



HAL
open science

SO 2 -Extrusive 1,4-(Het)Aryl Migration: Synthesis of α -Aryl Amides and Related Reactions

Nicolas G.-Simonian, Amandine Guérinot, Janine Cossy

► **To cite this version:**

Nicolas G.-Simonian, Amandine Guérinot, Janine Cossy. SO 2 -Extrusive 1,4-(Het)Aryl Migration: Synthesis of α -Aryl Amides and Related Reactions. *Synthesis: Journal of Synthetic Organic Chemistry*, 2022, 10.1055/s-0040-1720035 . hal-04076896

HAL Id: hal-04076896

<https://hal.science/hal-04076896v1>

Submitted on 21 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

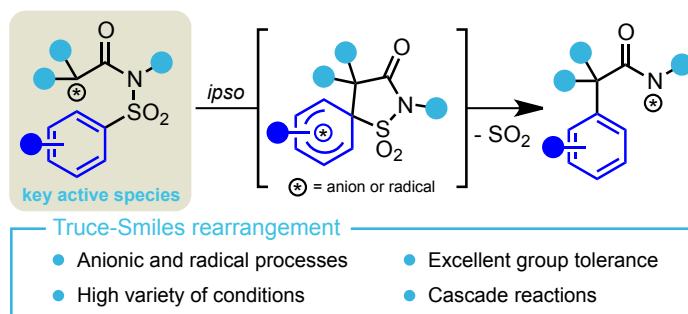
L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

SO₂-Extrusive 1,4-(Het)Aryl Migration: Synthesis of α -Aryl Amides and Related Reactions

Nicolas G.-Simonian^a
Amandine Guérinot^{**a}
Janine Cossy^{**a}

^a Molecular, Macromolecular Chemistry and Material-UMR 7167
ESPCI Paris, CNRS, PSL Research University
10 rue Vauquelin, 75231 Paris Cedex 05, France

amandine.guerinot@espci.fr, janine.cossy@espci.fr^b



Received:
Accepted:
Published online:
DOI:

Abstract (Het)Aryl migration has emerged as a key synthetic tool and has particularly been exploited for the synthesis of α -aryl amides. This method overcomes the existing α -arylation methods, which are not always compatible with the introduction of (het)aryl groups possessing bulky or electrophilic substituents. This review focuses on SO₂-extrusive (het)aryl migration in the frame of α -aryl amide synthesis. Anion- and radical-mediated transformations are reported including the synthesis of polycyclic compounds through cascade reactions.

1 Introduction
2 Anionic aryl migration
3 Radical aryl migration
4 Conclusion

Key words α -aryl amides; aryl migration; cascade reactions

1- Introduction

α -Aryl amides are present in some important marketed drugs (**Figure 1**). For example, penicillin G has been the first molecule of the penicillin family discovered by A. Fleming in 1928 and this discovery has been one of the most important breakthrough in medicine.¹ Amoxicillin, the most prescribed antibiotic for children infections as well as the β -blocker atenolol feature an α -aryl amide.² In addition, the α -aryl amide motif can be considered as an α -aryl carboxylic acid analog, an important pharmacophore present in non-steroidal anti-inflammatory drugs.³ Reduction of α -aryl amides to β -aryl amines also leads to useful biologically active compounds.⁴

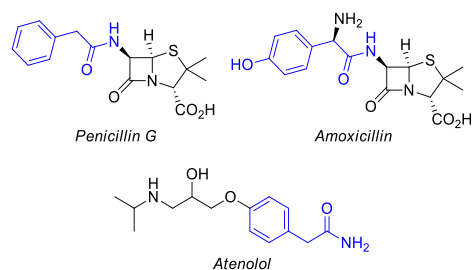


Figure 1. Examples of biologically active α -aryl amides.

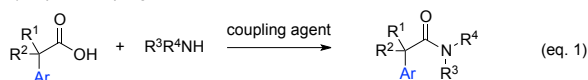
Due to the pharmaceutical importance of α -aryl amides, a lot of methods have been developed to access these compounds (**Scheme 1**). The most straightforward method is a peptidic coupling of an α -aryl carboxylic acid with an amine (**Scheme 1**, eq 1). However, the synthesis of α -aryl carboxylic acids can be problematic, restricting the scope of this direct method.

As an alternative, in 1998, Hartwig *et al.* described a palladium-catalyzed enolate arylation using aryl halides. This method has known a high number of developments over the last 20 years (**Scheme 1**, eq 2).⁵ A wide range of derivatives including esters, ketones and amides could be involved with no pre-required functionalization in the α -position of the carbonyl moiety. However, some limitations are encountered due to the use of a strong base to generate the enolate. This problem has been partially addressed later on by using zinc enolates, which can be synthesized by a Reformatsky-like reaction from an α -halo amide.⁶

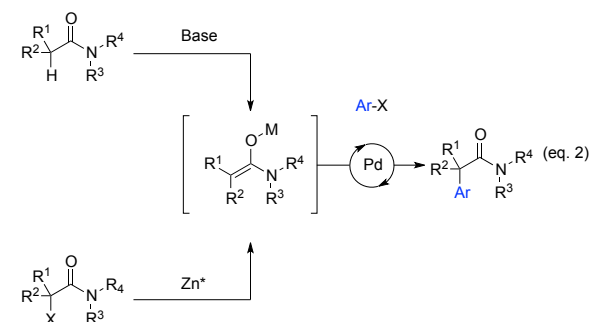
α -Aryl amides can also be synthesized using a metal-catalyzed cross-coupling reaction between an α -halo amide and an aryl organometallic (**Scheme 1**, eq 3).⁷ Even if these coupling reactions are powerful, the need for a halogen atom α to the amide can be viewed as a drawback. Another limitation of both

enolate arylation and cross-coupling reactions is their sluggishness when the aryl group is sterically hindered.⁸

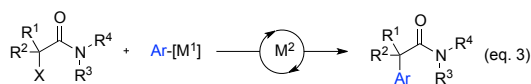
1) Peptidic coupling



2) Enolate coupling



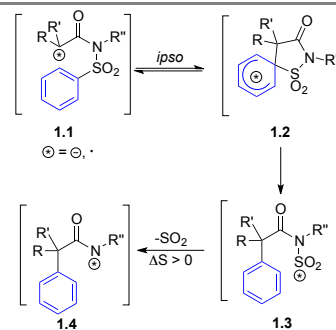
3) Cross-coupling of α -halo amides



X = Cl, Br; [M¹] = B, Zn, Mg, Si; M² = Pd, Ni, Co

Scheme 1. Synthesis of α -aryl amides by cross-coupling reactions.

Since its discovery by W. N. Speckamp *et al.* in 1972,⁹ desulfonylative 1,4 aryl migration has been deeply studied. Particularly, aryl migration proceeding with SO₂ extrusion represents a fourth method to access α -aryl amides (**Scheme 2**).^{10, 11} Once generated in the α position of a *N*-arylsulfonamide, an anion or a radical, **1.1**, can be in equilibrium with the spirocyclic intermediate **1.2** resulting from an *ipso* addition on the aryl ring. This spirocyclic intermediate can undergo a fragmentation and finally collapse to a α -arylated intermediate **1.3**, after SO₂ extrusion, which makes this reaction irreversible. Due to favorable geometrical factors, the acylsulfonamide linkage is particularly adapted to these kind of 1,4 aryl migrations as it allows positioning the aryl ring in an optimal position towards the reactive species –i.e. radical or carbanion- (N–S(O)₂–Ar angle = ca. 109° according to Valence Shell Electron Pair Repulsion (VSEPR) theory).¹² Compared to other amide α -arylation methods (enolate arylation, cross-coupling reaction), this intramolecular reaction based on an *ipso* addition proved to be less sensitive to the migrating aryl group steric hindrance, broadening the scope of α -aryl amide synthesis. In addition, this process can lead to the transient formation of very reactive intermediates, such as amidyl radicals, which can be exploited in subsequent cascade reactions (*vide infra*).

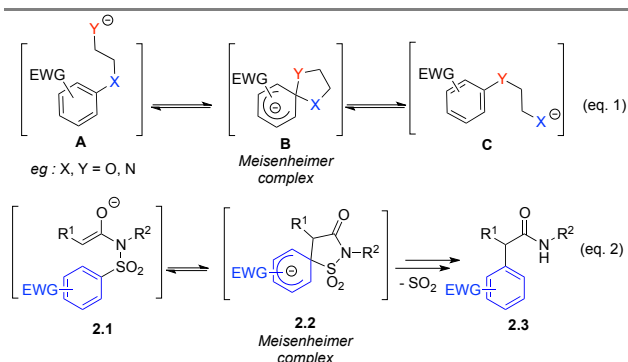


Scheme 2. Desulfonylative 1,4-aryl migration.

This review will focus on the formation of α -aryl amides through gas-extrusive aryl migration, highlighting the capacity of such rearrangements in tackling some synthetic challenges. This review will be divided into two main sections according to the nature of the key reactive species (anion or radical). Within each section, the reactions will be classified according to the method used for the generation of the key reactive species.

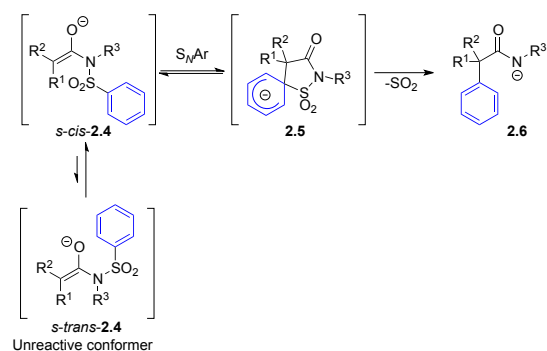
2- Anionic aryl migration

Pioneering examples of desulfonylative 1,4-aryl migration for the synthesis of α -aryl amides involved anionic species **2.1**. Such reaction is supposed to proceed *via* a S_NAr of an amide enolate onto the *ipso* position of the aryl group present in the sulfonamide to result in a Meisenheimer complex **2.2**. A subsequent two-step fragmentation/SO₂ extrusion occurring via a NSO₂^{•-} species delivers α -aryl amide **2.3**.¹³ Recently, some studies pointed out that most S_NAr reactions should follow a concerted mechanism, the Meisenheimer complex being a transition state rather than an intermediate.¹⁴ The mechanism of 1,4-(het)aryl migration is till under debate. On one hand, NMR and kinetic studies conducted on the classical anionic Smiles rearrangement, involving *N*-aryl ethylenediamines or aminoethylphenyl ethers of type **A**, showed a stepwise mechanism, with the Meisenheimer complex **B** being an intermediate (**Scheme 3**, eq. 1).¹⁵ On the other hand, some density functional theory (DFT) calculation indicates a concerted mechanism for similar transformations.¹⁶ In the case of the formation of α -aryl amides, it is hard to determine if the Meisenheimer complex **2.2** is an intermediate or a transition state (**Scheme 3**, eq. 2). The presence of a strong electron-withdrawing substituent on the migrating aryl ring such as a nitro group should favor a stepwise mechanism by decreasing the relative energy of **2.2**, but the exact nature of the Meisenheimer complex may depend on the substrate structure. In the following sections, the Meisenheimer complexes will be arbitrarily represented as intermediates.



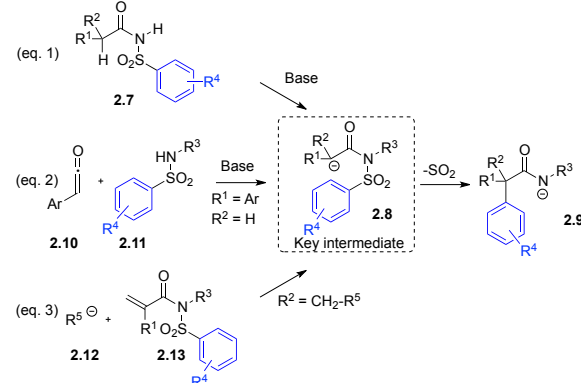
Scheme 3. Mechanism for anionic aryl migration.

One of the most intuitive and straightforward strategy to functionalize the α position of a carbonyl is a deprotonation followed by a rearrangement or by the addition of an electrophile. Besides deprotonation, alternative methods exist to generate an anion in the α position of a carbonyl such as a Michael addition on an α,β -unsaturated carbonyl compound. Whatever the generation of the anion, the resulting enolate **2.4** can react according to a S_NAr mechanism on the aryl ring of the sulfonamide, generating the spirocyclic intermediate **2.5**. After extrusion of SO_2 , the deprotonated amide **2.6** is formed and then can evolve to the corresponding α -aryl amide either by protonation or by trapping with electrophiles (**Scheme 4**). According to this mechanism, two requirements have to be fulfilled for the reaction to proceed. Firstly, the conformer that can undergo the *ipso* substitution is the one possessing the SO_2Ar group in the *s-cis* position with respect to the orbital containing the electrons of the carbanion. This conformational requirement is generally not a problem as delocalization of the anion in the C–O bond does not allow delocalization of the doublet of the nitrogen, decreasing the double bond character of the C–N bond and, in consequence, its rotation energy barrier.¹⁷ This energy barrier is also decreased by the presence of the electron-withdrawing SO_2 group.¹⁸ Secondly, the aryl group has to be electrophilic enough to allow the formation of the spirocyclic intermediate **2.5** according to a S_NAr mechanism. Hence, most examples of anionic 1,4-aryl migration only work with electron-poor aryl rings (NO_2 -substituted phenyl rings, pyridine *N*-oxides, etc.).^{19,20} In addition, when the enolate is directly generated by deprotonation of the amide, the use of a relatively strong base may not be compatible with the presence of acidic or electrophilic functions.



Scheme 4. General principle of the anionic desulfonylative 1,4-aryl migration for the synthesis of α -aryl amides.

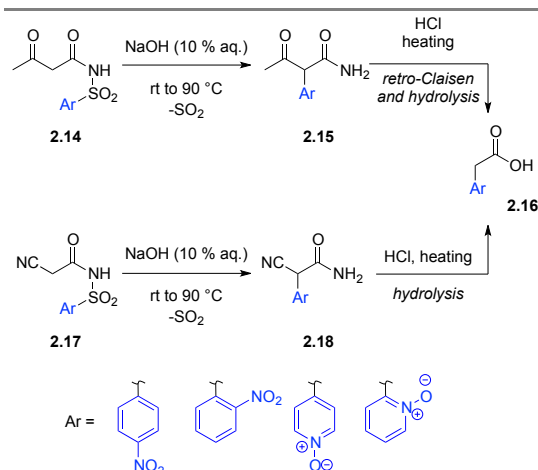
Several reactions involving an anionic desulfonylative 1,4-aryl migration have been developed to synthesize α -aryl amides (**Scheme 5**). All of them involve the key amide enolate intermediate that can be prepared by direct deprotonation of an amide (**Scheme 5**, eq. 1),¹⁹ by addition of a sulfonamide on a ketene (**Scheme 5**, eq. 2)²⁰ or by a conjugate addition of a nucleophile on an acrylamide (**Scheme 5**, eq. 3)²¹.



Scheme 5. Methods for the preparation of α -aryl amides through an anionic desulfonylative 1,4-aryl migration.

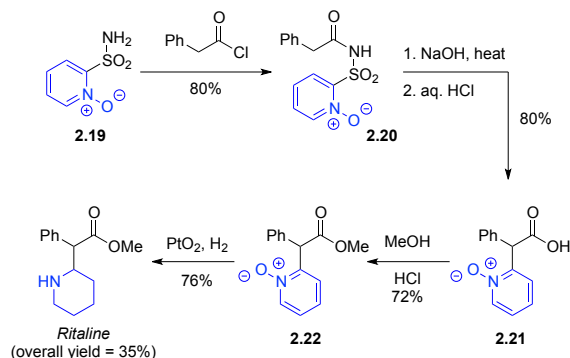
2.1 Generation of amide enolates by deprotonation

Rearrangement of nitrosulfonyl guanidines and nitrosulfonyl ureas are known since 1947²² but it is only between 1954 and 1964 that Dohmori and co-workers published a series of articles related to 1,4-aryl migrations performed on *N*-sulfonylamides under basic conditions.¹⁹ When aryl sulfonylamides **2.14** or **2.17**, bearing an electron-withdrawing group α to the amide and on the migrating aromatic ring, were treated with sodium hydroxide, the corresponding α -aryl amides **2.15** or **2.18** were respectively obtained (**Scheme 6**). These α -aryl amides were usually converted into the corresponding carboxylic acids **2.16** after a retro-Claisen reaction and/or a hydrolysis/decarboxylation sequence under acidic conditions. The presence of an acetyl or a cyano group α to the amide facilitates the deprotonation step to give the key enolate intermediate, which then undergoes a desulfonylative 1,4-aryl migration. Only electron-poor (hetero)aromatics such as nitrobenzenes or pyridine *N*-oxides were able to react and produce the corresponding α -aryl amides.^{19f} Aryl groups bearing weaker electron-withdrawing substituents such as a cyano group only produce non-rearranged hydrolysis products. The authors have investigated the mechanism of the reaction and proposed a desulfonylative 1,4-aryl migration. They also proved that the reaction was an intramolecular process by using competitive experiments.



Scheme 6. Dohmori and co-workers pioneering work.¹⁹

This rearrangement was applied to an efficient synthesis of a psychostimulant, *ritaline*[®], used in attention deficit hyperactivity disorder and narcolepsy (**Scheme 7**).^{19e} *N*-Sulfonyl amide **2.20** was obtained from the corresponding pyridine *N*-oxide sulfonamide **2.19**. The rearrangement/hydrolysis sequence was then performed and the α -pyridine oxide carboxylic acid **2.21** was isolated (80%). Subsequent esterification followed by reduction of the pyridine oxide moiety led to *ritaline*[®] with an overall yield of 35% over the four steps.



