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# Arynes, diaryliodonium salts and azine N-oxides in transition metal-free electrophilic N-arylation

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The main approach to the synthesis of aromatic and heteroaromatic amines is based on palladium- and copper-catalyzed N-arylation reactions. Although these methods are highly efficient and provide extensive opportunities for the synthesis of (het)arylamines with various structures and properties, they have some limitations related to the catalysts used and reaction conditions. This review addresses alternative approaches to N-(het)arylation that have been extensively developed in the past decade and are based on the use of arynes, diaryliodonium salts and azine N-oxides as electrophilic (het)arylating agents. Because of mild reaction conditions and no need for catalysts and strong bases, these N-(het)arylation methods are attractive for various synthetic applications and open up new possibilities for the preparation of valuable organic compounds inaccessible *via* traditional catalytic methods. The attention is focussed on publications of the last decade.
The bibliography includes 112 references.

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## 1. Introduction

Structural units of aromatic amines and their heterocyclic analogues are widespread in natural products, drugs, agrochemicals, dyes, functional materials and other compounds used in different applied fields. Besides, (hetero)aromatic amines serve as key building blocks in organic synthesis. One of the most commonly employed synthetic approaches to these compounds is based on NH-arylation of different substrates accompanied by $C_{Ar}-N$ bond formation.[1] Main methods for the synthesis of (het)arylamines within this approach involve the coupling of aryl halides and aryl pseudohalides with N-nucleophiles in the presence of catalysts based on palladium[2,3] and copper[4,5] compounds. Intramolecular versions of catalytic N-arylation reactions serve as key steps in the synthesis of valuable heterocyclic compounds.[6–9] Other methods for the $C_{Ar}-N$ bond formation are based on amination of organoboron compounds[10] and also on electrophilic[11] and transition metal-catalyzed CH-amination[12] of aromatic substrates.

Although the catalytic methods for $C_{Ar}-N$ bond formation are quite efficient, they have certain drawbacks.[13] Harsh reaction conditions and the necessity of using strong bases substantially limit the range of substituents and functional groups that may be present in the substrates. Catalytic methods of N-arylation are not economically and environmentally sustainable because of the use of expensive, difficult-to-synthesize and toxic transition metal salts[14] and ligands required for the preparation of catalysts. The development of alternative methods for $C_{Ar}-N$ bond formation, primarily without the use of transition metal-based catalysts, can help in addressing these shortcomings.

An aryl substituent can be introduced at the nucleophilic centre using other electrophilic arylating agents, in particular arynes (dehydrobenzenes),[15] diaryliodonium salts (diaryl-$\lambda^3$-iodanes)[16,17] and azine N-oxides.[18] Arylating properties of these reactants have been known for decades, and the reactions of these compounds with selected types of N-nucleophiles have been summarized in several general reviews.[15–18] Meanwhile, a considerable progress made in recent years in developing methods for N-arylation involving these reactants resulted in the appearance of diverse versatile and efficient approaches to the synthesis of aro-

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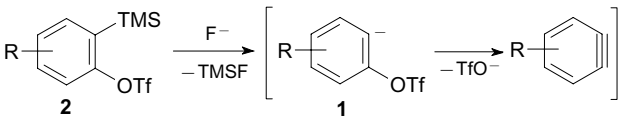
matic and heteroaromatic amines. In some cases, the employment of N-arylation reactions involving arynes, diaryliodonium salts and azine N-oxides not only makes it possible to avoid some limitations inherent in catalytic reactions but also opens up new opportunities for the synthesis of intricate organic compounds with a wide range of applications, which are inaccessible by catalytic methods.

This review covers studies published in the past decade and summarizes considerable recent advances in the development of synthetic approaches to transition metal-free amination of aromatic substrates using arynes, diaryliodonium salts and N-oxides. In this review, the advantages of electrophilic reagents for N-arylation are disclosed, with particular regard to specific features and shortcomings of these methods for the synthesis of aromatic amines. Selected aspects of the mechanism of arylation reactions are discussed.

## 2. N-Arylation using arynes

Arynes are electron-deficient and highly reactive compounds that are used for the synthesis of 1,2-disubstituted benzenes with complex structures.[15, 19, 20] Due to high electrophilicity and extreme strain of the C≡C triple bond, arynes are easily inserted into element – element bonds giving polysubstituted aromatic structures, which are difficult to prepare by other methods.[21, 22] The studies dealing with reactions of primary and secondary amines with arynes to form aniline derivatives, which were published before 2003, have been extensively reviewed by Pellissier and Santelli,[21] who considered the use of arynes in organic synthesis. In recent years, studies in this area have been intensified due apparently to a wide use of 2-(trimethylsilyl)aryl triflates [2-(trimethylsilyl)aryl trifluoromethanesulfonates] as precursors of substituted arynes in synthetic chemistry.[21] Since arynes exhibit extremely high reactivity, they should be generated *in situ* in the presence of the second reaction component. Conventional methods of generation involve the use of strong bases or (more rarely) strong oxidants, which imposes restrictions on synthetic applications of these arynes. On the contrary, the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates **2** through the intermediate formation of anion **1** (Scheme 1) occurs under very mild conditions. Consequently, the generation of arynes by this method can be accomplished in the presence of a number of functional groups sensitive to strong bases and oxidants.[21]

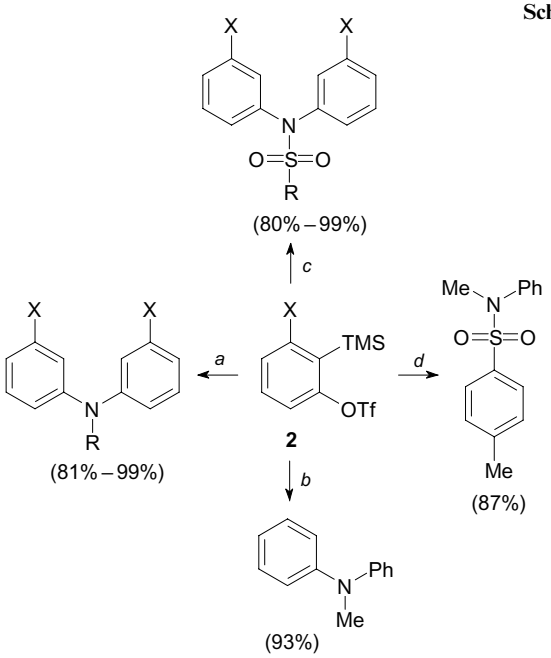
**Scheme 1**




Tf = $CF_3SO_2$, TMS = $Me_3Si$

In 2003, Liu and Larock[23] described the insertion of arynes into the C – N bond of primary and secondary amines and sulfamides (Scheme 2). Arynes were generated from appropriate 2-(trimethylsilyl)aryl triflates **2** in the presence of CsF. The reaction performed at room temperature afforded arylation products in high yields.

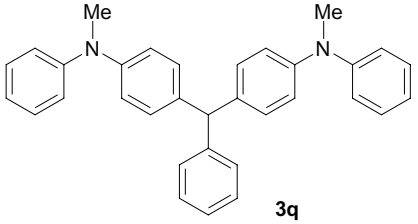
**Scheme 2**




(*a*) $RNH_2$, CsF (4 equiv.), 23 °C, 1 – 3 h; (*b*) for X = H: PhMeNH, CsF (2 equiv.), 23 °C, 1 h; (*c*) $RSO_2NH_2$, CsF (4 equiv.), 23 °C, 1 h; (*d*) for X = H: TsNHMe, CsF (2 equiv.), 23 °C, 1 h; X = H, MeO; R = Alk, Ar; Ts = 4-$MeC_6H_4SO_2$

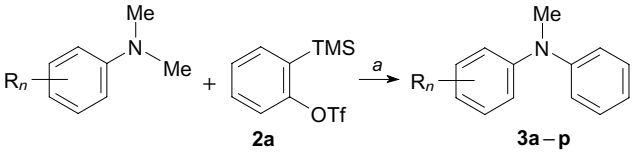
More recently, this approach has been further developed.[24 – 27] In 2013, Bhojgude *et al.* proposed a simple and selective method for N-arylation of aromatic tertiary amines using arynes as a source of an aromatic moiety (Scheme 3).[28] Thus, aryne is generated from 2-(trimethylsilyl)phenyl triflate (**2a**) by treatment with KF and 18-crown-6 in the presence of ammonium bicarbonate as an additive and is then subjected to the reaction with *N*,*N*-dimethylaniline giving *N*-methyl-*N*-phenylaniline (**3a**) in 98% yield. The use of ammonium bicarbonate as a source of protons leads to a substantial increase in the yield of the arylation product; in the absence of this additive, the yield of this product is 33%. The method was shown to be versatile with regard to aromatic substrates with different structures; besides, it exhibits high chemoselectivity. Even the diamine Leucomalachite green is efficiently subjected to N-arylation to form compound **3q** in 78% yield.

**Structure 3q**




It should be emphasized that halogen atoms are tolerant (see the synthesis of amines **3c**,**d**,**i**) to these conditions, which is not the case for related reactions catalyzed by transition metals.[28]

**Scheme 3**

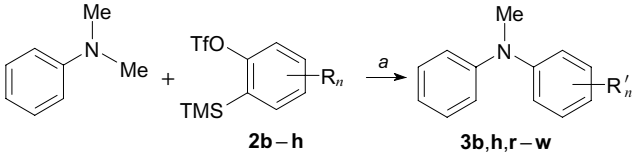



(*a*) KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), $NH_4HCO_3$ (1 equiv.), THF, 60 °C, 12 h; Th is thienyl

| Compounds **3** | $R_n$ | Yield (%) |
|---|---|---|
| **a** | H | 98 |
| **b** | 4-Me | 92 |
| **c** | 4-Br | 85 |
| **d** | 4-I | 85 |
| **e** | 4-CN | 60 |
| **f** | 4-$CO_2$Et | 86 |
| **g** | 4-CHO | 30 |
| **h** | 3-Me | 96 |
| **i** | 3-Br | 94 |
| **j** | 2-$CO_2$Me | 65 |
| **k** | 3,5-$Me_2$ | 81 |
| **l** | 4-$CH_2P(O)(OEt)_2$ | 87 |
| **m** | 4-(CH=CHTh-2-(*E*)) | 93 |
| **n** | C≡CPh | 82 |
| **o** | 2,3-Benzo | 87 |
| **p** | 2,3-($CH_2$=CH–CH=$CSO_2Cl$) | 61 |

The study of a series of aryne precursors **2** (Scheme 4, Table 1) demonstrated that 4,5-disubstituted dehydrobenzenes generated from substrates **2b**–**d** containing groups of different electronic nature produce diphenylamine derivatives **3r**–**t** in high yields. Symmetrically 3,6-dimethylated precursor **2e** is also easily transformed into compound **3u**. Moreover, 3-methoxydehydrobenzene, which is generated from compound **2f**, and dehydronaphthalene produced from triflate **2g** give exclusively regioisomers **3v**,**w**, respectively, in high yields. The employment of the aryne generated from precursor **2h** resulted in the formation of an inseparable mixture of isomers **3b**,**h**.[28]

**Scheme 4**




(*a*) KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), $NH_4HCO_3$ (1 equiv.), THF, 60 °C, 12 h

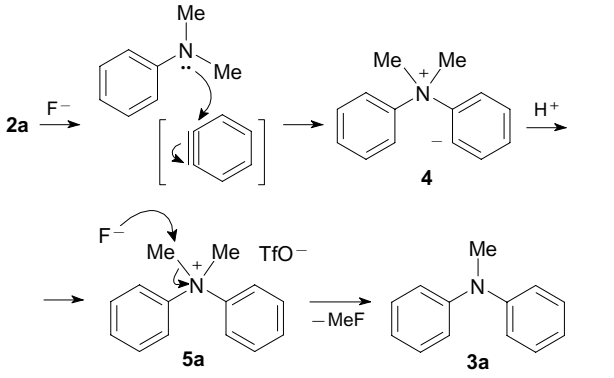
The nucleophilic addition of *N*,*N*-dimethylaniline to aryne affords zwitterionic intermediate **4**, which is protonated to form dimethyldiphenylammonium salt **5a** (Scheme 5). The demethylation is induced by a fluoride ion and gives N-arylation product **3a**.

There is the following strong evidence for the formation of salt **5a**. Under certain conditions, the reaction of tertiary amine — *N*,*N*-dimethyl-*p*-toluidine — with aryne precursor **2c** in the presence of CsF affords quaternary ammonium salt **5b** c in high yield and N-arylation product **3x** in low

**Table 1**. N-Arylation of *N*,*N*-dimethylaniline with substituted arynes (see Scheme 4).[28]

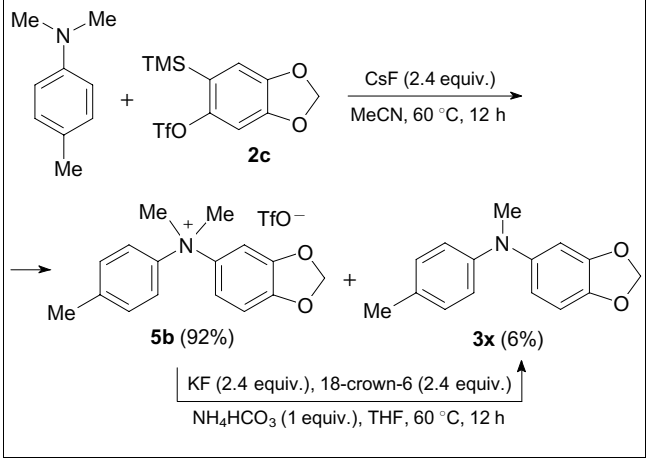
| Aryne precursor | $R_n$ | Product | $R'_n$ | Yield (%) |
|---|---|---|---|---|
| **2b** | 4,5-$Me_2$ | **3r** | 3,4-$Me_2$ | 93 |
| **2c** | 4,5-($OCH_2O$) | **3s** | 3,4-($OCH_2O$) | 94 |
| **2d** | 4,5-$F_2$ | **3t** | 3,4-$F_2$ | 88 |
| **2e** | 3,6-$Me_2$ | **3u** | 2,5-$Me_2$ | 64 |
| **2f** | 3-OMe | **3v** | 3-OMe | 94 |
| **2g** | 3,4-Benzo | **3w** | 3,4-Benzo | 96 |
| **2h** | 4-Me | **3b** + **3h** | 4-Me and 3-Me | 93 |

**Scheme 5**




yield. Moreover, under the reaction conditions, salt **5b** is transformed into the same arylation product in 73% yield (Scheme 6).[28]

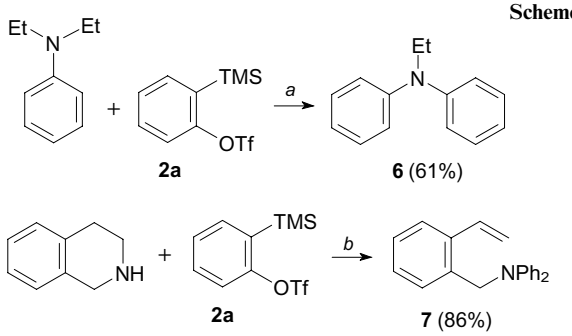
**Scheme 6**




Substrates for N-arylation are not limited to *N*,*N*-dimethylaniline derivatives. The reaction with *N*,*N*-diethylaniline affords arylation product **6** through the elimination of ethylene. Under these conditions (but at a different ratio of reactants), tetrahydroisoquinoline undergoes a similar sequence of transformations giving styrene derivative **7** (Scheme 7).[28]

The reaction of 4-hydroxymethylisoindolines with arynes giving isobenzofurans **8** also proceeds through the

**Scheme 7**




(*a*) KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), THF, 60 °C, 12 h;
(*b*) KF (4.8 equiv.), 18-crown-6 (4.8 equiv.), THF, 60 °C, 12 h

**Table 2**. N-Phenylation of tertiary amines containing various numbers of alkyl and aryl substituents with aryne precursor **2a** (see Scheme 9).[30]

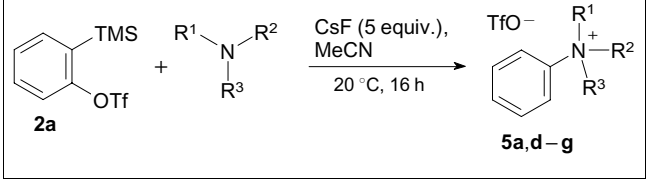
| Product | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| **5a** | Me | Me | Ph | 86 |
| **5d** | Et | Et | Et | 78 [a] |
| **5e** | Me | Ph | Ph | 61 |
| **5f** | Ph | Ph | Ph | 0 |
| **5g** | *p*-Tol [b] | *p*-Tol | *p*-Tol | 0 |

[a] The reaction proceeds only in the MeCN – MeOH mixture;
[b] *p*-Tol = 4-$MeC_6H_4$.

intermediate formation of the quaternary ammonium salt (Scheme 8).[29] Varlamov *et al.*[29] succeeded in terminating the reaction of 2-(4-fluorophenyl)isoindoline with dehydrobenzene at the formation of salt **5c**.[29]

The reaction mechanism involving the formation of quaternary ammonium intermediates that was proposed [29] and later confirmed.[30] Different tertiary amines — trialkyl-, dialkylaryl-, alkyldiaryl- and triarylamines — were subjected to the reaction with aryne precursor **2a**. The success of this approach to the synthesis of quaternary ammonium salts largely depends on the nucleophilicity of the ternary amine used (Scheme 9, Table 2).

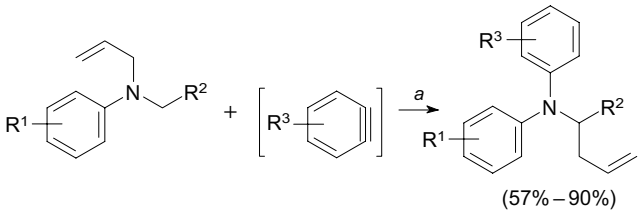
**Scheme 9**




It is surprising at first glance that the reaction with the most nucleophilic triethylamine under standard conditions did not afford expected product **5d**. A thorough analysis of the reaction mixture demonstrated that the reaction produces highly basic zwitterionic intermediate and the latter is subjected to undesirable elimination. In order to suppress this process, methanol was used as a source of protons. This made it possible to isolate salt **5d** in good yield. Under no reaction conditions, were tetraarylammonium salts **5f**,**g** obtained due apparently to extremely low nucleophilicity of the amines used.

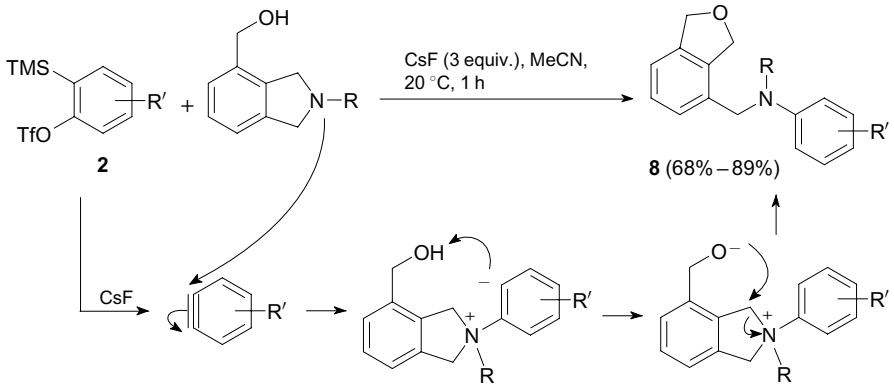
The arylation of tertiary allylamines with arynes may be accompanied by the Stevens rearrangement (Scheme 10).[31]

**Scheme 10**

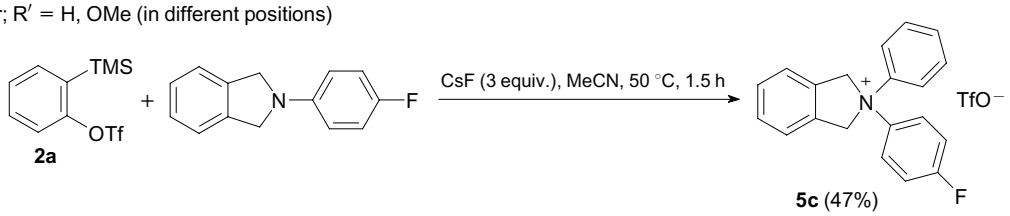



(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 30 °C, 12 h;
$R^1$ = Me, OMe, Hal; $R^2$ = $CO_2$Et, CN, Bz; $R^3$ = F, Me, *etc.*

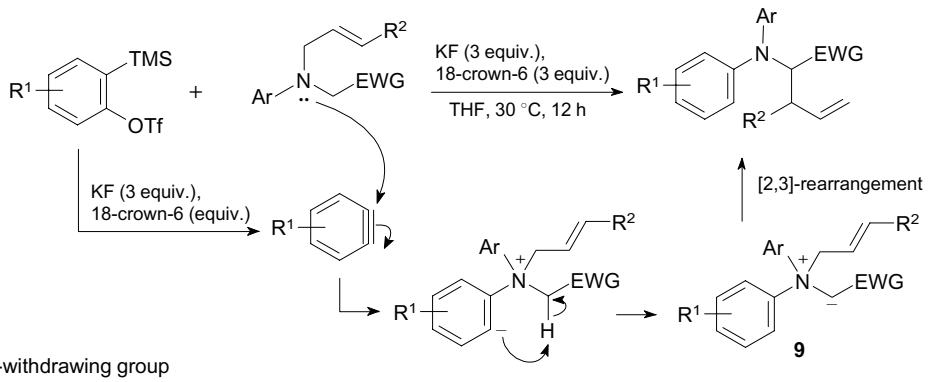
**Scheme 8**




R = Alk, Ar; R′ = H, OMe (in different positions)



**Scheme 11**

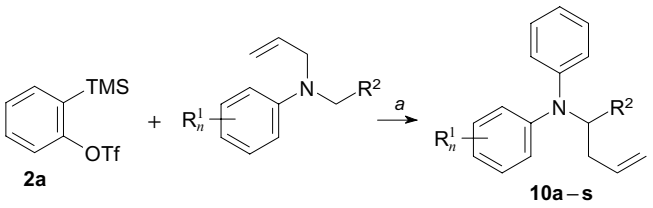



EWG is an electron-withdrawing group

Ammonium ylide was shown to be a key intermediate in the [2,3]-Stevens rearrangement. This intermediate is traditionally generated from appropriate ammonium salts by treatment with strong bases [32] or under transition metal catalysis conditions.[33] Harsh conditions for preparation of ammonium salts and the necessity of using strong bases significantly limit the synthetic potential of this method. An alternative way of generating ammonium ylides **9** is based on arylation of tertiary allylamines with arynes (Scheme 11).[31]

Advantages of this method are the simultaneous formation of two new bonds (C–C and C–N), the absence of transition metals and strong bases, mild conditions and high yields of the synthesized multifunctional compounds **10a–s** (Scheme 12, Table 3).[31]

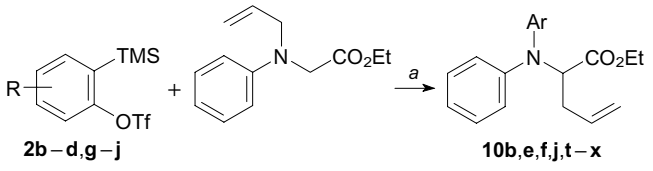
**Scheme 12**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 30 °C, 12 h

The use of different aryne precursors **2b–d,g–j** in the reaction with *N*-allyl-*N*-phenylglycine ethyl ester has substantially extended the range of homoallylamines **10b,e,f,j,t–x**. Compounds **10j,t–v** were isolated in the individual state; the other products were formed as mixtures of two isomers (Scheme 13, Table 4).

