulfinyl migration cycloisomerisation cascade of alkyne-tethered ynamides **40** in the presence of XPhosgold catalyst to afford a series of novel 4-sulfinylated pyrroles **41** in yields up to 85% (Scheme 10).[26] Notably, this reaction process is the first example of a general [1,3]-sulfonyl migration from the nitrogen centre to the β-carbon of ynamides, followed by umpolung 5-*endo-dig* cyclisation of the ynamide α-carbon atom to the gold-activated alkyne, and final deaurative [1,5]-sulfinylation. Control experiments in conjunction with DFT calculations were used to deduce an operative reaction pathway.

The de-sulfinylated pyrroles **45** and **46** were generated from *N*-mesyl protected yne-ynamides **42** and **43** respectively under the optimised conditions (Scheme 9a), highlighting the role of adventitious water in the protodeauration of the organo-Au intermediate **44**. Furthermore, the transformation of **43** in the presence of D_2O afforded [D]**47** indicating that a deuterium quench of **44** is preferred to the consecutive migration of the methyl sulfinyl cation motif in the pyrrole ring. A crossover experiment between **42** and **48** (1 : 1) generated **49** and **50** exclusively, indicating that both the [1,3]-sulfonyl and [1,5]-sulfinyl migration are intramolecular processes (Scheme 9b). No sulfinylated pyrrole **53** was observed when the pyrrole **45** was reacted in the presence of **51**, highlighting that intermolecular deaurative sulfinylation is unlikely (Scheme 9c). The reaction of **54** in the presence of [^{18}O]-labelled H_2O under the optimised conditions did not yield the [^{18}O]-labelled **56**, with **55** instead exclusively formed, indicating that an intramolecular oxygen transfer could be utilised in the mechanistic pathway (Scheme 9d).

DFT calculations proved useful in further understanding the mechanistic features of the cascade process (Scheme 10). The gold complex (**IM1**) was chosen as reference for the free energy, while coordination of the gold catalyst to the ynamide affords the isomerised allene-type complex (**IM2**). Attack of the sulfonyl oxygen onto the ynamide β-carbon yields the cyclic sulfoniminium (**IM3**), while extrusion of the sulfinylium ion $PhSO^+$ affords the heterodiene complex (**IM4**). Migration of AuL^+ to the propargyl triple bond generates a 1,2-azadiene (ketinimine) core (**IM5**), while subsequent 5-*endo-dig* cyclisation generates the 2*H*-pyrrole complex (**IM6**), which is strongly exergonic by 27.0 kcal mol^{-1}. Migration of the $PhSO^+$ to the nitrogen atom of the pyyrole ring affords **IM7**, which lies very

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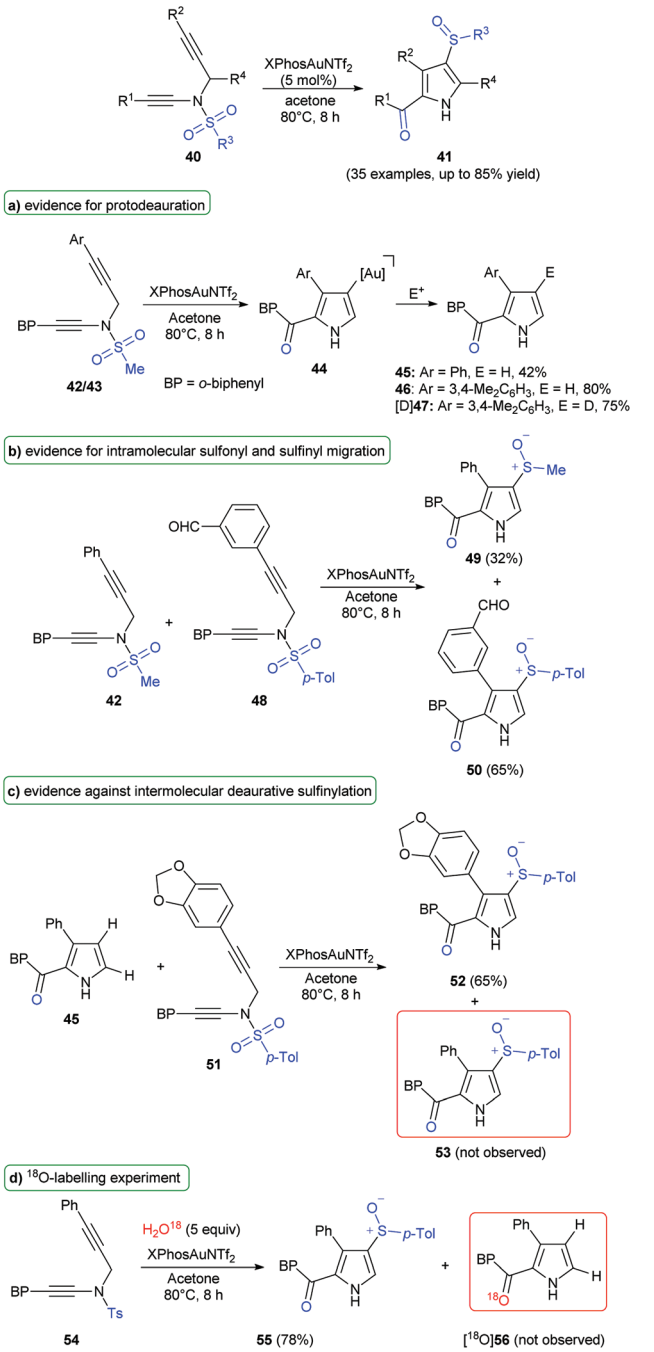
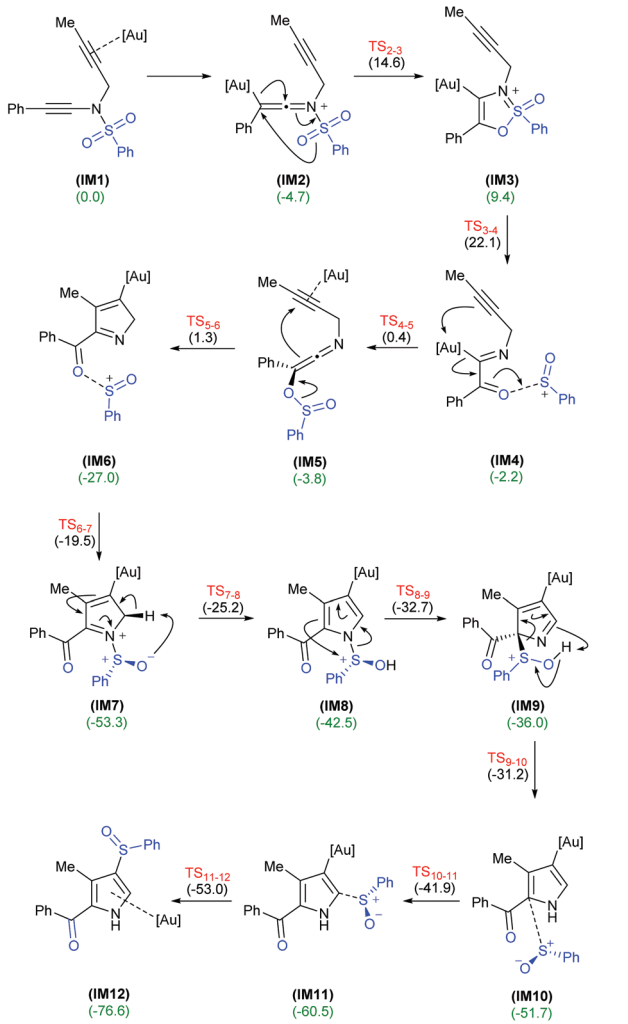


Scheme 9 Control experiments for mechanism elucidation.



Scheme 10 Calculated energy profile of the umpolung cycloisomerisation migration cascade process (ΔG_{298}, kcal mol^{-1}).

low on the potential energy surface (−53.3 kcal mol^{-1}). The sulfoxide oxygen is utilised as a base to shuttle one of the hydrogen atoms of the CH_2 group to the nitrogen atom of the pyrrole ring to afford **IM10**, despite being energetically unfavourable. The sulfonimidate-oxygen assisted 1,4-H shift *via* **TS$_{7\text{-}8}$** at −25.2 kcal mol^{-1} was found to be feasible affording **IM8**. Subsequent [1,2]-migration of the [PhSOH]$^+$ moiety, followed by [1,5]-H shift generates **IM10**, while antarafacial [1,4]-S shift of the PhSO$^+$ to afford **IM11** was observed to be favourable requiring 9.8 kcal mol^{-1} of free energy. To complete the transformation, a suprafacial [1,2]-S shift affords the **IM12** located at −76.6 kcal mol^{-1} on the PES.

2.1.2 Silver-catalysed sulfonyl migration. The synthesis of pyrazoles **58**/**59** *via* the silver(I)-catalysed rearrangement of propargyl *N*-sulfonylhydrazones **57**, involving a 1,3- or 1,5-sulfonyl migration, was described by the Chung group.[27] Using this methodology efficient and regioselective synthesis of 1,3- and 1,5-disubstituted, and 1,3,5-trisubstituted pyrazoles can be achieved in moderate to excellent yields (Scheme 11). Notably, in the absence of a sulfonyl moiety no pyrazole formation is observed. An intermolecular sulfonyl migration was elucidated by means of crossover experiments. Interestingly, deuterium incorporation studies highlighted an unexpected scrambling of deuterium at the C(4) and C(5) positions in the pyrazole product **61**; this was rationalised through the silver(I) allene intermediate **63** (Scheme 11). Loss of a deuterium ion causes the π-intermediate **62** to rearrange to a silver-substituted allene intermediate **63**. Subsequently, recombination with **63** affords intermediate **64**, which can isomerise to regenerate the π-intermediate **65**, which when cyclised gives pyrazole deriva-

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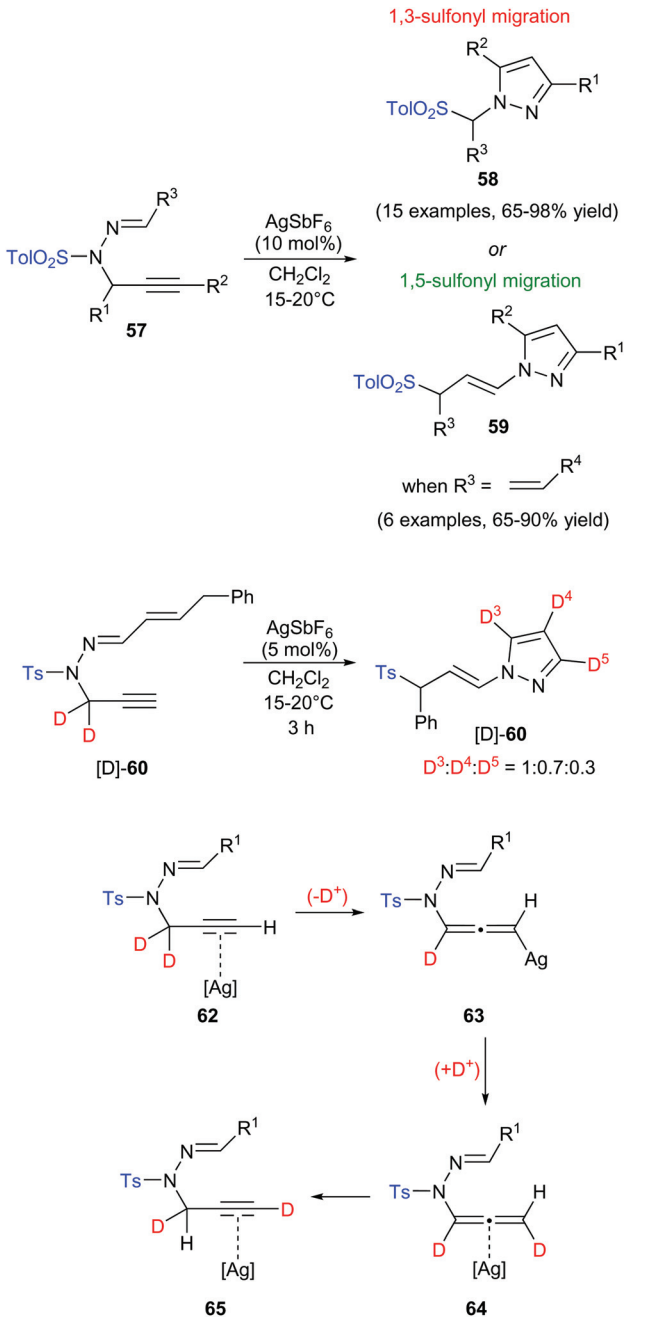
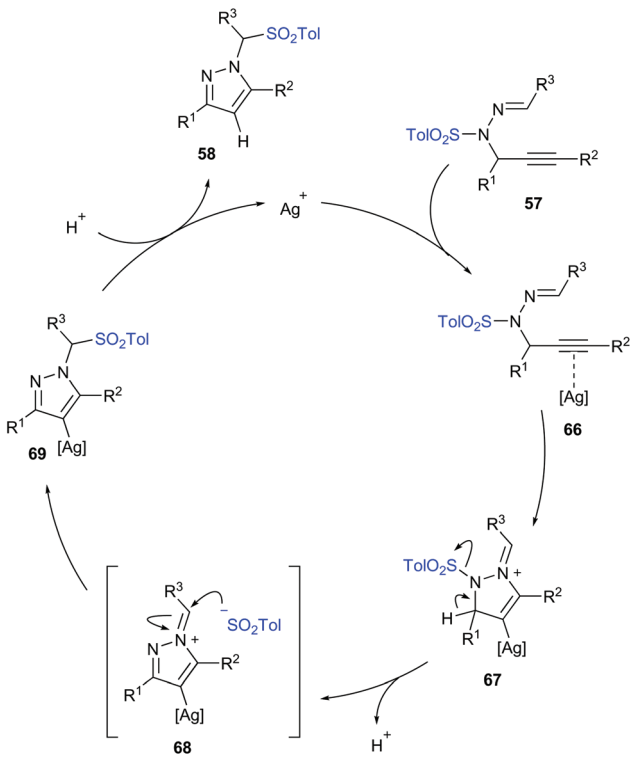


Scheme 11 Silver(I)-catalysed synthesis of pyrazoles from propargyl *N*-sulfonylhydrazones *via* 1,3- or 1,5-sulfonyl migration; proposition of a silver(I)-substituted allene intermediate.



Scheme 12 Postulated mechanism for the silver(I)-catalysed synthesis of pyrazoles from propargyl *N*-sulfonylhydrazones *via* 1,3- or 1,5-sulfonyl migration.

tives with deuterium incorporated at both the C(4) and C(5) positions.

Taking the above into account the following mechanism was postulated (Scheme 12). Upon coordination of the electrophilic silver source to the alkyne moiety of **57**, nucleophilic cyclisation occurs yielding the silver(I) intermediate **67**. Deprotonation leads to elimination of the sulfonyl moiety affording the ion pairs **68**. The sulfinate anion attacks the electrophilic iminium carbon completing the 1,3-sulfonyl migration. In instances in which the imine substituent is extended by conjugation, the sulfonate anion attacks the β-carbon leading to 1,5-sulfonyl migration being preferred. Finally, protodemetallation of **69** regenerates the catalytic silver species and gives the pyrazole products **58**.

The Wan group subsequently reported the silver(I)-catalysed cyclisation of *N*-sulfonyl propargylamides **70** for the synthesis of 4-(sulfonylmethyl)oxazoles **71** in moderate to good yields (Scheme 13).[28] The introduction of an aryl acyloxy directing group proved critical in realising the key silver-mediated [3,3]-rearrangement. Crossover experiments indicated that the sulfonyl migration may occur in both an intra- and intermolecular manner. The following plausible mechanism was presented (Scheme 13). Coordination of the silver(I) cation to the alkyne moiety of the propargylamide **70** as well as the acyloxy directing group generates the π-complex **72**. Due to the increased electrophilicity of the alkyne moiety an intramolecular nucleophilic attack of the amide oxygen occurs *via* a 6-*endo-dig* cyclisation giving the intermediate **73**. Subsequent collapse of the cyclic intermediate **73** affords the allene intermediate **74**. Nucleophilic attack of the nitrogen atom on the allene affords the 5-membered cyclic zwitterionic intermediate **75**. It is envisaged that the 1,3-sulfonyl migration occurs at this point in both an intra- and intermolecular manner, to give the rearranged 4-(sulfonylmethyl)oxazole **71**.

The Wan group further demonstrated that silver catalysis can be used in conjunction with trifluoromethyl-substituted

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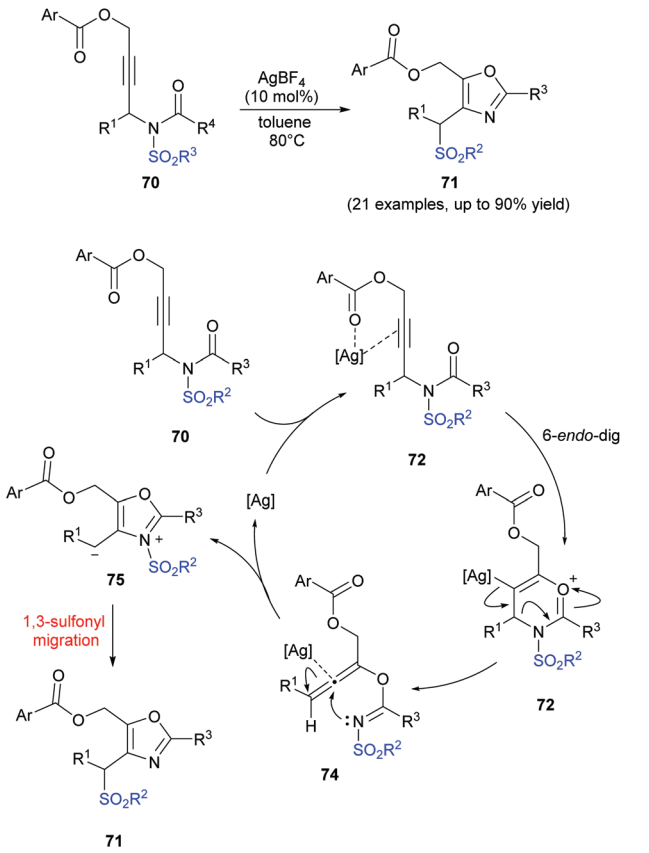
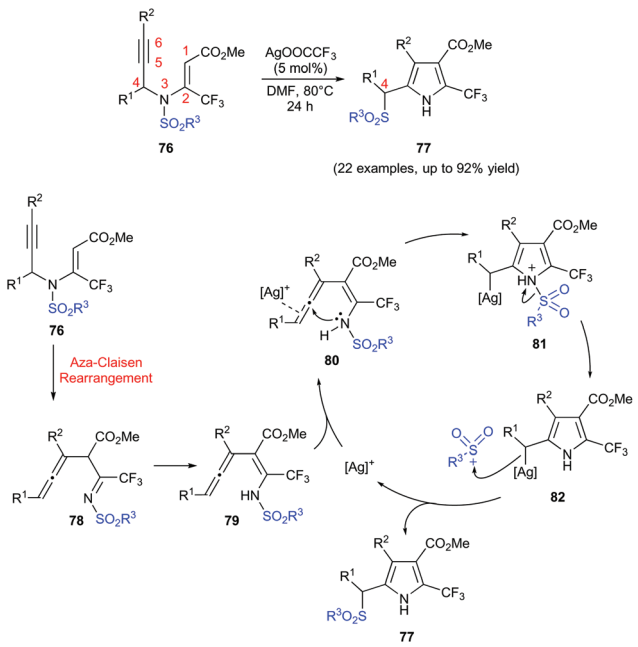


Scheme 13 Silver-catalysed cyclisation of propargylamides in the generation of functionalised oxazoles *via* 1,3-sulfonyl migration.



Scheme 14 Generation of 2-trifluoromethyl-5-(arylsulfonyl)methyl pyrroles *via* silver-catalysed 1,3-sulfonyl migration.

3-aza-1,5-enynes **76** to generate highly functionalised pyrroles **77** containing a trifluoromethyl group at the 2-position in a selective manner (Scheme 14).[29] Analogous to the group's previously mentioned report, a 1,3-sulfonyl migration again occurs. Both electron-rich and electron-deficient aryl moieties were well tolerated at R^1, however, the reaction does not work with alkyl substituents at this position. The alkynyl substituent could be readily diversified, with both alkyl and aryl groups tolerated. Crossover experiments indicated an intermolecular process for the sulfonyl migration, while a deuterium incorporation experiment was consistent with the absence of C–H bond cleavage at the C-4 position. As a result, the following mechanism was proposed (Scheme 14). Initial aza-Claisen rearrangement of **76** affords the intermediate **78**, which upon isomerisation gives the allene **79**. Coordination of the silver(I) catalyst with the allene intermediate **79** leads to cyclisation of the silver complex **80**, affording the cationic pyrrole **81**. Cleavage of the N–S bond ensues affording the intermediate **82** and the sulfinate anion. Regioselective recombination displaces the silver(I) cation in an intermolecular manner and in doing so generates the rearranged pyrrole **77**.

2.1.3. Transition metal-catalysed sulfonyl migration using *N*-sulfonylhydrazones. *N*-Sulfonylhydrazones undergo a range of transition-metal-catalysed and transition-metal-free transformations. The breadth of reactivity and synthetic application of this family of compounds has been reviewed extensively in recent years,[30–32] however, the overwhelming majority of reports involve either retention of the sulfonyl moiety at nitrogen or decomposition with elimination of the sulfonyl moiety. Notwithstanding, *N*-sulfonylhydrazones have recently been observed to be synthetically useful precursors to both allyl and vinyl sulfones, utilising sulfonyl migration in atom-economical syntheses. In this section, recent advances in the reactivity of these compounds utilising transition-metal catalysis, incorporating sulfonyl migration, will be considered.

2.1.3.1. Copper-catalysed sulfonyl migration using N-sulfonylhydrazones. Mao *et al.* developed a high-yielding stereoselective synthesis of terminal and α,β-unsaturated (*E*)-vinyl sulfones **84** from *N*-sulfonylhydrazones **83** *via* a radical pathway (Scheme 15).[33] The radical pathway was confirmed by the addition of TEMPO to the standard reaction conditions, which completely inhibited the formation of the sulfonyl migration product. The role of the sulfonyl free radical was further confirmed by the addition of 1,1-diphenylethylene (DPE), an alternative radical scavenger, with **85** isolated as the major product in 72% yield completely replacing formation of **84**. A small amount of water was required for an efficient transformation to occur; when anhydrous $Cu(OAc)_2$ was used a 35% reduction in yield was observed for **84** (R^1 = R^2 = Ph) when compared to when one drop of water was added. The mechanism is postulated to proceed *via* isomerisation of the *N*-tosylhydrazone **83** to **86**. Coordination of the copper catalyst to the alkene promotes the decomposition of **87**, with concomitant extrusion of diazene and the free tosyl radical affording the complex **88**. Recombination of **88** and the tosyl radical affords the carbenoid **89**, which undergoes O–H insertion with

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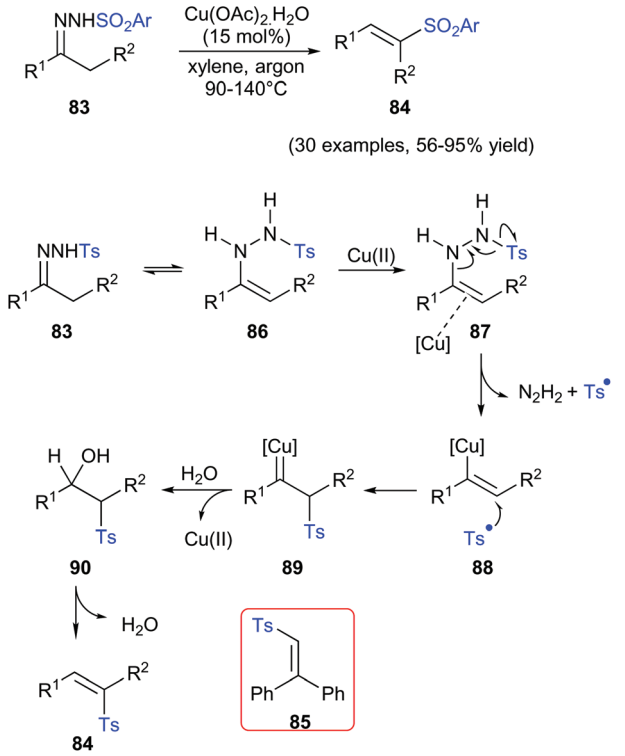
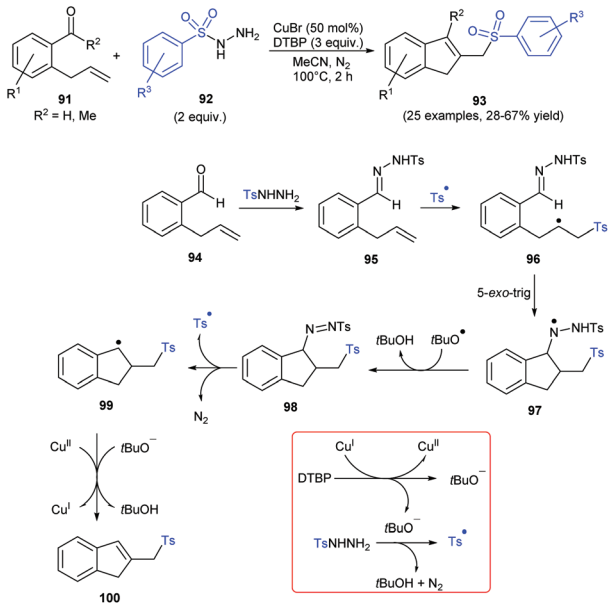


Scheme 15 Copper-catalysed stereoselective synthesis of (*E*)-vinyl sulfones *via* the radical reaction of *N*-tosylhydrazones.



Scheme 16 Access to sulfonylmethyl 1*H*-indenes *via* copper-mediated sulfonyl radical-enabled 5-*exo*-*trig* cyclisation of alkenyl aldehydes.

water to afford the alcohol **90**. *trans*-Elimination of water stereoselectively affords the desired (*E*)-vinyl sulfone.

The Zhang group reported the one-pot generation of 2-sulfonylmethyl 1*H*-indenes **93** in moderate yields *via* a copper-mediated sulfonyl radical-enabled cyclisation of *N*-arylsulfonyl hydrazones (Scheme 16).[34] A radical process was confirmed through the suppression of the reaction pathway on the addition of the radical scavengers TEMPO or 1,4-benzoquinone (BQ). Starting with the benzaldehyde **94**, in the absence of either CuBr or DTBP, the major product isolated was the *N*-sulfonylhydrazone **95**, highlighting the key role of the copper salt and oxidant in the reaction process. Stopping the reaction after 5 minutes afforded exclusively **95**, with complete consumption of starting material. The *N*-tosylhydrazone **95** was demonstrated to afford the indene **100** on treatment with $TsNHNH_2$ under the standard conditions. In the absence of a second equivalent of $TsNHNH_2$ the desired product was afforded in 10% yield, highlighting that efficient sulfonyl radical attack at the terminal vinyl carbon requires the second equivalent of $TsNHNH_2$.

Considering this the following mechanism was proposed. Condensation of $TsNHNH_2$ with the aldehyde **94** affords the *N*-tosylhydrazone **95**. A tosyl radical is generated *in situ* *via* the DTBP and copper-mediated oxidative decomposition of the second equivalent of $TsNHNH_2$. Subsequent addition of the sulfonyl radical to the terminal alkenyl carbon of **95** affords the intermediate radical **96**. Intramolecular 5-*exo*-*trig* cyclisation and hydrogen abstraction affords **98**, which loses dinitrogen and a tosyl radical to give **99**. Finally, a copper-mediated single electron transfer oxidation, and subsequent elimination *via* β-H abstraction by *tert*-butoxide affords the indene product **100**.

The Wang group described the copper(I)-catalysed one-step cross-coupling of terminal alkynes **101** with *N*-sulfonylhydrazones **102** to afford α,β-disubstituted vinyl sulfones **103** in moderate to excellent yields (Scheme 17).[35] Notably, the reaction proceeds readily for various *N*-tosylhydrazones with both electron-donating and electron-withdrawing groups tolerated on the aryl ring, albeit in lower yield when electron-withdrawing groups are present. Both naphthyl- and alkysulfonyl derivatives are also well tolerated, while both the ester substituent and the electronics of the aryl ring of the terminal alkyne can readily be altered with no deleterious effect. A radical-mediated transformation was excluded based on the absence of inhibition of the reaction on addition of TEMPO or BHT to the optimised reaction medium. Both the alkyne **110** and allene **111** afforded the desired product **112** when treated with *p*-toluenesulfinate in the presence of triethylamine. Notably, the alkyne **110** did not furnish any product in the absence of base, confirming the role of the allene intermediate **111** in the reaction cascade.

In light of these findings and previous reports the authors postulated the following mechanism (Scheme 17). Base-mediated decomposition of the *N*-tosylhydrazone **104** affords the tosylate anion and diazo compound **105**. Subsequent reaction of **105** with the copper acetylide **107** affords the carbenoid **108** which undergoes migratory insertion of the alkynyl moiety to the α-carbon to give the intermediate **109**. Protonation of **109** releases the copper cation which becomes available for the next catalytic cycle and generates the internal alkyne **110**. Deprotonation with triethylamine affords the allene intermedi-

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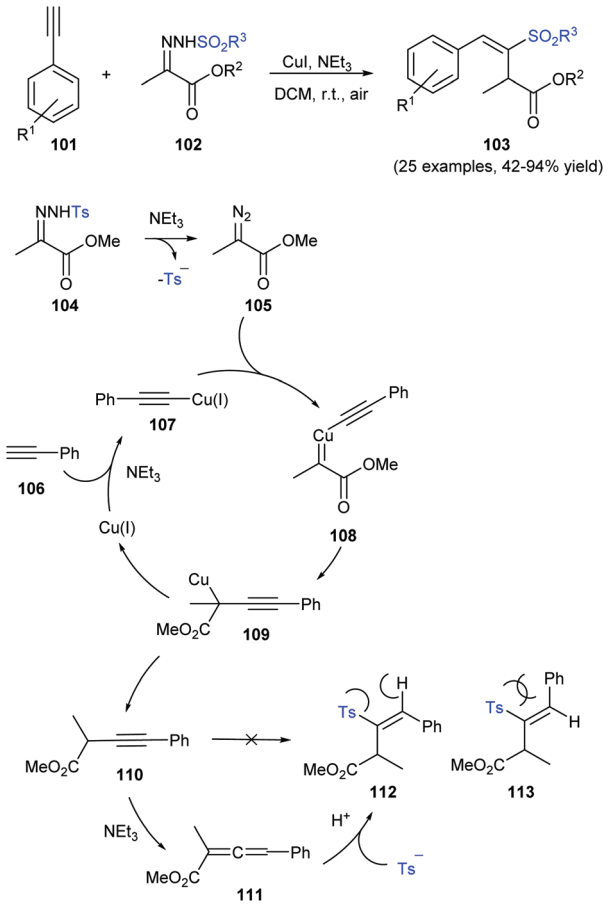
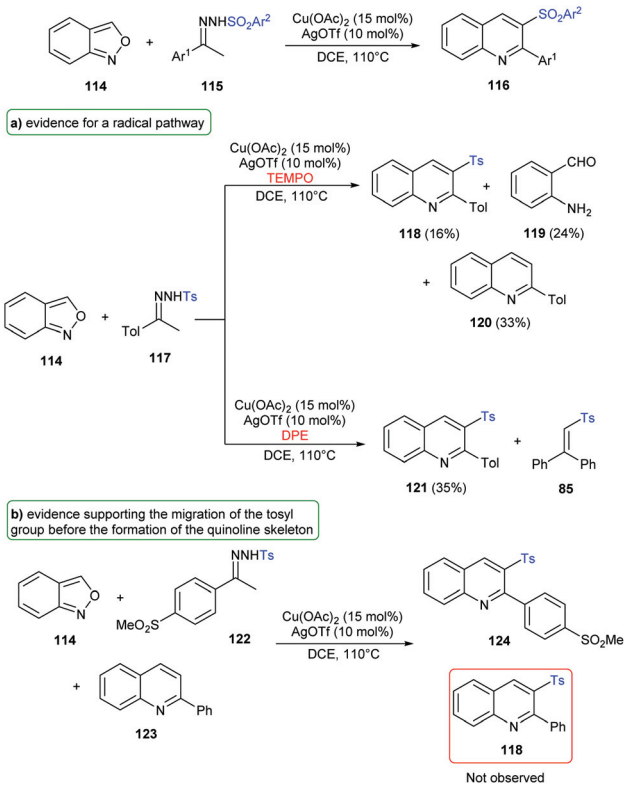


Scheme 17 One-step copper(I)-catalysed cross-coupling of terminal alkynes with *N*-sulfonylhydrazones affording α,β-disubstituted vinyl sulfones.



Scheme 18 Copper(II)/silver(I)-catalysed formation of 2-aryl 3-sulfonyl disubstituted quinoline derivatives *via* the reaction of *N*-sulfonylhydrazones and anthranils.

ate **111** which reacts with the tosyl anion in a regioselective manner, completing the sulfonyl migration, and affording the product **112**. The stereoselectivity of the reaction can be explained by the steric hindrance between the tosyl and phenyl moieties that inhibits the formation of the *Z*-isomer **113**.

The Ji group described a copper(II)/silver(I)-catalysed domino reaction of anthranils **114** with *N*-sulfonylhydrazones **115** to afford a series of 2-aryl-3-sulfonyl disubstituted quinoline derivatives **116** in moderate yields (Scheme 18).[36] To elucidate a mechanism the authors carried out a series of control experiments. The presence of TEMPO suppressed the reaction of **114** and **117** affording the desired product **118** in only 16% yield, while also forming the decomposition product **119** and the quinoline **120**. Additionally, in the presence of the alternative radical scavenger DPE, the trapped vinyl sulfone product **85** was observed by LC-MS confirming the presence of a sulfonyl radical in the mechanistic pathway. When **114** and **122** were reacted in the presence of the quinoline **123** no formation of **118** was observed highlighting that the sulfonyl migration occurs prior to the formation of the quinoline skeleton.

In light of the above the authors proposed that the zwitterion **114** reacts with the *N*-tosylhydrazone **126** under thermal conditions to afford the diazo intermediate **127** with expulsion of a tosyl radical (Scheme 19). Loss of nitrogen from the diazo compound **127** effected by the copper catalyst gives the carbenoid **128**, which subsequently coordinates with the anthranil **114** to give **129**. Carbene migratory insertion ensues to form **130**, while the following N–O bond cleavage affords the tautomer pair **131** and **132**. Addition of the tosyl radical to the terminal alkenyl carbon of **132** leads to the intermediate **133**, which cyclises in the presence of the AgOTf catalyst to yield the rearranged quinoline **125**.

Xu and co-workers recently reported the synthesis of 4-methyl 2*H*-chromene derivatives **135** from alkyne tethered *N*-sulfonyl hydrazones **134** using copper catalysis (Scheme 20).[37] Notably, in the absence of copper spiro-4*H*-pyrazoles (*e.g.* **139**) are instead the major products. Monitoring of the reaction progress by ^{1}H NMR allowed the identification of the 3*H*-pyrazole **137**, which was isolable. Furthermore, reacting **137** with one equivalent of CuI under thermal conditions gave **138** and **139** in 44% and 55% conversion respectively, highlighting that the 3*H*-pyrazole **137** is a key intermediate in both potential transformations. The formation of **138** in this instance, which does not require a catalyst, suggested that dinitrogen extrusion could be preceded by anion exchange (Ts^-/I^-) and/or coordination of the copper catalyst with **137**. As such, using CuOTf as catalyst, both the copper complex **140** and the triflyl addition product **141** were observed by ESI-MS. Crossover experiments indicated not only that the sulfonyl

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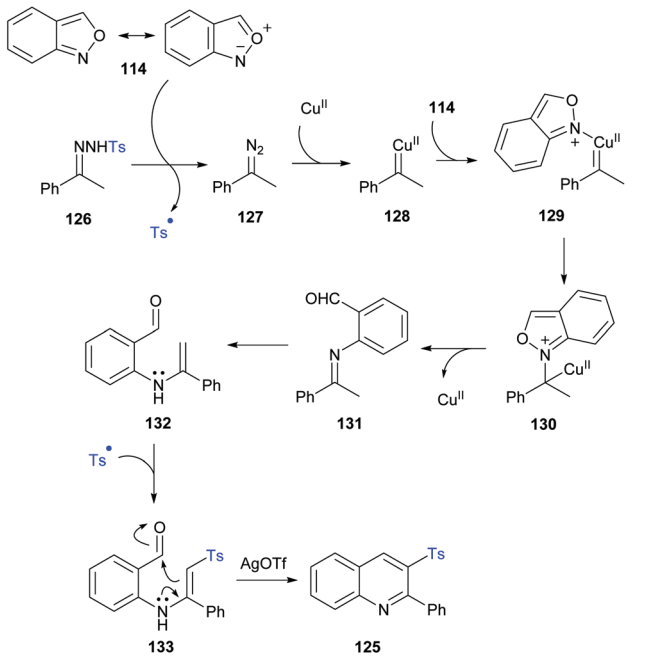
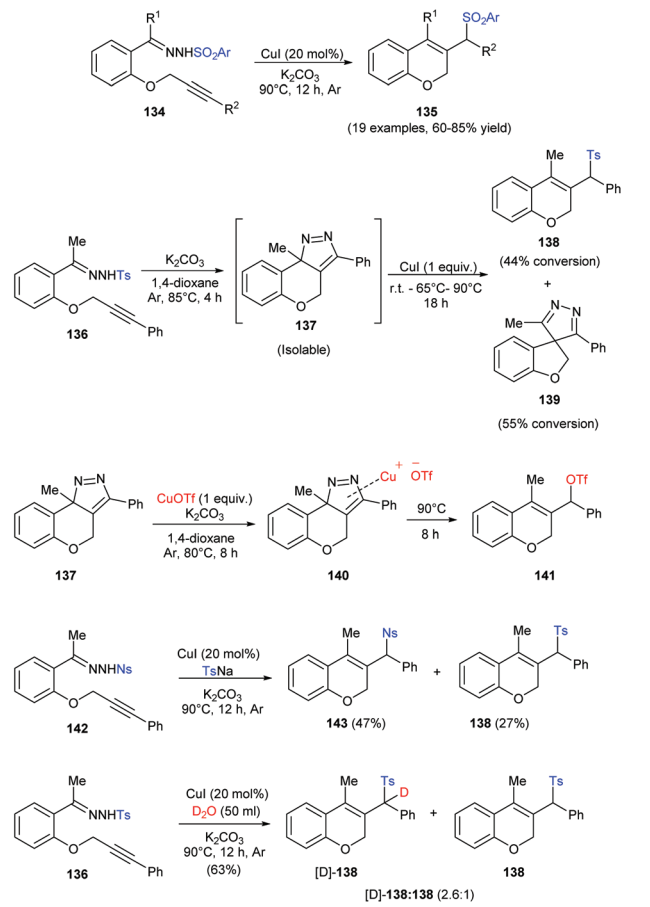
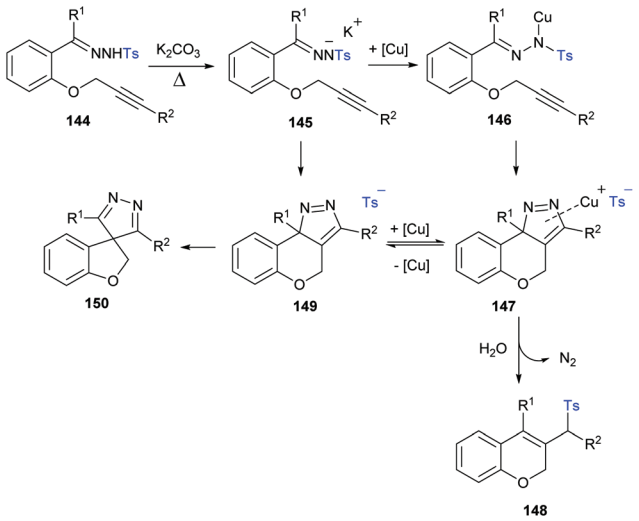


Scheme 19 Proposed mechanism for the copper(II)/silver(I)-catalysed formation of 2-aryl-3-sulfonyl quinolines.



Scheme 20 Copper-catalysed synthesis of 4-methyl 2*H*-chromenes alkyne tethered *N*-sulfonyl hydrazones.



Scheme 21 Proposed mechanism for the copper-catalysed transformation of alkyne tethered *N*-sulfonyl hydrazones to 4-methyl 2*H*-chromene derivatives.

migration is an intermolecular process but also that it is likely that the counter ion is either in close proximity or associated to the intermediate during the transformation, and that the catalytic rate of reaction is faster than the counter ion exchange; this is as a result of observing that the less nucleophilic nosyl anion afforded a significantly higher combined yield than that of the tosyl anion (Scheme 20). Isolation of the deuterated product **[D]-138** rationalised the protonation after recombination with the tosyl anion. Further evidence for the reaction pathway was obtained *via* the identification of the intermediates **145** and **146** by ^{1}H NMR and HRMS (see Scheme 21).

Considering this the following mechanism was proposed (Scheme 21). K_2CO_3-mediated deprotonation of the *N*-sulfonyl hydrazone **144** affords the potassium salt **145**. Subsequent ion exchange affords the copper complex **146**, which undergoes a [3 + 2] cycloaddition/dinitrogen extrusion/sulfonyl anion recombination to give the desired product **148** *via* **147**. Alternatively, dissociation of the copper catalyst could occur leading to the rearranged spiro-product **150** *via* van Alphen–Hüttel rearrangement of **149**.