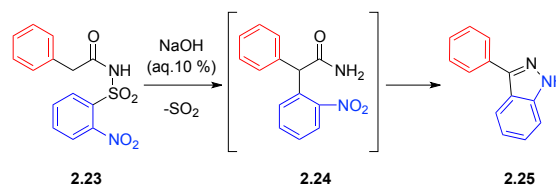
Scheme 7. Synthesis of *ritaline*[®].^{19e}

To get more insights into the mechanism of the aryl migration, the authors used gravimetric analysis to perform kinetic studies. The amount of SO₂ released was measured by adding BaCl₂ to the crude reaction mixture to precipitate BaSO₄. Using a large excess of sodium hydroxide led to a pseudo-first order kinetic profiles and the rate constant could be determined. Some of these results are reported in **Table 1**. When the R group, α to the amide moiety, is a cyano or an acetyl group, the rate determining step is the 1,4-aryl migration. The migration of a pyridine *N*-oxide is faster than the migration of a nitrophenyl and, among the nitro-substituted aryl groups, the *ortho*-nitrophenyl groups migrate faster than the *para*-nitrophenyl groups. This result can be rationalized by the addition of attractive mesomeric and inductive effects of the nitro substituent, enhancing the reactivity of an *ortho*-nitrophenyl group in the S_NAr-like process.

Table 1. Kinetic effects in Dohmori reaction.

	Increasing reaction rate			
	Ar =			
(R = CN)				
k (min ⁻¹)	2.21	n.d.	$3.2 \cdot 10^{-2}$	$2.13 \cdot 10^{-2}$
(R = Ac)				
k (min ⁻¹)	2.34	$4.28 \cdot 10^{-1}$	$1.19 \cdot 10^{-1}$	$9.08 \cdot 10^{-2}$

When the R group α to the amide is a phenyl ring, the reaction is much slower regardless of the nature of the migrating aryl group ($k = ca. 4 - 6 \cdot 10^{-4} \text{ min}^{-1}$). In this case, the α protons are less acidic ($pK_a \approx 26$ vs. 17 - 18 when R = CN or C(O)Me) and the deprotonation becomes the rate determining step.²³ The authors showed that changing the phenyl in the α position of the amide by a more electron-poor 2-nitrophenyl gave the rearranged product in quantitative yield within a short reaction time. The slower reaction observed with R = Ph can favor divergent reactivity leading to attractive heterocyclic compounds. For example, when *N*-sulfonylamide **2.23**, bearing a phenyl group in the α position of the amide and an *ortho* nitro phenyl migrating group, was treated under basic conditions, the rearranged product **2.24** could not be isolated as it evolved spontaneously to indazole **2.25** (**Scheme 8**). This reaction was the first example of indazole synthesis involving an initial 1,4-aryl migration. Other examples have been reported later on (*vide infra* in section 2.2).



Scheme 8. Indazole synthesis by Dohmori *et al.*¹⁹

The pioneering work of Dohmori and co-workers paved the way for further developments (*vide infra*) but some drawbacks appeared. The migrating aryl group has to be electrophilic enough to undergo an aromatic nucleophilic substitution, which is an ubiquitous feature of anionic aryl migration. Moreover, the generation of the key enolate through deprotonation requires the presence of an electron-withdrawing group α to the amide to increase the acidity of the protons. Without such electron-withdrawing group, side reactions can appear due to a too slow generation of the key enolate intermediate. Due to these two requirements, the scope of the migration is strongly affected.

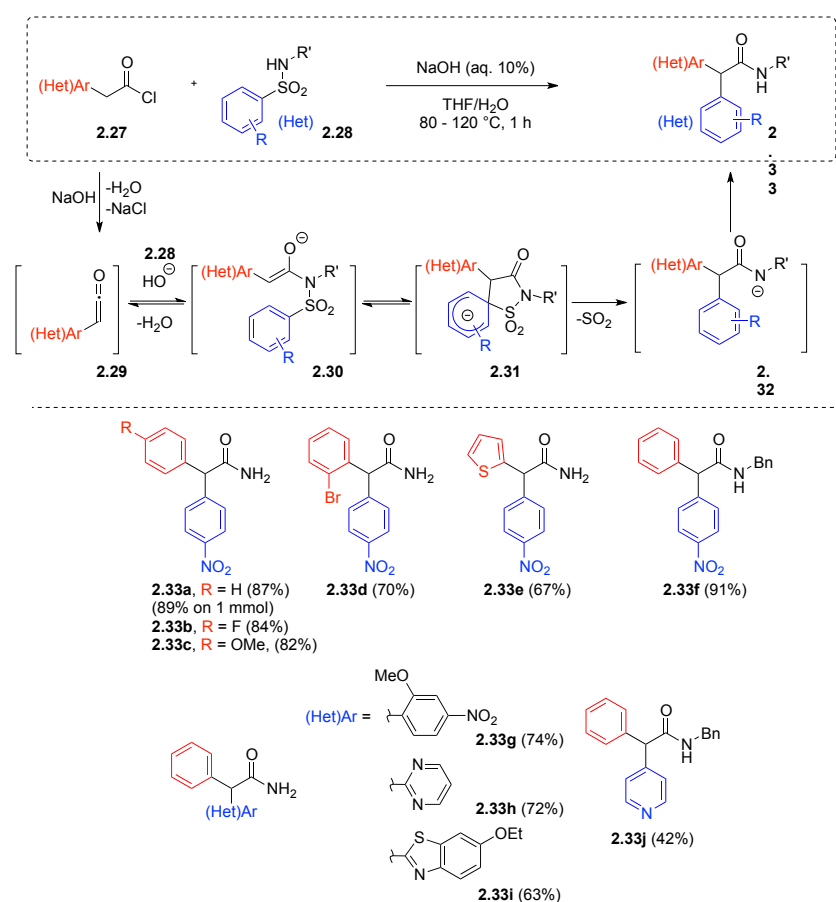
2.2 Generation of amide enolates by addition of a sulfonamide on a ketene

Recently, Greaney and co-workers, published the synthesis of α,α' -bis-aryl amides proceeding *via* a desulfonylative 1,4-aryl migration (**Scheme 9**).²⁴ The key intermediate was produced by addition of a sulfonamide on a ketene, generated *in situ* from the corresponding acyl chloride under basic conditions. The resulting enolate then underwent a rearrangement furnishing

the corresponding α,α' -bis-aryl amides with moderate to excellent yields.²⁰

The authors hypothesized that acyl chloride **2.27** would react with the base *via* an E1_{CB} to generate ketene **2.29**. Addition of sulfonamide **2.28** on this ketene would lead to enolate **2.30** which would react through a S_NAr mechanism on the SO₂-aryl group to yield spirocyclic intermediate **2.31**. Desulfonation of **2.31** would lead to the deprotonated amide **2.32** that would give α -aryl amide **2.33** after protonation. It is worth mentioning that the use of *i*PrNEt₂ instead of sodium hydroxide only led to the condensation product resulting from the protonation of enolate **2.30**. Among the bases tested, sodium hydroxide was the only one able to promote the rearrangement. This is surprising as most of the bases commonly used for *in situ* generation of ketene are amines or pyridines. The authors were able to isolate the α,α' -bis-aryl amide **2.33a** in 87% yield (89% on 1 mmol)

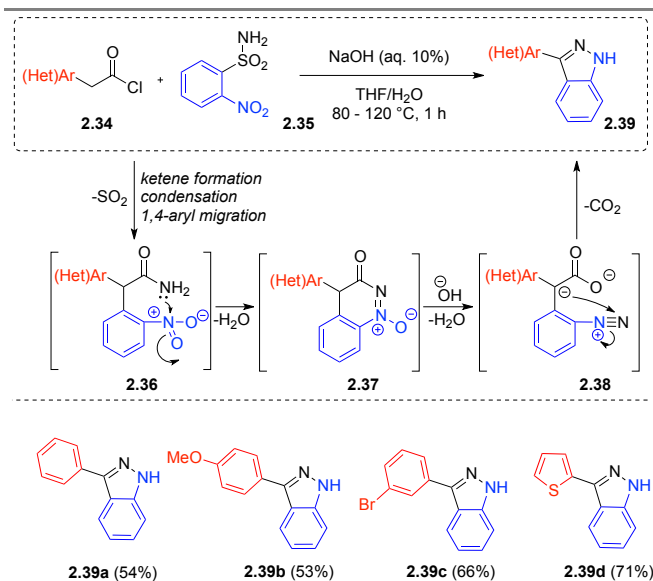
yield on a 1 mmol scale). Electron-withdrawing groups as well as electron-donating groups on the aryl group present at the α -position of the starting acyl chloride were well tolerated and α,α' -bis-aryl amides **2.33b** and **2.33c** were isolated in 84% and 82% yield respectively. The reaction proceeded smoothly even in the presence of a sterically hindered aryl group or a heteroaromatic in the α -position (**2.33d**: 70%; **2.33e**: 67%). The presence of a substituent on the nitrogen of the sulfonamide **2.28** was well tolerated and amide **2.33f** (R' = Bn) was isolated with an excellent yield of 91%. Several aryl groups were able to migrate efficiently, including heteroaromatics, delivering amides **2.33g-2.33i** in good yields. However, similarly to the previous observations by Dohmori *et al.*, the migration of a pyridine proved to be difficult (**2.33j**, 42%).



Scheme 9. Synthesis of α,α' -bis-aryl amides by Greaney *et al.* through desulfonative anionic 1,4 aryl migration.²⁰ THF = tetrahydrofuran.

In addition, as previously observed by Dohmori and co-workers, the reaction involving *ortho*-nitrosulfonamide **2.35** did not lead to α,α' -bis-aryl product but to indazole **2.39** (**Scheme 10**). To rationalize the formation of this indazole, the authors proposed that, after the aryl migration, a nucleophilic attack of the amide onto the nitro group could take place leading to compound **2.37** after the loss of a molecule of water. Intermediate **2.37** would then react with a hydroxide ion to give diazonium **2.38**, which would evolve to indazole **2.39** after nucleophilic attack of the carboxylate enolate onto the diazonium followed by a decarboxylation. The authors were able to synthesize indazoles **2.39a-2.39d** with good yields ranging from 53% to 71%, regardless the nature of the (het)aryl group at the α position of the acyl chloride. This method

allows an easy access to indazoles, which are biorelevant scaffolds.



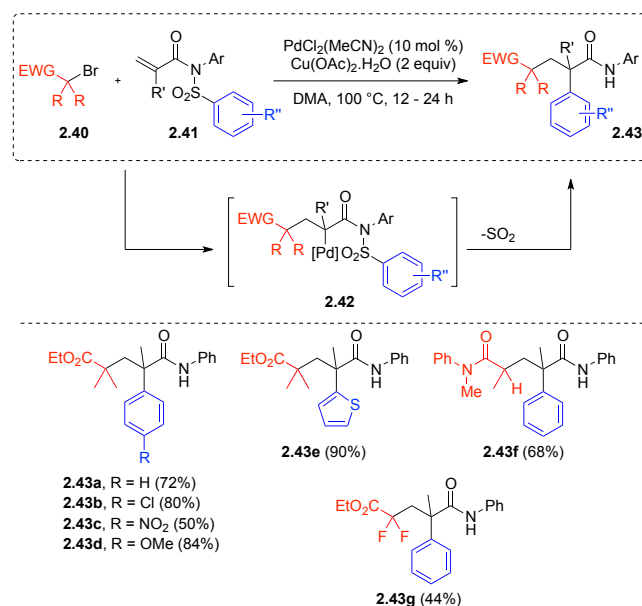
Scheme 10. Indazole synthesis by Greaney *et al.*²⁰ THF = tetrahydrofuran.

By avoiding the deprotonation step α to the amide, the generation of the key enolate intermediate through the addition of a sulfonamide on a ketene broadens the scope of the anionic aryl migration. The migrating aromatic still needs to be activated toward $S_N\text{Ar}$ (*i.e.* electron-poor) but a significant scope extension was achieved, notably to the migration of pyridines. The successful formation of indazoles is quite complementary with the work reported by Dohmori and co-workers.

2.3 Generation of amide enolates by a Heck type reaction on acrylamides

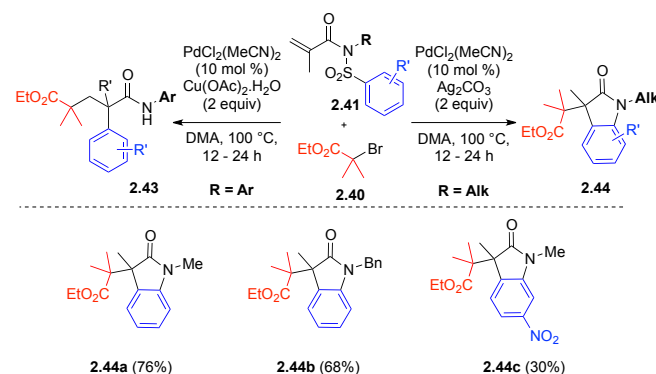
In 2015, Li and co-worker published a synthesis of α -aryl amides involving a 1,4-aryl migration triggered by a 1,4-addition of an organopalladium species onto an acrylamide, under oxidative conditions in the presence of a copper(II) complex (**Scheme 11**).²¹ According to the authors' hypothesis, a first reaction between bromide **2.40** and $(\text{MeCN})_2\text{PdCl}_2$ would furnish an organopalladium species that would then perform the carbopalladation of the acrylamide **2.41** double bond leading to palladium enolate **2.42**. This latter would produce α -arylamide **2.43** after a desulfonylative 1,4-aryl migration sequence. The authors were able to synthesize amide **2.43a** (72%). A $\text{C}(\text{sp}^2)\text{-Cl}$ bond was non-reactive under these conditions and amide **2.43b** was isolated with a good yield (80%). However, when the aryl group was substituted by a nitro group, the yield dropped to 50%, maybe due to catalyst poisoning. Surprisingly, electron-rich aromatics were able to migrate and the authors isolated amide **2.43d** featuring a *p*-OMe aryl group with a very good yield (84%). This result could question the anionic nature of the transformation that is usually restricted to the migration of electron-poor aryl groups. An α -heteroaryl amide incorporating a thiophene group, *e.g.* **2.43e**, was synthesized in 90% yield using these conditions [$(\text{MeCN})_2\text{PdCl}_2$, $\text{Cu}(\text{OAc})_2$, DMA]. Moving from an α -bromo ester to an α -bromo amide partner led to diamide **2.43f** (68%). Similarly, the authors synthesized nitrile and ketone containing amides (not shown). However, di-fluorobromo ester **2.40g** led to amide **2.43g** with a moderate yield (44%).

The proposed anionic mechanism for this transformation is questionable as it does not account for the effective migration of electron-rich aryl groups that should not be reactive in a $S_N\text{Ar}$ type process. The presence of a stoichiometric amount of a copper complex in the reaction mixture may not be innocent and could transmetalate one of the intermediates, for example **2.42**. The resulting copper enolate could be in equilibrium with a radical intermediate that could induce a radical aryl migration. As we will discuss in Section 3 (*vide infra*), the 1,4-migration of electron-rich aryl groups is a typical feature of radical-mediated desulfonylative 1,4-aryl migration.



Scheme 11. Pd-catalyzed Heck-type transformation/1,4-aryl migration sequence.²¹ DMA = *N,N*-dimethylacetamide.

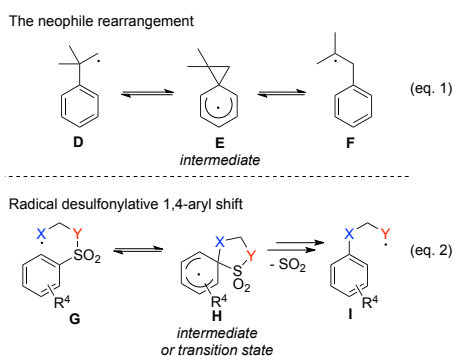
The most remarkable feature in this transformation is the divergence of reactivity observed for *N*-alkyl and *N*-aryl acrylamides (**Scheme 12**). Treatment of *N*-alkyl acrylamides, under close conditions to those used for *N*-aryl acrylamides (Ag_2CO_3 versus $\text{Cu}(\text{OAc})_2$) led to oxindoles derivatives **2.44**. Under these conditions, oxindoles **2.44a** and **2.44b** were isolated in 76% and 68% yields respectively. The nitro compound **2.44c** was isolated in a moderate yield of 30%, probably due to catalyst poisoning. This divergence of reactivity was further observed in radical 1,4-aryl migration (*vide infra*) and can be considered as an additional clue in favor of a radical mechanism.



Scheme 12. *N*-Substituent-driven divergence of reactivity.²¹ DMA = *N,N*-dimethylacetamide.

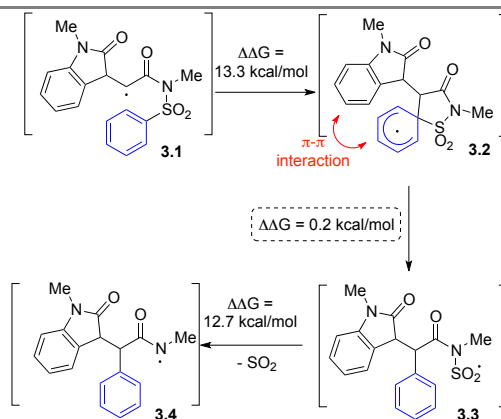
3- Radical aryl migration

In 1911, the first radical 1,2-aryl migration was reported by Wieland *et al.* Thirty years later, Urry and Karasch discovered the neophile rearrangement and, thereafter, this rearrangement has been thoroughly studied.^{10d,10i} The mechanism of this transformation was deeply investigated and theoretical calculations as well as Electron Paramagnetic Resonance (EPR) spectroscopy clearly identified the spirocycle **H** as an intermediate (**Scheme 13**, eq. 1).²⁶ These pioneering works made a significant breakthrough in organic synthesis opening the way to the development of numerous rearrangements based on an aryl migration process. Among the aryl migration with gas extrusion, desulfonylative radical 1,4-aryl migration is by far the most documented reaction in the literature and several reviews have been published.^{11a,c,d,e,g} In contrast with the neophile rearrangement, the nature of the spirocycle **H** - *i.e.* a transition state or an intermediate - involved in the desulfonylative radical 1,4-aryl migration remains unclear (**Scheme 13**, eq. 2). Depending on the substrate, theoretical calculations sometimes pointed **H** as an intermediate,²⁷ sometimes as a transition state.²⁸ In both cases, after a fragmentation and consecutive SO₂ release, spirocycle **H** leads to radical **I**.¹³



Scheme 13. Mechanism for radical aryl-shift.

