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Harnessing the oxidative potential of iodobenzene diacetate in unlocking azacyclic diversity (C_3–C_6 rings)

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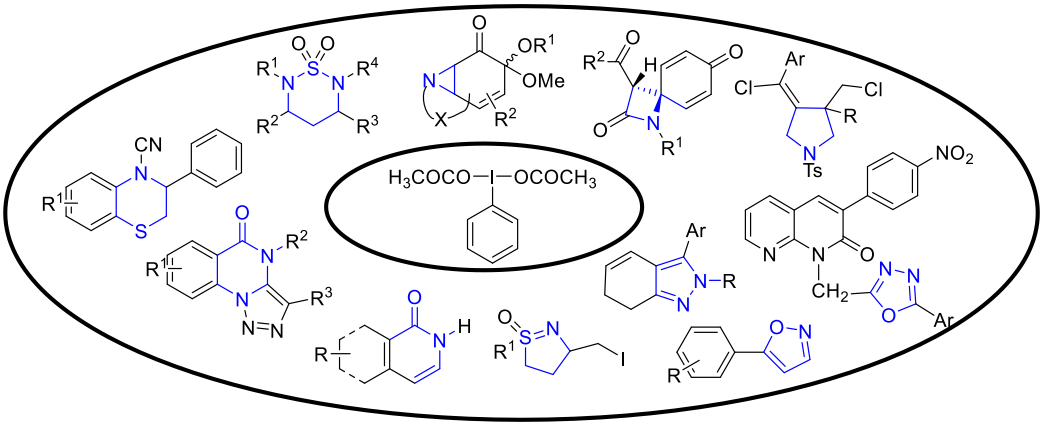
Abstract

(Diacetoxyiodo)benzene ($PhI(OCOCH_3)_2$), (DAIB or DIB) also known as phenyliodine(III) diacetate (PIDA) or iodobenzene diacetate (IBD) stands as one of the most versatile and widely employed hypervalent iodine reagents in organic synthesis. Renowned for its strong oxidizing properties, PIDA has become a cornerstone in modern methodology, extending far beyond its established utility to play a pivotal role in heterocyclic ring construction. This review focuses specifically on its role in synthetic methodologies that enable the construction of nitrogen-containing heterocyclic rings, providing a critical and comprehensive analysis of advances reported from 2013 to till date.



Keywords: Hypervalent iodine reagents, phenyliodine(III) diacetate (PIDA), nitrogen containing, heterocyclic rings

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1. Introduction

Hypervalent iodine reagents are vital tools in modern organic synthesis, functioning as versatile reagents and catalysts. Their chemistry parallels transition-metal systems, enabling innovative methodologies, while also offering unique transformations unattainable with non-iodine reagents. The field's significance is underscored by extensive recent literature, including numerous books and reviews.[1–25] Hypervalent iodine reagents have attracted significant attention in the organic chemistry community owing to their remarkable versatility, high selectivity, mild reaction conditions, environmental compatibility, and ready commercial availability compared to many traditional reagents. Their synthetic utility arises from their ability to promote selective oxidation as well as bond formation and cleavage processes, including oxidation, halogenation, amination, C–H activation

and functionalization, cross-coupling reactions, phenolic dearomatization, rearrangements, and the construction of spiro- and other heterocyclic frameworks.[26–41] Consequently, hypervalent iodine reagents have been extensively employed in the synthesis of complex molecules, including natural products and key intermediates.[42,43] In recent years, substantial progress has been made with new classes of hypervalent iodine compounds, such as pseudocyclic reagents, benziodoxole sulfonates, water-soluble and recyclable iodine reagents, and polymer-supported systems, further expanding their applicability, including reactions in aqueous media and catalytic processes.[44–48] These compounds contain iodine in higher oxidation states, most commonly +1, +3, +5, and +7, which impart strong electrophilic character. Organic iodine (III) reagents, constitute the most widely used class and include phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), phenyliodine(III) dibenzoate, iodosylbenzene, [hydroxy(tosyloxy)iodo]benzene (HTIB), 1-hydroxy-1,2-benziodoxol-3(1H)-one (IBA), and related benziodoxole derivatives.

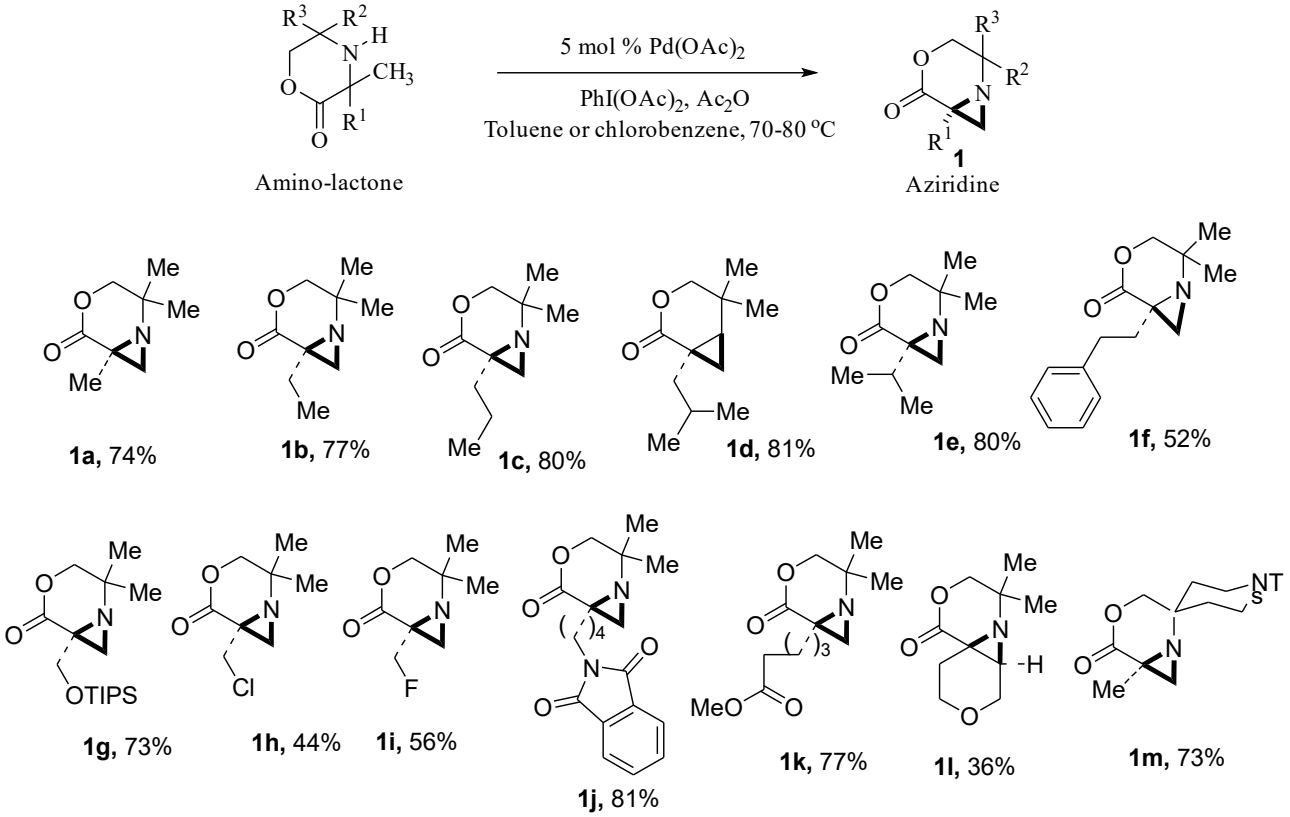
Among these, PIDA has emerged as the prototypical [bis(acyloxy)iodo]arene reagent, valued for its stability, ease of handling, and broad functional group tolerance. Its ability to act as a mild yet powerful oxidant has enabled a wide range of transformations, including oxidative cyclizations, C–H functionalizations, and rearrangements that are particularly effective in heterocycle construction.[49–61] As such, PIDA continues to serve as a benchmark reagent in hypervalent iodine chemistry, providing a foundation for both classical methodologies and the development of newer, more specialized iodine (III) systems.

Against this background, the present review focuses on recent developments in the use of the iodine (III) reagent PIDA, with special emphasis on its role for the synthesis of diverse nitrogen containing heterocyclic scaffolds; literature coverage is through the end of 2013 to till date.

2. Reactions offering cyclic products

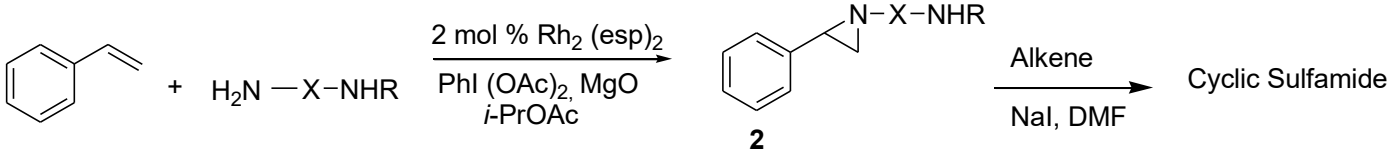
2.1. 3-Membered compounds with one heteroatom (nitrogen): aziridines

Selective transformation of aliphatic secondary amines, the morpholines, containing methyl group proximal to the unprotected nitrogen into the strained three-membered heterocycles, aziridines **1**, on treatment with palladium(II) acetate in the presence of $PhI(OAc)_2$ oxidant is reported by McNally *et al*. (2014). The reaction offers C-H functionalization platform via the formation of four-membered intermediates before reductive elimination to form C-N bond. The reaction has a broad tolerance for a variety of substituents on the reactant morpholinone. Alkyl substituents and substituents containing aromatic rings, protected hydroxyl, sensitive chloromethyl and fluoromethyl motifs, esters and protected amines are well tolerated in the aziridination reaction. The reaction is also compatible with methylene C-H bonds, the substrates containing substituents other than methyl groups distal to the carbonyl motif as in piperidine substituted morpholinone and amines not possessing lactone framework but the product formed is not aziridine instead acetoxylation occurs. (Scheme 1)[62]