2.1.3.2. Palladium-catalysed sulfonyl migration using N-sulfonylhydrazones. Allylic sulfones are accessible *via* palladium-catalysed cross-coupling of aryl and vinyl iodides **151** and **154** with *N*-sulfonylhydrazones **152** and **155**, involving carbene migratory insertion and regioselective addition of the released sulfonyl anion (Scheme 22).[38,39] For example, using $Pd(OAc)_2$ and triphenylphosphine as catalyst, and BTAC as phase-transfer additive, a series of allylic sulfones **156** were generated in moderate to high yields, with electron-deficient and electron-rich aryl rings all well tolerated, as well as a range of sulfonyl moieties. The reactions are believed to proceed *via* initial base-mediated decomposition of the *N*-tosylhydrazone **159** to afford the diazo **160** with concomitant release of the tosylate salt. The diazo **160** reacts with the vinylpalladium iodide complex **158** to form the carbenoid **161**, which under-

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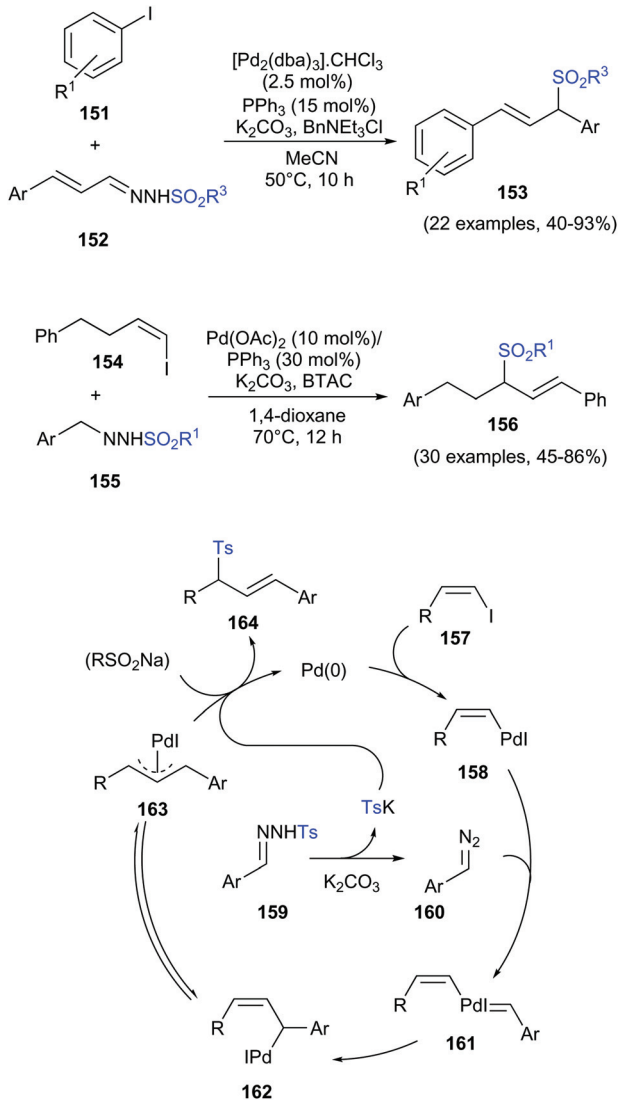
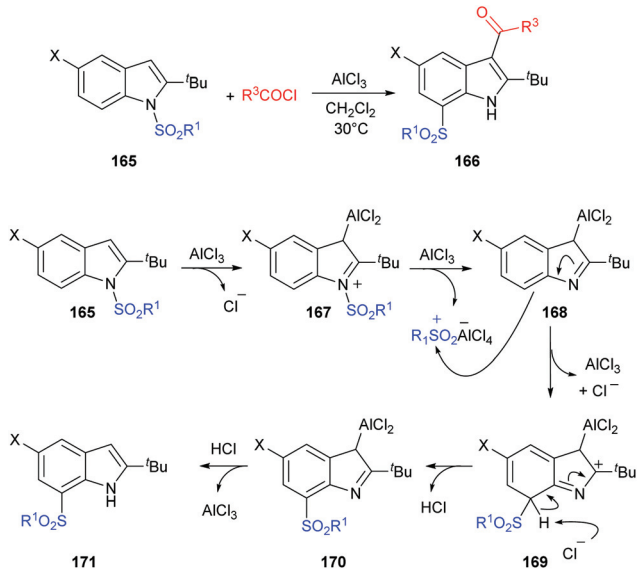


Scheme 22 Generation of allylic sulfones *via* palladium-catalysed cross-coupling of aryl iodides and *N*-tosylhydrazones.

goes migratory insertion to afford the η^1-allylpalladium intermediate **162**. Isomerisation to the η^3-allylpalladium complex **163** is followed by selective nucleophilic addition of the tosylate anion to give **164** as the exclusive product.

2.1.4. Miscellaneous metal-catalysed sulfonyl migration. The introduction of a sulfonyl group to the C-7 position of indoles can be achieved in moderate to good yields through the aluminium trichloride-mediated regioselective 1,3-sulfonyl migration of *N*-sulfonyl indoles **165** (Scheme 23).[40] The sulfonyl migration was found to proceed smoothly when an electron-donating group was present at the C-5 position of **165**, however the regioselectivity of the transformation was attenuated by the presence of electron-withdrawing groups with some formation of the 3-sulfonyl indole observed. The presence of the bulky *tert*-butyl group at the C2 position appears to assist the cleavage of the N–S bond allowing the sulfonyl migration to occur; when a *n*-butyl substituent was present at



Scheme 23 $AlCl_3$-mediated 1,3-sulfonyl migration of *N*-sulfonyl indoles; access to 7-sulfonyl indoles.

C2 no migration was observed, despite the acylation readily occurring. In the absence of acyl chloride the sulfonyl migration still readily occurred, highlighting the key role of $AlCl_3$ in the reaction. The mechanism was proposed to involve a non-concerted, intermolecular sulfonyl migration based on the outcome of crossover experiments. Thus, the reaction seems to proceed *via* $AlCl_3$-assisted activation of the indolyl double bond followed by cleavage of the N–S bond to give **168** which subsequently undergoes sulfonylation at the C7 position to give **171** *via* **170**, completing the sulfonyl migration.

The Zhan group reported the copper(I)-catalysed stereoselective synthesis of (1*E*,3*E*)-2-sulfonyl-1,3-dienes **173** from *N*-propargylic sulfonylhydrazones **172** involving a stereoselective sulfonyl migration (Scheme 24).[41] When employing catalytic $[Cu(PPh_3)I]_4$ in refluxing toluene yields of 51–92% were achieved, with electron-poor sulfonylhydrazones leading to higher yields than electron-rich analogues. Aryl groups at both R^2 and R^4 bearing electron-withdrawing and electron-donating substituents were also well tolerated.

Crossover experiments indicated that the migration of the sulfonyl group is an intermolecular process. Based on these observations the authors hypothesised that the mechanism involves initial 6-*endo-dig* addition of the sulfonylhydrazone onto the copper(I)-alkyne complex **174** to generate the intermediate **175** which collapses to the allenic intermediate **176**, completing the initial [3,3]-rearrangement. Intermediate **176** is unstable and readily loses dinitrogen, leaving ion pair **177**. Finally, the tosyl anion regioselectively and stereoselectively attacks the central sp carbon atom of the allenic moiety, with subsequent electron transfer affording the (1*E*,3*E*)-2-sulfonyl-1,3-diene **173** (Scheme 24). The release of nitrogen is most likely the trigger for the sulfonyl migration.

Zhan and co-workers reported the zinc chloride mediated synthesis of 4-(sulfonyl)-methyl-1*H*-pyrazoles **179** in excellent

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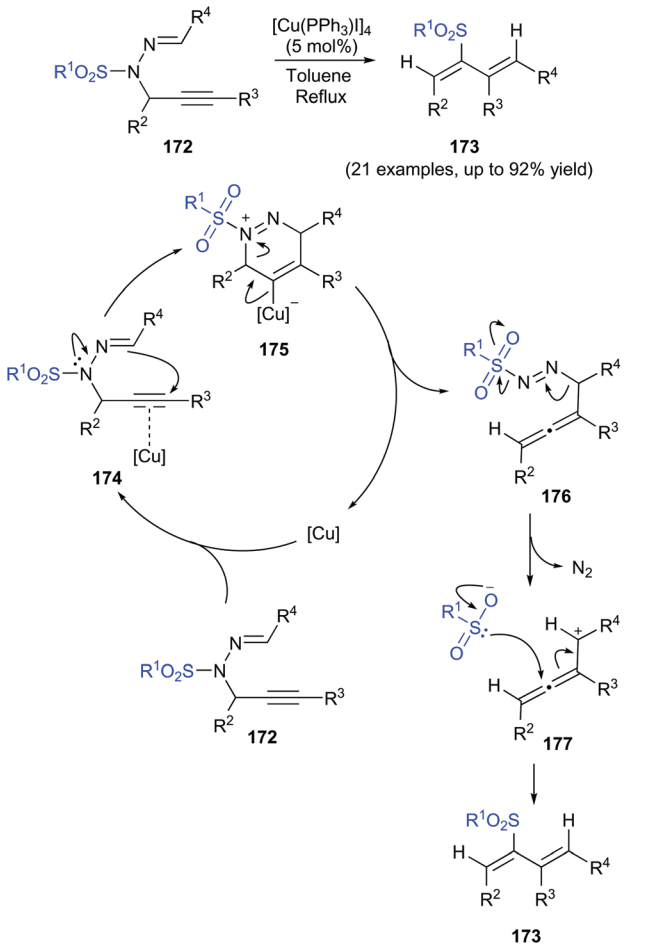
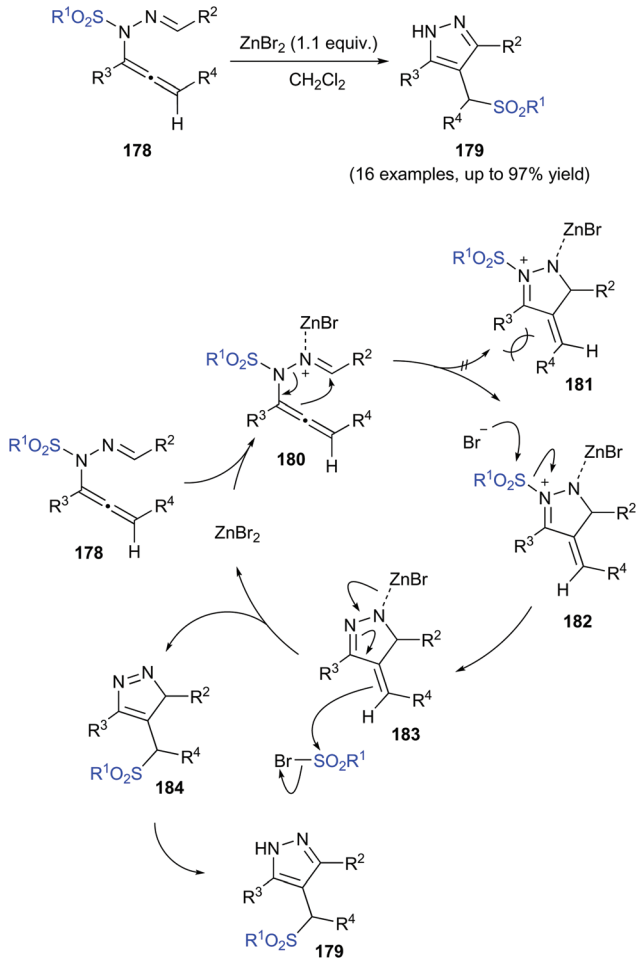


Scheme 24 Copper(I)-catalysed stereoselective synthesis of (1*E*,3*E*)-2-sulfonyl-1,3-dienes utilising migration of the sulfonyl group.



Scheme 25 Selective synthesis of 4-(sulfonyl)-methyl-1*H*-pyrazoles from *N*-allenic sulfonylhydrazones *via* 1,4-nitrogen to carbon sulfonyl migration (see also Scheme 66).

yields from *N*-allenic sulfonylhydrazones **178** *via* a formal 1,4-nitrogen to carbon sulfonyl migration (Scheme 25).[42] Crossover experiments utilising two different *N*-allenic sulfonylhydrazones highlighted an intermolecular process for the sulfonyl migration. Mesyl, tosyl and benzenesulfonyl substituents were tolerated. The authors postulated that coordination of $ZnBr_2$ to the azomethine nitrogen atom of **178** induces a nucleophilic addition of the central allenyl carbon to the azomethine carbon to give exclusively (*E*)-**182**. Formation of (*Z*)-**181** is inhibited due to steric hindrance between the R^3 and R^4 substituents. Bromide assists the N–S bond scission to generate the intermediate **183** and tosyl bromide, which then reacts with the endocyclic alkene moiety to complete the formal 1,4-tosyl migration, and in doing so generates **184**. Tautomerisation affords the rearranged aromatic pyrazole **179**.

2.2. Single electron-mediated sulfonyl migration

2.2.1. Radical-mediated sulfonyl migration. The Maulide group observed an unexpected nitrogen to carbon 1,3-sulfonyl migration of a tosyl group when attempting to expand the scope of electrophilic Claisen rearrangements to aza-derivatives. While alkyl and alkenyl oxygen-based substrates underwent straightforward Claisen rearrangement to afford a series of hydrocoumarins, aza-derivatives **185–187** did not afford the expected α-substituted lactams **191**, but instead the amidinium derivatives **188–190** (Scheme 26).[43] Both the allyl and benzyl derivatives **185** and **186** underwent tosyl migration, while the propargyl derivative **187** underwent an additional cyclisation with concurrent tosyl migration. It was postulated that the tosyl migration occurs as a result of a radical pathway, with homolytic cleavage of N–S bond in the intermediate **193**. It was suggested that recombination of the radical pair **194** to afford **188** may be faster than diffusion, and that this process is more favourable energetically than migration of the allyl group.

The thermal 1,3- and 1,5-sulfonyl migrations of *N*-arenesulfonylphenothiazines **195** and *N*-arenesulfonylphenoxazines **196** were realised by the Xu group (Scheme 27).[44] Under neutral, thermal conditions a series of sulfonyl substituted phenothiazine **197**/**199** or phenoxazine derivatives **198**/**200** are afforded with moderate yields and regioselectivities. Crossover experiments indicated that the sulfonyl migration was an intermolecular process while a

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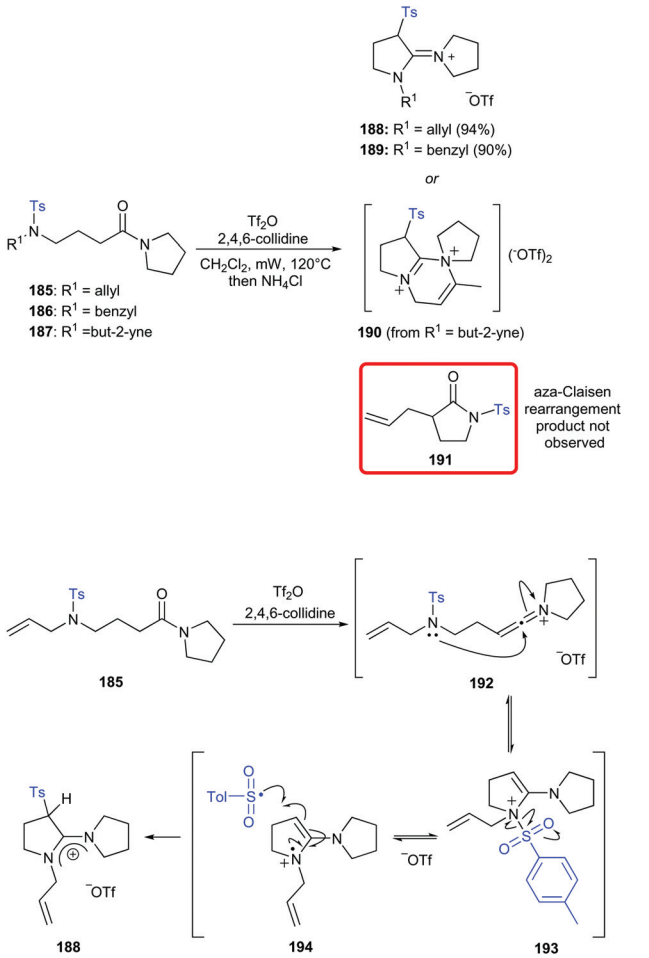
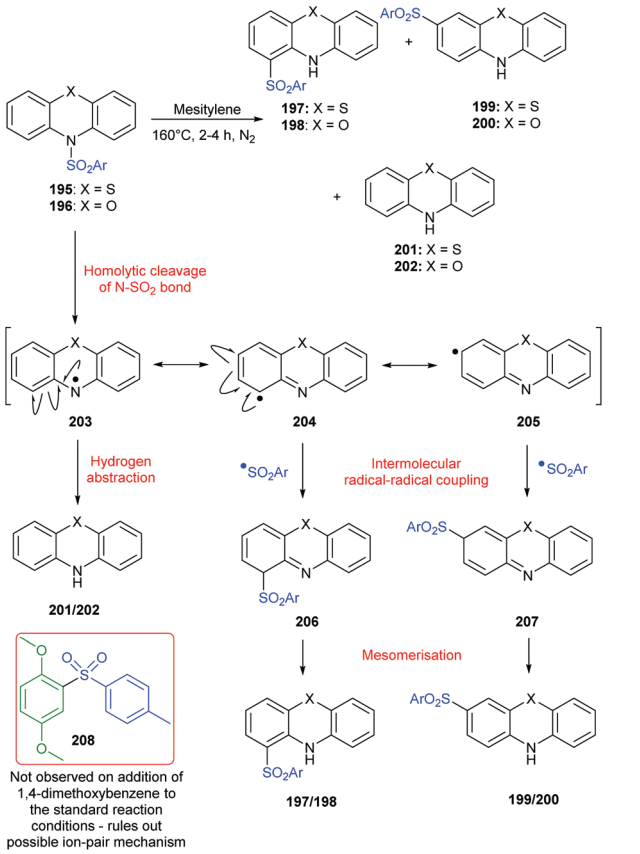


Scheme 26 Generation of amidinium derivatives *via* 1,3-tosyl migration.



Scheme 27 Radical–radical coupling reaction mechanism for the 1,3- and 1,5-sulfonyl migrations of *N*-arenesulfonyl-phenothiazines and phenoxazines.

radical–radical coupling reaction mechanism was proposed based on competitive trapping experiments using electron-rich 1,4-dimethoxybenzene, which ultimately allowed the ruling out of a possible ion-pair mechanism. As such, homolytic cleavage of the N–S bond affords the free radical **203** and a sulfonyl radical. The radical intermediate **203** can readily interconvert between the resonance structures **204** and **205** through electron delocalisation. Recombination of the sulfonyl radical with **204** or **205**, leads to formal 1,3- and 1,5-sulfonyl migrations to give intermediates **206** and **207**. Finally, isomerisation of these intermediates affords the rearranged phenothiazine or phenoxazine products **197–200**. The formation of the dissociation products **201**/**202**, *via* abstraction of a hydrogen atom from a neighbouring molecule, such as solvent, provides further supportive evidence for the radical mechanism.

The She group developed a sequential catalysed cycloaddition of N-heterocyclic carbene (NHC) activated 1,3-dioxoisoindolin-2-yl 2-phenyl acetate **210** and α,β-unsaturated imines **209** in which the *N*-hydroxyphthalimide (NHPI) by-product **212** of the first reaction catalysed a further nitrogen to carbon 1,3-sulfonyl migration of the tosyl group (Scheme 28).[45] Notably, the enantiomeric composition of the major product **211** from the cycloaddition step was retained through the subsequent sulfonyl migration to afford the desired product **213** in moderate yields and high enantioselectivities. The efficiency of the NHC/NHPI catalytic cascade process was found to be strongly dependant on the electronic nature of the R^2 substituent, with electron donating groups on the aromatic ring affording final products in significantly higher yields after 2 steps. While the mechanism of the sulfonyl migration is not fully understood, a radical mechanism was deemed most likely, as the addition of the radical scavenger TEMPO completely inhibited the migration.

Wang *et al.* reported the di-*tert*-butyl peroxide-mediated radical rearrangement of *N*-sulfonyl-*N*-aryl propynamides **214** to afford 3-sulfonyl-2-(1*H*)-quinolinones **215** in moderate to good yields with good functional group compatibilities, with a 1,3-sulfonyl migration from nitrogen to carbon a key step (Scheme 29).[46] Crossover experiments indicated the involvement of an intermolecular process, while a radical pathway was postulated based on the inhibition of the reaction cycle upon the addition of the radical scavengers TEMPO, BHT or galvinoxyl. The intramolecular and intermolecular kinetic isotope effect (KIE) was determined to be 1.08 and 1.04 respectively, indicating that the rate determining step was un-

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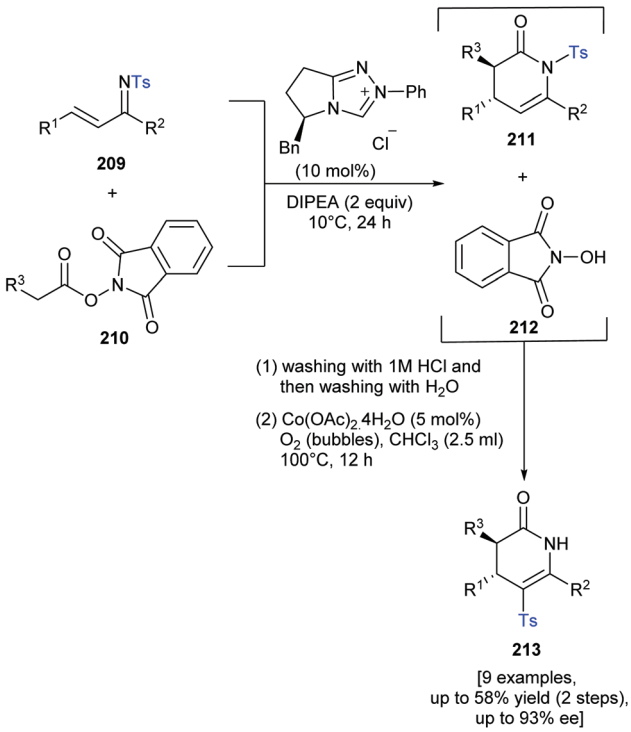
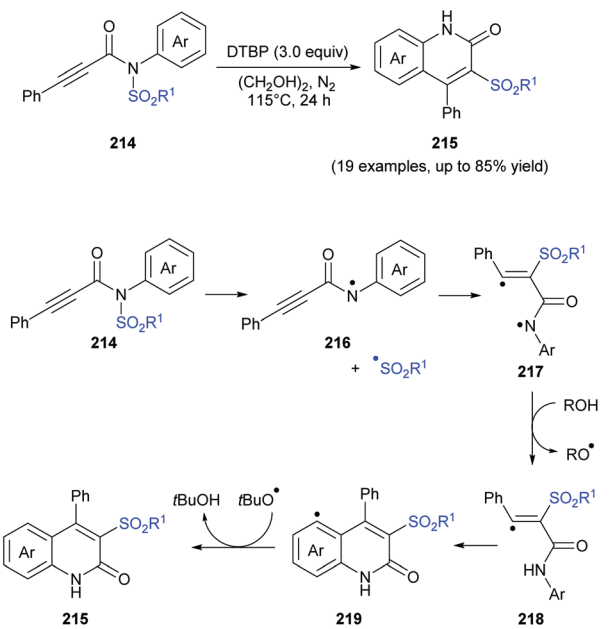


Scheme 28 Application of upstream by-product NHPI as catalyst for sequential 1,3-sulfonyl migration.

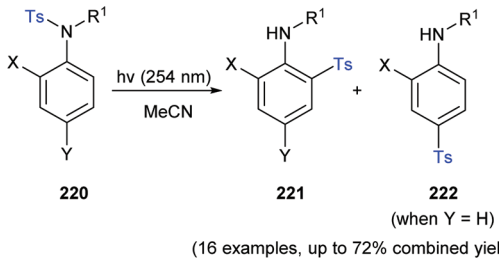


Scheme 29 Di-*tert*-butyl peroxide mediated radical rearrangement of *N*-sulfonyl-*N*-aryl propynamides; observation of a formal 1,3-sulfonyl migration.

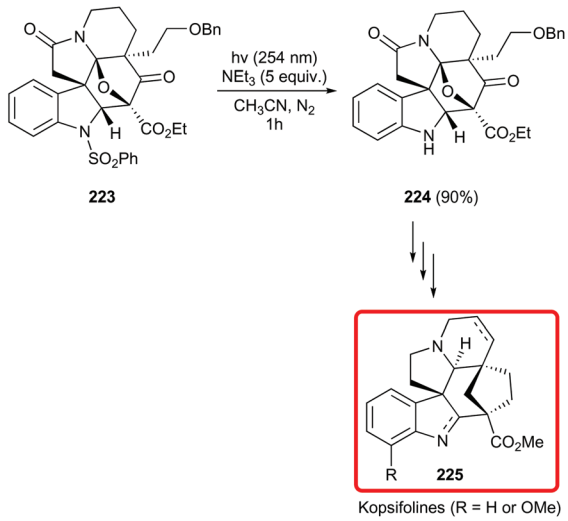
likely to involve the cleavage of the aromatic C–H bond, while also suggesting that either a radical or electrophilic aromatic substitution pathway was involved. Considering this the authors proposed that homolytic scission of the N–SO_2 bond leads to the radical **216** and a sulfonyl radical. Addition of the sulfonyl radical to the alkyne group of radical **216** generates the diradical **217**, which abstracts a hydrogen atom from the solvent, to give the radical **218**. A 6-*endo-dig* cyclisation affords the cyclised radical **219**, which on abstraction of a hydrogen by a *tert*-butoxyl radical affords the 3-sulfonyl-2-(1*H*)-quinolinone **215**.

2.2.2. Photoinduced sulfonyl migration. Photochemical irradiation of *N*-sulfonyl anilines **220** was found to promote thia-Fries-type rearrangements to afford mixtures of regioisomeric *ortho*- and *para*-aminophenyl sulfone derivatives **221** and **222** in moderate yields, *via* nitrogen to carbon 1,3- or 1,5-sulfonyl migration (Scheme 30).[47] *N*-Alkylation of the sulfonanilides **220** increased the yield of the rearranged products, while the presence of electron-withdrawing groups on the aromatic ring did not greatly lower the yields.

In their efforts to establish a total synthesis of the kopsifoline alkaloid framework **225**, Padwa and co-workers observed an unanticipated desulfonylation of **223**, while attempting to carry out a photochemical rearrangement. The desulfonylation proceeded efficiently, affording **224** in 90% yield (Scheme 31).[48,49]



Scheme 30 Photochemical thia-Fries-type rearrangement of *N*-sulfonyl anilines.



Scheme 31 Photoinduced desulfonylation strategy toward the synthesis of the kopsifoline alkaloid framework.

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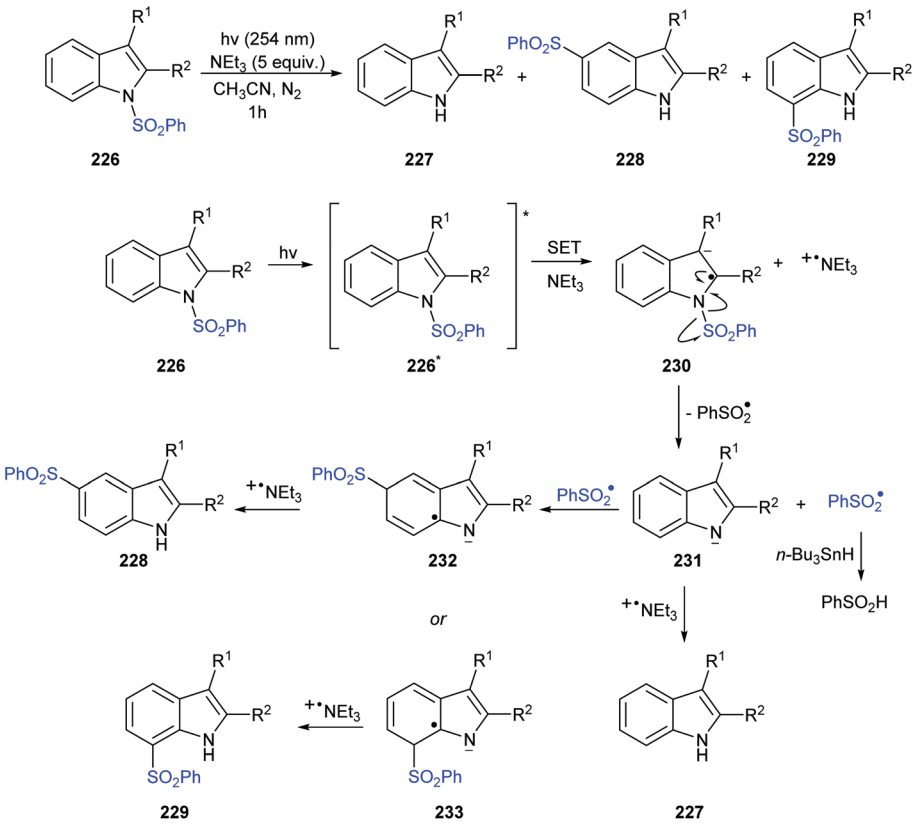

Scheme 32 Mechanism for the photoinduced thia-Fries type rearrangement of indoles.

Due to the efficiency of this reaction, and the mild conditions required, the authors sought to extend the scope of the reaction to a series of related indoles **226**, however a significant reduction in yield was observed for this class of compound due to the competing formation of both *ortho*- and *para*-photo Fries rearrangement products **228** and **229** (Scheme 32). In most instances the *para*-rearrangement by-product **228**, the result of a formal 1,5-sulfonyl migration, was the major isomer formed. The reaction is likely initiated by single electron transfer from triethylamine to the electronically excited indole **226*** leading to the triethylamine radical cation and the indole radical anion **231** (*via* the indole radical **230**). Proton transfer from the radical cation of triethylamine affords the desired desulfonylated indole **227**. In competing processes, the phenylsulfonyl radical can also add to the aromatic framework of the radical anion **231** to afford the transient intermediates **232** or **233**. Subsequent electron transfer from **232** and **233** to the triethylamine radical cation affords the *ortho*- and *para*-sulfonylated indoles **228** and **229**. The competing thia-Fries pathway can be suppressed by addition of *n*-Bu_3SnH, which allows capture of the sulfonyl radical *via* hydrogen atom transfer.

Smith and coworkers reported the first selective example of a nitrogen to carbon 1,3-sulfonyl migration of dihydropyridones **234** *via* prolonged storage and heating, however, most notable was the quantitative isomerisation observed under photochemical conditions (Scheme 33).[50,51] Highlights of the methodology include a high degree of tolerance for both *N*- and *C*-substituent diversification around the dihydropyridinone ring, to afford the corresponding rearranged *C*-sulfonyl products **235** in moderate to high yields with no erosion of stereochemical integrity. Significant efforts to rationalise the mechanism of the sulfonyl migration were made by the authors. Crossover experiments elucidated an intermolecular event, while adding TEMPO under the standard conditions led to complete suppression of the sulfonyl transfer, indicating a radical mechanism. Rather than a straightforward homolytic N–S bond cleavage to give a sulfonyl radical and radical **236** followed by recombination at carbon to give the rearranged product **235**, electron paramagnetic resonance (EPR) spectroscopy indicated the presence of a larger radical that was assigned as the intermediate benzylic radical **237**. Therefore the authors proposed that after the homolytic cleavage, the sulfonyl radical adds to the dihydropyridinone **234** generating the benzylic radical **237** which can extrude a sulfone radical to generate the neutral imine **238**. Tautomerisation of **238** affords the rearranged dihydropyridinone **235**.

The Rutjes group discovered the first example of a photoinduced rearrangement of 1,2-benzothiazole-1,1-diones **240** to form 3-amino-1-benzothiophene-1,1-dione derivatives **241** in excellent yields *via* a nitrogen to carbon 1,3-sulfonyl migration (Scheme 34).[52] Based on literature precedent for the photoinduced cleavage of sulfonamides the authors postulated the following radical mechanism.[53–56] Irradiation of **240** induces

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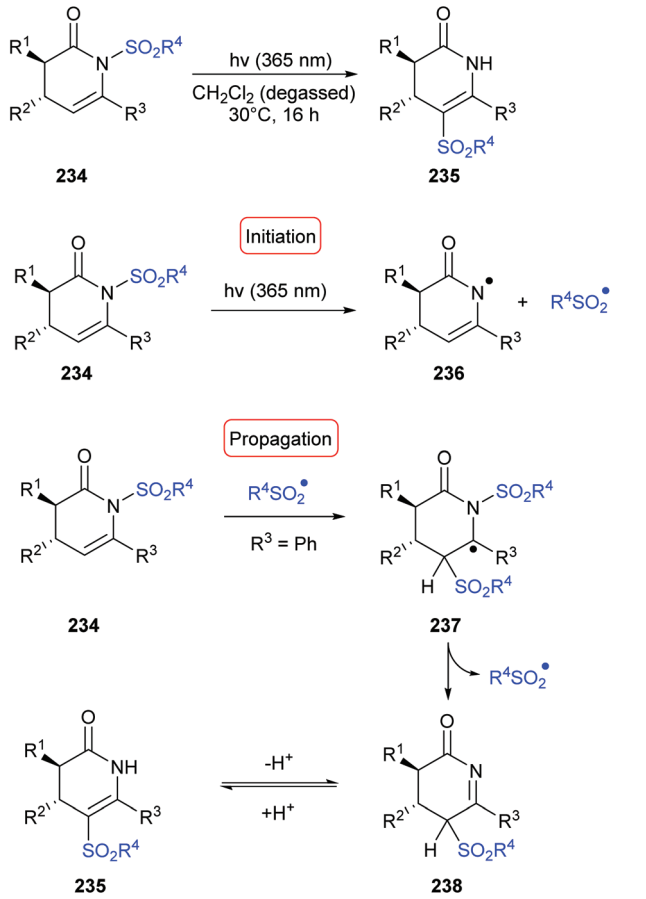
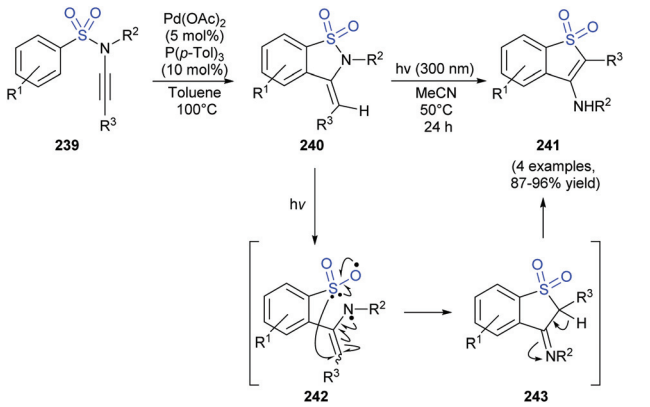
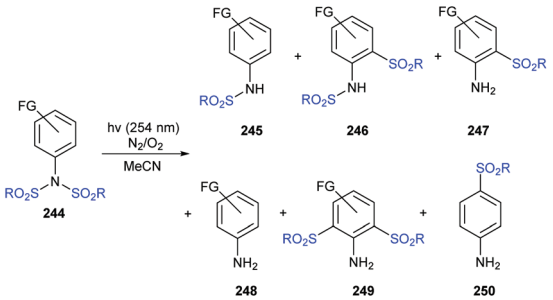


Scheme 33 Photoisomerisation of *N*-sulfonyldihydropyridinones; observation of a visible light induced 1,3-sulfonyl migration.



Scheme 34 Photochemical rearrangement of 1,2-benzothiazole-1,1-diones to 3-amino-1-benzothiophene-1,1-diones; observation of a nitrogen to carbon 1,3-sulfonyl migration.

homolytic cleavage of the N–S bond which generates the diradical **242**. Recombination of the sulfinate radical with the C-terminus of the enaminyl radical generates the imine **243**, which subsequently tautomerises to generate the rearranged 3-amino-1-benzothiophene-1,1-dione **241**. The requisite substrates **240** for the photoinduced sulfonyl migration were



Scheme 35 Irradiation of *N*-aryl sulfonimides; observation of single and double photo thia-Fries rearrangement.

demonstrated to be accessible through a palladium-catalysed regioselective and highly stereoselective intramolecular hydroarylation of sulfonyl ynamines **239**.

Torti *et al.* described the use of *N*-arylsulfonimides **244** as potential nonionic photoacid generators able to photorelease up to two equivalents of sulfonic acids for each mole of substrate under deaerated conditions in acetonitrile.[57,58] The product distribution of the reaction under deaerated conditions proved to be complex with all compounds formed arising from the cleavage of the S–N bond to afford both photo thia-Fries rearrangement products **246**, **247**, **249** or **250** and desulfonylated products **245** or **248** (Scheme 35).

In order to further understand the photoreactivity of the *N*-arylsulfonamides **244**, and to investigate secondary photochemical pathways, laser flash photolysis (LFP) and electron paramagnetic resonance (EPR) spectroscopy experiments were performed. Considering the supporting evidence of these studies the authors tentatively proposed the following mechanism (Scheme 36). Initial irradiation of **244** causes excitation to the singlet state ^{1}**244**, which undergoes homolytic cleavage of the N–S bond to generate the sulfamido **251** and sulfonyl **252** radicals, the presence of which were confirmed by both time-resolved absorption and EPR spectroscopy (path A). Once formed, the radicals **251** and **252** can undergo either thia-Fries rearrangement as a result of recombination (path D) to afford **246** *via* intermediate **253**, or escape from the solvent cage to release sulfonic acids. The photoreactive sulfonamide **246** can undergo a second thia-Fries rearrangement to generate the rearranged aniline **249** (path D″), however desulfonylation appears to have no role (path D′). In contrast, hydrogen abstraction by the sulfamido radical **251** from the reaction medium affords the sulfonamide **245** (path C). The favoured pathway, between path C and D, is dependent on both the functional groups present on the aryl ring and the reaction medium. The single thia-Fries rearrangement product **246** is preferred in less polar solvents and in the presence of electron-donating groups (NMe_2, OMe) on the aromatic ring.

The *N*-arylsulfonamide **245** is also photoactive and can undergo both thia-Fries rearrangement to afford the rearranged aniline **247** (path C″), or desulfonylation to give **248** (path C′). The thia-Fries rearrangement is favoured for electron-rich sulfonamides, while for unsubstituted

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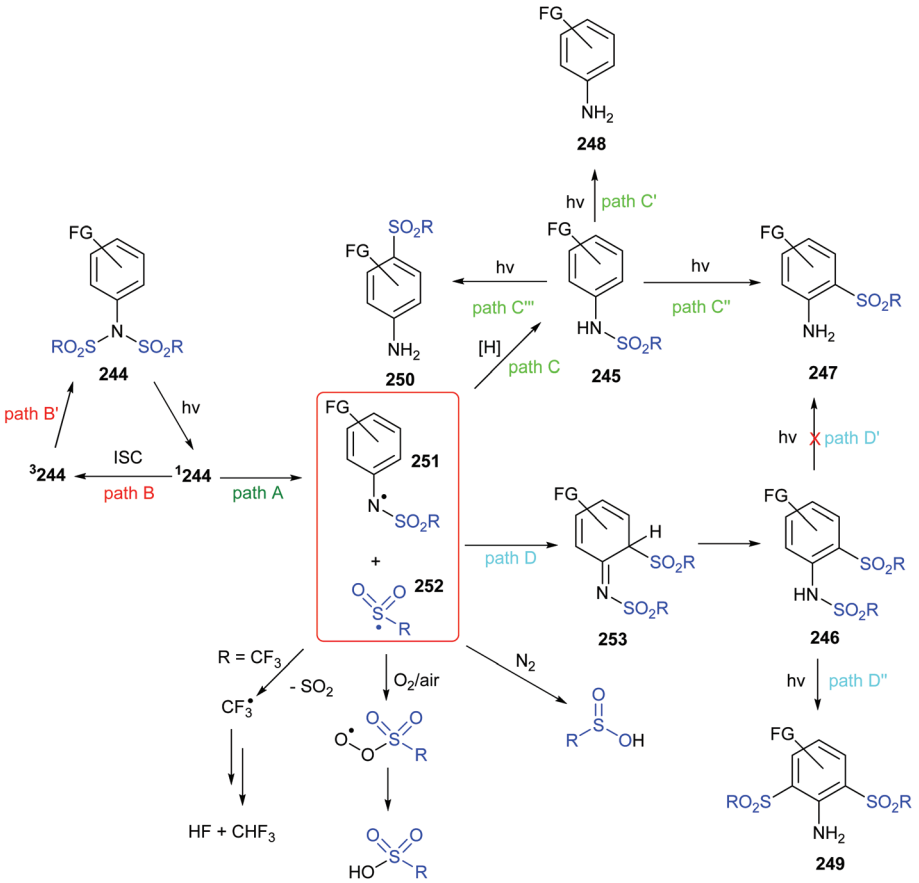
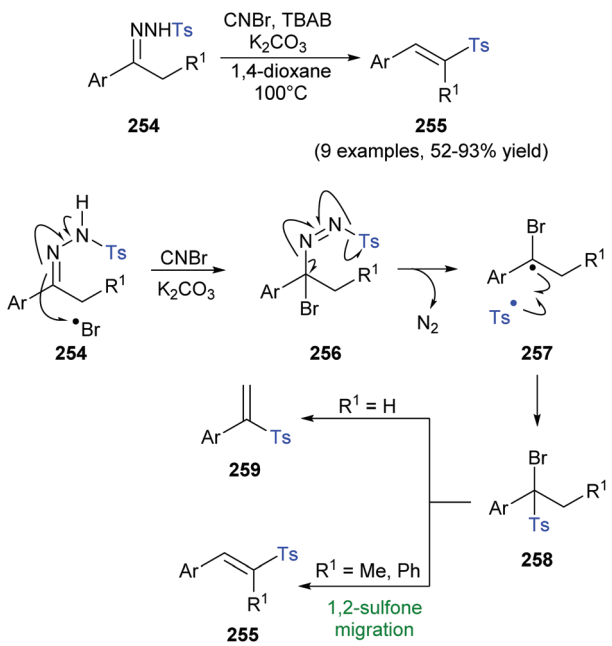


Scheme 36 Mechanism for the photochemical reactivity of *N*-arylsulfonimides under inert and aerated conditions.