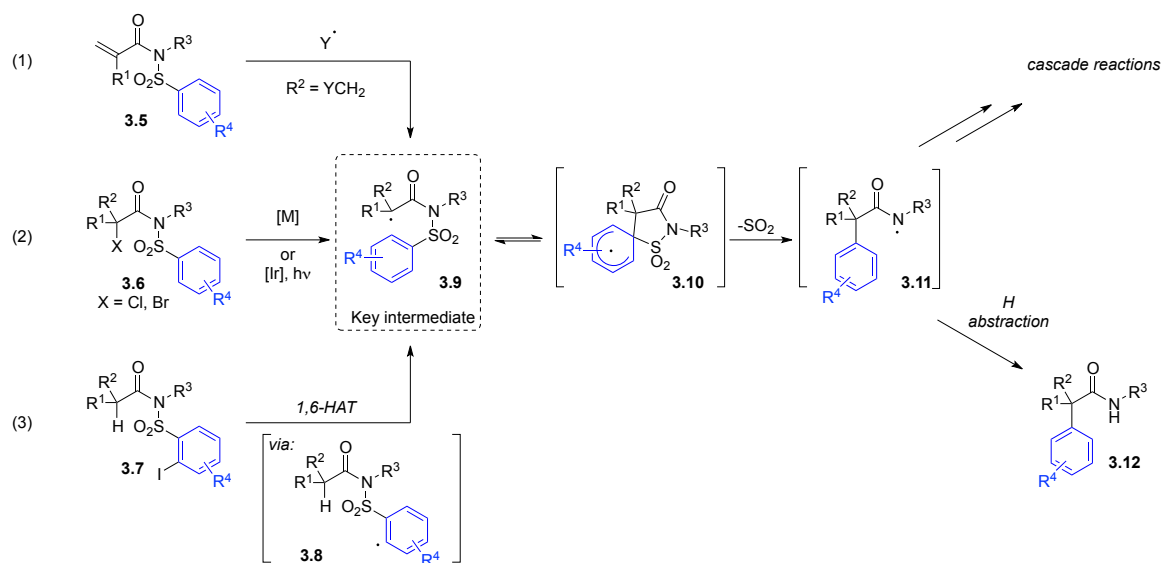
In 2020, Hénon *et al.* performed theoretical calculations to investigate the mechanism of desulfonylative radical 1,4-aryl migration for the synthesis of α -aryl amides (**Scheme 14**).²⁷ The authors identified the spirocycle **3.2** as an intermediate. However, this result should be taken with caution and cannot be generalized since a π - π interaction between the delocalized radical and the oxindole moiety may decrease the relative energy of **3.2**. In the following sections, the spirocyclic radicals will be arbitrarily written as intermediates.



Scheme 14. Theoretical calculations by Hénon *et al.*²⁷

Over the past decade, the synthesis of α -aryl amides and derivatives through desulfonylative radical 1,4-aryl migration has been under rapid development. Indeed, several classical methods have been developed to generate a radical α to the carbonyl moiety. This radical is, by nature, less polarized than a formal charge and has an electrophilic character. This could expand the scope of gas-extrusive aryl migration strategies, especially for the migration of electron-rich aryl groups.

Carbon-centered radical **3.9** is a key intermediate of radical desulfonylative 1,4-aryl migration involving *N*-arylsulfonyl amides (**Scheme 15**). Radical **3.9** can be in equilibrium with the spirocyclic intermediate **3.10**, which can produce the amidyl radical **3.11** after SO₂ extrusion. This amidyl radical can either abstract a hydrogen atom from a species present in the reaction mixture, leading to the desired α -arylated amide **3.12**. Alternatively, this radical can induce intramolecular cascade reactions, such as addition onto unsaturations to produce polycyclic products. Three strategies have been developed through the past years to form the key radical intermediate, two of them being the most popular ones (**Scheme 15**, eq. 1 and 2). The first one consists of the addition of a radical **Y**, generated *in situ*, onto an acrylamide of type **3.5**. The advantage of this method is the large diversity of radicals that can be employed. The second strategy generates the key intermediate **3.9** through the homolytic cleavage of the C-X bond of an α -halo amide **3.6**, induced either by a transition metal complex or an iridium photocatalyst under visible-light irradiation. Recently, a third strategy emerged based on a 1,6-hydrogen transfer from radical **3.8**, which is generated from the corresponding aryl iodide **3.7** (**Scheme 15**, eq. 3). This method displays the advantage of avoiding the α -functionalization of the amide.



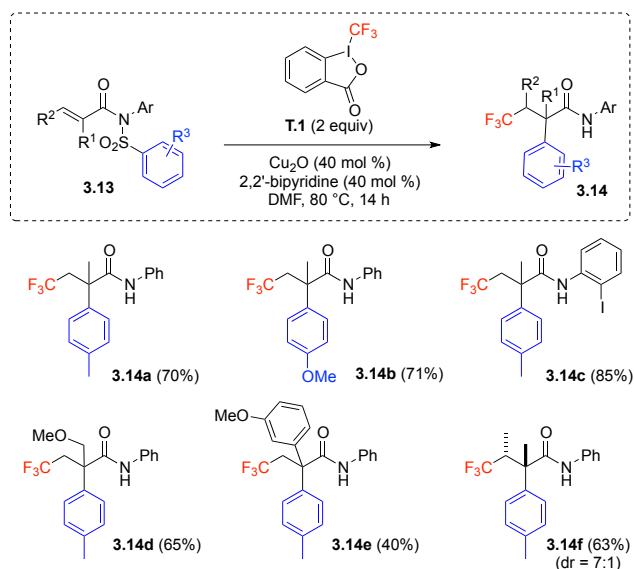
Scheme 15. Strategies for the synthesis of α -aryl amides by radical desulfonylative 1,4-aryl migration. HAT = hydrogen atom transfer.

3.1 Addition of radicals to acrylamides

3.1.1 Formation of α -aryl amides

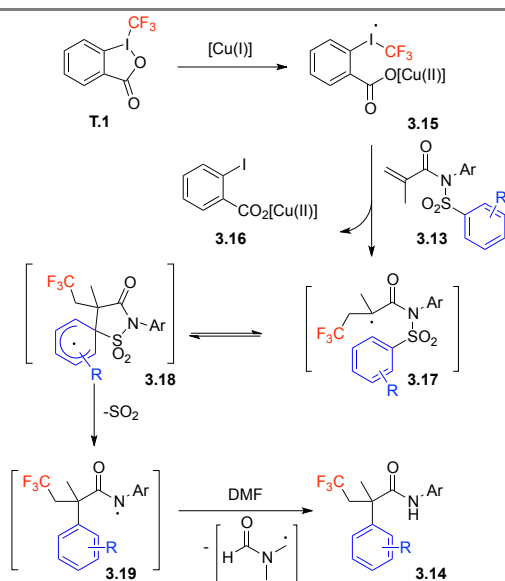
Carbon-centered radicals

In 2013, Nevado and co-workers were the first to publish a method to access α -aryl amides through 1,4-aryl migration starting from an acrylamide (**Scheme 16**)²⁹ In the presence of a copper complex, CF_3 radicals were generated from the Togni reagent **T.1** and could subsequently add onto acrylamides **3.13** to form a radical α to the amide leading, after a desulfonylative aryl migration, to β -trifluoro- α -aryl amides **3.14**. The authors were able to isolate amide **3.14a** with a good yield (70%). Unlike anionic 1,4-aryl migration, radical aryl migration enabled electron-rich aryl groups to migrate affording amide **3.14b** with a *p*-methoxy phenyl group at the α position of the amide (71%). As the reaction tolerated C(sp²)-I bond, amide **3.14c** was obtained in 85% yield, and the presence of the iodine atom would enable further reactions, extending the synthetic utility of the method. Having a R¹ substituent different from a proton in the α position of the acrylamide is mandatory, probably to stabilize the transient radical formed at this position. This R¹ substituent can possess a methyl ether (**3.14d**, 65%). However, having an aryl group in this position probably decreases the reactivity of the key intermediate as α,α' -bis-aryl amide **3.14e** was obtained with a moderate yield (40%). When the double bond of the acrylamide was disubstituted (R² \neq H), a mixture of diastereoisomers was obtained (**3.14f**, 63%, dr = 7:1). An aryl substituent on the nitrogen of the amide is needed to produce α -aryl amides whereas an alkyl substituent leads to a divergence of reactivity with the formation of oxindoles (vide infra).



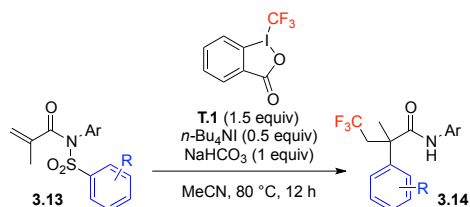
Scheme 16. Synthesis of β -trifluoromethyl α -aryl amides by Nevado *et al.*²⁹ DMF = *N,N*-dimethylformamide.

The putative mechanism of this transformation would start by the reaction of the Togni reagent with a copper(I) complex giving the iodine centered radical **3.15** (**Scheme 17**). This radical would lead to the CF_3 radical, which could react with acrylamide **3.13** to give the key intermediate **3.17** and the copper(II) carboxylate **3.16**. The radical **3.17** would be in equilibrium with the spirocyclic intermediate **3.18**, which would produce the amidyl radical **3.19** after SO_2 extrusion.³⁰ Finally, the amidyl radical **3.19** could perform a hydrogen abstraction from DMF to give α -aryl amide **3.14**.



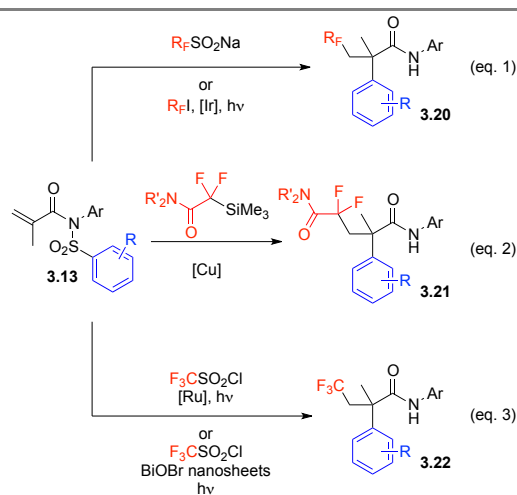
Scheme 17. Putative mechanism for the synthesis of β -trifluoromethyl α -aryl amides from acrylamides and Togni reagent.²⁹ DMF = *N,N*-dimethylformamide.

The same year, the same team published a similar method avoiding the use of a transition metal catalyst (**Scheme 18**).³¹ Treatment of acrylamides **3.13** with the Togni reagent in the presence of *n*-Bu₄NI and a base (NaHCO₃) yielded β -trifluoromethyl α -aryl amides **3.14**. The authors suggested the formation of a cation at the α position of the amide after reaction with a super-electrophilic iodine species generated from the Togni reagent and iodine. Nevertheless, the formation of a cation α to the carbonyl is not common and the generation of CF₃ radicals under similar conditions (Bu₄NI, **T.1**) has been previously described,³² suggesting that a radical aryl migration could also be operative.



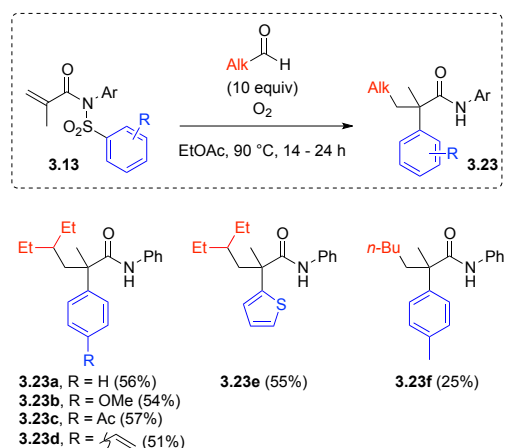
Scheme 18. Metal-free synthesis of β -trifluoromethyl α -aryl amides.³¹

Since fluoroalkyl compounds are of importance in medicinal chemistry,³³ several methods to prepare β -fluoroalkyl α -aryl amides from acrylamides using a 1,4-aryl migration have been developed (**Scheme 19**). The required fluoroalkyl radical can be generated from the corresponding fluoroalkyl sulfinate or fluoroalkyl iodide in the presence of an iridium photocatalyst under visible light irradiation (**Scheme 19**, eq. 1).^{34, 35} A copper-mediated difluoroacetamidation has also been reported (**Scheme 19**, eq. 2).³⁶ In this case, the active radical was generated from the corresponding trimethylsilane difluoro acetamido derivative and then added on acrylamide **3.13**. It is also possible to generate a CF₃ radical from trifluoromethylsulfonyl chloride in the presence of a ruthenium photocatalyst under visible light irradiation (Scheme 19, eq. 3).³⁷ A very interesting generation of a trifluoromethyl radical has been achieved using BiOBr nanosheets and trifluoromethylsulfonyl chloride under light irradiation ($\lambda = 280$ -780 nm) (**Scheme 19**, eq. 3).³⁸



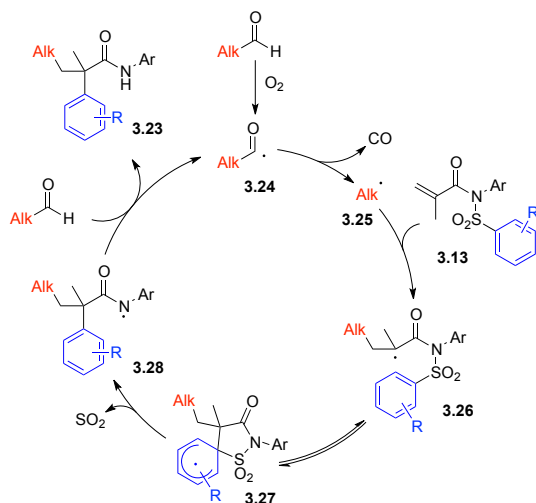
Scheme 19. Fluoroalkyl radical insertion on *N*-arylsulfonyl acrylamides triggering a radical 1,4-aryl shift.³⁴⁻³⁸

From these pioneering studies involving fluoroalkyl radical, a range of similar methods, using different carbon-centered radicals, were developed to access a diversity of β -substituted α -aryl amides from acrylamides. In 2015, Guin and co-workers developed a reaction affording β -alkyl α -aryl amides **3.23** from alkyl aldehydes and acrylamides **3.13** under a dioxygen atmosphere (**Scheme 20**).³⁹ The reaction of aliphatic aldehydes with oxygen allowed the generation of alkyl radicals that are able to add on the double bond of an acrylamide. The authors were able to isolate amides **3.23** generally with acceptable yields. α -Phenyl-amide **3.23a** was isolated with a yield of 56%. Both electron-rich and electron-poor aryl groups were able to migrate and amides **3.23b**, bearing a *p*-OMe aryl group, and **3.23c**, bearing a *p*-acetyl aryl group, were isolated in 54% and 57% yields respectively. Worthy of note, the satisfying yield obtained for **3.23c** emphasizes the tolerance of the reaction toward electrophilic groups such as ketones. Interestingly, amide **3.23d** bearing a styrenic moiety, usually reactive toward radicals, could be isolated in 51% yield. The α -thiophenyl amide **3.23e** was obtained (55%), showing the ability of heteroaromatics to migrate, opening the way to the synthesis of pharmaceutically relevant compounds. However, primary alkyl radicals reacted poorly under these conditions and amide **3.23f** was isolated with a low yield (25%). This may be explained by the low stability of primary radicals.⁴⁰



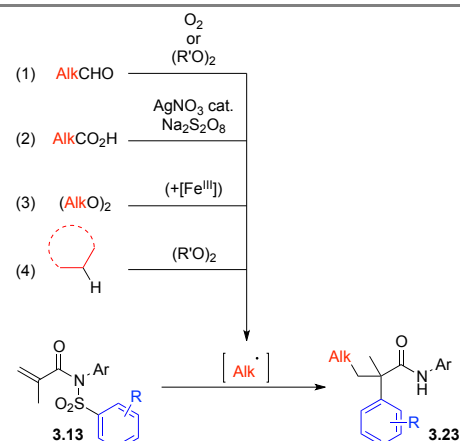
Scheme 20. Alkyl radical triggered 1,4-aryl migration upon addition on acrylamides.³⁹

The authors suggested that the reaction between dioxygen and an aliphatic aldehyde would afford acyl radical **3.24**, which would give the alkyl radical **3.25** after carbon monoxide extrusion (**Scheme 21**). This radical would add to acrylamide **3.13** yielding the key intermediate **3.26**. Radical **3.26** could then undergo the desulfonylative 1,4-aryl migration sequence leading to amidyl radical **3.28** through spirocyclic intermediate **3.27**. The authors then hypothesized that amidyl radical **3.28** could abstract a hydrogen atom from the aliphatic aldehyde to give the α -aryl product **3.23** and the regeneration of the acyl radical **3.24**.