**Scheme 13**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 30 °C, 12 h

The aryne-induced [2,3]-Stevens rearrangement was also investigated in relation to enantiomerically pure *N*-allylproline methyl ester [enantiomeric excess (*ee*) > 99%]. The treatment of this ester with dehydrobenzene under standard conditions produced *N*-phenylproline derivative **11** containing the chiral quaternary carbon atom in high yield with high enantiomeric purity (Scheme 14).[31]

The addition of tertiary allylamines to arynes can be accompanied, apart from the Stevens rearrangement, by the aza-Claisen rearrangement (Scheme 15).[34] The corresponding quaternary zwitterionic intermediates **9′** generated through the addition of tertiary allylamine to aryne can undergo a rearrangement *via* the intramolecular 6-endo-$S_N2'$ reaction (path *a*) giving anilines **12a–c**. An alternative path *b* is also possible: the zwitterionic intermediate is initially protonated by the solvent and the subsequent aza-Claisen rearrangement gives the same anilines.

**Table 3**. Products of the dehydrobenzene-induced Stevens rearrangement (see Scheme 12).[31]

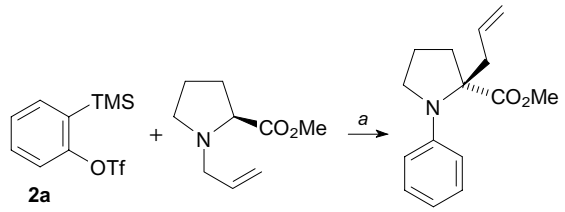
| Product | $R^1_n$ | $R^2$ | Yield (%) |
|---|---|---|---|
| **10a** | 4-OMe | $CO_2Et$ | 88 |
| **10b** | 4-Me | $CO_2Et$ | 86 |
| **10c** | 4-Br | $CO_2Et$ | 83 |
| **10d** | 4-Cl | $CO_2Et$ | 80 |
| **10e** | 4-F | $CO_2Et$ | 90 |
| **10f** | 3-Me | $CO_2Et$ | 75 |
| **10g** | 3-Br | $CO_2Et$ | 57 |
| **10h** | 3-Cl | $CO_2Et$ | 72 |
| **10i** | 3,4-$(OMe)_2$ | $CO_2Et$ | 85 |
| **10j** | 3,4-$F_2$ | $CO_2Et$ | 83 |
| **10k** | 3-Cl-4-F | $CO_2Et$ | 77 |
| **10l** | 3,4,5-$(OMe)_3$ | $CO_2Et$ | 65 |
| **10m** | H | CN | 80 |
| **10n** | H | $CO_2Me$ | 79 |
| **10o** | H | $CO_2Bn$ | 84 |
| **10p** | H | $CO_2Bu^t$ | 82 |
| **10q** | H | Bz | 91 |
| **10r** | H | C(O)Tol-*p* | 85 |
| **10s** | H | $C(O)C_6H_4Br$-4 | 88 |

**Table 4**. Synthesis of homoallylamines by the aryne-induced Stevens rearrangement (see Scheme 13).[31]

| Aryne precursor | $R_n$ | Product | Ar | Yiel (%) (ratio of isomers) |
|---|---|---|---|---|
| **2b** | 4,5-$Me_2$ | **10t** | 3,4-$Me_2C_6H_3$ | 79 |
| **2c** | 4,5-($OCH_2O$) | **10u** | 3,4-($OCH_2O$)$C_6H_3$ | 73 |
| **2d** | 4,5-$F_2$ | **10j** | 3,4-$F_2C_6H_3$ | 70 |
| **2g** | 3,4-Benzo | **10v** + **10w** | 2-Naph and 1-Naph | 69 (> 20 : 1) |
| **2h** | 4-Me | **10f** + **10b** | *m*-Tol and *p*-Tol | 80 (1 : 1) |
| **2i** | 4,5-Benzo | **10v** | 2-Naph | 72 |
| **2j** | 4-F | **10e** + **10x** | 4-$FC_6H_4$ and 3-$FC_6H_4$ | 78 (2 : 1) |

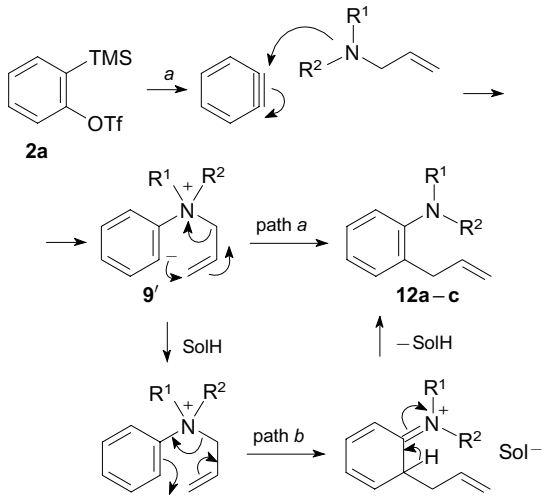
**Note**. Naph is naphthyl.

**Scheme 14**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 30 °C, 2 h

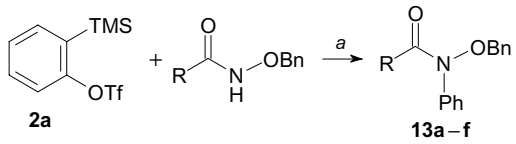
**Scheme 15**




(*a*) CsF, PhMe, MeCN, 110 °C, 48 h; **12**: $R^1$ = Me, $R^2$ = Ph (**a**, 91% yield); $R^1$ = $R^2$ = Et (**b**, 65%); $R^1 – R^2$ = $(CH_2)_5$ (**c**, 92%); SolH is a protic solvent

Apart from amines, compounds bearing various nitrogen-containing functional groups can serve as substrates for N-arylation with arynes. Thus, the insertion of arynes into the N – H amide bond was accomplished in relation to alkoxy amides (hydroxamic acid esters).[35] Methods for the synthesis of N-alkyl-substituted hydroxamic acids are well known, whereas approaches to the preparation of *N*-aryl hydroxamates **13a – f**, particularly those involving amino acids and peptides, are poorly developed. The method based on the insertion of arynes into the N – H amide bond of *O*-benzyl hydroxamates[35] has the following advantages: the reaction occurs under mild conditions with high regioselectivity and gives products in good yields; compounds containing various reactive functional groups (C=O, C=C, furan ring, a fragment of unsubstituted N-indole) can serve as substrates (Scheme 16).

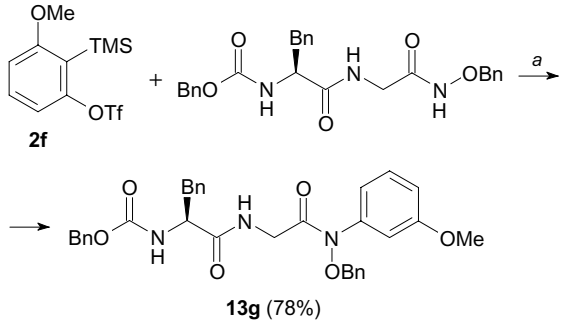
**Scheme 16**




(*a*) CsF (2.4 equiv.), MeCN, 23 °C; R = 2-Fu (**a**, 53% yield), 3-Ind (**b**, 89%); (*E*)-4-$ClC_6H_4CH$=CH (**c**, 89%), 4-$OHCC_6H_4$ (**d**, 52%), Me (**e**, 83%), Ph (**f**, 99%); Fu is furyl, Ind is indolyl

It should be noted that the N-arylation of compounds containing several N – H amide bonds is a selective process and involves the hydroxamic group giving, *e.g.*, compound **13g** (Scheme 17).[35]

**Scheme 17**

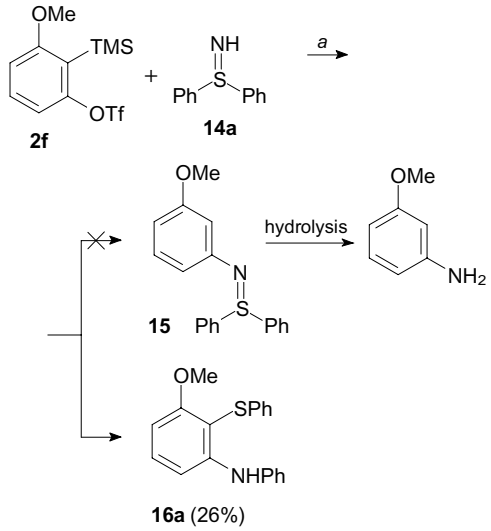



(*a*) CsF (2.4 equiv.), MeCN, 23 °C

Sulfilimines are efficient substrates for N-arylation with arynes. It is noteworthy that the reaction of *S*,*S*-diphenylsulfilimine (**14a**) with dehydrobenzene generated from triflate **2f** affords *o*-phenylsulfanylaniline **16a** (confirmed by X-ray diffraction), although in low yield, instead of the expected *N*-arylsulfilimine **15** (Scheme 18).[36]

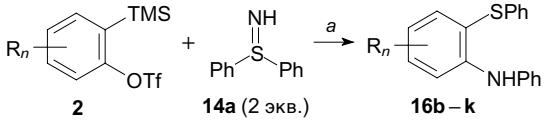
These results demonstrate that the C – S bond formation occurs simultaneously with the formation of the C – N bond between the electrophilic carbon atom of aryne and the nucleophilic nitrogen atom of sulfilimine. Besides, the reaction is accompanied by the migration of one of phenyl groups of sulfilimine **14a** from the sulfur atom to nitrogen. *o*-Sulfanylanilines **16** were prepared in high yields by the reaction using 2 equiv. of *S*,*S*-diarylsulfilimines **14** and the KF – 18-crown-6 system, which is required for the generation of aryne, in THF at 60 °C. The reaction performed at room temperature in the absence of crown ether affords compounds **16** in much lower yields (Scheme 19).[36]

**Scheme 18**




(*a*) CsF (2 equiv.), MeCN, 23 °C, 15 h

**Scheme 19**




(*a*) KF (2 equiv.), 18-crown-6 (2 equiv.), THF, 60 °C, 15 h

The optimized conditions allow the synthesis of a wide range of structurally diverse *o*-sulfanylanilines **16b – k**, in some cases as mixtures of isomers, starting from appropriate triflates.[36]

Various sulfilimines (**14b – i**) also readily react with 3-methoxydehydrobenzene to form 2-sulfanylaniline derivatives **16l – s** (Scheme 20, Table 5).[36]

**Scheme 20**

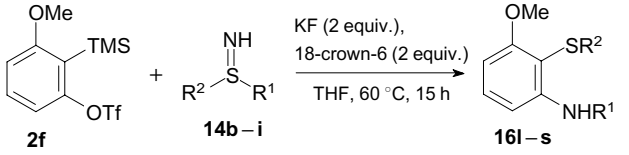


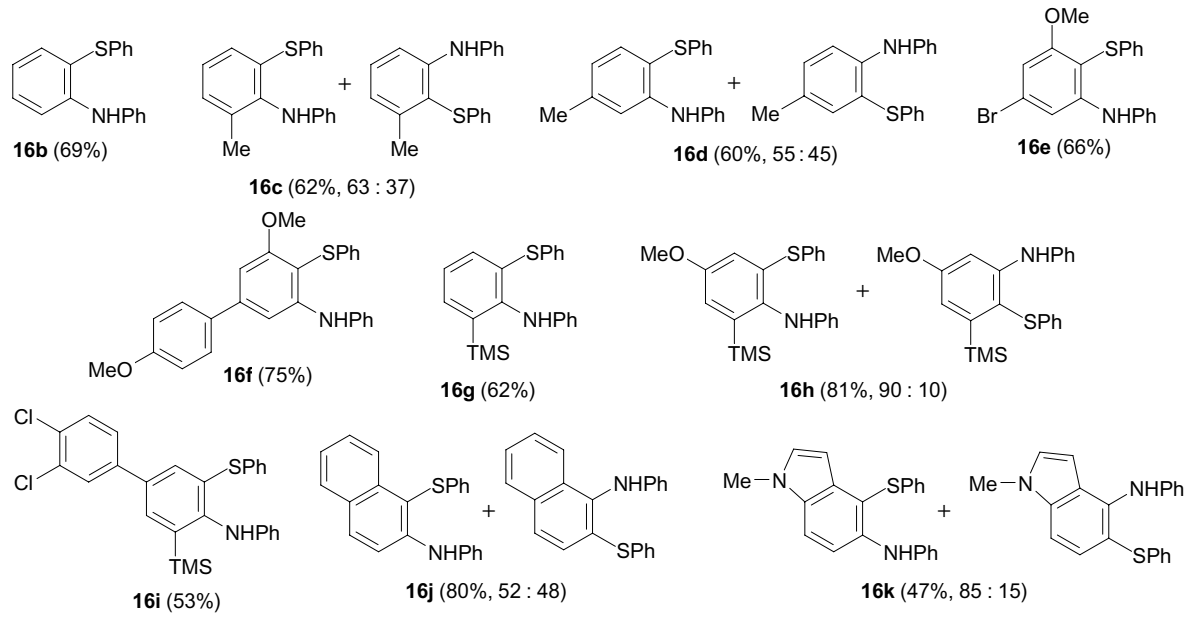

**Table 5**. Reactions of 3-methoxydehydrobenzene with sulfilimines (see Scheme 20).[36]

| Sulfilimine | Product | $R^1$ | $R^2$ | Yield (%) |
|---|---|---|---|---|
| **14b** | **16l** | *p*-Tol | *p*-Tol | 69 |
| **14c** | **16m** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | 54 |
| **14d** | **16n** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 67 |
| **14e** | **16o** | 4-$BrC_6H_4$ | 4-$BrC_6H_4$ | 71 |
| **14f** | **16p** | 4-$BzC_6H_4$ | *p*-Tol | 66 |
| **14g** | **16q** | 4-$O_2NC_6H_4$ | Ph | 60 |
| **14h** | **16r** | Ph | cyclo-$C_3H_5$ | 50 |
| **14i** | **16s** | Me (see [a]) | *p*-Tol | 43 |

[a] In the product, $R^1$ = H.

*o*-Sulfanylanilines **16** were prepared in good yields by the reactions with symmetrically substituted *S*,*S*-diphenylsulfilimines containing both electron-donating (**14b**,**c**) and electron-withdrawing (**14d**,**e**) substituents in benzene rings. It is noteworthy that the reactions with unsymmetrical sulfilimines (**14f**,**g**) bearing substituents of different electronic nature are accompanied by the selective migration of the phenyl group containing the electron-withdrawing substituent. Apparently, this migration occurs *via* the intramolecular nucleophilic *ipso*-attack, which is facilitated by the presence of the electron-withdrawing substituent. The

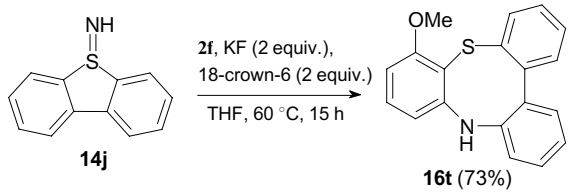
**Structures 16b – k**



reaction with *S*-methyl-*S*-(*p*-tolyl)sulfilimine (**14i**) proceeds in an unusual manner and is accompanied by the elimination of the methyl group and the formation of 3-methoxy-2-(*p*-tolylthio)aniline (**16s**).

It should be noted that the reaction of 3-methoxydehydrobenzene with fused sulfilimine **14j** produces a unique eight-membered thiazocine derivative **16t** *via* ring expansion (Scheme 21).[36]

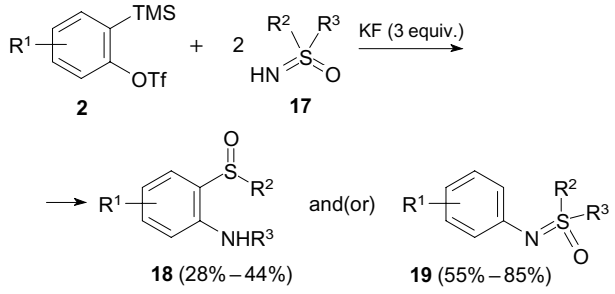
**Scheme 21**




Presumably, the reaction involving *S*,*S*-diarylsulfilimine (considered for substrate **14f**) and aryne **A** proceeds through the formation of the four-membered cyclic intermediate **B**, which is either generated *via* the nucleophilic addition of sulfilimine to aryne **A** through the formation of the zwitterionic intermediate **C** followed by cyclization or is produced directly through [2 + 2]-cycloaddition. The S – N bond cleavage in the intermediate **B** giving intermediate **D** followed by the intramolecular *ipso*-attack of the nucleophilic nitrogen atom on the more electron-deficient aryl group gives rise to *o*-sulfanylaniline **16p** (Scheme 22).[36]

*S*,*S*-Diarylsulfoximines **17** can be used as substrates in related reactions with arynes; however, the outcome of these reactions depends on the character of substituents at the sulfur atom, resulting in the formation of products **18** and(or) **19** (Scheme 23).[37]

**Scheme 23**




The reactions of *S*,*S*-diarylsulfoximines **17a – d** with 3-chloro- and 3-methoxy-1,2-dehydrobenzenes generated by treatment of triflates **2k**,**f**, respectively, with the KF – 18-crown-6 system in THF at 60°C give *o*-sulfinylanilines **18a – d** as the major products regardless of the electronic nature of aryl substituents (Scheme 24, Table 6). Like the reactions of arynes with sulfilimines, the reactions of unsymmetrical sulfoximine **17d** containing aromatic substituents of different electronic nature involve the migration of the phenyl group containing an electron-withdrawing substituent ($CF_3$ group).[37]

**Scheme 24**

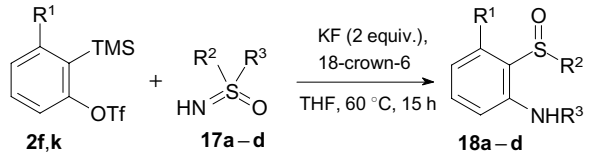


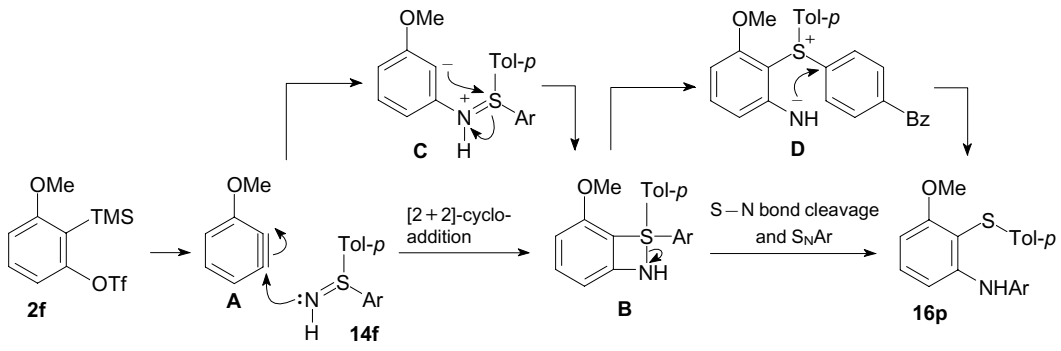

**Table 6**. Reactions of arynes with *S*,*S*-diarylsulfoximines (see Scheme 24).[37]

| Aryne precursor | $R^1$ | Sulfoximine | $R^2$ | $R^3$ | Product | Yield (%) |
|---|---|---|---|---|---|---|
| **2k** | Cl | **17a** | *p*-Tol | *p*-Tol | **18a** | 28 |
| **2f** | OMe | **17b** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | **18b** | 43 |
| **2f** | OMe | **17c** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | **18c** | 44 |
| **2f** | OMe | **17d** | *p*-Tol | 4-$F_3CC_6H_4$ | **18d** | 43 |