N-arylsulfonamides **245** (FG = H) both desulfonylation to generate aniline **248** or thia-Fries rearrangement to give the *para*-substituted aniline **250** can occur.

2.2.3. Non-metal-catalysed radical-mediated sulfonyl migration of *N*-sulfonylhydrazones. In 2014, the Prabhu group reported the generation of (*E*)-vinyl sulfones **255** from the reaction of *N*-tosylhydrazones **254** with cyanogen bromide and TBAB; involving 1,2-tosyl migration for derivatives bearing a methyl or aryl substituent at R^1 (Scheme 37).[59] The reaction is thought to proceed *via* generation of a bromine radical from the reaction of CNBr–TBAB, which adds to **254** affording the bromo-azo-sulfone **256**, which releases dinitrogen and a tosyl radical to afford **257**. Recombination of the tosyl radical and **257** affords the isolable intermediate **258**, which undergoes either dehydrohalogenation to give the vinyl sulfone **259** when R^1 = H, or a 1,2-sulfone migration in addition to elimination of HBr to afford **255**. Crossover experiments were used to confirm an intermolecular tosyl migration.

Luo *et al.* described a $PhI(OAc)_2$-mediated stereoselective synthesis of (*E*)-vinyl sulfones **261** from aliphatic and aryl *N*-sulfonyl hydrazones **260** in moderate to high yields (Scheme 38).[60] Both electron-withdrawing and electron-donating aryl moieties at R^1 were well tolerated, while the methodology was further applied to a range of aromatic heterocyclic



Scheme 37 Generation of vinyl sulfones *via* the reaction of *N*-tosylhydrazones with CNBr and aliphatic quaternary ammonium salts; observation of an intermolecular tosyl migration.

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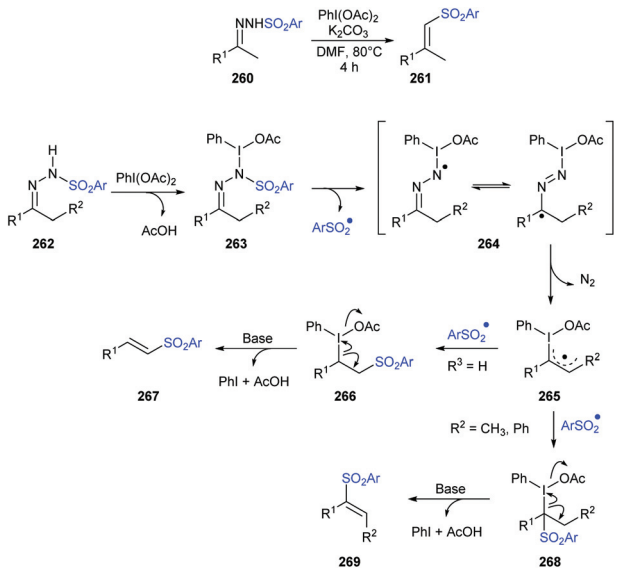
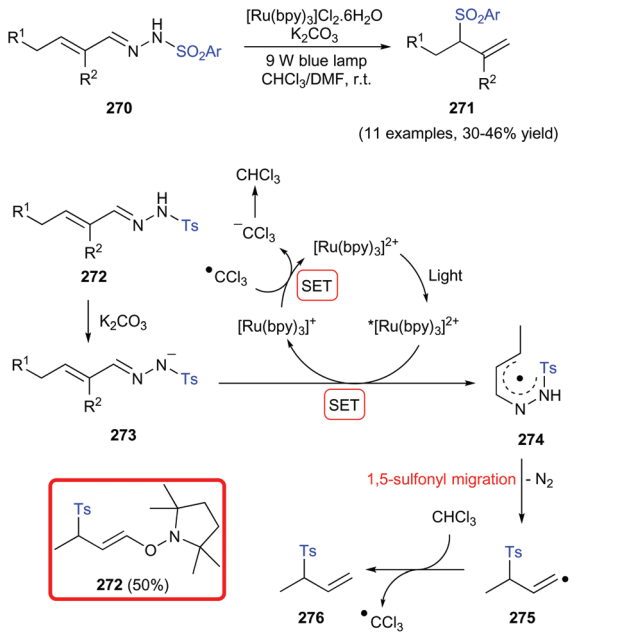


Scheme 38 $PhI(OAc)_2$-mediated synthesis of (*E*)-vinyl sulfones from aliphatic and aromatic *N*-sulfonyl hydrazones.



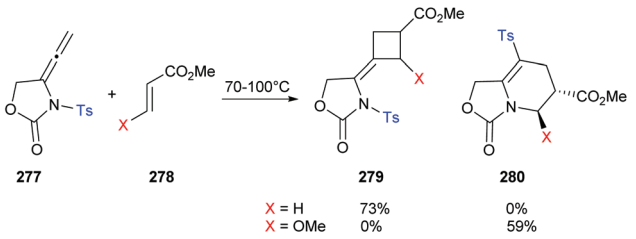
Scheme 39 Visible-light-mediated photocatalytic transformation of α,β-unsaturated *N*-sulfonylhydrazones to allylic sulfones.

derivatives. A radical mechanism was envisaged based on the inhibition of the reaction on the addition of the radical scavenger TEMPO. As such, the authors postulated that the hypervalent iodine intermediate **263** forms in the presence of $PhI(OAc)_2$, which undergoes homolytic N–S bond cleavage to afford a sulfonyl radical and **264**. Subsequent elimination of dinitrogen from **264** affords the radical intermediate **265**, which on recombination with the sulfonyl radical affords **268** (or **266** when R^2 = H). Base-mediated reductive elimination of **266**/**268** affords either the α- or β-substituted vinyl sulfones **267** or **269**.

Deagostino and co-workers described the first visible-light-mediated transformation of α,β-unsaturated-*N*-sulfonylhydrazones **270** to allylic sulfones **271** with optimal results achieved using $[Ru(bpy)_3]Cl_26H_2O$ as photocatalyst (Scheme 39).[61] Tosyl, mesyl, and triflyl moieties were well tolerated. Interestingly, on addition of TEMPO, to the standard reaction conditions, **272** was isolated confirming that the process involves a vinyl radical intermediate. A radical chain mechanism was excluded based on observation that no reaction occurs in the presence of AIBN, while the use of the more reactive benzoyl peroxide produced a complex mixture of products. In light of these results the authors postulated the following mechanism. Treatment of the *N*-tosylhydrazone **272** with base affords the anion **273**. Visible-light promotes the excitation of the photocatalyst, and it is the excited state $*[Ru(bpy)_3]^{2+}$ that induces the single electron oxidation of **273** to give the N-centered radical **274**. A formal 1,5-sulfonyl migration, suggested to occur *via* a 6-membered transition state, leads to the expulsion of dinitrogen and the formation of the vinyl tosylate radical **275**. Abstraction of a hydrogen atom from the solvent, as confirmed *via* deuterium incorporation studies using $CDCl_3$, generates the final product **276** and a CCl_3 radical that promotes the regeneration of the photocatalyst $[Ru(bpy)_3]^{2+}$.

2.3. Non-metal-catalysed sulfonyl migration

In 1997, the Tamaru group reported the thermal [2 + 2] cycloaddition of allenesulfonamides with electron deficient alkenes and alkynes to yield substituted cyclobutene derivatives, for example the reaction of **277** with methyl acrylate afforded the cyclobutane **279** in 73% yield (Scheme 40, X = H).[62] In an extension of this study, the authors were surprised to find that when the alkene substrate was an enol ether, such as methyl β-methoxyacrylate **278** (R = OMe), that a completely different pathway was operational, with the tetrahydropyridine **280** isolated as the major product and no evidence for the expected cyclobutane product (Scheme 40, R = OMe).[63] Notably, this pathway involved an unexpected 1,3-nitrogen to carbon sulfonyl migration, while enol ethers including acyclic and cyclic aldehyde enol ethers and acyclic and cyclic ketone–enol ethers all reacted similarly. Using this methodology highly functionalised tetrahydropyridines could be accessed in moderate to excellent yields (Scheme 41).[64]



Scheme 40 Novel addition–cyclisation reaction of 4-vinylidene-1,3-oxazolidin-2-ones and enol ethers; observation of a 1,3-sulfonyl migration.

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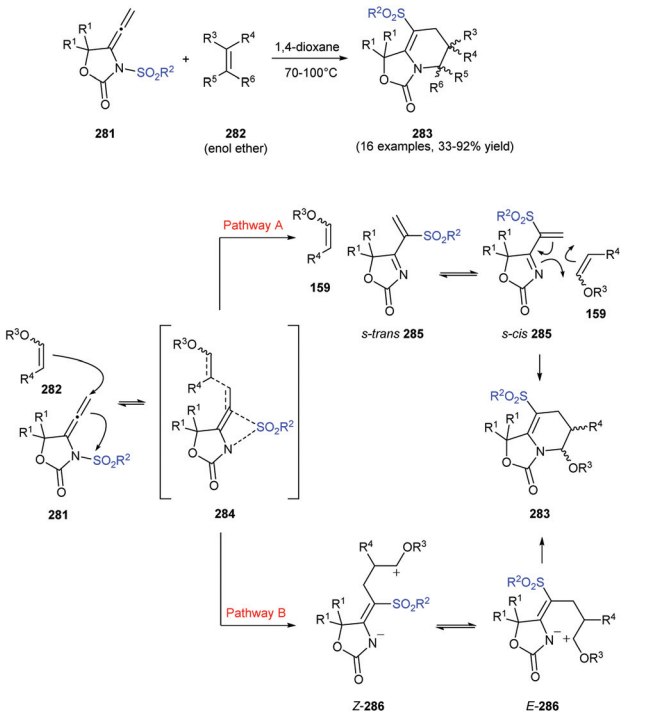


Scheme 41 Possible mechanistic pathways for the selective formation of tetrahydropyridines.

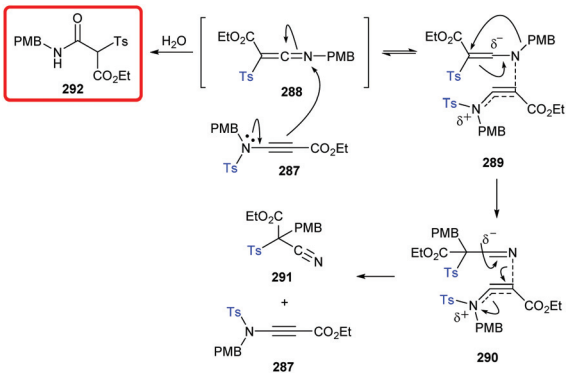
The reaction mechanism is believed to proceed through the transition state **284** in which the cumulative effect of the electron density of the C1′–C2′ alkene bond being pushed into the sulfonamide moiety and the electron density being drawn away from the carbamate through conjugation with the C4′–C1′ alkene bond significantly weakens the N–S bond, allowing for the 1,3-sulfonyl migration and the generation of s-*trans*-1-azabutadiene **285**. Subsequent isomerisation of the terminal double bond to s-*cis* **285**, allows for a facile hetero-Diels–Alder reaction with the enol ether **282** to afford the tetrahydropyridine product **283** (Scheme 41, path A). In certain instances the enol ether was observed to isomerise during the reaction with the allenesulfonamides **281** with both *E*- and *Z*-isomers recoverable; however, no isomerisation was observed in the absence of **281**. In contrast, the allenesulfonamide **281** readily isomerised to 3-tosyl-4-vinyl-4-oxazolin-2-one under thermal conditions *via* a 1,3-H shift in the absence of enol ether highlighting that allenesulfonamide **281** promotes the isomerisation of the enol ether, while the enol ether is crucial in promoting the 1,3-sulfonyl migration. For enol ethers that are highly electron-donating (*e.g.*, ketone enol ethers and furans) it is possible that pathway B could be operational to some extent due to being more able to stabilise the zwitterionic species **286**.

Subsequent studies by the group highlighted that allyl silanes and hydrosilanes react in an analogous manner, albeit with reduced efficiency, despite being much poorer nucleophiles than enol ethers.[65] Further extension to hetero-nucleophiles including alcohols and thiols afforded both 1,3-sulfonyl migration products in addition to significant amounts of non-sulfonyl migration products as a result of simple addition to the Cα=Cβ bond. Indoles were observed to undergo a similar reaction profile, however the addition occurs through the alkenyl carbon, rather than the nitrogen atom, akin to an electrophilic aromatic substitution.[64]

Wudl reported the first example of an uncatalysed 1,3-sulfonyl migration from a sulfonamide **287** to a keteneimine **288** under thermal conditions.[66] Notably, the rearrangement of the ynamide **287**, which proceeds cleanly either in the melt or in solution at 100–120 °C, involves the migration of both the tosyl group and the *p*-methoxybenzyl (PMB) group from the nitrogen atom to the same β-carbon, to afford the nitrile **291** in an isolated yield of 92%. Variable temperature ^{1}H NMR was readily used to follow the progress of the rearrangement in the non-aromatic solvent decalin. This demonstrated that the rearrangement occurs *via* the observable intermediate **289**, which also demonstrates that the 1,3-sulfonyl migration occurs first. The identity of the keteneimine intermediate **288** was further inferred as it hydrolysed readily on contact with water to afford the amide **292**, which was characterised by X-ray crystallography. Quantum mechanical calculations suggest that strong resonance stabilisation of the transition state facilitates the sulfonyl migration (Scheme 42). Both rearrangement processes were calculated to be thermodynamically favoured.

The Zhang group described the thermal aza-Claisen rearrangements of *N*-allyl ynamides **293** to allyl-keteneimine intermediate **295** *via* the aza-Claisen transition state **294**, with subsequent spontaneous 1,3-sulfonyl migrations affording quaternary nitriles **296** in moderate yields (7 examples, 45–64%) (Scheme 43).[67] The sulfonyl migration was not observed when R^2 = TIPS, with the generated silyl keteneimine **298** sufficiently stable to not undergo subsequent sulfonyl migration. Monitoring of the reaction progress by ^{1}H NMR did not reveal any of the allyl-keteneimine intermediate **295**, suggesting rapid sulfonyl migration at 110 °C.

The authors attempted to extend this methodology to ynamides of type **299** possessing a propargylic stereocenter, with the possibility to undergo a stereoselective 1,3-sulfonyl migration leading to either **302** or **302′** (Scheme 44). They



Scheme 42 1,3-Sulfonyl migration of a sulfonyl group from sulfonamide to keteneimine.

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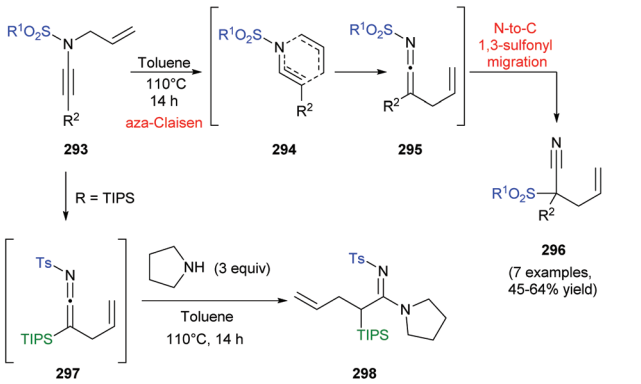
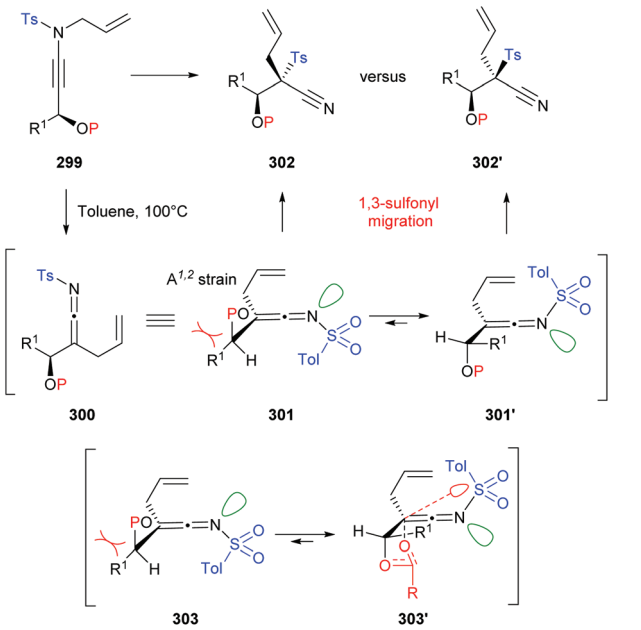


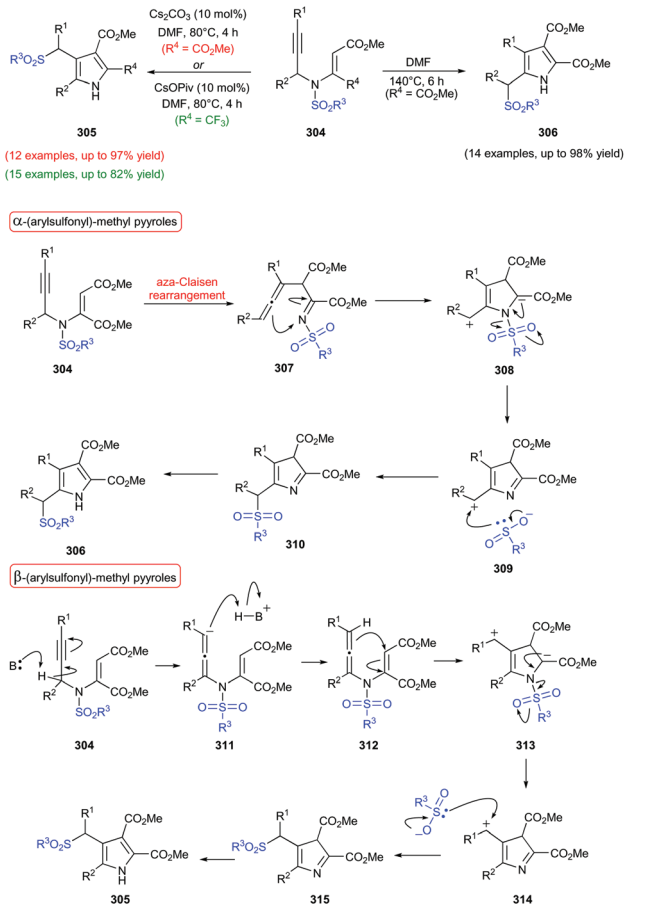
Scheme 43 Thermal aza-Claisen rearrangement of *N*-allyl ynamides and subsequent 1,3-sulfonyl migration.



Scheme 44 Attempted diastereoselective *N*-to-*C* 1,3-sulfonyl migration.

reasoned that the conformational preference of the allylketeneimine intermediate **301** or **301′** would dictate the level of selectivity, with the $A^{1,2}$-strain present in **301** potentially meaning that the conformer **301′** would be preferred. If so, this preference could result in facially selective 1,3-sulfonyl migration to give **302′**. They further hypothesised that suitable modification of the protecting group (P) could lead to the conformational preference shown for **303′** in which anchimeric assistance could also result in facially selective 1,3-sulfonyl migration. In the event, however, the highest diastereomer ratio achieved was 2 : 1.

The Wan group reported the highly regioselective sulfonyl group migration in the synthesis of functionalised pyrroles.[68] A significant feature of the work is that the regioselectivity of the sulfonyl migration can be tuned with high selectivity for



Scheme 45 1,3- and 1,4-sulfonyl migration in the generation of both α- and β-(arylsulfonyl)methyl pyrroles under thermal and basic conditions respectively.

the formation of both α- and β-(arylsulfonyl)methyl pyrroles **306** and **305** in excellent yields (Scheme 45). Under thermal conditions, the azaenyne derivative **304** is transformed into **307** *via* an aza-Claisen rearrangement. Due to the electron-withdrawing character of both the double bond and the sulfonyl group the nitrogen atom is rendered electrophilic, leading to ring closure to afford the zwitterionic intermediate **308** through nucleophilic attack of the allene moiety. Cleavage of the N–S bond leads to the ion pair **309**, which recombines to complete the 1,3-sulfonyl migration. The presence of the ion-pair **309**, and the intermolecular nature of the migration was confirmed by crossover experiments. Finally, isomerisation of **310** affords the α-(arylsulfonyl)-methyl pyrrole **306**.

In the presence of base, namely $CsCO_3$, β-(arylsulfonyl) methyl pyrroles **305** were the favoured rearrangement products indicative of an alternate mechanism for the transformation (Scheme 45). Under basic conditions the propargyl group of **304** is converted to the allene intermediate **312** *via* protonation of **311**. Subsequent ring closing affords the zwitterionic intermediate **313**, with the electrophilic carbocation instead γ- to the nitrogen atom. Akin to the thermal reaction an intermolecular sulfonyl migration was elucidated, hence elimin-

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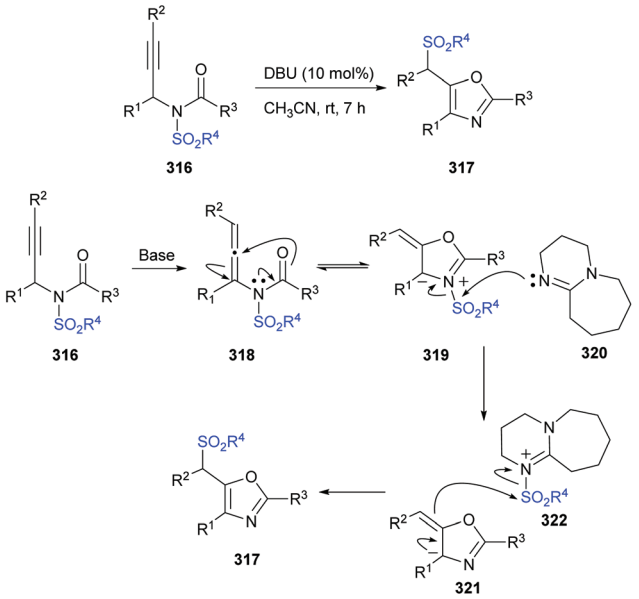
ation of the sulfonyl moiety gives the ion-pair **314**, which on recombination completes the 1,4-sulfonyl migration. Isomerisation of **315** affords the β-(arylsulfonyl)methyl pyrrole **305**. The group subsequently reported that this methodology could be extended to the synthesis of 2-trifluoromethyl-4-(arylsulfonyl)methyl pyrroles **305** (R^4 = CF_3), with crossover and competition experiments indicating the likelihood of the same mechanism, however, in this instance CsOPiv was the optimal base (Scheme 45).[29]

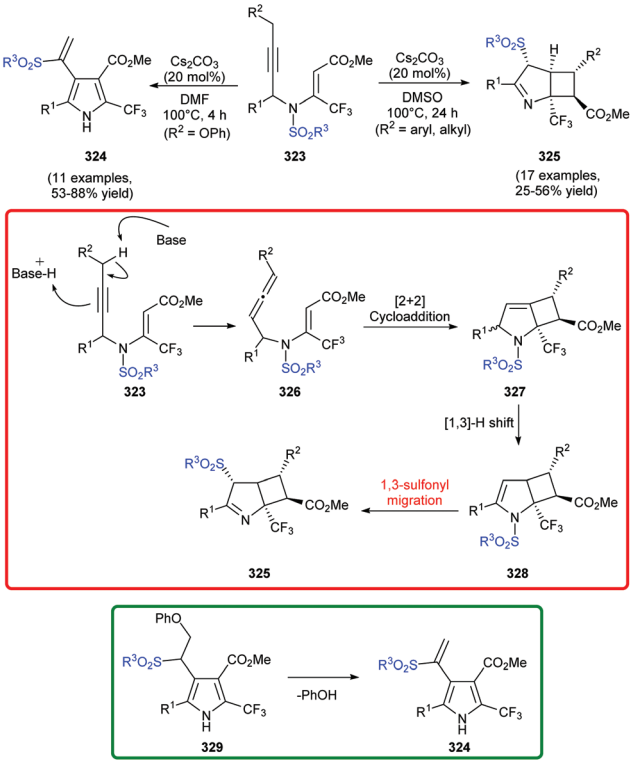
Using this precedent, the authors reasoned that the replacement of the alkenyl group with an acyl group could provide a route towards base-catalysed cycloisomerisation to access sulfonylmethyl-substituted oxazoles. With this in mind the authors reacted a series of *N*-sulfonyl propargylamides **316** in the presence of catalytic DBU affording various 5-(sulfonylmethyl)oxazoles **317** in up to 98% yield.[69] The allene intermediate **318** was determined to be a key intermediate in the mechanistic cycle, while monitoring of the conversion process by HPLC highlighted the presence of a further intermediate, that despite not being isolable, the authors reasoned was the zwitterionic species **319**. Key to the mechanistic cycle is a formal 1,4-sulfonyl migration which by means of crossover experiments was determined to be an intermolecular process. While not fully understood, the DBU is likely pertinent to facilitating the dissociation of the sulfonyl group (Scheme 46).

In a further extension to this methodology the group rationalised that incorporating an additional methylene group at the C-7 position of 3-aza-1,5-enynes could be utilised in complex heterocycle synthesis. Accordingly, a series of 2-azabicyclo[3.2.0]hept-2-enes **325** were synthesised *via* base-catalysed cycloisomerisation of the requisite substrates **323** in moderate yields (Scheme 47).[70] Similar to their previous studies, a 1,3-sulfonyl migration was observed. Consistent with the results of deuterium labelling experiments the following mechanism was formulated. Deprotonation of the less sterically hindered C-7 position (compared to the more acidic C-4 proton) generates the allene intermediate **326**. [2 + 2] Cycloaddition affords the bicyclic intermediate **327**, which undergoes sequential [1,3]-H shift and 1,3-sulfonyl migration to afford the desired 2-azabicyclo[3.2.0]hept-2-ene **325**. Interestingly, when the R^2 substituent in **323** is a phenoxy group the product formed is the vinyl-substituted pyrrole **324**, with 1,4-sulfonyl migration a crucial step (Scheme 47). The mechanism for this transformation is thought to be the same as the one presented for the synthesis of β-(arylsulfonyl)-methyl pyrroles **305** in Scheme 45. Once the pyrrole **329** is formed elimination of phenol affords the vinyl group in the product **324**.

The synthesis of tetrasubstituted imidazoles **333** *via* a two-step one-pot approach from the three-component reaction of propargyl amines **330**, sulfonyl azides **332** and alkynes **441** utilising 1,3-sulfonyl migration has been described (Scheme 48).[71] Initially, the keteneimine **334** is generated *in situ* by means of a copper catalysed azide–alkyne cycloaddition between the alkyne and tosyl azide. Nucleophilic addition of the propargyl amine **335** to the ketenimine **334** affords the intermediate **336**. In the second step, the allene **337** is generated through the deprotonation of the propargyl moiety, which subsequently undergoes a 6π-electron electrocyclic ring closure (6π-ECR) to give the zwitterionic structure



Scheme 46 DBU-catalysed cycloisomerisation of *N*-sulfonyl propylargylamides *via* 1,4-sulfonyl migration.



Scheme 47 Base-catalysed selective synthesis of 2-azabicyclo[3.2.0]hept-2-enes and sulfonyl vinyl-substituted pyrroles from 3-aza-1,5-enynes *via* 1,3- and 1,4-sulfonyl migrations respectively.

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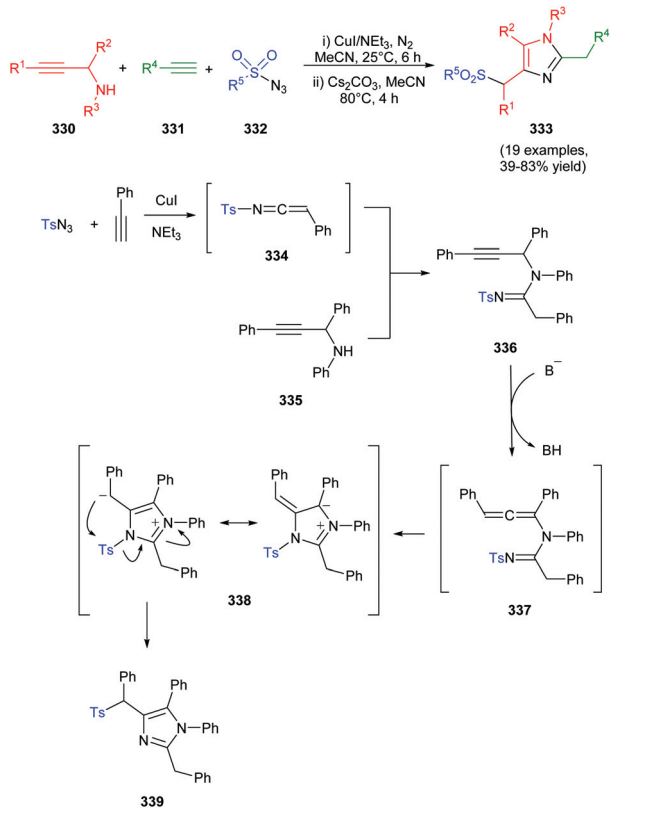
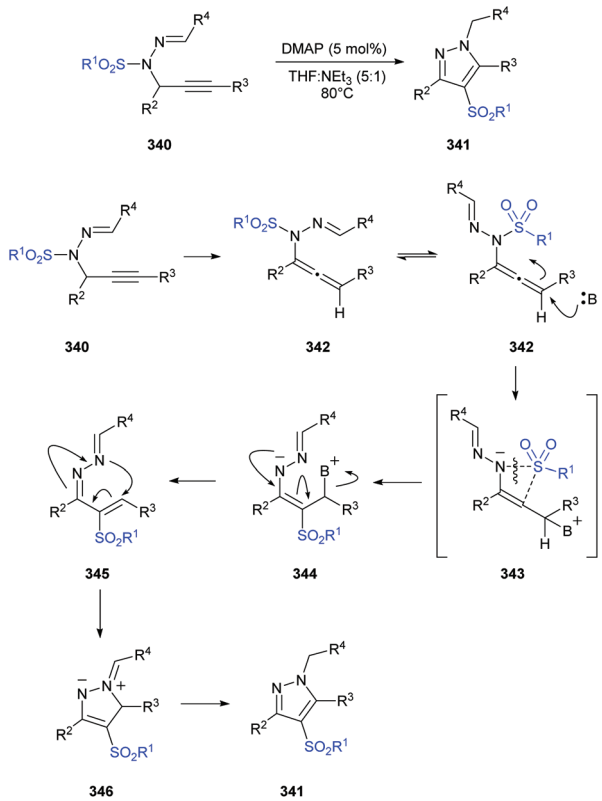


Scheme 48 One-pot synthesis of tetrasubstituted imidazoles utilising intramolecular 1,3-sulfonyl migration.



Scheme 49 Lewis base catalysed synthesis of 4-sulfonyl-1*H*-pyrazoles involving 1,3-sulfonyl migration.

338. Finally, an intramolecular 1,3-sulfonyl migration completes the process affording the imidazole product **339**. Crossover experiments supported the intramolecular nature of the sulfonyl migration.

Following the Zhan group's seminal report regarding the reactivity of *N*-propargylic sulfonylhydrazones in the presence of copper catalysts, they further demonstrated that compounds of this type could undergo Lewis base catalysed reaction to give 4-sulfonyl-1*H*-pyrazoles **341** in moderate to good yields, with allenic sulfonamide formation and 1,3-sulfonyl migration key steps in the transformation (Scheme 49).[72] DMAP in a mixed solvent system of tetrahydrofuran and triethylamine at 80 °C proved to be the optimal conditions for the transformation with yields up to 92% achieved. As per their initial optimisation study, the allenic sulfonamide **342** was formed exclusively at room temperature in 0.5 h indicating that it is likely a key intermediate in the cascade process. This was confirmed by reacting the allenic sulfonamide **342** under the optimised conditions with the pyrazole **341** formed in 97% yield. Notably, in the absence of DMAP no reaction occurred at room temperature indicating that both the allenamide formation and cyclisation reactions are catalysed by DMAP.

Considering this the authors proposed the following mechanism (Scheme 49). The propargylic amide moiety of **340** is transformed into the allenic sulfonamide intermediate **342** in the presence of DMAP. Nucleophilic addition of the Lewis base to the sp^2 terminus of the allene moves electron density towards the sulfonamide moiety to give the transition state **343**, leading to the breakage of the N–S bond forming **344**, completing an intramolecular 1,3-sufonyl migration as supported by crossover experiments. Elimination of the Lewis base affords the α,β-unsaturated imine **345** which undergoes intramolecular 1,4-addition to form the zwitterionic species **346**. Finally, 1,3-hydride shift and electron transfer occur to give the rearranged pyrazole **341**.

The base-mediated decomposition of a series of bicyclic amide-substituted furfuryl tosylhydrazones **347** was observed to lead to formal nitrogen to carbon 1,5-sulfonyl migration affording sulfone derivatives **348** with the furan ring remaining intact (Scheme 50).[73] Competition experiments suggested that the sulfonyl migration most likely proceeds in an intermolecular manner. The authors postulated that the mechanism proceeds *via* the base-mediated generation of the anion **349** which decomposes to the diazo compound **350** with concomitant extrusion of the tosyl group. Loss of nitrogen from the diazo moiety affords the electrophilic carbene **351**, which mediates ring opening of the furan ring to generate the enynyl-ketoamide **352**. Regioselective nucleophilic addition of the tosyl group to the α,β-unsaturated system of **352** regenerates the furan ring giving **353** which is converted to the final rearranged product **348** following protonation and aromatisation.

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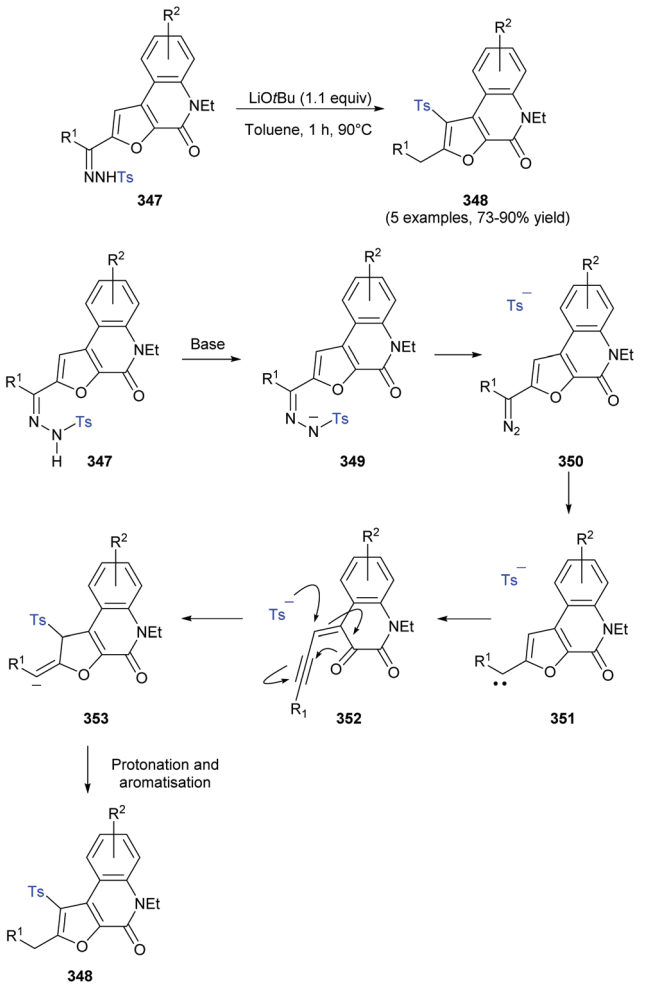
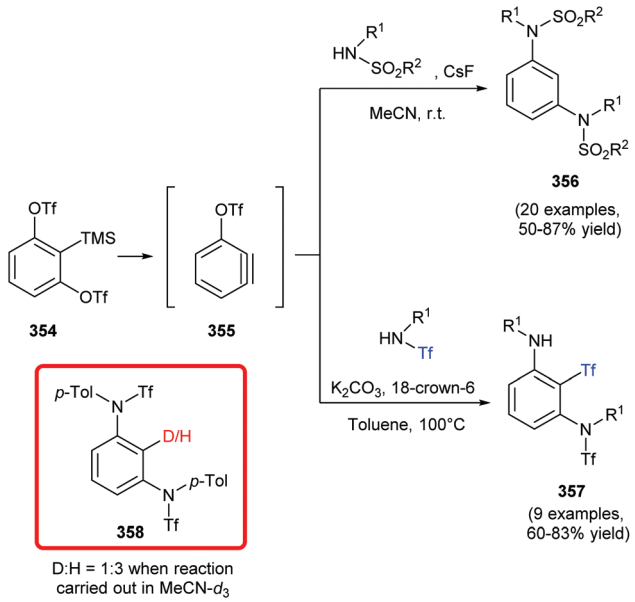
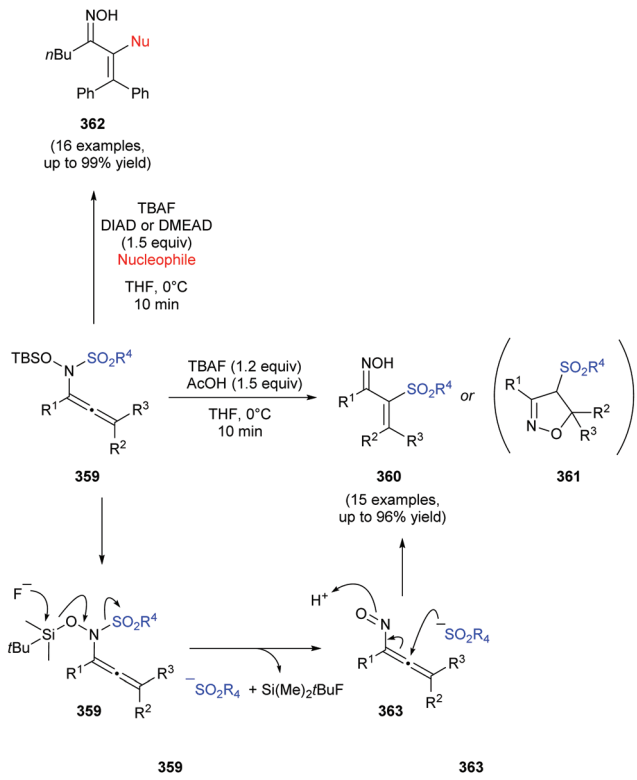


Scheme 50 Observation of a 1,5-nitrogen to carbon tosyl migration to afford sulfone derivatives from furfuryl tosylhydrazones.



Scheme 51 1,3-Sulfonyl migration *via* aryne precursors.



Scheme 52 Synthesis of α-substituted enoximes *via* fluoride mediated deprotection of nitrosoallenes.

Li reported the diamination of the domino aryne precursor **354**[74,75] with sulfonamides, affording 1,3-diaminobenzenes **356** in moderate to good yields (Scheme 51).[76] Interestingly, in their investigation to ascertain the origin of the proton at the 2-position, a deuterium-labeling experiment in MeCN-d_6 indicated that the proton comes from both the solvent and the N–H bond of the amine starting material (25% deuterium incorporation, compound **358**). The authors therefore rationalised that this methodology could be further applied to the synthesis of 1,2,3-trisubstituted benzenes **357** by capturing an electrophile rather than a proton. Indeed, by carrying out the reaction in the inert solvent toluene, and in the presence of K_2CO_3 and 18-crown-6 as activating agents, a formal 1,3 nitrogen to carbon sulfonyl migration of the triflyl group readily occurred in good yields. Extension of the methodology to the migration of a tosyl group proved unsuccessful.