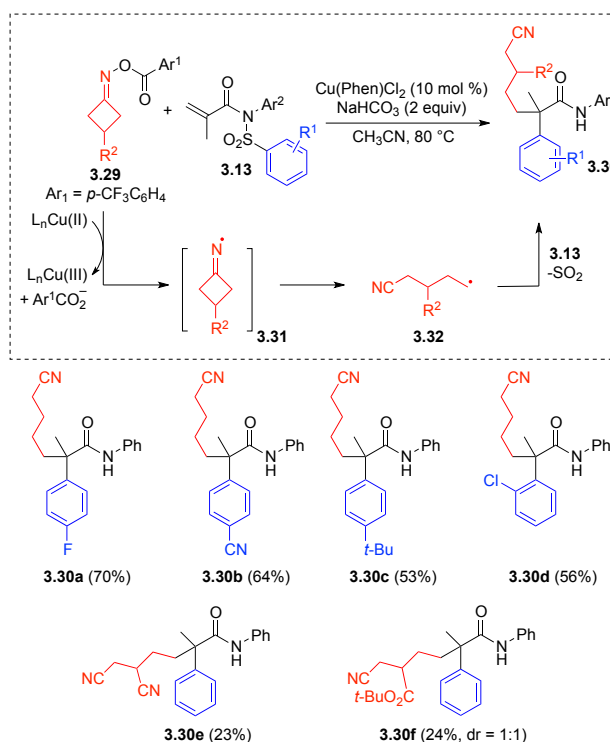
Scheme 21. Putative mechanism proposed by Guin *et al.*³⁹

Starting from acrylamides, many other methods have been published to synthesize β -alkyl α -aryl amides using a radical addition/desulfonylation/1,4-aryl migration sequence (**Scheme 22**). Acyclic alkyl radicals can be generated from aldehydes either by reaction with oxygen (*vide supra*) or with peroxides (**Scheme 22**, eq. 1).^{39,34, 41} Decarboxylation of carboxylic acids under oxidative conditions [AgNO_3 , $\text{Na}_2\text{S}_2\text{O}_8$] can also lead to alkyl radicals (**Scheme 22**, eq. 2).⁴² Otherwise, alkyl radicals can be generated from peroxides at high temperature and methyl radicals can be formed from di-*tert*-butyl peroxides using iron(III) catalysis (**Scheme 22**, eq. 3).^{43,44} Moreover, cyclic alkyl radicals can result from an intermolecular hydrogen abstraction starting from the corresponding cycloalkanes and peroxides. All these radicals were able to trigger a desulfonylation/1,4-aryl migration sequence after addition to acrylamides **3.13** (**Scheme 22**, eq. 4).⁴⁵ Addition of the tertiary radical derived from AIBN to acrylamides has also been reported.⁴⁶



Scheme 22. Synthesis of α -aryl amides by alkyl radical addition on acrylamides followed by desulfonylation/1,4-aryl migration sequence.^{34, 39, 41-46}

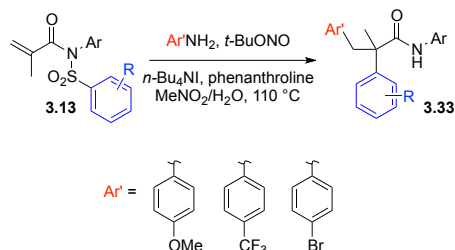
In 2021, Liang *et al.* reported an elegant method to generate alkyl radicals through a copper-catalyzed ring-opening of cycloalkanone oxime derivatives **3.29**.⁴⁷ The iminyl radical resulting from the N-O bond cleavage spontaneously generated a carbon-centered alkyl radical after a β -C-C bond scission and this radical was able to add on the double bond of a *N*-arylsulfonyl acrylamide thus triggering the desulfonylation/aryl migration sequence. Following this cascade reaction, a diversity of α -aryl amides featuring an alkyl nitrile moiety was isolated. Several functional groups were tolerated on the benzenesulfonyl group and both electron-rich and electron-poor aryl groups could be involved in the migration step (**3.30a-3.30d**). The scope of cyclic oxime derivatives was restricted as the presence of electron-withdrawing groups at the C3 position affected the yield of the transformation (**3.30e-3.30f**).



Scheme 23. Generation of alkyl radicals through copper-catalyzed ring-opening of cycloketone oxime derivatives.⁴⁷

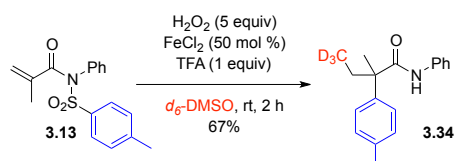
The generation of an aryl radical followed by its addition to an acrylamide, promoting the desulfonylative 1,4-aryl migration was

also reported (**Scheme 24**).⁴⁸ In this case, the radical was formed from the diazo compound prepared *in situ* by treatment of aniline derivatives with *tert*-butylnitrite. As expected for a radical-mediated 1,4-aryl migration, the reaction is not sensitive to the electron density of the migrating aryl group as both electron-poor and electron-rich aryl groups can migrate. The reaction seems also to be tolerant toward C(sp²)-Br bonds, allowing further transformations.



Scheme 24. Desulfonylative radical 1,4-aryl migration triggered by an aryl radical addition on acrylamides.⁴⁸

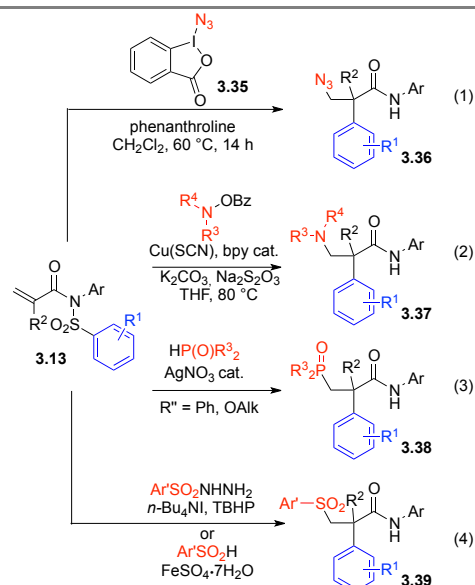
An isolated example of deuterated methyl group incorporation through radical addition/desulfonylative 1,4-aryl migration was reported (**Scheme 25**).⁴⁹ Deuterated DMSO was used as the source of CD₃ radical under oxidative conditions and acrylamide **3.13** was converted in the deuterated α -aryl amide **3.34** with a synthetically useful yield (67%). This reaction paves the way to an easy access to deuterated compounds, which can be useful intermediates.



Scheme 25. Synthesis of β -trideuteromethyl α -aryl amide from an acrylamide.⁴⁹ TFA = trifluoroacetic acid. DMSO = dimethylsulfoxide.

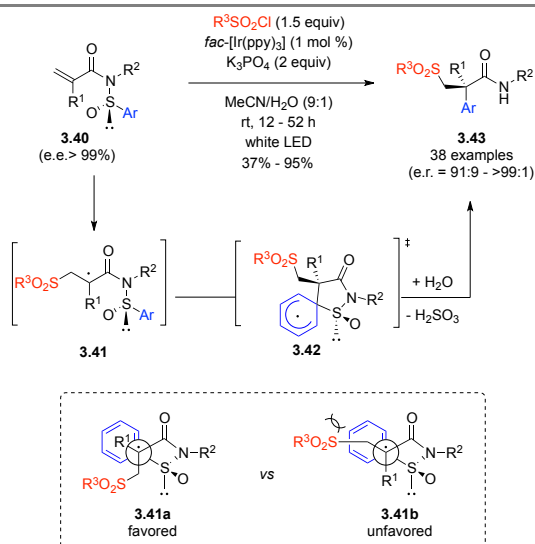
Heteroatom-centered radicals

Heteroatom centered radicals are also able to promote the desulfonylative 1,4-(het)aryl migration sequence through addition on acrylamides. Azide radical generated from benziodoxole **3.35** has been employed to produce β -azide α -aryl amides **3.36** (phenanthroline, CH_2Cl_2 , $60\text{ }^\circ\text{C}$, 14 h) (**Scheme 26**, eq. 1).^{50,51} *O*-Benzoylhydroxylamines were used as aminyl radical precursors to deliver β -amino α -aryl amides **3.37** under copper(I) catalysis (**Scheme 26**, eq. 2).⁵² Phosphorus-centered radicals have also been used (**Scheme 26**, eq. 3). Associated to a catalytic amount of silver nitrate, phosphorus hydrides could give $\text{P}(\text{O})\text{R}''_2$ radicals that could add to acrylamide **3.13** yielding β -phosphine oxide α -aryl amides ($\text{R}'' = \text{Ph}$) or β -phosphonate ester α -aryl amides ($\text{R}'' = \text{OAlk}$) **3.38**.^{50,51} Methods allowing the synthesis of β -arylsulfonyl α -aryl amides **3.39** have also been reported using $\text{Ar}'\text{SO}_2$ radicals (**Scheme 26**, eq. 4).⁵³ These latter radicals can be generated from sulfonylhydrazine derivatives in the presence of $n\text{-Bu}_4\text{NI}$ and peroxides (TBHP)^{53b} or from the corresponding sulfinic acid and an iron(II) complex.^{53a}



Scheme 26. Desulfonylative radical 1,4-aryl migration triggered by addition of an heteroatom-centered radical on an acrylamide.⁵⁰⁻⁵³ TBHP = *tert*-butyl hydroperoxide.

In 2021, a crucial breakthrough was made by Nevado *et al.*, who were the first to disclose the synthesis of enantio-enriched α -aryl amides using a radical 1,4-aryl migration. The absence of gas extrusion during the process excludes this method from the scope of the present review, but the importance of this discovery as well as its tight connection with desulfonylative processes make it important to mention. The method based on a chirality transfer, realized from optically active *N*-sulfinylacrylamides **3.40**, afforded **3.43** with high enantiomeric ratios (**Scheme 27**).⁵⁴ A *S*-centered radical, generated from the corresponding sulfonyl chloride in the presence of an iridium photocatalyst, under light irradiation, was able to add onto the acrylamide and yielded β -sulfinyl α -aryl amide after the 1,4-aryl migration proceeding with sulfite anion release. Worthy of note, *C*-centered radicals can also be used in this transformation. DFT calculations showed that the reaction proceeds *via* a spirocyclic early transition state **3.42** in which the C-C_{Ar} bond is relatively long (2.12 Å) and the C_{Ar}-SO bond is relatively short (1.86 Å). The *ipso* addition of radical **3.41** is the enantio-determining step and the stereochemical outcome of the reaction takes its origin in the existence of a steric repulsion between the -CH₂SO₂R³ group and the aryl group, favoring **3.41a**.

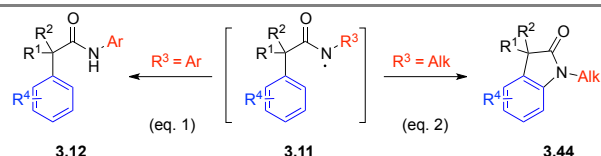


Scheme 27. Nevado *et al.* synthesis of enantio-enriched α -aryl amides.⁵⁴ ppy = 2-phenylpyridine. LED = light emitting diode.

Addition of a radical on an acrylamide is a powerful way to generate a key radical intermediate able to trigger a desulfonylation/1,4-aryl migration sequence. It is compatible with a wide range of radicals allowing the introduction of a variety of functions β to the amide. However, this method has some drawbacks and, particularly, the key radical intermediate has to be stabilized, requiring the presence of an alkyl group α to the carbonyl moiety of the acrylamide. Furthermore, the evolution of the resulting amidyl radical seems to be highly dependent on the nature of the *N*-substituent and the reaction is only feasible with *N*-aryl amides. Indeed, as developed in the next section, when the nitrogen atom of the amide is substituted with an alkyl chain, oxindoles were obtained.

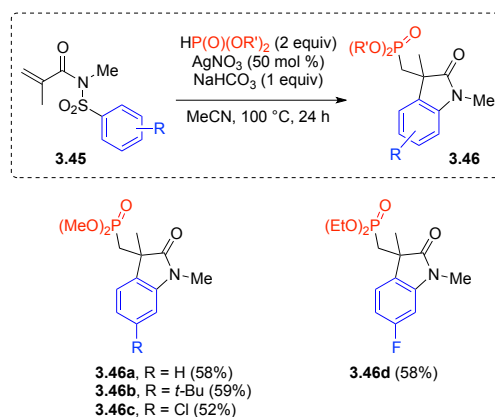
3.1.2 Formation of oxindoles

The nature of the *N*-substituent plays a crucial role with regard to the behaviour of the amidyl radical **3.11** formed after the radical addition/desulfonylative aryl migration sequence. In the presence of a *N*-aryl substituent, the amidyl radical usually abstracts a hydrogen atom from the solvent resulting in the formation of the α -arylamide **3.12** (**Scheme 28**, eq. 1). In contrast, when an alkyl group is present on the nitrogen atom, the amidyl radical is prone to cyclize onto the aryl ring that has previously undergone the migration, leading to oxindole **3.44** (**Scheme 28**, eq. 2). This observed divergence of reactivity could be attributed to a modulation of the stability of the amidyl radical depending on the nature of the *N*-substituent. The addition of the amidyl radical on the aromatic could be seen as a reversible process.⁵⁵ In the presence of an *N*-aryl amidyl radical, the aryl ring would induce a stabilization of the *N*-centered radical favoring the open chain form and finally the formation of the α -arylamide. In contrast, in the presence of a *N*-alkyl group, the radical is less stabilized and the closed form should be favored explaining the major formation of the oxindole. However a modulation in term of reactivity of the amidyl radical depending on the electronics and steric hindrance of the nitrogen substituent should not be excluded. This divergence of reactivity is observed in most cases but still depends on the reaction conditions since exceptions were encountered.^{60,61,66,72}



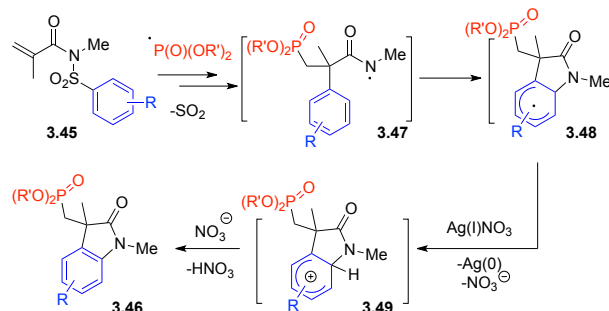
Scheme 28. Divergence of reactivity depending on the *N*-substituent.

In 2013, in the course of their work on desulfonylative 1,4-aryl shift promoted by radical addition on acrylamides, Nevado and co-workers were the first to discover this divergence of reactivity.²⁹ In 2014, the same group developed a method allowing the incorporation of a phosphonate ester moiety on acrylamides **3.45** leading to the formation of oxindoles **3.46** (**Scheme 29**).⁵⁰ The authors were able to isolate the phosphonate ester containing oxindoles **3.46a-3.46d** and the yield of the transformation does not seem to depend on the nature of the migrating aryl group. The reaction is tolerant to C(sp²)-Cl and C(sp²)-F bonds leading to products **3.46c** (52%) and **3.46d** (58%).



Scheme 29. Nevado *et al.* synthesis of oxindoles.²⁹

Mechanistic studies were performed and the following mechanism was proposed (**Scheme 30**). A phosphorus-based radical could be generated under the optimized conditions [HP(O)(OR')₂, AgNO₃, NaHCO₃, MeCN, 100 °C] and this radical could add to acrylamide **3.45** to trigger the desulfonylative 1,4-aryl migration leading to *N*-alkyl amidyl radical **3.47**. This radical is hypothetically more nucleophilic than *N*-aryl radicals, and thus could add on the aryl group present in the α -position of the amide to generate bicyclic radical **3.48**. In the presence of AgNO₃, the radical could be oxidized to the cationic intermediate **3.49**, identical to a Wheland complex. This arenium intermediate led to oxindole product **3.46** after proton elimination. Based on Kinetic Isotopic Effect (KIE) and labeling experiments, the desulfonylation/1,4-aryl migration sequence was identified as the rate determining step.



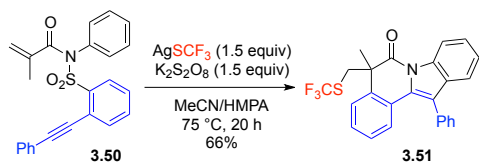
Scheme 30. Putative mechanism for the formation of oxindoles.²⁹

Inspired by this seminal study, several examples of oxindole formation through the same type of sequence were disclosed. Different radicals were used to initiate the cascade reaction such as acyl radicals, nitrogen dioxide radicals and arylsulfonyl radical.⁵⁶

3.1.3 Formation of (poly)cyclic products by cascade reactions

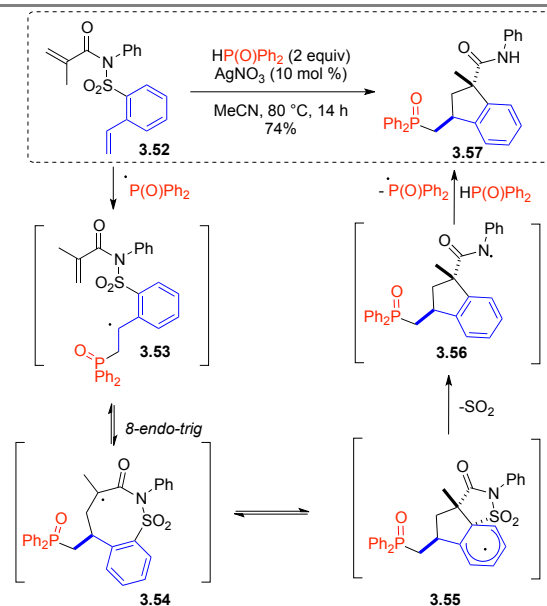
Cascade reactions involving radical additions on multiple bonds

The ability of radicals to add on unsaturations such as triple or double bonds has been exploited to induce cascade reactions subsequent to the desulfonylative 1,4-aryl migration. For example, the presence of an alkyne substituent, *ortho* to the sulfonamide group on the migrating aryl group, could lead to the formation of indoloisoquinolones. Nevado and co-workers were the first to report this reactivity in 2015 (**Scheme 31**).⁵⁷ The combination of silver trifluoromethylthiolate with potassium persulfate would generate SCF₃ radicals in the reaction mixture, which could add to acrylamide **3.50**, affording, after a cascade reaction, indoloisoquinolone **3.51** (66%). The authors were also able to perform similar reactions using CF₃, P(O)Ph₂ and N₃ radicals.⁵⁸



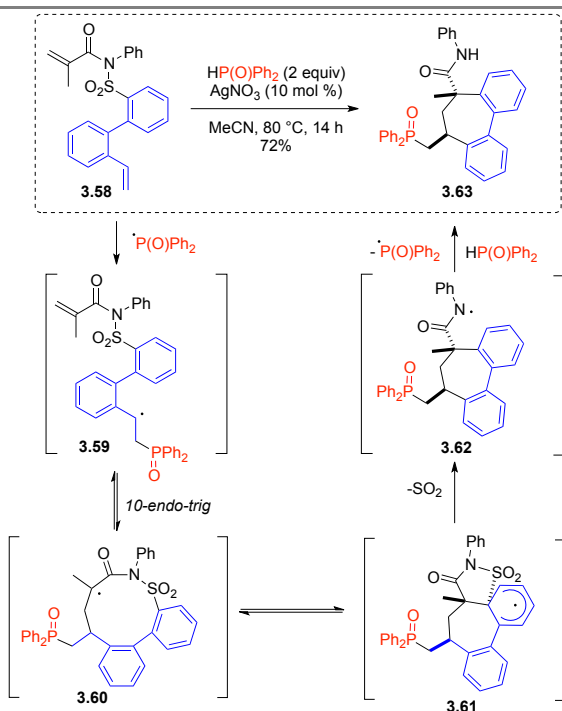
Scheme 31. Formation of indoloisoquinolones by Nevado *et al.*⁵⁷ HMPA = hexamethylphosphoramide.