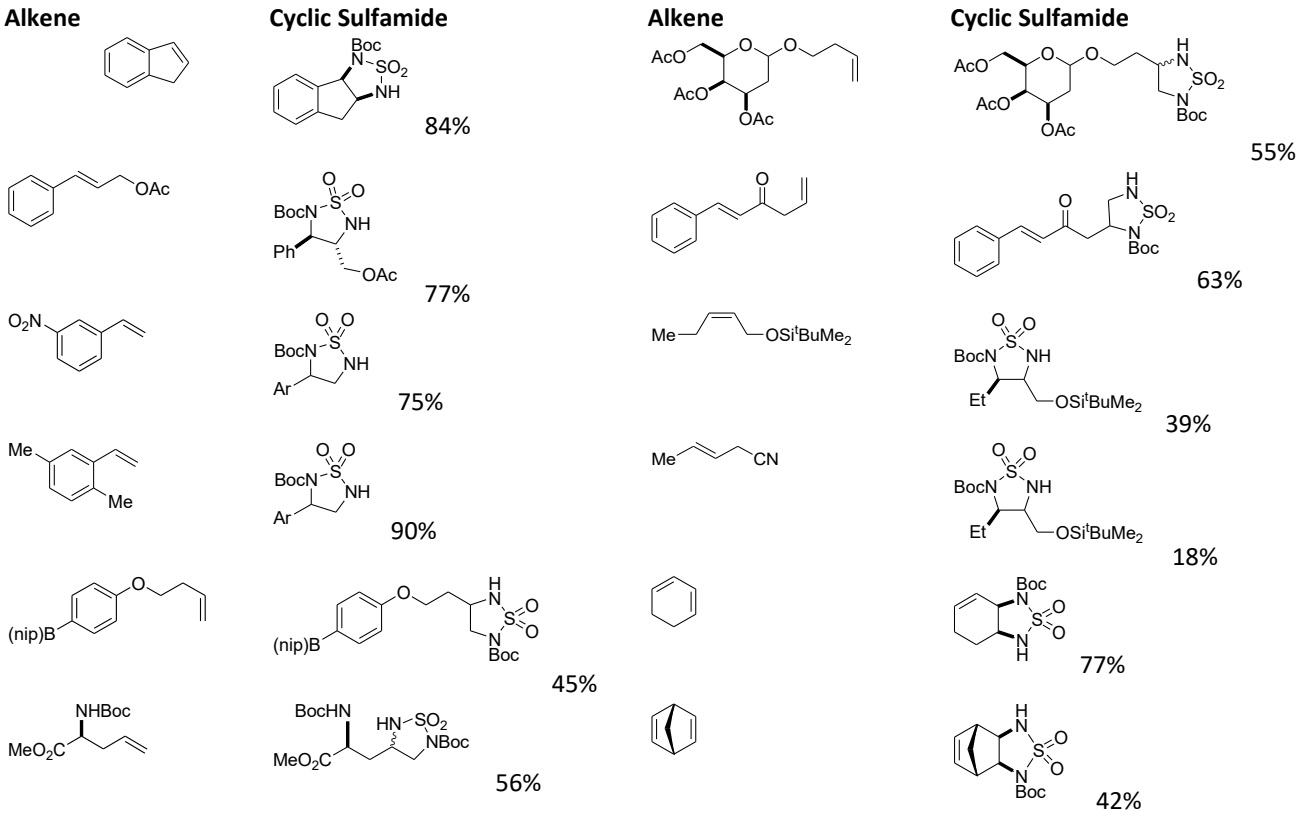


Scheme 1. Conversion of morpholine into aziridine using $Pd(OAc)_2$/$PhI(OAc)_2$

Alkenes on treatment with bifunctionalized N-source $NH_2S(O)_2NHBoc$ using dirhodium catalyst $Rh_2(esp)_2$ bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) (2 mol%) and hypervalent iodine oxidant $PhI(OAc)_2$, MgO offered the products of C-N bond formation, the aziridines **2** which were further isomerized to the corresponding cyclic sulfamides in the presence of NaI-DMF at room temperature. The optimized protocol can also be performed in a single vessel by adding a solution of NaI in DMF, once the aziridination is complete, to obtain the corresponding sulphonamide products as the single isomers from a range of mono and disubstituted alkenes including the acyclic and cyclic ones (Scheme 2). The results with terminal alkenes are of high yield compared to cis- or trans disubstituted olefins and reaction is found to be most efficient with styrene-type reactants. The N-protected cyclic sulfamide derivatives are considerably labile for ring-opening to furnish mono-Boc diamine upon heating in aqueous pyridine and the effectiveness of the overall vicinal deamination technology is underscored in the preparation of natural products (±)-enduracididine and (±)-allo-enduracididine.[63]



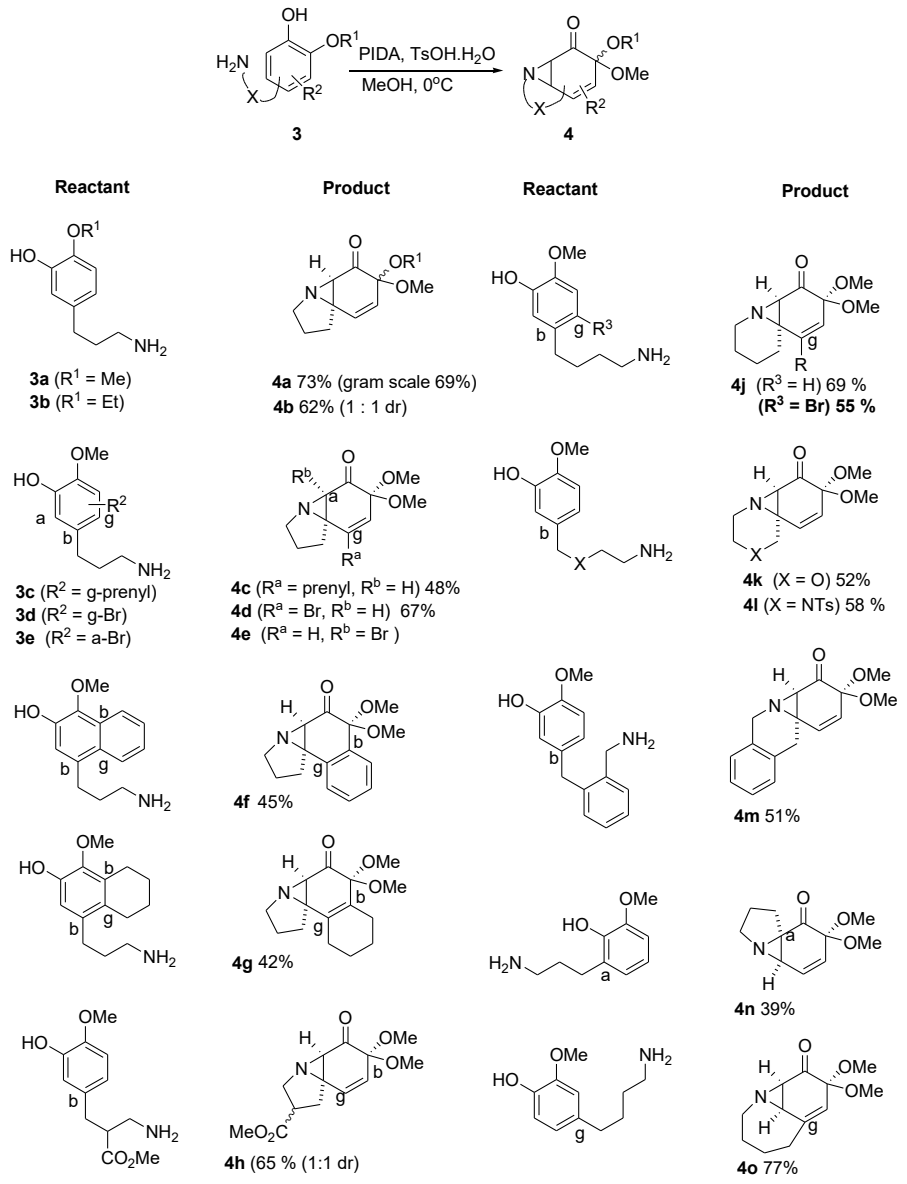
X = CO; R= Boc, CH_2Ph, CO_2Me



Scheme 2: Styrene aziridination using bifunctional nitrogen sources

The synthetic utility of hypervalent iodine (III) reagent (PIDA) in oxidative dearomatization and in situ aziridination of phenolic amines to functionalized unactivated aziridines has been explored. Oxidation of meta-phenolic amines by PIDA in methanol affords 5,3,6-tricyclic aziridine **4**. β, γ-Disubstituted subunit smoothly afforded the architecturally interesting 5,3,6,6-tetracyclic aziridines **4f** and **4g** in 45% and 42% yield respectively.

The oxidative dearomatization and aziridination of ortho-phenolic amines with primary amino group at the α position of the phenolic ring yields 5,3,6- tricyclic aziridine in 39% yield. While para-phenolic amine having a primary amino substituent at the γ position of phenolic core gave 7,3,6-tricyclic aziridine in 77% yield (Scheme 3).[64]

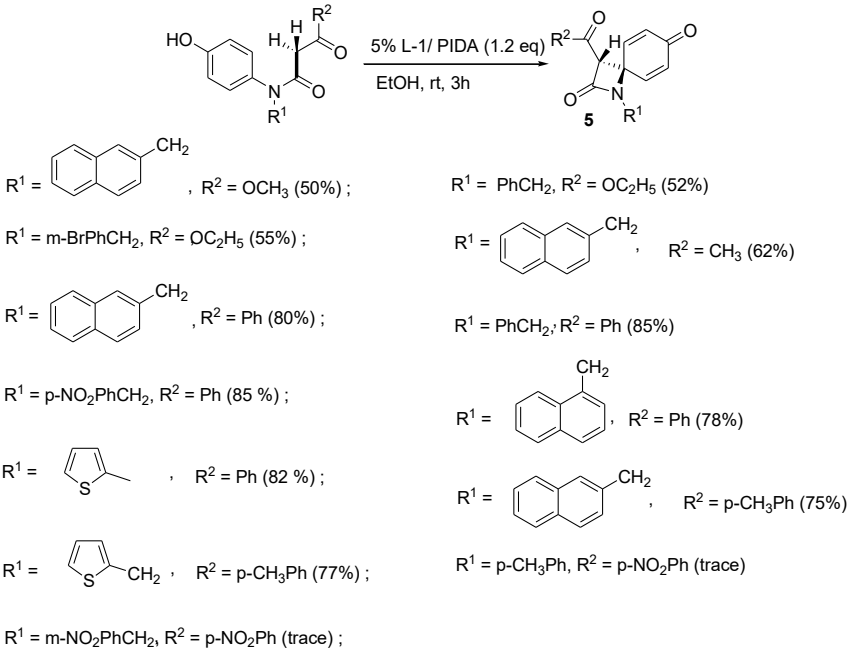


Scheme 3: IBD mediated aziridation of phenolic amines

2.2 4-Membered compounds with one heteroatom (nitrogen): β-lactams

Xu and coworkers synthesised β-lactam derivatives **5** by employing homochiral porous MOFs as heterogeneous catalysts and PIDA oxidant in ethanol through C-C oxidative coupling reaction. The authors prepared enantiopure organic ligands as (S)-H_3PIA and (R)-H_3PIA (5-(2-carboxypyrrolidine-1-carbonyl) isophthalic acid) and used them for constructing the molecular organic frameworks namely, two enantiomeric pairs of HMOFs, namely, $[Cu_3((S)$- PIA)2(1,4-dioxane)$(H_2O)_2]\cdot$2(1,4-dioxane)$\cdot H_2O$ (L-1), $[Cu_3((R)$-PIA)$_2$(1,4-dioxane)$(H_2O)_2]\cdot$2(1,4-dioxane)$\cdot H_2O$ (D-1), $[Cu_4((S)$-PIA)$_2$.5$(H_2O)_3]\cdot$x(guest) (L-2) and $[Cu_4((R)$-PIA)$_2$.5$(H_2O)_3]\cdot$x(guest) (D-2). Out of the L1 and D1, it was found that for catalyst L-1, the reaction is found to be applicable for a variety of functional groups. The effect of R^2 group of phenol amides is very prominent, with alkoxy or alkyl group, moderate yields of the products are obtained while with phenyl or 4-methyl phenyl

the reaction is more efficient and yields are more than 75% and strong electron-withdrawing nitryl phenyl is capable of producing the products only in trace amounts.[65] (Scheme 4)

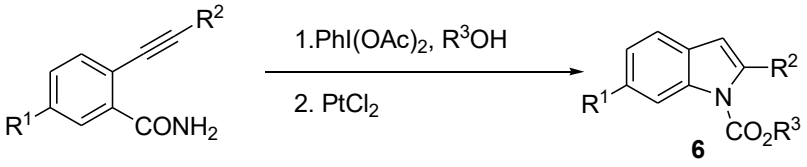


Trace yield on the basis of TLC detection and rest yields were isolated

Scheme 4: Homochiral porous MOFs- IBD in the synthesis of β-lactam derivatives

2.3. 5-membered compounds with with one/two/three heteroatoms

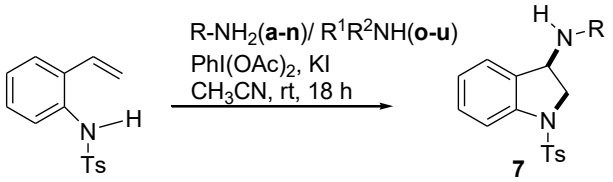
2.3.1. 5-membered compounds with one heteroatom (nitrogen). Okamoto *et al* in 2014 developed PIDA promoted Hofmann-type rearrangement of 2-alkynylbenzamides in the synthesis of indoles **6**. The study of effect of electronic nature of substituents revealed that yields of the products (82-91%) were independent of the electronic nature of the substituents. Although, the terminal alkyne was unsuitable under these conditions (Scheme 5). [66]

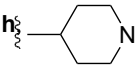
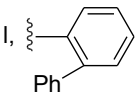
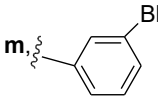
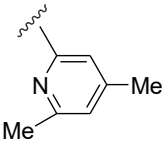


R^1 = F, R^2 = *n*-Bu, R^3 = Et (84%), R^1 = NO_2, R^2 = *n*-Bu, R^3 = Et (91%)
R^1 = OMe, R^2 = *n*-Bu, R^3 = Et (82%), R^1 = H, R^2 = Ph, R^3 = Et (84%)
R^1 = H, R^2 = *p*-Tol, R^3 = Et (66%), R^1 = H, R^2 = -$(CH_2)_3$OTs, R^3 = Et (100%)
R^1 = H, R^2 = *n*-Bu, R^3 = Bn (90%), R^1 = H, R^2 = H, R^3 = Et (33%)