Kakiuchi's team developed a synthesis of α-functionalised enoximes **360** *via* nitrosoallenes **363**,[77] a group of compounds pioneered by the group,[78,79] through a fluoride-mediated deprotection of the silyl moiety and tandem elimination of sulfinate from *N*-sulfonyl hydroxylamines **359** (Scheme 52). Recombination of the sulfinate with the electrophilic moiety of the allene **363**, completes a formal intermolecular 1,3-sulfonyl migration, with subsequent *O*-protonation affording α-sulfonyl enoximes **360** in high yields. In some instances, where all substituents on the allenylamides **359** were aryl groups,

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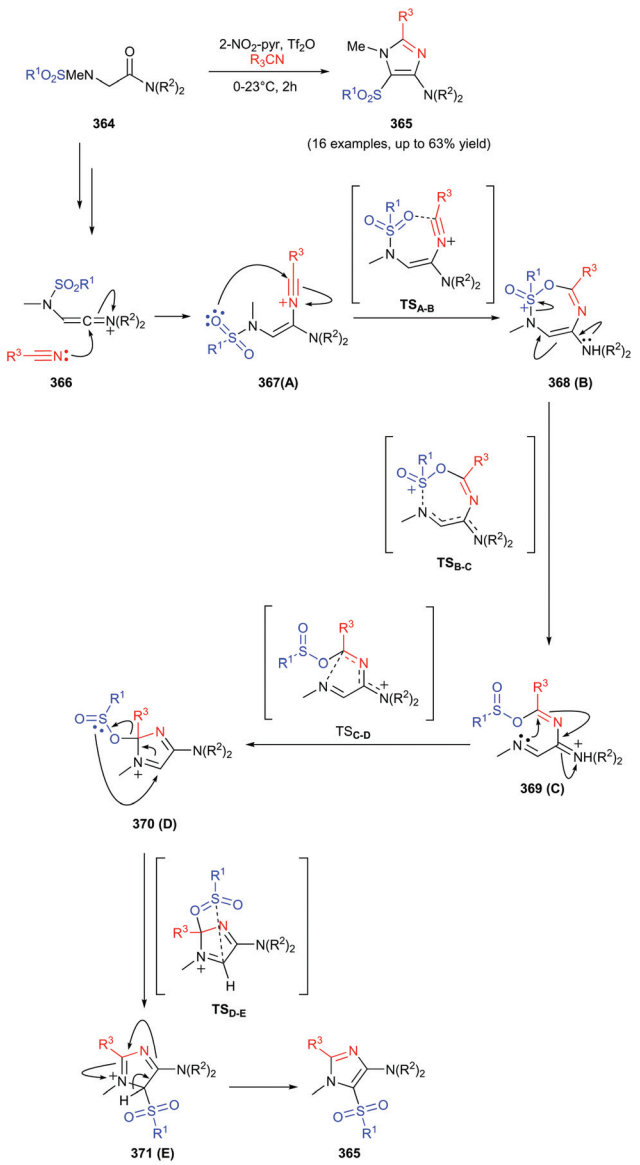
2-isoxazolines **361** were afforded as major products derived from the cyclocondensation of the initially fomed vinylsulfones **360**. The group further established that by adding an azodicarboxylate as a sulfinate scavenger that the protocol could be extended to allow functionalisation of the α-position by various nucleophiles in moderate to excellent yields (compounds **362**).

The utility of triflic anhydride-mediated amide activation of a series of α-aminoamides **364** to generate tetrasubstituted imidazoles **365** in moderate yields was demonstrated to proceed *via* a mechanistically intriguing [2,3]-sigmatropic rearrangement of a sulfinate intermediate, promoting a formal 1,2-sulfonyl migration from nitrogen to carbon (Scheme 53).[80] Quantum-chemical calculations were used to rationalise the overall mechanistic transformation. Initially, triflic anhydride activation of the α-aminoamide **364** and subsequent nucleophilic addition of acetonitrile to the keteneiminium ion **366** affords intermediate **367**. A 7-*endo-dig* cyclisation of **367** *via* nucleophilic attack of the sulfonamide oxygen onto the nitrilium moiety gives the intermediate **368**. Cleavage of the N–S bond ensues giving the sulfinate **369** which subsequently cyclises to **370** which then undergoes a [2,3]-sigmatropic rearrangement, reminiscent of a retro-Mislow–Evans-type rearrangement,[81] to complete the formal 1,2-sulfonyl migration to give **371**. Deprotonation of intermediate **371** affords the final rearranged imidazole **365** through aromatisation. While the computational analysis indicated that the 7-*endo-dig* cyclisation is endergonic (ΔG_{A-B} = +14 kcal mol^{-1}), the subsequent cleavage of the N–S bond (ΔG_{B-C} = −25.8 kcal mol^{-1}) and the [2,3]-sigmatropic rearrangement (ΔG_{D-E} = −21.4 kcal mol^{-1}) provides significant thermodynamic stabilisation.



Scheme 53 Generation of tetrasubstituted 5-aminoimidazoles *via* formal 1,2-sulfonyl migration.

The Bharatam group reported a mechanistically interesting 1,3-sulfonyl migration from nitrogen to carbon within the pyrrole framework, the first example of such a rearrangement for this heterocycle class. They demonstrated that *N*-sulfonyl-2-arylpyrroles **373** undergo a 1,3-sulfonyl migration in pivalic acid to afford 2-aryl-3-sulfonylpyrroles **374** in moderate to excellent yields.[82] They further realised that this sulfonyl migration could be incorporated into a one-pot tandem palladium-catalysed oxidative arylation of the 2-position of *N*-sulfonylpyrroles **372**, followed by regioselective sulfonyl migration (Scheme 54).

While further clarity is required, the authors tentatively proposed an operative intramolecular nucleophilic displacement pathway based on a series of experimental observations and computational results. An intermolecular process was deemed unlikely based on crossover experiments. The addition of CsF, benzylsulfonate or benzenesulfonyl chloride to the *N*-sulfonylpyrroles **375**, **376** and **377** afforded neither **381** or **382**, which would be expected if an intimate ion-pair mechanism were operational. The sulfonyl migration occurs readily in the presence of TEMPO, suggesting that the reaction does not involve the formation of a free-radical. Interestingly, when *N*-tosylpyrroles **383–385** (*i.e.* unsubstituted, 2-substituted or 2,5-disubstituted without an aryl substituent) were heated under the optimised conditions no reaction was observed. Notably, the reaction was found to be completely inhibited in the absence of an aryl group at the 2-position, while blockage of the *ortho*-position of the aryl ring, as seen for the reaction of *N*-tosyl-2-pentafluorophenylpyrrole **389**, had the same effect. Deuterium incorporation studies indicated that C–H bond breaking was unlikely to be involved in the sulfonyl migration, but that an aryl group at the 2-position is crucial for the migration to occur, which suggests an intramolecular C-2 aryl group assisted sulfonyl migration is operational for this transformation.

Javorskis and Orentas described the chemoselective deprotection of neutral and electron-deficient sulfonamides **391** under acidic conditions using trifluoromethanesulfonic acid (Scheme 55A).[83] Interestingly, when this deprotection strategy

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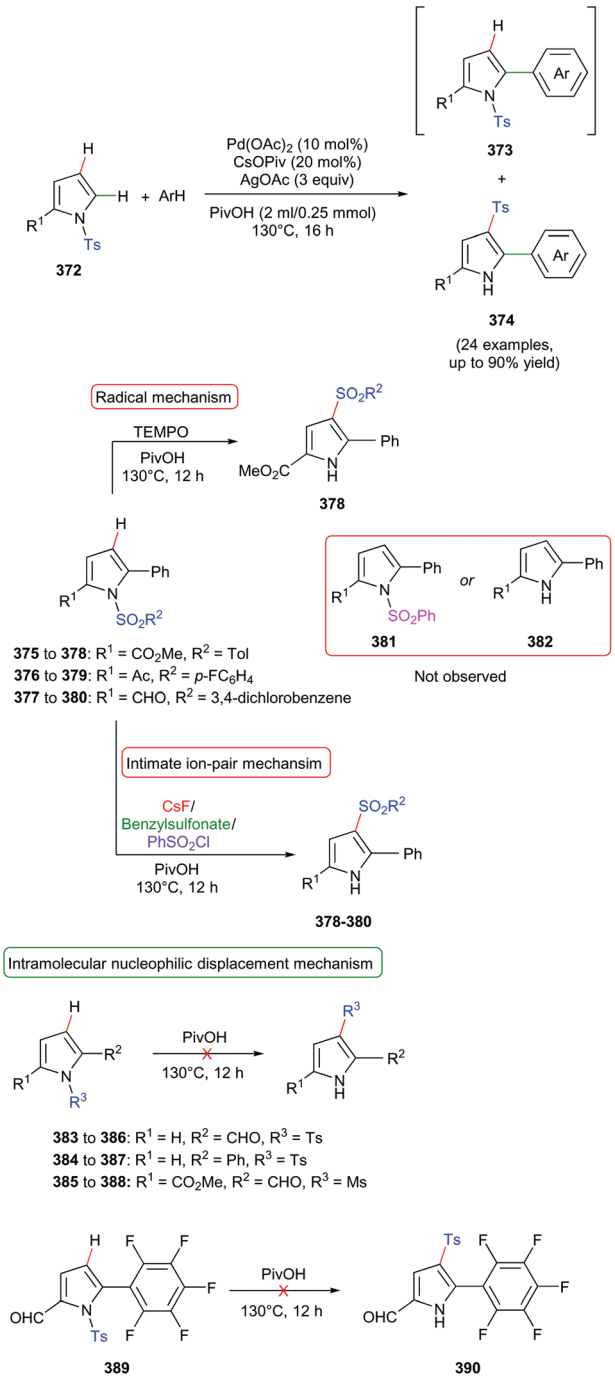
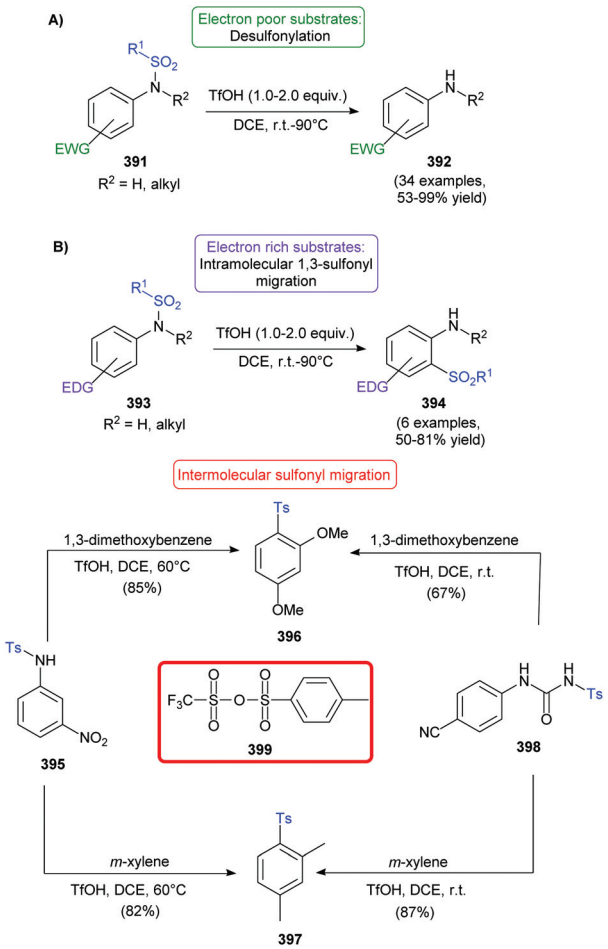


Scheme 54 One-pot tandem oxidative arylation and sulfonyl migration of pyrroles; mechanistic studies supporting an intramolecular nucleophilic displacement mechanism.

was applied to electron-rich *N*-arylsulfonamides **393** a completely different reaction profile was observed, with a 1,3-sulfonyl migration preferred (Scheme 55B). Notably, mesyl, tosyl and nosyl substituents were well tolerated. An independent crossover experiment confirmed that this sulfonyl migration is most likely an intramolecular process. On the basis of the mechanism proposed for the hydrolysis of neutral and electron-deficient *N*-arylsulfonamides, which involves the formation of



Scheme 55 Chemoselective deprotection of sulfonamides under acidic conditions; observation of a 1,3-sulfonyl migration.

the mixed anhydride **399** as a side-product, the authors hypothesised that the high reactivity of the mixed anhydride **399** may facilitate an intermolecular sulfonyl group migration. Verification of this assumption was achieved *via* deprotection of the electron-deficient aniline **395** in the presence of electron-rich arenes, 1,3-dimethoxybenzene and *m*-xylene, which afforded the sulfones **396** and **397** respectively through a Friedel–Crafts sulfonylation. In subsequent optimisation studies the *N*-sulfonylated urea **398** was determined to undergo desulfonylation much more readily, allowing access to the mixed anhydride **399** under more facile conditions.

The Hoye group reported the generation of tetrahydroquinolines **402** from hexadehydro-Diels–Alder substrates **400** through a cascade cyclisation and sulfonyl migration.[84] For substrates **400** bearing a trimethylene linker between the alkyne and sulfonamide a newly fused piperidine ring is generated, with a formal 1,3-sulfonyl migration of a tosyl group also observed (6 examples, 83–92% yield) (Scheme 56). Variation of the sulfonyl group in certain instances led to suppression of the sulfonyl migration (Scheme 57). For mesyl substituted substrates **400**, the desulfonylated tetrahydroquinolines **406** were generated, through elimination of sulfene from the zwitter-

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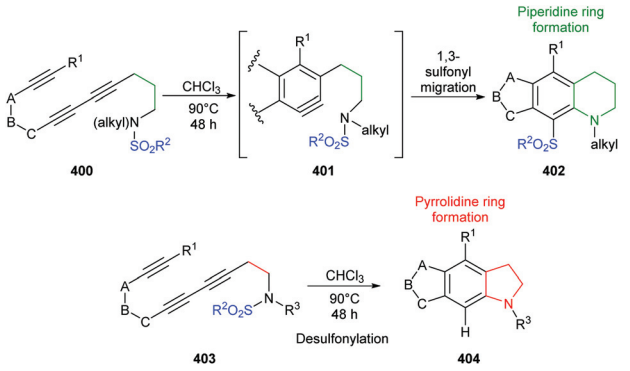
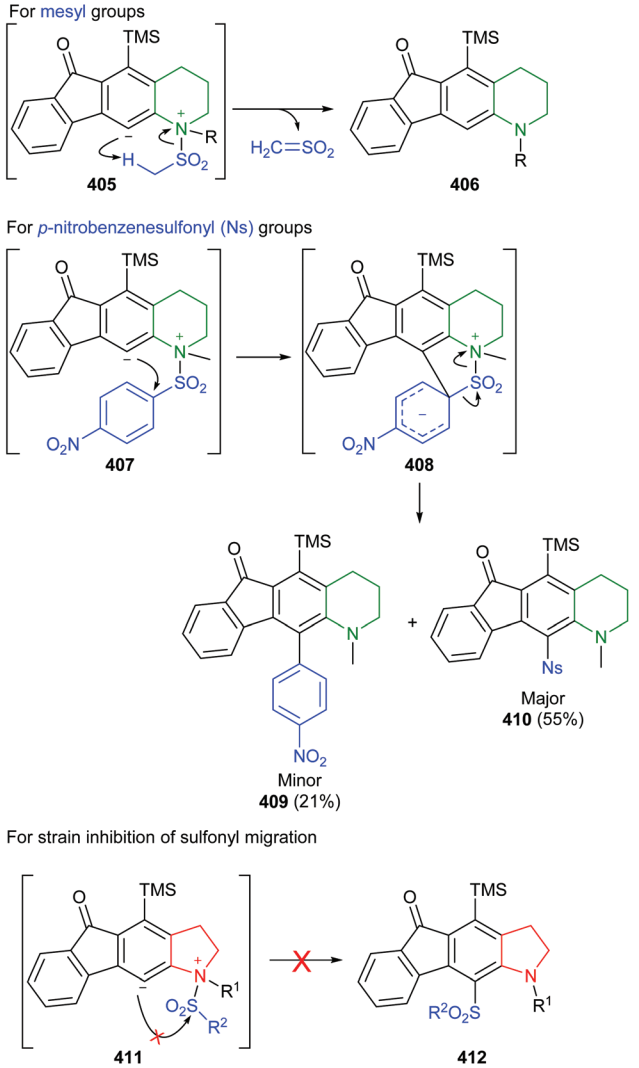


Scheme 56 Synthesis of tetrahydroquinolines and indolines accompanied by 1,3-sulfonyl migration or desulfonylation *via* sulfonamide-trapping reactions of thermally generated benzynes.

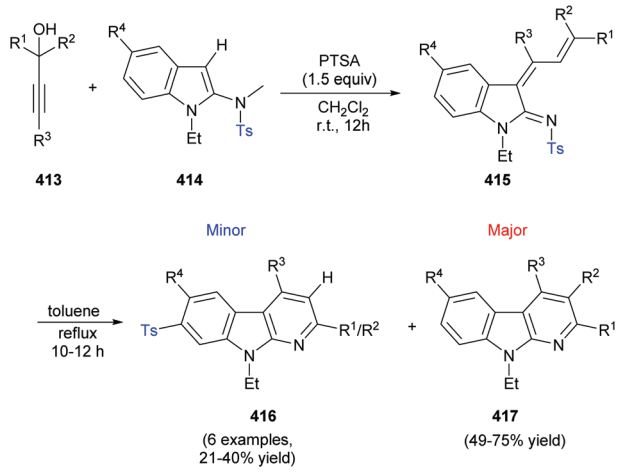


Scheme 57 Mechanistic rationales for desulfonylation of mesyl groups, migration of *p*-nitrobenzene from nosyl group and inhibition of sulfonyl migration for indoline derivatives.

ionic intermediate **405**. Substitution with a nosyl group afforded the expected rearrangement product **410** as the major product, but its formation was accompanied by the generation of the *p*-nitrophenyl-substituted biaryl compound **409** in which sulfur dioxide has been eliminated. This variant of the Truce–Smiles rearrangement[85] is thought to take place *via ipso*-attack *para* to the nitro group in **407**. The zwitterionic intermediate **408** loses SO_2 to form **409**. Interestingly, incorporation of the shorter dimethylene tether between the diyne moiety and the sulfonamide of **403** afforded exclusively desulfonylated indolines **404** regardless of the sulfonyl moiety (mesyl and tosyl both studied) (Scheme 55). This was attributed to the increased strain in the transition state that would lead to the 5-membered zwitterion **411**, and hence the product **412** was not formed (Scheme 57).

Selvaraj and Swamy reported the generation of 6-sulfonyl substituted α-carbolines **416** *via* a Brønsted acid-mediated reaction of 2-sulfonamidoindolines **414** and propargylic alcohols **413**, *via* a formal 1,6-tosyl migration (Scheme 58).[86] Despite the moderate yields achieved (21–40%), and the selective formation of α-carbolines **417** *via* competing 1,2-aryl migration, this was the first example of the direct introduction of a sulfonyl moiety to the C-6 position of the indole framework in the absence of a metal catalyst. A crossover experiment between the conjugated sulfonamidoindoline **415** (R^1, R^2 = Tol; R^3 = Ph, R^4 = H) and sodium benzenesulfinate did not lead to the incorporation of the sulfonyl moiety at the C-6 position of the indole system, while the migration product was acquired when **415** was heated to reflux in the presence of *p*-toluenesulfonic acid. Considering this, the authors suggested that the incorporated tosyl moiety has exclusively migrated from the indole framework.

In light of these observations the authors proposed the following mechanism to account for the observed tosyl migration (Scheme 59). The allenic carbocation **418** is formed *via* Brønsted acid-mediated Meyer–Schuster rearrangement of **413**, which undergoes a Friedel–Crafts reaction with the indoline



Scheme 58 Regioselective tosyl group migration from indole 2- to 6-position.

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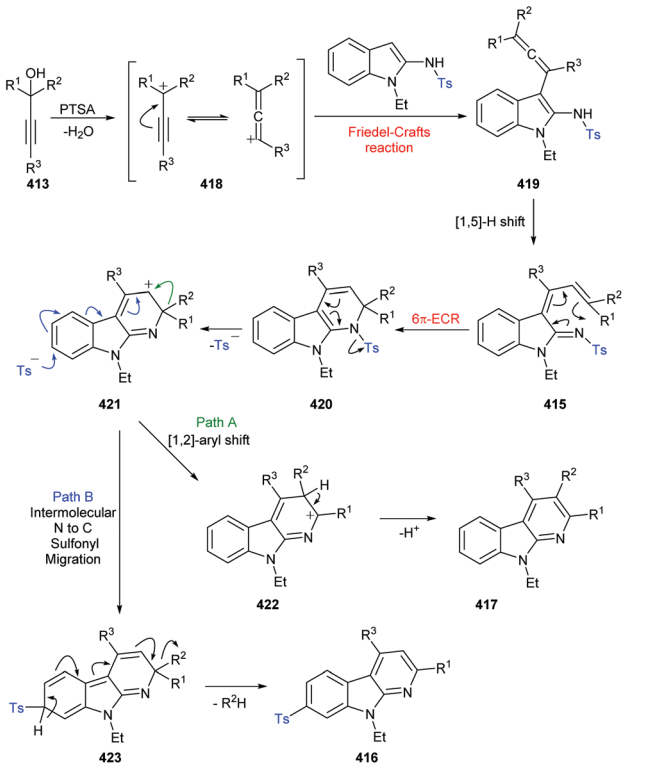
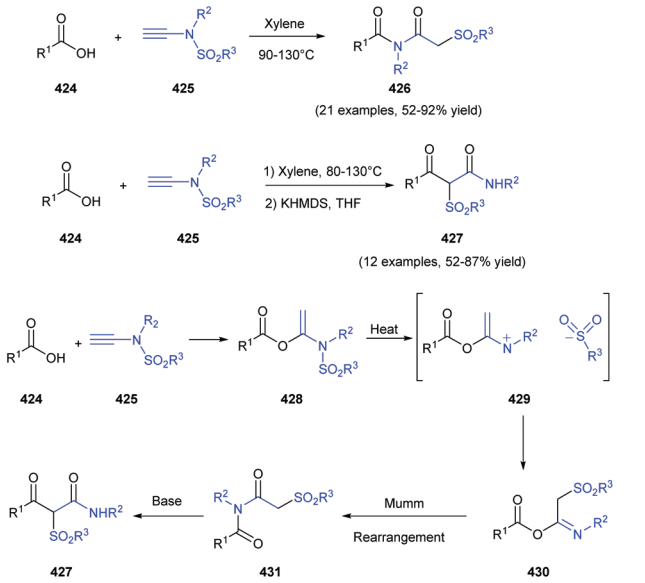


Scheme 59 Formation of α-carbolines from the reaction of propargyl alcohols and sulfonamido-indoles; observation of an unexpected 1,6-tosyl migration.

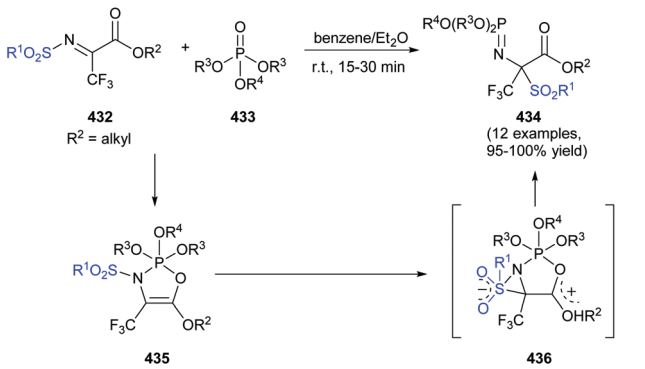
414 to afford the conjugated intermediate **419**. Subsequent [1,5]-hydride shift affords the tosylimine **415**, which was isolable. A 6π-electrocyclic ring closure, followed by elimination of the tosylate anion gives the carbocation **421** which can undergo two divergent pathways. Firstly, and preferentially, a [1,2]-aryl shift affords **422** which upon aromatisation gives the major α-carboline product **417**. Alternatively, regioselective addition of the tosylate to the C-6 position of the indole affords **423**, with subsequent elimination of an aryl group affording the aromatised product **416**.

Shen *et al.* reported the coupling of carboxylic acids **424** and ynamides **425** to form α-acyloxyenamides **428**, with subsequent 1,3-sulfonyl migration and Mumm rearrangement observed at high temperatures leading to imides **426** in moderate to excellent yields (Scheme 60A).[87] In the presence of base, the functionalised imides undergo additional rearrangement to give β-keto amides **427** in moderate to good yields in a one-pot process (Scheme 60B). Crossover experiments demonstrated that the thermally induced 1,3-sulfonyl migration of the α-acyloxyenamide **428** involves cleavage of the N–S bond, generating an ion pair **429** that undergoes intermolecular rearrangement to afford the intermediate **430** (Scheme 60).

Sulfonyl-substituted trifluoroalanine derivatives **434** can be accessed in almost quantitative yields *via* nitrogen to carbon 1,2-sulfonyl migration from the reaction of vicinal sulfonyliminocarboxylates **432** and phosphites **433** (Scheme 61).[88]



Scheme 60 Coupling of carboxylic acids with ynamides to afford imides and amides *via* sulfonyl migration and subsequent rearrangement.



Scheme 61 Access to sulfonyl-substituted trifluroalanine derivatives *via* 1,4-cycloaddition and 1,2-sulfonyl migration.

Monitoring the progress of the reaction by ^{31}P and ^{19}F NMR spectroscopy revealed the presence of two pentacoordinate phosphorus intermediates which were transformed over time to the iminophosphorane **434**. Based on the NMR data the authors assigned the intermediate stereoisomeric phosphorane **435**, generated through the 1,4-cycloaddition of **432** and **433**. Accordingly, it was proposed that the transformation from the intermediate **435** to **434** involves intramolecular nucleophilic attack of the sp^2-hybridised carbon on the sulfonyl moiety, which is favoured by the cumulative effect of the alkoxy and phosphoryloxy substituents, which on subsequent breakdown completes a formal 1,2-sulfonyl migration. Replacement of the ester moiety by a trifluoromethyl group completely inhibits the reaction, supporting the likelihood of intermediate **435** being generated *via* cycloaddition.

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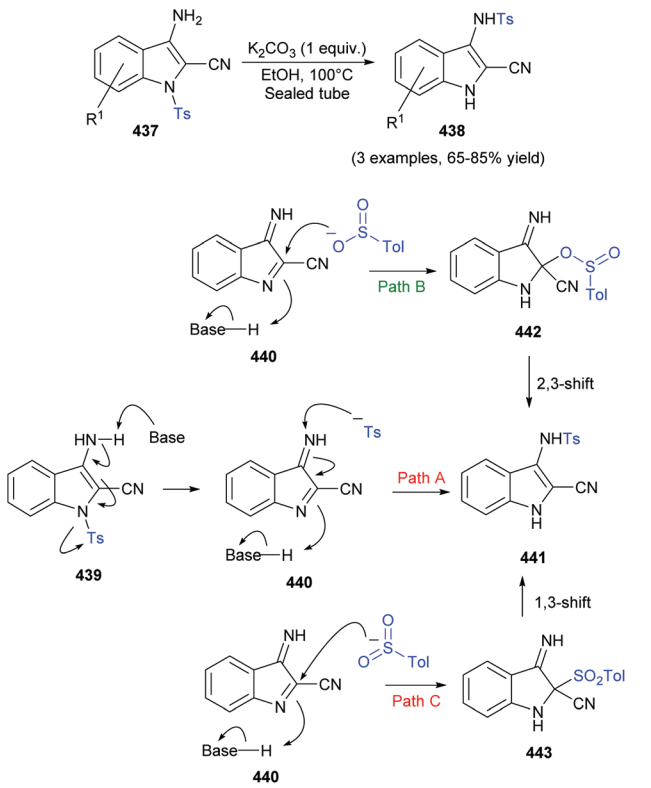
3. Nitrogen to nitrogen sulfonyl migration

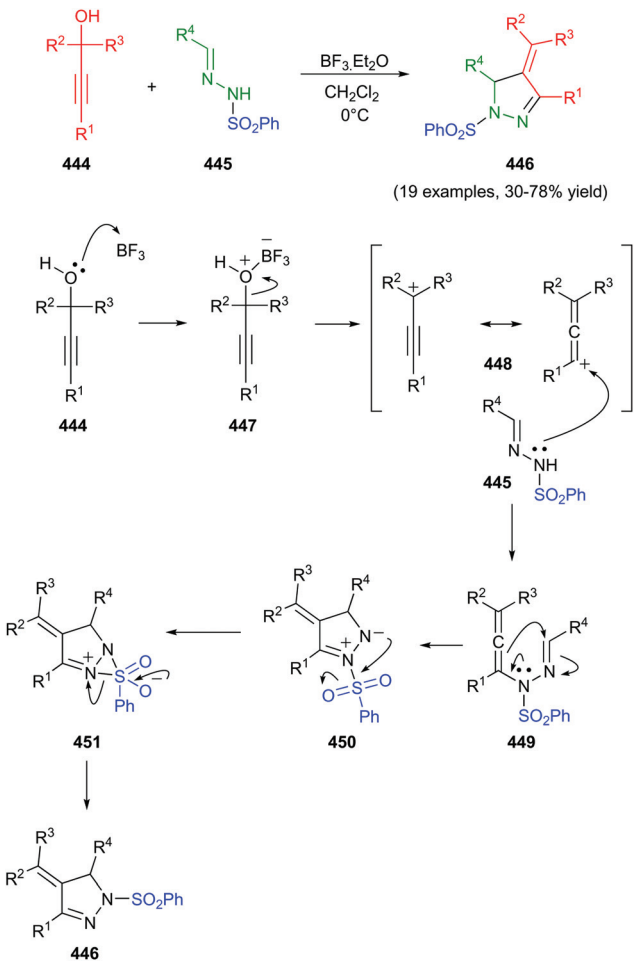
Michaelidou and Koutentis observed a surprising 1,4-nitrogen to nitrogen tosyl migration in their attempts to detosylate the indoles **437** under basic conditions; 3-(*N*-tosylamino)indoles **438** were isolated in moderate to good yields (Scheme 62).[89] While several mechanistic pathways can be considered to explain the transformation, the authors favoured path B, in which base-catalysed elimination of tosylate affords the imine **440** (Scheme 62). Their preference was for the ambidentate tosylate to directly add to the indolimine at the C-2 position through the oxygen atom to afford the sulfinate ester **442**. Subsequent isomerisation *via* either a concerted 2,3-sigmatropic rearrangement or a stepwise ion pair process affords the desired product, completing the formal 1,4-nitrogen to nitrogen tosyl migration. This proposed pathway was preferred as path C would involve a less favourable four-membered transition state to complete the 1,3-sulfonyl migration, compared to the five-membered analogue required for path B, while intermediate **442** would also be less sterically crowded than **443** at the C-2 indole position (Scheme 62). The direct addition of tosylate to the indolimine **440** (path A) was disfavoured due to electrophilicity of the nitrogen atom being offset by the conflicting local dipole and lone pair repulsion centered at that atom.



Scheme 62 Base-mediated 1,4-nitrogen to nitrogen tosyl migration of 3-amino-1-tosylindole-2-carbonitriles.

The Lewis acid mediated tandem reaction of propargyl alcohols **444** and *N*-sulfonylhydrazones **445** to afford dihydropyrazoles **446** in moderate to good yields *via* a nitrogen to nitrogen 1,2-sulfonyl migration was reported by Wang and co-workers (Scheme 63).[90] Lewis acid mediated conversion of the tertiary alcohol **444** to the allenic carbocation **448** occurs by Meyer–Schuster rearrangement.[91] The allenic carbocation **448** is trapped by *N*-sulfonylhydrazone **445** to afford the *N*-sulfonylallenamide **449**. Cyclisation *via* nucleophilic addition of the internal carbon of the allene to the electron-deficient carbon of the hydrazone can be envisaged to construct the cyclised intermediate **450**. The sequence is completed by intramolecular 1,2-sulfonyl migration to afford the dihydropyrazole **446** *via* **451**. The intramolecular nature of the sulfonyl migration was confirmed by the addition of sodium *p*-toluene sulfinate to the standard reaction conditions, with no incorporation of the tosyl group observed.

In 2013, the Dong group reported the regioselective synthesis of polysubstituted 4-amino- and 6-amino-2-iminopyridines **452** *via* copper-catalysed three-component reaction of sulfonyl azides, alkynes, and 2-[(amino)methylene]malono-



Scheme 63 Formation of dihydropyrazoles from the Lewis acid-catalysed tandem reaction of *N*-sulfonyl hydrazones and propargyl alcohols *via* intramolecular 1,2-nitrogen to nitrogen sulfonyl migration.

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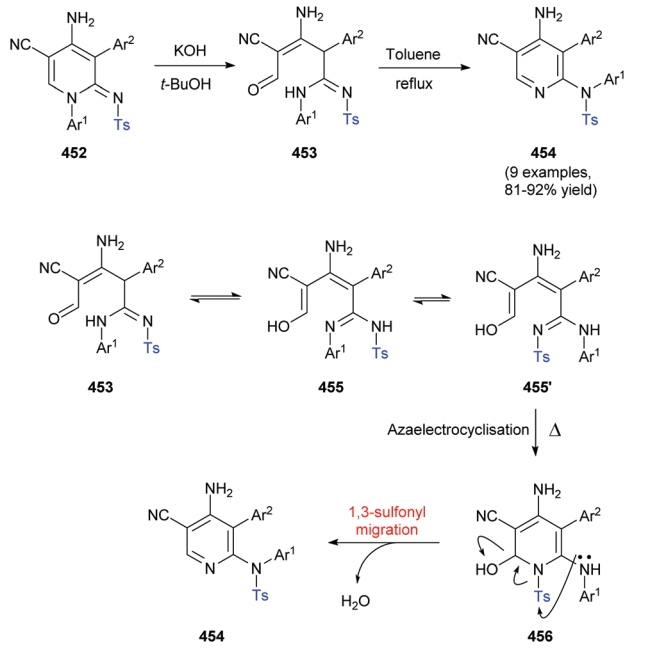
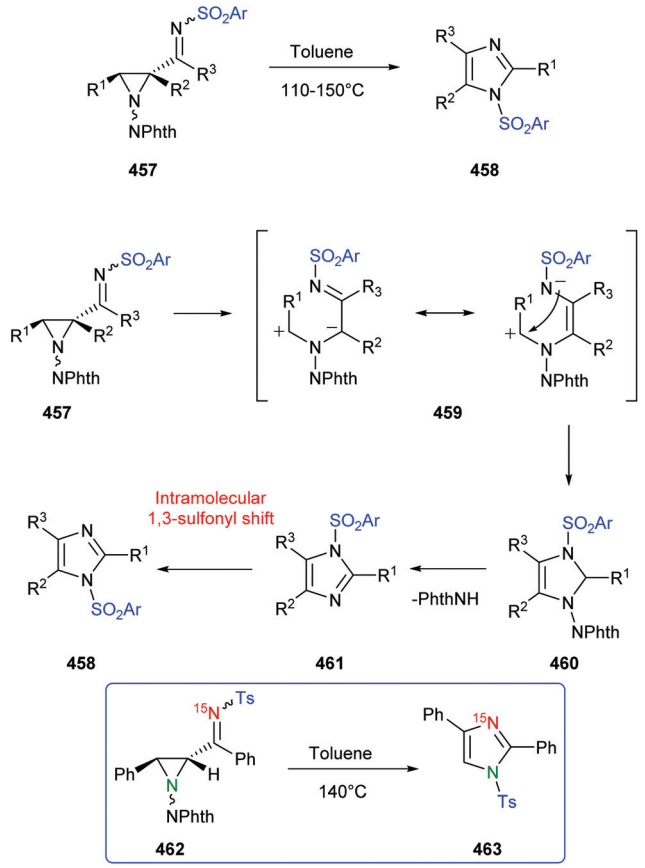


Scheme 64 Thermal rearrangement of 5-oxo-pent-3-enimidamides to 4-aminopyridines *via* 1,3-nitrogen-to-nitrogen sulfonyl migration.



Scheme 65 Thermal ring expansion of 2-sulfonylimidoyl-1-phthalimidoaziridines into *N*-sulfonylimidazoles involving 1,3-nitrogen to nitrogen sulfonyl migration.

nitriles.[92] Subsequently, during examination of the synthetic potential of these substrates, the same group observed that that these pyridine derivatives readily undergo base-mediated regioselective ring opening to afford 5-oxo-pent-3-enimidamides **453** in high yields.[93] Under thermal conditions, rearrangement involving a rare nitrogen-to-nitrogen 1,3-sulfonyl migration affords 4-aminopyridines **454** in excellent yields (Scheme 64). It is thought that **455′**, the enol tautomer of **453**, being a polysubstituted azatriene, undergoes a 6π-azaelectrocyclisation[94–96] at high temperatures to give the 1,2-dihydropyridine intermediate **456**. Subsequently, a 1,3-nitrogen-to-nitrogen tosyl migration generates the aromatic 4-aminopyridine **454**, after loss of water (Scheme 64).

The thermal ring expansion of 2-sulfonylimidoyl-1-phthalimidoaziridines **457** to generate *N*-sulfonylimidazoles **458**, involving a 1,3-nitrogen to nitrogen sulfonyl migration, in moderate to good yields has been described (Scheme 65).[97] To confirm the nitrogen to nitrogen sulfonyl migration the ^{15}N-labelled aziridine **462** was prepared, which when heated afforded the ^{15}N-labelled imidazole **463** with the tosyl group on the unlabelled nitrogen. By virtue of crossover experiments the sulfonyl migration was determined to be an intramolecular process. The mechanism is postulated to involve ring opening of the aziridine ring of **457**, which affords the azomethine ylide **459**. A 1,5-electrocyclisation to imidazoline **460** precedes elimination of the phthalimide moiety to give the sterically hindered imidazole **461**. Isomerisation *via* an in intramolecular 1,3-sulfonyl migration affords the less sterically hindered rearranged imidazole **458**.

Interestingly, while the Zhan group observed a 1,4-nitrogen to carbon sulfonyl migration for the $ZnCl_2$-mediated reaction of *N*-allenic sulfonylhydrazones **178** (see Scheme 25),[42] a 1,2-nitrogen to nitrogen sulfonyl migration was observed in the presence of $FeCl_3$ as a catalyst with the same substrate class (Scheme 66).[42] As with the zinc-catalysed reaction, intermolecular sulfonyl migration was supported by crossover experiments. Analogous to the $ZnCl_2$ catalysed reaction, the intermediate **469** is generated in the same manner from **465**, however, under this set of conditions elimination of $FeCl_2$ facilitates direct nucleophilic addition of the nitrogen atom to tosyl chloride completing a formal 1,2-nitrogen to nitrogen sulfonyl migration to give the rearranged pyrazole **470**.

The Beak group reported the application of the endocyclic restriction test in the evaluation of the geometries of nucleophilic substitutions at the sulfonyl moiety of aryl sulfonamides **471**/**472** to afford alkyl sulfonamides **473**/**474** *via* base-catalysed nitrogen to nitrogen migration (Scheme 67).[98] By incorporating a short molecular tether (X = CH_2, **472**) linking the nucleophilic amine and the sulfonyl leaving group, the geometry is restrained. Therefore, the simultaneous apical entering of the nucleophile and leaving of the sulfonyl moiety affording a trigonal biypyramidal transition state structure is disfavoured; hence an intermolecular migration is most likely. In contrast a long tether [X = $O(CH_2)_{11}$, **471**] which is much more flexible would make such a transition state more likely, and as

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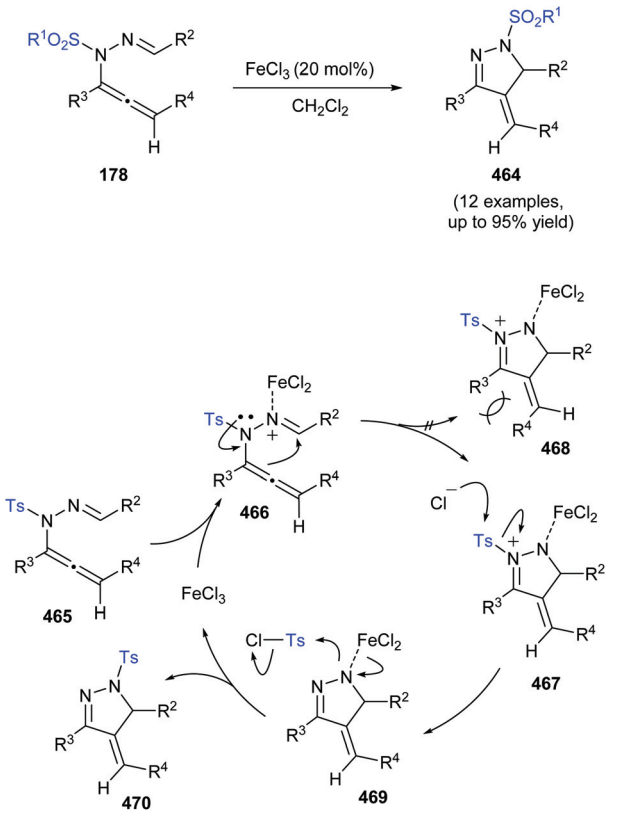
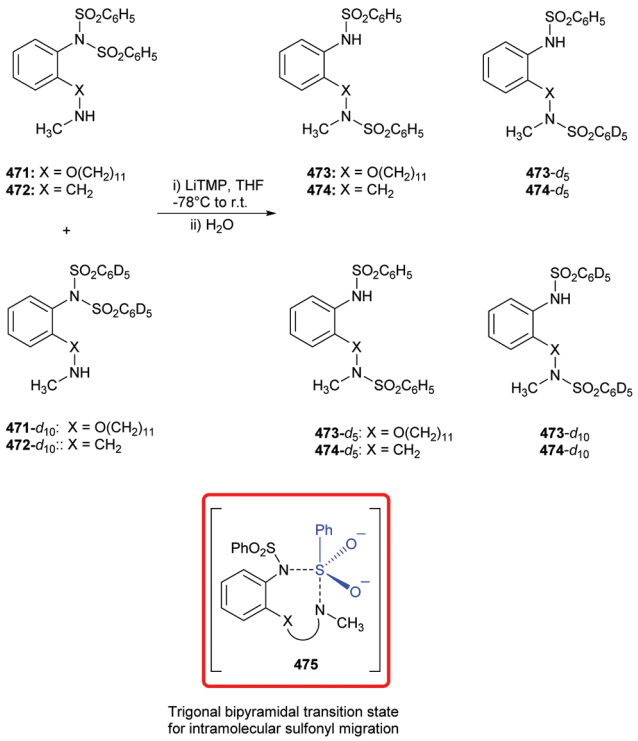


Scheme 66 Selective synthesis of (*E*)-4,5-dihydro-1*H*-pyrazoles from *N*-allenic sulfonylhydrazones *via* 1,2-nitrogen to nitrogen sulfonyl migration.



Scheme 67 Evaluation of the geometries of nucleophilic substitutions at the sulfonyl moiety of aryl sulfonamides using the endocyclic restriction test.

a result an intramolecular migration may become the operative pathway.