Under the same conditions, the reaction of 3-methoxydehydrobenzene with *S*-alkyl- and *S*,*S*-dialkylsulfoximines affords *N*-(3-methoxyphenyl)sulfoximines **19a – f** in good yields (Schemes 25 and 26, Table 7).[37]

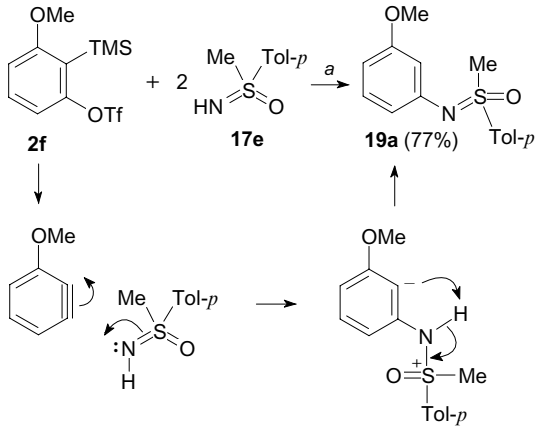
Dehydrobenzene and its 4,5-dimethoxy derivative also react with sulfoximine **17e** to give *N*-phenyl- (**19g**) and *N*-(4,5-dimethoxyphenyl)sulfoximines (**19h**) in moderate yields (see Table 7). The reaction of 3-(trimethylsilyl)dehydrobenzene generated from triflate **2m** with sulfoximine **17e** produces a mixture of regioisomers, with the *ortho*-isomer predominating due to the electron-donating inductive effect of the trimethylsilyl group.[37]

**Scheme 22**



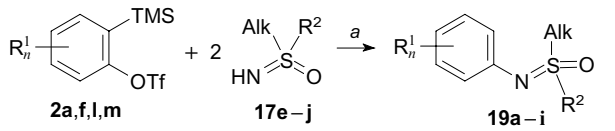

Ar = $C_6H_4Bz$-4

**Scheme 25**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 24 h

**Scheme 26**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 24 h

**Table 7**. Arylation of *S*-alkylsulfoximines with triflates **2** (see Scheme 26).[37]

| Aryne precursor | $R^1_n$ | Sulfoximine | Alk | $R^2$ | Product | Yield (%) |
|---|---|---|---|---|---|---|
| **2f** | 3-OMe | **17e** | Me | *p*-Tol | **19a** | 77 |
| **2f** | 3-OMe | **17f** | Me | 4-$MeOC_6H_4$ | **19b** | 74 |
| **2f** | 3-OMe | **17g** | Me | 4-$ClC_6H_4$ | **19c** | 62 |
| **2f** | 3-OMe | **17h** | Me | 2-Th | **19d** | 55 |
| **2f** | 3-OMe | **17i** | Bn | Bn | **19e** | 85 |
| **2f** | 3-OMe | **17j** | $(CH_2)_4$ | | **19f** | 60 |
| **2a** | H | **17e** | Me | *p*-Tol | **19g** | 52 |
| **2l** | 4,5-$(OMe)_2$ | **17e** | Me | *p*-Tol | **19h** | 54 |
| **2m** | 6-TMS | **17e** | Me | *p*-Tol | **19i** [a] | 45 |

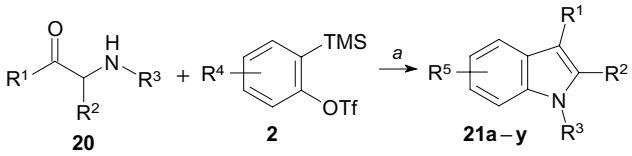
[a] A mixture of isomers containing the TMS group at positions 2 and 3 in a ratio of 73 : 27.

Similar results on the synthesis of *N*-arylsulfoximines using arynes [KF (2.5 equiv.), THF, 23 °C, 2 – 4 h, 42% – 77% yields] were reported by Aithagani *et al.*[38]

The N-arylation of amines with arynes was used in the synthesis of heterocyclic compounds. For instance, an efficient method for the preparation of polysubstituted N-arylindoles **21** was developed based on cycloaddition of α-amino ketones **20** to arynes (Scheme 27, Tables 8 and 9).[39]

This approach is applicable to α-amino ketones containing both electron-donating and electron-withdrawing substituents in different positions. Substituted aryne precursors

**Scheme 27**




(*a*) 1) KF (3 equiv.), 18-crown-6 (3 equiv.), MeCN, 1 – 4 h; 2) $H_3O^+$

**Table 8**. Synthesis of indoles **21** by the cyclization of α-amino ketones with unsubstituted dehydrobenzene (see Scheme 27, $R^4 = R^5 = H$).[39]

| Product | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| **21a** | Ph | Ph | Ph | 97 |
| **21b** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | Ph | 73 |
| **21c** | 4-$BrC_6H_4$ | 4-$BrC_6H_4$ | Ph | 74 |
| **21d** | Ph | Ph | 4-$ClC_6H_4$ | 82 |
| **21e** | 4-$BrC_6H_4$ | Ph | Ph | 83 |
| **21f** | *p*-Tol | *p*-Tol | Ph | 91 |
| **21g** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | Ph | 85 |
| **21h** | *p*-Tol | *p*-Tol | 4-$MeOC_6H_4$ | 93 |
| **21i** | Ph | Ph | *p*-Tol | 86 |
| **21j** | Ph | Ph | 4-$MeOC_6H_4$ | 92 |
| **21k** | Ph | 4-$MeOC_6H_4$ | Ph | 89 |
| **21l** | 4-$BrC_6H_4$ | 4-$MeOC_6H_4$ | Ph | 88 |
| **21m** | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | 4-$MeOC_6H_4$ | 86 |
| **21n** | 4-$BrC_6H_4$ | 4-$BrC_6H_4$ | 4-$MeOC_6H_4$ | 74 |
| **21o** | Ph | 4-$F_3CC_6H_4$ | Ph | 88 |
| **21p** | 3-$MeOC_6H_4$ | 3-$BrC_6H_4$ | Ph | 99 |
| **21q** | 3-$BrC_6H_4$ | 2-$MeOC_6H_4$ | Ph | 99 |
| **21r** | 2-Fu | Ph | Ph | 63 |
| **21s** | 2-Fu | 4-$MeOC_6H_4$ | Ph | 66 |
| **21t** | 4-$ClC_6H_4$ | Me | Ph | 72 |
| **21u** | Me | Et | Ph | 51 |

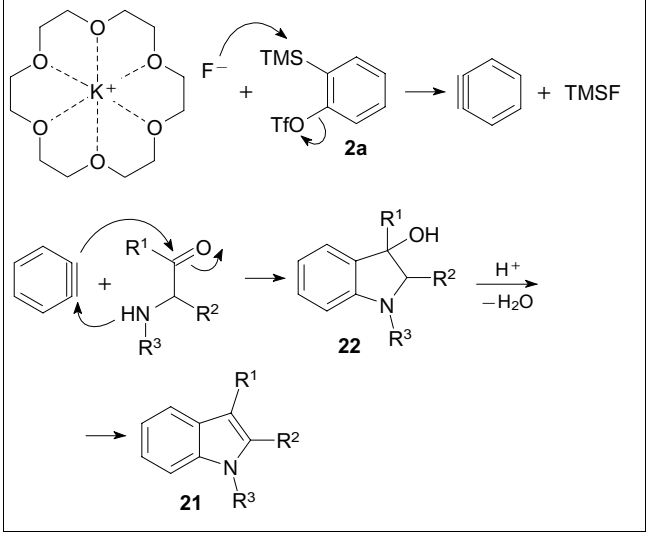
**Table 9**. Substituted arynes in the synthesis of indoles **21** from α-amino ketones **20a** (see Scheme 27, $R^1 = R^2 = R^3 = Ph$).[39]

| Aryne precursor | $R^4$ | Product | $R^5$ | Yield (%) |
|---|---|---|---|---|
| **2b** | 4,5-$Me_2$ | **21v** | 5,6-$Me_2$ | 87 |
| **2l** | 4,5-$(OMe)_2$ | **21w** | 5,6-$(OMe)_2$ | 88 |
| **2i** | 4,5-Benzo | **21x** | 5,6-Benzo | 90 |
| **2f** | 3-OMe | **21y** | 4-OMe | 95 |

can also be employed for this purpose. Symmetrical arynes generated from precursors **2b**,**i**,**l** react with amino ketone **20a** ($R^1 = R^2 = R^3 = Ph$) to form polysubstituted indoles **21v – x** in high yields; the corresponding reaction with aryne generated from 3-methoxy(trimethylsilyl) triflate (**2f**) proceeds regioselectively to form indole **21y** as the only reaction product (see Table 9).[39]

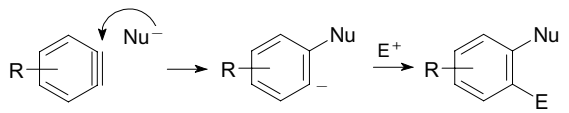
According to the proposed mechanism, the initial insertion of aryne into the N – H bond of amino ketone is accompanied by cyclization involving the carbonyl group to form substituted indoline **22**, which undergoes aromatization in an acidic medium (Scheme 28).[39]

**Scheme 28**




The multicomponent coupling reactions involving arynes are of particular interest.[40] These reactions comprise the initial addition of a nucleophile to dehydrobenzene followed by the interception of the anionic intermediate with an electrophile (provided the nucleophilic and electrophilic functional groups do not belong to the same molecule) to give finally 1,2-disubstituted benzenes (Scheme 29).

**Scheme 29**



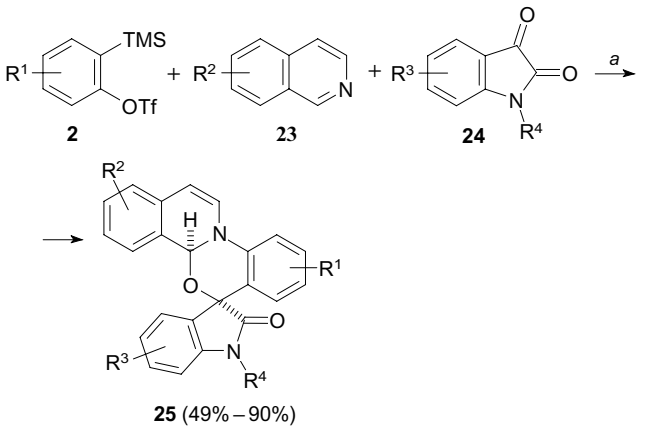

Nu is nucleophile, E is electrophile

The multicomponent reaction of arynes, isoquinolines **23** and isatins **24** provides a unique opportunity to synthesize heterocyclic compounds with complex structures. This reaction was used to prepare spirooxazinoisoquinolines **25** in good yields as a mixture of stereoisomers (Scheme 30, one of stereoisomers is shown).[41, 42]

The reactions of unsubstituted isoquinoline and isatin using triflates **2a**,**c**,**d** produced spirooxazinoisoquinolines **25a – c** (the major isomer is shown).[41, 42]

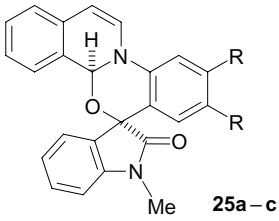
Related reactions are known for other carbonyl compounds. In particular, multicomponent reactions of arynes, (iso)quinolines and different aldehydes or ketones produce benzoxazino(iso)quinolines **26** in good yields with high diastereoselectivity (Scheme 31).[43]

**Scheme 30**




(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 70 °C, 24 h

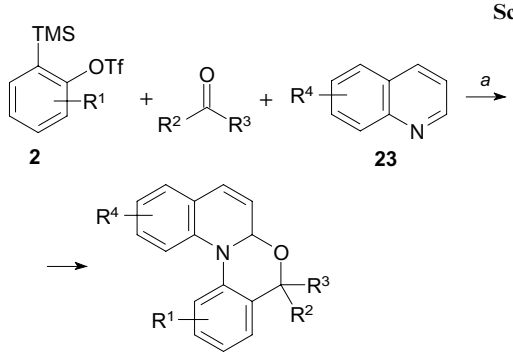
**Structures 25a – c**




| Aryne precursor | R or R – R | Product | Yield (%) | Isomer ratio |
|---|---|---|---|---|
| **2a** | H | **25a** | 71 | 4 : 1 |
| **2c** | $CH_2OCH_2$ | **25b** | 67 | 10 : 1 |
| **2d** | F | **25c** | 70 | 12 : 1 |

As an example, let us mention compounds prepared from triflate **2a**, appropriate ketones and unsubstituted quinoline (**26a – e**) or isoquinoline (**27a**) (*dr* is diastereomeric ratio).

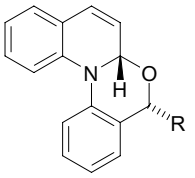
**Scheme 31**



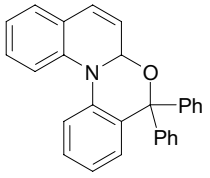

(*a*) KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), THF, from –10 to 70 °C, 12 h; $R^1$ = F, OMe, *etc.*; $R^2$, $R^3$ = Alk, Ar; $R^4$ = H, Me

According to the proposed mechanism, zwitterionic intermediate **28** generated from aryne and isoquinoline adds to the C=O bond of ketone to form oxazinoisoquinoline derivative **27** *via* a concerted process (Scheme 32). An

**Structures 26, 27**

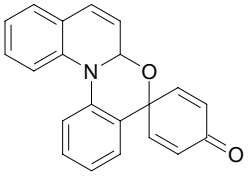


**26a–c**

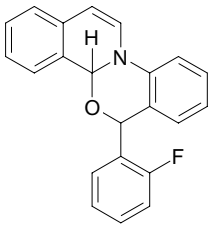


**26d** (54%)

R = Ph (**a**, 82% yield, *dr* = > 20 : 1), 2-Th (**b**, 57%, *dr* = 1 : 1), cyclo-$C_6H_{11}$ (**c**, 89%, *dr* = > 20 : 1)



**26e** (59%)

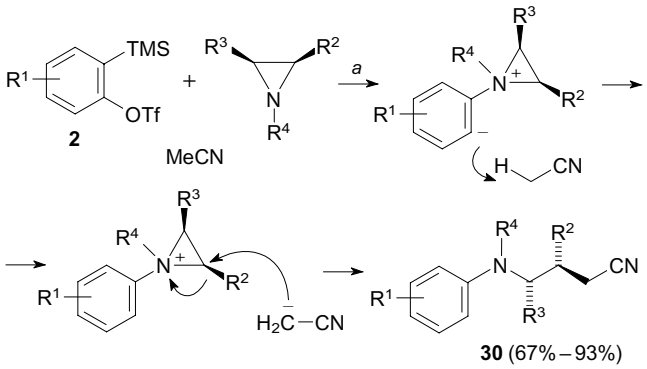


**27a** (64%, *dr* = 3 : 1)

alternative mechanism involves the two-step reaction of zwitterion **28** with the carbonyl compound giving intermediate **29** followed by the transformation of the latter into heterocycle **27** through the ring closure.[43]

The application of aziridines as nucleophiles in multicomponent coupling with arynes was described by Larionov and co-workers.[44] In this reaction, acetonitrile used as the solvent acts also as the third component of the reaction giving finally *N*-aryl-γ-aminobutyronitriles **30** in good yield

**Scheme 33**



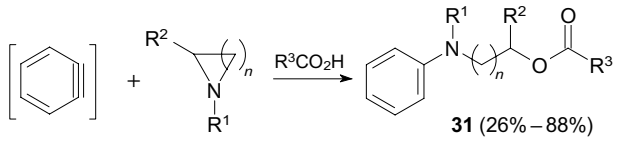
**30** (67%–93%)

(*a*) CsF (6 equiv.), PhMe, 65 °C; $R^1$, $R^2$, $R^3$, $R^4$ = Alk, Ar, *etc.*

(Scheme 33). The reaction involves the initial generation of the aziridinium zwitterion.[44] Suh and Chenoweth also employed acetonitrile and dichloromethane as reactants in the reaction with arynes.[45]

Multicomponent reactions of arynes with aziridines or azetidines in the presence of carboxylic acids afford *N*-aryl-β(γ)-amino alcohol derivatives **31** (Scheme 34).[46] This reaction was used to prepare, for example, derivatives **31a–h**.[46]

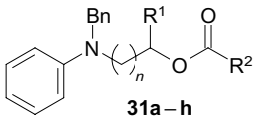
**Scheme 34**



**31** (26%–88%)

$R^1$, $R^2$, $R^3$ = Alk, Ar, *etc.*; *n* = 1, 2

**Structures 31a–h**



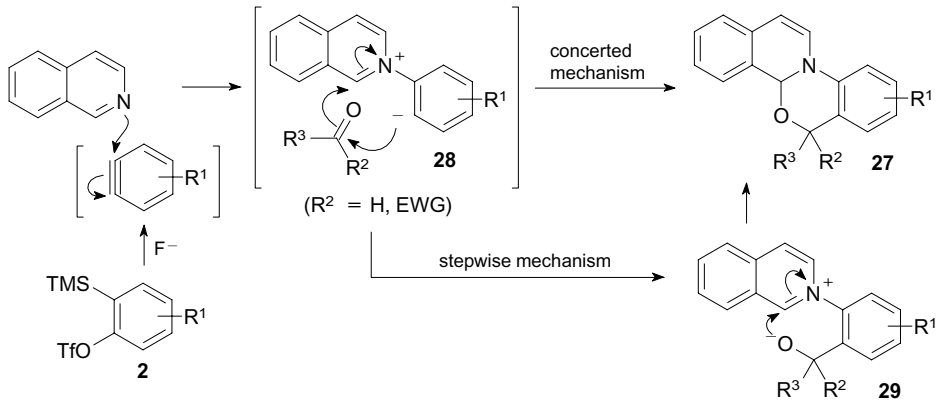
**31a–h**

| Compound | $R^1$ | $R^2$ | *n* | Yield (%) |
|---|---|---|---|---|
| **a** | Ph | 2-$IC_6H_4$ | 1 | 84 |
| **b** | Ph | 2-Th | 1 | 72 |
| **c** | Ph | Pyrrol-2-yl | 1 | 72 |
| **d** | Ph | Me | 1 | 76 |
| **e** | Ph | n-$C_5H_{11}$ | 1 | 60 |
| **f** | $EtCO_2$ | Ph | 1 | 78 |
| **g** | Ph | Et | 1 | 73 |
| **h** | Ph | Benzo[*b*]furan-2-yl | 2 | 80 |

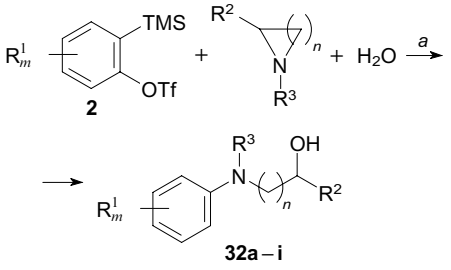
The reaction using trifluoroacetic acid in the presence of water directly produces *N*-aryl-β(γ)-amino alcohols, including compounds **32a–i**, in moderate to high yields (Scheme 35, Table 10).[47]

According to the proposed mechanism, the formation of *N*-aryl-β(γ)-amino alcohol derivatives involves the protonation of the initially formed zwitterion **33** by carboxylic acid giving quaternary ammonium salt **34** containing a carboxylate anion. The cleavage of the heterocycle through the nucleophilic attack of the carboxylate anion on the carbon atom of the cationic moiety of quaternary ammonium salt

**Scheme 32**



**Scheme 35**



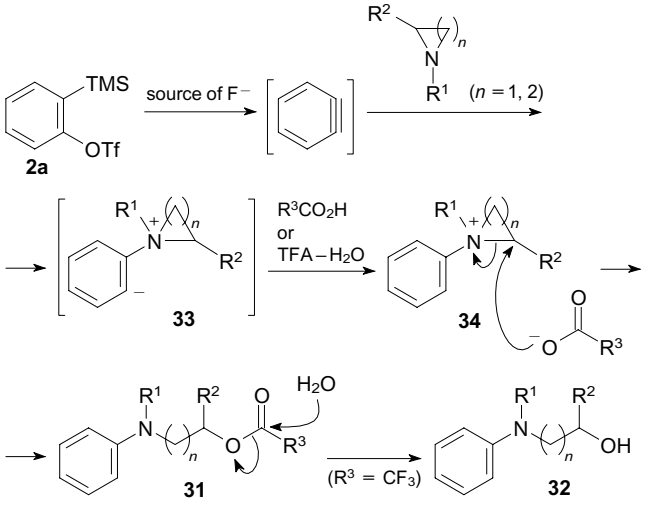
(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), TFA (1 equiv.), THF, from −10 to 20 °C, 12 h; TFA is trifluoroacetic acid

**Table 10**. Synthesis of *N*-aryl-β(γ)-amino alcohols **32** by the multicomponent coupling of arynes, aziridines (azetidines) and trifluoroacetic acid in the presence of water (see Scheme 35).[47]

| Product | $R^1_m$ | $R^2$ | $R^3$ | *n* | Yield (%) |
|---|---|---|---|---|---|
| **32a** | H | Ph | Bn | 1 | 72 |
| **32b** | H | Ph | 2-$FuCH_2$ | 1 | 48 |
| **32c** | H | 4-$BrC_6H_4$ | Bn | 1 | 69 |
| **32d** | H | 1-Naph | Bn | 1 | 64 |
| **32e** | H | OH | Bn | 1 | 91 |
| **32f** | H | HO(PhC≡C)$_2$C | Bn | 1 | 82 |
| **32g** | 3,4-$F_2$ | Ph | Bn | 1 | 65 |
| **32h** | H | Ph | Bn | 2 | 71 |
| **32i** | 3,4-Benzo | Ph | Bn | 2 | 51 |