With the same objective of initiating cascade reactions, a double bond was introduced *ortho* to the sulfonamide of the migrating aryl ring of *N*-arylsulfonyl acrylamides (**Scheme 32**). In the presence of HP(O)Ph₂ and silver nitrate, indane **3.57** was obtained in 74% yield from *o*-styryl acrylamides **3.52**.⁵¹ According to the proposed mechanism, the phosphorous-centered radical P(O)Ph₂ would add first on the styrenyl double bond to give the benzylic radical **3.53**, which would lead to radical **3.54** after an 8-*endo-trig* cyclization. The resulting radical α to the sulfonimide, would be able to induce a desulfonylation/1,4-aryl migration sequence to give the amidyl radical **3.56** *via* the tricyclic intermediate **3.55**. The resulting amidyl radical would then abstract a hydrogen atom from HP(O)Ph₂ to give indane **3.57** and regenerate a P(O)Ph₂ radical at the same time, allowing the use of a catalytic amount of silver nitrate. This last step has been supported by deuterium labeling experiments.



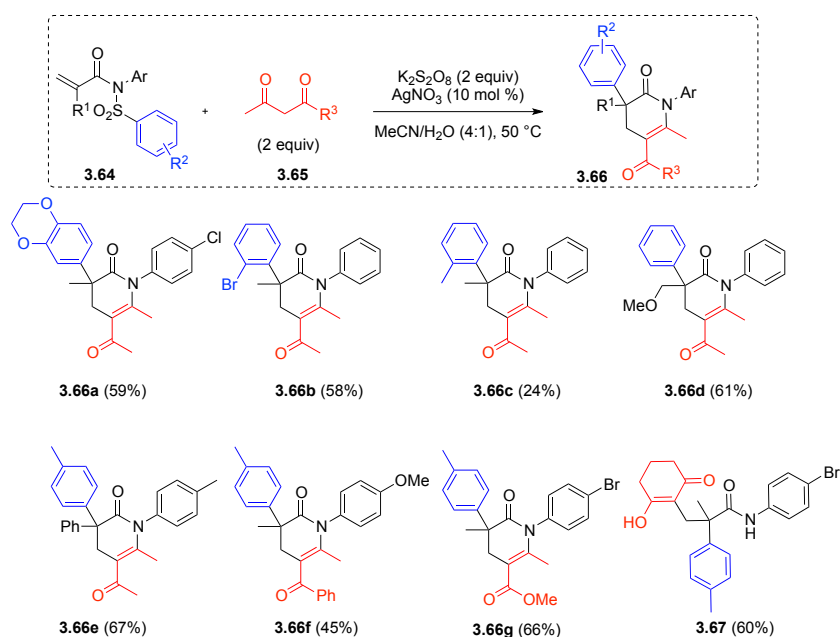
Scheme 32. Synthesis of indane by cascade reactions.⁵¹

To push this reactivity forward, the authors replaced the styrenyl moiety on the acrylamide by a bis-aryl including a styrenic group (**Scheme 33**).⁵¹ When acrylamide **3.58** was treated under the same conditions [HP(O)Ph₂ (2 equiv), AgNO₃ (10 mol %), MeCN, 80 °C, 14 h], the tricyclic compound **3.63**, incorporating a central 7-membered ring was isolated in 72% yield. Once again, the first step would be the addition of the phosphorus-centered radical to the double bond of the styrenyl moiety to afford the radical **3.59**. A subsequent 10-*endo-trig* cyclization on the acrylamide would lead to the 10-membered ring **3.60** possessing a radical α to the *N*-arylsulfonyl amide. This radical could undergo a desulfonylation/1,4-aryl migration sequence *via* tetracyclic intermediate **3.61** to afford the amidyl radical **3.62**. This radical would regenerate the P(O)Ph₂ radical by hydrogen atom abstraction from HP(O)Ph₂ to give the 7-membered ring product **3.63**.



Scheme 33. Synthesis of 7-membered rings by cascade reaction.⁵¹

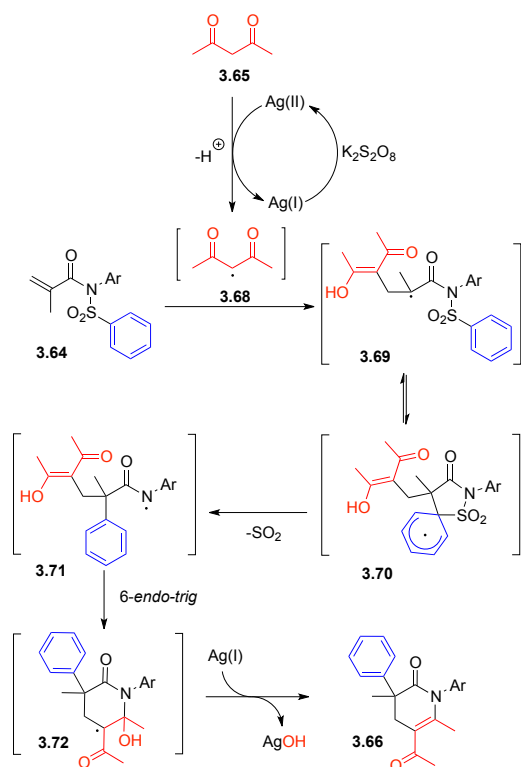
Another family of cascade reactions exploiting the reactivity of the generated amidyl radical with unsaturations was developed to access a variety of dihydropyridinones (Scheme 34).⁵⁷ When acrylamides **3.64** were treated with 1,3-dicarbonyl compounds **3.65** in the presence of a catalytic amount of AgNO_3 , associated to an excess of $\text{K}_2\text{S}_2\text{O}_8$, heterocycles **3.66** were isolated. Halides (Cl, Br) were well tolerated when present on the *N*-aryl substituent and/or on the migrating aryl group. The reaction became sluggish with a hindered *o*-tolyl migrating group, as **3.66c** was obtained with a low yield (24%). A variety of groups (Ph, Me, OMe) were well tolerated at the α position of the acrylamide (R^1). Methyl ether **3.66d** was obtained with a decent yield (61%) as well as the *gem*-



Scheme 34. Synthesis of dihydropyridinones by cascade reaction.⁵⁷

diaryl dihydropyridinone **3.66e** (67%). Using non-symmetrical 1,3-dicarbonyl compounds ($\text{R}^3 \neq \text{Me}$) afforded regioselectively the product incorporating the most sterically hindered carbonyl moiety in its structure. For instance, product **3.66f**, including an acetophenone moiety, was obtained with a yield of 45%. Under these conditions, a β -ketoester was also successfully transformed into dihydropyridinone **3.66g** (66% yield). When a cyclic 1,3-dicarbonyl compound was used, no cyclisation occurred and an α -arylated product, such as **3.67**, was obtained, resulting from a desulfonation/1,4-aryl migration with no subsequent cascade reaction.

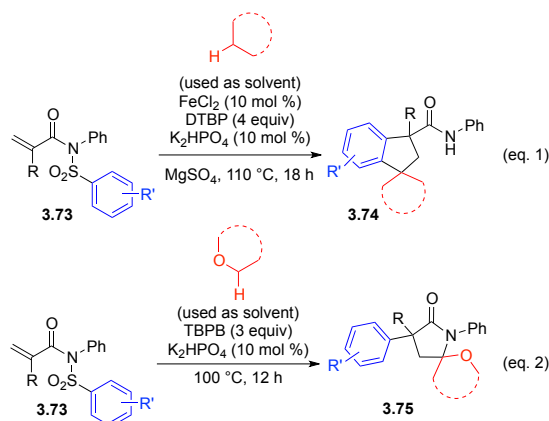
From a mechanistic point of view, Nevado *et al.* proposed that the formation of the dicarbonyl radical **3.68** would arise from the oxidation of the dicarbonyl **3.65** by a silver(II) species, obtained by oxidation of a silver(I) complex with potassium persulfate. Radical **3.68** could add to acrylamide **3.64** to generate the radical intermediate **3.69** able to trigger the desulfonation/1,4-aryl migration sequence yielding the amidyl radical **3.71**. The authors proposed that this radical could undergo a 6-*endo-trig* cyclization on the keto-enol moiety affording radical **3.72**. However, giving the electrophilicity of the amidyl radical, a 5-*exo-trig* cyclization on the more electron-rich carbon would have been more likely. A reduction of the amidyl radical followed by the addition of the resulting anion on a ketone could be seen as an alternative mechanistic hypothesis to explain the formation of **3.72**. Intermediate **3.72** could be deoxygenated to the dihydropyridinone product **3.66** by reaction with a silver(I) species releasing a silver hydroxo complex (Scheme 35).



Scheme 35. Putative mechanism for the formation of dihydropyridinones.⁵⁷

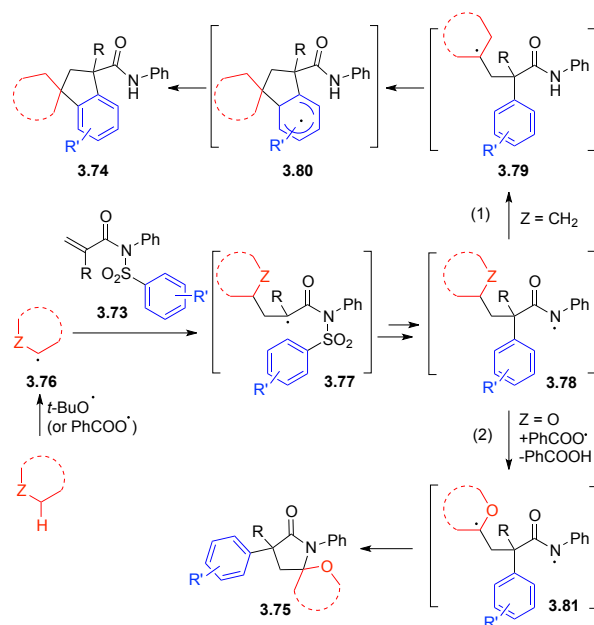
Cascade reactions involving hydrogen atom transfer

In 2017, an interesting radical cascade reaction induced by a 1,4-aryl migration and involving a hydrogen atom transfer was reported (**Scheme 36**).⁵⁹ When a cycloalkyl radical, generated from a cycloalkane in the presence of an iron(II) salt, di-*tert*-butylperoxide (DTBP) and K_2HPO_4 , adds to acrylamides **3.73**, β -spirocyclic indanes **3.74** were formed instead of the expected α -aryl amides (**Scheme 36**, eq. 1). Different R' substituents on the migrating aryl group ($R' = \text{Me, OMe, Cl}$) were tolerated. A variety of cycloalkanes could be used from cyclopentane to cyclooctane. Interestingly, when cycloalkanes were replaced by cyclic ethers, under metal-free conditions and in the presence of *tert*-butyl peroxybenzoate (TBPB), γ -spiro α -aryl pyrrolidinones **3.75** were formed (**Scheme 36**, eq. 2).



Scheme 36. Cascade reactions involving a hydrogen atom transfer.⁵⁹ DTBP = di-*tert*-butyl peroxide. TBPB = *tert*-butyl peroxybenzoate.

Addition of TEMPO to the reaction mixture completely inhibited the reaction and this observation suggested a free-radical-mediated transformation. Kinetic isotope effect experiments were also performed using C_6D_{12} and a k_H/k_D ratio of 3.5 was measured, suggesting that the rate determining step involves a C–H bond cleavage of the cycloalkane. These experiments are in favor of a mechanism involving the formation of the cycloalkyl radical **3.76** that could add to acrylamide **3.73** to give intermediate **3.77** (**Scheme 37**). Radical **3.77** could follow the desulfonylation/1,4-aryl migration sequence described above to afford the amidyl radical **3.78**. When a cyclic alkane was involved (**Scheme 37**, $Z = \text{CH}_2$, Path 1) **3.78** would undergo a 1,5-hydrogen atom transfer yielding radical **3.79**. This radical could intramolecularly add to the aromatic ring to give the delocalized radical **3.80** that could finally evolve to the β -spiro indane **3.74**. When the R substituent α to the amide is an aromatic group different from the migrating aryl ring, the cyclization of **3.79** in **3.80** faced a regioselectivity issue and a mixture of products was generally obtained. When a cyclic ether was used instead of a cycloalkane (**Scheme 37**, $Z = \text{O}$, Path 2), **3.78** could undergo an intermolecular hydrogen atom abstraction by PhCOO^\bullet leading to the bis-radical intermediate **3.81**. The coupling of these two radicals could give pyrrolidinone **3.75**. The authors hypothesized that the stabilization effect of the oxygen is the cause of this reactivity divergence, making the intermolecular hydrogen abstraction easier on cyclic ethers. One could also attribute this divergence of reactivity to the more oxidizable character of radicals α to oxygen, resulting in the oxonium ion after an oxidation event. The latter could then be intramolecularly attacked by the amide to afford the observed product.



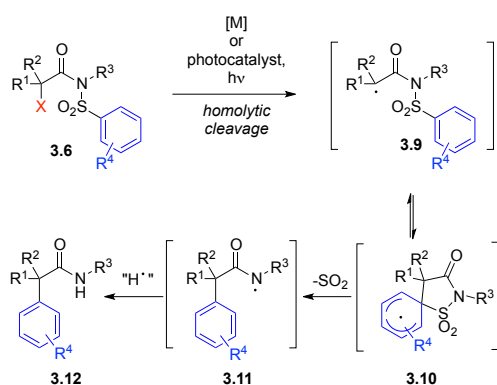
Scheme 37. Putative mechanism for formation of indanes and pyrrolidinones involving a hydrogen atom transfer.⁵⁹

The radical nature of the transformation and the transient formation of highly reactive amidyl radical allow a wide range of cascade reactions to occur. This rich divergence of reactivity depending on the substrate and conditions, broadly enlarges the scope of these synthetic methods, making it a useful tool for organic chemists.

3.2 Homolytic cleavage of C-X bond of α -haloamides

3.2.1 Formation of α -aryl amides

Alkyl halides have been broadly employed as precursors of carbon-centered radicals, the work of Urry and Karasch being a pioneering example.¹⁰ⁱ Indeed, α -halo amide **3.6** can be converted to the key radical intermediate **3.9** by homolytic cleavage of the C-X bond promoted by a transition metal complex or a photocatalyst under light irradiation (Scheme 38). The alkyl radical is then in equilibrium with the spirocyclic intermediate **3.10**, which can evolve to the amidyl radical **3.11** after SO₂ extrusion, which shifted the equilibrium towards **3.11**. Amidyl radical **3.11** can then lead to α -aryl amide **3.12** after hydrogen abstraction.

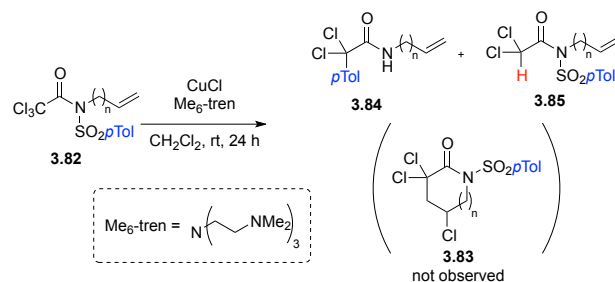


Scheme 38. General principle for the synthesis of α -aryl amides through desulfonylative radical 1,4-aryl shift on α -halo amides.

From trichloroacetamides – seminal work

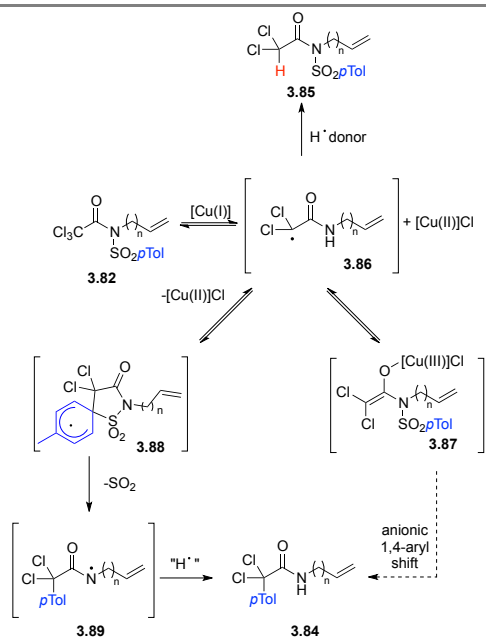
In 2009, Clark *et al.* intended to synthesize macrolactams from trichloroacetamides bearing a double bond on the *N*-alkyl substituent (Table 2).⁶⁰ By treatment of trichloroacetamides **3.82** with a copper(I) salt, they expected the formation of a radical in the α position of the carbonyl that may be involved in an *endo*-trig cyclization to deliver the corresponding lactam **3.83**.⁶¹ However, the formation of **3.83** was not observed and, instead, α -aryl amide **3.84** resulting from a desulfonylative 1,4-aryl migration was produced along with the dehalogenated product **3.85**. The number of methylene groups [(CH₂)_n] between the double bond and the nitrogen atom was varied. By decreasing the number of CH₂ groups, the formation of α -aryl amide **3.84** was favored over the reduction product **3.85**. In addition, by increasing the number of CH₂ groups a loss in the global yield was observed while the yield in favor of the reduction product **3.85** seems to be constant regardless the number of CH₂ groups (28 – 34%).

Table 2. Treatment of trichloroacetamides with CuCl.^{60,61} Me₆-tren = *N*¹,*N*¹-bis(2-(dimethylamino)ethyl)-*N*²,*N*²-dimethylethane-1,2-diamine.