Scheme 5: Conversion of alkynyl benzamides to indoles

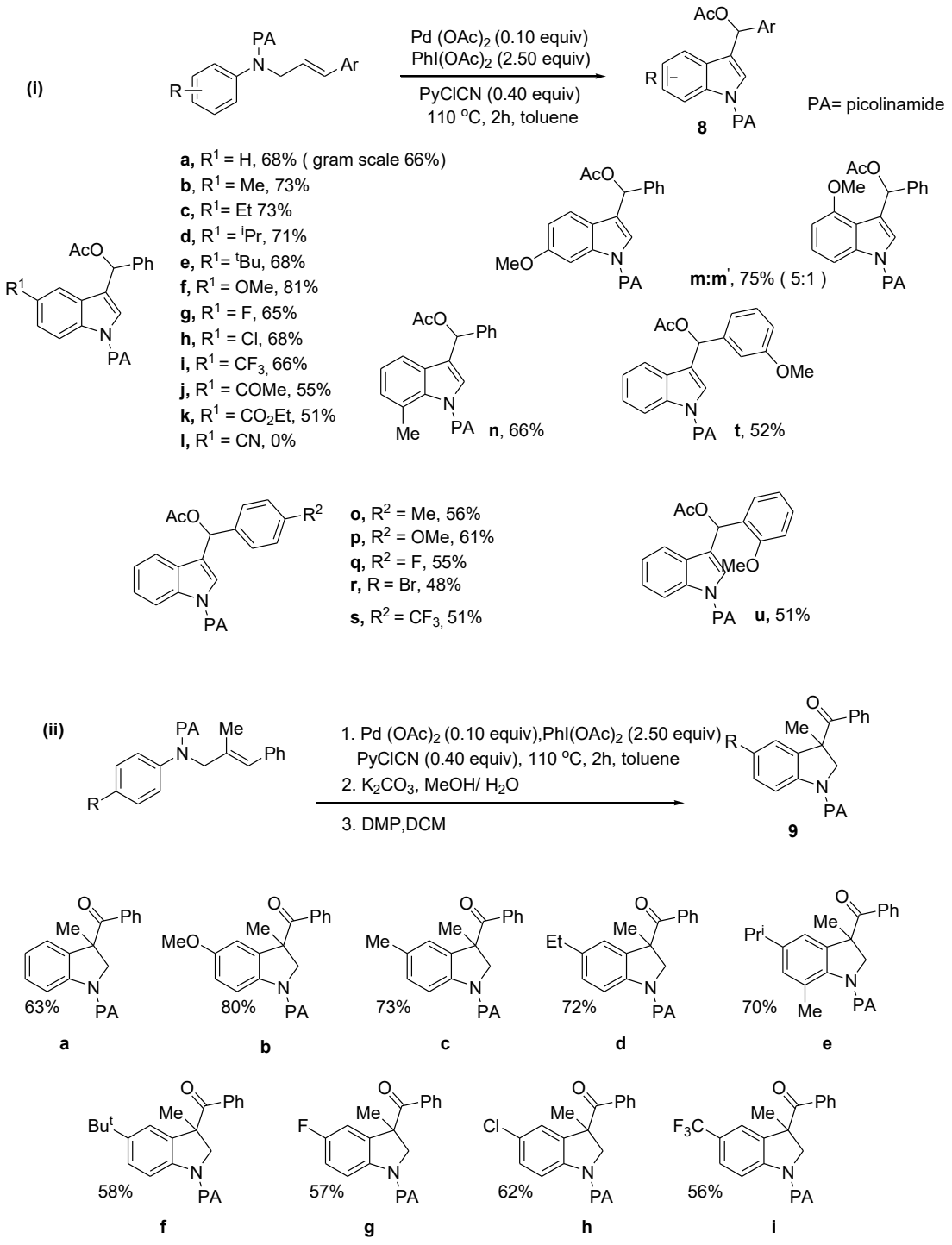
Synthesis of 3-aminoindoline derivatives **7** is achieved from terminal alkenes (1 equiv.) and a nucleophilic mono- or disubstituted amine (2 equiv.) using PIDA (2 equiv.), KI (1.2 equiv.) at ambient temperature without amine preactivation or protection through combined inter-/intramolecular oxidative deamination. The reaction was carried out on a 0.18 mmol scale in CH_3CN (0.1 M) at room temperature. The reaction can be performed with (i) alkylamines- amines having terminal alkene (**c**), pyridine (**e**), oxetane (**i**) (ii) aliphatic amines (**f-h**), however with *t*-butylamine only 20% yield was obtained (iii) arylamines (**k-m**), 2-aminotoludine gave only 42% yield (iv) disubstituted amines (**o-u**) (Scheme 6)[67].



R = **a**, cyclopentyl; **b**, Bn (64%); **c**, allyl (78%); **d**, $CH_2CH_2CH_2OCH_3$ (72%); **e**, C_7H_9N (62%); **f**, cyclohexyl (73%); **g**, Ph_2CH (57%); **h**,  N−CO_2Et(91%); **i**, C_3H_3O (3-oxetanyl) (94%); **j**, t-Bu (20%); **k**, Ph (68%); **l**,  (79%); **m**,  (79%); **n**,  (42%) **o**, C_4H_8 (pyrrolidine) (64%); **p**, C_8H_8 (isoindoline) (73%); **q**, C_4H_8O (morpholine) (78%); **r,** $C_{14}H_{14}$(dibenzylamine) (72%); **s,** C_9H_{10} (*N*-allylaniline) (82%); **t**, C_9H_{10} (N-allylaniline) (59%); **u**, C_9H_{10} (tetrahydroisoquinoline) (64%)

Scheme 6: Synthesis of 3-aminoindolines by using PIDA in room temperature

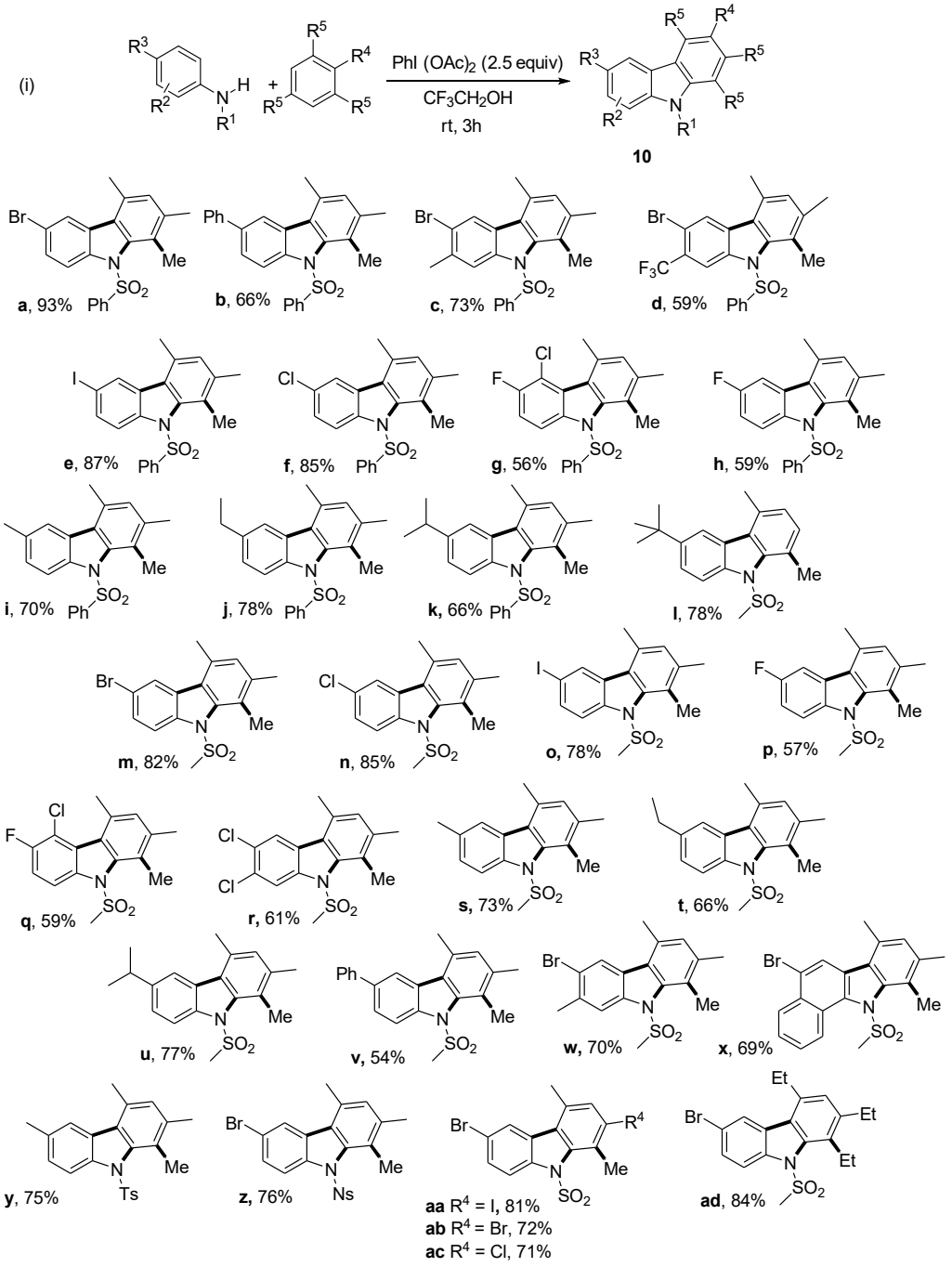
Karnakanti *et al* have studied oxidative arylacetoxylation of alkenes to obtain indole derivatives (**8**) from the cinnamyl anilines and indoline derivatives (**9**) from 2-methyl substituted cinnamyl anilines using palladium acetate and PIDA. The difunctionalization reaction is believed to proceed via arene palladation, olefin insertion, oxidation to hypervalent palladium(IV) intermediate using PIDA, followed by sequential acetoxylation and reductive elimination to obtain **8** (Scheme 7). With cinnamyl anilines, isomerization was obstructed and acetoxylation occured to offer **9**.[68]

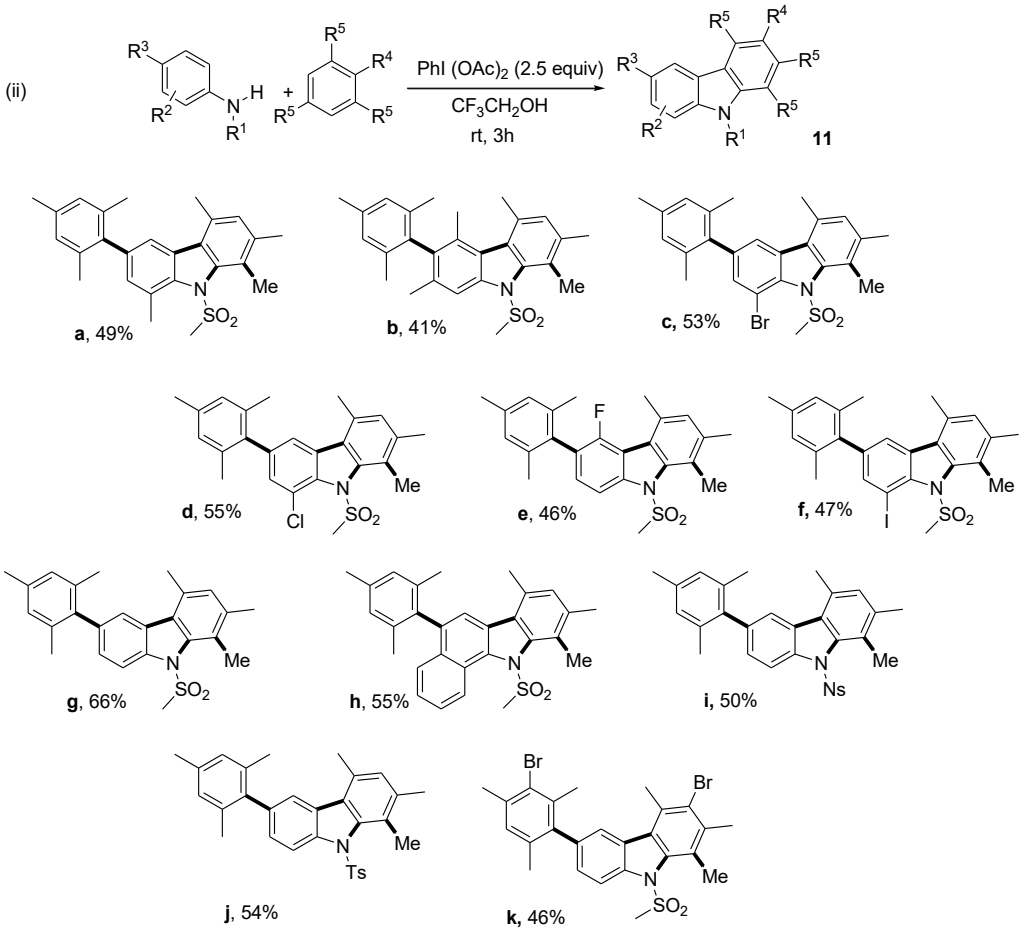


Scheme 7: Arylacetoxylation of alkenes to prepare indole and indoline derivatives