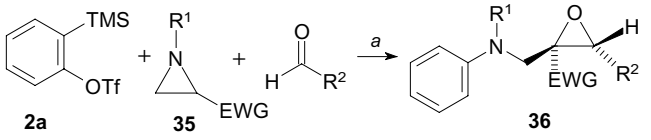
**34** affords O-acyl derivative of *N*-aryl-β-amino alcohol **31**.[46] In the presence of water in the reaction mixture, trifluoroacetates of *N*-aryl-β-amino alcohols **31** ($R^3 = CF_3$) are readily hydrolyzed to give the corresponding amino alcohols **32** (Scheme 36).[47]

**Scheme 36**



The three-component coupling of arynes, aziridines **35** containing an electron-withdrawing substituent and aldehydes produces *N*-aryl-β-amino epoxides, including compounds **36a – j**, in satisfactory yields with good diastereoselectivity (Scheme 37, Table 11).[48]

**Scheme 37**



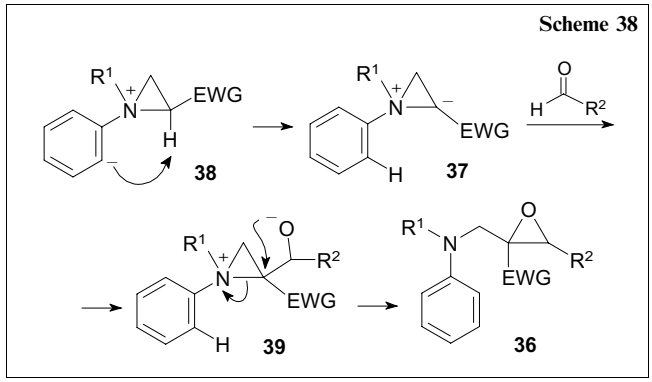
(*a*) KF (3 equiv.), 18-crown-6 (3 equiv.), THF, 30 °C, 12 h

**Table 11**. Products of the three-component coupling of dehydrobenzene, aziridines and aldehydes (see Scheme 37, EWG = CN).[48]

| Product | $R^1$ | $R^2$ | Yield (%) | *dr* |
|---|---|---|---|---|
| **36a** | $Bu^i$ | *p*-Tol | 60 | 90 : 10 |
| **36b** | $Bu^i$ | Ph | 59 | 88 : 12 |
| **36c** | $Bu^i$ | 4-$NCC_6H_4$ | 67 | 87 : 13 |
| **36d** | $Bu^i$ | 3-$MeOC_6H_4$ | 55 | 87 : 13 |
| **36e** | $Bu^i$ | 3-$BrC_6H_4$ | 61 | 85 : 15 |
| **36f** | $Bu^i$ | 2-$FC_6H_4$ | 60 | 87 : 13 |
| **36g** | $Bu^i$ | 2-$O_2NC_6H_4$ | 67 | 70 : 30 |
| **36h** | $Bu^i$ | 3,4-$Cl_2C_6H_3$ | 70 | 87 : 13 |
| **36i** | $Bu^i$ | 2-Naph | 74 | 88 : 12 |
| **36j** | $Bu^t$ | cyclo-$C_6H_{11}$ | 58 | > 95 : 5 |

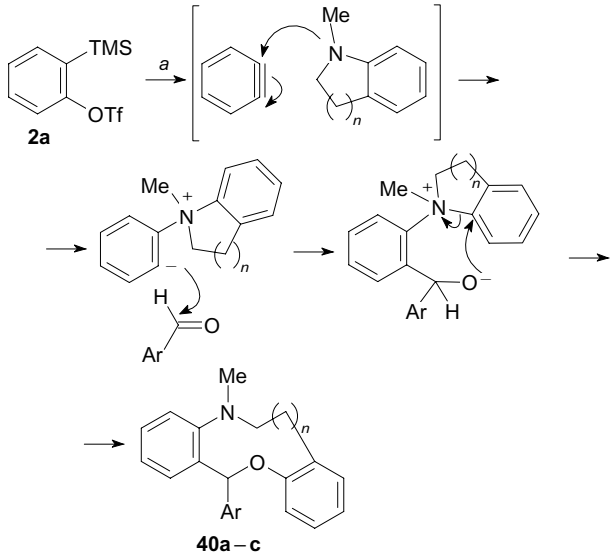
α-Amino epoxides serve as key building blocks in the synthesis of aminocarbohydrates and polyhydroxy-α-amino acids. This aryne strategy allows the one-step synthesis of such compounds from readily available substrates in the absence of metal-containing catalysts. The reaction presumably proceeds through the formation of cyclic ylide intermediate **37** stabilized by an electron-withdrawing substituent. This intermediate is generated *via* an intramolecular proton transfer in the initial adduct **38**. The subsequent addition of ylide **37** to the aldehyde carbonyl group affords zwitterionic intermediate **39** followed by the ring opening of aziridine *via* the intramolecular nucleophilic attack, which is accompanied by the simultaneous oxirane ring closure to form aminomethyl epoxide **36** (Scheme 38).[48]

**Scheme 38**



The aryne strategy to functionalize and complicate molecular structures provides an approach to the preparation of compounds, the synthesis of which using other methods, including those with transition metal-based catalysts, would be labourious. Thus, nine- and ten-membered dibenzo[1.5]oxaza heterocycles, *e.g.*, compounds **40a–c**, were synthesized (Scheme 39) by the three-component coupling using 1-methylindoline or 1-methyl-1,2,3,4-tetrahydroquinoline as substrates, different aryne precursors and aromatic aldehydes.[49]

**Scheme 39**

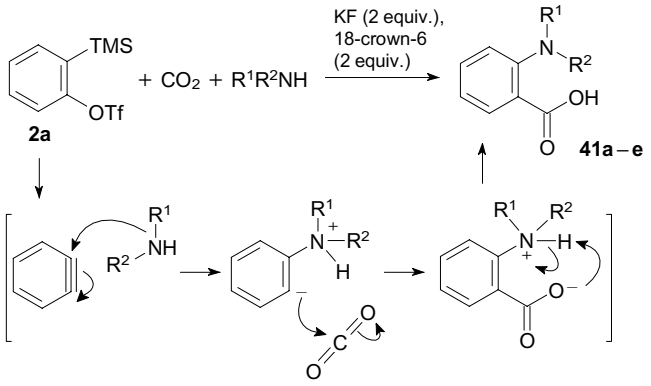


(*a*) CsF, 18-crown-6, THF, 15 h; $n$ = 1: Ar = Ph (**a**, 52% yield), 4-$ClC_6H_4$ (**b**, 69%); $n$ = 2, Ar = 4-$BrC_6H_4$ (**c**, 59%)

An efficient one-pot synthesis of N-substituted anthranilic acids **41a–e** is based on the coupling of arynes with aliphatic secondary amines and carbon(IV) oxide (Scheme 40).[50]

The use of aromatic tertiary amines as nucleophilic agents allows the synthesis of N-substituted anthranilic acid esters **42** or **43** (Scheme 41).[51] The formation of a particular reaction product is determined by the electronic nature of the substituent in the aromatic ring of tertiary amine. For instance, aryl anthranilates **43** are generated from amines containing an electron-withdrawing substituent *via* the intramolecular nucleophilic aromatic substitution ($S_NAr$). In the absence of an electron-withdrawing substituent in the aromatic ring, methyl esters of anthranilic acid derivatives **42** are generated *via* the intramolecular nucleophilic aliphatic substitution involving the carboxylate anion (see Scheme 41).[51]

**Scheme 40**

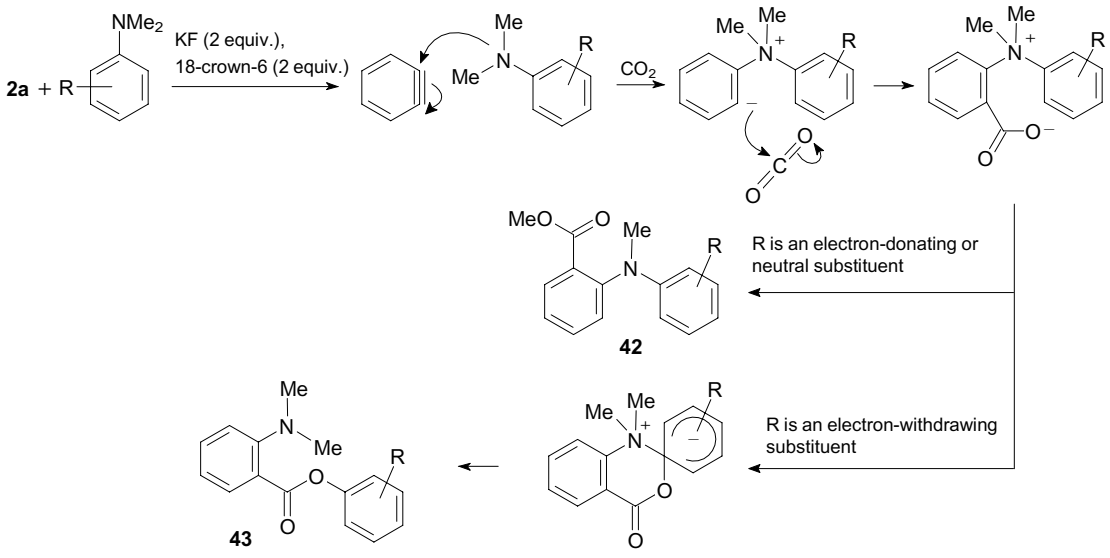


$R^1 = R^2$ = Et (**a**, 54% yield), $Pr^n$ (**b**, 84%), $Pr^i$ (**c**, 79%), $R^1$ = Me, $R^2$ = cyclo-$C_6H_{11}$ (**d**, 74%); $R^1–R^2$ = $(CH_2)_2$ (**e**, 7%)

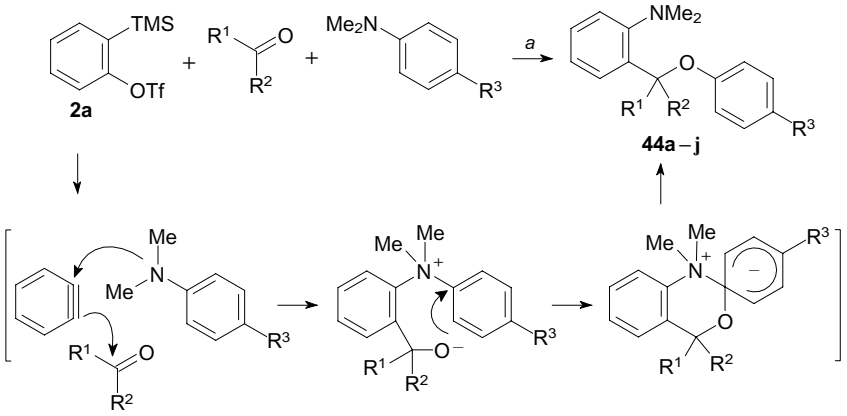
Related multicomponent coupling reactions of arynes, aldehydes (or activated ketones) and aromatic tertiary amines are accompanied by the formal migration of the amino group and proceed through the intermediate intramolecular nucleophilic aromatic substitution. This method was used to synthesize, *e.g.*, ethers **44a–j** (Scheme 42).[52]

The applicability of one-pot transformations involving arynes to prepare complex organic molecules was demonstrated in relation to the reaction of triflate **2a** with N-substituted imidazoles giving anthracene-containing arylamines **45a–e**.[53] The tandem reaction proceeds under very mild conditions. The proposed mechanism involves two sequen-

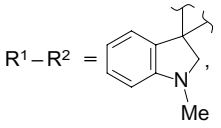
**Scheme 41**



**Scheme 42**



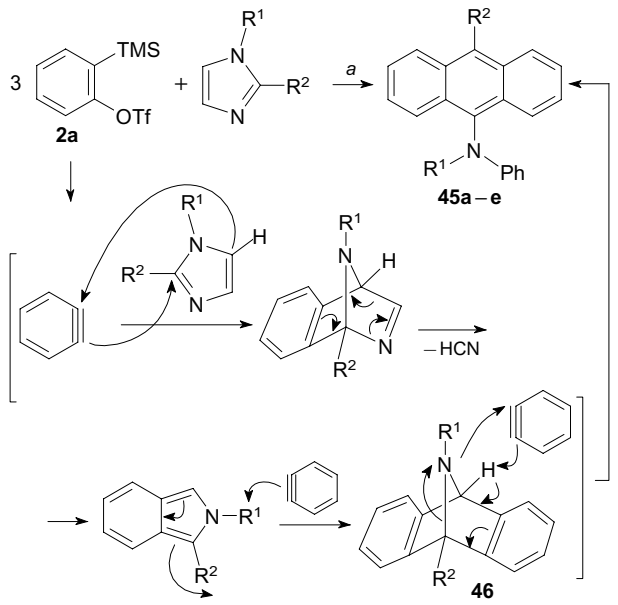
(*a*) KF (2.4 equiv.), 18-crown-6 (2.4 equiv.), THF; $R^1 = R^3 = H$: $R^2$ = Ph (**a**, 54% yield), 4-$F_3CC_6H_4$ (**b**, 79%), 4-$O_2NC_6H_4$ (**c**, 80%), 2-Th (**d**, 63%), n-$C_9H_{19}$ (**e**, 27%), cyclo-$C_6H_{11}$ (**f**, 27%); $R^1 = H$, $R^2$ = 4-$NCC_6H_4$, $R^3 = EtCO_2$ (**g**, 63%); $R^1$ = Ph, $R^3 = H$: $R^2 = F_3C$ (**h**, 62%), Bz (**i**, 30%);



$R^3$ = H (**j**, 72%)

tial Diels – Alder reactions with the participation of one imidazole molecule and two dehydrobenzene molecules giving tertiary amine **46** and the nucleophilic addition of the latter to the third dehydrobenzene molecule as the final step (Scheme 43).[53]

**Scheme 43**



(*a*) CsF, MeCN, 50 °C, 12 h; $R^1 = R^2$ = Me (**a**, 70% yield); $R^2 = H$: $R^1$ = Ph (**b**, 47%), 4-$ClC_6H_4$ (**c**, 45%), 4-$MeOC_6H_4$ (**d**, 57%); $R^1$ = Et, $R^2$ = Ph (**e**, 66%)

N-Unsubstituted β-lactams react with arynes to form N-substituted acrydones **47**. The proposed reaction mechanism involves the N-arylation of β-lactam followed by the intramolecular nucleophilic addition to the carbonyl group finally giving 2,3-dihydroquinolin-4-one. The reaction of the latter with two aryne molecules is accompanied by ethylene elimination to form acrydone **47** (Scheme 44).[54]

The cycloisomerization of triynes and tetraynes connected by a three-atom tether provides an alternative route for the generation of fused arynes. This process, known as the hexadehydro-Diels – Alder reaction, proceeds on moderate heating and does not require any reagent for the direct generation of arynes (Scheme 45). Ross and Hoye[55] investigated the reactions of polycyclic arynes that were generated through the hexadehydro-Diels – Alder reaction with different N-nucleophiles.

For instance, the three-component reaction of tetrayne **48**, 1,4-diazabicyclo[2.2.2]octane (DABCO) and benzotriazole produced piperazine derivatives **49a**,**b**. It was proposed that the synthesis of these compounds involves a sequence of the following transformations: 1) the generation of aryne **50** *via* the hexadehydro-Diels – Alder reaction, 2) the addition of DABCO to aryne **50** giving zwitterionic intermediate **51** and 3) the transformation of the latter into ion pair **52**. The ring cleavage of the quaternary ammonium salt with DABCO *via* the nucleophilic attack affords substituted piperazines **49** (Scheme 46).[55]

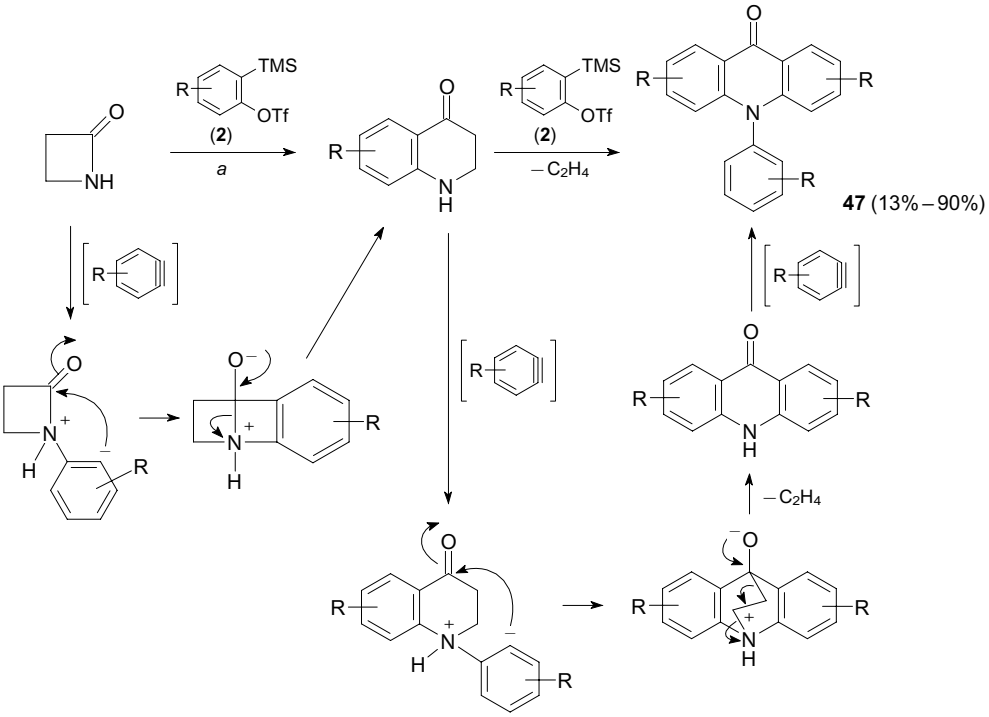
The ring cleavage of the quaternary ammonium salt with DABCO in ion pair **52** can be induced by O-nucleophiles, including complex natural products, such as estradiol (**53**) and vitamin E (**54**) (Scheme 47).[55]

The successful application of DABCO in the above-described reactions gave impetus to further studies on the use of tertiary amine-containing alkaloids as nucleophilic components in reactions with arynes. For instance, the heating of tetrayne **48** with 1.5 equiv. of tropinone (**55**) affords adduct (±)-**56** (Scheme 48). The reaction mechanism involves the Hofmann cleavage of the initially formed zwitterion **57** resulting in the formation of the cycloheptenone moiety.[55]

The related reaction of the alkaloid scopolamine (**58**) proceeds with retention of the epoxide and ester functions to give an equimolar mixture of diatereomers **59** in a total yield of 48% (Scheme 49). This method was employed to modify other natural products containing the tertiary amino group — quinidine, reserpine, sinomenine and brucine.[55] In general, it should be noted that this synthetic approach provides direct selective functionalization of natural products, thus allowing the design of new drugs based on natural pharmacophores.

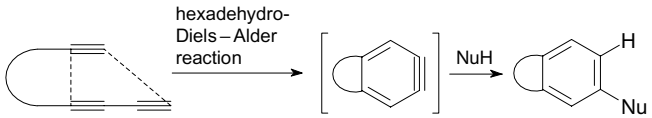
The above of participation of arynes in N-arylation of different classes of nitrogen-containing compounds demonstrate a considerable potential of this type of electrophilic agents in the synthesis of functionalized anilines. The arylation of tertiary amines and the application of *in situ* generated N-arylated quaternary ammonium salts in synthetically valuable cascade transformations have attracted considerable interest in recent years.[56] Tertiary amines often serve as bases in different transition metal-catalyzed reactions; however, examples of their arylation similar to that of

**Scheme 44**




(*a*) CsF (7 equiv.), MeCN, 23 °C; R = Alk, Hal, OAlk, *etc.* (in different positions)

**Scheme 45**

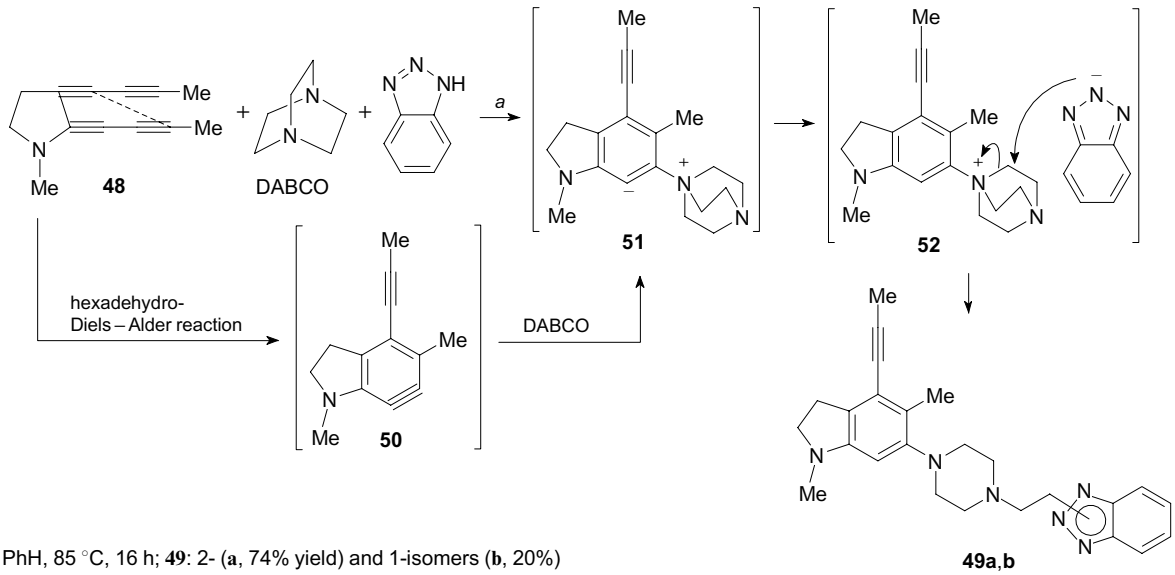



primary and secondary amines are unknown. Reactions of highly reactive arynes with N-nucleophiles can be performed under mild conditions employing gentle methods for their generation [from *o*-(trimethylsilyl)phenyl triflates or by the hexadehydro-Diels – Alder reaction]. Besides, a broad range of functionalized substrates can be used in these processes. Some aryne precursors are commercially available but their structural diversity is small. The main limitation of this N-arylation approach is related to problems with regioselectivity that arise when using unsymmetrical arynes. Thus, in almost all cases, the arylation with 4-substituted arynes affords nearly equimolar mixtures of regioisomers.