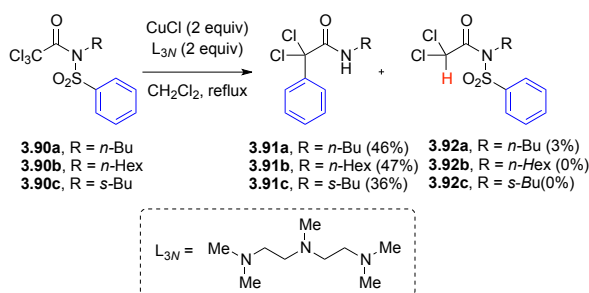
Entry	n =	Yield 3.84 + 3.85 (3.84 / 3.85)
1	3	71% (61:39)
2	4	62% (49:51)
3	6	54% (37:63)

A mechanism depicted in Scheme 39 can be proposed to explain these results. In the presence of a copper(I) salt, an equilibrium between α -trichloroacetamide **3.82** and the corresponding radical **3.86** could be established. This equilibrium has been thoroughly studied because of its implication in Atom Transfer Radical Polymerization (ATRP).⁶² Kinetic studies indicated that this halogen abstraction proceeds according to an inner sphere single-electron transfer.⁶³ At this stage, the reduction product **3.85** could arise from a direct hydrogen atom abstraction by the radical **3.86**. Alternatively, radical **3.86** could be in equilibrium with the spirocyclic intermediate **3.88**, which could give amidyl radical **3.89** after an aryl migration with SO₂ extrusion. This radical could perform a hydrogen atom abstraction to afford the α -aryl product **3.84**. The presence of a double bond in the amidyl radical **3.89** can also lead to side reactions, such as radical cyclization (not shown). This is particularly true when the number of CH₂ groups is large enough and this may explain the decrease of the yield in **3.84** when the number of CH₂ groups is increased. Based on the results reported in the previous section of this review, one could ask why having a *N*-alkyl substituent on the nitrogen atom of the amide did not produce the oxindole. Several hypotheses can be proposed to explain this difference of reactivity. The presence of a copper(II) complex could stabilize the amidyl radical **3.89** that can be in equilibrium with the copper(III) amide. In addition, the reaction between the radical **3.86** and the copper(II) complex could result in enolate **3.87**, which could then evolve through an anionic desulfonylative 1,4-aryl migration to provide **3.84**. However, the observed migration of electron-neutral/rich aromatics under these conditions does not favor this last hypothesis. Nevertheless, some results obtained for the migration of electron-poor aryl groups, such as NO₂-substituted phenyl groups, could be explained by the existence of two competing mechanisms.



Scheme 39. Putative mechanism for the desulfonylative radical 1,4-aryl migration on trichloroacetamides.^{60,61}

To avoid any side reactions, Clark *et al.* removed the double bond present on the *N*-alkyl substituent and explored the reactivity of various *N*-alkyl trichloroacetamides (**Scheme 40**). When *N*-alkyl trichloroacetamides **3.90a-3.90c** were treated with copper chloride and an amine-based ligand, α -aryl amides **3.91a-3.91c** were isolated with moderate yields (36% to 47%). Under the same conditions, trichloroacetamide **3.90a** led to α -aryl amide **3.91a** (46%) along with traces of the reduction product **3.92a** (3%). In contrast, no reduction product was observed starting from **3.90b** and **3.90c**. The yields were better than the ones obtained with an unsaturated *N*-substituent but were still low. Nevertheless, this seminal work proved that α -aryl amides can be generated from α -halo amides *via* a radical 1,4-aryl migration and paved the way for further development.

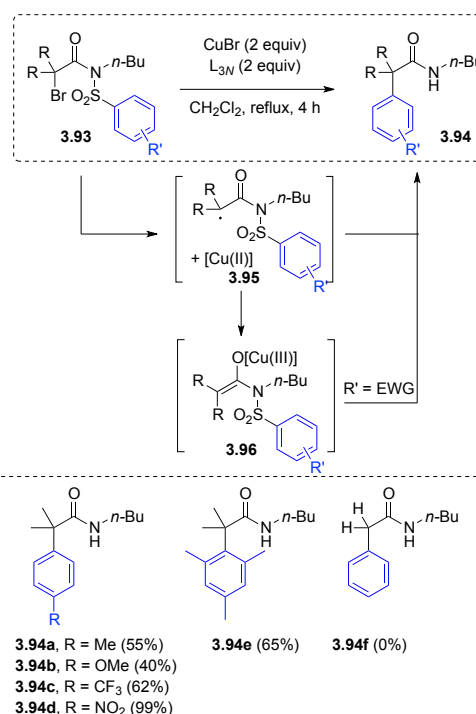


Scheme 40. Desulfonylative radical 1,4-aryl migration on trichloroacetamides by reaction with copper(I).^{60a} $L_{3N} = N^1$ -(2-(dimethylamino)ethyl)- N^1, N^2, N^2 -trimethylethane-1,2-diamine.

From α -bromo amides

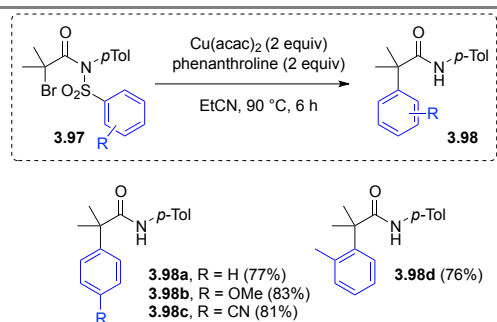
In the pioneering work by Clark *et al.*, trichloroacetamides afforded α, α -dichloro- α -arylamides. Even if the chlorine-carbon bond could be reduced afterward, the presence of the chlorine atoms can be viewed as a restriction for substrate diversity. Instead, using α -bromo amide may enlarge the reaction scope and facilitate the radical formation as the carbon bromine bond is generally more easily cleaved than the carbon-chlorine one. Based on these

considerations, Clark *et al.* moved to α -bromo *N*-arylsulfonyl amides **3.93**, which were treated under similar conditions than trichloroacetamides [CuBr (2 equiv), N^1 -(2-(dimethylamino)ethyl)- N^1, N^2, N^2 -trimethylethane-1,2-diamine (L_{3N} , 2 equiv), CH_2Cl_2 , reflux] to give the corresponding α -aryl amides **3.94** with moderate to good yields (**Scheme 41**).^{60b} Electron-rich as well as electron-poor aryl groups were able to migrate and a quantitative yield was obtained in the presence of a *p*-nitro substituent on the migrating aryl group (**3.94d**). This result could suggest that the copper complex could perform two consecutive single electron transfers to form a copper enolate **3.96** that could be involved in an anionic aryl migration (*vide supra*). Hindered α -aryl amides such as α -mesityl amide **3.94e** could be obtained (65%). However, the reaction was limited to tertiary bromides as α -bromo amide **3.93f**, featuring a primary bromide, led to a mixture of reduced product and primary sulfonamide that could come from a $E1_{CB}$ elimination on a putative enolate intermediate through two consecutive single electron transfers.



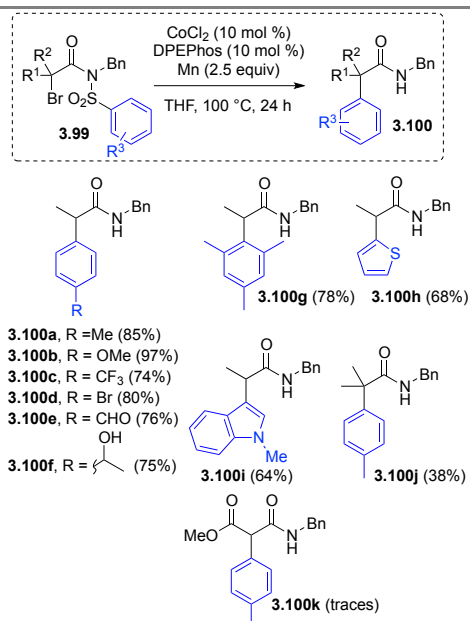
Scheme 41. Synthesis of α -aryl amides from *N*-arylsulfonyl α -bromo amides.^{60b} $L_{3N} = N^1$ -(2-(dimethylamino)ethyl)- N^1, N^2, N^2 -trimethylethane-1,2-diamine.

In 2017, Chuang *et al.* published a similar method using a copper(II) complex in the presence of phenanthroline (**Scheme 42**).⁶⁴ At high temperature in EtCN, this system allowed the transformation of α -bromo amides **3.97** into the corresponding α -aryl amides **3.98** in good yields regardless the electron density of the migrating aryl group. Both electron-poor and electron-rich aryl groups were able to migrate affording α -aryl amides **3.98a-3.98c** in yields ranging from 77% to 83%. Hindered aromatics proved able to migrate and the *ortho*-tolyl product **3.98d** was isolated with a yield of 76%. No example of *N*-alkyl α -aryl amide formation was reported and the use of a tertiary bromide seems to be mandatory. It is noteworthy that the reaction tolerated the presence of electrophilic function such as a nitrile in the substrate and even as the solvent.



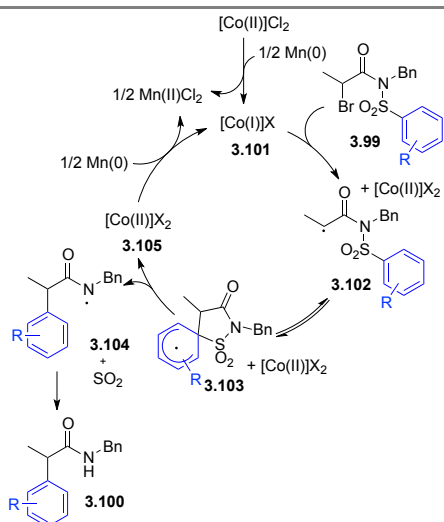
Scheme 42. Synthesis of α -aryl amides by Chuang *et al.*⁶⁴ acac = acetylacetonate.

The main drawback of these reactions is the need of an excess of copper complexes, strongly affecting the atom-economy of the reaction. In the past few years, the ability of earth-abundant transition metal, such as cobalt or iron, to generate alkyl radicals from alkyl halides in a catalytic fashion has been demonstrated.⁶⁵ Based on these considerations, a cobalt-catalyzed desulfonylative 1,4-aryl migration process applied to α -bromo *N*-arylsulfonyl amides was recently developed (**Scheme 43**).⁶⁶ α -Bromo amides **3.99** were treated with cobalt chloride in the presence of a bis-phosphine ligand and manganese as a reductant to lead to the corresponding α -aryl amides **3.100**.⁶⁷ The rearrangement is supposed to be initiated by a low-valent cobalt-induced radical formation from the bromide. Electronic effects on the migrating aromatic group did not seem to have an effect on the yield of the reaction since α -aryl amides possessing a *p*-methoxyphenyl (**3.100b**) and a *p*-trifluoromethylphenyl (**3.100c**) groups were obtained with 97% and 74% yield respectively. The reaction was tolerant toward C(sp²)-Br bond, electrophilic functions such as aldehydes, or hydroxyl groups. It has been possible to form hindered α -aryl amides such as α -mesityl amide **3.100g**, which was isolated in 78% yield. Heteroaromatics such as thiophene or indole were also suitable migrating groups. However, some limitations were identified. The reaction is sluggish when a tertiary bromide was used and amide **3.100j** was isolated with a low yield (38%). This result could be explained either by difficulties in generating the radical due to steric hindrance around the C-Br bond or by extra stabilization of the transient radical, inducing side reactions. Primary bromides were also unable to react under these conditions probably because of the lack of stability of the resulting primary radical intermediate. The 1,4-aryl migration failed when an electron-withdrawing group was present at the α -position of the amide as the formation of the primary sulfonamide BnNHSO₂Ar was observed. The presence of the electron-withdrawing group could facilitate the reduction of the transient radical, leading to the corresponding enolate, which would eliminate the BnNSO₂Ar group according to a E1_{CB} mechanism.



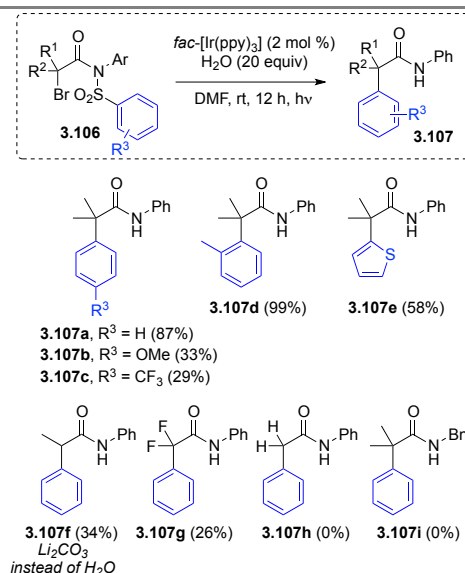
Scheme 43. Cobalt-catalyzed synthesis of α -aryl amides from *N*-arylsulfonyl α -bromo amides through a desulfonylative radical 1,4-aryl migration.⁶⁶ DPEPhos = bis[(2-diphenylphosphino)phenyl] ether. THF = tetrahydrofuran.

Complementary experiments involving radical probes highlighted the formation of a radical intermediate. In addition, an isolated cobalt(I) complex was shown to be able to induce the 1,4-aryl migration when introduced in stoichiometric amount. Based on these studies and previous literature reports, the following mechanism was proposed (**Scheme 44**). Cobalt(I) species **3.101** could be generated from cobalt(II) chloride in the presence of manganese and this low-valent cobalt(I) complex could be stabilized by the bis-phosphine ligand (not shown in the scheme). A single electron transfer from **3.101** to the α -bromoamide would occur to afford the key radical intermediate **3.102**. This latter could then undergo a desulfonylative 1,4-aryl migration, processing with the formation of the transient spirocyclic intermediate **3.103**, affording the amidyl radical **3.104** and a Co(II) complex **3.105**. The amidyl radical could abstract a hydrogen atom from the solvent to produce α -aryl amide **3.100**. Cobalt(II) complex **3.105** could be reduced by Mn(0) to the active Co(I) **3.101**, closing the catalytic cycle.



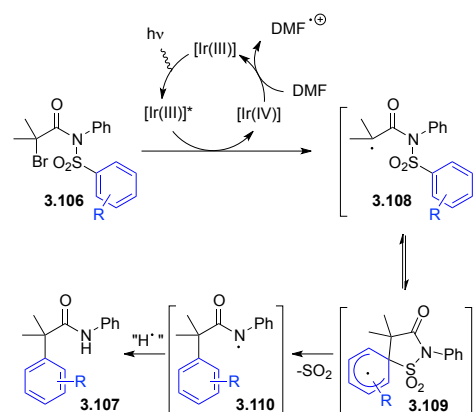
Scheme 44. Putative mechanism for the cobalt-catalyzed synthesis of α -aryl amides from *N*-arylsulfonyl α -bromo amides through a desulfonylative radical 1,4-aryl shift.⁶⁶

Photocatalysis has been identified as a promising activation mode for the formation of *C*-centered radical from alkyl halide.⁶⁸ The resulting radical can then be involved in rearrangements such as desulfonylative 1,4-aryl migration. In 2016, Zhang, Wan and co-workers reported the synthesis of α -aryl amides **3.107** from α -bromo amides **3.106** using an iridium photocatalyst and a 23 W light bulb (**Scheme 45**).⁶⁹ Organic photocatalysts were inefficient while addition of water proved to be beneficial. Under these optimized conditions, α -phenyl amide **3.107a** was obtained with a good yield of 87% from the corresponding bromide. Surprisingly, the migration of *p*-methoxy and *p*-trifluoromethyl phenyl groups proceeded with low yields (33% and 29% respectively), which is hard to explain. It is noteworthy that the *p*-trifluoromethylphenyl containing α -aryl amide **3.107c** was obtained along with the desulfonylated α -bromo amide. On the other hand, hindered α -aryl amide such as **3.107d** bearing an *o*-methyl phenyl group was obtained in almost quantitative yield. Heteroaromatics were able to migrate as thiophenyl amide **3.107e** was obtained with a moderate yield (58%). The *gem*-dimethyl moiety at the α position of the amide seems to be important to ensure an efficient reaction, probably because of the stabilization of the radical intermediate. Indeed, amide **3.107f** and the *gem*-difluoro compound **3.107g** were obtained only with low yields of 34% and 26% respectively. Primary bromides were not compatible under these conditions and **3.107h** was not formed. Having an aryl substituent on the nitrogen atom also seems mandatory as *N*-benzyl amide **3.107i** was not formed.



Scheme 45. Photocatalytic synthesis of α -aryl amides from *N*-arylsulfonyl α -bromoamides.⁶⁹ ppy = 2-phenylpyridine. DMF = *N,N*-dimethylformamide.

From a mechanistic point of view, the absorption of a photon by the iridium complex would lead to an excited complex $[\text{Ir}(\text{III})]^*$. This excitation would severely lower the RedOx potential of the couple ($E_{1/2}[\text{Ir}(\text{IV})/\text{Ir}(\text{III})] = +0.77 \text{ V versus } E_{1/2}[\text{Ir}(\text{IV})/\text{Ir}(\text{III})^*] = -1.73 \text{ V}$)⁷⁰ rendering the excited $\text{Ir}(\text{III})^*$ complex able to reduce the C-Br bond of amides **3.106** to yield the radicals **3.108** and an iridium(IV) complex (**Scheme 46**). This latter could oxidize DMF to regenerate the initial iridium(III) complex. Radicals **3.108** would be in equilibrium with the spirocyclic intermediates **3.109**, which would give the amidyl radicals **3.110** after SO_2 extrusion. The amidyl radicals **3.110** could then perform a hydrogen abstraction to afford the α -aryl amides **3.107**. Alternatively, a reduction of **3.110** by an $\text{Ir}(\text{III})^*$ complex followed by protonation of the resulting anion can be envisioned.