PIDA-assisted selective alkyl group migration in intermolecular dehydrogenative annulation for carbazole synthesis has been studied. The coupling reaction of 1,3,5-trialkylbenzenes with different sulfonyl substituted anilides in 2,2,2-trifluoroethanol (TFE) afforded multisubstituted carbazoles. 1,2,4-Alkyl-

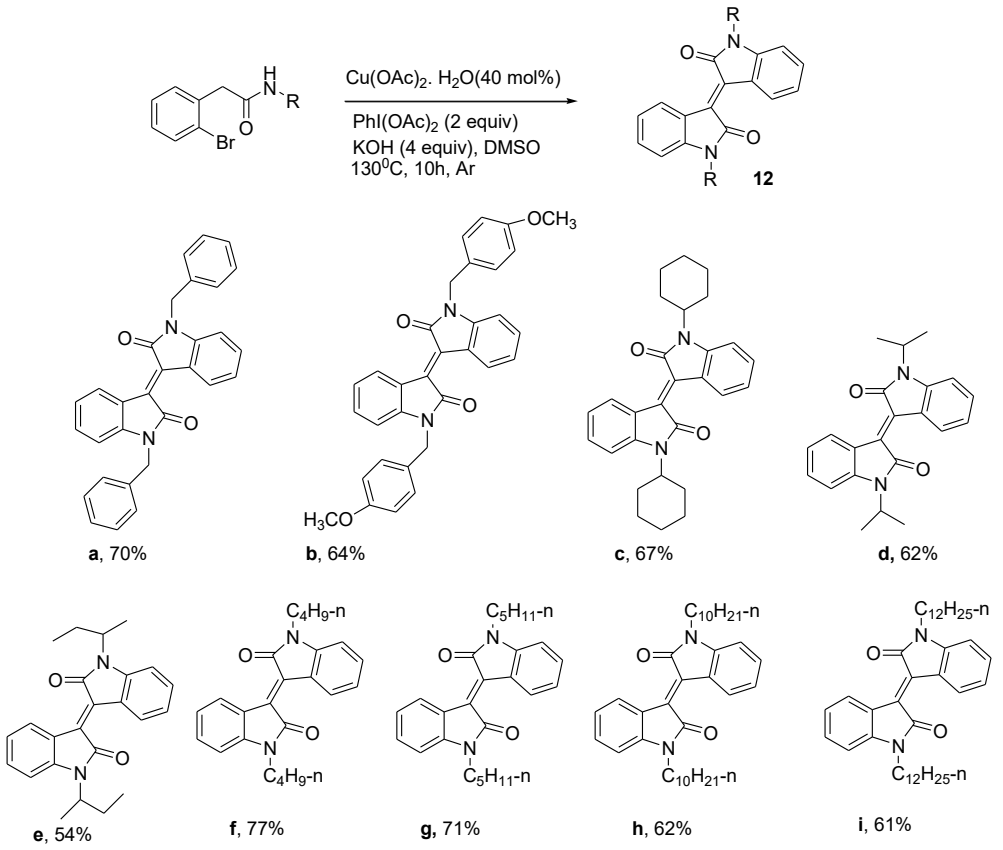
substituted carbazoles **10** containing electron-withdrawing substituents as well as electron-donating substituents (in 56-93% yields) were isolated. In addition, various disubstituted anilides also undergo similar reaction to give the corresponding carbazole products. The reaction with the substrates possessing H at the para position of sulfoanilide group is successful, however, the reaction proceeds with 3 equivalents of PIDA and the products **11** (42-66% yields) were obtained (Scheme 8)[69]





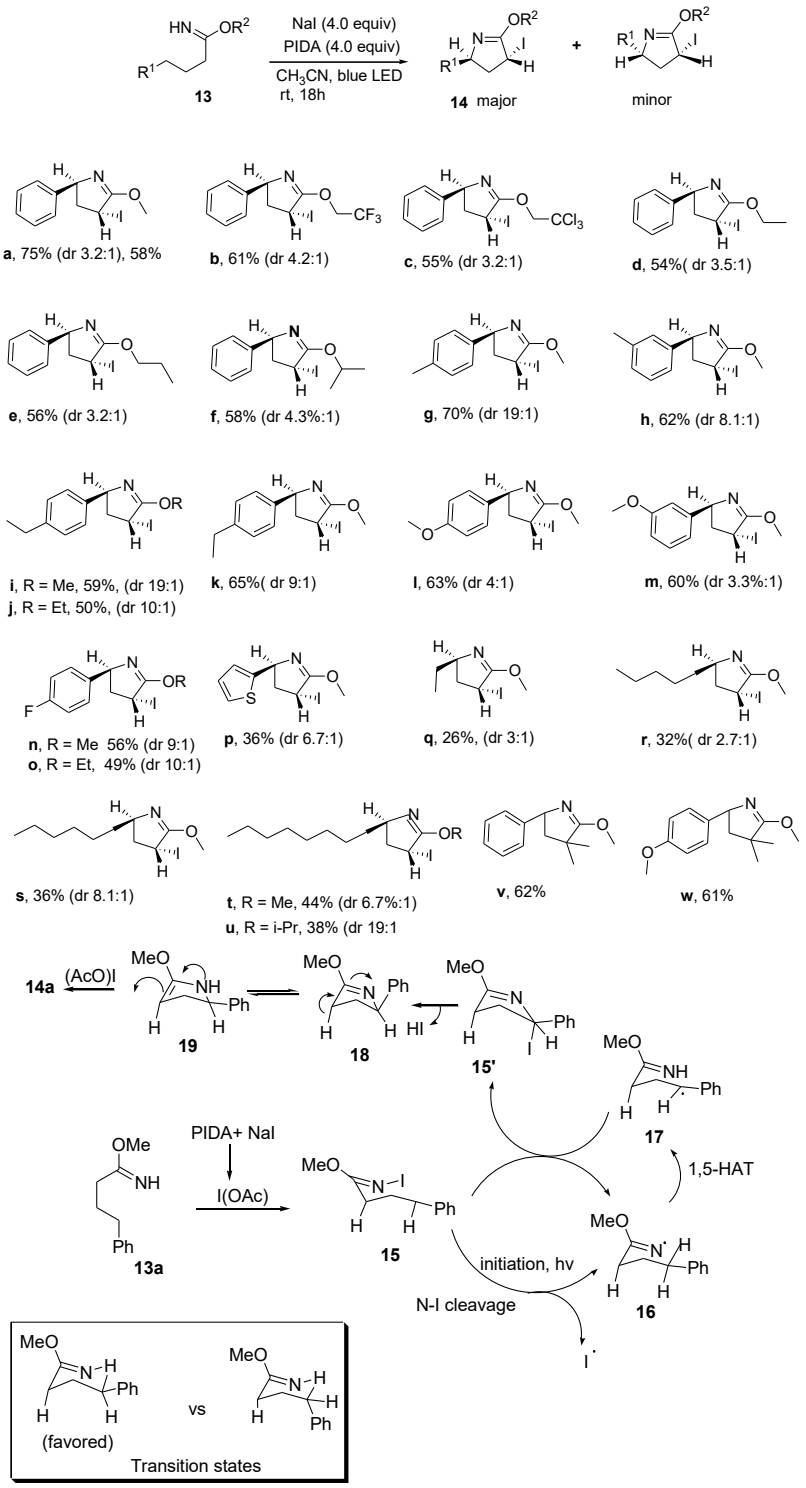
Scheme 8: $PhI(OAc)_2$-CF_3CH_2OH mediated coupling reaction of N-sulfonylanilides with 1,3,5-trialkylbenzenes (i) anilides with various sulfonyl substituents (ii) anilides with unsubstituted *para* position

The hypervalent I(III) assisted cyclization, oxidation and condensation of *o*-bromophenylacetamides under basic conditions using PIDA in DMSO to afford isoindigo derivatives **12** has been reported by Liu et al 2018. Use of copper (II) acetate monohydrate was necessary alongwith PIDA-KOH-DMSO. The desired reaction proceeds only in the presence of PIDA and copper(II) salt. Using other bases, K_2CO_3 or K_3PO_4, the reaction did not occur well (Scheme 9)[70]



Scheme 9. Synthesis of isoindigo derivatives from *o*-bromophenylacetamides using PIDA-$Cu(OAc)_2$. H_2O

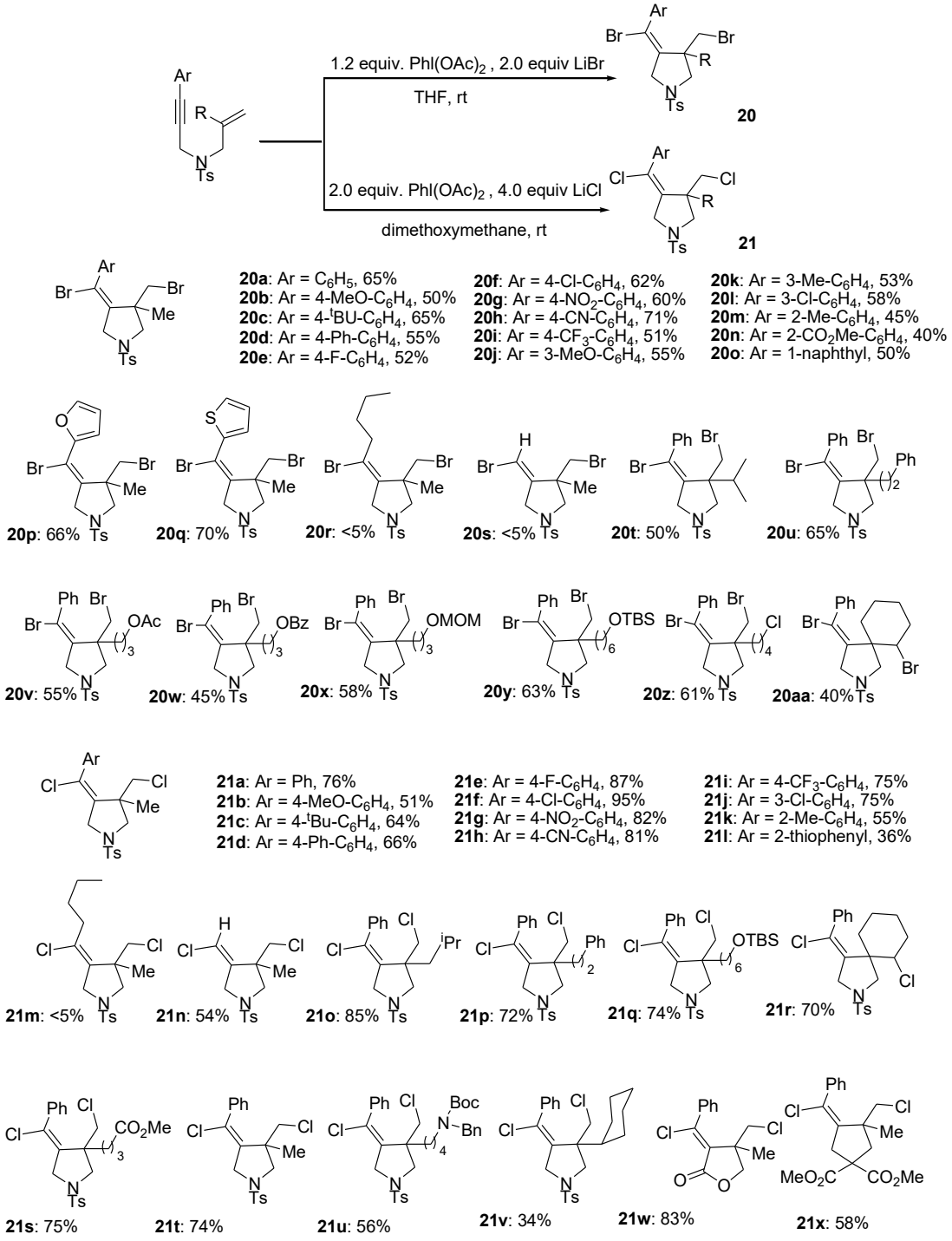
Kumar and coworkers developed a visible-light mediated chemoselective protocol for the synthesis of 4-iododihydropyrrole derivatives **14** from alkylimidates **13** using NaI/PIDA under blue LED light (λ_{max} = 455 nm). The intramolecular γ-C (sp^3)-H amidation reaction is proposed to proceed through the formation of N-iodobutylimidate **15** which is transformed to imidate N-radical **16** by N-I homolytic cleavage. The radical **16** through 1,5-hydrogen-atom-transfer (1,5-HAT) from the γ-C-H atom turns to carbon radical **17** which after abstracting iodine atom from A generates iodinated intermediate **15'** from which the key intermediate 1-pyrroline **18** is formed after nucleophilic attack of the imidate group onto the C-I bond. Tautomerization of **18** to **19** followed by nucleophilic attack by iodinemonoacetate (IOAc) gives the desired iododihydropyrrole via the less hindered thermodynamically favoured transition state. The reaction is applicable to (i) alkylimidates containing different O-alkyl groups, for instance, methyl, trifluoroethyl, trichloroethyl, ethyl, *n*-propyl and isopropyl groups (**b-f,** Scheme 10). With the ethyl-, n-propyl-, and isopropyl-substituted alkylimidates containing two possible sites of γ-C-H functionalization, the chemoselective products were formed due to the C-H BDE (BDE: bond dissociation energy) for the benzyl over the methyl or ethyl groups, (ii) 4-arylbutylimidates **g-k** containing electron-donating group, at the meta and para positions of the phenyl ring, halofunctional group such as fluoro at the para position of the aromatic ring gave the desired products. The reaction also works with hetarylimidate, long-chain aliphatic imidates containing stronger C-H bonds (BDE: benzylic 90 kcal/mol vs aliphatic 97 kcal/mol) and sterically hindered alkylimidates.[71]