## 3. Arylation using diaryliodonium salts

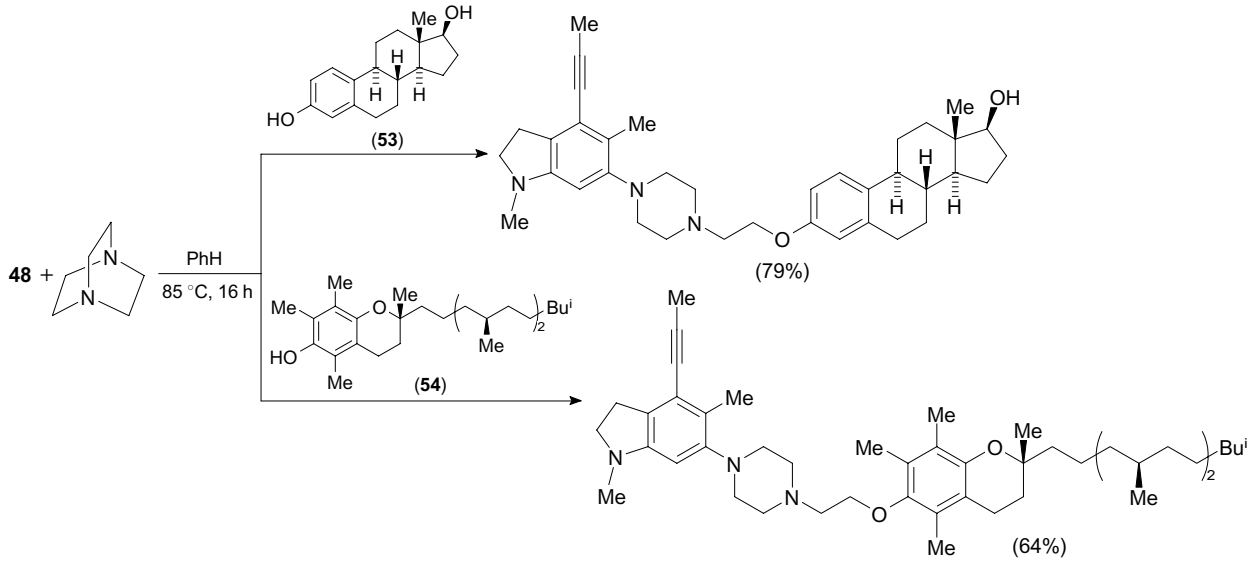
The properties of hypervalent iodine compounds are similar to those of transition metal complexes. However, as opposed to the latter, hypervalent iodine compounds are

**Scheme 46**

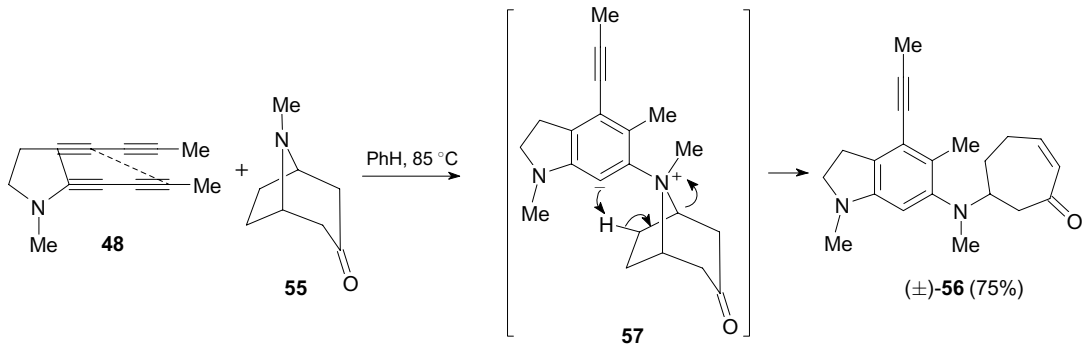



(*a*) PhH, 85 °C, 16 h; **49**: 2- (**a**, 74% yield) and 1-isomers (**b**, 20%)

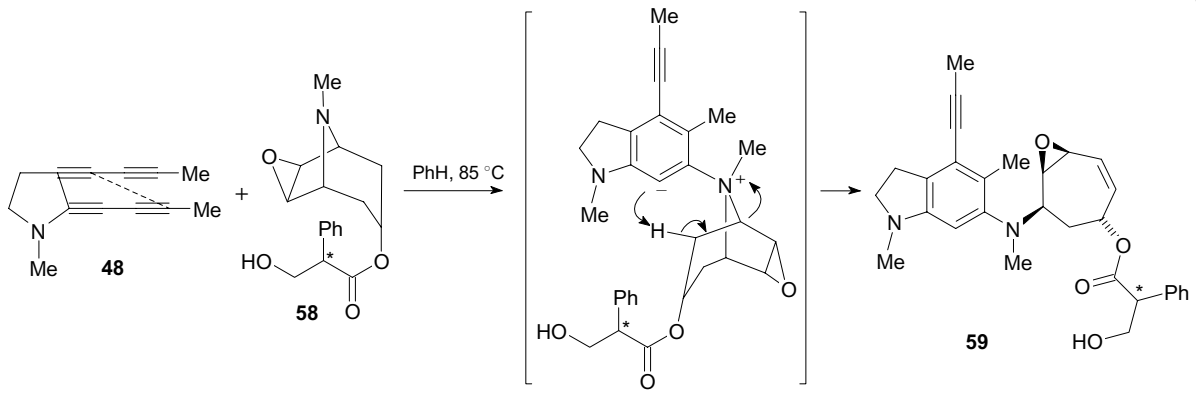
**Scheme 47**




**Scheme 48**



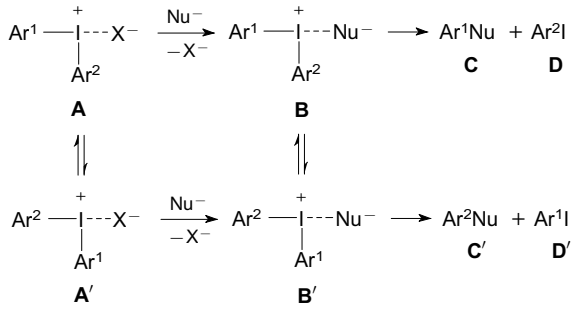

**Scheme 49**




more environmentally benign. These reagents are widely employed for performing various transformations in organic synthesis with high efficiency.[57] In particular, a lot of valuable methods were developed for arylation using diaryliodonium salts (diaryl-$\lambda^3$-iodanes) as efficient electrophilic arylating agents.[16, 17, 57]

The most probable mechanism of arylation in reactions of nucleophiles with diaryliodonium salts **A** in the absence of transition metal based-catalysts involves the intermediate formation of $\lambda^3$-iodane **B** through ligand exchange (Scheme 50). Both the starting diaryliodonium salts **A** and intermediate $\lambda^3$-iodanes **B** are characterized by the dynamic nature manifested in the pseudo-rotation of two aryl substituents (structures **A** and **A′**, **B** and **B′**). Then the arylation product **C** is formed through the coupling of a nucleophilic ligand with an equatorial aryl group, while the apical aryl group acts as a ligand for $\lambda^3$-iodane and is finally eliminated as the aryl iodide **D** (see Scheme 50). In the case of unsymmetrical diaryliodonium salts, the selectivity of aryl group transfer to the nucleophilic ligand in $\lambda^3$-iodane is determined by electronic and steric factors and depends on the nature of both diaryliodonium salts and nucleophilic

**Scheme 50**

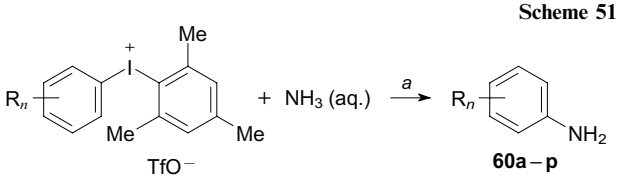


reagents.[58] In most cases, the reversal of selectivity of aryl group transfer to a nucleophilic atom was observed in non-catalytic and catalytic N-arylation reactions with diaryliodonium salts.[59]

Since arylation reactions with diaryliodonium salts always afford, apart from arylation products, 1 equiv. of aryl iodide, these reactants are characterized by a low atom-economy. Nevertheless, in most cases, aryl iodide can easily be separated from the arylation product and used in the subsequent operational cycle. Diaryliodonium salts are air- and moisture-stable and non-toxic. Therefore, they are attractive reactants for electrophilic arylation, particularly on the industrial scale. In recent years, several efficient, facile and environmentally benign procedures were developed for the synthesis of diaryliodonium salts,[16, 17, 57, 60, 61] including those performed in continuous-flow reactors, which provides a powerful impetus for the further development of methods of organic synthesis involving these reactants.[62]

Catalytic N-arylation reactions are known to be inefficient in aqueous media.[2] As opposed to this, Li and Liu[63] developed a method for arylation of ammonia with diaryliodonium triflates in aqueous media, which is a common procedure for the synthesis of anilines with different structures (Scheme 51).[63] The authors of the cited study used unsymmetrical iodonium salts generated from the appropriate aryl iodides and mesitylene (1,3,5-trimethylbenzene, MesH). The selectivity of aryl group transfer to the nitrogen atom is determined by steric effects — in all cases, the transfer of the most sterically hindered substituent is observed (anti-*ortho* effect) giving 2,4,6-trimethyliodobenzene along with anilines **60a–p**. It is noteworthy that the reaction with the symmetrical salt $Mes_2I^+TfO^-$ as the arylating agent produced 2,4,6-trimethylaniline (**60o**) in good yield, *i.e.*, steric hindrance does not adversely affect arylation. The electronic effects of substituents in the starting salts have almost no influence on the outcome of the arylation of ammonia. Thus, anilines **60** containing both electron-donating and electron-withdrawing substituents are generated in high yields.[63]

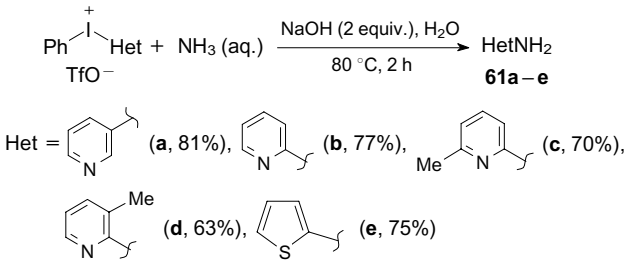
**Scheme 51**



(*a*) NaOH (2 equiv.), $H_2O$, 80 °C, 2 h; $R_n$ = H (**a**, 98% yield), 4-F (**b**, 90%), 4-Cl (**c**, 96%), 4-Br (**d**, 91%), 4-Me (**e**, 90%), 4-OMe (**f**, 94%), 4-$NO_2$ (**g**, 91%), 4-Ph (**h**, 95%), 4-$CO_2$Me (**i**, 80%), 4-Ac (**j**, 84%), 4-CN (**k**, 93%), 3-Br (**l**, 86%), 2-Me (**m**, 62%), 3,4-$(OMe)_2$ (**n**, 87%), 2,4,6-$Me_3$ (**o**, 71%), 2,3-benzo (**p**, 90%)

This reaction was extended to (hetaryl)phenyliodonium salts, which allowed the synthesis of a series of heterocyclic amines **61a–e** (Scheme 52).[63]

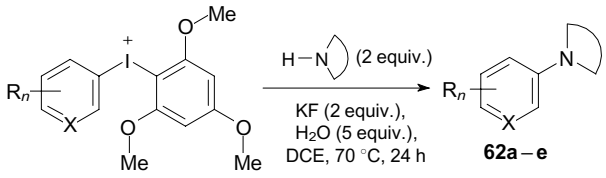
**Scheme 52**



The reversal of selectivity of aryl group transfer to a nucleophilic ligand was observed in the reaction of diaryliodonium salts with sodium nitrite as a nucleophile giving rise to nitrobenzenes.[64] In this case, the transfer of the most sterically hindered substituent occurs. Simple, sterically unhindered nitrobenzenes can be synthesized using either symmetrical diaryliodonium salts or diaryliodonium salts containing aryl groups with substantially different electronic properties. In the latter case, the transfer of the most electron-deficient aryl group is always observed.[64]

In 2016, Sandtorv and Stuart[65] developed a procedure for the arylation of aliphatic secondary amines with diaryliodonium salts (Scheme 53).

**Scheme 53**



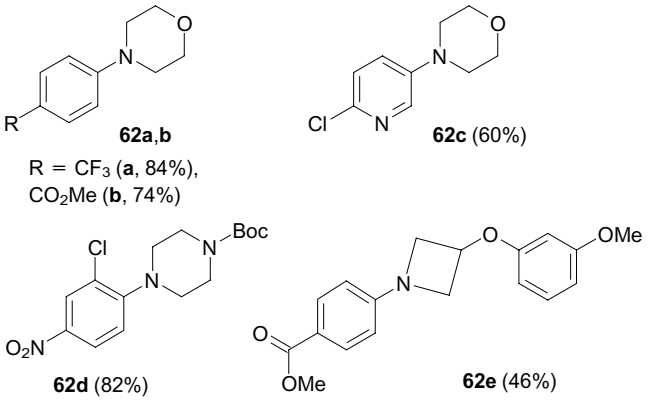
X = CH, N; DCE is dichloroethane

Earlier, this transition metal-free arylation reactions were considered to be difficult to accomplish.[59, 62] Potassium fluoride as the base and unsymmetrical diaryliodonium salts containing the 2,4,6-trimethoxyphenyl substituent, which is simultaneously electron-rich and sterically hindered, were found to be the optimal reactants. The application of these reactants made it possible to prepare substituted anilines and pyridine — compounds **62a–e**.[65]

Diaryliodonium salts can also be used for the arylation of much less nucleophilic anilines, although under more severe conditions (DMF, 130 °C).[66] The transfer of the most electron-deficient and least sterically hindered aryl substituent is preferable in this process.

Amides can also be used as nitrogen-containing nucleophiles in N-arylation reactions with diaryliodonium salts. Thus, anions of secondary acyclic amides **63a–j** are aryated with diaryliodonium salts under mild conditions. This method has a wide scope and allows the synthesis of tertiary

**Structures 62a–e**



**62a**,**b**

R = $CF_3$ (**a**, 84%),
$CO_2Me$ (**b**, 74%)

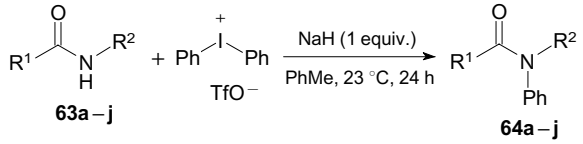
**62c** (60%)

**62d** (82%)

**62e** (46%)

Boc = $CO_2Bu^t$

**Scheme 54**



**63a–j**

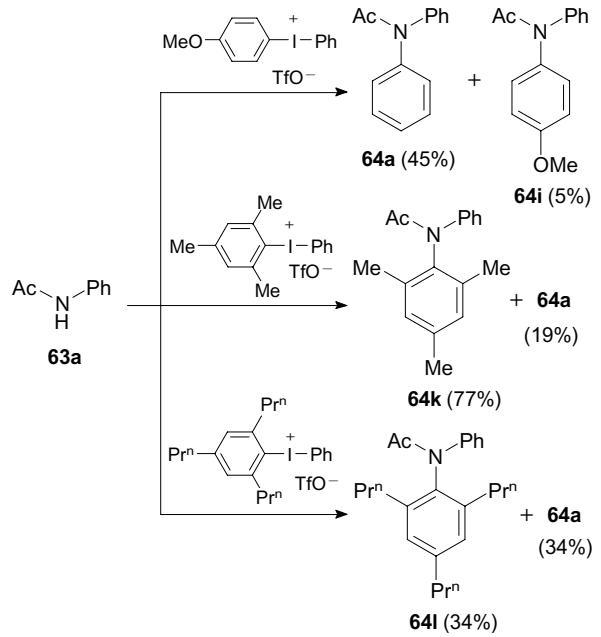
**64a–j**

$R^2$ = Ph: $R^1$ = Me (**a**, 75% выход ), Et (**b**, 72%), $Pr^i$ (**c**, 73%), cyclo-$C_6H_{11}$ (**d**, 82%), H (**e**, 61%); $R^1$ = Me: $R^2$ = 4-$O_2NC_6H_4$ (**f**, 87%), 4-$BrC_6H_4$ (**g**, 87%), *p*-Tol (**h**, 80%), 4-$MeOC_6H_4$ (**i**, 85%); $R^1$ = Ph, $R^2$ = 4-$MeOC_6H_4$ (**j**, 73%)

amides **64a–j** containing different aryl substituents (Scheme 54).[67]

The N-arylation of secondary amide anions is quite independent of the electronic nature of the substituents in the starting amide. The transfer of sterically hindered (*ortho* effect) and electron-deficient aryl groups is preferable in this process. (It should be noted that steric hindrance precludes N-arylation of amides in transition metal-catalyzed reactions.[68]) The reactions exhibiting selectivity of arylation of *N*-phenylacetamide (**63a**) with unsymmetrical iodonium salts[67] are shown in Scheme 55.

**Scheme 55**



**63a**

**64a** (45%)

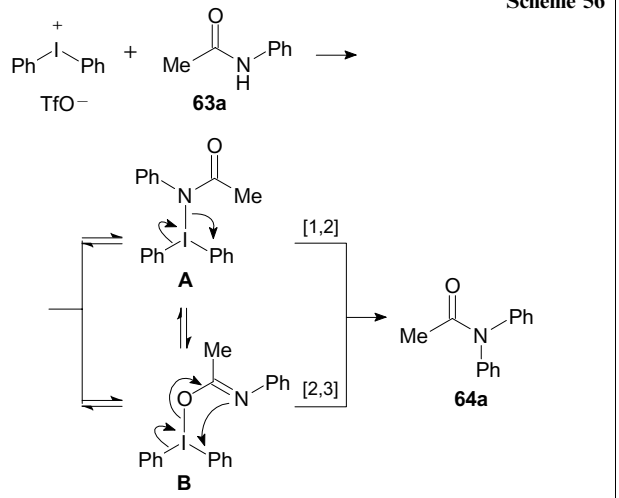
**64i** (5%)

**64k** (77%)

**64l** (34%)

The proposed mechanism of arylation of secondary amides (Scheme 56)[67] involves the formation of two possible intermediates (**A** and **B**), which are in a fast equilibrium. The intermediate **A** should form N-arylation product **64a** *via* a normal ligand coupling, *i.e.*, *via* the [1,2]-rearrangement; the intermediate **B**, *via* the [2,3]-rearrangement.

**Scheme 56**



**63a**

**A**

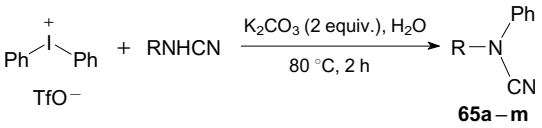
**B**

**64a**

The intramolecular N-arylation of β-phenylethylamines containing a protecting group [Cbz (benzyloxycarbonyl), Boc, Ac, $CO_2NEt_2$] at the nitrogen atom and the $\lambda^3$-iodane moiety in the *ortho* position affords indolines.[69] The authors of the cited study employed 10 mol.% 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) as an inhibitor of radical decomposition of the diaryliodonium salt and prepared cyclization products in high yields (84% in the presence of TEMPO *versus* 30% in the absence of this additive).

Diaryliodonium salts were employed for the preparation of N-arylated cyanamides, which have valuable properties and are widely used in synthetic,[70] coordination[71] and medicinal chemistry.[72] Recently, a method was developed for N-arylation of cyanamides based on their reactions with diaryliodonium hexafluorophosphates in the presence of copper salts as catalysts.[73] The necessity of performing the reaction exclusively under an inert atmosphere complicates the experimental procedure. The N-arylation of cyanamides with diaryliodonium salts can be accomplished in the absence of catalysts.[74] The arylation of both aryl- and alkylcyanamides with diaryliodonium triflates proceeds under mild conditions in aqueous or water–organic media in the presence of $K_2CO_3$ without using an inert atmosphere and affords arylated products **65a–m** (Scheme 57). The outcome of the reaction is independent of the electronic nature of substituents in the aryl moiety of the starting *N*-arylcyanamides. Actually, compounds **65e** (R = 4-OMe) and **65f** (R = 4-F) are generated in similar yields (92% and 89%, respectively). Despite the fact that aliphatic cyanamides are easily hydrolyzed, their arylation products were obtained, although in moderate or low yields (compounds **65h–j**,**l**,**m**). Sterically hindered *tert*-butylcyanamide reacts to form only trace amounts of cyanamide **65k**.