To test this assumption a double-labelled crossover experiment was performed between an equimolar mixture of unlabelled **471** and labelled **471**-d_{10} at 0.1 and 0.01 M. Following isolation and analysis of the isotopic composition of the products by FABMS it was determined that at a concentration of 0.1 M the sulfonyl migration occurs in both an intra- and intermolecular manner. However, at a dilution of 0.01 M a significant increase in intramolecular substitution is observed (Scheme 67). This increase at higher dilution is consistent with a first-order (intramolecular) reaction which becomes competitive with a second-order (intermolecular) reaction which occurs more readily at higher concentrations. Repeating the double-labelled crossover experiment with the less flexible arylsulfonamides **472** and **472**-d_{10} at 0.01 M determined that the sulfonyl migration is instead an intermolecular process. These results are consistent with the requirement of an almost linear arrangement of the nucleophile and leaving group at sulfur in the transition state, with a trigonal bipyramidal structure **475** with a large bond angle between the incoming and leaving groups a reasonable candidate for the transition state for such reactions.

4. Nitrogen to oxygen sulfonyl migration

4.1. Transition metal-catalysed sulfonyl migration

Boominathan *et al.* described the iron-catalysed cascade generation of 5*H*-benzo[*b*]carbazole derivatives **477** utilising an intramolecular 1,4-nitrogen to oxygen sulfonyl migration (Scheme 68).[99] The following mechanism was tentatively suggested by the authors. Keto–enol tautomerisation of the ketone **476** occurs, with subsequent coordination of the iron catalyst to the alkyne **478** facilitating a 5-*exo-dig* cyclisation and protodemetallation to afford the vinylidene intermediate **479**. Keto–enol tautomerisation of this intermediate generates the enol **480**, which, after 6π-electrocyclisation gives the ring-closed intermediate **481**. Aerial oxidative aromatisation[100–103] gives the hydroxy 5*H*-benzo[*b*]carbazole intermediate **482**, which was isolable. Coordination of the iron catalyst with the sulfonyl group of intermediate **482** gives the intermediate **483**, which due to the increased electrophilicity at sulfur undergoes an intramolecular nucleophilic attack of the phenolic OH giving the 5-membered intermediate **484**. Finally, the iron-driven scission of the N–S bond completes the 1,4-sulfonyl migration from nitrogen to oxygen. The intramolecular nature of the sulfonyl migration was supported by the results of crossover experiments. Notably, no sulfonyl migration was observed for the reaction of the intermediate **482** in the absence of the iron catalyst, highlighting that the catalyst is required for both the cascade process and the sulfonyl migration.

The Blanc group reported the synthesis of 1-azabicycloalkane derivatives **487** *via* a gold-catalysed desulfonylative cyclisation.[104] Notably, *N*-sulfonyl azacyclic ynone derivatives **485** can

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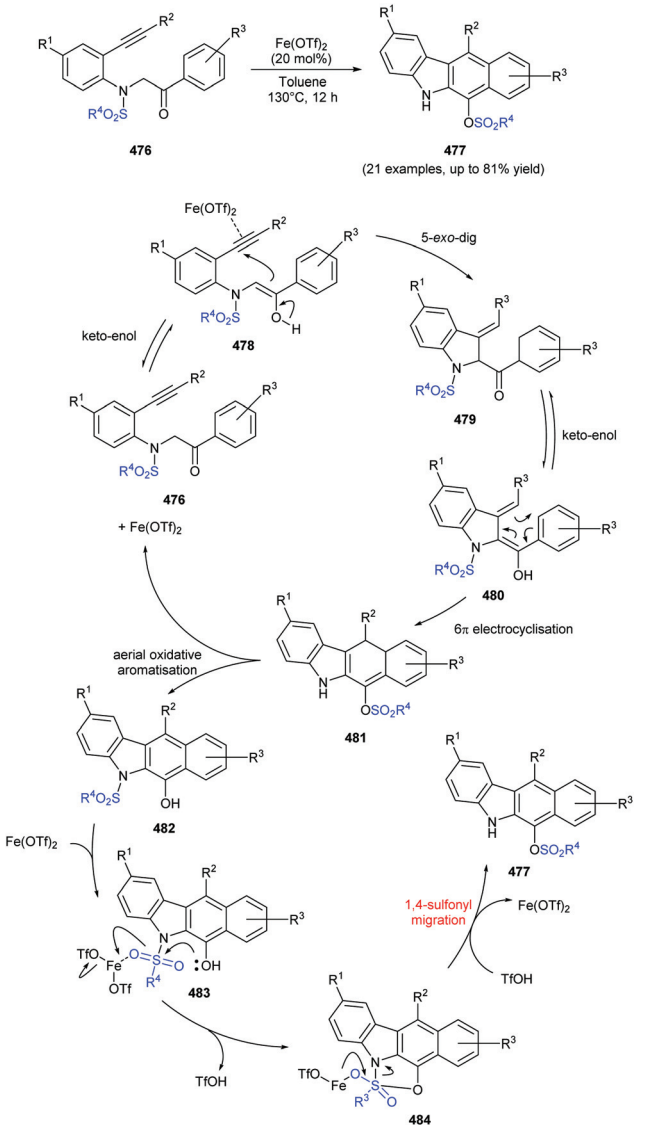
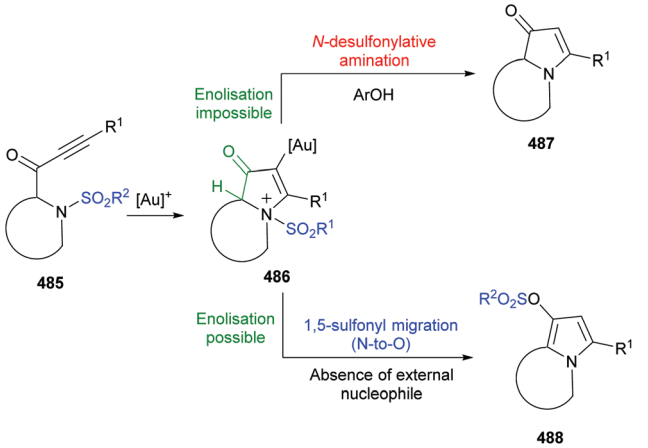
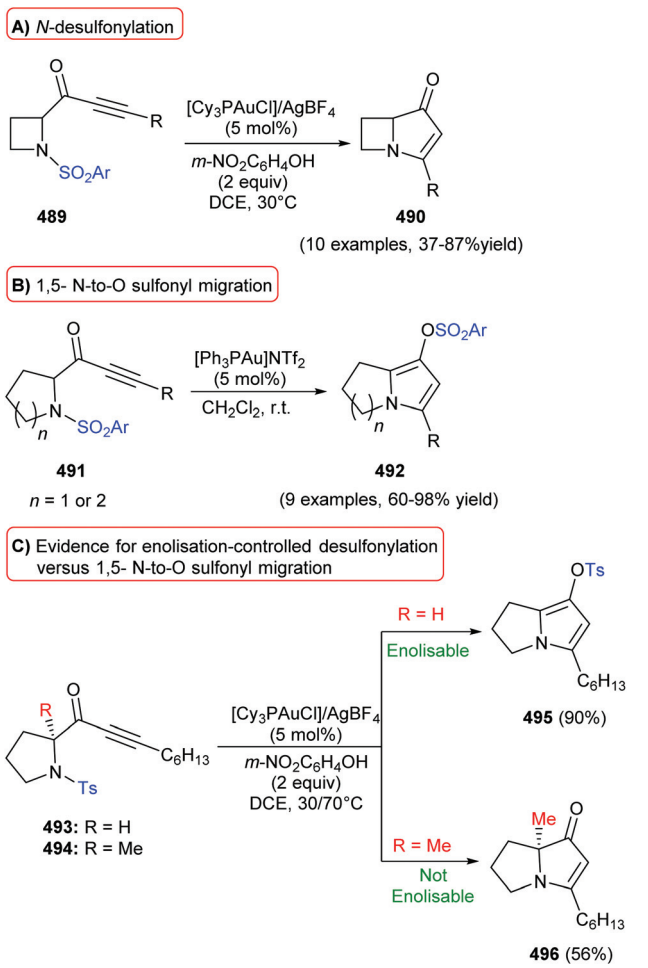


Scheme 68 Iron-catalysed cascade generation of benzo[*b*]carbazoles followed by 1,4-nitrogen to oxygen sulfonyl migration.



Scheme 69 Overview of gold(I)-catalysed *N*-desulfonylation or regioselective 1,5-sulfonyl migration.



Scheme 70 Gold(I)-catalysed *N*-desulfonylation *versus* intramolecular 1,5-nitrogen to oxygen sulfonyl migration and the role of enolisation on the reaction outcome.

readily undergo two divergent reaction pathways; the pathway followed is strongly dependant on whether a suitable protic oxygen-nucleophile is added, and the ability of the substrate to enolise (Scheme 69).

In the presence of $[Cy_3PAuCl]/AgBF_4$ as catalyst and an excess of *m*-nitrophenol, the azabicyclic products **490** were generated in moderate to good yields *via* *N*-desulfonylation of the ammonium intermediate **486** (Scheme 69/70A). Expanding the scope of the reaction to more flexible substrates, which are more readily enolisable, an alternative 1,5-nitrogen to oxygen sulfonyl migration occurred in the presence of triphenylphosphine gold(I) triflimidate and in the absence of external nucleophile. Using this approach pyrrolizine or indolizine derivatives **492** were accessible in moderate to high yields (Scheme 70B). Crossover experiments unambiguously confirmed that the 1,5-sulfonyl migrations proceeds intramolecu-

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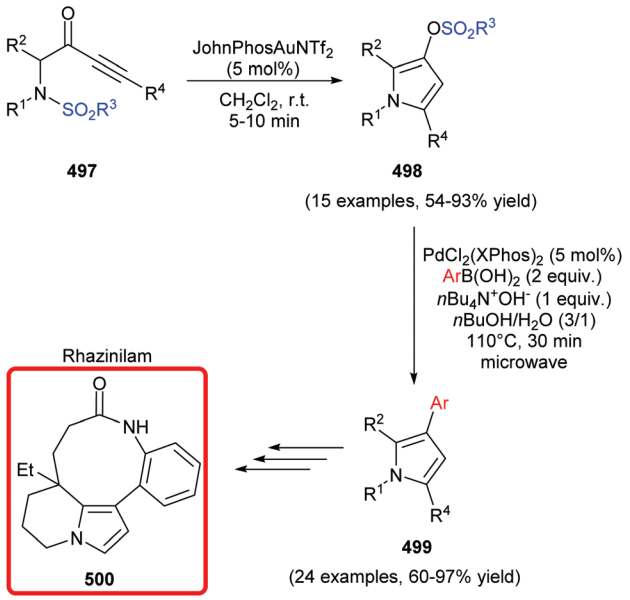


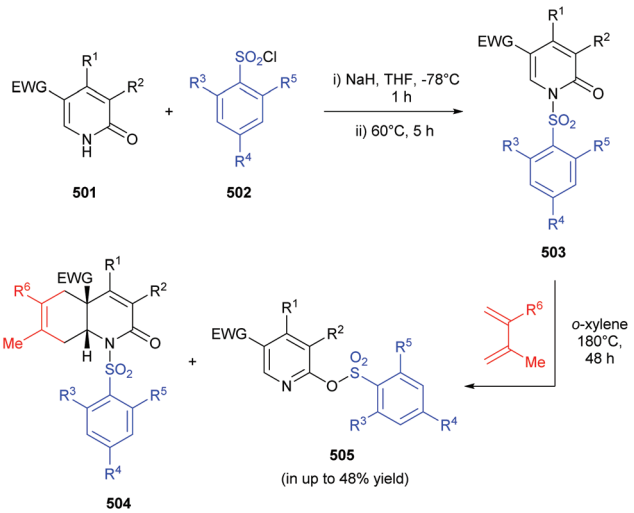
Scheme 71 Total synthesis of rhazinilam through gold-catalysed cycloisomerisation–sulfonyl migration and palladium-catalysed Suzuki–Miyaura coupling of pyrrolyl sulfonates.

larly. Notably, enolisation could be used as a switch between the *N*-desulfonylation pathways as demonstrated by the subjection of enolisable compound **493** and non-enolisable compound **494** to the optimised desulfonylation conditions (Scheme 70C). As expected the *N*-desulfonylation product **496** was obtained from non-enolisable **394**, while the enolisable **493** readily afforded the 1,5-sulfonyl migration product **495** in 90% yield.

The same group subsequently extended their gold-catalysed cycloisomerisation–sulfonyl migration cascade strategy to the formation of the key pyrrole ring in the total synthesis of the anticancer monoterpenoid indole alkaloid rhazinilam **500** (Scheme 71).[105] The required extension of the methodology to incorporate various *N*-alkylated *N*-sulfonyl 1-aminobut-3-yn-2-ones **497** proved successful, this time with the JohnPhosAuNTf$_2$ proving more efficient than the Gagosz catalyst for both acyclic and cyclic substrates. Using this methodology the substrates **497** formed the desired 1,2,4-trisubstituted pyrrolyl sulfonates **498** in high yields (up to 93%) in less than 10 minutes. Crucial to the total synthesis was the subsequent palladium-catalysed coupling of the pyrrolyl tosylates and related sulfonates with boronic acids, a first-in-class example of a challenging Suzuki–Miyaura coupling of pyrrolyl sulfonates.

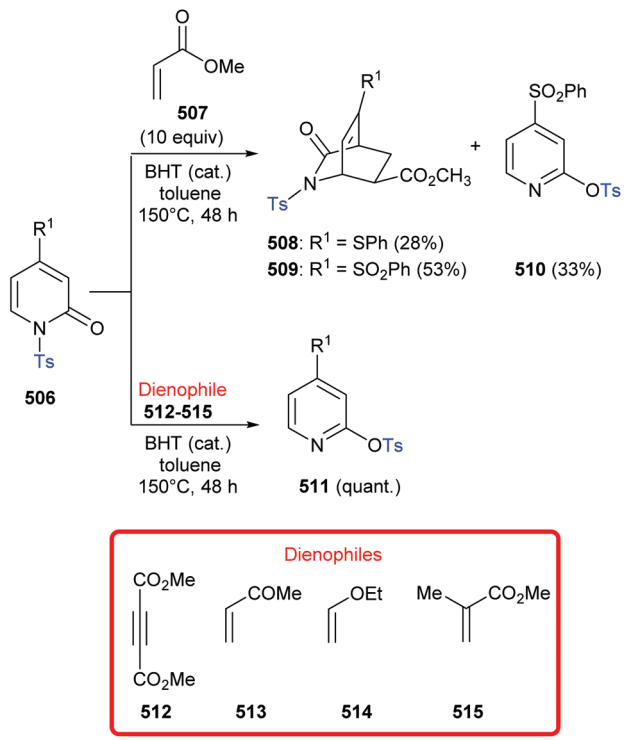
4.2. Non-metal-catalysed sulfonyl migration

In studies on the Diels–Alder cycloadditions of 2-methyl- and 2,3-dimethyl-1,3-butadienes with 1-arylsulfonyl-2(1*H*)-pyridones **503** as dienophiles, Fujita and co-workers observed significant amounts of the 1,3-nitrogen to oxygen sulfonyl migration by-products **505** (Scheme 72).[106] In a later study, the Yang group observed that the thermally driven sulfonyl



Scheme 72 Generation of sulfonate by-products **505** *via* thermal 1,3-nitrogen to oxygen sulfonyl migration in Diels–Alder cycloadditions between 1-arylsulfonylpyridones and dienes.

migration of pyridones **506** can completely supress cycloaddition when using dienophiles such as dimethyl acetylenedicarboxylate **512**, methyl vinyl ketone **513**, ethyl vinyl ether **514** or methyl methacrylate **515**, whereas when methyl acrylate **507** is employed the cycloaddition is favoured albeit with significant amounts of sulfonyl migration product **510** also observed (Scheme 73).[107]



Scheme 73 Selective 1,3-nitrogen to oxygen tosyl migration of pyridones in the presence of dienophiles under thermal conditions.

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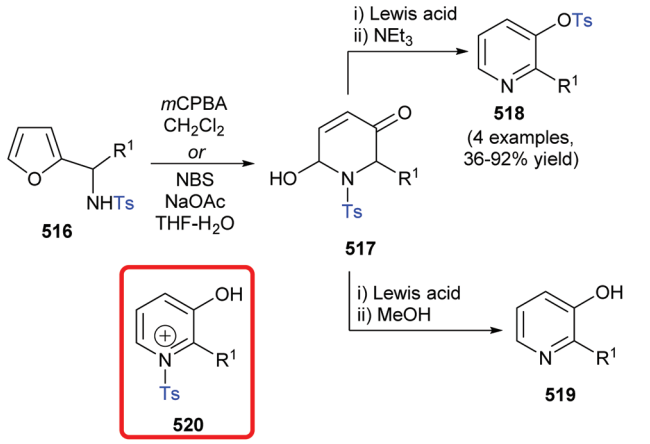
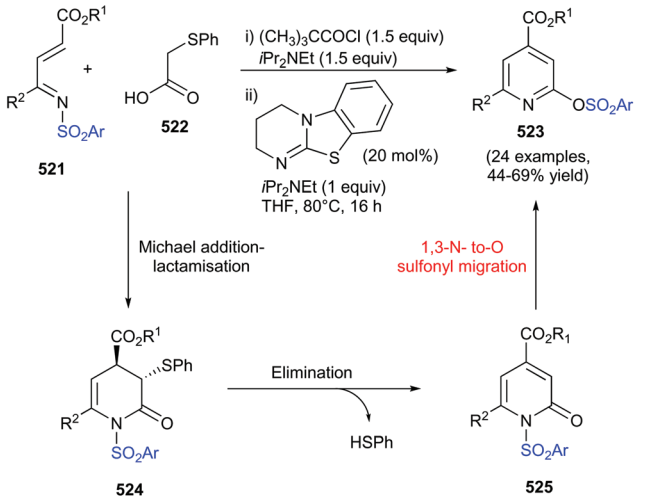


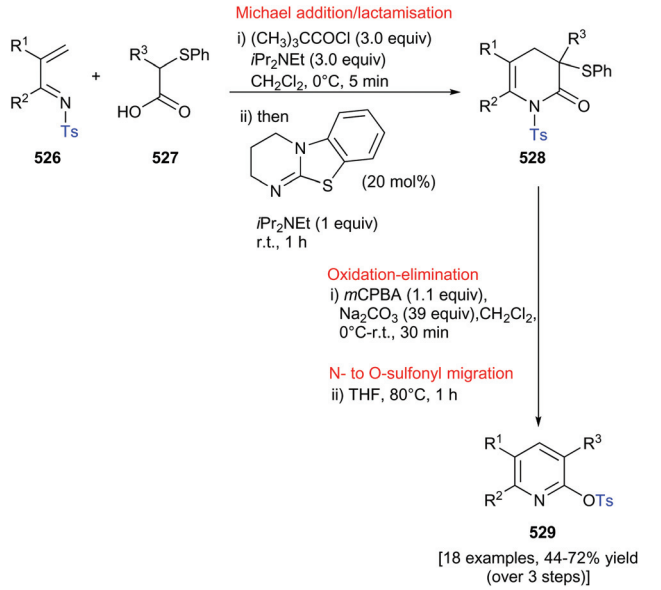
Scheme 74 Synthesis of 3-sulfonyloxypyridines *via* oxidative ring expansion of α-furyl sulfonamides and formal 1,4-sulfonyl migration.

Perry and co-workers described an oxidative cascade, involving an oxidative ring expansion of α-furyl sulfonamides **516**, acid-catalysed aromatisation and a formal 1,4-sulfonyl migration from nitrogen to oxygen to generate 3-sulfonyloxypyridines **518** in moderate to excellent yields (Scheme 74).[108] The authors propose that aromatisation of the pyridinone **517** occurs *via* acid-catalysed dehydration and enolisation to give the pyridinium salt intermediate **518**. Addition of triethylamine is believed to mediate the intermolecular 1,4-sulfonyl migration. When the reaction was quenched with methanol the 3-hydroxypyridine **519** was instead the major product, and sulfonyl migration product was not observed (Scheme 74).

The Smith group developed an isothiourea-catalysed, one-pot synthesis of 2,4,6-substituted pyridines **523** bearing a 2-sulfonate moiety, amenable to further transformations, from (phenylthio)acetic acid **522** and a range of α,β-unsaturated ketimines **521** (Scheme 75).[109] This reaction involves inter-



Scheme 75 Isothiourea-mediated one-pot synthesis of functionalised pyridines *via* 1,3-nitrogen to carbon sulfonyl migration.



Scheme 76 Synthesis of di-, tri-, and tetrasubstituted pyridines from (phenylthio)carboxylic acids and 2-[aryl(tosylimino)methyl]acrylates.

molecular Michael addition/lactam formation, elimination of thiophenol, and finally 1,3-*N*-to *O*-sulfonyl migration. The results of crossover studies indicated that the sulfonyl migration is consistent with an intramolecular process.

The group later extended this methodology by incorporating alkyl 2-[aryl(tosylimino)methyl]acrylates **526** as Michael acceptors to prepare 2,3,6-pyridine tosylates **529** (Scheme 76).[110] Utilising α-substituted pheylthioacetic acids **527** in combination with Michael acceptors bearing no β-substituent also facilitated the generation of 2,3,5,6-functionalised pyridines **529**. In these reactions the elimination of PhSH did not occur in either the presence of base or at elevated temperatures. To circumvent this, an additional oxidative step was added to the reaction sequence to generate the sulfoxide, which underwent elimination much more readily. Thermal conditions proved sufficient to enable the final *N*- to *O*-sulfonyl migration to afford the functionalised pyridines **529** in yields of 44–69% across three steps.

During a study relating to the sulfonylation of quinazoline-4(3*H*)-ones and related tetrahydrobenzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones, Gütschow and co-workers observed an unexpected nitrogen to oxygen 1,3-sulfonyl migration during the cyclisation of **531** under thermal conditions; the *O*-sulfonylated isomer **533** was isolated as the major product, rather than the expected **532** (Scheme 77).[111] The sulfonyl migration was further proved by heating **532** in acetonitrile and monitoring the reaction progress by HPLC. The sulfonyl migration was determined to proceed readily *via* first order kinetics to give the *O*-sulfonylated product **533**. However, the heating of **534**, bearing a hydrogen substituent at the 2-position, resulted in no reaction. These results support that the *N*-sulfonylated products are the thermodynamically favoured isomers when the 2-position is unsubstituted, while for substituted derivatives

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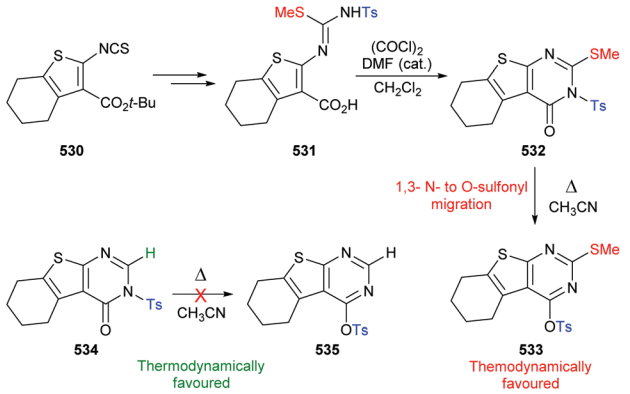
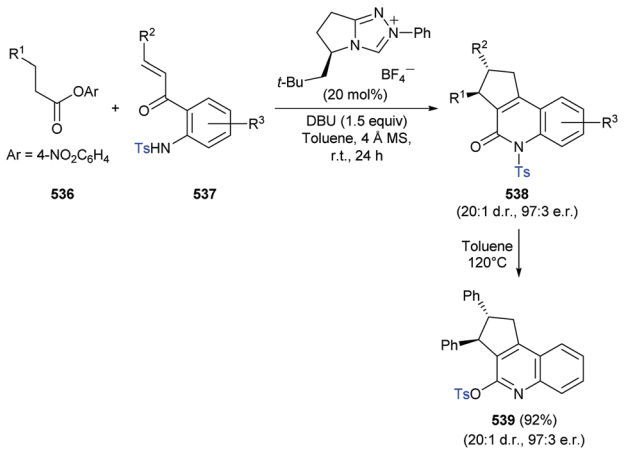


Scheme 77 Generation of *O*-sulfonylated thieno[2,3-*d*]pyrimidines *via* unexpected thermal intramolecular 1,3-sulfonyl migration.

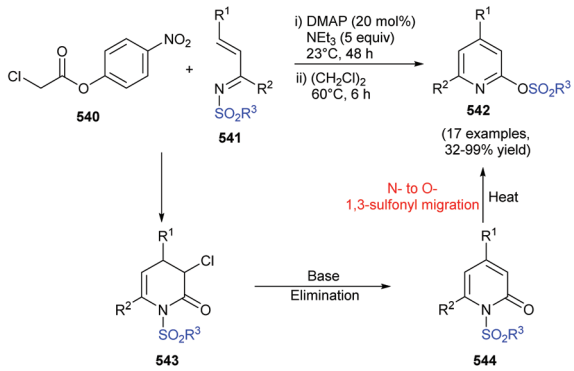
the *O*-sulfonylated isomers are thermodynamically favoured. Crossover experiments indicated that the 1,3-sulfonyl migration is most likely an intramolecular process.

Chi and co-workers developed a one-step, chemo-, stereo- and enantioselective cascade reaction to synthesise multicyclic oxoquinoline-type heterocycles **538** *via* an N-heterocyclic carbene catalysed activation of the β sp^3-carbon atom of the ester **536** as a key step (Scheme 78).[112] During derivatisation of the oxoquinoline **538**, the group demonstrated that a 1,3-*N*- to *O*-sulfonyl migration proceeds readily under thermal conditions to afford the quinoline derivative **539** in 92% yield. The enantiomeric and diastereomeric ratios remained intact through the migration.

Trisubstituted pyridines **542**, bearing a 2-sulfonate moiety amenable to further synthetic manipulation, are accessible *via* a DMAP-catalysed activation of α-chloroacetic ester **540** in the presence of unsaturated imines **541** containing a tosyl protecting group that undergoes a thermal nitrogen- to oxygen 1,3-sulfonyl migration (Scheme 79).[113] Optimal results were achieved using **541** bearing electron-withdrawing substituents,



Scheme 78 Access to oxoquinoline heterocycles *via* N-heterocyclic carbene-catalysed ester activation for selective reaction with an enone.



Scheme 79 Access to pyridines *via* DMAP-catalysed activation of α-chloroacetic ester with unsaturated imines.

with a significant reduction in yield observed when electron-donating substituents were incorporated. Imines containing heterocyclic moieties also readily participated in the reaction, however the use of α-branched chloroacetates with an α-alkyl substituent completely inhibited the reaction pathway. The mechanism postulated involves the reaction of the DMAP-activated α-chloroacetic ester **540** with the unsaturated imine **541** leading to the lactam intermediate **543**. E2-elimination affords the adduct **544** which undergoes *N*- to *O*-sulfonyl migration at elevated temperature to give the desired product **542**. It is likely that the driving force for the sulfonyl migration is the aromatisation of the heterocyclic ring.

5. Oxygen to carbon sulfonyl migration

5.1 Photoinduced sulfonyl migration

The photoinitiated radical fragmentation and rearrangement of vinyl tosylates resulting in efficient formation of aromatic and aliphatic β-ketosulfones **546** and **549** was reported by Xie *et al.*[114] Aromatic vinyl tosylates **545** and aliphatic vinyl tosylates **548** both underwent these visible-light promoted transformations with excellent and moderate to good yields respectively, albeit with different photoinitiators in each instance. Eosin B **547** proved optimal for the aromatic series, while 9-fluorenone **550** was preferable in the case of aliphatic vinyl tosylates (Scheme 80).

A trapping experiment, using the radical scavenger TEMPO, revealed complete suppression of the reaction, and 99% recovery of the starting material, indicative of a radical mechanism. Crossover experiments indicated that the 1,3-sulfonyl migration is an intermolecular process. A photoinduced chain mechanism was deemed likely as a result of quantum efficiency calculations, while DFT calculations for the initiation process were compatible with energy transfer between the initiator and the vinyl tosylate substrate. Considering this, the putative mechanistic pathway was presented (Scheme 81). Homolytic cleavage of the O–S bond in the vinyl tosylate **551** occurs through energy transfer from the

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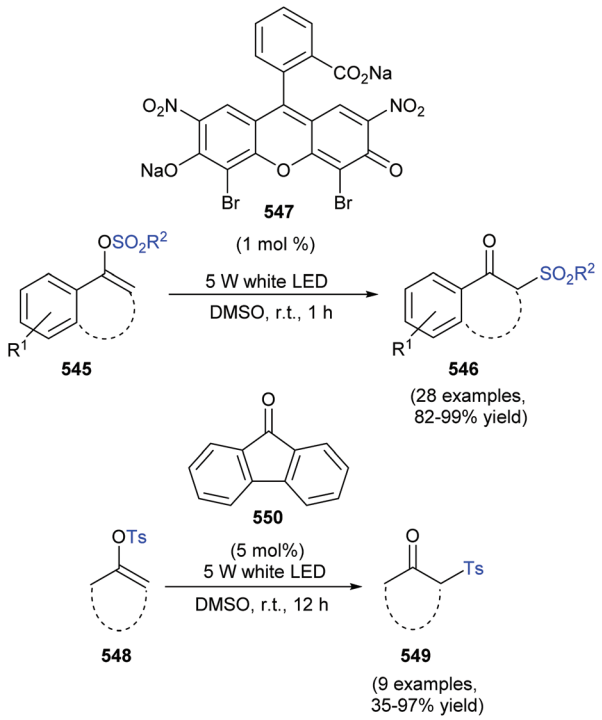
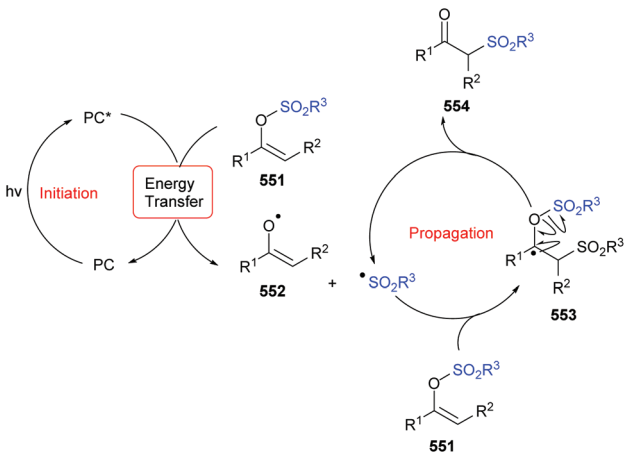


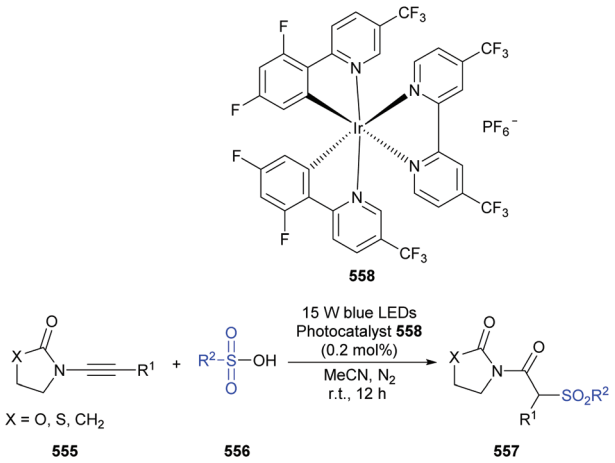
Scheme 80 Photoinduced rearrangement of vinyl tosylates to β-ketosulfones *via* 1,3-sulfonyl migration.



Scheme 81 Proposed mechanism for the photoinduced rearrangement of vinyl tosylates to β-ketosulfones *via* 1,3-sulfonyl migration.

excited photosensitiser, to generate an enol radical **552** and a sulfonyl radical. The sulfonyl radical adds to another vinyl tosylate **551** affording the intermediate **553**, which on elimination of a further sulfonyl radical affords the β-ketosulfone **554** and sulfonyl radical for the subsequent reaction cycle.

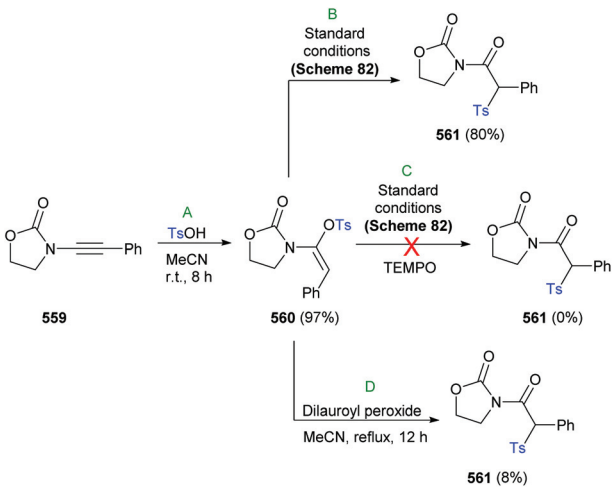
The Feng group reported an iridium-catalysed visible-light promoted oxo-sulfonylation of ynamides **555** with sulfonic acids **556**, leading to functionalised α-sulfonylated amides **557** in moderate to good yields (Scheme 82).[115] Generally, ynamides bearing an electron-rich aromatic ring delivered the



Scheme 82 Visible-light promoted oxo-sulfonylation of ynamides with sulfonic acids.

desired products in good yields, while substrates with an electron-deficient aromatic ring gave lower yields. Aryl halides, fused aromatics and heterocyclic substituents were well tolerated, while both electron-rich and electron-poor alkyl and aromatic sulfonic acid derivatives could be incorporated to furnish a diverse range of α-sulfonylated amides.

In order to garner information regarding the mechanism the authors carried out a series of control experiments (Scheme 83). Toluenesulfonic acid readily reacted with the ynamide **559** to give the vinyl tosylate **560** in almost quantitative yield (Scheme 83A). This vinyl tosylate could be converted into the α-sulfonylated amide **561** under the standard reaction conditions in high yields, confirming its role as an intermediate in the tandem reaction pathway (Scheme 83B). Performing the reaction in the presence of TEMPO, a radical scavenger, completely inhibited the reaction, supporting the generation of a radical intermediate in the rearrangement step



Scheme 83 Control experiments supporting a radical mediated oxygen to carbon sulfonyl migration in the synthesis of α-sulfonylated amides.

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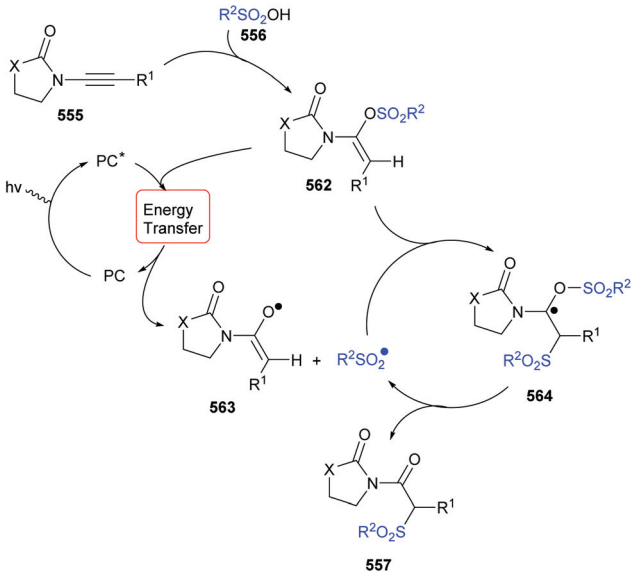
(Scheme 83C). A radical mechanism was additionally confirmed through the reaction of **560** with dilauroyl peroxide as a radical initiator in place of the iridium photocatalyst **558** which also led to **561**, albeit in a significantly lower yield (Scheme 83D). Crossover experiments indicated that the sulfonyl migration was an intermolecular process.

In further investigation of the working mode of the photocatalyst (single electron transfer *vs.* energy transfer), cyclic voltammetry experiments indicated that the vinyl tosylate intermediate **560** has a higher reduction potential than the excited state of the photocatalyst (PC*), indicating that a single electron transfer cannot occur under the standard conditions. Stern–Volmer quenching experiments confirmed that the vinyl tosylate **560**, and not the ynamide **559** or tosic acid, could quench the excited photocatalyst. A DFT calculation of the triplet energy of **560** was calculated to be 100.1 kJ mol^{-1}, a value that is within the range expected to be accessed by the iridium photocatalyst (250.3 kJ mol^{-1}) as a triplet sensitiser. These results in combination support an energy transfer mechanism for the photocatalyst's working mode. Furthermore, a light on/off experiment confirmed that the reaction requires continuous irradiation to achieve reaction completion, while the quantum yield of 10.0 for the rearrangement of **560** to **561** indicated a radical chain propagation mechanism.

In light of these findings the following mechanism was proposed (Scheme 84). Electrophilic addition of sulfonic acid to ynamide **555** gives vinyl sulfonate **562** in a regioselective manner. Subsequently, activation of the sulfonate **562** occurs through the energy transfer process from the excited photocatalyst (PC^*). Homolytic cleavage of the C–S bond of the activated vinyl sulfonate **562** generates the sulfonyl radical and enol radical **563**. Selective addition of the sulfonyl radical to the electron rich alkene group of vinyl sulfonate **562** leads to the α-sulfonylated amide **557** *via* β-scission of the radical intermediate **564**, which regenerates a sulfonyl radical enabling a radical chain propagation.

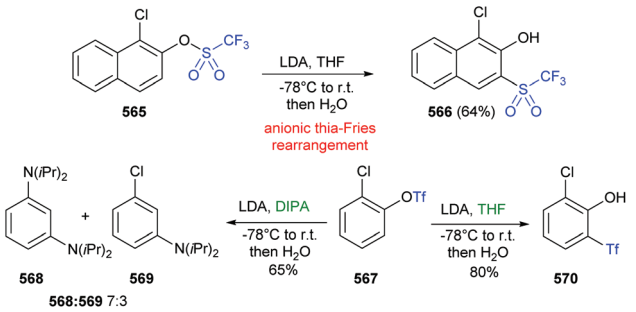


Scheme 84 Proposed mechanism for the visible-light-promoted oxo-sulfonylation of ynamides with sulfonic acids.

5.2. Thia-Fries rearrangement

The thia-Fries rearrangement is a sulfur based sub-class of the well-known Fries rearrangement, in which aromatic sulfonates or sulfonanilides rearrange to afford *ortho*- or *para*-substituted hydroxy or amino sulfones respectively. The rearrangement, named after Karl Fries, who published the seminal report in 1908, has subsequently been demonstrated under cationic, anionic and radical/light-induced conditions. Notably, over the last 20 years the most significant highlight in this area was the development of the anionic-thia Fries rearrangement for sulfonates at both aromatics and organometallics. An overview of the anionic Fries rearrangement, including the thia-Fries subclass, was recently undertaken by Korb and Lang.[116] This section will further describe anionic and non-anionic thia-Fries rearrangement.

5.2.1. Anionic thia-Fries rearrangement. While attempting the palladium-catalysed cross-coupling of 1-chloro-2-naphthalene triflate **565** with a pyridyl zinc halide, generated *in situ* using LDA/$ZnCl_2$, a notable side product was identified as the *ortho*-hydroxyarylsulfone **566**. This result, reported by Lloyd-Jones in 2003, described the first example of an anionic thia-Fries rearrangement of aryl triflates.[117] Further optimisation revealed that it is in fact LDA, and hence a base, that mediates the rearrangement, with the *ortho*-hydroxyarylsulfone **566** obtained in 64% yield (Scheme 85). Aryl triflates bearing moderately electron-withdrawing groups, particularly *ortho* to the triflate, readily underwent the thia-Fries rearrangement, whereas analogues containing electron-donating groups at the *ortho*-position favoured aryne generation. Notably, solvent effects are crucial in controlling the reaction outcome. For example, *o*-chlorophenyl triflate **567** exclusively affords the thia-Fries rearrangement product **570** in the presence of THF, however, the use of DIPA which is an effective aryne scavenger gives a mixture of both the mono- and bis-anilines **568** and **569** (Scheme 85). However, even in instances in which excess DIPA is not employed one must contend with the generation of DIPA from the deprotonation of the aryl triflate.



Scheme 85 Discovery of the first anionic this-Fries rearrangement.

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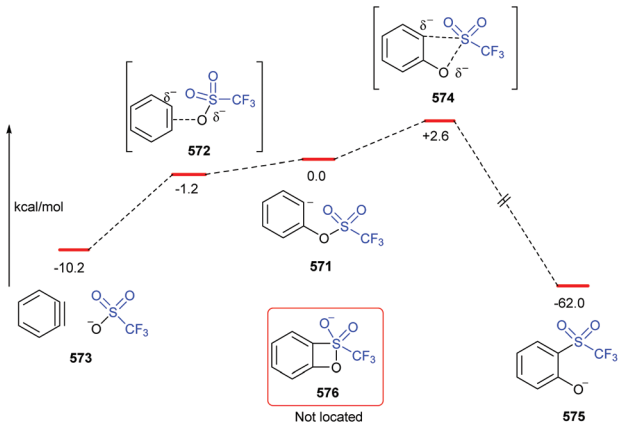
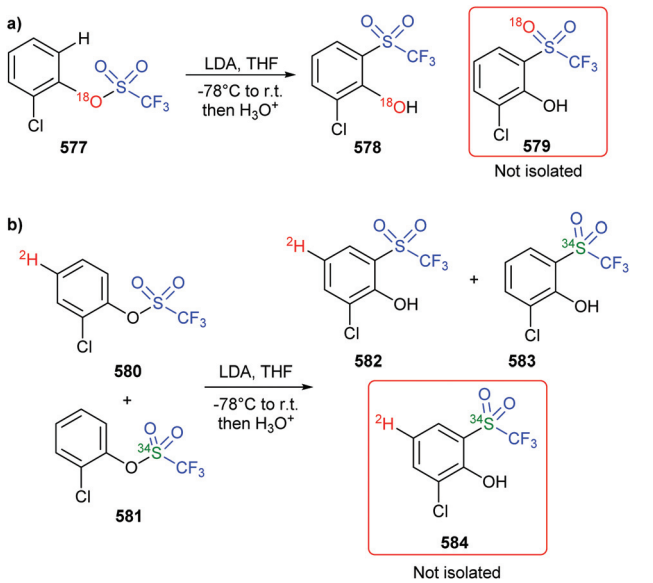


Scheme 86 Computed relative energies (in kcal mol^{-1}) for the elimination or thia-Fries rearrangement of **571** in a THF continuum.