Scheme 10: Synthesis of 4-iodo-3,4-dihydropyrrole derivatives and mechanistic aspects

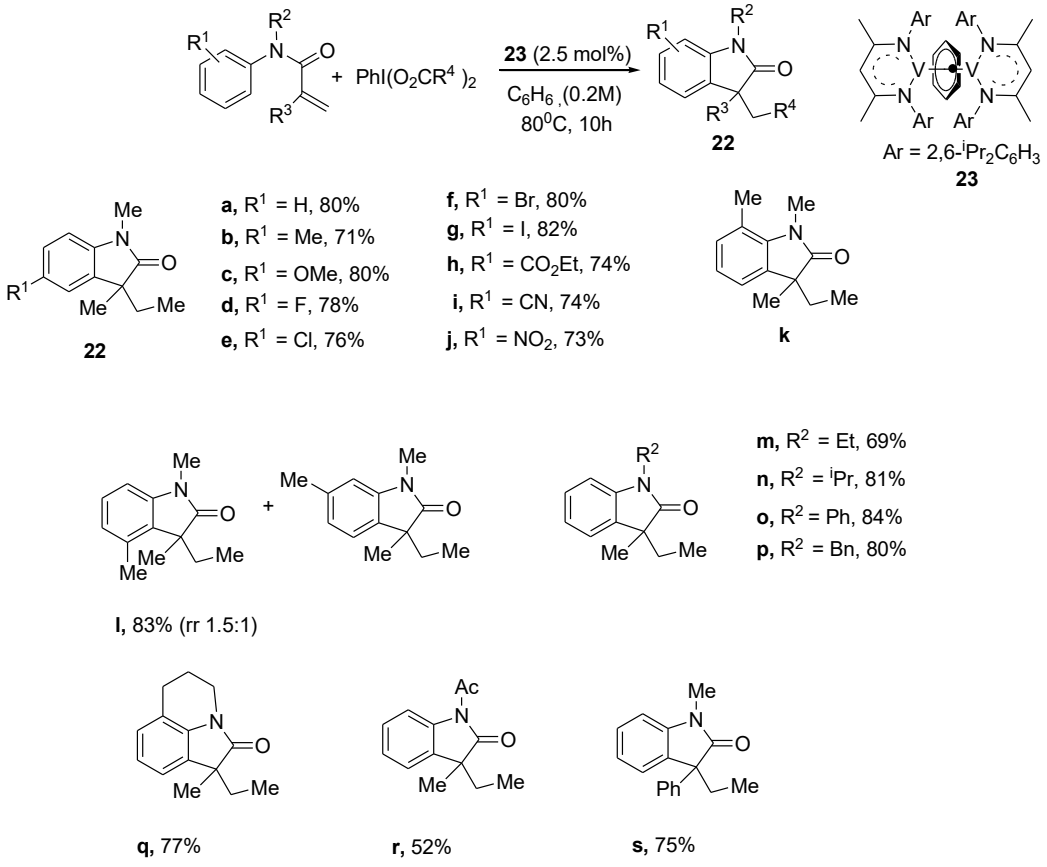
A highly stereoselective PIDA promoted dihalogenative cyclization of 1,6-enynes in the presence of lithium hailde has been described, the reaction with 2 equivalents of LiBr and PIDA (1.2 equiv) in THF, gave cyclized dibrominated **20** in 40-71% yields and the reaction tolerated the variety of substituents with product

independent of steric and electronic factors in 1, 6-enynes. While in dichlorinative cyclization with 2 equiv of PIDA and 4 equiv of LiCl in dimethoxymethane at room temperature for 16 h afforded the products **21** in 36-95% yields. By this method Dong et al., explored a metal-free pathway for cyclization of 1,6-enynes via a radical mechanism, leading to a functionalized cyclic products (Scheme 11).[72]



Scheme 11: Dihalogenative cyclization of 1,6-enyne compounds using PhI $(OAc)_2$ and lithium halide

Zhang et al. in 2021 have reported the alkene alkylarylation using iodobenzene diacetate to obtain quaternary carbon-centered indolinones **22**. A benzene-bridged divanadium complex (μ-η6:η6-C_6H_6)[V(Nacnac)]$_2$ **23** was used for the decarboxylative alkylation. The reaction worked well with either electron-withdrawing or electron-releasing substituents on the benzene ring. Also, the reaction was found to be successful with ortho- or meta-substituted N-aryl-N-methylmethacrylamides and regioisomeric indolinones were obtained in good yields. Further, the reactants having aliphatic or aromatic substituents on the nitrogen offered the expected products in good to excellent yields. It is important to note that N-benzyl-N-phenylmethacrylamide was found to be highly reactive to give the indoline as the exclusive product as a result of 5-exo cyclization on aniline. The rigid reactant 1-methacryloyl-1,2,3,4-tetrahydroquinoline gave the expected tricyclic product. The N-phenylmethacrylamide with electron-deficient acetyl substituent also faced the reaction smoothly to offer N-acetyl indolinone. In addition, for R^3, replacing methyl to phenyl gave the expected product in good yield (Scheme 12).[73]

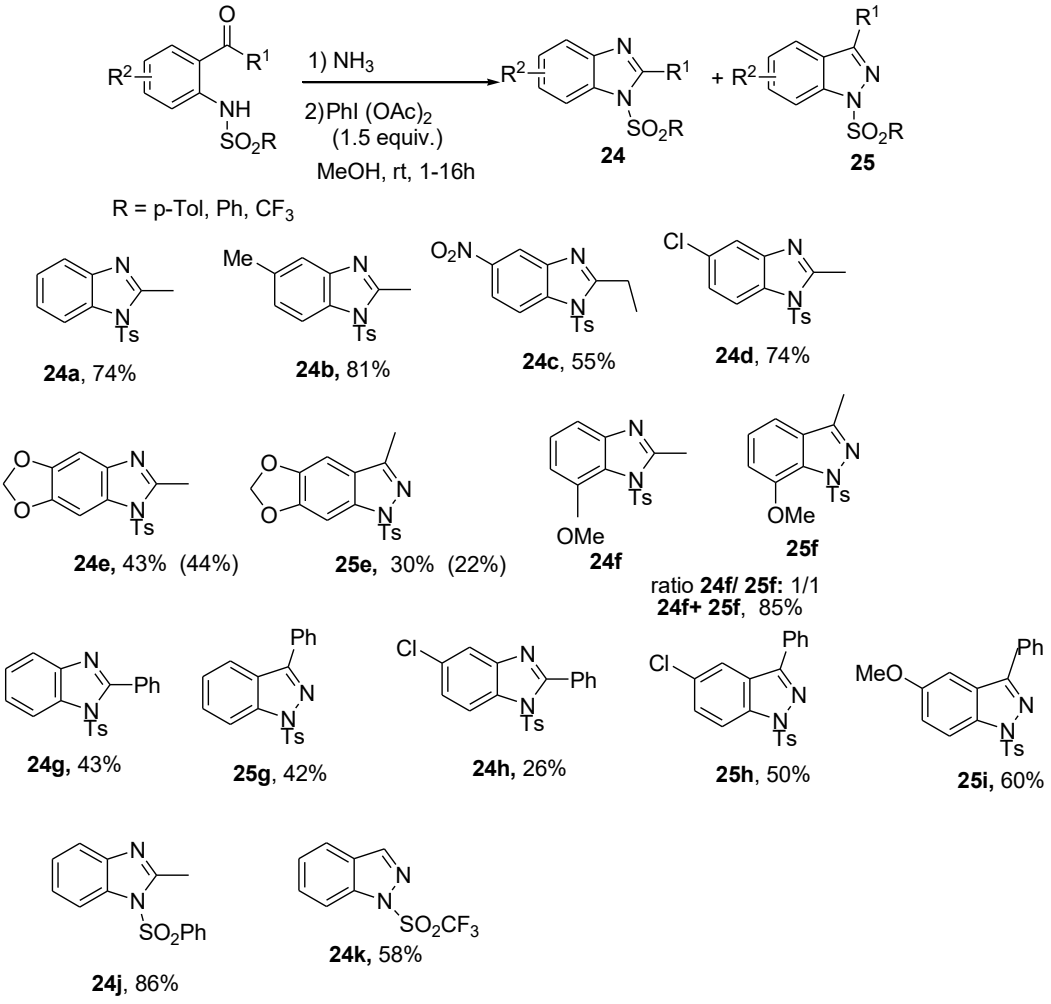


Scheme 12: Conversion of alkenes to indolinones using divanadium complex

2.3.2 5-membered compounds with two heteroatoms

2.3.2.1 With two nitrogens. The application of iodobenzene diacetate in Beckmann-type rearrangement of *o*-aminoaryl N-H ketimines in synthesis of functionalized N-Ts benzimidazoles has been explored by Zhang et al., in 2015. The reaction occurred in two steps: first, ortho-aminoaryl ketones react with ammonia in methanol to form o-aminoaryl N-H ketimines. These ketimines undergo cyclization in methanol with (PhI(OAc)$_2$) as an

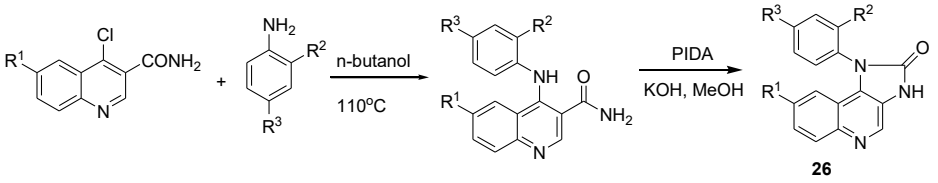
oxidant, yielding benzimidazoles **24**. Depending on the substituents, the [1,2]-migration of the aryl moiety leading to benzimidazoles **25** compete with the formation of indazoles through an intramolecular cyclization (Scheme 13).[74]



Scheme 13: PIDA mediated Beckmann-type rearrangement of o-aminoaryl N-H ketimines