**Scheme 57**

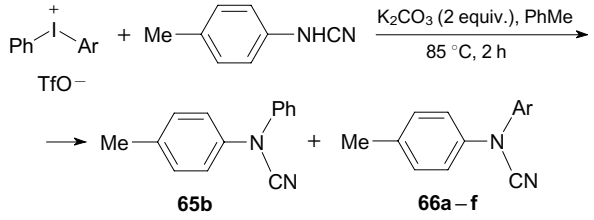



**65a–m**

R = H (**a**, 93% yield), *p*-Tol (**b**, 91%), *m*-Tol (**c**, 91%), *o*-Tol (**d**, 89%), 4-$MeOC_6H_4$ (**e**, 92%), 4-$FC_6H_4$ (**f**, 89%), 2-$FC_6H_4$ (**g**, 91%), Bn (**h**, 62%), $Bu^n$ (**i**, 74%), $Pr^i$ (**j**, 44%), $Bu^t$ (**k**, traces), cyclo-$C_6H_{11}$ (**l**, 70%), cyclo-$C_3H_5$ (**m**, 5%)

The N-arylation of cyanamides can be accomplished using both symmetrical and unsymmetrical diaryliodonium salts (Scheme 58, Table 12). In the case of unsymmetrical salts, the more electron-withdrawing aryl group is transferred preferably, and the reaction affords both *N*-phenylcyanamide **65b** and its analogues **66a–f**.[74]

**Scheme 58**




**65b** **66a–f**

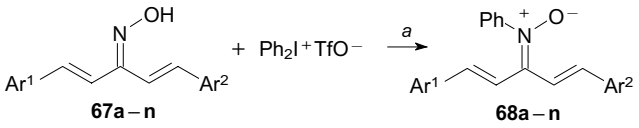
Oximes are widely used as reactants in organic synthesis.[75] Recently, Anderson and co-workers[76] developed a procedure for the generation of α,β-unsaturated *N*-aryl ketonitrones based on copper salt-catalyzed N-arylation of oximes with arylboronic acids. Despite efficiency, this method has drawbacks: harsh conditions, long reaction time, the use of complex ligands. Besides, the reaction products are difficult to purify from trace impurities of copper compounds used as catalysts. The transition metal-free N-arylation of oximes with diaryliodonium salts is devoid of these drawbacks.[77]

α,β-Unsaturated *N*-aryl ketonitrones have a considerable synthetic potential due to the presence of a conjugated double bond. Therefore, they are of great interest as building blocks for the construction of complex molecules.[78, 79] For this reason, the development of an efficient procedure for the N-arylation of oximes with diaryliodonium salts is of great importance. A wide range of α,β-unsaturated ketone oximes **67a–n** were employed in the N-arylation involving diphenyliodonium triflate under optimized conditions to prepare N-oxides **68a–n** (Scheme 59, Table 13).[77]

**Table 12**. N-Arylation of *N*-(*p*-tolyl)cyanamide with unsymmetrical diaryliodonium salts (see Scheme 58).[74]

| Product | Ar | Ratio **65b** : **66** | Yield (%) |
|---|---|---|---|
| **66a** | 4-$Bu^tC_6H_4$ | 2.4 : 1 | 96 |
| **66b** | 4-$AcNHC_6H_4$ | 6.8 : 1 | 86 |
| **66c** | 4-$O_2NC_6H_4$ | < 1 : 20 | 97 |
| **66d** | 2-Th | > 99 : 1 | 84 |
| **66e** | 4-$IC_6H_4$ | 1.5 : 1 | 97 |
| **66f** | 2,5-$Me_2C_6H_3$ | 1.2 : 1 | 89 |

**Scheme 59**




**67a–n** **68a–n**

(*a*) KOH (1.5 equiv.), $CCl_4$, 23 °C, 0.5–24 h

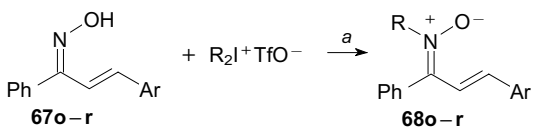
**Table 13**. N-Arylation of unsaturated oximes with diphenyliodonium triflate (see Scheme 59).[77]

| Compounds **67**, **68** | $Ar^1$ | $Ar^2$ | Yield (%) |
|---|---|---|---|
| **a** | Ph | Ph | 75 |
| **b** | 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | 65 |
| **c** | *p*-Tol | *p*-Tol | 81 |
| **d** | 4-$F_3CC_6H_4$ | 4-$F_3CC_6H_4$ | 76 |
| **e** | 3-$BrC_6H_4$ | 3-$BrC_6H_4$ | 46 |
| **f** | 2-$BrC_6H_4$ | 2-$BrC_6H_4$ | 68 |
| **g** | 2-Fu | 2-Fu | 75 |
| **h** | 2-Th | 2-Th | 75 |
| **i** | Ph | 4-$MeOC_6H_4$ | 46 |
| **j** | Ph | 4-$F_3CC_6H_4$ | 75 |
| **k** | Ph | 4-$BrC_6H_4$ | 75 |
| **l** | Ph | 3-$BrC_6H_4$ | 77 |
| **m** | Ph | 2-$BrC_6H_4$ | 60 |
| **n** | Ph | PhCH=CH | 67 |

The addition of a radical trap (TEMPO) to the reaction mixture of oxime **67a** and diphenyliodonium salt resulted in an increase in the yield of nitrone **68a** to 78% within 24 h. This argues against the radical mechanism. The possibility of preparing nitrone **68a** on a gram scale was also demonstrated with these reagents.

Under these conditions, the N-arylation of chalcone oximes **67o–r** with diaryliodonium salts affords products **68o–r** in moderate yields; these products were isolated as a mixture of two geometric isomers, with the *E*-isomer predominating (Scheme 60; the major isomer is shown).[77]

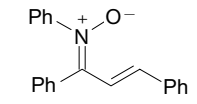
**Scheme 60**



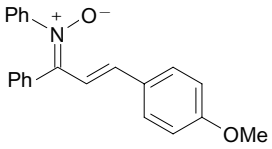

**67o–r** **68o–r**

(*a*) KOH (1.5 equiv.), $CCl_4$, 23 °C, 0.5–24 h

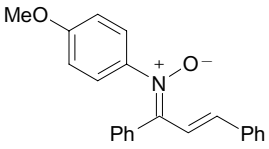
**Structures 68o–r**



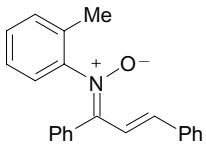
**68o** (65%, *E* : *Z* = 10 : 1)



**68p** (42%, *E* : *Z* = 12 : 1)



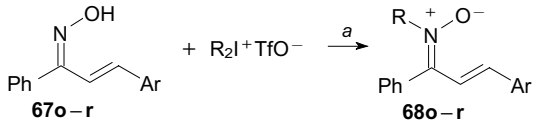
**68q** (53%, *E* : *Z* = 8 : 1)



**68r** (31%, *E* : *Z* = 8 : 1)

Under mild conditions, the reaction involving isatin oxime as the substrate selectively gives (*Z*)-*N*-aryl oxindole nitrones **69a**–**n**. This process can be performed using various diaryliodonium salts, including those with sensitive functional groups (Scheme 61, Table 14).[80] The reactions of diaryliodonium salts containing substituents of different electronic nature are equally efficient. In reactions with unsymmetrical diaryliodonium salts, a more electron-withdrawing aryl moiety is transferred to the oxime nitrogen atom. Substituents in isatin oximes have no significant effect on the reaction; the yields of arylation products for substrates with both electron-donating and electron-withdrawing groups are high (78%–99%).

**Scheme 61**



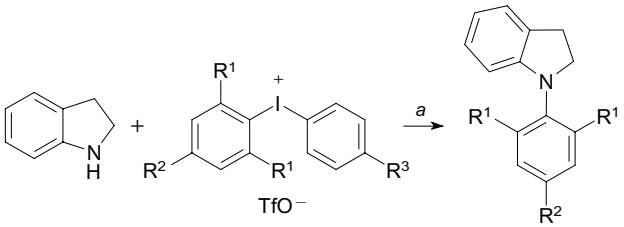
(*a*) KOH (1.5 equiv.), $CCl_4$, 23 °C, 0.5–24 h

**Table 14**. N-Arylation of isatin oxime with diaryliodonium salts (see Scheme 61).[80]

| $R^1_n$ | $R^2_m$ | Product | Yield (%) |
|---|---|---|---|
| H | H | **69a** | 98 |
| 4-OMe | 4-OMe | **69b** | 60 |
| 4-Me | 4-Me | **69c** | 92 |
| 4-Bu$^t$ | 4-Bu$^t$ | **69d** | 94 |
| 4-Cl | 4-Cl | **69e** | 90 |
| 4-F | 4-F | **69f** | 97 |
| 4-$CF_3$ | 4-$CF_3$ | **69g** | 97 |
| 3,5-$Me_2$ | 3,5-$Me_2$ | **69h** | 93 |
| 2-Me | 2-Me | **69i** | 99 |
| H | 4-OMe | **69j** | 79 |
| 4-Br | 4-OMe | **69k** | 85 |
| 3-Br | 4-OMe | **69l** | 97 |
| 2-Br | 4-OMe | **69m** | 83 |
| 4-$CO_2$Me | Ph | **69n** | 99 |

N-Arylindoline derivatives are of interest as structural components in organic electronic devices.[81] One of facile methods for the synthesis of these compounds is based on N-arylation of indolines with diaryliodonium salts (Scheme 62).[82] The maximum, though on average moderate, yields of arylation products **70** were achieved when performing the reaction in 2,2,2-trifluoroethanol as the solvent. Diaryliodonium salts containing substituents of different electronic nature exhibit different arylating capability (Table 15). Thus, compared to unsubstituted diphenyliodonium triflate, its analogue containing the electron-donating methyl group at position 4 gives indoline **70b** in lower yield (41%). In the reaction with bis(4-methoxyphenyl)iodonium triflate ($R^1$ = H, $R^2$ = $R^3$ = OMe), the corresponding N-arylated indoline **70c** was not isolated. The reactions with 4-bromo- and 4-trifluoromethyl-substituted diaryliodonium salts gave *N*-arylindolines **70d**,**e** in moderate yields. In the reaction with (mesityl)phenyliodonium triflate, a mixture of arylation products **67a**,**f** was obtained in a low overall yield.[82]

**Scheme 62**



(*a*) $F_3CCH_2OH$, 75 °C

**70a–f**

**Table 15**. N-Arylation of indolines with diaryliodonium salts (see Scheme 62).[82]

| $R^1$ | $R^2$ | $R^3$ | Time /h | Product | Yield (%) |
|---|---|---|---|---|---|
| H | H | H | 14 | **70a** | 83 |
| H | Me | Me | 48 | **70b** | 41 |
| H | OMe | OMe | 88 | **70c** | 0 |
| H | Br | Br | 22 | **70d** | 65 |
| H | $CF_3$ | $CF_3$ | 4 | **70e** | 62 |
| Me | Me | H | 24 | **70f** | 5 (see [a]) |

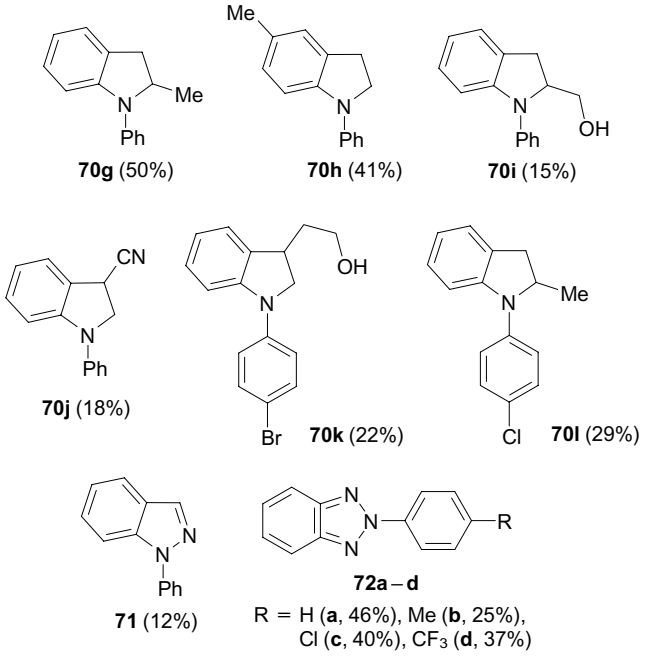
[a] The reaction also affords *N*-phenylindoline (**70a**) in 16% yield.

The N-arylation reactions of indolines, indazole and benzotriazole were performed under the same conditions, resulting in the formation of products **70g**–**l**, **71** and **72a**–**d**.[82]

Like indolines, substituted *N*-arylcarbazoles are of great interest as functional building blocks for the construction of optoelectronic devices,[83] particularly, organic light-emitting devices (OLED).[84] One of efficient approaches to the synthesis of these compounds is based on N-arylation of substituted carbazoles **73a**–**f** with diaryliodonium triflates in the presence of potassium *tert*-butoxide as a base in toluene (Scheme 63, Table 16).[85]

This approach was used to prepare N-arylated carbazoles **74a**–**f** containing aryl groups with both electron-donating and electron-withdrawing substituents.

**Structures 70 – 72**




**Scheme 63**

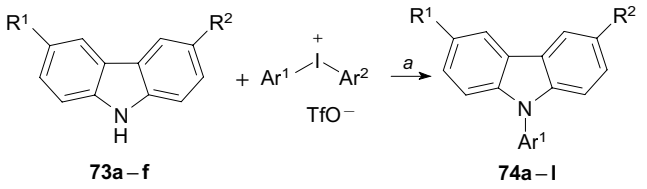


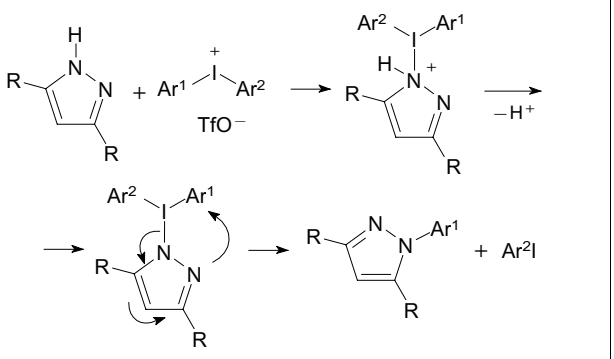

**Table 16**. N-Arylation of substituted carbazoles with iodonium salts (see Scheme 63).[85]

| Substrate | | | Reactant | | Product | Yield (%) |
|---|---|---|---|---|---|---|
| No. | $R^1$ | $R^2$ | $Ar^1$ | $Ar^2$ | | |
| **73a** | H | H | Ph | Ph | **74a** | 86 |
| **73a** | H | H | 4-$ClC_6H_4$ | 4-$ClC_6H_4$ | **74b** | 72 |
| **73a** | H | H | 4-$BrC_6H_4$ | 4-$BrC_6H_4$ | **74c** | 73 |
| **73a** | H | H | 4-$FC_6H_4$ | 4-$FC_6H_4$ | **74d** | 66 |
| **73a** | H | H | 2,4-$Me_2C_6H_3$ | 2,4-$Me_2C_6H_3$ | **74e** | 55 |
| **73a** | H | H | 4-$Bu^tC_6H_4$ | 4-$Bu^tC_6H_4$ | **74f** | 74 |
| **73a** | H | H | Mes | Mes | **74g** | Traces |
| **73a** | H | H | Ph | Mes | **74a** | 84 |
| **73b** | Cl | Cl | Ph | Ph | **74h** | 78 |
| **73c** | Br | Br | Ph | Ph | **74i** | 92 |
| **73d** | Br | H | Ph | Ph | **74j** | 84 |
| **73e** | $F_3C$ | H | Ph | Ph | **74k** | 75 |
| **73f** | MeO | H | Ph | Ph | **74l** | 80 |

Steric hindrance caused by *ortho*-substituents in diaryliodonium salts has a considerable influence on the N-arylation. For instance, the reaction involving bis(2,4-dimethylphenyl)iodonium triflate affords product **74e** in 55% yield, while the reaction with bis(mesityl)iodonium triflate does not give the arylation product. The selectivity of the reaction of the unsymmetrical salt $MesPhI^+TfO^-$ is controlled by steric factors: the transfer of the sterically unhindered aryl substituent and the formation of compound **74a** (anti-*ortho* effects) were observed.[85]

*N*-Arylpyrazoles are important structural units of many agrochemicals and pharmaceuticals. Therefore, the development of methods for the synthesis of these compounds is of great importance.[86, 87] Gonda and Novák[86] described the N-arylation of NH-pyrazoles with diaryliodonium salts under very mild conditions using aqueous ammonia as a base. The procedure for arylation of enols with diaryliodonium salts developed earlier[88] was extended to the arylation of N-unsubstituted pyrazoles.[86] The authors started from the assumption that the presence of the second (adjacent) nitrogen atom in the pyrazole molecule will be beneficial for arylation (Scheme 64).[86, 89] Besides, the coordination of a diaryliodonium salt at the pyrazole nitrogen atom facilitates the deprotonation and allows the use of a weak base (ammonia) for this purpose.[86]

**Scheme 64**



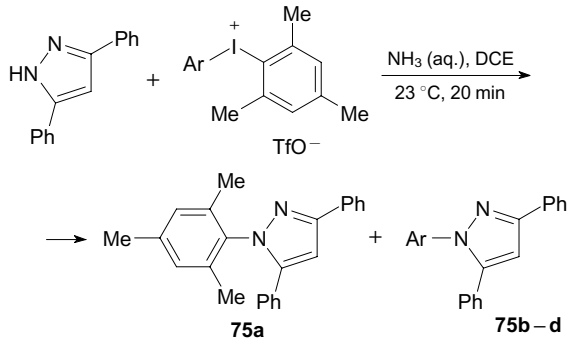

As opposed to the arylation of indolines and carbazoles, the arylation of pyrazoles with unsymmetrical (aryl)mesityliodonium triflates is controlled by the *ortho* effects. Thus, in most cases, a high preference for the mesityl group transfer to the pyrazole nitrogen atom was observed, as illustrated by the synthesis of compounds **75a – d** (Scheme 65).[89]

Diaryliodonium salts can be employed for the selective N-arylation of quinolin-4-ones under mild conditions giving, for example, compounds **76a – c** (Scheme 66).[90]

The reactions of potassium phthalimide and related compounds with diaryliodonium salts afford the corresponding *N*-arylimides, *e.g.*, compound **77a – o** (Scheme 67).[91] In this case, 3 equiv. of the starting perfluoro-substituted potassium phthalimide are used, and the reaction does not require heating.