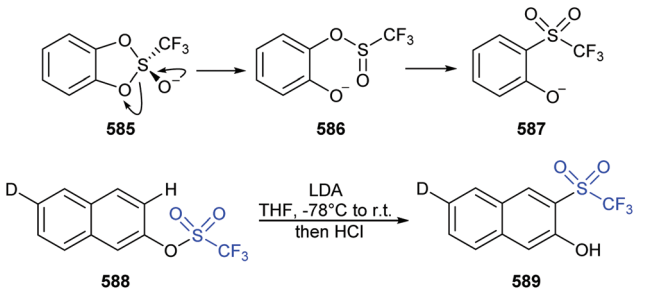
In order to rationalise the reactivity of aryl triflates towards thia-Fries rearrangement or elimination, Lloyd-Jones and co-workers carried out computational studies and labelling studies.[118] Gas phase and single point calculations, including a continuum description of the THF solvent, were performed for the pathways leading to the rearrangement and elimination of $[C_6H_4OTf]^-$ (Scheme 86). The sulfonyl migration was predicted to be a highly exothermic process (62.0 kcal mol^{-1}), while a 1,2-oxethietane intermediate **576** could not be located. Instead, the sulfonyl migration was observed to proceed *via* a single and early transition state **574** in which the C–S and S–O bond distances shorten and lengthen respectively, relative to the reference starting material **571**. The significantly lower energy of the rearranged phenolate **575** relative to the reference substrate **571** excludes retro-Fries rearrangements as an operative mechanism. Alternatively, the loss of triflate is predicted to be only mildly exothermic (10.2 kcal mol^{-1}). Interestingly, the similar energies of the transition states **572** and **574** indicate that a thermodynamic rather than a kinetic process may be operational, due to reversible elimination of triflate.

To test whether reversible addition/elimination of the triflate group to the aryne was occurring, ^{18}O-labelled triflate **577** was reacted under the standard conditions, however, only ^{18}O-labelled phenol **578**, generated through the expected anionic thia-Fries rearrangement was obtained, with no evidence for the ^{18}O/^{16}O scrambling product **579** that would be expected *via* a reversible process (Scheme 87a). A crossover experiment between ^{2}H-lablelled triflate **580** and ^{34}S-labelled triflate **581** did not generate any of the ^{2}H/^{34}S-lablled phenol **584** anticipated if an intermolecular mechanism was operational, hence the sulfonyl migration was deemed to be an intramolecular process (Scheme 87b).

The potential for a sulfinite based mechanism, in which one could consider an intramolecular attack of an anionic triflate at the sulfonyl oxygen to afford a trifluoromethylsulfinite **586**, *via* intermediate **585**, was also investigated as a plausible route (Scheme 88).[118] As organosulfinites undergo isomerisation to sulfones *via* heterolytic ion-pair recombination, it



Scheme 87 (a) ^{18}O-Scrambling experiment eliminating reversible aryne formation mechanism; (b) crossover experiment indicating an intramolecular sulfonyl migration.



Scheme 88 Evidence disconfirming the likelihood of a sulfinite-based mechanism for the anionic thia-Fries rearrangement.

would be expected that isomerisation would readily occur for a trifluoromethylsulfinite and a phenolate **586**.[119] However, anionic thia-Fries rearrangement of the deuterium labelled **588** afforded exclusively **589**, with no evidence for isomerisation effectively ruling out the possibility of a sulfinite-based mechanism.

Notably, while both the elimination and rearrangement processes nominally produce diisopropylamine (DIPA) from the reaction between the aryl triflate and LDA, the concentration of free base can have a significant impact on the course of the reaction outcome due to the strong complexation of the DIPA to the lithium cation in the rearranged product as well as its consumption by the aryne to produce $ArN(iPr)_2$. Interestingly, carrying out the reaction of **588** in the presence of DIPA-free LDA affords the rearrangement product **589** in 30% yield and the aryne-derived amine **590** in 44% yield (Scheme 89).[118] Repeating the reaction in the presence of 1,3-diphenylisobenzofuran (DPIBF), an aryne trapping reagent, affords the naphthyne-DPIBF cycloadduct **591** in 99% yield with no thia-

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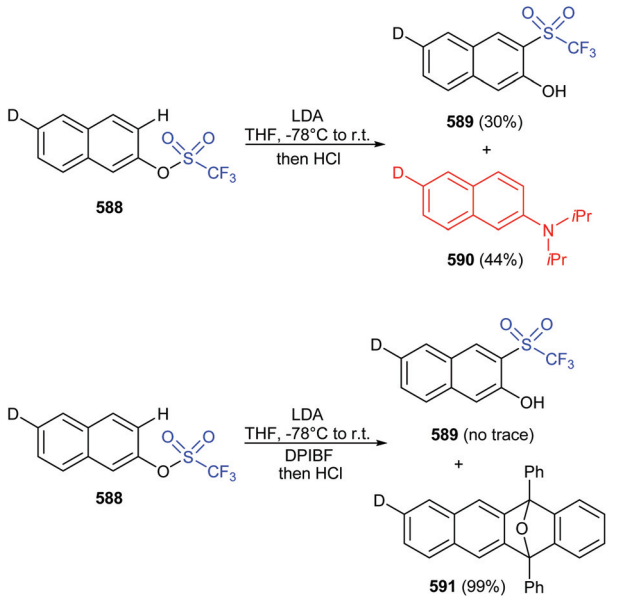
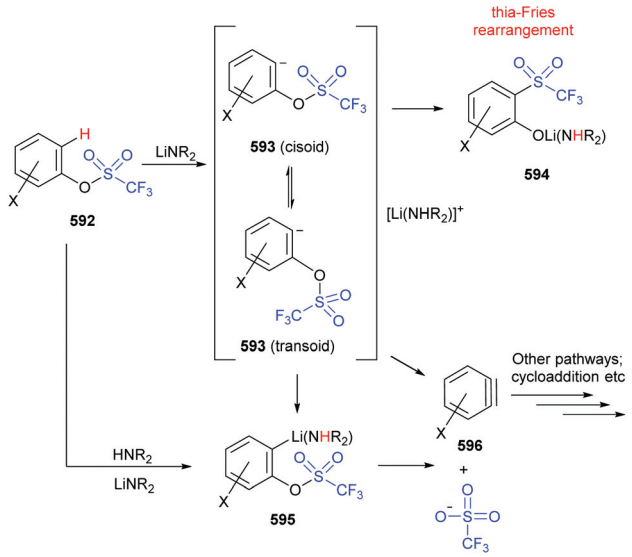


Scheme 89 Effect of concentration of free DIPA on anionic thia-Fries rearrangement and aryne generation.



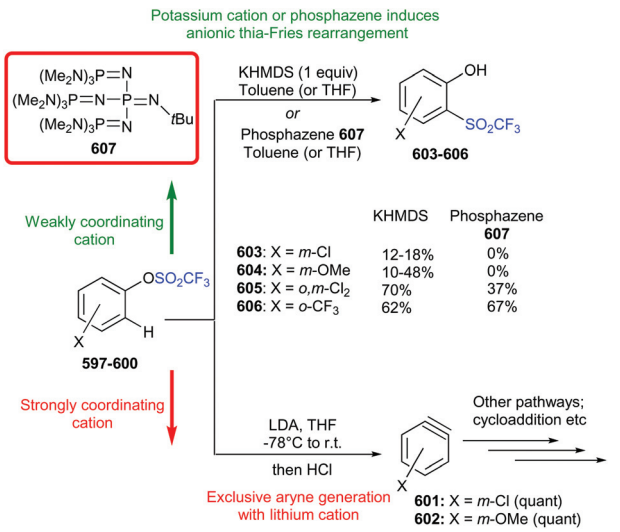
Scheme 90 Proposed mechanistic pathways for the reaction of aryl triflates with LDA; anionic thia-Fries rearrangement and aryne generation.

Fries rearrangement product **589** observed as a result of DPIBF bypassing DIPA consumption which leads to a rise in DIPA concentration (Scheme 89). Therefore, the presence of a metalated compound, required for aryne generation, is favoured when the lithium cation is stabilised by the amine. The amine, in this instance DIPA, can be formed through either the deprotonation process or by being employed in excess. This finding, that DIPA catalyses aryne formation, is in agreement with Huisgen and Sauer's earlier work on the kinetics of aryne formation from Ar–X which highlighted that HNR_2 catalyses *ortho* metalation efficiently.[120]

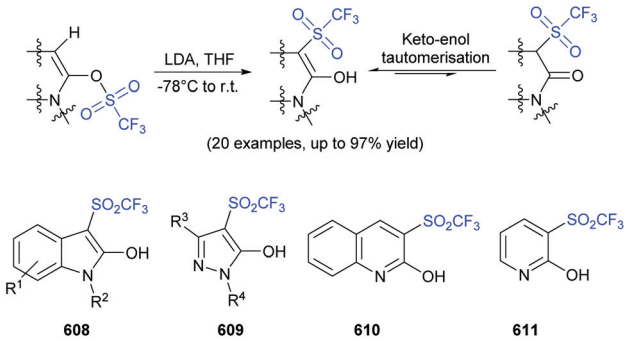
As a result of these findings two disparate mechanistic pathways are operational for the reaction of aryl triflates with LDA, namely an anionic pathway leading to anionic thia-Fries rearrangement and a DIPA-catalysed metalation pathway leading to aryne generation (Scheme 90).[118] In the first instance, the anion **593** which can adopt two conformations of similar energies, plays a key role in the sulfonyl group migration. For unsubstituted aryl triflates (X = H) the cisoid conformation that is required for rearrangement is slightly higher in energy (+0.4 kcal mol^{-1}) than its transoid counterpart, however this can be overcome through the incorporation of electron withdrawing moieties *ortho* (and *para*) to the triflate group which inhibits competing metalation. In contrast, *meta* substituents actively destabilise the aryl anion **593** which favours elimination to **596** *via* **595**, while the employment of excess DIPA further facilitates elimination to generate the aryne **596**, with a concomitant decrease in the thia-Fries rearrangement product **594**.

In light of the clear evidence that metalation favours aryne generation the authors postulated that the use of more weakly coordinating metal cations, such as the larger potassium cation, would instead favour rearrangement. As such, by using potassium hexamethyldisilazane (KHMDS) as base in place of LDA, the aryl tosylates **597–600** which had previously exclusively afforded aryne-based products with LDA (as well as LiHMDS) afforded the thia-Fries rearrangement products **603–606** albeit in low to moderate yields, highlighting the key role that the metal cation plays in distinguishing between the two pathways (Scheme 91).[118] In certain instances, the non-ionic base phosphazene **607**,[121] proved suitable in inducing thia-Fries rearrangement however stringently dry conditions are required or competing side reactions can occur.

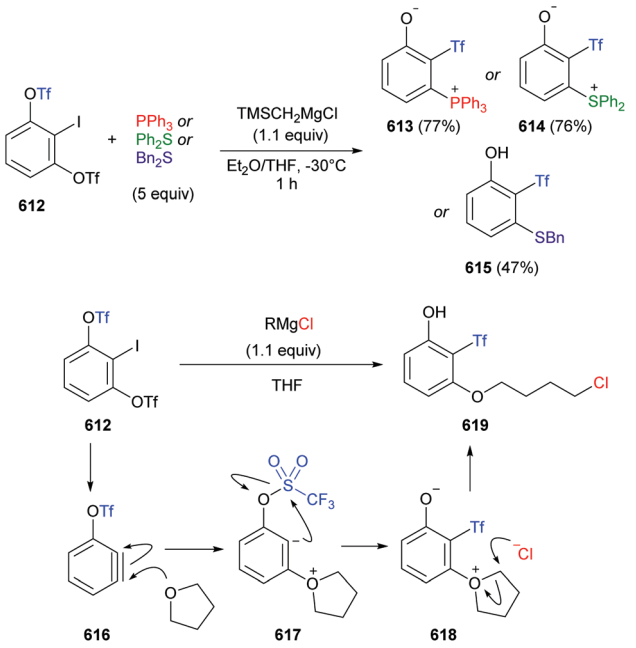
Notably, Lloyd-Jones and co-workers have successfully utilised the anionic-thia Fries rearrangement in the development



Scheme 91 Inhibition of aryne pathway *via* use of less coordinating metal cations; anionic thia-Fries rearrangement in the presence of KHMDS and phosphazene **607**.



Scheme 92 Regioselective synthesis of heteroaryl triflones *via* LDA-mediated anionic thia-Fries rearrangement.



Scheme 93 Generation of aryl triflones *via* thia-Fries rearrangement.

of sulfone containing BINOL and BINAPHOS ligands for use in catalytic enantioselective indium-mediated allylations[122] and palladium-catalysed hydrophosphorylations.[123]

The first example of the application of the anionic thia-Fries rearrangement in heteroaromatic compounds was reported by Shibata and co-workers in 2012.[124] Using LDA as base a series of rearranged nitrogen containing heterocycles including oxindole **608**, pyrazolone **609**, quinoline **610** and pyridine triflones **611** was synthesised in moderate to good yields, with all products existing as the enol-tautomer rather than the amido form as confirmed by NMR studies (Scheme 92). This transformation proceeds in higher yields than those in the pioneering work of Lloyd-Jones for the rearrangement of phenyl and naphthyl triflates.[117]

In their studies on the reactivity of 3-triflyloxybenzyne **616**, the Hosoya group observed that in the absence of an arynophile, **616** reacted with the solvent rather than dimerizing (Scheme 93).[125] Thus the reaction in THF afforded the chlorobutoxy triflone **619**. The reaction proceeds by regioselective nucleophilic addition of THF to the benzyne **616** to afford the zwitterionic intermediate **617**, which subsequently undergoes anionic thia-Fries rearrangement to give **618**. Ring opening of the oxonium ion *via* addition of chloride from the Grignard reagent affords the rearranged triflone **619** upon protonation of the phenoxide anion (Scheme 93). The methodology was amenable to variation of the nucleophile; rearranged zwitterionic aryl triflones **613** and **614** were generated through regioselective nucleophilic addition of PPh_3 and PhS_2 to 3-triflyloxybenzyne **616**, while Bn_2S afforded the non-ionic triflone **615**, following debenzylation.

To broaden the applicability of 3-triflylbenzyne, the group further explored the reactivity in Diels–Alder cycloadditions of 3-triflyloxyarynes bearing an additional functionalisable group, such as a halide.[126] However, their initial attempt to generate the cycloadduct **621** from the triflate **620** and furan did not proceed efficiently using the previously optimised conditions, with a similar amount of the triflone **622** being generated *via* competing anionic thia-Fries rearrangement (Table 1, entry 1). The authors, therefore, screened for conditions to try to inhibit the thia-Fries rearrangement pathway. A significant improvement was attained by utilising non-polar solvents such as hexane and toluene, with further increases in yield and selectivity observed by increasing the amount of activator and decreasing the reaction temperature (Table 1, entries 6 and 7). While not fully understood, it is likely that the non-polar solvents destabilise the anionic intermediate required for thia-Fries rearrangement, while enhancing the Mg–C bond formation which facilitates the elimination to the aryne.

In a subsequent publication the Hosoya group reported the isolation of the thia-Fries rearrangement by-product **626** in significant amounts (up to 32%) when using the 5,6-thienobenzyne precursor **624** in cycloaddition reactions (Scheme 94).[127] It is likely that this side reaction is facilitated by the strongly electron-withdrawing trifluoromethyl group, which contributes by stabilising the anionic intermediate generated *via* the iodine-magnesium exchange reaction. Interestingly, the analogous cycloadditions of 6,7-thienobenzyne precursors under the same conditions proceed with significantly greater selectivity, with no evidence for thia-Fries rearrangement observed.

In 2013, Greaney and co-workers reported a tandem anionic thia-Fries rearrangement-cyclisation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate benzyne precursors **629** to form phenoxathiine-dioxide derivatives **630** in moderate yields as single regioisomers (Scheme 95).[128] The phenoxathiine derivatives were only afforded when halogen substituents were present *ortho* to the triflate moiety, a result which is in line with Lloyd-Jones' earlier work that demonstrated that electron-withdrawing groups *ortho* to the sulfonate are crucial for anionic thia-Fries rearrangement.[117] However, in this instance the halogenated triflates **629** can undergo both thia-Fries rearrangement and aryne generation in the same reaction and further react together in a tandem manner. This observation is in direct contrast with Lloyd-Jones' observation that the two

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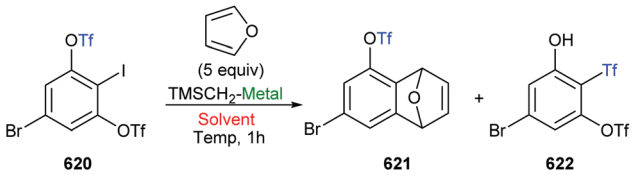
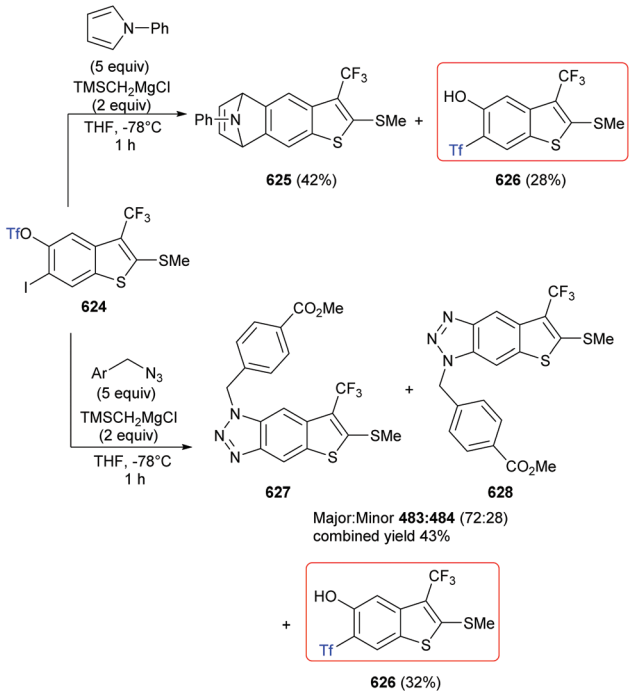
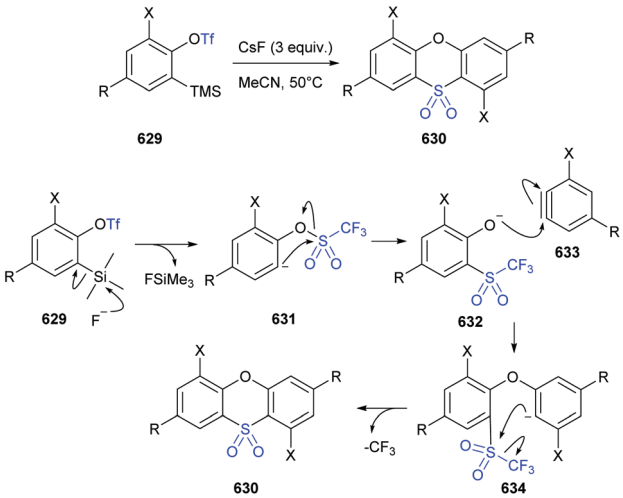
Table 1 Influence of solvent on inhibition of thia-Fries rearrangement



Entry	$TMSCH_2$-metal (equiv.)	Solvent	Temp (°C)	Yield **621** (%)	Yield **622** (%)	**621 : 622**
1	$TMSCH_2MgCl$ (1.5)	Et_2O	−30	44	44	—
2	$TMSCH_2Li$ (1.5)	Et_2O	−30	32	24	57 : 43
3	$TMSCH_2MgCl{\cdot}LiCl$ (1.5)	Et_2O	−30	25	19	57 : 43
4	$TMSCH_2MgCl{\cdot}LiCl$ (1.5)	Toluene	−30	54	4	93 : 7
5	$TMSCH_2MgCl{\cdot}LiCl$ (1.5)	*n*-Hexane	−30	67	7	91 : 9
6	$TMSCH_2MgCl{\cdot}LiCl$ (2.4)	Toluene	−50	70	4	95 : 5
7	$TMSCH_2MgCl{\cdot}LiCl$ (2.4)	*n*-Hexane	−30	83	4	95 : 5



Scheme 94 [4 + 2] cycloadditions of 5,6-thienobenzyne precursors; competing anionic thia-Fries rearrangement of the phenylene ring.



Scheme 95 Formation of phenoxathiine-dioxide derivatives *via* tandem anionic thia-Fries rearrangement-cyclisation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate benzyne precursors.

processes are orthogonal to each other at low temperatures. Considering this, the following mechanism was postulated (Scheme 95): C–Si bond cleavage is mediated by treatment with fluoride, which induces an anionic thia-Fries rearrangement of the resulting anion **631** to form the phenolate **632**. The aryne **633**, generated through the fluoride mediated elimination of the triflate and trimethylsilyl moieties, reacts with the phenolate **632** to generate the anionic intermediate **634**. Cyclisation of **634** *via* nucleophilic addition of the phenyl anion onto the trifluoromethane sulfonate moiety affords the phenoxathiine-dioxide product **630**. The dual mode of the triflate starting materials **629** with respect to anionic thia-Fries rearrangement and aryne formation in the one pot was supported *via* crossover experiments.

5.2.2. Remote anionic thia-Fries rearrangement. The NaH-mediated remote anionic 1,5-thia-Fries rearrangement, which constitutes a formal 1,5-sulfonyl migration from oxygen to carbon, allowing the regioselective synthesis of 2-(2-hydroxyphenyl)-3-indole triflones and 3-sulfonyl indoles **636** was described by the Shibata group (Scheme 96).[129] Notably, this first example of a remote anionic thia-Fries rearrangement tolerated both electron-withdrawing and electron-donating groups at various positions on the phenyl ring, while also tolerating the presence of bromo- and chloro-substituents due to the reaction not requiring strong alkyllithium bases. Strong base is not required for this reaction because, unlike conventional anionic Fries rearrangement, which is initated by a carbanion, this method is initiated by a nitranion.

No migration was observed with either *N*-methylindole **639** or 3-methylindole **640** when subjected to the optimised con-

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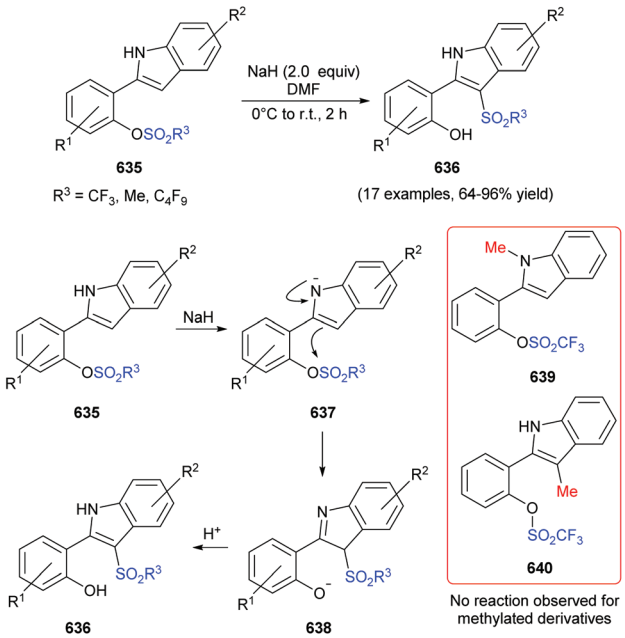
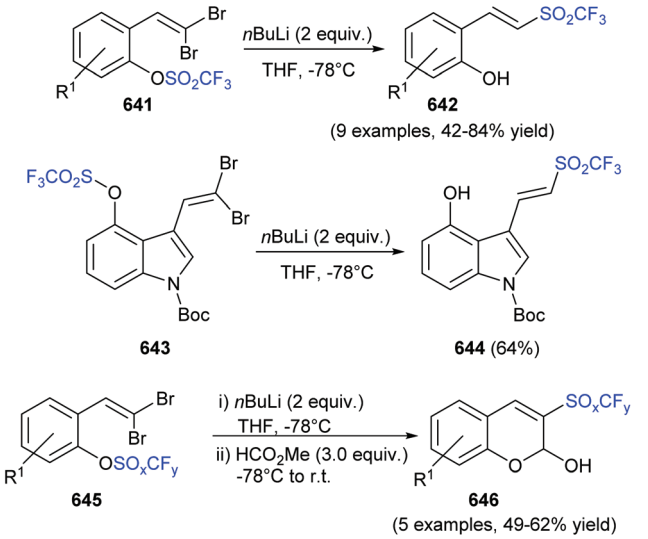
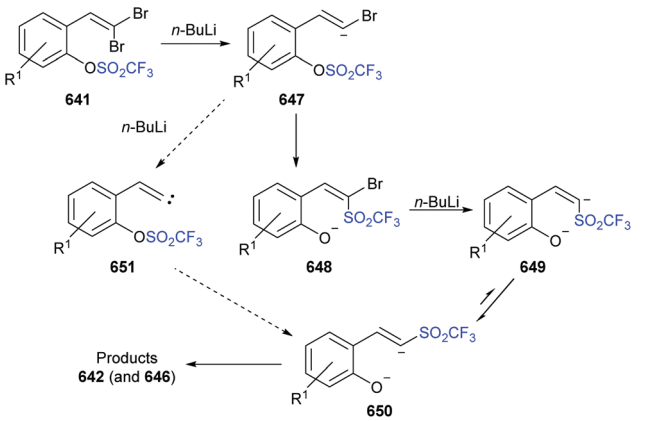


Scheme 96 Remote anionic Fries rearrangement of sulfonates: regioselective synthesis of indole triflones.



Scheme 97 1,5- and 1,6-triflyl migration of *gem*-dibromovinyl compounds.



Scheme 98 Proposed mechanism for the 1,5-triflyl migration of *gem*-dibromovinyl compounds.

ditions, while competition experiments demonstrated the likelihood of an intramolecular 1,5-sulfonyl migration. Therefore, the following mechanism was proposed (Scheme 96). Deprotonation of **635** by NaH affords the nitrogen anion **637**, which undergoes intramolecular 1,5-sulfonyl migration to give intermediate **638**, which following protonation and tautomerisation affords the rearranged indole **636**.

The Shibata group also demonstrated the synthesis of a series of vinyl triflones **642** in a stereoselective manner *via* remote anionic thia-Fries rearrangement from a series of *gem*-dibromovinyl substrates (Scheme 97).[130] Employing two equivalents of *n*-BuLi, the requisite substrates **641** afforded exclusively *E*-vinyl triflones **642** in moderate to good yields, *via* 1,5-triflyl migration, with both electron-donating and electron-withdrawing substituents on the aryl ring well tolerated. The triflyl moiety was crucial to the transformation; no migration was observed for the analogous methanesulfonates. Interestingly, the indole derivative **643** also readily underwent rearrangement, and is the first example of an anionic 1,6-migration. The methodology could also be utilised in a tandem reaction with methyl formate as an electrophilic partner which led to cyclisation after the rearrangement, affording heteroaryl triflones **646** in moderate yields.

Based on these results the authors postulated that lithium–bromine exchange of the substrate **641** and *n*-BuLi affords the anion **647** (Scheme 98), which undergoes remote anionic thia-Fries rearrangement, induced by the electron-withdrawing nature of the trifluoromethyl group, to afford the phenolate **648**. The presence of the electron-withdrawing triflyl moiety activates the remaining bromine in **648** to undergo lithium–bromine exchange with the second equivalent of *n*-BuLi to afford the intermediate **649** which rapidly isomerises to the more thermodynamically stable intermediate **650**. This isomerisation explains the stereoselective generation of the *E*-vinyl triflones **642** and the cyclised products **646**.

5.2.3. Anionic thia-Fries rearrangement of organometallic complexes. In 2006, as part of their efforts to generate (η^6-aryne)chromiumtricarbonyl complexes, the Butenschön group studied the reactions of chromiumtricarbonyl complexes of arene triflates. They were surprised to find that none of the expected product **652** was observed under standard basic conditions. Instead, they uncovered the first examples of anionic thia-Fries rearrangement of organometallic substrates to afford a series of *ortho*-(trifluoromethylsulfonyl)phenol chromium complexes **653** in high yields (Scheme 99).[131] Notably, the reaction tolerates both electron-rich and *ortho*-substituted substrates **651** that would normally be expected to favour elimination of the triflate. The preference for the thia-Fries rearrange-

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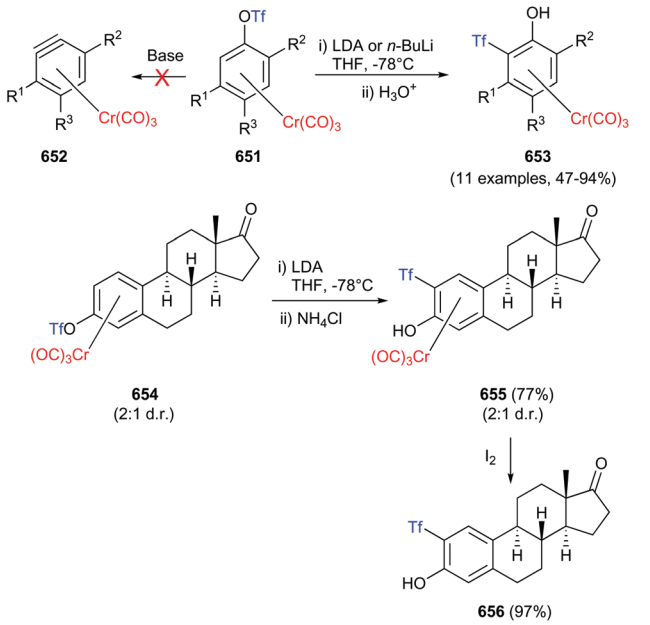
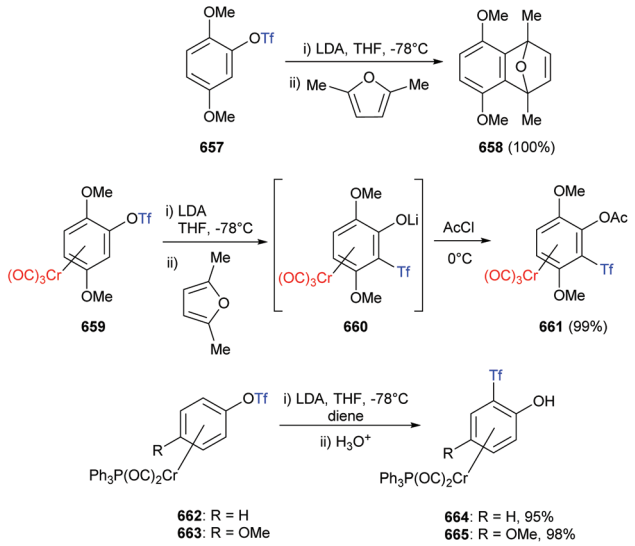


Scheme 99 First example of an anionic thia-Fries rearrangement at organometallics.

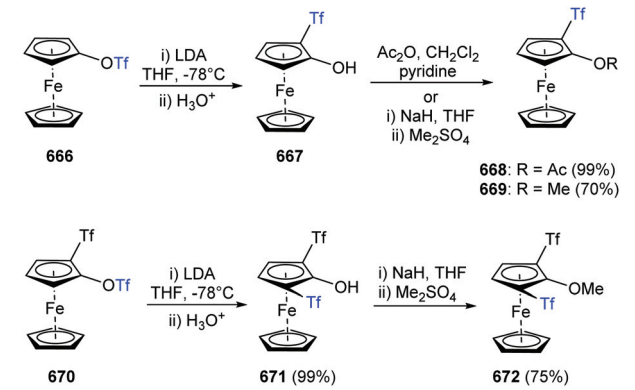


Scheme 100 Attempted compensation of the electron withdrawing effect of the tricarbonylchromium complex; no inhibition of the anionic thia-Fries rearrangement observed.

ment is likely attributable to the electron-withdrawing effect of the chromiumtricarbonyl moiety, which is better satisfied by the formation of the rearranged phenolate. The methodology was subsequently applied to the structurally complex estrone **654** (Scheme 99). Under standard basic conditions regioselective thia-Fries rearrangement occurred to afford the phenolic estrone complex **655** in 77% yield. Iodine-mediated decomplexation afforded the desired steroid **656** in 97% yield.

In an attempt to compensate for the highly electron-withdrawing tricarbonylchromium moiety, which was believed to be the main factor inhibiting aryne generation, the authors hypothesised that the introduction of further strongly electron-donating groups may generate more electron-rich triflates more susceptible to elimination.[132] Therefore, the triflate **657**, bearing two methoxy substituents, was prepared and subjected to basic conditions in the presence of 2,5-dimethylfuran as trapping reagent (Scheme 100). The desired cycloadduct **658** was isolated in quantitative yield demonstrating the suitability of triflate **657** to undergo base-mediated triflate elimination. On the other hand, the analogous reaction of the tricarbonylchromium complex **659** instantaneously afforded the anionic-thia Fries rearrangement product **660** exclusively, and upon acylation the product **661** was isolated in quantitative yield. As part of the same investigation, two (triphenylphosphine)dicarbonylchromium complexes, **662** and **663** were investigated. Despite the fact that it has been shown that replacement of one carbonyl ligand by triphenylphosphine reverses the electron-withdrawing effect of the chromium moiety,[133] when **662** or **663** were treated with LDA in THF at −78 °C in the presence of trapping reagents, the anionic thia-Fries rearrangement was again the exclusive pathway, leading to **664** and **665** in almost quantitative yields (Scheme 100).[132] As a result it can be concluded that electronics do not exert a significant effect on the outcome of the reaction, with organochromium complexes favouring anionic thia-Fries rearrangement.

In a further attempt to favour aryne formation, the Butenschön group attempted to use ferrocene derivatives in lieu of chromium complexes, hoping that the more electron-rich ferrocene derivatives might circumvent the problems encountered when using the highly electron-withdrawing tricarbonylchromium group. However, in spite of the more electron-rich substrate, ferrocenyl triflate **666** underwent a highly efficient anionic thia-Fries rearrangement instead of triflate elimination (Scheme 101).[134] Lowering the temperature of the reaction from −78 °C to as low as −117 °C did not lead to any formation of ferrocyne product. This was the first example of an anionic thia-Fries rearrangement in a five-membered ring. The remarkable efficiency of the transformation was further



Scheme 101 Attempted use of electron-rich ferrocenyl triflate derivatives to achieve ferrocyne formation; first example of anionic thia-Fries rearrangement in a five-membered ring.

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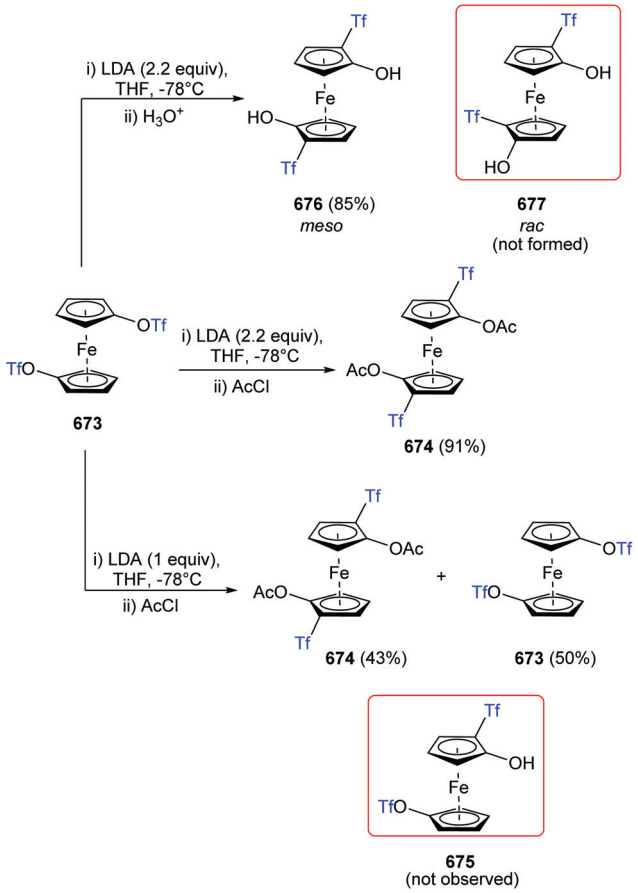
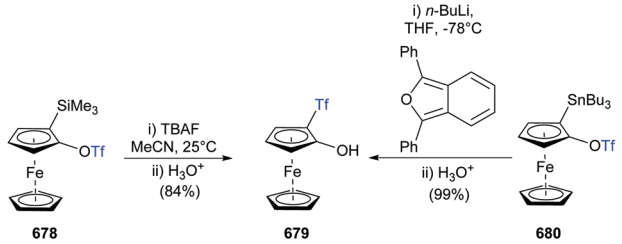


Scheme 102 Double anionic thia-Fries rearrangement of 1,1′-ferrocenediyl ditriflate **673**.

demonstrated by the reaction of the more electron-poor ferrocene triflate **670**, which also readily underwent rearrangement in quantitative yields (Scheme 101).

Interestingly, when 1,1′-ferrocenediyl ditriflate **673** was treated with 2.2 equivalents of LDA at −78 °C a double anionic thia-Fries rearrangement occurred giving **676** in 85% yield.[134] Although this reaction could yield two diasteromeric rearrangement products, *meso*-**676** and *rac*-**677**, only the *meso* diastereomer was observed, *i.e.* the reaction proceeds with complete diastereoselectivity (Scheme 102). To further probe this exceptional diastereoselectivity the authors attempted to obtain the single anionic thia-Fries rearrangement product **675** by instead using 1 equivalent of LDA. However, the reaction gave an almost equimolar mixture of the starting material **673** and the double rearrangement product **674** after acylation, highlighting that the rate of the second anionic thia-Fries rearrangement is significantly faster than that of the first (Scheme 102).

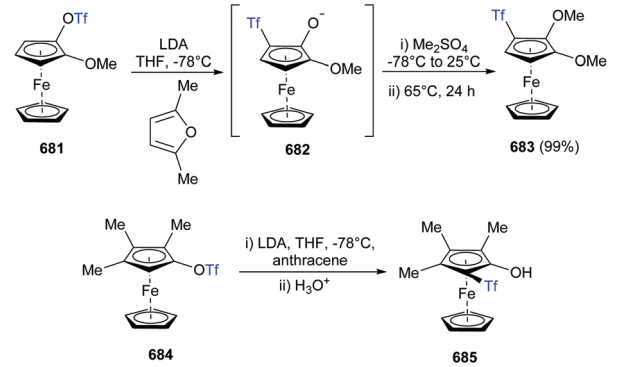
In order to probe the effect of *ortho*-lithiation on the reaction outcome the authors prepared 2-(trimethylsilyl)ferrocenyl triflate **678** for comparison. Upon treatment with TBAF in acetonitrile at 25 °C, exclusive anionic thia-Fries rearrangement occurred immediately to afford **679** in 84% yield (Scheme 103).[135] Metalation of the *ortho*-position was considered as an alternative to anion formation, hence the tributylstannyl compound **680** was treated with *n*-BuLi to induce metal exchange to the respective lithio compound. However, exclusive anionic thia-Fries rearrangement was again observed affording **679** in quantitative yield (Scheme 103). This was described as the first example of an anionic-thia Fries rearrangement induced by *ortho* metalation.



Scheme 103 First example of anionic thia-Fries rearrangement induced by *ortho* metalation.

In light of the anionic thia-Fries rearrangement occurring for ferrocenyl triflates upon both *ortho* deprotonation as well as *ortho* metalation, the authors sought to determine how electron-rich the ferrocenyl triflate can be tailored to still allow the reaction. Even the more electron-rich methoxy derivative **681** also afforded exclusively the anionic-thia Fries rearrangement product **683** in quantitative yield (Scheme 104).[135] Therefore, it is clear that excess electron density in the ferrocene system does not prevent rearrangement. Sterics were hypothesised to be a possible factor that may favour ferrocyne formation *via* elimination, however, treatment of the trimethyl derivative **684** under standard basic conditions in the presence of anthracene as cycloaddition trapping reagent afforded exclusively the anionic thia-Fries rearrangement product **685** (Scheme 104). Notably, while triflate elimination is the most prominent method for the generation of arynes, there is little correlation between aromatic systems and their analogous organometallic derivatives. As a result, the procurement of organometallic arynes remains an ongoing research pursuit.

Prior to Lloyd-Jones' discovery of the anionic thia-Fries rearrangement in 2003, the Minami group observed an oxygen



Scheme 104 Exclusive anionic thia-Fries rearrangement of ferrocenyl triflates despite incorporation of electron-donating groups.