Ladani and Patel have reported a study on intramolecular cyclization and Hofmann rearrangement upon treatment of 4-(substituted-phenylamino)-6-substituted-quinoline-3-carboxamide with PIDA in KOH/methanol at room temperature for 1 h affording 1-and 8-substituted-1H-imidazo[4,5-c] quinolin-2(3H)-one derivatives **26**. The screening studies of these imidazo[4,5-c] quinolones **26** for various pharmacological activities viz., antimicrobial (antibacterial activity against Streptococcus pneumoniae, Bacillus subtilis, Clostridium tetani, E. coli, Salmonella typhi. Vibrio cholera and antifungal activity against Candida albicans, Aspergillus flavus, antitubercular (M. tuberculosis $H_{37}Rv$) and antimalarial activity (P. falciparum) have been reported. Compounds viz., 8-methyl-1-phenyl-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one, 1-(4-chlorophenyl)-8-methyl-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one, 1-(2-fluorophenyl)-8-methyl-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one, 8-chloro-1-(4-fluorophenyl)-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one, 8-fluoro-1-(p-tolyl)-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one and 8-fluoro-1-(4-fluorophenyl)-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one exhibited moderate inhibition

against M. tuberculosis $H_{37}Rv$ as compared to standard drugs. The antimalarial activity was shown by almost all types of compounds. 8-Fluoro-1-(4-methoxyphenyl)-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one and 8-fluoro-1-(2-(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-c]quinolin-2(3*H*)-one contributed excellent antifungal activity against C. albicans. All the compounds showed moderate to very good antibacterial activity (Scheme 14).[75]

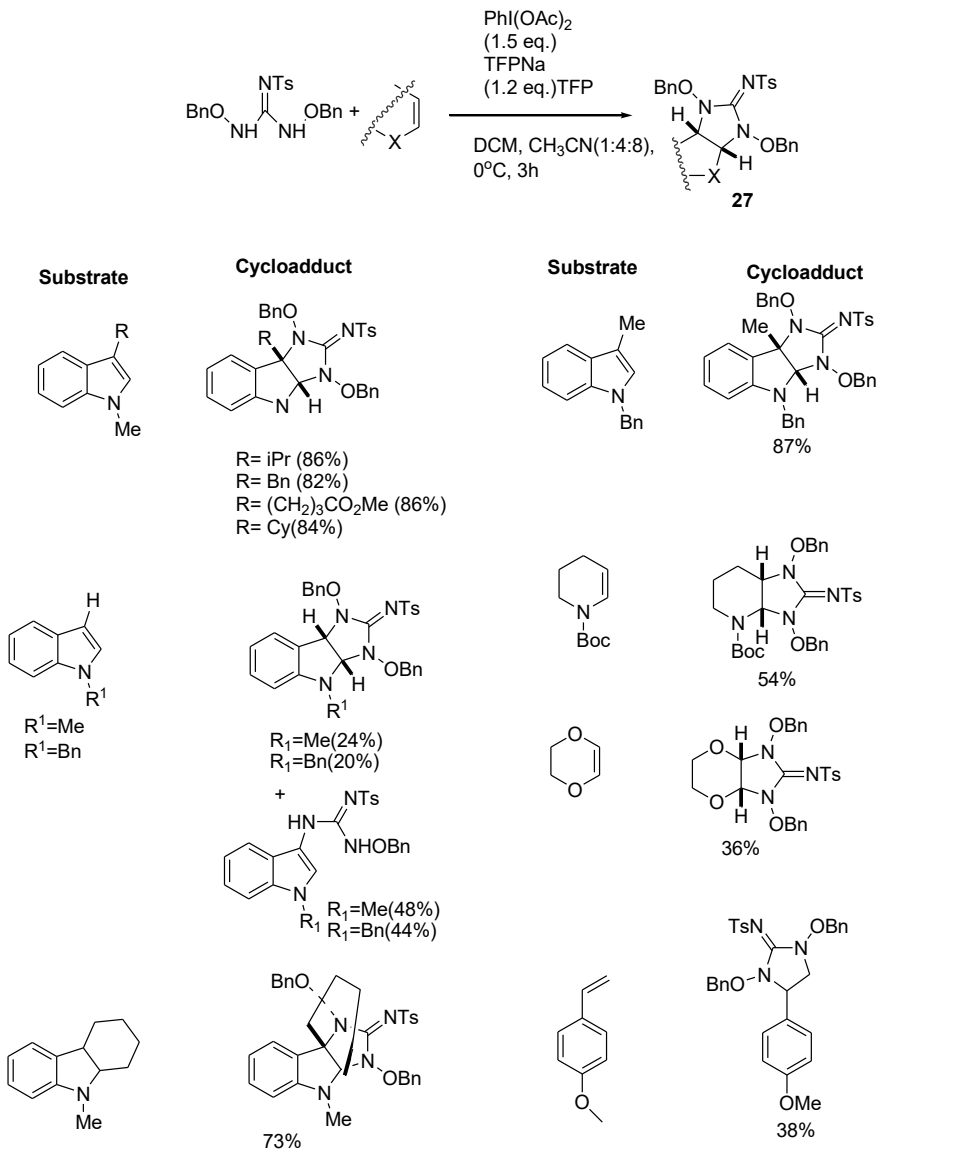


$R^1 = CH_3$, Cl,F; R^2= H, F, CF_3; R^3= H,CH_3, OCH_3, Cl, F

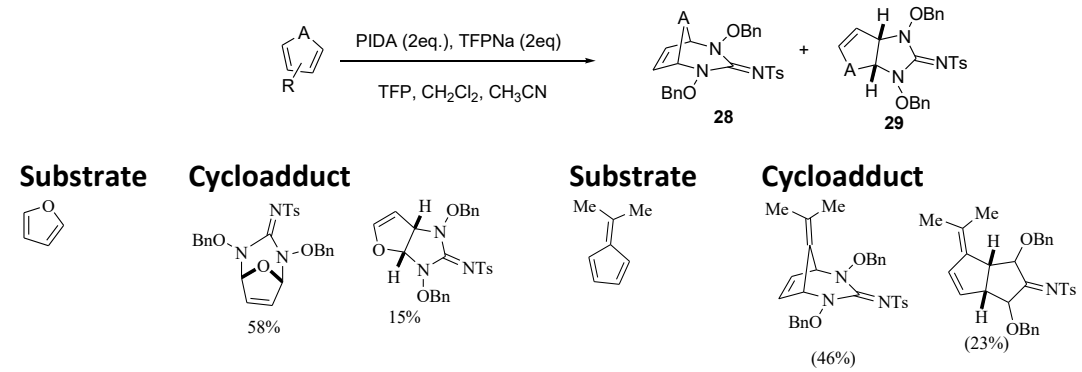
$R^1 = CH_3$, R^2=R^3=H, 76%
$R^1 = CH_3$, R_2=4-CH_3, R_3=H, 78%

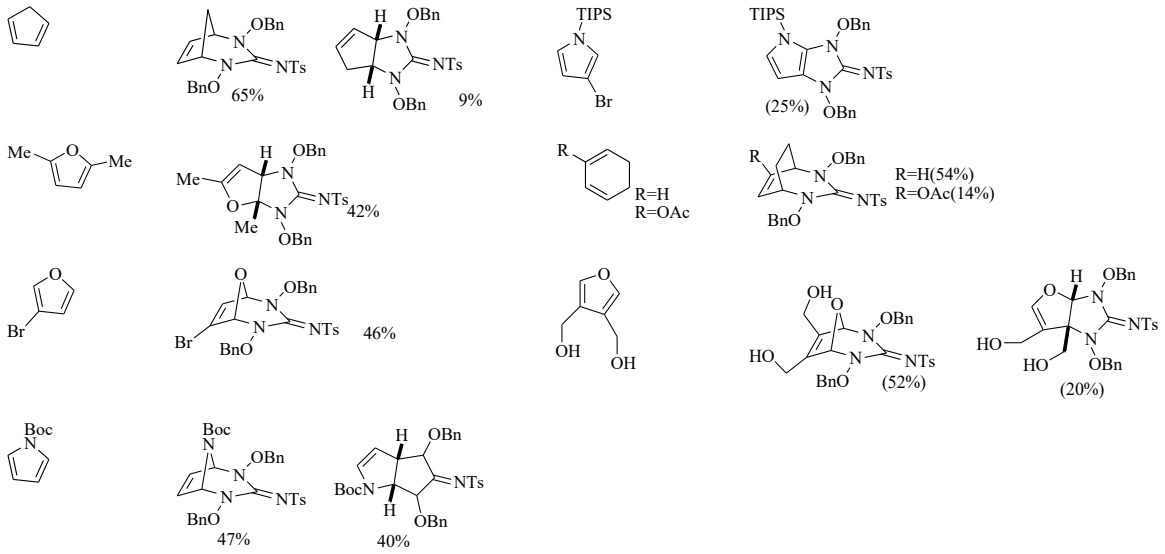
Scheme 14: Intramolecular cyclization of 4-(substituted-phenylamino)-6-substituted-quinoline-3-carboxamide

Kovvuri and coworkers (2020) demonstrated a versatile method for the synthesis of cyclic guanidines via 1,3-dipolar cycloadditions viz., (3+2) and (4+3) of 2-amido-1,3-diaminoallyl cations with various alkenes and dienes respectively. The study highlighted the utility of PIDA as an oxidant with sodium tetrafluoropropoxide (NaTFP) in dichloromethane and acetonitrile to promote the reaction. A number of cyclic guanidines such as N-Boc-piperidine-fused guanidine **27** and dioxane fused guanidine **28**, **29** with varying yields have been synthesized (Scheme 15, Scheme 16). The flexibility of the approach was that the method permitted the incorporation of different substituents on the indole nitrogen to obtain a variety of cyclic guanidines including bridged and fused structures.[76]



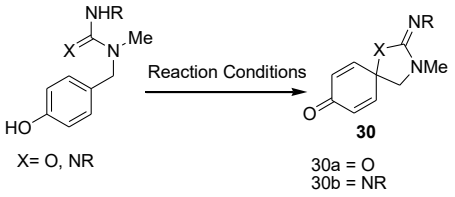
Scheme 15. PIDA mediated synthesis of cyclic guanidines via 1,3-dipolar cycloaddition





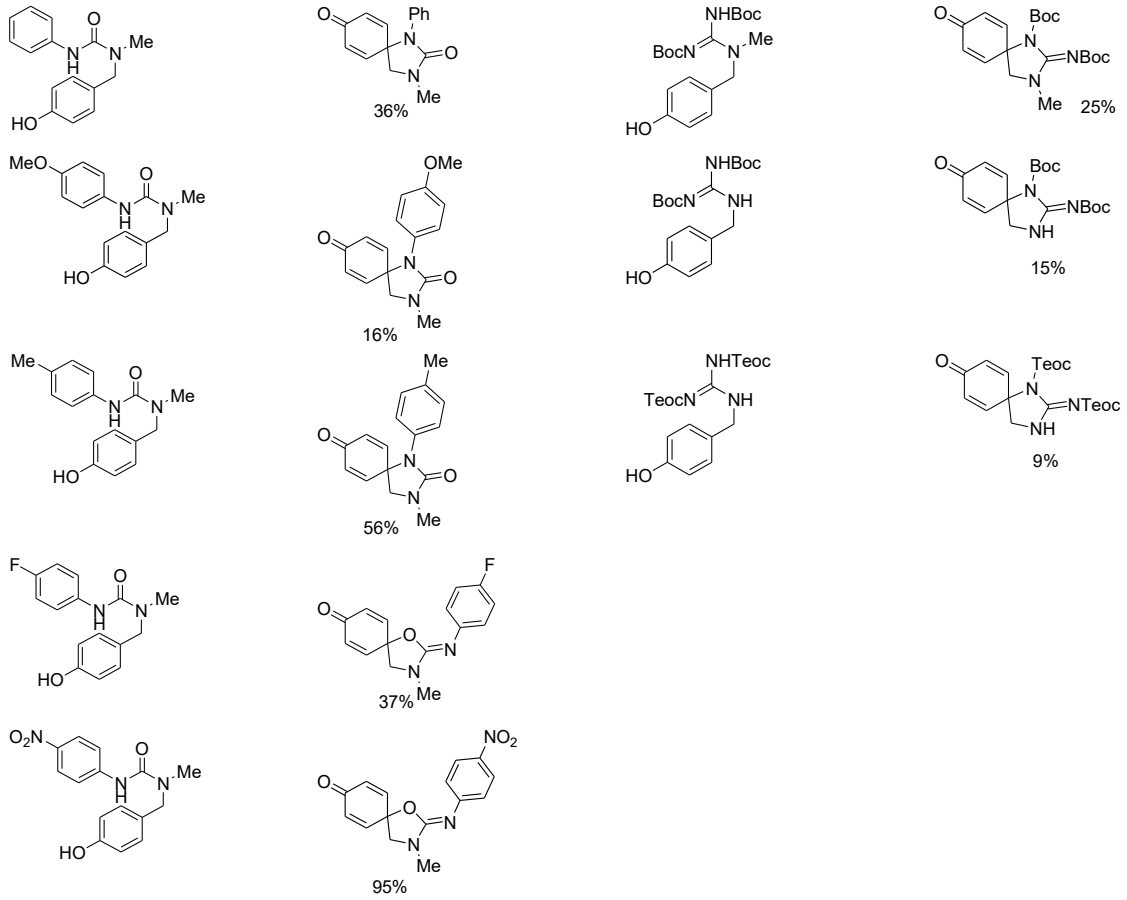
Scheme 16: PIDA mediated synthesis of cyclic guanidines via (4 + 3)/(3 + 2) cycloaddition