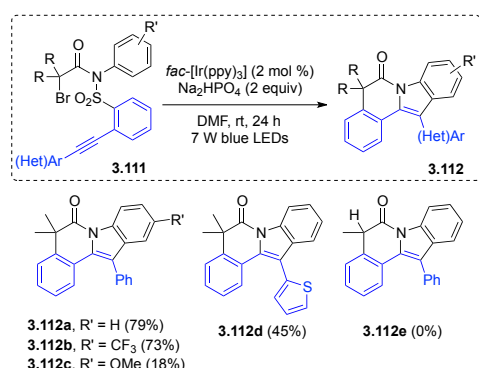


Scheme 46. Putative mechanism for the photocatalytic synthesis of α -aryl amides from *N*-arylsulfonyl α -bromoamides.⁶⁹ DMF = *N,N*-dimethylformamide.

3.2.2 Formation of (poly)cyclic products by cascade reactions

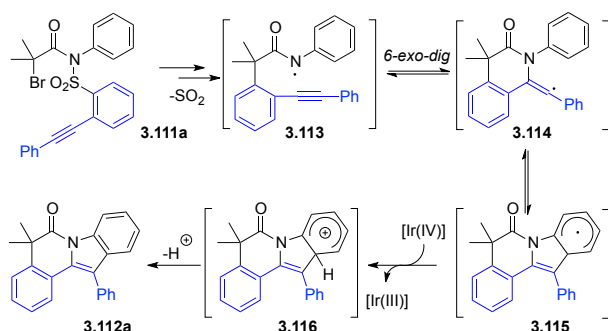
As observed in the desulfonylative aryl migration induced by radical addition on acrylamides, radical cascade reaction can take place from α -bromo amides. In 2020, Zhang *et al.* showed that, in the presence of an alkyne on the migrating aryl group, tetracyclic indoloisoquinolones **3.112** can be obtained from the corresponding α -bromo amide **3.111** (**Scheme 47**).⁷¹ The reaction

proceeds in the presence of a base and an iridium(III) photocatalyst under visible light irradiation, at room temperature in DMF. This process is restricted to internal alkynes and the electronic properties of the *N*-aryl substituent has an important influence on the outcome of the reaction. Both products **3.112a** and **3.112b** possessing a neutral or electron-poor *N*-aryl substituent were obtained in good yields while electron-rich *N*-aryl amide **3.111c** gave indoloisoquinolone **3.112c** with a low yield (18%). The reaction was tolerant toward the presence of heterocyclic substituents on the alkyne and the thiophenyl derivative **3.112d** was obtained in a decent 45% yield. However, α -secondary bromo amides were unable to react under these conditions and, for example, compound **3.112e** could not be synthesized.



Scheme 47. Formation of indoloisoquinolones by Zhang *et al.*⁷¹ ppy = 2-phenylpyridine. DMF = *N,N*-diethylformamide. LED = light emitting diode.

Mechanistically, an iridium induced homolytic cleavage of the C-Br bond followed by a desulfonation/1,4-aryl migration sequence would provide the amidyl radical **3.113** from **3.111a** (**Scheme 48**). This amidyl radical could then undergo a 6-*exo-dig* cyclization to give alkenyl radical **3.114**, which could add onto the *N*-aromatic ring to give intermediate **3.115**. Subsequent oxidation of this radical by an iridium(IV) complex would regenerate the active iridium(III) photocatalyst and would afford arenium **3.116**, which would give the polycyclic compound **3.112a** after re-aromatization.

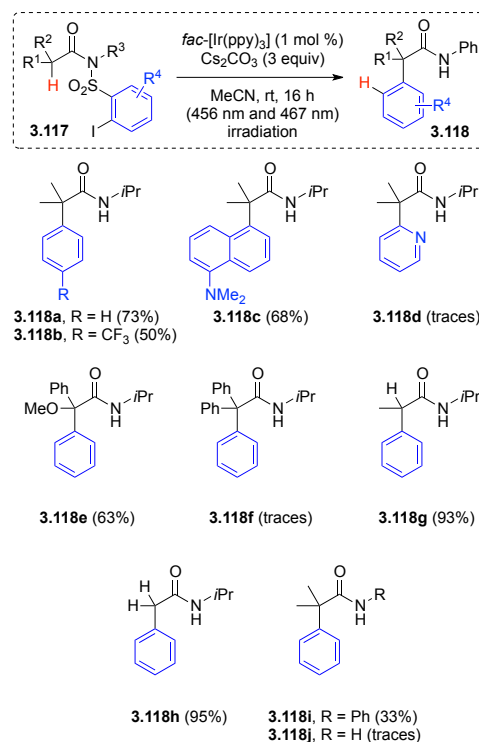


Scheme 48. Putative mechanism for the formation of indoloisoquinolones⁷¹

3.3 Homolytic cleavage/HAT sequence on *o*-iodo-substituted *N*-aryl sulfonamides

Recently, another strategy allowing the generation of the radical intermediate α to the amide moiety has been proposed by Studer *et al.* based on the use of sulfonamides possessing an *o*-iodide substituent on the migrating phenyl group.⁷² The authors

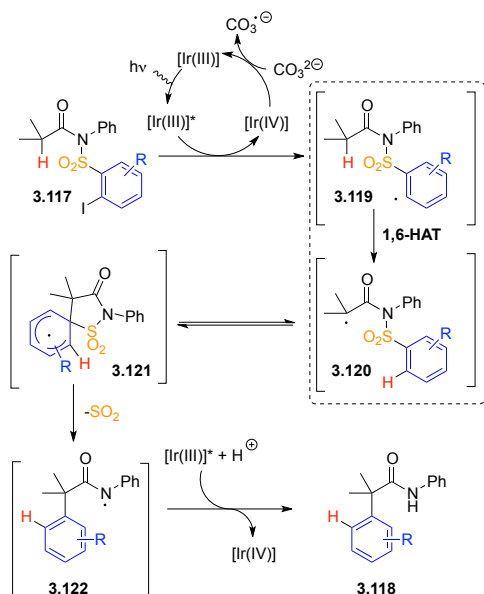
hypothesized that the homolytic cleavage of the C-I bond followed by a 1,6-hydrogen atom transfer would deliver the targeted radical α to the amide moiety. Based on this hypothesis, amides **3.117** were treated with an iridium photocatalyst in the presence of a base to give the corresponding α -aryl amides **3.118** (**Scheme 49**). This system was able to promote the migration of electron-poor as well as electron-rich aromatics and α -aryl amides **3.118a-3.118c** were obtained in yields ranging from 50% to 73%. However, α -heteroaryl amides such as pyridine **3.118d** could not be synthesized using this method. The presence of a methyl ether was tolerated as α -methoxy α -aryl amide **3.118e** was isolated in 63% yield. However, this method was not suitable to access triaryl amide such as **3.118f**, certainly due to the low reactivity of the radical intermediate. This reaction appeared to be very tolerant toward α -substitution of the starting amide. Indeed, the migration was shown to similarly occur on tertiary, secondary or primary carbon atoms α to the carbonyl moiety. However, the choice of the *N*-substituent of the amide seems limited as the presence of a *N*-phenyl substituent led to the corresponding α -aryl amide **3.118i** with a low yield (33%) and only traces of the primary amide **3.118j** were observed. Overall, this reaction is the most versatile method for the formation of α -aryl amide through aryl shift regarding amides α -substitution. Nevertheless, the need of an iodide atom on the migrating aryl group can be viewed as a limit in term of aryl diversity.



Scheme 49. Desulfonylative radical 1,4-aryl migration to access α -aryl amides featuring a 1,6-hydrogen atom transfer.⁷² ppy = 2-phenylpyridine.

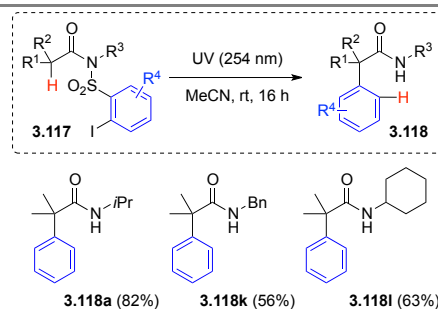
Based on mechanistic studies including cyclic voltammetry, the authors suggested that the reduction of the carbon iodine bond of *N*-arylsulfonyl amide **3.117** could be ensured by the photoexcited iridium(III)* complex and would lead to the aryl radical **3.119** and to an iridium(IV) complex (**Scheme 50**). The reaction between the iridium(IV) complex and carbonate dianion coming from Cs_2CO_3 would regenerate an iridium(III) species. Aryl radical **3.119** could undergo a 1,6-hydrogen atom transfer (1,6-HAT) leading to the

radical intermediate **3.120**. Desulfonylative 1,4-aryl migration processing through spirocyclic intermediate **3.121** would give the amidyl radical **3.122**. This amidyl radical could be reduced by the excited iridium(III)* complex and the resulting anion would then be protonated to afford α -aryl amide **3.118**.



Scheme 50. Putative mechanism for the desulfonylative radical 1,4-aryl migration to access α -aryl amides featuring a 1,6-hydrogen atom transfer.⁷²

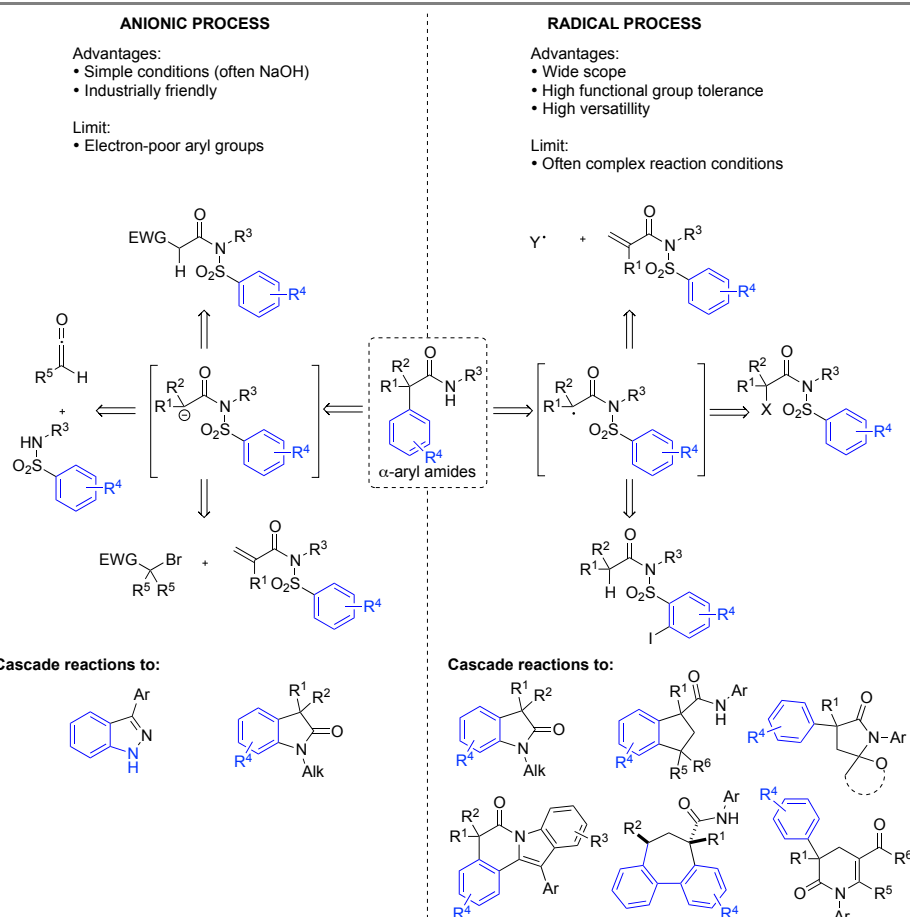
In the same publication,⁷² Studer *et al.* proposed alternative conditions to perform the homolytic cleavage of the C-I bond (**Scheme 51**). Simple irradiation of the substrate bearing an *o*-iodophenyl group **3.117** using UV light could lead to the same radical **3.119**, which could follow the same pathway yielding to the amidyl radical **3.120**. Formation of the α -aryl amide **3.118** could arise from hydrogen abstraction of **3.122** from the solvent. A slightly better yield in **3.118a** was obtained compared to iridium photocatalytic conditions (82% versus 73%). *N*-alkyl amides **3.118k** and **3.118l** were isolated in moderate yields (56% and 63% respectively). These conditions are much simpler and less expensive than the ones involving the iridium photocatalyst, however, it seems that the scope is narrower.



Scheme 51. UV irradiation induced variant of Studer *et al.* reaction. UV = ultraviolet light.⁷²

4- Conclusion

Gas-extrusive 1,4-aryl migration involving *N*-arylsulfonyl amides emerged as an attractive method to synthesize α -aryl amides. This reaction can be particularly useful for the synthesis of α -heteroaromatic or hindered α -aryl amides for which traditional methods such as enolate arylation or metal-catalyzed coupling are sluggish. The anionic process, which was first developed, is attractive due to simple experimental procedures. However, this process suffers from a narrow scope due to the restriction to electron-poor migrating aryl groups. Radical-mediated process has been extensively developed after its disclosure by the Nevado group in 2013. The scope of this transformation is much larger compared to the anionic rearrangement and most of the developed methods have been found to be very tolerant especially toward the presence of electrophilic functional groups. Formation of a reactive transient amidyl radical opened the possibility of cascade reactions and gave access to a variety of polycyclic scaffolds such as oxindoles, indanes, pyrrolidinones or dihydropyridinones. The seminal work by Nevado and co-worker towards the synthesis of optically active α -aryl amides through a 1,4-aryl migration greatly enhances the synthetic potential of such transformations. In light of these recent developments, gas-extrusive 1,4-(het)aryl migration is appearing as a promising synthetic tool to access not only α -aryl amides but also more complex polycyclic molecules that can be incorporated in biologically active scaffolds. If a great number of milestones have been reached, one can expect others to appear in the near future.



Scheme 52. Overview of 1,4-aryl-shift reactions performed on *N*-arylsulfonyl amides.

For example, this approach has not been expanded to the migration of alkenyl or alkynyl sulfonamides. Several examples of vinylogous anionic shifts have been described⁷³ but none of them has been involving amide enolate so far.⁷⁴ Applying this strategy using either an anionic or a radical transformation could afford valuable α -vinyl or α -alkynyl amides that are not easily available otherwise.

Several groups attempted to develop a CO extrusive aryl migration starting from acrylimides. However, in most cases, the radical generated in the α position of the imide is preferentially involved in a 1,6-addition on the aryl group rather than an *ipso* cyclization, leading to a cyclic imide, probably due to geometrical factors.^{75,50,76} While extrusion of carbon monoxide does not seem to be a good way to promote 1,4-aryl migration to form α -aryl amides, a CO₂ extrusive process applied to an amide bearing a *N*-C(O)OAr group could be envisioned.

Based on recent reports by Nevado *et al.*, *N*-sulfinyl acrylamides or *N*-sulfinyl α -halo amides could be employed in either simple

stereoselective 1,4-aryl migration or more sophisticated cascade reactions to afford a large diversity of enantio-enriched molecules.

Acknowledgment

N. G.-S. thanks the French Ministère de l'Enseignement Supérieur, de la Recherche et de l'Innovation (MESRI) for financial support.

Conflict of Interest

The authors declare no conflict of interests.

References

Biosketches



Nicolas G.-Simonian was born in 1994 in Massy, France. He graduated as an engineer from ESPCI Paris in 2017 and received his M. Sc. in molecular chemistry in 2018 from Sorbonne University, Paris, France. He started his Ph. D. thesis in 2018, under the supervision of Dr Amandine Guérinot and Prof. Janine Cossy at ESPCI. He is working on the development of sustainable synthetic methods using earth-abundant metal catalyst. Recently, he focused on the application of radical aryl migration.



Amandine Guérinot graduated as chemical engineer from ESPCI Paris in 2007 and received her Ph. D. in 2010 from the University Pierre et Marie Curie under the supervision of Dr Sébastien Reymond and Prof. Janine Cossy. She joined the group of Prof. Sylvain Canesi at UQAM, Montreal as a postdoctoral associate and then moved to ICMMO, Orsay, France for a postdoctoral stay with Prof. Vincent Gandon. After a postdoctoral fellowship with Dr Laurent Micouin (Paris Descartes University), she was appointed Associate Professor in 2013 at ESPCI Paris. Her research interests include sustainable catalysis, photocatalysis and dynamic covalent chemistry.



Janine Cossy did her undergraduate and graduate studies at the University Champagne-Ardenne in Reims under the supervision of Prof. Pète. After a postdoctoral stay with Prof. Trost, at the University of Wisconsin (USA), she returned to Reims where she became, in 1990, research director at CNRS. In the same year, she moved to Paris where she was appointed Professor of Organic Chemistry at the ESPCI Paris. Janine Cossy's research interests focus on the synthesis of natural products and/or biologically active molecules and on the development of synthetic methods.

¹ a) Fleming, A. *Br. J. Exp. Pathol.* **1929**, *10*, 226–236; b) Ligon, B. L. *Seminars in Pediatric Infectious Diseases* **2004**, *15*, 52–57.

² Handsfield, H. H.; Clark, H.; Wallace, J. F.; Holmes, K. K.; Turck, M. *Antimicrob. Agents Chemother.* **1973**, *3*, 262–265.

³ Hart, F. D.; Huskisson, E. C. *Drugs* **1984**, *27*, 232–255.

⁴ a) Jullian, V.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1997**, 1091–1097. b) Honda, T.; Namiki, H.; Satoh, F. *Org. Lett.* **2001**, *3*, 631–633. c) Wang, M.-X.; Zhao, S.-M. *Tetrahedron Lett.* **2002**, *43*, 6617–6620.

⁵ a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546–6553. b) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234–245. c) Cossy, J.; de Filippis, A.; Gomez-Pardo, D. *Org. Lett.* **2003**, *5*, 3037–3039. d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676–707. e) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082–1146. f) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 4190–4193. g) Zheng, B.; Jia, T.; Walsh, P. J. *Adv. Synth. Catal.* **2014**, *356*, 165–178.

⁶ See for example: a) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176–11177. b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976–4985. c) Cossy, J.; de Filippis, A.; Gomez-Pardo, D. *Org. Lett.* **2003**, *5*, 3037–3039. d) Cossy, J.; de Filippis, A.; Gomez-Pardo, D. *Synlett* **2003**, 2171–2174. e) de Filippis, A.; Gomez-Pardo, D.; Cossy, J. *Synthesis* **2004**, 2930–2933. f) Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105–4108. g) Michon, C.; Béthegnies, A.; Capet, F.; Roussel, P.; de Filippis, A.; Gomez-Pardo, D.; Cossy, J.; Agbossou-Niedercom, F. *Eur. J. Org. Chem.* **2013**, 4979–4985.