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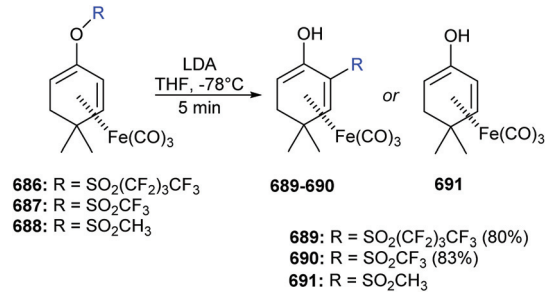
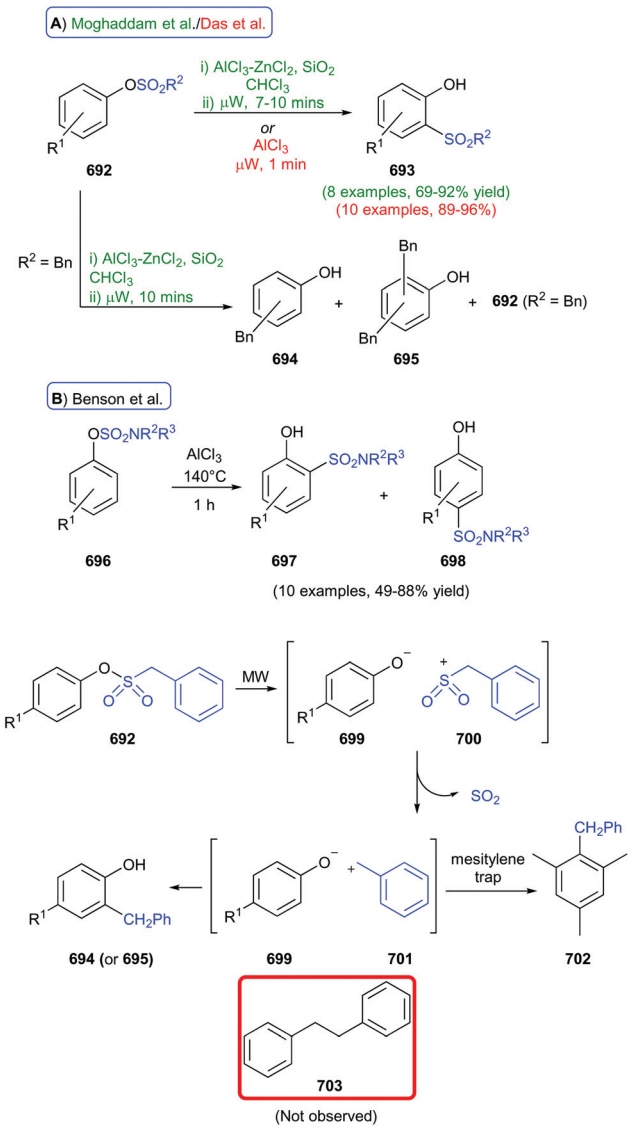


Scheme 105 *O*- to *C*-1,3-sulfonyl migration in iron-complexed non-aromatic cyclohexadienes.

to carbon 1,3-sulfonyl migration of both phosphonates and sulfonates in cyclohexadiene systems (Scheme 105).[136] Notably, iron coordination to the 1,3-diene with either a phosphate or sulfonate moiety allows *ortho* deprotonation of the C-3 position, which facilitates the overall 1,3-sulfonyl migration. The rearrangement proceeds rapidly and efficiently under basic conditions with **689** and **690** afforded in high yields after five minutes. However, when the migrating group contained acidic protons, *e.g.* a methanesulfonyl group, no migration was observed, and the iron dienol complex **691** was favoured instead. Crossover experiments for the phosphonate derivatives determined that the migration is likely an intramolecular process.

5.2.4. Non-anionic thia-Fries rearrangement. While the last two decades have seen considerable attention devoted to the development of the understanding of the anionic thia-Fries rearrangement, significantly less attention has been afforded to thia-Fries rearrangements *via* metal catalysis, microwave or photoirradiation techniques.

Moghaddam and Das almost simultaneously reported the high yielding thia-Fries rearrangement of aryl sulfonates **692** in the presence of anhydrous aluminium trichloride under microwave conditions (Scheme 106A).[137,138] Moghaddam's method involved using an $AlCl_3$-$ZnCl_2$ supported on silica gel in conjunction with microwave irradiation with similar efficiencies and yields. Das also demonstrated that the methodology could readily be used for the analogous reaction of aryl sulfonanilides with similar efficiencies and yields obtained. When Moghaddam *et al.* later attempted to extend their methodology to incorporate aryl benzylsulfonates, a pseudo-thia-Fries rearrangement was instead observed, with the *ortho*- and *para*-benzylated phenols **694**, and the dibenzylated phenols **695** isolated.[139] Unlike the photochemical thia-Fries rearrangement, which is known to proceed *via* a radical mechanism, the authors postulated that the reaction occurs *via* initial heterolytic cleavage of the O–S bond to generate a phenolate and a benzylsulfonyl cation which decomposes by elimination of SO_2 to afford the active benzyl cation (Scheme 106). The cationic mechanism was supported by the capture of the hypothesised benzyl cation by the cation scavenger mesitylene to afford **702**. Furthermore, no evidence for the presence of the benzyl radical coupling product diphenylethane **703** was observed, also supporting the cationic mechanism. Benson *et al.* subsequently reported the $AlCl_3$-mediated thermal thia-Fries type rearrangement of aryl sulfamates **696** to generate aryl sulfonamides **697** and **698** in moderate to high yields (Scheme 106B).[140]



Scheme 106 Non-anionic thia-Fries rearrangement.

Sharghi *et al.* reported the use of $Al_2O_3/MeSO_3H$,[141] and subsequently graphite/$MeSO_3H$[142] mixtures as novel reagents for a solvent-free thermal thia-Fries rearrangement of aryl tosylates **704** to afford hydroxy aryl sulfones in high yields (Scheme 107A). An intermolecular ionic mechanism was presented by the authors, with the presence of a sulfonyl cation intermediate, confirmed *via* trapping of the cation with electron-rich *m*-xylene. Furthermore electron-poor *meta*- and *para*-nitro derivatives **704** failed to undergo rearrangement providing further evidence for the proposed mechanism.

Crevatín *et al.* reported the photo-thia-Fries rearrangement for a series of 9*H*-carbazol-2-yl-sulfonates **707** to afford the

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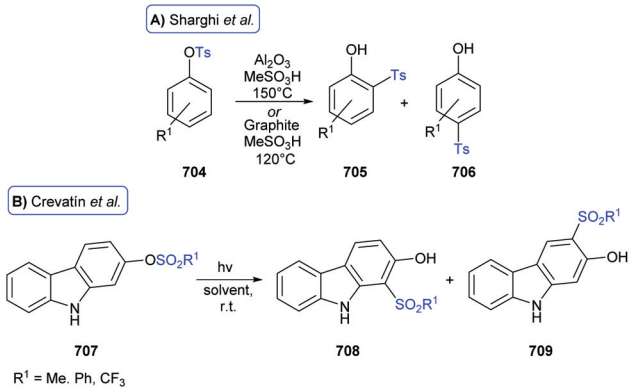


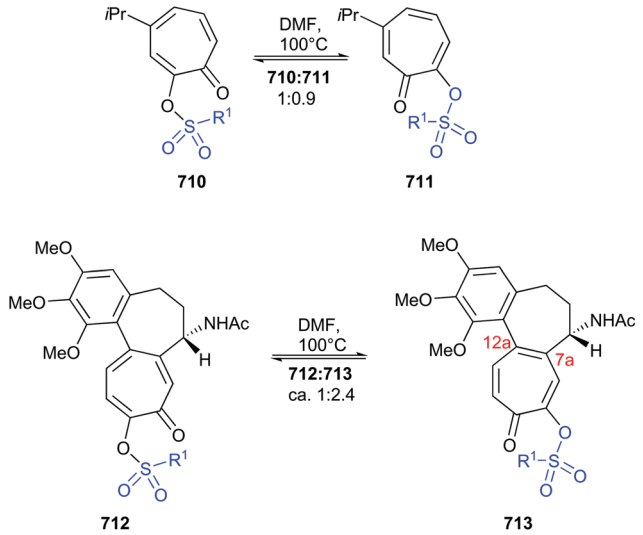
Scheme 107 Non-anionic thia-Fries rearrangement.

respective alkyl- and arysulfones **708** and **709** (Scheme 107B).[143] Under photoirradiation, regardless of reaction solvent utilised (MeCN, MeOH, benzene, cyclohexane), the *ortho*-rearranged products **708** and **709** were obtained in a molar ratio of approx. 2 : 1, with **708** always being the favoured isomer. Semi-empirical and *ab initio* optimisation of the 2-hydroxy-9*H*-carbazole radical were used to rationalise the regioselectivity of the reaction, with a slightly higher charge density observed at C(1) when compared to C(3). Furthermore, hydrogen bonding with the carbazole N–H may assist with the migration to C(1); this is not possible for rearrangement to C(3) due to geometry.

6. Oxygen to oxygen sulfonyl migration

Cavazza and Pietra reported the first examples of fluxional sulfonates, in which a formal thermal 1,4-oxygen to oxygen sulfonyl migration for tosyl and mesyl substituents was observed for troponoid **710** and colchicinoid **712** derivatives (Scheme 108).[144] In all instances an equilibrium was observed. For example, when the tosylate of β-thujaplicine **710** was heated in DMF at 100 °C a 1 : 1.09 mixture of **710** and 2-tosyloxy-6-isopropyltropone **711** was afforded after 2.5 hours. Isolation of pure **711**, followed by heating under the aforementioned conditions, again afforded a 1 : 0.9 mixture of **710** : **711** confirming the equilibrium process. A similar effect was observed for the colchicine **712**/isocolchicine **713** system, amongst other derivatives, in this case the equilibrium favoured the isomer bearing a double bond between C7a and C12a (**712** : **713** *ca.* 1 : 2.4) (Scheme 108).

The mechanism can be rationalised *via* an intramolecular nucleophilic addition of the carbonyl oxygen atom to the electron-deficient sulfur atom of the sulfonyl moiety, generating a trigonal bipyramidal intermediate bearing negatively-charged oxygen atoms occupying the apical positions. Molecular mechanics calculations indicate that such an intermediate would have low strain, which is in contrast with the high strain that would be expected of a trigonal bipyramidal transition state



Scheme 108 Fluxional sulfonyl derivatives of troponoids and colchicinoids; observation of a formal 1,4-oxygen to oxygen sulfonyl migration.

formed *via* a concerted entering and leaving of the respective oxygen atoms. Also, the highly polarised character of the rate-determining transition state is borne out by the fact that a higher rate of reaction was observed in DMF than toluene.

In their efforts to access the aglaroxin C analogue **716**, of the rocaglate family of natural products, Zhang *et al.* hypothesised that the tosyl-enol rocaglate **714** could undergo base-mediated conjugate addition with benzamidine, followed by elimination of the tosyl moiety to give the enamine **715** which upon ring closure would afford the desired pyrimidinone product **716** (Scheme 109).[145] When the reaction was carried out using NaH as base, the isolated product was in fact the amidino-rocaglate **721**. The authors attributed this transformation to an intercepted retro-Nazarov reaction. Deprotonation of **714** affords the anionic intermediate **717** which undergoes an intramolecular 1,4-oxygen to oxygen tosyl migration to give the enolate **718**. Elimination of the tertiary tosylate generates the stabilised oxyallyl cation **719**. Nucleophilic addition of amidine and subsequent cyclisation affords the product **721**. Using this methodology, a series of amidino- and amino-rocaglates were synthesised (46 examples, up to 93% yield).

7. Carbon to carbon sulfonyl migration

7.1. N-heterocyclic carbene-catalysed sulfonyl migration

Atienza *et al.* described the N-heterocyclic carbene (NHC) catalysed 1,2-sulfonyl migration of 1,1-bis(sulfonyl)ethylene derivatives **722** and their subsequent reactivity with 1,3-dipoles (predominantly nitrones **723**) to generate a series of highly functionalised isoxazolidine derivatives **724** as single diastereomers in good to excellent yields (Scheme 110).[146] Mechanistic

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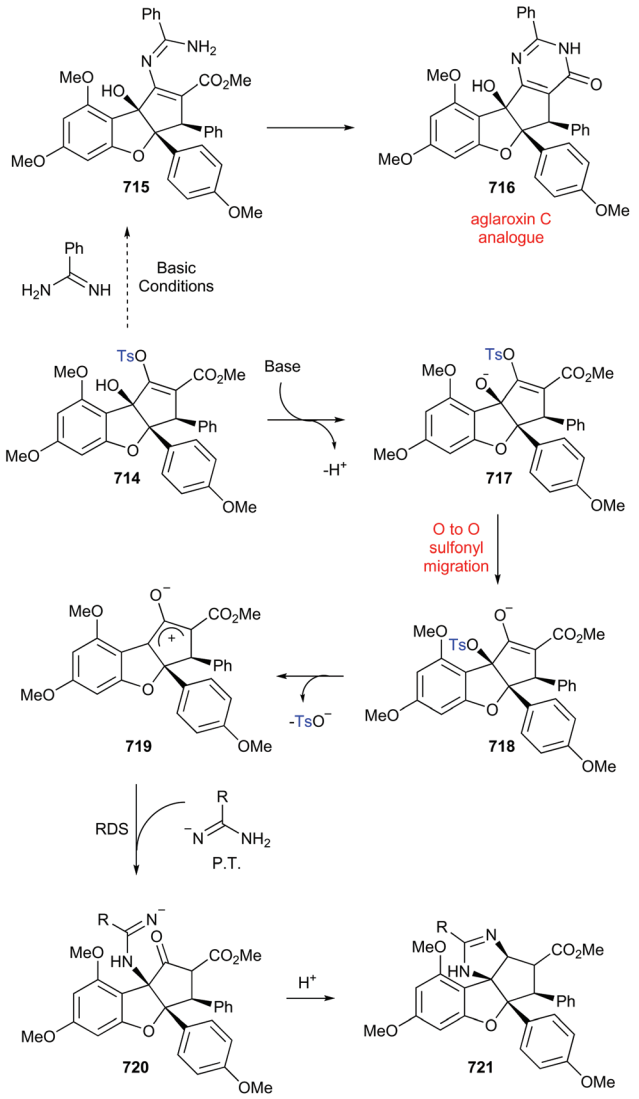
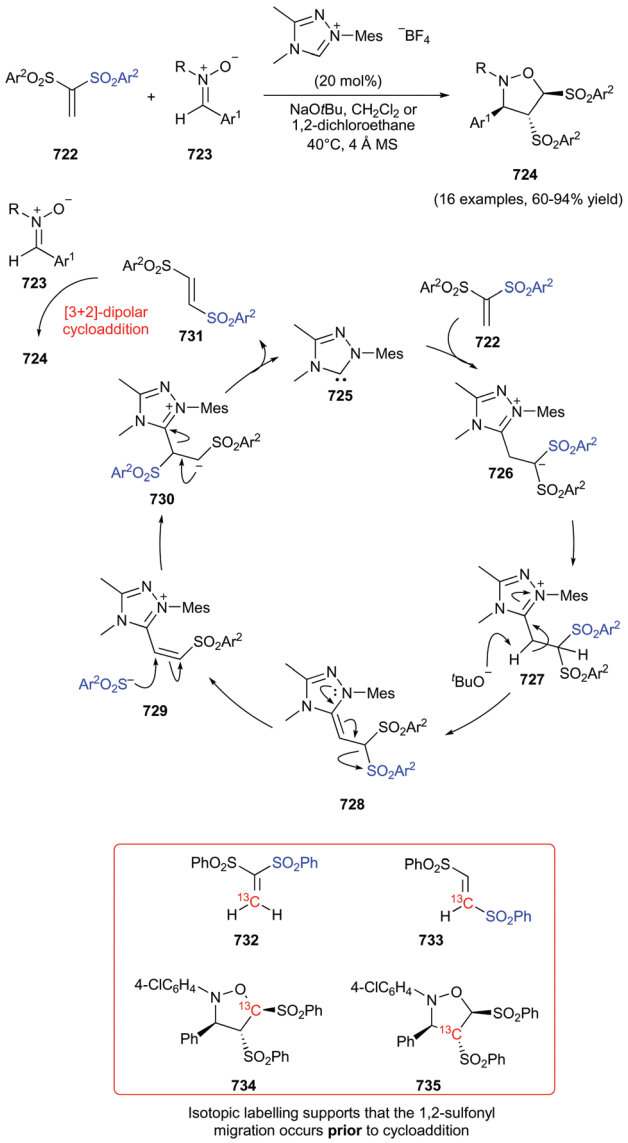


Scheme 109 Generation of amidino-rocaglate derivatives *via* an intercepted retro-Nazarov reaction; observation of a 1,4-oxygen to oxygen sulfonyl migration.



Scheme 110 N-Heterocyclic carbene-catalysed 1,2-sulfonyl migration of vinyl sulfones.

studies informed that the sulfonyl migration was an intermolecular process as supported by crossover experiments. Furthermore, the NHC catalyst **725** was not necessary for the [3 + 2]-dipolar cycloaddition to occur, however its presence was crucial for the isomerisation of the 1,1-bis(sulfonyl)ethylene derivative **722** to the rearranged *trans*-1,2-bis-alkene **731** as illustrated in Scheme 110. In addition, ^{13}C-labelling of **732** highlighted that the 1,2-sulfonyl migration occurs prior to the cycloaddition step as evidenced by isolation of a mixture of labelled products **734** and **735**. Notably, if only the ^{13}C-labelled vinyl sulfone isomer was present at the cycloaddition step isotopic labelling would only be observed at one position in the product.

Yamada and co-workers described the N-heterocyclic-carbene-mediated cyclisation of sulfonylalkynols **736** with concomitant 1,2-sulfonyl migration to afford 5- and 6-membered oxacycles **737** in high yields (Scheme 111).[147] While *N*-formylalkynamides cyclised smoothly under the same conditions, *N*-sulfonylalkynamide derivatives required the use of NHC **740** in conjunction with proton sponge as the base. The mechanism is believed to proceed *via* the allenyl sulfone intermediate **742** which is generated *in situ* on reaction of the sulfonylalkynol **741** with base. Applying this intermediate to the standard reaction conditions led to isolation of the desired product in high yield. Nucleophilic addition of the NHC to **742**, followed by a proton transfer affords the intermediate **743** which cyclises with accompanying tosylate extrusion to give **744**. This tosylate reacts with another equivalent of the allene intermediate **742** to give the intermediate **745**, which completes the formal 1,2-sulfonyl migration. A final cyclisation affords the desired vinyl sulfone **746**. That tosylate initiates the productive cycle was supported by carrying out the reaction in

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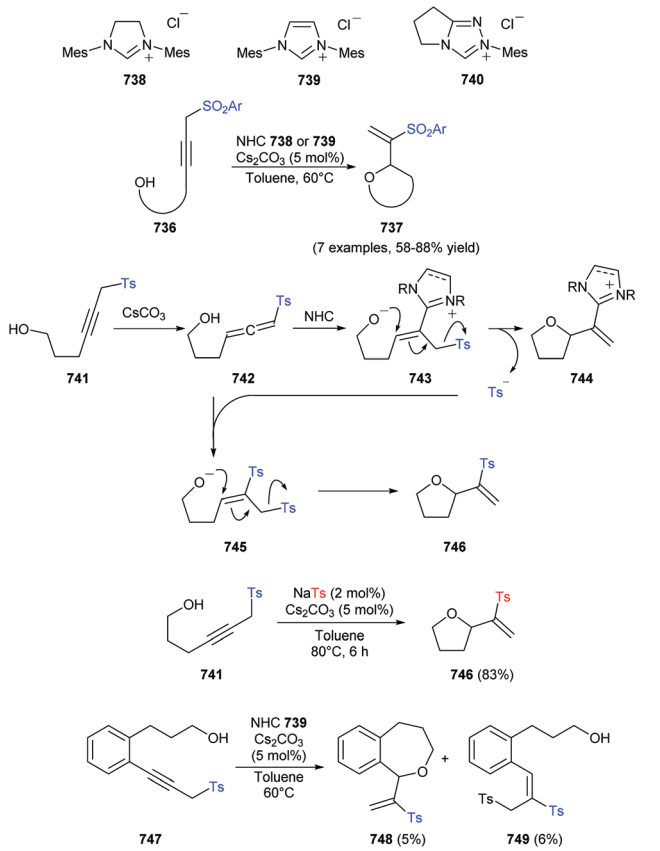
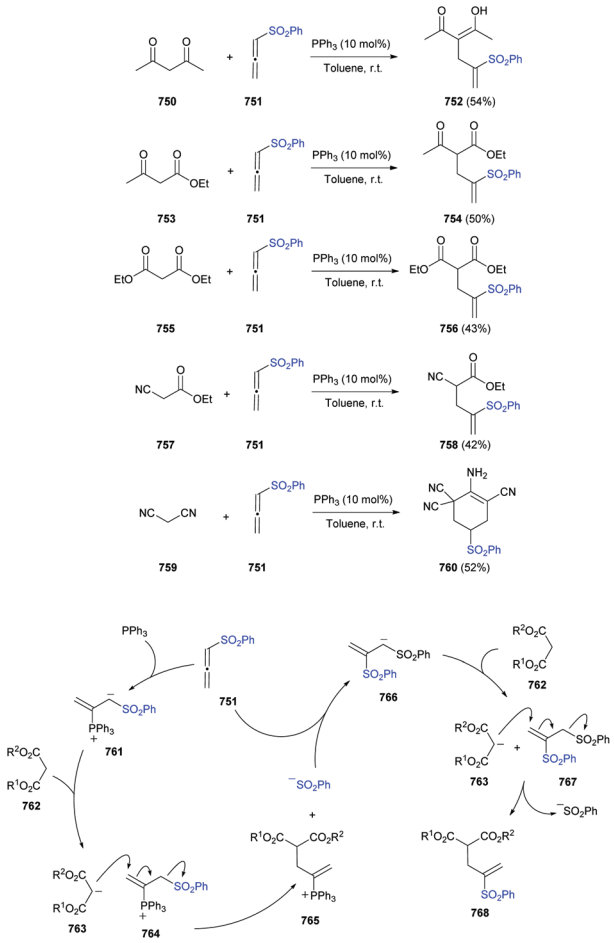


Scheme 111 NHC-mediated cyclisation of sulfonylalkynols forming oxacycles with accompanying 1,2-sulfonyl migration.



Scheme 112 Triphenylphosphine-catalysed 1,2-sulfonyl migration of electron-deficient allenes in their reaction with active methylene compounds affording vinyl sulfones.

the presence of *p*-toluenesulfinate (2 mol%) in the absence of the NHC mediator. This experiment afforded the desired product **746** in 83% yield. The isolation of the disulfone **749** when the propargyl sulfone **747** was reacted under the standard conditions (in refluxing toluene) supports the formation of **745** as an intermediate in the reaction pathway. The group subsequently reported that the reaction can be carried out with either catalytic triphenylphosphine or DMAP in place of the N-heterocyclic carbene.[148]

7.2. Triphenylphosphine-catalysed sulfonyl migration

Lu *et al.* described the triphenylphosphine-catalysed 1,2-sulfonyl migration of electron-deficient allenes **751** in their reaction with active methylene compounds to give vinyl sulfones in moderate yields (Scheme 112).[149] While mechanistic studies were not undertaken the authors postulated that the migration occurs *via* the *in situ* generation of the sulfinate anion as described in Scheme 112. Upon its formation it is readily conceivable that the nucleophilic sulfinate could add to the allene **751** to form the vinyl anion **766**, which can deprotonate the active methylene compound **762** to form the allylic sulfone **767**. Subsequent addition of the anion **763** to **767** leads to elimination of the allylic sulfone, generating the desired rearranged product **768**.

Hampton and Harmata reported the use of triphenylphosphine as a nucleophilic catalyst in the isomerisation of allenic sulfones **769** to afford 2-arylsulfonyl 1,3-dienes with catalytic phenol used as a proton shuttle (Scheme 113).[150] The formal carbon to carbon 1,2-sulfonyl migration was rationalised by the following mechanism as previously described: nucleophilic addition of triphenylphosphine to the β-carbon of the allene substrate **771** affords **772** which is protonated by phenol to give the phosphonium salt **773**; the phenoxide anion deprotonates **773** which leads to the elimination of the tosylate anion, which undergoes nucleophilic addition to the β-carbon of the allene substrate **771** affording the anionic intermediate **775**; subsequent protonation by phenol, and deprotonation of **776** releases tosylate for the next catalytic cycle while generating the desired product **777**.

In a subsequent report the authors provided a series of supporting experiments confirming the likelihood of the presented mechanism (Scheme 114).[151] Crossover experiments indicated an intermolecular sulfonyl migration, while the reaction was observed to proceed in the absence of triphenylphosphine when an external source of sulfinate anion was

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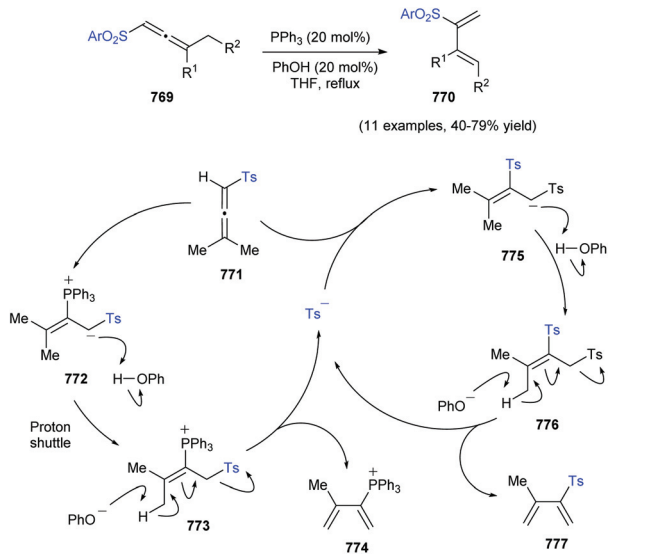
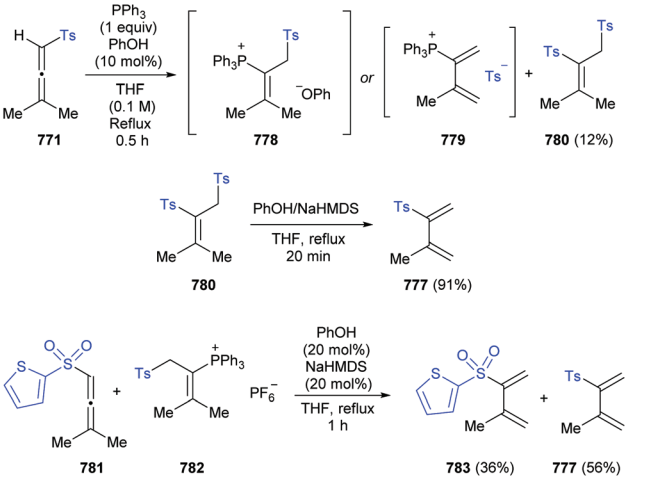


Scheme 113 Isomerisation of allenic sulfones affording 2-arylsulfonyl 1,3-dienes catalysed by triphenylphosphine.

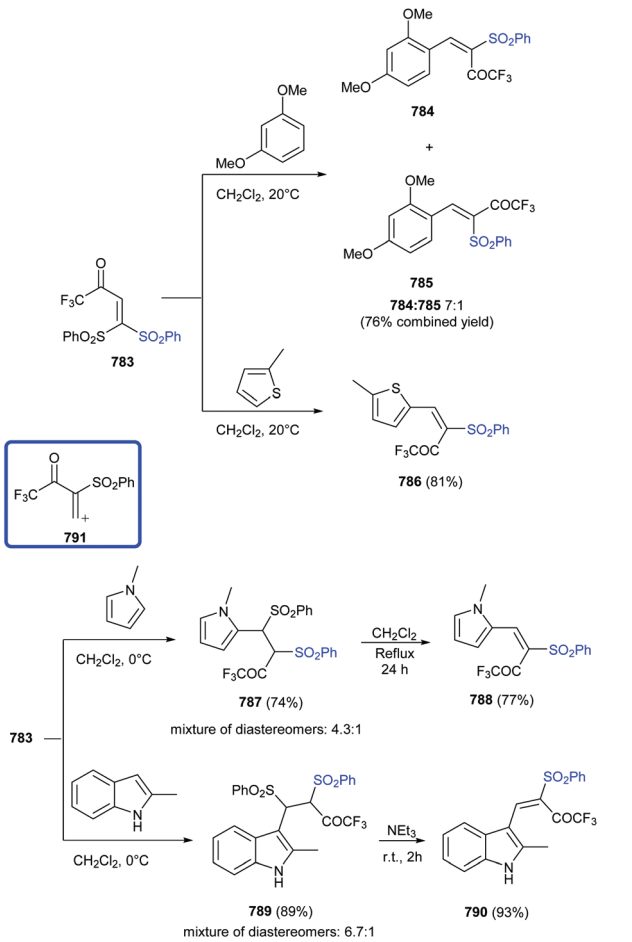


Scheme 114 Hampton and Harmata's supporting evidence for the proposed mechanism for the triphenylphosphine-catalysed isomerisation of allenic sulfones to 2-arylsulfonyl 1,3-dienes.

added in the presence of the proton shuttle phenol. While the phosphonium salt intermediates did not prove amenable to isolation, tentative evidence for the presence of either **778** or **779** was provided by ^{31}P NMR for the reaction of the allene **771** with one equivalent of triphenylphosphine. In this reaction, the proposed intermediate, the disulfone **780** was isolated in 12% yield. To ensure that this intermediate could lead to the dienyl product **777**, it was prepared independently and treated with *in situ* generated sodium phenoxide which afforded the desired product **777** in 91% yield. The authors were able to independently synthesise the phosphonium salt **782**, which compared favourably to the ^{31}P NMR data for the proposed intermediate **778** or **779**. To prove unequivocally that this salt was indeed an intermediate of the proposed reaction pathway it was reacted with the allene **781** in a crossover experiment in the presence of *in situ* generated sodium phenoxide. Notably, both **783** and **777** were formed consistent with the phosphonium salt **778** being an intermediate in the migratory process. DFT studies carried out by the Li group were consistent with the Hamata group's proposed mechanism for this process, and particularly support the role of phenol as proton shuttle.[152]

7.3. Miscellaneous sulfonyl migration

Krasovsky *et al.* developed a novel electrophilic reagent, β-trifluoroacetylketene diphenyldithioacetal *S*,*S*′-tetroxide **783**, that allowed access to a range of previously undescribed 1,1,1-trifluoro-4-aryl-3-(phenylsulfonyl)but-3-en-2-ones **584–586**, **788** and **790** *via* Michael-like additions of electron-rich aromatic derivatives (Scheme 115).[153] The highly electrophilic reagent **783** readily reacted with 1,3-dimethoxybenzene and 2-methylthiophene to afford the ketones **584–586** in high yields under mild conditions. Notably, the reaction occurs *via* an unusual 1,2-sulfonyl migration and elimination of one sulfonyl moiety.



Scheme 115 β-Trifluoroacetylketene diphenyldithioacetal *S*,*S*′-tetroxide as a synthetic equivalent for **791** in electrophilic aromatic substitution; observation of a 1,2-carbon to carbon sulfonyl migration.

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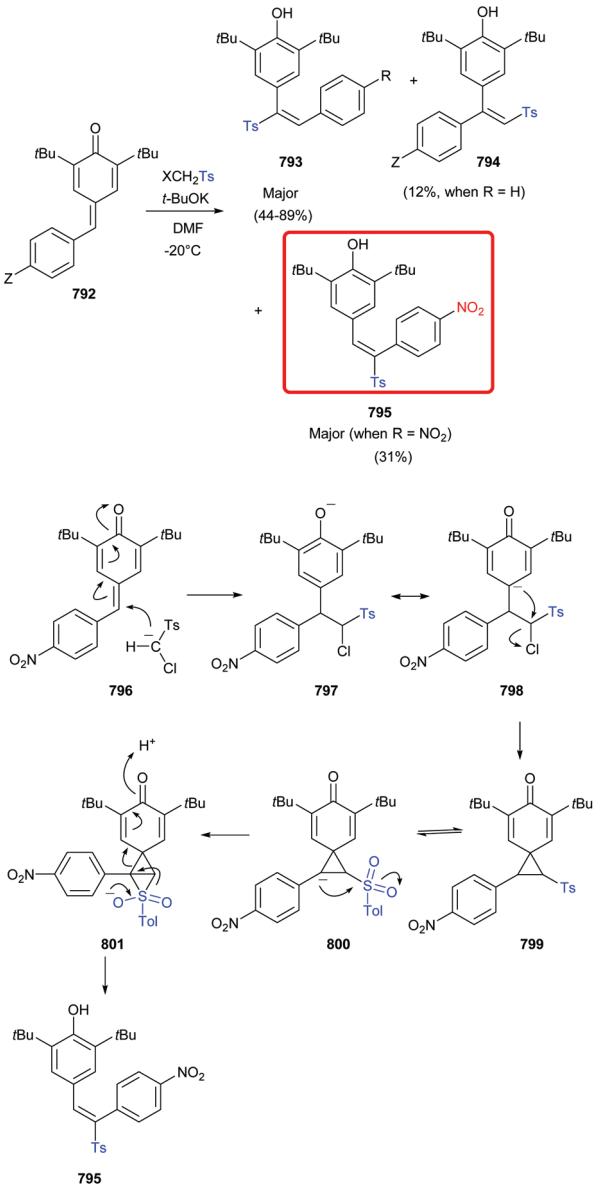
As such, the electrophilic ketone **783** is a synthetic equivalent for the cationic synthon **791** in reactions with electron-rich aromatics. Interestingly, reaction of **783** with the more electron-rich 2-methylindole and *N*-methylpyrrole occured with rearrangement, but no elimination, at low temperatures to afford a mixture of diastereomeric ketones **787** and **788** with good stereoselectivity. Elimination of the β-phenylsulfonyl moiety could be induced thermally for pyrrole derived ketone **787**, whereas basic conditions were required for the analogous reaction of the indolyl derivative **789**. Mechanistic studies were not part of this investigation.

In their studies on the reactivity of carbanions derived from α-substituted-methyl tolyl sulfones with quinone methides **792** as Michael acceptors, Groszek and Lemek observed an unusual 1,2-tosyl migration when a *para*-nitro substituent was incorporated on the phenyl ring of the quinone scaffold **792** (Scheme 116).[154] The authors tentatively proposed the formation of the spirodienone **799** as an unstable intermediate, which undergoes a divergent reaction pathway due the electron-withdrawing nature of the nitro group. This nitro moiety significantly increases the acidity of the benzylic proton relative to the other substituents studied (Z = H, NMe_2, OMe). In the presence of excess base the nitro group facilitates deprotonation allowing the anion **800** to cyclise to the hypervalent sulfur intermediate **801** *via* nucleophilic addition to the sulfur of the sulfonyl moiety.[144,155,156] Subsequent ring-opening and protonation leads to aromatisation and the acquisition of the rearranged product **795**.

Following their success achieving the enantioselective generation of chiral cyclopropenes from ethyl diazoacetate and various terminal alkynes using the $Rh_2(OAc)(DPTI)_3$ catalyst,[157] the Corey group sought to extend this methodology to include tosyl derivatives to further study the effects of strain in unsaturated cyclopropenes. Using the highly selective rhodium catalyst the chiral tosyl substituted cyclopropenes **804–806** were afforded in 91%, 94% and 78% ee respectively (Scheme 117).[158] Interestingly, when the 2-*n*-amyl-2-cyclopropenyl 4-tolyl sulfone **804** was purified by chromatography on silica gel, or allowed to stir with silica gel in benzene, complete racemisation was observed. Measurements of the kinetics of the thermal racemisation of **804** at 70 °C in each of the solvents benzene, cyclohexane and acetonitrile afforded very similar first-order rate constants, indicating that a polar dissociation mechanism *via* the formation of a cyclopropenium toluene–sulfinate ion pair was unlikely. Instead, a reversible [2,3]-sigmatropic rearrangement was proposed by the authors (Scheme 117). The reverse process, that is a sulfinate–sulfone allylic rearrangement, is well-known in the literature.

Evidence supporting the reversible [2,3]-sigmatropic rearrangement of **804** in the solution phase was provided by carrying out a trapping experiment with anhydrous CD_3OD (Scheme 118). Methanolysis of **804″** or *ent*-**804″** produced the isolable deuterated methyl toluenesulfinate **810**, and the cyclopropenol **808**, which despite being too unstable to isolate led to the β-deuterated α,β-enal **809** and the deuterated methyl acetal **811**. These results unequivocally support the generation



Scheme 116 Observation of a formal 1,2-sulfonyl migration from carbon to carbon *via* hypothesised hypervalent sulfur intermediate **801**.

of the sulfinate **804″**, formed *via* the first 2,3-sulfone-sulfinate allylic rearrangement. The instability of the cyclopropenol **808** is a direct consequence of high ring strain (approx. 55 kcal mol^{-1}) and the availability of a carbonyl-forming elimination process that can alleviate the strain. Ring strain can also explain the ring cleavage process that converts the sulfone **804‴** to the deuterated methoxy sulfone **813** *via* intermediate **812**. It is likely that the silica gel, acting as a weak protic acid, catalyses the racemisation through hydrogen bonding with one of the oxygen atoms of the migrating sulfonyl group in the transition state.

The synthetic value of sulfonyl migrations was utilised in Zakharov's enantioselective total synthesis of lycopodine **820**.[159,160] The observed 1,3-sulfonyl migration was the first

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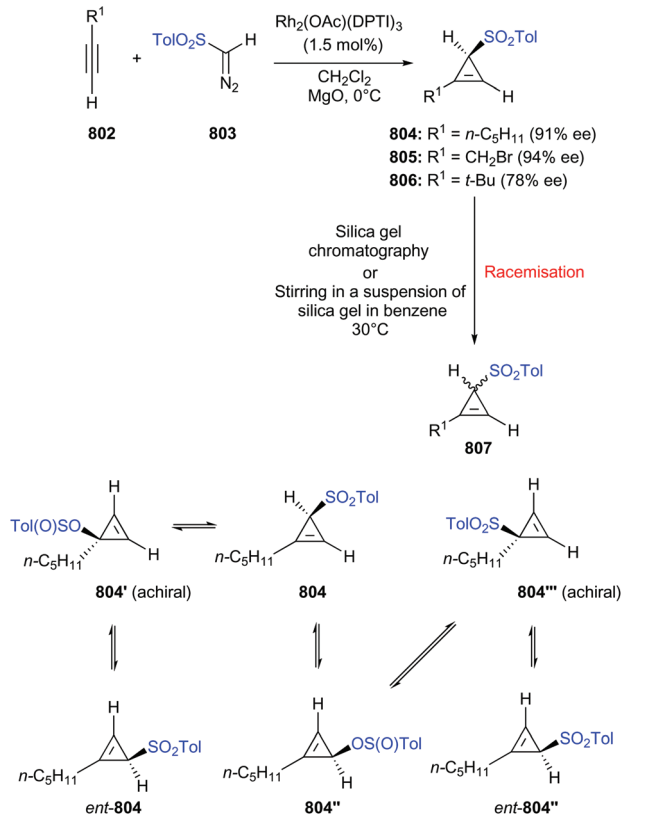
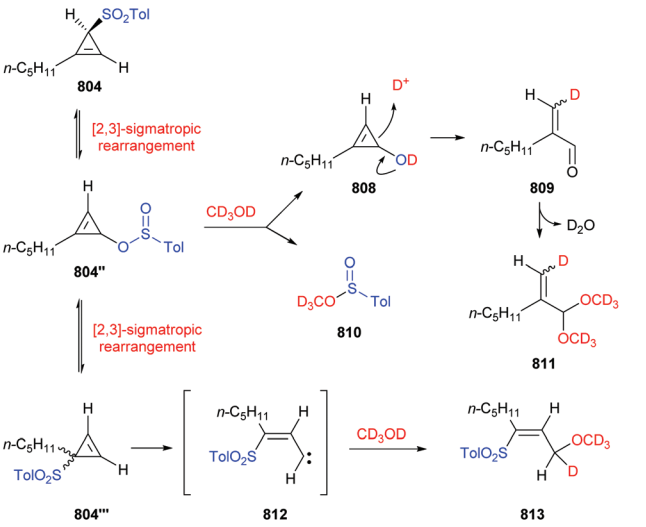
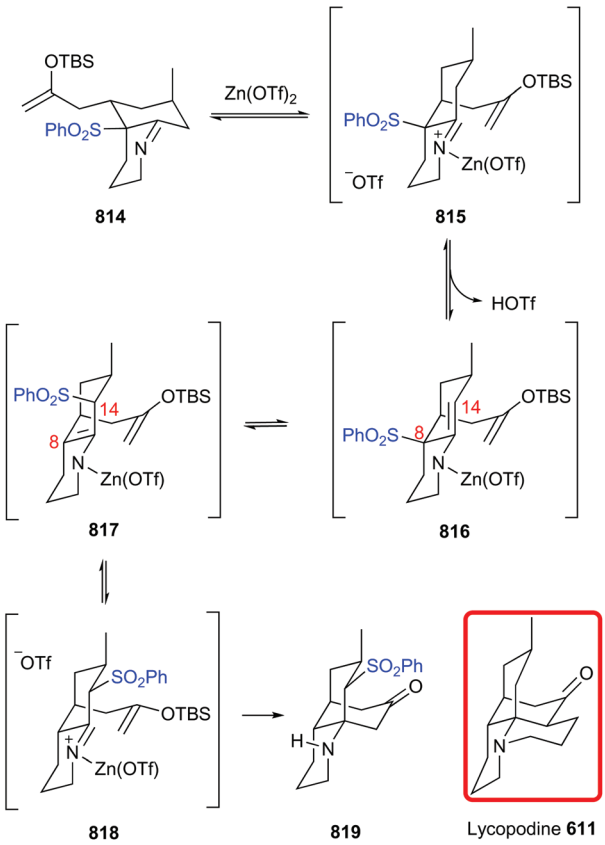


Scheme 117 Reversible 2,3-sulfone-sulfinate allylic rearrangement; formal 1,2-sulfonyl migration.