The application of PIDA in the dearomatization of benzylic ureas and guanidines is examined to give spirofused heterocycles **30**. In benzylureas with 1 equiv PIDA, 1.2 equiv Cs_2CO_3 in HFIP at room temperature, an addition of 0.2 equiv of PIDA after 5 h gave spirofused cyclohexadienones in 16-95% yield. The studies revealed that imidazolones were obtained from the ureas with electron-rich aryl groups while oxazolines from derivatives with electron-poor aryl group involved cyclization via the oxygen. In benzyl guanidines 1 equiv PIDA, 1 equiv Cs_2CO_3 in HFIP at room temperature led to the isolation of 9-25% dearomatized products. It was found that the N-methyl bis Boc guanidine underwent dearomatization to afford spirocyclic derivative in modest yield. The corresponding NH derivative also provided the desired spirocyclic derivative in low yield. Teoc derivative afforded spirocyclic product with mono deprotection whereas complex reaction mixture was obtained in the mono Cbz adduct and the anisole precursor than spirocyclic derivatives. (Scheme 17).[77]



Reaction Conditions:
When X=O
[a]PIDA (1.0 equiv), Cs_2CO_3 (1.2 equiv), HFIP, rt.
[b]An additional 0.2 equiv of PIDA was added after 5 h.
When X= NR
[a]PIDA (1.0 equiv), Cs_2CO_3 (1.2 equiv), HFIP, rt.

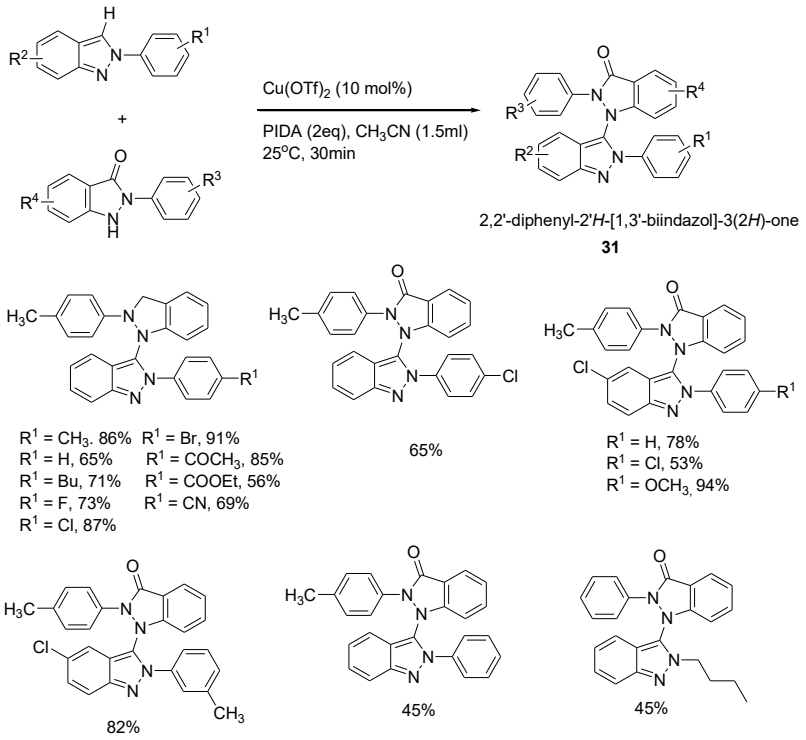
Oxidative dearomatization of benzyl ureas		**Oxidative dearomatization of benzyl guanidines**	
Substrate	**Product (30a, X=O)**	**Substrate**	**Product (30b, X=NR)**



Teoc-2-(trimethylsilyl)ethoxycarbonyl (Teoc)

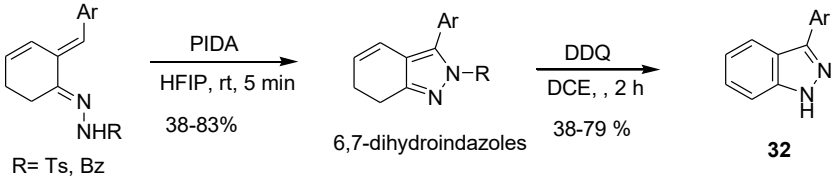
Scheme 17: Role of PIDA in the dearomatization of benzylurea and benzyl guanidine

Zhang et al. in 2023 executed PIDA mediated copper ($Cu(OTf)_2$) catalyzed C–H amination for synthesizing indazole containing indazol-3(2H)-one derivatives **31**. The reaction undergoes C3 amination of 2H-indazoles with 2H-indazoles and indazol-3(2H)-ones in acetonitrile at room temperature for 30 min via radical mechanism affording indazoles in moderate to excellent yields. The mechanistic studies suggest that the reactions proceed through a radical pathway by PIDA acing as both oxidant and radical initiator and coupling of indazoles with indazolones occurs (**Scheme 18**). TEMPO as well as BHT inhibited the product formation. The reaction tolerated electron withdrawing, electron donating, heterocyclic and alkyl groups at the N2 position of 2H-indazoles. Whereas, electron donating substituents viz., Me and OMe at C-6 position are inferior to C5 position of 1H-indazol-3(2H)-one.[78]



Scheme 18: Synthesis of indazole-containing indazol-3(2*H*)-ones by regioselective C−H amination of 2*H*-indazoles

A two-step method for synthesizing synthetically and pharmaceutically useful 3-aryl-1*H*-indazoles was reported by Li et al. The process begins with the PIDA-mediated intramolecular C–N coupling of acylhydrazone derivatives of (*E*)-2-methylidene-3-cyclohexenones to afford 6,7-dihydroindazoles in moderate to high yields (49–83%). Subsequently, an oxidative aromatization using DDQ under reflux conditions not only converted the dihydroindazoles to the aromatic ring but also triggered the *in situ* cleavage of the N-protecting group, efficiently yielding a range of 1-unsubstituted 3-aryl-1*H*-indazoles (**32**) in 38–79% yields (Scheme 19). This protocol offers a mild and metal-free approach with good substrate tolerance, making it especially valuable for applications in medicinal chemistry.[79]

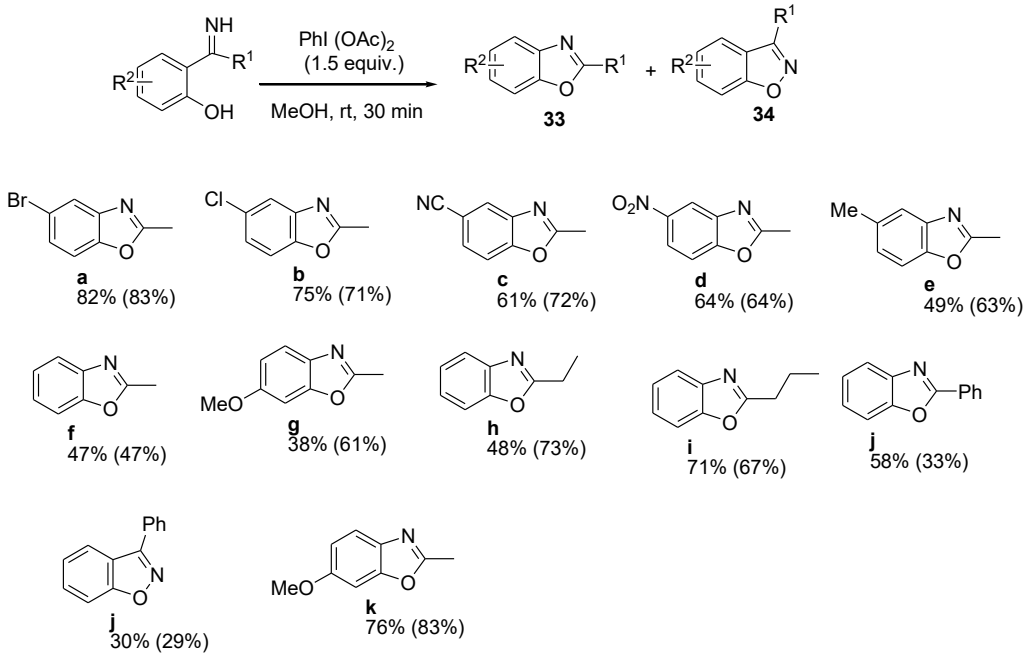


Compound	Ar	Isolated yield, %	Compound	Ar	Isolated yield, %
32a	Ph	43	**32i**	4-PhC_6H_4	67
32b	2-MeC_6H_4	44	**32j**	4-ClC_6H_4	73
32c	2-ClC_6H_4	38	**32k**	4-BrC_6H_4	63

32d	2-BrC_6H_4	55	**32l**	3,4-$(OMe)_2C_6H_3$	62
32e	3-MeC_6H_4	76	**32m**	3,4-$Cl_2C_6H_3$	64
32f	3-ClC_6H_4	60	**32n**	1-Naphthyl	58
32g	4-MeC_6H_4	53	**32o**	2-Naphthyl	75
32h	4-OMeC_6H_4	61	**32p**	2-Thienyl	78

Scheme 19: PIDA-mediated C–N coupling cyclization for the synthesis of 3-aryl-1*H*-indazoles

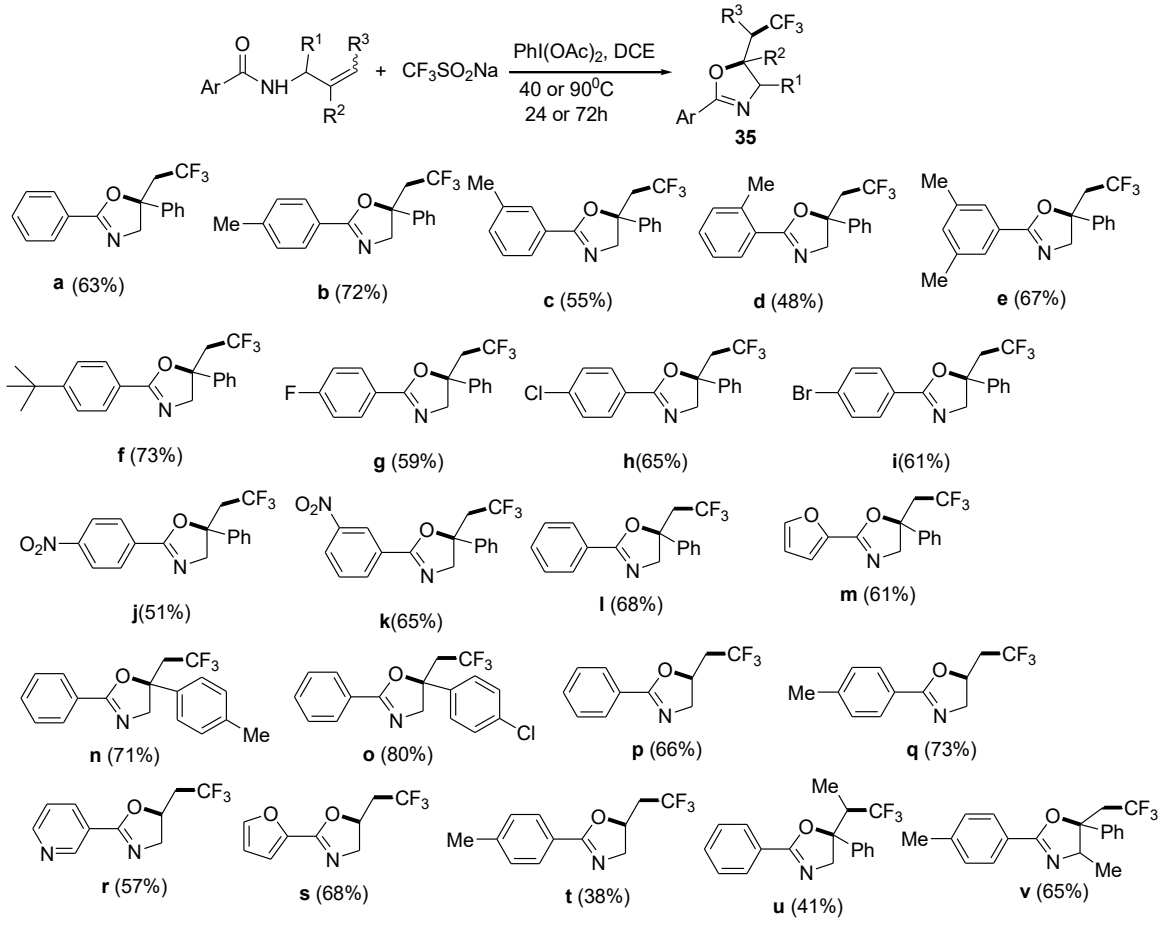
2.3.2.2 *With one nitrogen and one oxygen.* The application of PIDA in Beckmann-type rearrangement of *o*-hydroxy ketimines in synthesis of functionalized benzoxazoles has been explored (Zhang et al. 2015). The reaction of imines with PIDA in methanol gave benzoxazole in 82% yield. It was found that an electron-donating group on the phenyl ring with 0.5 equiv of triethylamine yielded benzoxazole in 61% yield as compared to the absence of triethylamine (38% yield). Similarly, the effect of triethylamine was explored with different substituents on the phenyl ring. Depending on the substituents, the [1,2]-migration of the aryl moiety leading to benzoxazoles **33** can compete with the formation of benzisoxazoles **34** through an intramolecular cyclization (Scheme 20).[74]