It is noteworthy that the selectivity of aryl group transfer is determined by the *ortho* effect, due to which this reaction can be applied to synthesize sterically hindered anilines after the removal of the imide protecting group (Scheme 68).[91]

**Scheme 65**

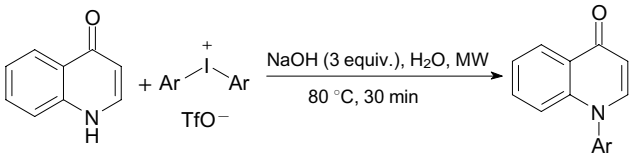



**75a** **75b – d**

**75**: Ar = 1-Naph (**b**), 4-$BzC_6H_4$ (**c**), 4-$O_2NC_6H_4$ (**d**)

| Ar | Products (ratio) | Yield (%) |
|---|---|---|
| *o*-Tol | **75a** | 92 |
| 2-$FC_6H_4$ | **75a** | 100 |
| 2-$ClC_6H_4$ | **75a** | 100 |
| 2-$BrC_6H_4$ | **75a** | 100 |
| 2,4,6-$(MeO)_3C_6H_2$ | **75a** | 82 |
| 1-Naph | **75a** + **75b** (17.2 : 1) | 91 |
| 4-$BzC_6H_4$ | **75a** + **75c** (11.4 : 1) | 99 |
| 4-$O_2NC_6H_4$ | **75a** + **75d** (3.2 : 1) | 99 |

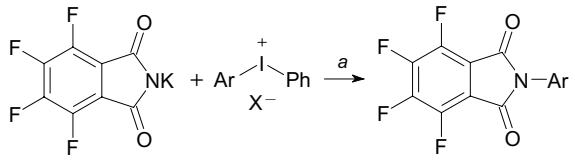
**Scheme 66**




**76a – c**

Ar = 3-$MeOC_6H_4$ (**a**, 78% yield), 3-$BrC_6H_4$ (**b**, 75%), 4-$AcC_6H_4$ (**c**, 79%); MW is microwave irradiation

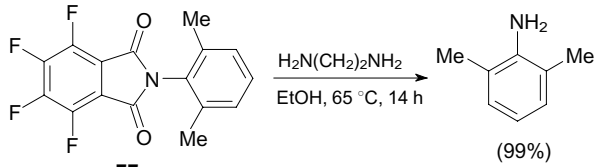
**Scheme 67**




**77a – o**

(*a*) PhMe, 100 °C, 5 – 24 h; Ar = Ph (**a**, 75% yield), Mes (**b**, 68%), 2,6-$Me_2C_6H_3$ (**c**, 79%), 2,3,5,6-$Me_4C_6H$ (**d**, 80%), 2,4,6-$Et_3C_6H_2$ (**e**, 90%), $C_6Me_5$ (**f**, 71%), 2,6-$Me_2$-4-$Bu^t$-$C_6H_2$ (**g**, 70%), 2,4,6-$Me_3$-3-$BrC_6H$ (**h**, 73%), 2,6-$Cl_2C_6H_3$ (**i**, 51%), 2,4,6-$Pr^i_3C_6H_2$ (**j**, 70%), 2,4,6-$Cl_3C_6H_2$ (**k**, 61%), 2,3,6-$Cl_3C_6H_2$ (**l**, 67%), 2,3,5,6-$Cl_4C_6H$ (**m**, 75%), $C_6Cl_5$ (**n**, 67%), 2-$O_2N$-6-$MeC_6H_3$ (**o**, 87%); X = $PF_6$, TsO, TfO

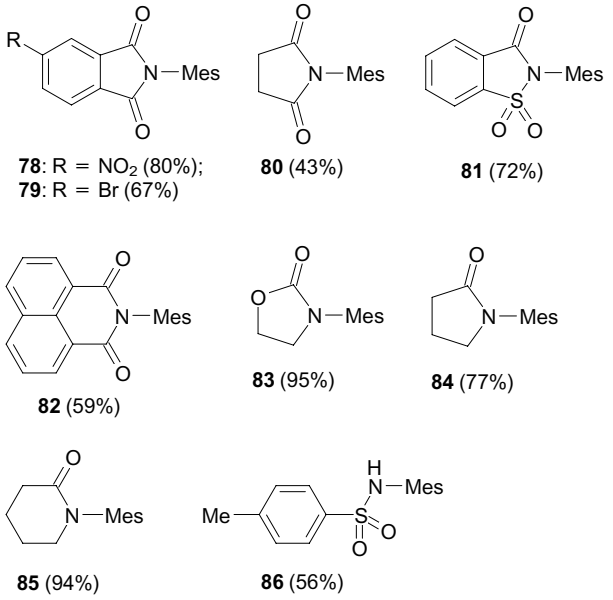
**Scheme 68**




**77c** (99%)

This amination protocol is not limited to potassium phthalimide and tetrafluorophthalimide. Thus, the reaction of bis(mesityl)iodonium triflate as the arylating agent with 4-nitro- and 4-bromophthalimides produces aniline derivatives **78** and **79**, respectively, in high yields. Succinimide, 1,8-naphthalimide, saccharine, as well as pharmacologically valuable oxazolidinones and lactams, served as additional possible N-nucleophiles, resulting in the formation of N-arylated products **80** – **86**.[91]

**Structures 80 – 86**



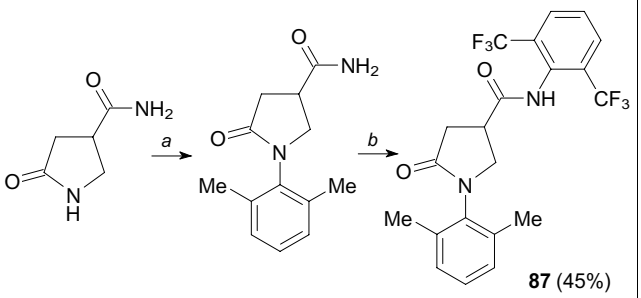

**78**: R = $NO_2$ (80%); **79**: R = Br (67%) **80** (43%) **81** (72%)

**82** (59%) **83** (95%) **84** (77%)

**85** (94%) **86** (56%)

The efficiency of this strategy was demonstrated in relation to the three-step synthesis of N,N′-diarylated pyrrolidinone amide **87** — an important biologically active compound (Scheme 69).[91]

**Scheme 69**



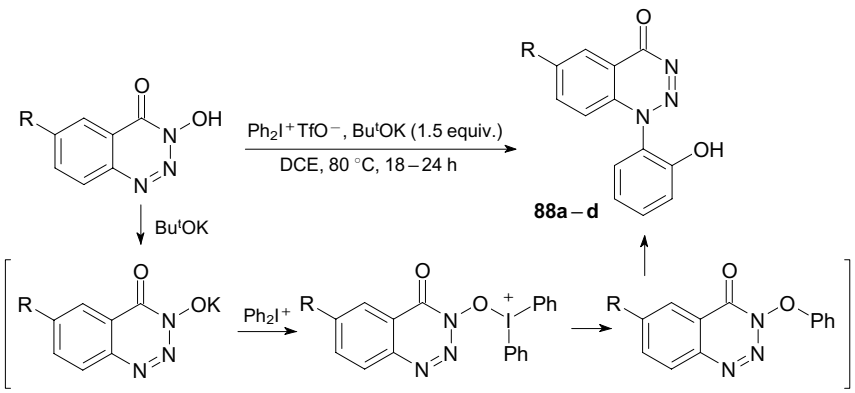

**87** (45%)

(*a*) 1) NaH, THF, from 0 to 20 °C, 1 h; 2) 2,6-$Me_2C_6H_3$(Ph)IOTs, DMF, 100 °C, 16 h; (*b*) 3,5-$(F_3C)_2C_6H_3$I, CuI (10 mol.%), $K_3PO_4$, dioxane, 110 °C

Some reactions involving diaryliodonium salts are accompanied by rearrangements. For example, the reaction of *N*-hydroxybenzo[1.2.3]triazin-4(3*H*)-ones with diaryliodonium salts giving *N*-arylbenzo[1.2.3]triazin-4(1*H*)-one derivatives **88a** – **d** is based on the [3,3]-rearrangement (Scheme 70).[92]

Examples of reactions considered in this section demonstrate the efficiency of the employment of diaryliodonium salts as arylating agents for different types of N-nucleo-

**Scheme 70**




R = H (**a**, 88% yield), Me (**b**, 61%), I (**c**, 79%), Cl (**d**, 70%)

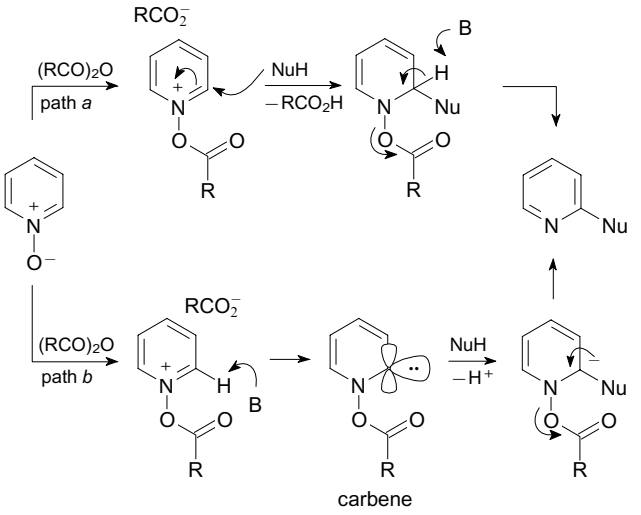
philes. In most cases, the application of unsymmetrical diaryliodonium salts is characterized by high selectivity of aryl group transfer, which is determined by the structures of both the substrate and arylating agents. A high preference for the transfer of the strongest electron-withdrawing aryl substituent is generally observed, thus relating, to a certain (although low) extent, N-arylation reactions involving diaryliodonium salts to classical nucleophilic aromatic substitution ($S_NAr$) reactions. Reactions of anionic nucleophiles usually involve the transfer of the most sterically hindered substituent (*ortho* effect), whereas the reversal of selectivity (anti-*ortho* effect) is typical of reactions of neutral N-nucleophiles. Generally, the N-arylation with diaryliodonium salts not only provides an efficient alternative to catalytic N-arylation strategies but also complement the latter reactions, in particular, in the synthesis of sterically hindered anilines.

## 4. Pyridine N-oxides in N-hetarylation reactions

Pyridine, like other azines, can form N-oxides with unique chemical properties.[18,93–95] Pyridine N-oxides are widely used as reactants in synthetic chemistry of heterocyclic compounds due to their high reactivity toward both electrophilic and nucleophilic agents. To promote reactions with nucleophiles, pyridine N-oxides are initially activated reactions with electrophilic (generally, acylating or sulfonylating) agents, resulting in their transformation into more reactive *N*-acyl(sulfonyl)oxypyridinium salts. The reactions of thus pre-activated pyridine N-oxides provide an important synthetic tool for the preparation of various substituted pyridines, including aminopyridines.

In the general case, the formation of pyridine derivatives *via* deoxygenative functionalization of appropriate N-oxides can involve two successive transformations (Scheme 71, B is a base). In both cases, the initial activation of N-oxide (shown for acylation) leads to an increase in both the electrophilicity of position 2 and polarity of the C(2)–H bond. One of possible pathways (path *a*) involves the addition of the nucleophile at position 2 and subsequent deprotonation accompanied by restoration of aromaticity giving rise to 2-substituted pyridine. An alternative pathway (path *b*) involves the initial proton abstraction from the C(2) atom of N-oxide to form a highly reactive carbene intermediate, which is attacked by a nucleophilic reagent.[18,93–95] The acylation of the N-oxide oxygen atom promotes activation not only of α positions but also of the γ position of the pyridine ring for nucleophilic attack. In realtity, many reactions of pyridine N-oxides afford mixtures of regioisomeric substitution products.

**Scheme 71**

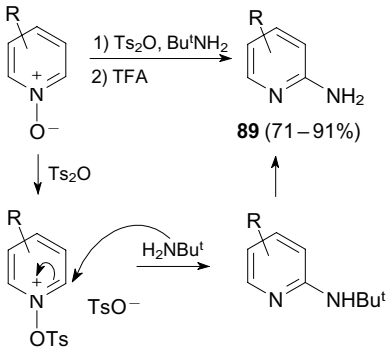



The review on the methods for the synthesis of 2-substituted pyridines[95] published in 2013 includes a chapter devoted to 2-amination, which summarizes amination reactions published up to 2011. In particular, various activating agents for N-oxides and different N-nucleophiles employed in amination reactions were considered. Some of the studies given below were discussed in the cited review.

In 2007, a general and efficient one-pot method was developed for the first time for the transformation of pyridine N-oxides into 2-aminopyridines **89** in high yields with high regioselectivity (Scheme 72).[96] This method is based on commercially available *tert*-butylamine and $Ts_2O$ and is compatible with many functional groups in the substrate. The use of $Bu^tNH_2$ proved to be essential for suppressing side reactions, such as dimerization and tosylation of reaction products, as well as for preventing transformations involving the activating agent and amine. It was noted that this process has high regioselectivity. Thus, the 2-/4-isomer ratio was higher than 50 : 1. The treatment of the reaction mixture with trifluoroacetic acid in the final

step resulted in the removal of the *tert*-butyl group and the formation of primary amines. This two-step one-pot reaction was successfully applied for the synthesis of amino derivatives of functionalized pyridines, quinolines and isoquinolines.[96]

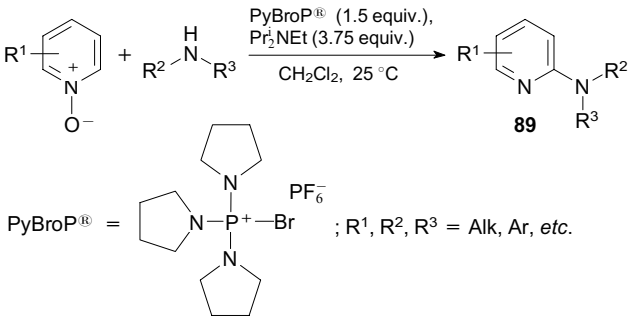
**Scheme 72**




R = H, 3-Me, 4-Me, 4-Cl, 4-OMe, 2-$CO_2$Me, 4-$CO_2$Me, 2-Py, *ect.*; Py is pyridyl

Later, Londregan *et al.*[97] developed a general facile one-pot procedure for the synthesis of 2-aminopyridines **89** from appropriate N-oxides in the presence of bromotris(pyrrolidino)phosphonium hexafluorophosphate (PyBroP®), which acts as a mild and efficient activator of N-oxides in reactions with nucleophilic agents. The best outcome of amination was achieved by using sterically unhindered aliphatic amines, while this reaction with heterocyclic compounds, such as imidazole or pyrazole, is not efficient (Scheme 73). The amination occurs exclusively at the α position, 2,6-lutidine is not subjected to amination, while 3-picoline gives a mixture of regioisomers.[97]

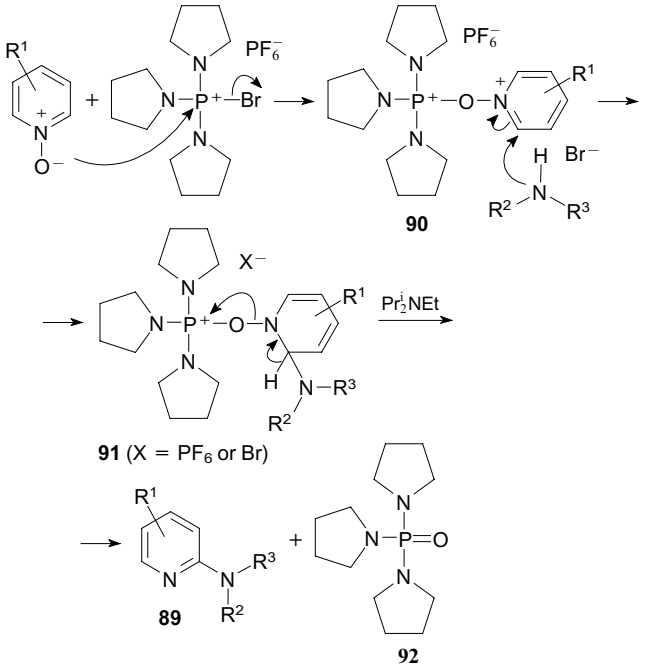
**Scheme 73**



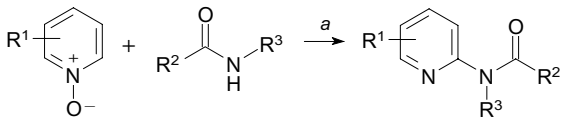

The mechanism of PyBroP®-mediated amination of pyridine N-oxides is outlined in Scheme 74. Presumably, the nucleophilic reagent adds to pyridine complex **90** to form intermediate **91**, and the amortization of the latter with a base affords substituted 2-aminopyridine and phosphoryltripyrrolidine **92** as the only by-product.

The reaction of *in-situ* generated imidoyl chlorides with pyridine N-oxides gives acylated 2-aminopyridine derivatives **93** (Scheme 75).[98] Imidoyl chlorides and their derivatives are produced by the reaction of secondary amides with oxalyl chloride and 2,6-lutidine in $CH_2Cl_2$ at 0 °C. The heating of the reaction mixture to room temperature followed by the addition of pyridine N-oxide affords N-acylated 2-aminopyridines in moderate to high yields.

**Scheme 74**



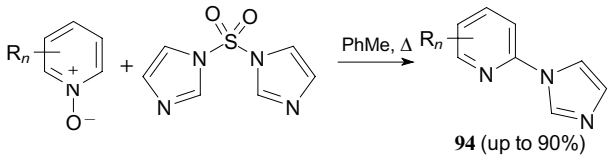

**Scheme 75**




(*a*) 1) Oxalyl chloride, 2,6-lutidine, $CH_2Cl_2$, 0 °C; 2) from 0 to 20 °C; $R^1$ = H, 4-Me, 4-Ph, 4-OBn, 2-Me, 3-Me; $R^2$, $R^3$ = Alk, Ar

A one-pot procedure for the transformation of pyridine N-oxides into 2-imidazolopyridines **94** in excellent yields is based on the treatment with sulfuryl imidazole at elevated temperature (Scheme 76).[99]

**Scheme 76**

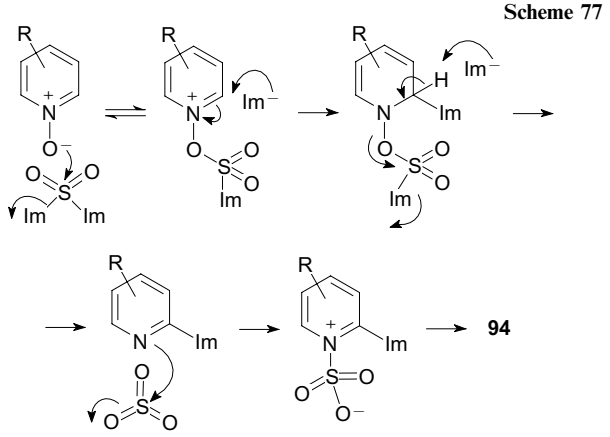



$R_n$ = H, 4-Ph, 3-CN, 4-CN, 2-OMe, 4-OMe, 2-Me, 3-I, 3,4-$Me_2$, 3,5-$Me_2$, 2-Py

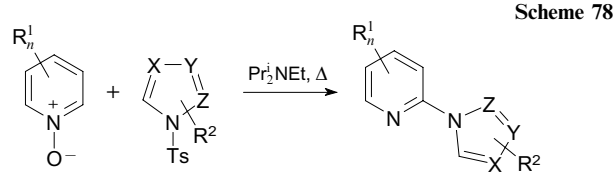
A plausible mechanism for this transformation is presented in Scheme 77 (Im is imidazol-1-yl).[99]

Later, this approach was extended to the deoxygenative coupling of pyridine N-oxides with azoles using N-tosylazole reagents. This procedures allows the introduction of 1,2,4- and 1,2,3-triazole, imidazoles and electron-deficient pyrazole moieties at position 2 of pyridines. About 30 such

**Scheme 77**



**Scheme 78**



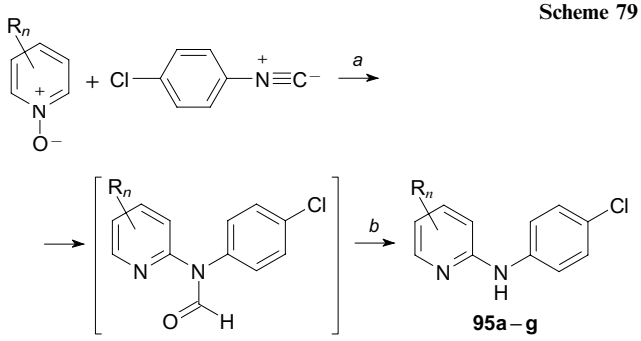
$R^1_n$ = H, 4-Ph, 3,5-$Me_2$, 3-OMe, 4-OMe, 4-$NMe_2$;
$R^2$ = H, $NO_2$, $CO_2Et$, CN; X, Y, Z = N or CH

compounds were synthesized in yields of up to 93% (Scheme 78).[100]

Since the publication of the review,[95] the amination of pyridine N-oxides was reported in several studies. Thus, the efficient activator PyBroP® (Ref. 97) mentioned above was used to prepare macrocyclic peptides from pyridine N-oxides.[101]

In 2014 Vamos and Cosford [102] proposed a one-pot two-step method for the synthesis of *N*-aryl-2-aminopyridines from N-oxides based on the reaction of the latter with activated isonitriles without the isolation of intermediate *N*-formyl-2-aminopyridines. By studying the reaction of methylisonicotinate *N*-oxide ($R_n$ = 4-$CO_2Me$) with phenylisonitrile, the researchers found that the best reaction outcome can be achieved using a powerful silylating agent (TMSOTf) in an acetonitrile – DMF solvent mixture microwaved at 150 °C for 15 min. Later, these conditions were applied to different N-oxides, which were reacted with 4-chlorophenylisonitrile to form substituted aminopyridines **95a – g** (Scheme 79; the positions of substituents in the product are indicated).[102]

**Scheme 79**

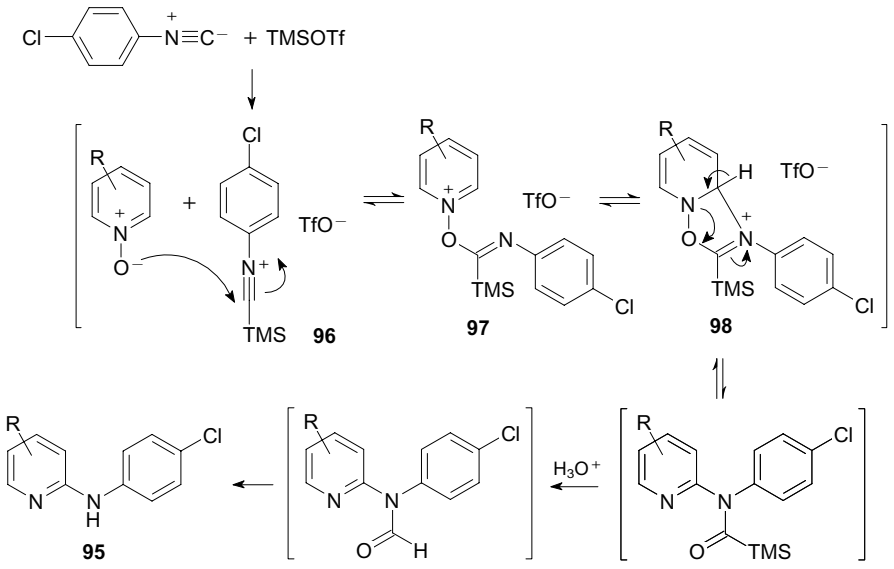


(*a*) TMSOTf (1 equiv.), MeCN – DMF (3 : 1), MW, 150 °C, 15 min;
(*b*) 1 M HCl, THF;
$R_n$ = H (**a**, 71% yield), 4-$CO_2Me$ (**b**, 60%), 4-$NO_2$ (**c**, 67%), 4-OMe (**d**, 19%), 4-CHO (**e**, 0%), 6-Me (**f**, 48%), 3,5-$Br_2$ (**g**, 41%)

The yields of N-aminopyridines depend on the structure of the starting N-oxides. Thus, the highest yields were achieved for compounds with electron-withdrawing substituents. An attempt to synthesize aminopyridine **95e** staring from the 4-formyl derivative failed because of instability of the substrates under the reaction conditions. 3,4-Disubstituted pyridine or isoquinoline N-oxides form mixtures of regioisomers due to amination at both possible α positions.