Scheme 118 Trapping experiment with CD_3OD confirming the sulfinate **804''** as an intermediate, evidence supporting a 2,3-sulfone-sulfinate allylic rearrangement.

example of a rearrangement of this type involving an α-sulfonyl imine. The proposed mechanism for the rearrangement is as follows (Scheme 119). Treatment of the silyl enol ether **814** with zinc triflate likely affords the zinc complex **815**



Scheme 119 The utilisation of a 1,3-sulfonyl migration in the enantioselective total synthesis of lycopodine.

which can tautomerise to the metallo-enamine **816**, which is considered to be the intermediate that undergoes the 1,3-migration of the sulfonyl moiety from C8 to C14. This rearrangement might occur through (i) heterolytic or homolytic cleavage of the C–S bond to yield an intimate ion-pair or radical pair respectively, followed by recombination at the C14 position; (ii) [2,3]-sigmatropic rearrangement to a sulfinate ester which reorganises to the sulfone **817**; or (iii) formation of a 1,1-dioxothietane intermediate and subsequent ring opening. Protonation of the enamine in a diastereoselective fashion and epimerisation at C14 generates intermediate **818** which *via* an intramolecular Mannich reaction yields the tricyclic product **819**.

The Robina group reported a sulfonyl moiety catalysed anionic [3 + 2] cycloaddition of allenyl sulfones **751** and sulfonyl imines **821** to afford 2-aryl-4-phenylsulfonyl-3-pyrrolines **822** in moderate yields (Scheme 120).[161] A nucleophilic mediator, in this instance $NaNO_2$, was required for the reaction to occur. The authors suggested that in order to rationalise the high regioselectivity of the transformation that the intermediate **826** must be involved in the process. They reasoned that this could be achieved *via* conjugate addition of *in situ* generated benzenesulfinate anion to the allenyl sulfone **751**. Nucleophilic addition of the anionic intermediate **823** to the *N*-sulfonylimine **824** forms the nitranion **825**. A 5-*endo-trig*

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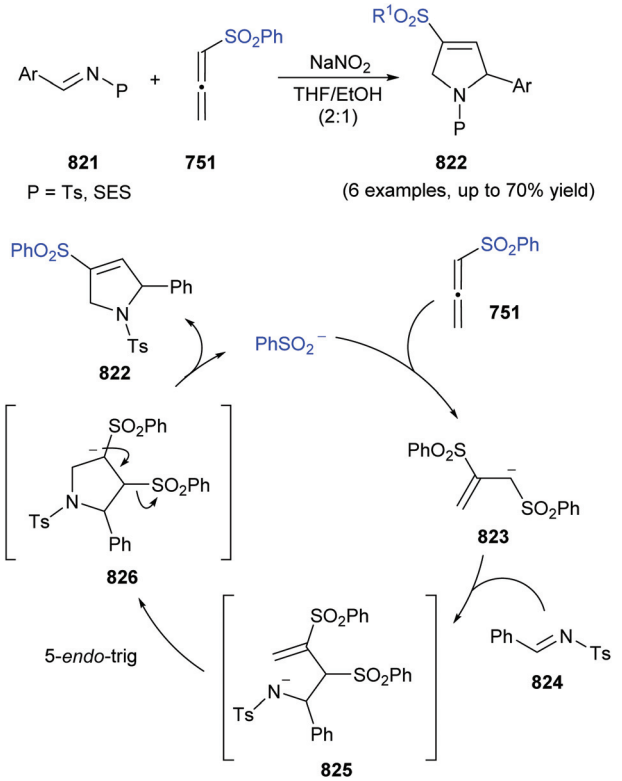
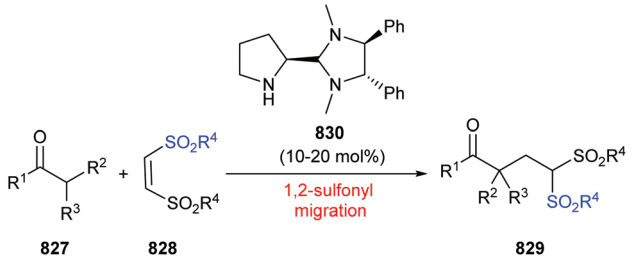
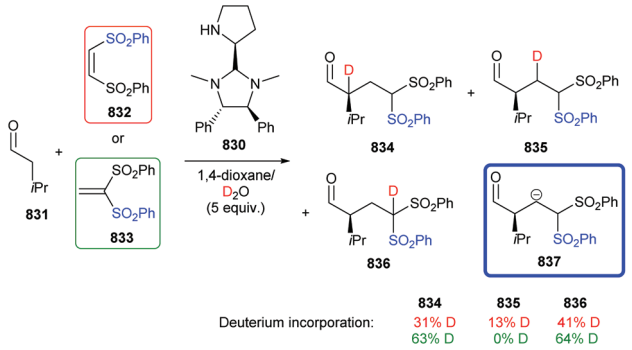


Scheme 120 Sulfonyl moiety-catalysed anionic [3 + 2] cycloaddition of allenyl sulfones and sulfonyl imines affording 2-aryl-4-phenylsulfonyl-3-pyrrolines.



Scheme 121 Organocatalyst mediated 1,2-carbon to carbon sulfonyl migration resulting from nucleophilic addition to bis activated vinyl-sulfones.



Scheme 122 Mechanistic studies supporting the formation of the anion intermediate **837**.

cyclisation, and subsequent β-elimination of the sulfonyl moiety affords the desired rearranged pyrroline **822**. The route toward the initial formation of benzenesulfinate is unclear, however it is believed to be promoted by addition of the nucleophilic mediator $NaNO_2$ to **751**, which could then react *via* several pathways to afford the necessary sulfinate anion.

Alexakis reported an intriguing 1,2-carbon to carbon sulfonyl migration resulting from nucleophilic addition to bis activated vinyl-sulfones **828**.[162,163] Various nucleophiles including aldehydes, ketones, malonates, keto-esters and nitro-esters activated by different organocatalytic sources (enamine, Brønsted base, thiourea) can promote this migration in moderate to excellent yields and enantioselectivities (Scheme 121). The authors reasoned that the mechanism likely proceeds *via* an anionic intermediate, formed upon Michael addition of the nucleophile and doubly activated vinyl sulfone. Indeed, anion trapping, by performing the reaction using *cis*-1,2-bis(phenylsulfonyl)ethene **832** in the presence of deuterium oxide, highlighted the existence of such an intermediate **837**, with the products **834–836** displaying deuterium incorporation at the α-, β- and γ-positions in 31%, 13% and 41% respectively (Scheme 122). A control experiment using 1,1-bis-(phenylsulfone)ethene **833** led to deuterium incorporation at the α- and γ-positions only in 63% and 64% respectively.

Considering these observations, the following mechanism was postulated. Michael addition, or [2 + 2] cycloaddition, affords the anionic intermediate **839**. Depending on the substrate and the relative conformation of the sulfone and the adjacent anion, two disparate mechanistic outcomes can be considered. If the lone pair and the sulfone moiety are preferentially antiperiplanar after an *anti*-addition, as can be seen in the Newman projection **848**, the elimination of sulfinic acid will be favoured. Alternatively, if the lone pair is in the proximity of the sulfonyl moiety after a *syn* addition as is the case for **846**, then the 1,2-sulfonyl migration will preferentially occur (Scheme 123). Protonation of the rearranged intermediate affords the desired product. Notably, the observation that the selectivity for the sulfonyl migration is enhanced by utilising larger nucleophiles is consistent with the proposed mechanism.

Subsequently, Rios demonstrated the application of this 1,2-sulfonyl migration in the asymmetric organocatalytic Michael addition of azlactones **850** to *cis*-1,2-bis(phenylsulfonyl)ethene **832** as a synthetically useful method for the generation of direct precursors to enantioenriched quaternary α-alkyl-α-amino acids **851** (Scheme 124).[164] The thiourea-based catalyst of Takemoto and co-workers (*S*,*S*)-**852** was determined to be the optimal catalyst for the transformation,[165] producing yields of up to 82% and enantiomeric excesses of up to 95%.

2-(Sulfonylmethyl)arylpyrroles **855** were observed to be accessible from α-allyl-β-ketosulfones **853** *via* a $PdCl_2/CuCl_2/NH_4OAc$-mediated domino Wacker-type aminocyclisation *via* selective 1,4-sulfonyl migration with moderate to good yields

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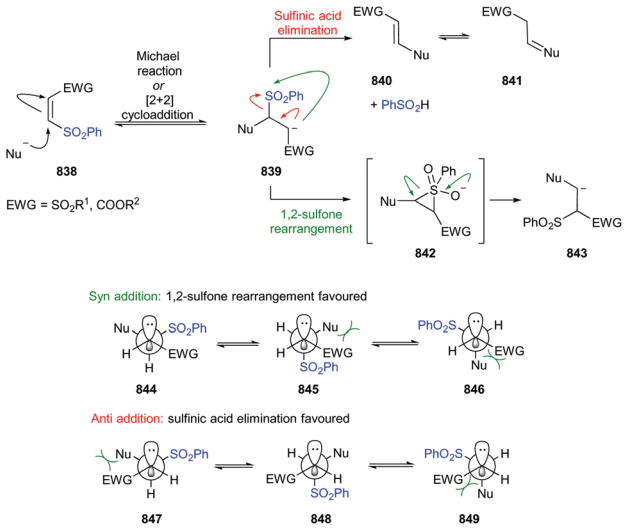
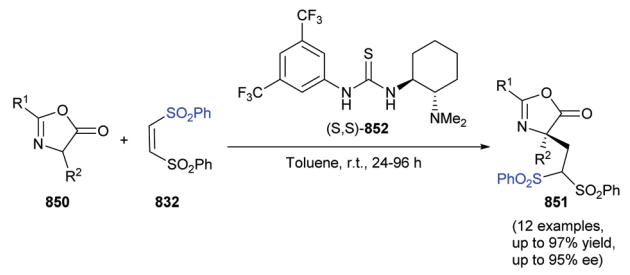


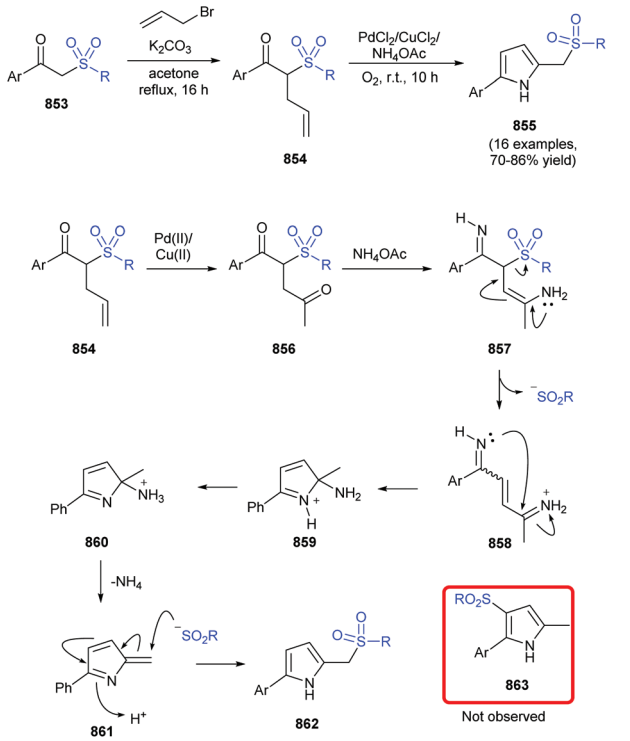
Scheme 123 Proposed mechanism for the 1,2-sulfonyl migration; stereochemistry of the transient anion.

(Scheme 125).[166] Regardless of the conditions employed through optimisation, no evidence for the pyrrole **863**, derived from a 1,3-sulfonyl migration was observed. Complexation of the $PdCl_2/CuCl_2$-catalyst system to the olefin **854** was found to yield the Wacker oxidation product **856**. Condensation of **856** with NH_4OAc affords intermediate **857**, which subsequently undergoes desulfonylation, cyclisation and tautomerisation to give **860**. Elimination of ammonia leads to the generation of the fulvene skeleton **861**, which undergoes regioselective addition of the sulfinate, which gives the pyrrole product **862** *via* protonation of **861**, completing the overall 1,4-sulfonyl migration. Crossover experiments, whereby both the aryl group and the sulfonyl group were varied, supported the intermolecular nature of the sulfonyl migration and the presence of the fulvene skeleton **861** as a key intermediate.

The Yu group developed a copper-catalysed cyclisation of allenoates **864** with activated isocyanides **865**, that invloved 1,3-sulfonyl migration, leading to di- or tri-substituted pyrroles **866** in moderate to good yields (Scheme 126).[167] The authors proposed that the transformation starts with Cu_2O mediated C–H bond activation of the isocycanide **867** to give the copper-isocyanide complex **868** with concomitant formation of H_2O.



Scheme 124 Application of a 1,2-sulfonyl migration in the synthesis of direct precursors to enantioenriched quaternary α-alkyl-α-amino acids.



Scheme 125 $PdCl_2/CuCl_2/NH_4OAc$-mediated domino Wacker-type aminocyclisation of α-allyl-β-ketosulfones *via* selective 1,4-sulfonyl migration.

Subsequent [3 + 2]-dipolar cycloaddition of this intermediate with the allenoate **869** affords the intermediate **870**, which following protonolysis leads to the formation of **871** and the regeneration of the copper catalyst. A copper-assisted elimination of tosylate produces the cationic intermediate **872**, which upon recombination affords the rearranged pyrrole complex **873**. The intermolecular nature of the sulfonyl migration was further established by means of crossover experiments. Protonolysis of **873** leads to the final pyrrole product **874** and regeneration of the copper catalyst.

Bi and co-workers described the silver-catalysed generation of 1,4,5-trisubstituted imidazoles **877** *via* isocyanide–isocyanide [3 + 2]-dipolar cycloaddition in which a 1,2-tosyl migration was observed (Scheme 127).[168] Notably, both electron-rich and electron-deficient aryl groups on the aryl isocyanides **875**, as well as sterically demanding groups, were well tolerated with moderate to high yields obtained in all instances. Furthermore, both aryl and alkyl α-substituted tosylmethyl isocyanide derivatives **876** reacted readily. The addition of either TEMPO or BHT did not inhibit the reaction, indicating that the mechanism does not proceed *via* a radical process (Scheme 127). When the reaction was carried out in the presence of D_2O, 74% deuterium incorporation was observed, highlighting that trace amounts of water in the solvent may provide a proton in the imidazole products **877**. No deuterated imidazole [D]-**880** was isolated when the substrate [D]-**879** was reacted under standard conditions, confirming that the active methine group is involved in proton abstraction.

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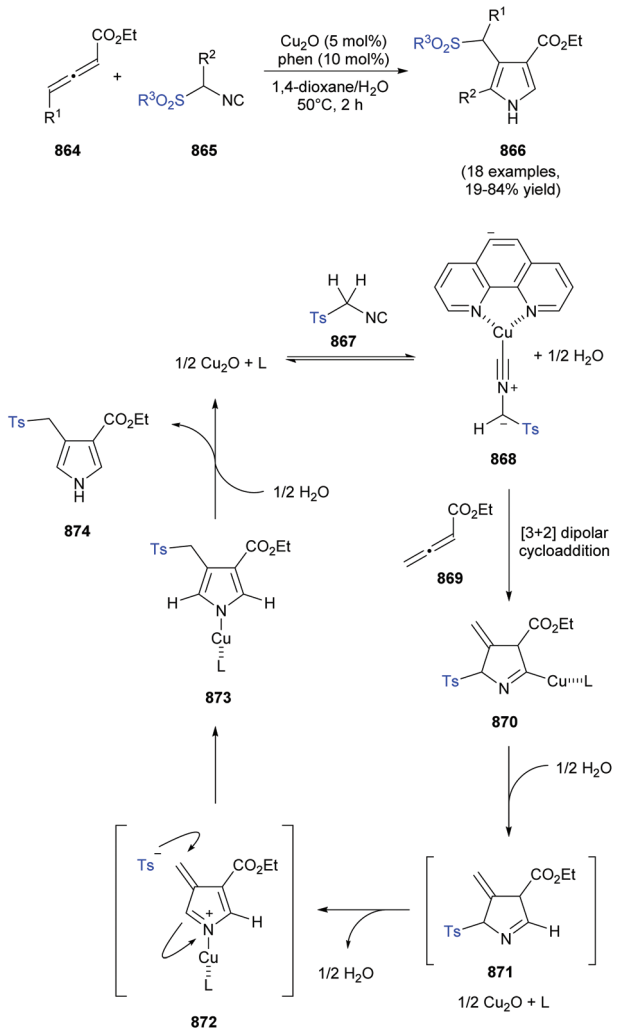
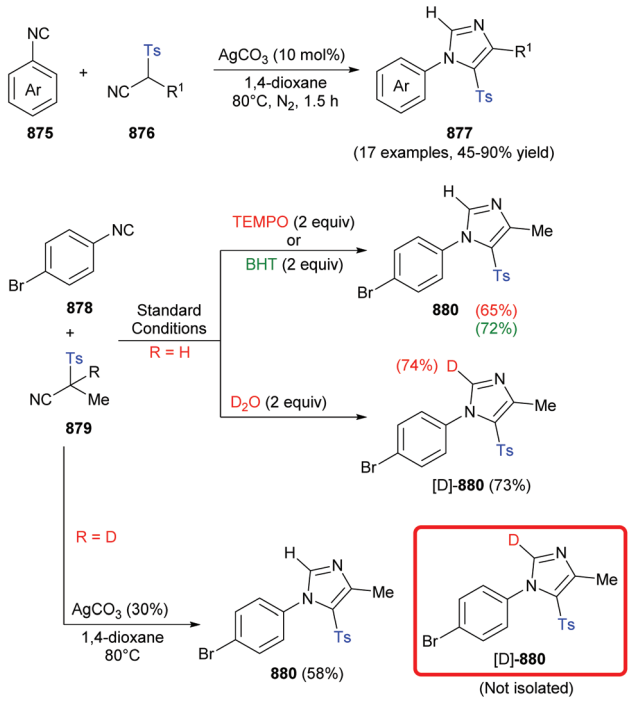


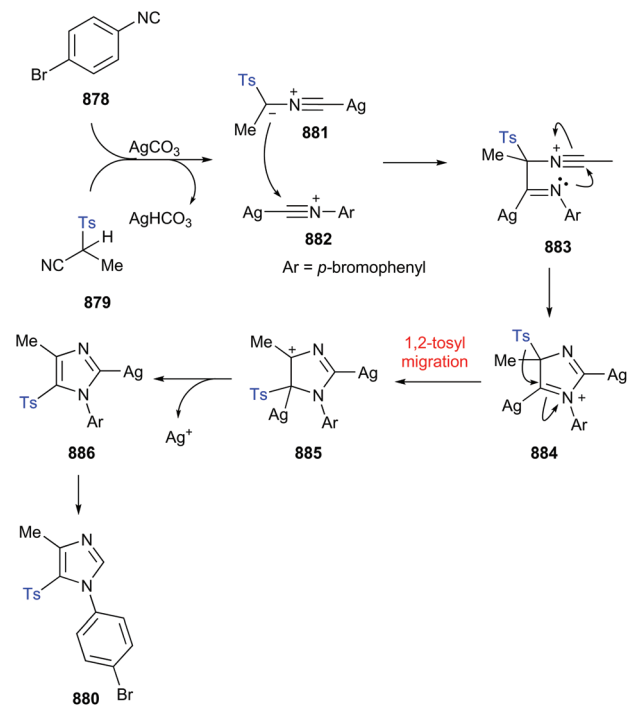
Scheme 126 Copper-catalysed cyclisation of allenoates with activated isocyanides featuring a carbon–carbon 1,3-sulfonyl migration.



Scheme 127 Silver-catalysed formation of 1,4,5-trisubstituted imidazoles *via* isocyanide–isocyanide [3 + 2]-dipolar cycloaddition with accompanying 1,2-tosyl migration.

The authors postulated that coordination of the silver catalyst to the isocyanides **878** and **879** generates the silver complexes **881** (following abstraction of a proton and concurrent generation of $AgHCO_3$) and **882**, which subsequently undergo [3 + 2]-dipolar cycloaddition to give the cyclic nitrilium ion **884** (Scheme 128). 1,2-Tosyl migration affords the carbocation intermediate **885** followed by loss of the silver cation and subsequent protonation forms the rearranged imidazoles **880** with concomitant regeneration of the silver catalyst.

The Xu group disclosed the first example of the preparation of *ortho*-alkylaryl triflones **889** *via* the insertion of arynes into C–SO_2CF_3 bonds through a tandem nucleophilic attack/intramolecular carbon to carbon 1,3-sulfonyl migration (Scheme 129).[169] Using KF/18-crown-6 as fluoride source a series of *ortho*-alkylaryl triflones **889** were generated in moderate to high yields, with the presence of an electron-withdrawing substituent on the benzyl triflones **888** essential for efficient reaction. A plausible mechanism involves the fluoride-mediated generation of the aryne **890** and carbanion **891**,



Scheme 128 Proposed mechanism for silver-catalysed formation of 1,4,5-trisubstituted imidazoles *via* isocyanide–isocyanide [3 + 2]-dipolar cycloaddition.

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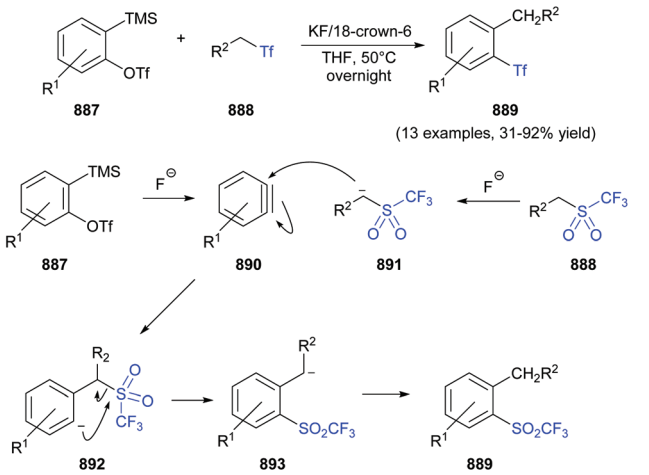

Scheme 129 Preparation of *ortho*-alkylaryl triflones *via* insertion of C–SO_2CF_3 bonds into arynes through a tandem nucleophilic attack/intramolecular carbon to carbon 1,3-sulfonyl migration.

which upon nucleophilic addition forms the intermediate **892** (Scheme 129). Subsequent carbon to carbon 1,3-sulfonyl migration of the triflyl group, presumably *via* an intramolecular process, akin to an anionic thia-Fries rearrangement, affords the rearranged *ortho*-alkylaryl triflone **889**. Notably, the corresponding reaction of substituted benzyl methanesulfones did not afford the desired aryl methanesulfones, highlighting the importance of the triflyl group in the transformation.

Access to novel atropisomeric 3-tosyl-1-enyl-cyclopropyl-diphenylphosphine oxide derivatives **896** and **897** *via* a one-pot transition metal free coupling of *N*-tosylhydrazones **894** and phosphinyl allenes **895** was recently developed by Wu and co-workers.[170] Notably, the multistep cascade reaction occurs by initial radical hydrazonyl N–S bond cleavage, followed by sequential radical C(sp^3)–OAr bond cleavage, carbon to carbon 1,3-sulfonyl migration and atropisomeric cyclopropanation to afford the desired products in moderate to high yields in excellent diastereoselectivity (Scheme 130). The initial radical cleavage of the hydrazonyl N–S bond is enabled by the combination of catalytic 1,10-phenanthroline and potassium carbonate, and while significant attention was afforded to the elucidation of the mechanism for this step it is beyond the scope of this review. Consequently, we will focus exclusively on the attempts to elucidate the mechanism for the sulfonyl migration step. For clarity, the full proposed mechanism is included in Scheme 131.

A radical mechanism was invalidated by the addition of TEMPO, under otherwise standard conditions, to the isolable intermediate **898** which afforded the rearranged product **899** with no inhibition observed (Scheme 130A). A stoichiometric amount of K_2CO_3 was shown to be necessary for optimal conversion to rearranged product, with a reduction in the amount of base inhibiting the cascade process (Scheme 130B). This finding strongly suggests that the base promotes the sulfonyl migration. A crossover experiment between **898** and sodium 4-methoxybenzenesulfinate **900** afforded a statistical mixture of products **899** and **901** supporting an intermolecular sulfonyl migration (Scheme 130C). A kinetic isotope effect value (k_H/k_D) of 1.5 was determined for the parallel reactions of **904** and **904-D**[6] under standard conditions, with incorporation of deuterium observed over all the alkenyl positions (Scheme 130D). This KIE suggests that the rate-determining step probably involves the sulfonyl rearrangement but does not involve the previous C(sp^3)–H bond cleavage. With this experimental evidence in mind the following mechanism is postulated (Scheme 130E): base induced elimination of the tosyl moiety affords the tosyl anion and the allene **906**, which isomerises to **907** in the presence of stoichiometric base.[171] Nucleophilic addition of the tosyl anion promotes the elimination of the base and completes the formal 1,3-sulfonyl migration to afford **899**.

Our group has an ongoing interest in the reactivity of α-thio-β-chloroacrylamides,[172] a family of highly functionalised sulfur-containing compounds that can undergo a large range of synthetic transformations such as oxidation,[173] addition-substitution,[174] Diels–Alder cycloaddition[175] and [3 + 2]-dipolar cycloaddition.[2,176] Notably, during studies regarding their reactivity as dipolarophiles in [3 + 2]-dipolar cycloaddition reactions with both electron-rich and electron-poor terminal α-diazoalkanes it was observed that the degree of oxidation at sulfur played a critical role in the outcome of the reaction. While the outcome of the cycloadditions at the sulfide and sulfoxide level can be readily rationalised due to the nucleophilic character of sulfides and the leaving group potential of sulfoxides, the observation of a formal carbon to carbon 1,2-sulfonyl migration for the sulfone derivatives is unprecedented in pyrazoline heterocyclic structures (Scheme 132).

While the mechanism for the formation of the rearranged pyrazoles **923** is not fully understood, several mechanistic routes can be considered based on the confirmed regiochemistry of the products (Scheme 133). In all instances, regioselective [3 + 2]-dipolar cycloaddition of the crude α-sulfonyl-β-chloroacrylamide **925** leads to the initial pyrazoline **926** which readily undergoes elimination of HCl to give the intermediate cycloadduct **927**. It is likely that this elimination is facilitated by the presence of the electron-withdrawing ester moiety, with an $E_{1c}B$ elimination likely. To rationalise the formal 1,2-sulfonyl migration a [1,5]-sigmatropic rearrangement can be considered based on an earlier report by Fuchs *et al.* in which they reported the thermally induced rearrangement of a five-membered γ-sulfonyl enone to the rearranged sulfone in almost quantitative yield.[177] The authors rationalised the transformation through the formation of an enol intermediate which undergoes [1,5]-sigmatropic rearrangement. Notably, however, this reaction was carried out in toluene at 145 °C in a sealed tube, whereas the rearrangement observed in our work to generate **929** occurred at room temperature. Recently, Valdés and co-workers reported the synthesis of chiral pyrazoles through the [3 + 2]-dipolar cycloaddition of α-chiral tosylhydrazones with alkynes.[178] Interestingly, they observed that the initial cycloadduct underwent [1,5]-sigmatro-

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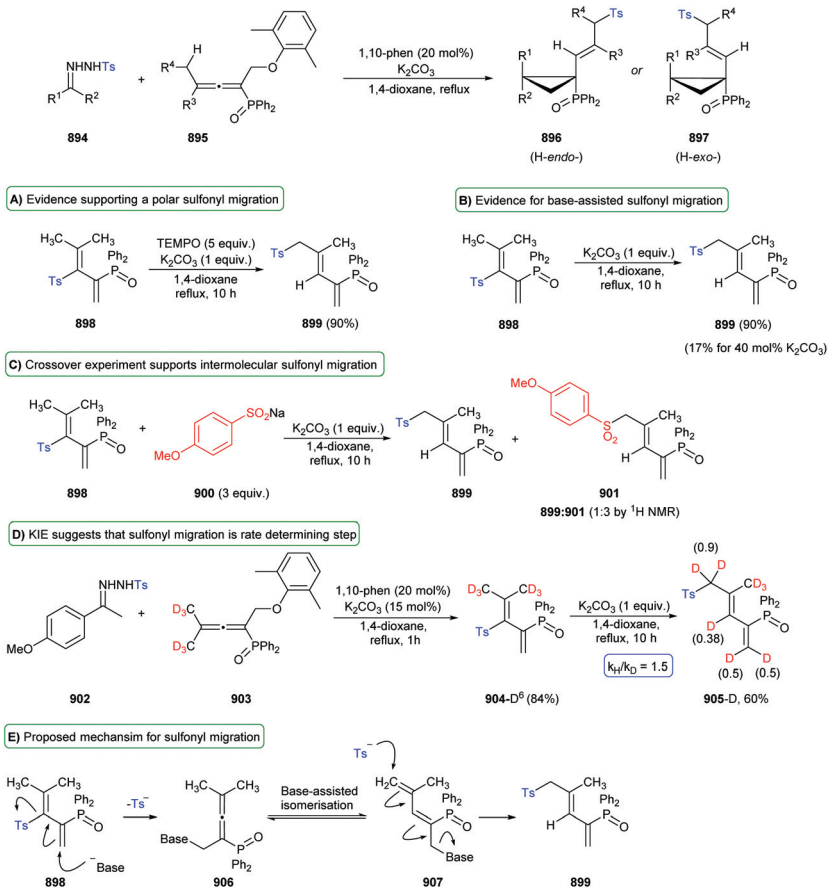
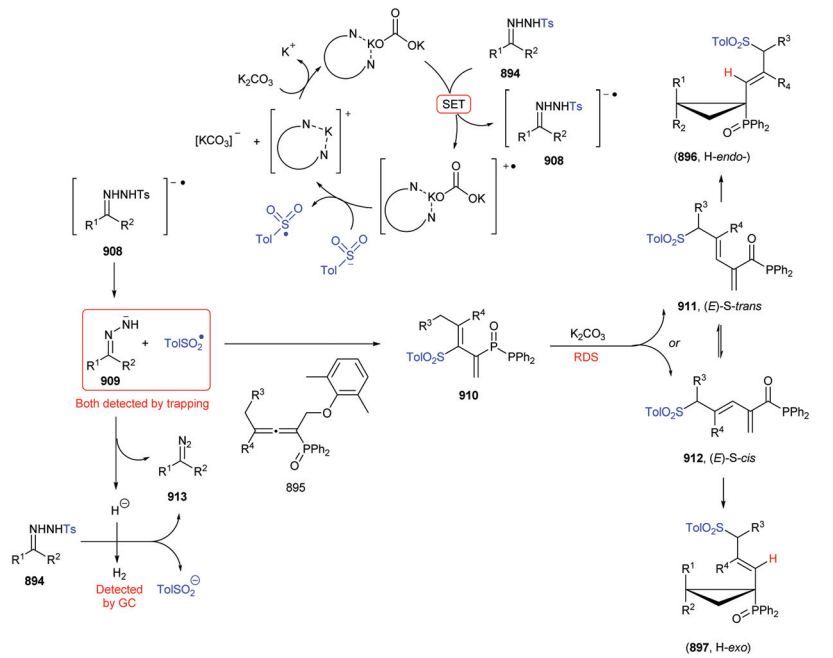


Scheme 130 Proposed mechanism for sulfonyl migration including experimental evidence.



Scheme 131 Overall proposed mechanism for the synthesis of atropisomeric 3-tosyl-1-enyl-cyclopropyl-diphenylphosphine oxide derivatives.

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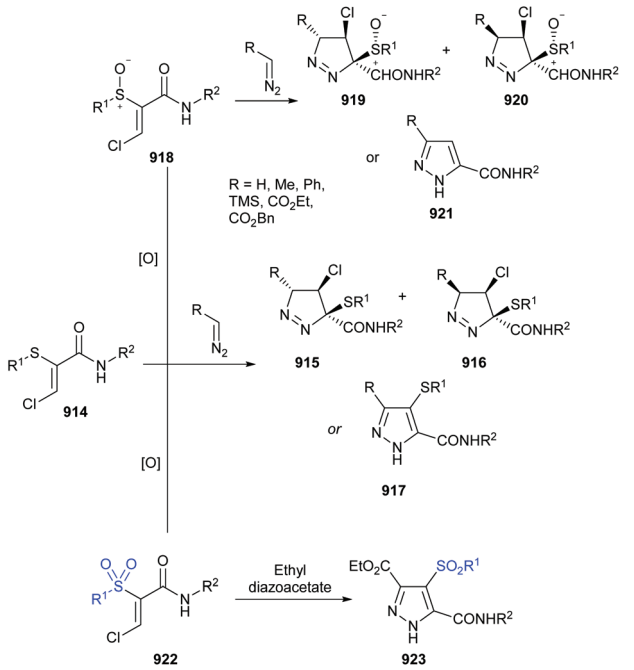


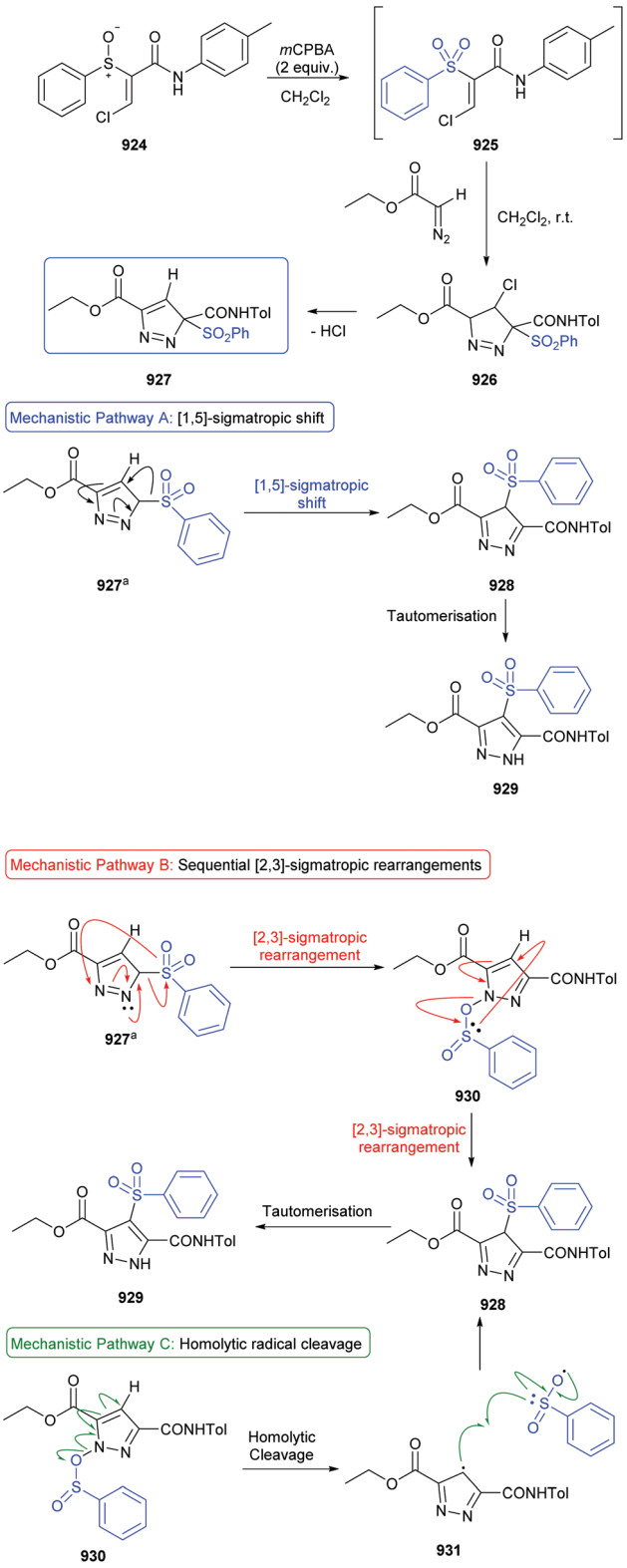
Scheme 132 [3 + 2]-dipolar cycloaddition of α-sulfenyl/sulfinyl/sulfonyl-β-chloroacrylamides with electron rich and electron deficient diazoalkanes.

pic rearrangement with migration of the alkyl group. Significantly, they observed that the [1,5]-sigmatropic rearrangement, which has two regioisomeric outcomes, preferentially, but not exclusively, results in migration to nitrogen rather than the C(4) carbon. Forcing conditions were also required for this transformation.

Alternatively, two sequential [2,3]-sigmatropic rearrangements of the sulfonyl moiety can be envisaged followed by re-aromatisation *via* tautomerisation at the end of the sequence to afford the pyrazole **929** (Scheme 133). The second [2,3]-sigmatropic rearrangement is somewhat akin to an allylic sulfinate–sulfone rearrangement. It is also plausible that homolytic cleavage of the weak N–O bond of the intermediate **930** could generate a radical pair **931** which on recombination forms the more stable C–S bond.

8. Summary and outlook

In this review, we have comprehensively collected reports of sulfonyl migrations over the past 20 years, highlighted the development of insight into synthetic and mechanistic aspects of these sulfonyl shifts, and categorised them based on the migration type, namely nitrogen–carbon, nitrogen–oxygen, nitrogen–nitrogen, oxygen–carbon, oxygen–oxygen and carbon–carbon. While most sulfonyl migrations prior to the beginning of the 21st century were discovered as side reactions, and regularly as isolated cases, the last 20 years has seen a significant increase in the number of reports focusing on development of synthetic methodology based on the sulfonyl



Scheme 133 [3 + 2]-dipolar cycloadditions of ethyl diazoacetate and α-sulfonyl-β-chloroacrylamides; observation of an unprecedented carbon to carbon 1,2-sulfonyl migration [a: –CONHTol not drawn in structure **927**].

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migration. Efforts to understand the mechanisms of these often 'unexpected' reactions have garnered significant recent attention including by means of crossover studies, competition experiments, isotopic-labelling, density functional theory calculations and electron paramagnetic resonance spectroscopy, although many sulfonyl migrations are only partially understood at this point. Despite progress in this area, the potential for formal 1,2-, 1,3-, 1,4-, 1,5-, 1,6- and 1,7-sulfonyl migrations, both in an inter- and intramolecular fashion, *via* both radical and polar processes render challenging the prediction of the outcome of such reactions in a manner that would facilitate their predictable use in synthesis. Notwithstanding, the clear evidence discussed herein for the utility of sulfonyl migration, particularly in the synthesis of highly functionalised heterocycles, and notably in total synthesis, highlights the synthetic potential of sulfonyl migrations. Therefore, we believe that significant attention will be afforded to this expanding field of research in years to come.

Abbreviations

Å	Angstrom
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
B	Base
BHT	Dibutylhydroxytoluene
BINOL	1,1′-Bi-2-naphthol
Bn	Benzyl
BP	Biphenyl
BQ	1,4-Benzoquinone
BTAC	Behentrimonium chloride
iBu	iso-Butyl
n-BuLi	*n*-Butyllithium
*t*Bu	*tert*-Butyl
Bz	Benzoyl
°C	Degrees celsius
*m*CPBA	*meta*-Chloroperbenzoic acid
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIPA	Diisopropylamine
DMAP	4-Dimethylaminopyridine
DMEAD	Di-2-methoxyethyl azodicarboxylate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPBIF	1,3-Diphenylisobenzofuran
DPE	1,1-Diphenylethylene
dr	Diastereomeric ratio
DTBP	Di-*tert*-butylhydroperoxide
$E_{1C}B$	Elimination unimolecular conjugate base
ECR	Electrocyclic ring-closure
EDG	Electron-donating group
ee	Enantiomeric excess
equiv.	Equivalents
EPR	Electron paramagnetic resonance
ESI-MS	Electrospray ionisation-mass spectrometry
Et	Ethyl
EWG	Electron withdrawing group
FABMS	Fast atom bombardment mass spectrometry
ΔG	Change in Gibbs free energy
GC	Gas chromatography
h	Hours
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
hv	Photochemical energy
IM	Intermediate
kcal mol^{-1}	kilocalorie per mole
KHMDS	Potassium bis(trimethylsilyl)amide
KIE	kinetic isotope effect
kJ mol^{-1}	kilojoule per mole
LC-MS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamine
LED	Light emitting diode
LFP	Laser flash photolysis
LiTMP	Lithium tetramethylpiperidine
Me	Methyl
MeCN	Acetonitrile
Mes	Mesityl
min	Minutes
mol%	Mole percent
Ms	Mesyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NHC	N-Heterocyclic carbene
NHPI	*N*-Hydroxyphthalimide
nm	Nanometer
NMR	Nuclear magnetic resonance
Ns	Nitrobenzenesulfonyl
PC	Photocatalyst
PC*	Excited photocatalyst
PES	Potential energy surface
Ph	Phenyl
phen	1,10-Phenanthroline
Phth	Phthaloyl
Piv	Pivaloyl
PMB	*p*-Methoxybenzyl
iPr	Isopropyl
*n*Pr	Propyl
P.T.	Proton transfer
PTSA	*p*-Toluenesulfonic acid
pyr	Pyridine
RDS	Rate-determining step
rt	Room temperature
SET	Single-electon transfer
TBAB	Tetra-*n*-butylammonium bromide
TBAF	Tetra-*n*-butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Triflyl

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THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Tol	Tolyl
TS	Transition state
Ts	Tosyl
μW	Microwave

Conflicts of interest

There are no conflicts to declare.

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