⁷ a) Gooßen, L. J. *Chem. Commun.* **2001**, 669–670. b) Duan, Y.-Z.; Deng, M.-Z. *Tetrahedron Lett.* **2003**, *44*, 3423–3426. c) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595. d) Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 3556–3558. e) Liu, C.; He, C.; Shi, W.; Chen, M.; Lei, A. *Org. Lett.* **2007**, *9*, 5601–5604. f) Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029. g) Jin, M.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1012–1014. h) Tarui, A.; Shinohara, S.; Sato, K.; Omote, M.; Ando, A. *Org. Lett.* **2016**, *18*, 1128–1131. i) Barde, E.; Guérinot, A.; Cossy, J. *Org. Lett.* **2017**, *19*, 6068–6071. j) Li, J.; Berger, M.; Zawodny, W.; Simaan, M.; Maulide, N. *Chem* **2019**, *5*, 1883–1891. k) Koch, V.; Lorion, M. M.; Barde, E.; Bräse, S.; Cossy, J. *Org. Lett.* **2019**, *21*, 6241–6244. l) Lorion, M. M.; Koch, V.; Nieger, M.; Chen, H.-Y.; Lei, A.; Bräse, S.; Cossy, J. *Chem. Eur. J.* **2020**, *26*, 13163–13169.

⁸ A cross-electrophile cross-coupling leading to imide arylation has also been described, see: Durandetti, M.; Périchon, J.; Nédelec, J.-Y. *J. Org. Chem.* **1997**, *62*, 7914–7915.

⁹ a) Loven, R.; Speckamp, W. N. *Tetrahedron Lett.* **1972**, *16*, 1567–1570. b) Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 631–634. c) Köhler, J. J.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *18*, 635–638.

¹⁰ Seminal work on aryl migration: a) Henriques, R. *Berichte der deutschen chemischen Gesellschaft* **1894**, *27*, 2993–3005. b) Hinsberg, O. *Journal für Praktische Chemie* **1914**, *90*, 345–353. c) Hinsberg, O. *Journal für Praktische Chemie* **1915**, *91*, 307–324. d) Wieland, H. *Chem. Ber.* **1911**, *44*, 2550–2556. e) Warren, L. A.; Smiles, S. *J. Chem. Soc.* **1930**, 1327–1331. f) Levy, A. A.; Rains, H. C.; Smiles, S. *J. Chem. Soc.* **1931**, 3264–3269. g) Evans, W. J.; Smiles, S. *J. Chem. Soc.* **1935**, 181–188. h) Evans, W. J.; Smiles, S. *J. Chem. Soc.* **1936**, 329–331. i) Urry, W. H.; Kharasch, M. S. *J. Am. Chem. Soc.* **1944**, *66*, 1438–1440.

¹¹ Previous reviews on aryl migration: a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649–9667. b) Snape, T. J. *Chem. Soc. Rev.* **2008**, *37*, 2452–2458. c) Chen, Z.-M.; Zhang, X.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2015**, *44*, 5220–5245. d) Allart-Simon, I.; Gérard, S.; Sapi, J. *Molecules* **2016**, *21*, 878–888. e) Holden, C. M.; Greaney, M. F. *Chem. Eur. J.* **2017**, *23*, 8992–9008. f) Henderson, A. R. P.; Kosowan, J. R.; Wood, T. E. *Can. J. Chem.* **2017**, *95*, 483–504. g) Li, W.; Xu, W.; Xie, J.; Yu, S.; Zhu, C. *Chem. Soc. Rev.* **2018**, *47*, 654–667. h) Whalley, D. M.; Greaney, M. F. *Synthesis*, **2022**, *54*, 1908–1918. Book chapters: i) Plesniak, K.; Zarecki, A.; Wicha, J. In *Sulfur-Mediated Rearrangements II*; Schaumann, E., Ed.; Topics in Current Chemistry; Springer: Berlin, Heidelberg, 2007; pp 163–250. j) Jack Li, J. In *Name Reactions*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2009; pp 511–514. k) Kürti, L.; Czákó, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Inc., 2005; pp 416–417

- ¹² In contrast, when some CO extrusive radical aryl migrations were attempted starting from acrylimides, a 1,6 addition of the radical on the aryl group was favored over the *ipso* addition, see: Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504–507.
- ¹³ To gain in concision, the fragmentation and loss of SO₂ are generally represented as a single step but the two processes are not concerted.
- ¹⁴ Lennox, A. J. *J. Angew. Chem. Int. Ed.* **2018**, *57*, 14686–14688.
- ¹⁵ a) Bernasconi, C. F.; Gehriger, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 1092–1099. b) Sekiguchi, S.; Okada, K. *J. Org. Chem.* **1975**, *40*, 2782–2786. c) Knipe, A. C.; Lound-Keast, J.; Sridhar, N. *J. Chem. Soc., Chem. Commun.* **1976**, 765–766. d) Okada, K.; Sekiguchi, S. *J. Org. Chem.* **1978**, *43*, 441–447. e) Knipe, A. C.; Sridhar, N.; Lound-Keast, J. *Tetrahedron Lett.* **1979**, *20*, 2541–2544. f) Knipe, A. C.; Sridhar, N. *J. Chem. Soc., Chem. Commun.* **1979**, 791–792.
- ¹⁶ Yang, D.; Xie, C.-X.; Wu, X.-T.; Fei, L.-R.; Feng, L.; Ma, C. *J. Org. Chem.* **2020**, *85*, 14905–14915.
- ¹⁷ Kemnitz, C. R.; Loewen, M. *J. Am. Chem. Soc.* **2007**, *129*, 2521–2528.
- ¹⁸ Elguero, J.; Goya, P.; Rozas, I.; Catalán, J.; De Paz, J. L. G. *J. Mol. Struct.-THEOCHEM* **1989**, *184*, 115–129.
- ¹⁹ a) Naito, T.; Dohmori, R.; Nagase, O. *Yakugaku Zasshi* **1954**, *74*, 593–595. b) Naito, T.; Dohmori, R.; Sano, M. *Yakugaku Zasshi* **1954**, *74*, 596–599. c) Naito, T.; Dohmori, R.; Shimoda, M. *Pharm. Bull.* **1955**, *3*, 34–37. d) Naito, T.; Dohmori, R. *Pharm. Bull.* **1955**, *3*, 38–42. e) Naito, T.; Dohmori, R.; Kotake, T. *Chem. Pharm. Bull.* **1964**, *12*, 588–590. f) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 591–594. g) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 595–601. h) Dohmori, R. *Chem. Pharm. Bull.* **1964**, *12*, 601–606.
- ²⁰ Barlow, H. L.; Rabet, P. T. G.; Durie, A.; Evans, T.; Greaney, M. F. *Org. Lett.* **2019**, *21*, 9033–9035.
- ²¹ Fan, J.-H.; Yang, J.; Song, R.-J.; Li, J.-H. *Org. Lett.* **2015**, *17*, 836–839.
- ²² a) Backer, H. J.; Moed, H. D. *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 689–704. b) Backer, H. J.; Groot, J. *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1323–1347.
- ²³ a) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 4327–4331. b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.
- ²⁴ This group had already worked on this kind of strategy with sulfonamide addition on a benzyne: Holden, C. M.; Sohnel, S. M. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2016**, *55*, 2450–2453.
- ²⁵ See for example: a) Cao, Y.; Luo, C.; Yang, P.; Li, P.; Wu, C. *Med. Chem. Res.* **2021**, *30*, 501–518. b) Tandon, N.; Luxami, V.; Kant, D.; Tandon, R.; Paul, K. *RSC Adv.* **2021**, *11*, 25228–25257.
- ²⁶ a) Leardini, R.; Nanni, D.; Pedulli, G. F.; Tundo, A.; Zanardi, G.; Foresti, E.; Palmieri, P. *J. Am. Chem. Soc.* **1989**, *111*, 7723–7732. b) Asensio, A.; Dannenberg, J. J. *J. Org. Chem.* **2001**, *66*, 5996–5999.
- ²⁷ Khartabil, H.; Doudet, L.; Allart-Simon, I.; Ponce-Vargas, M.; Gérard, S.; Hénon, E. *Org. Biomol. Chem.* **2020**, *18*, 6840–6848.
- ²⁸ Azzi, E.; Ghigo, G.; Parisotto, S.; Pellegrino, F.; Priola, E.; Renzi, P.; Deagostino, A. *J. Org. Chem.* **2021**, *86*, 3300–3323.
- ²⁹ Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480–14483.
- ³⁰ Authors did not write an equilibrium between the key intermediate and the spiro compound.
- ³¹ Kong, W.; Casimiro, M.; Fuentes, N.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2013**, *52*, 13086–13090.
- ³² Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 10792–10795.
- ³³ a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529–2591. b) Barillari, C.; Brown, N. In *Bioisosteres in Medicinal Chemistry*; John Wiley & Sons, Ltd, 2012; pp 15–29.
- ³⁴ He, Z.; Tan, P.; Ni, C.; Hu, J. *Org. Lett.* **2015**, *17*, 1838–1841.
- ³⁵ Tang, S.; Yuan, L.; Deng, Y.-L.; Li, Z.-Z.; Wang, L.-N.; Huang, G.-X.; Sheng, R.-L. *Tetrahedron Lett.* **2017**, *58*, 329–332.
- ³⁶ Liu, K.; Sui, L.-C.; Jin, Q.; Li, D.-Y.; Liu, P.-N. *Org. Chem. Front.* **2017**, *4*, 1606–1610.
- ³⁷ Zheng, L.; Yang, C.; Xu, Z.; Gao, F.; Xia, W. *J. Org. Chem.* **2015**, *80*, 5730–5736.
- ³⁸ Liu, C.; Zhang, B. *RSC Adv.* **2015**, *5*, 61199–61203.
- ³⁹ Biswas, P.; Guin, J. *J. Org. Chem.* **2018**, *83*, 5629–5638.
- ⁴⁰ Chatgililoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991–2070.
- ⁴¹ Yu, J.-T.; Chen, R.; Zhu, J.; Cheng, J. *Org. Biomol. Chem.* **2017**, *15*, 5476.
- ⁴² Xia, X.-F.; Zhu, S.-L.; Chen, C.; Wang, H.; Liang, Y.-M. *J. Org. Chem.* **2016**, *81*, 1277–1284.
- ⁴³ Tan, F.-L.; Song, R.-J.; Hu, M.; Li, J.-H. *Org. Lett.* **2016**, *18*, 3198–3201.
- ⁴⁴ Yu, J.-T.; Hu, W.; Peng, H.; Cheng, J. *Tetrahedron Lett.* **2016**, *57*, 4109–4112.
- ⁴⁵ Zhang, H.; Pan, C.; Jin, N.; Gu, Z.; Hu, H.; Zhu, C. *Chem. Commun.* **2014**, *51*, 1320–1322.
- ⁴⁶ Zhang, M.; Sheng, W.; Ji, P.; Liu, Y.; Guo, C. *RSC Adv.* **2015**, *5*, 56438–56443.
- ⁴⁷ Li, M.; Wang, C.-T.; Bao, Q.-F.; Qiu, Y.-F.; Wei, W.-X.; Li, X.-S.; Wang, Y.-Z.; Zhang, Z.; Wang, J.-L.; Liang, Y.-M. *Org. Lett.* **2021**, *23*, 751.
- ⁴⁸ Ni, Z.; Huang, X.; Pan, Y. *Org. Lett.* **2016**, *18*, 2612–2615.
- ⁴⁹ Caporaso, R.; Manna, S.; Zinken, S.; Kochnev, A. R.; Lukyanenko, E. R.; Kurkin, A. V.; Antonchick, A. P. *Chem. Commun.* **2016**, *52*, 12486–12489.
- ⁵⁰ Kong, W.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5078–5082.
- ⁵¹ Kong, W.; Fuentes, N.; García Domínguez, A.; Merino, E.; Nevado, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 2487–2491.
- ⁵² Wang, J.-L.; Liu, M.-L.; Zou, J.-Y.; Sun, W.-H.; Liu, X.-Y. *Org. Lett.* **2022**, *24*, 309.
- ⁵³ a) Shi, L.; Wang, H.; Yang, H.; Fu, H. *Synlett* **2015**, *26*, 688–694; b) Qiu, J.-K.; Hao, W.-J.; Kong, L.-F.; Ping, W.; Tu, S.-J.; Jiang, B. *Tetrahedron Lett.* **2016**, *57*, 2414–2417.
- ⁵⁴ Hervieu, C.; Kirillova, M. S.; Suárez, T.; Müller, M.; Merino, E.; Nevado, C. *Nature Chem.* **2021**, *13*, 327–334.
- ⁵⁵ For some studies highlighting the aromatization of *N*-substituted cyclohexadienyl derivatives through C-N fragmentation, see: a) Kemper, J.; Studer, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4914–4917. b) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503.
- ⁵⁶ a) Niu, B.; Xie, P.; Zhao, W.; Zhou, Y.; Bian, Z.; Pittman Jr, C. U.; Zhou, A. *RSC Adv.* **2014**, *4*, 43525–43528. b) Niu, B.; Xie, P.; Bian, Z.; Zhao, W.; Zhang, M.; Zhou, Y.; Feng, L.; Pittman Jr, C. U.; Zhou, A. *Synlett* **2015**, *26*, 635. c) Wang, H.; Sun, S.; Cheng, J. *Org. Lett.* **2017**, *19*, 5844.
- ⁵⁷ Fuentes, N.; Kong, W.; Fernández-Sánchez, L.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2015**, *137*, 964–973.
- ⁵⁸ For similar cascade reactions, see: a) Su, X.; Huang, H.; Hong, W.; Cui, J.; Yu, M.; Li, Y. *Chem. Commun.* **2017**, *53*, 13324. b) Huang, H.; Li, Y. *J. Org. Chem.* **2017**, *82*, 4449.
- ⁵⁹ Hu, M.; Guo, L.-Y.; Han, Y.; Tan, F.-L.; Song, R.-J.; Li, J.-H. *Chem. Commun.* **2017**, *53*, 6081–6084.
- ⁶⁰ a) Clark, A. J.; Coles, S. R.; Collis, A.; Debure, T.; Guy, C.; Murphy, N. P.; Wilson, P. *Tetrahedron Lett.* **2009**, *50*, 5609–5612. b) Clark, A. J.; Coles, S. R.; Collis, A.; Fullaway, D. R.; Murphy, N. P.; Wilson, P. *Tetrahedron Lett.* **2009**, *50*, 6311–6314.
- ⁶¹ Clark, A. J.; Cornia, A.; Felluga, F.; Gennaro, A.; Ghelfi, F.; Isse, A. A.; Menziani, M. C.; Muniz-Miranda, F.; Roncaglia, F.; Spinelli, D. *Eur. J. Org. Chem.* **2014**, 6734–6745.
- ⁶² Konkolewicz, D.; Wang, Y.; Zhong, M.; Kryszewski, P.; Isse, A. A.; Gennaro, A.; Matyjaszewski, K. *Macromolecules* **2013**, *46*, 8749–8772.
- ⁶³ Isse, A. A.; Bortolamei, N.; De Paoli, P.; Gennaro, A. *Electrochimica Acta* **2013**, *110*, 655–662.
- ⁶⁴ Chuang, C.-P.; Chen, Y.-Y.; Chuang, T.-H.; Yang, C.-H. *Synthesis* **2017**, *49*, 1273.
- ⁶⁵ Kyne, S. H.; Lefèvre, G.; Ollivier, C.; Petit, M.; Cladera, V.-A. R.; Fensterbank, L. *Chem. Soc. Rev.* **2020**, *49*, 8501–8542.

-
- ⁶⁶ Gillaizeau-Simonian, N.; Barde, E.; Guérinot, A.; Cossy, J. *Chem. Eur. J.* **2021**, *27*, 4004–4008.
- ⁶⁷ The reactions were conducted at 100 °C in THF under pressure in sealed tubes.
- ⁶⁸ a) Zeitler, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9785–9789. b) Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chem.* **2010**, *2*, 527–532. c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2010**, *40*, 102–113. d) Xuan, J.; Xiao, W.-J. *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838. e) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617–1622. f) Pagire, S. K.; Föll, T.; Reiser, O. *Acc. Chem. Res.* **2020**, *53*, 782–791.
- ⁶⁹ Li, Y.; Hu, B.; Dong, W.; Xie, X.; Wan, J.; Zhang, Z. *J. Org. Chem.* **2016**, *81*, 7036–7041.
- ⁷⁰ a) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. In *Photochemistry and Photophysics of Coordination Compounds II*; Balzani, V., Campagna, S., Eds.; Topics in Current Chemistry; Springer: Berlin, Heidelberg, 2007; pp 143–203. b) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem* **2012**, *4*, 854–859.
- ⁷¹ Gao, X.; Li, C.; Yuan, Y.; Xie, X.; Zhang, Z. *Org. Biomol. Chem.* **2020**, *18*, 263–271.
- ⁷² Radhoff, N.; Studer, A. *Angew. Chem. Int. Ed.* **2021**, *60*, 3561–3565.
- ⁷³ a) Waldau, E.; Pütter, R. *Angew. Chem. Int. Ed.* **1972**, *11*, 826–828. b) Johnson, S.; Kovács, E.; Greaney, M. F. *Chem. Commun.* **2020**, *56*, 3222–3224.
- ⁷⁴ a) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817–3820. b) Chen, Y.-R.; Duan, W.-L. *J. Am. Chem. Soc.* **2013**, *135*, 16754–16757.
- ⁷⁵ Li, L.; Deng, M.; Zheng, S.-C.; Xiong, Y.-P.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2014**, *16*, 504–507.
- ⁷⁶ The prevalence of this 1,6-addition over extrusive 1,4-aryl migration through *ipso* addition could be due to geometric factors, the N–C(O)–Ar angle for an imide should be of ca. 120° whereas the N–S(O)₂–Ar angle for a sulfonimide should be of ca. 109°, according to VSEPR theory.
-