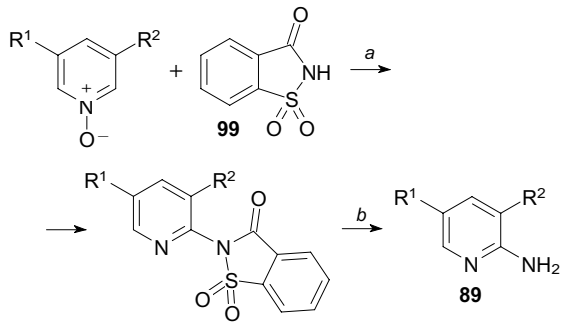
The reaction mechanism proposed by Vamos and Cosford [102] involves the addition of N-oxide to activated isonitrile **96** giving intermediate **97**. The reaction of the latter can occur at position 2 or 6 of the activated aromatic ring giving oxadiazoline [by the reaction at the C(2) atom]. The regioselectivity of this step is determined by the balance between the electron density distribution in the pyridine ring and steric effects of substituents (Scheme 80).[102]

**Scheme 80**



Primary 2-amino derivatives can be regioselectively synthesized from 3,5-disubstituted pyridines using commercially available and cheap saccharin (**99**) as a nitrogen source.[103] This method is characterized by regioselectivity, high yields and mild reaction conditions. The best yields of products **100a – g** were obtained in the reaction performed in $CH_2Cl_2$ at 0 °C using N-oxide under toluenesulfonyl chloride activation in the presence of *N*,*N*-diisopropylethylamine. Moreover, the initially formed adduct with saccharin can be subjected to mild hydrolysis *in situ* (Scheme 81, Table 17).[103]

**Scheme 81**




(*a*) $Pr^i_2NEt$ (2 equiv.), TsCl (1.2 equiv.), $CH_2Cl_2$, 0 °C;
(*b*) HCl (aq.), 80 °C

**Table 17**. Regioselectivity of amination of 3,5-disubstituted pyridine N-oxides with saccharin (see Scheme 81).[103]

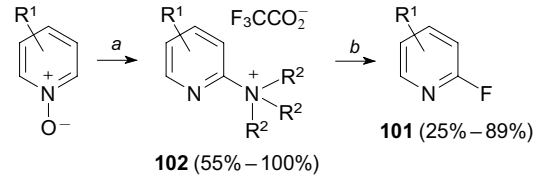
| Major product | | | Conversion (%) | 2-/6-Isomer ratio | Yield (%) (see [a]) |
|---|---|---|---|---|---|
| No. | $R^1$ | $R^2$ | | | |
| **100a** | 4-$BrC_6H_4O$ | 3,4-$(MeO)_2C_6H_3O$ | 94 | 2 : 1 | 91 [b] |
| **100b** | Br | PhO | 100 | 5.8 : 1 | 69 |
| **100c** | Br | 3,4-$(MeO)_2C_6H_3O$ | 95 | 84 : 1 | 73 |
| **100d** | Br | MeO | 97 | 11.8 : 1 | 77 |
| **100e** | $MeO_2C$ | $MeO(CH_2)_2O$ | 100 | 7.6 : 1 | 66 |
| **100f** | PhS | Br | 100 | 2.9 : 1 | 79 [b] |
| **100g** | H | MeO | 65 | 3 : 1 | 21 |

[a] The yield of the major product is given; [b] the yield of a mixture of isomers is given.

The amination of 5-alkyl(aryl)oxy-3-bromo-substituted substrates occurs predominantly at the *ortho* position relative to the electron-donating substituent at position 5. Unexpectedly, 3-bromo-5-phenylthiopyridine N-oxide is aminated at the *ortho* position relative to the bromine atom. Therefore, it was demonstrated that saccharin is ideally suited as a synthetic equivalent of ammonia for the regioselective amination of unsymmetrical 3,5-disubstituted pyridines.

The synthesis of 2-fluoropyridines **101**, including $^{18}F$ radioisotope-labelled derivatives, by means of the nucleophilic aromatic substitution created a need for the preparation of activated substrates. These substrates include quaternary trialkyl(2-pyridyl)ammonium salts **102**, which not only activate the substrate for nucleophilic substitution but also contain a good leaving group. Salts **102** were synthesized by the reaction of substituted pyridine N-oxides with tertiary alkylamines and pyridine (Scheme 82).[104]

**Scheme 82**

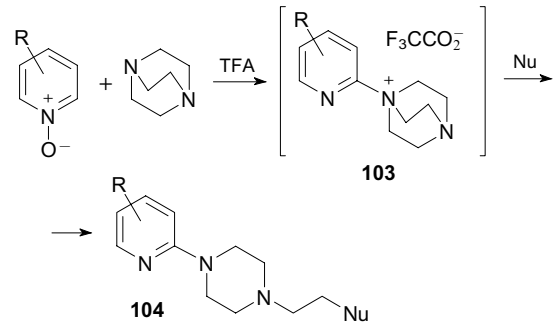



(*a*) $NR^2_3$ (5 – 6 equiv.), $(CF_3CO)_2O$ (3 equiv.), $CH_2Cl_2$, 0 – 25 °C;
(*b*) $Bu^n_4F$ or CsF (3 equiv.), DMF or THF, 60 – 90 °C ;
$R^1$ = Ar, Het, Br, OH; $NR^2_3$ = $NMe_3$, $BnNMe_2$, PyH

It should be noted that salts **102** are stable compounds isolated in moderate to high yields. The employment of these substrates substantially extends the scope of nucleophilic substitution of pyridine derivatives.

The one-pot synthesis of *N*-(2-azino)-*N′*-ethylpiperazine derivatives **104** involves quaternary salts **103**, which are *in situ* generated by the reaction of azine N-oxides with DABCO, and proceeds *via* the nucleophilic ring opening of the tertiary diamine (Scheme 83).[105]

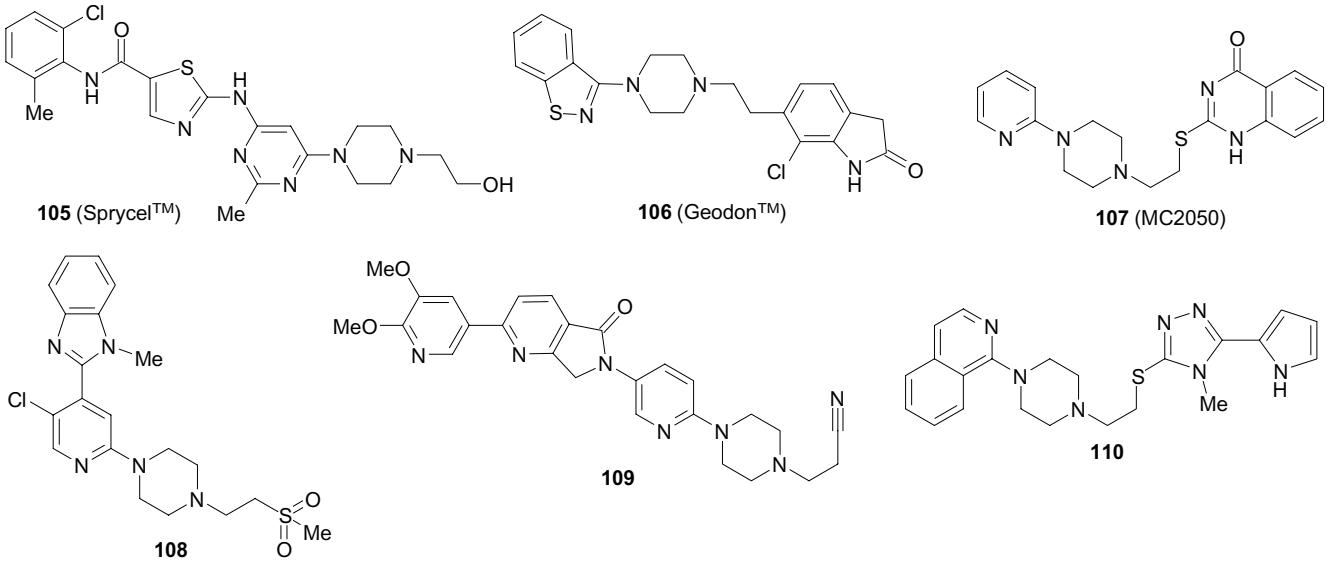
**Scheme 83**




R = EWG or EDG; EDG is an electron-donating group

The benefits of this approach are the efficiency, simplicity, mild conditions, environmental safety and the possibility of using substrates with both electron-withdrawing and electron-donating substituents. When considering the reactions of arynes with tertiary amines (see Section 2), we mentioned the generation of quaternary *N*-aryl-DABCO salts and their application in the synthesis of biologically important piperazine derivatives.[55, 105] We performed an independent study on the generation and synthetic applications of *N*-aryl-DABCO salts[106] and developed a new method for the synthesis of 1,4-disubstituted piperazine derivatives based on DABCO as a source of the *N*-ethylpiperazine moiety. *N*-Hetaryl-*N′*-ethylpiperazine is a structural moiety that is present in many potential pharmaceutical agents, as well as in medications.[106] These biologically active derivatives involve compounds **105** (anticancer drug), **106** (atypical antipsychotic drug), **107** (PARP-

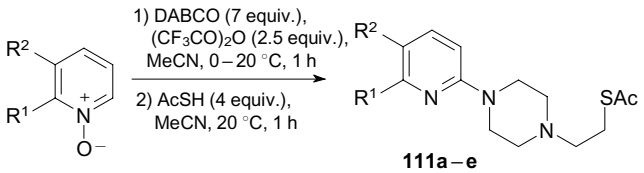
**Structures 105 – 110**



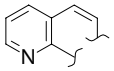

1 inhibitor), **108** (SMO inhibitor), **109** (PI3K inhibitor) and **110** (anti-neurodegenerative drug).

A series of *N*-(2-azino)-*N′*-ethylpiperazines, *e.g.*, compounds **111a – e**, were synthesized *via* the ring opening of DABCO with thioacetic acid (AcSH) as the nucleophile using a broad range of appropriate heterocyclic N-oxides (Scheme 84).[106] With a few exceptions, the amination occurs with high regioselectivity at the sterically unhindered α position of the pyridine ring.

**Scheme 84**

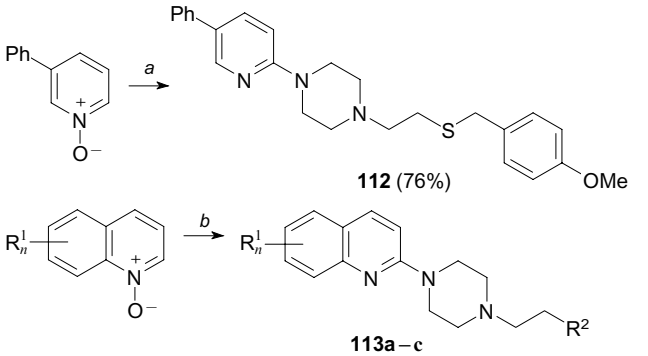



$R^1$ = H: $R^2$ = $CH_2CO_2Me$ (**a**, 45% yield), $NHC(O)CF_3$ (**b**, 71%), 1-methylbenzimidazol-2-yl (**c**, 50%); $R^1 – R^2$ is benzo (**d**, 96%);

 (**e**, 79%)

The employment of other S-nucleophiles in the ring opening reactions of DABCO made it possible to substantially extend the diversity of the reaction products, including pyridine derivatives **112** and quinoline derivatives **113a – c** (Scheme 85).[106]

**Scheme 85**

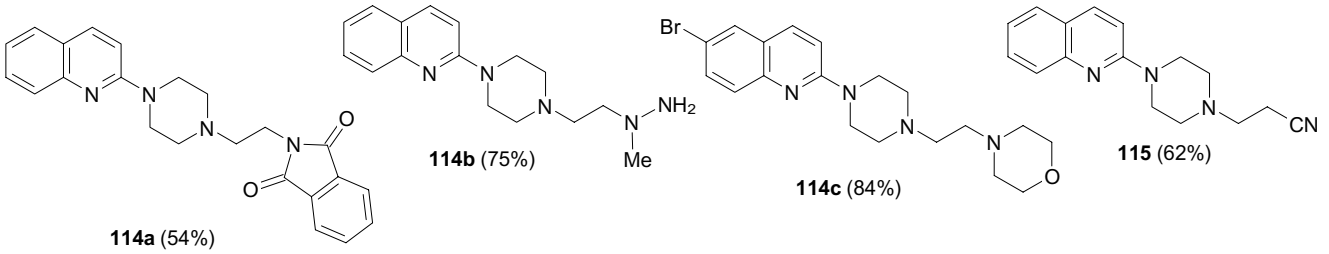



(*a*) 1) DABCO (7 equiv.), $(CF_3CO)_2O$ (2.5 equiv.), MeCN, 0 – 20 °C, 1 h; 2) 4-$MeOC_6H_4CH_2SH$ (4 equiv.), MeCN, 20 °C, 12 h;
(*b*) 1) DABCO (7 equiv.), $(CF_3CO)_2O$ (2.5 equiv.), MeCN, 0 – 20 °C, 1 h; 2) $R^2SH$ (4 equiv.), MeCN, 20 °C, 12 h; $R^1_n$ = H, $R^2$ = Ts (**a**, 22% yield); $R^1_n$ = 5-Cl-8-OMe, $R^2$ = SPh (**b**, 81%); $R^1_n$ = 6-Br, $R^2$ is benzothiazol-2-ylthio (**c**, 50%)

Apart from S-nucleophiles, N- and C-nucleophiles, *e.g.*, quinoline derivatives **114a – c** and **115**, were also employed in this reaction.

This procedures served as the basis for the one-pot synthesis of PARP-1 inhibitor **107** in 65% yield, while the procedure for the preparation of this compound developed earlier involved two steps and gave the target product in 45% yield.[107]

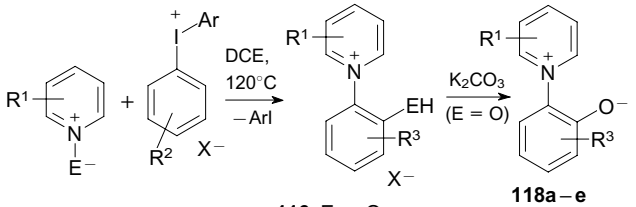
**Structures 114, 115**



The direct vicinal disubstitution of pyridines is an unusual reaction of diaryliodonium salts with pyridine N-oxides or N-amidates.[108] This new efficient one-step route to *ortho*-disubstituted benzenes (pyridinium phenols **116** and pyridinium anilines **117**) from available starting compounds is accomplished *via* arylation and 1,3-radical rearrangement on heating.

Pyridinium phenols and anilines are of great interest as synthetic building blocks,[109] valuable optical materials[110] and alkaloid components[111] (Scheme 86).

**Scheme 86**



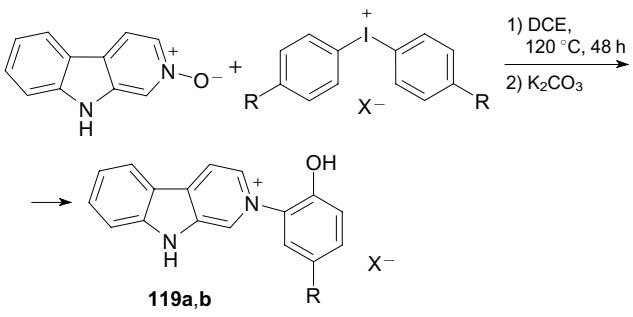

**116**: E = O;
**117**: E = $NSO_2Ar$

**118a–e**

Betaines **118** were synthesized in high yields by heating equimolar amounts of N-oxide and diaryliodonium salt to 120 °C followed by the addition of 1 equiv. of $K_2CO_3$. This method has a broad scope of applications and is suitable for various substituted N-oxides and diaryliodonium salts. Examples of such compounds are listed in Table 18.[108] It should be noted that the vicinal substitution of unsymmetrical diaryliodonium salt is controlled by steric factors.

The utilty of this transformation was demonstrated with the synthesis of two β-carboline alkaloids **119a**,**b** from β-carboline *N*-oxide (Scheme 87).[108]

**Scheme 87**



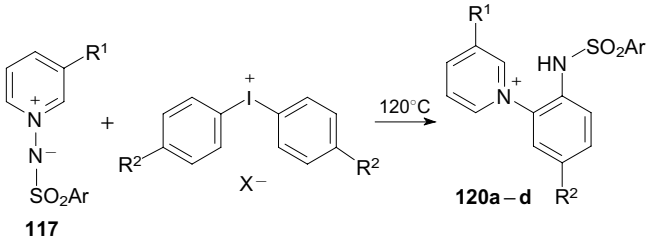

**119a**,**b**

R = H, X = $PF_6$ (**a**, 90% yield); R = Br, X = OTf (**b**, 87%)

**Table 18**. Products of vicinal disubstitution of diaryliodonium salts with pyridine N-oxides (see Scheme 86).[108]

| Iodonium salt | Product | $R^1$ | $R^3$ | Yield (%) |
|---|---|---|---|---|
| $Ph_2I^+PF_6^-$ | **118a** | 4-Me | H | 85 |
| $Ph_2I^+PF_6^-$ | **118b** | 3-F | H | 89 |
| $Ph_2I^+PF_6^-$ | **118c** | 4-CN | H | 58 |
| $(p\text{-Tol})_2I^+TfO^-$ | **118d** | 4-Me | 4-Me | 60 |
| $(o\text{-Tol})MesI^+TfO^-$ | **118e** | 4-Me | 2-Me | 45 |

**Scheme 88**




**117**

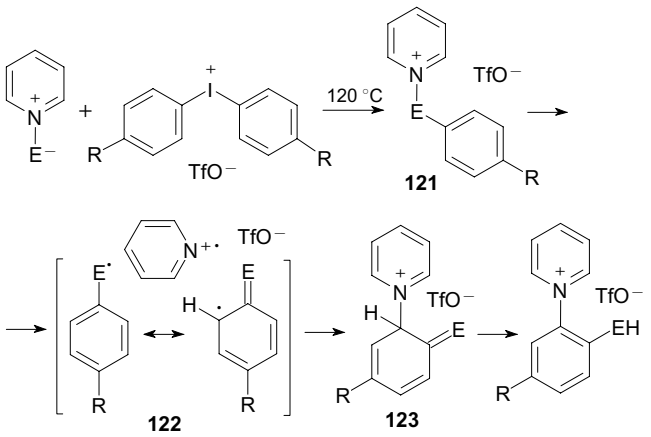
**120a–d**

X = $PF_6$ (for $R^2$ = H), OTf (for $R^2$ = Me); Ar = *p*-Tol: $R^1 = R^2$ = H (**a**, 45% yield); $R^1$ = Cl, $R^2$ = H (**b**, 78%); $R^1$ = OEt, $R^2$ = Me (**c**, 73%); Ar = 4-$BrC_6H_4$, $R^1$ = H, $R^2$ = Me (**d**, 75%)

Apart from N-oxides, amidates **117**t can be employed in these reactions.[108] For example, this approach was applied to prepare pyridinium anilines **120a–d** (Scheme 88).

A plausible mechanism for vicinal disubstitution, which was supported by special experiments and calculations (density functional theory, DFT), involves: 1) arylation of pyridine N-oxide or N-amidate with diaryliodonium salt giving intermediate **121**; 2) heat-induced homolytic cleavage of an N–O or N–N single bond in intermediate **121** to form a radical pair consisting of the pyridine radical cation and heteroatomic radical **122** (phenoxyl or its aza analogue); 3) recombination of radicals in a solvent cage to form the C–N bond in intermediate cation **123**; 4) tautomeric transformation of cation **123** into the reaction product (Scheme 89).

**Scheme 89**




**121**

**122**

**123**

E = O, $NSO_2Ar$

Although the application of azine N-oxides as arylating agents implies only the introduction of pyridine, quinoline, isoquinoline and some other related heterocyclic moieties into the molecule, these reactions are of importance in synthetic chemistry due to simplicity and no need for strong bases. Besides, in some cases the pyridine functionalization at the α position by means of catalytic methods is impracticable because of the formation of stable transition metal complexes.[112] It should also be noted that halogenated pyridines required for catalytic reactions are less commercially available and are more difficult to synthesize compared with N-oxides, which can easily be prepared by the one-step oxidation of pyridines.

## 5. Conclusion

The review summarize recent advances in the synthesis of various derivatives of aromatic and heteroaromatic amines using *in situ* generated arynes and also diaryliodonium salts and azine N-oxides as arylating agents. A common feature of these methods is that they do not require transition metal-based catalysts. Transition metal compounds, as well as phosphine ligands needed for the construction of active catalytic systems, are expensive and toxic. For this reason, catalytic methods are, in general, costly and, besides, need special techniques to purify target compounds from microimpurities of transition metals and ligands, thus increasing the cost price of the products. Another limitation of catalytic methods is associated with their low compatibility with a number of functional groups in the substrate molecule. The advantage of the non-catalytic methods considered in this review over catalytic procedures can be exemplified by the N-arylation of tertiary amines. Catalytic methods for arylation of primary and secondary amines giving secondary and tertiary arylamines, respectively, are well known and are widely used in routine synthetic chemistry. Under these conditions, quaternary N-aryl-substituted ammonium salts cannot be synthesized by N-arylation of tertiary amines. The arylation of tertiary amines with arynes and the amination of N-oxides with tertiary amines, as it was demonstrated in this review, can be efficiently applied for the *in situ* generation of aryl-containing quaternary ammonium salts. These salts have great synthetic potential and, in turn, can be employed in subsequent transformations for the preparation of organic compounds with different structures.

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