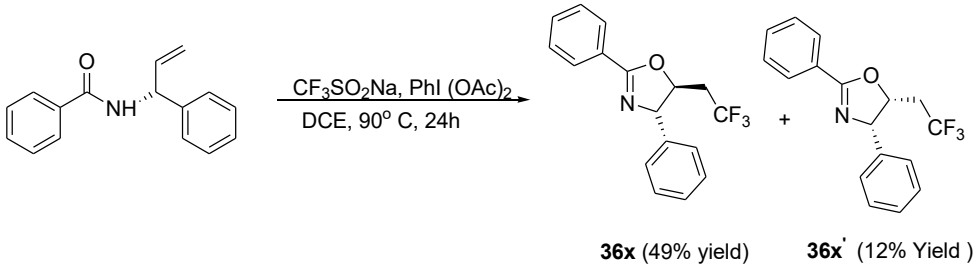
Scheme 20: Synthesis of benzoxazoles and benzisoxazoles from *o*-hydroxy ketimines using PhI$(OAc)_2$-MeOH

Yu et al., 2014 investigated the synthesis of trifluoromethylated oxazolines in PIDA induced intramolecular cyclization, intermolecular trifluoromethylation of alkenes followed by oxidation with PIDA under nitrogen atmosphere afforded 2,5-diphenyl-5-(2,2,2-trifluoroethyl)-4,5-dihydrooxazole **35** in 63% yield. Under similar conditions, for other substituted derivatives also corresponding oxazolines were isolated in 38-80% yields (Scheme 21). The studies showed that transition metals inhibited the reactivity of the substrates

instead of catalysing the reaction. The electronic effect studies showed that for substituents on the Ar of N-allylamides containing electron-donating groups showed slightly higher reactivity than those with electron-withdrawing groups, and ortho substituted substrate gave a lower yield due to steric hindrance. The substrates with R^2=aryl or hydrogen provided higher yields than with R^2= methyl and with an internal alkene gave 41% yield. The trifluoromethylation of (R)-N-(1-phenylallyl)benzamide with CF_3SO_2Na was performed under the standard conditions, to synthesise chiral oxazolines **36** (a pair of diastereoisomers of **36x** and **36x'**(dr=4:1) containing CF_3 groups. The pure products **36x** and **36x'**were obtained after isolation by a preparative TLC (Scheme 22).[80]

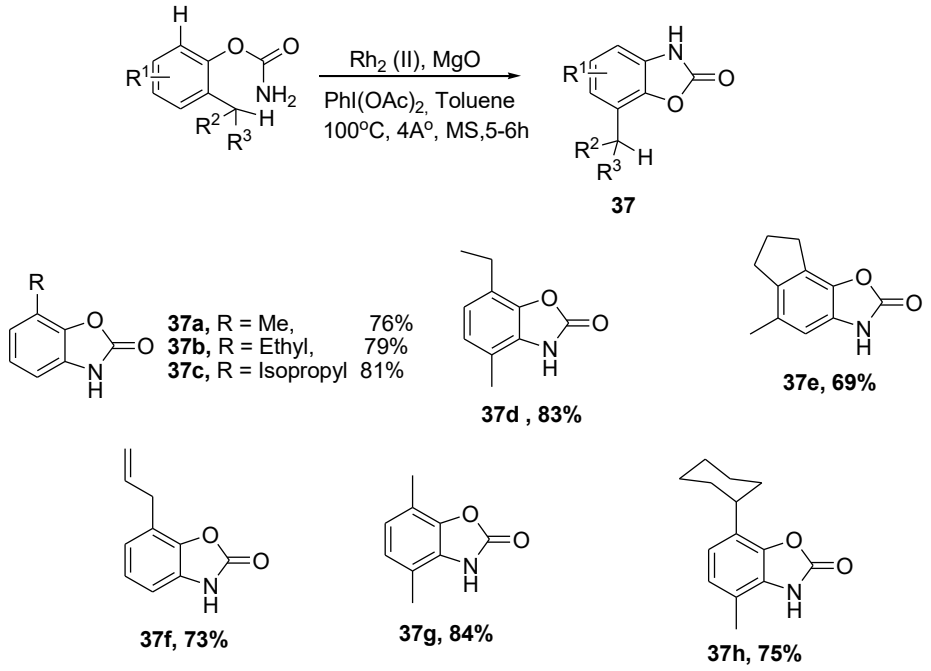


Scheme 21: PIDA induced intramolecular cyclization to synthesize trifluoromethylated oxazolines



Scheme 22: Trifluoromethylation of (R)-N-(1-phenylallyl)benzamide with CF_3SO_2Na to synthesise chiral oxazolines

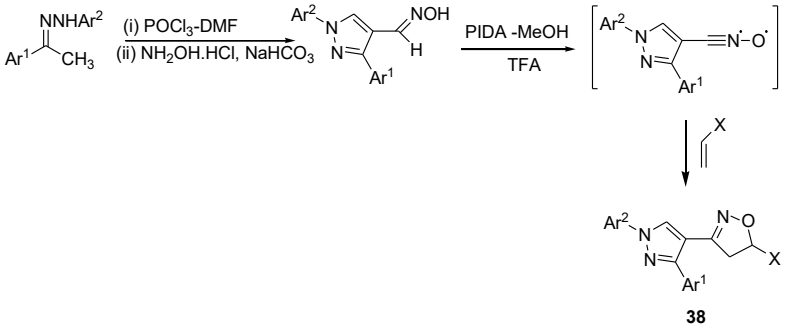
Intramolecular aryl C-H amidation of arylcarbamates in the presence of PIDA and Rh(II) catalyst, under inert atmosphere promoted the formation of benzoxazolones **37** via an intramolecular nitrene C-H insertion reaction (Singh et al., 2016). It was reported that no reaction took place except slight decomposition in the absence of rhodium catalyst under the similar reaction conditions. The reaction undergoes selective aromatic C (sp^2)-H amination over more labile *o*-C(sp^3)-H bonds. The optimization of reaction conditions revealed that toluene was the better solvent compared to DCM and of various metal catalysts viz., Ag, Pd, Cu, Fe and Rh studied, rhodium gave best results. Further, substituent effect studies revealed carbamate with electron donating substituents showed fast reaction with better yields compared to electron withdrawing substituted carbamates. Furhthermore, substrates with bulkier alkyl groups (t-butyl) led to more yields than with smaller alkyl groups (Scheme 23).[81]



Scheme 23: Formation of benzoxazolones via Rh_2(II)-catalyzed C (sp^2)-H amination on o-alkyl arylcarbamates

A useful synthetic methodology of PIDA mediated synthesis of pyrazolyl isoxazoline derivatives has been studied by Kumar and coworkers. Reaction of substituted pyrazolyl aldoximes with PIDA (1.1 equivalent) in methanol at room temperature for 10 minutes followed by treatment with activated alkenes in methanol (containing catalytic amount of TFA) and then stirring at room temperature for 30-40 minutes afforded corresponding pyrazolyl isoxazolines **38** in good yields (82-92% yields) (Scheme 24). These pyrazolyl isoxazolines were screened in vitro for their antibacterial activity against two Gram-positive bacteria viz., Staphylococcus aureus (MTCC 96), Bacillus subtilis (MTCC 121), and two Gram-negative bacteria viz.,

Escherichia coli (MTCC 1652) and Pseudomonas aeruginosa (MTCC 741) by agar well diffusion method with ciprofloxacin as standard and antifungal activity against two fungi, namely Aspergillus niger and Aspergillus flavus through poisoned food method using fluconazole as standard. Pyrazolyl isoxazolines with **38a**, **38e**, **38f** and **38l** showed good antibacterial and antifungal activities.[82]



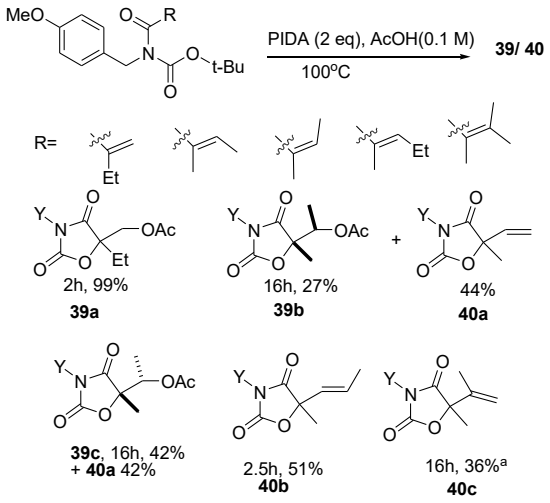
38

Compound	Ar^1	Ar^2	X	Yield %
38a	C_6H_5	C_6H_5	CN	90
38b	4-$CH_3C_6H_4$	C_6H_5	CN	86
38c	4-ClC_6H_4	C_6H_5	CN	87
38d	4-BrC_6H_4	C_6H_5	CN	92
38e	4-FC_6H_4	C_6H_5	CN	82
38f	4-$NO_2C_6H_4$	C_6H_5	CN	84
38g	C_6H_5	4-$NO_2C_6H_4$	CN	89
38h	4-$OCH_3C_6H_4$	4-$NO_2C_6H_4$	CN	88
38i	4-FC_6H_4	4-$NO_2C_6H_4$	CN	87
38j	C_6H_5	C_6H_5	$COOCH_3$	88
38k	4-$CH_3C_6H_4$	C_6H_5	$COOCH_3$	91
38l	C_6H_5	C_6H_5	$OCOCH_3$	85
38m	4-$CH_3C_6H_4$	C_6H_5	$OCOCH_3$	87

Scheme 24: Synthesis of pyrazolyl isoxazoline derivatives

PIDA promoted oxidative cyclization was explored by Duddupudi et al. (2020), the C-O bond formation of N-BOC-acrylamides with $PhI(OAc)_2$ gave 5,5-disubstituted oxazolidines-2,4-diones **39** in moderate to excellent yields. Diastereospecific products with N-BOC-2,3-dimethylacrylamides viz., 5-acetoxy-5-benzyloxazolidine-2,4-dione **40** were obtained by phenyl migration in N-Boc-2-phenylacrylamide under similar reaction conditions (Scheme 25). The reaction tolerated various electron withdrawing and electron donating N-substituents. It was found that the geometry of the alkene (E or Z isomer) significantly influenced the diastereoselectivity of the reaction. The study specifically examined E- and Z-substituted alkenes and their corresponding yields of diastereomeric products. The E-substituted alkene substrate underwent a diastereospecific reaction, producing a specific diastereomer in lower yield (27%). Additionally, another 5,5-disubstituted oxazolidine-2,4-dione was generated as a byproduct. The Z-isomer also yielded a diastereomer, with a similar yield to that of the E-isomer. This indicates that both geometries can lead to the formation of

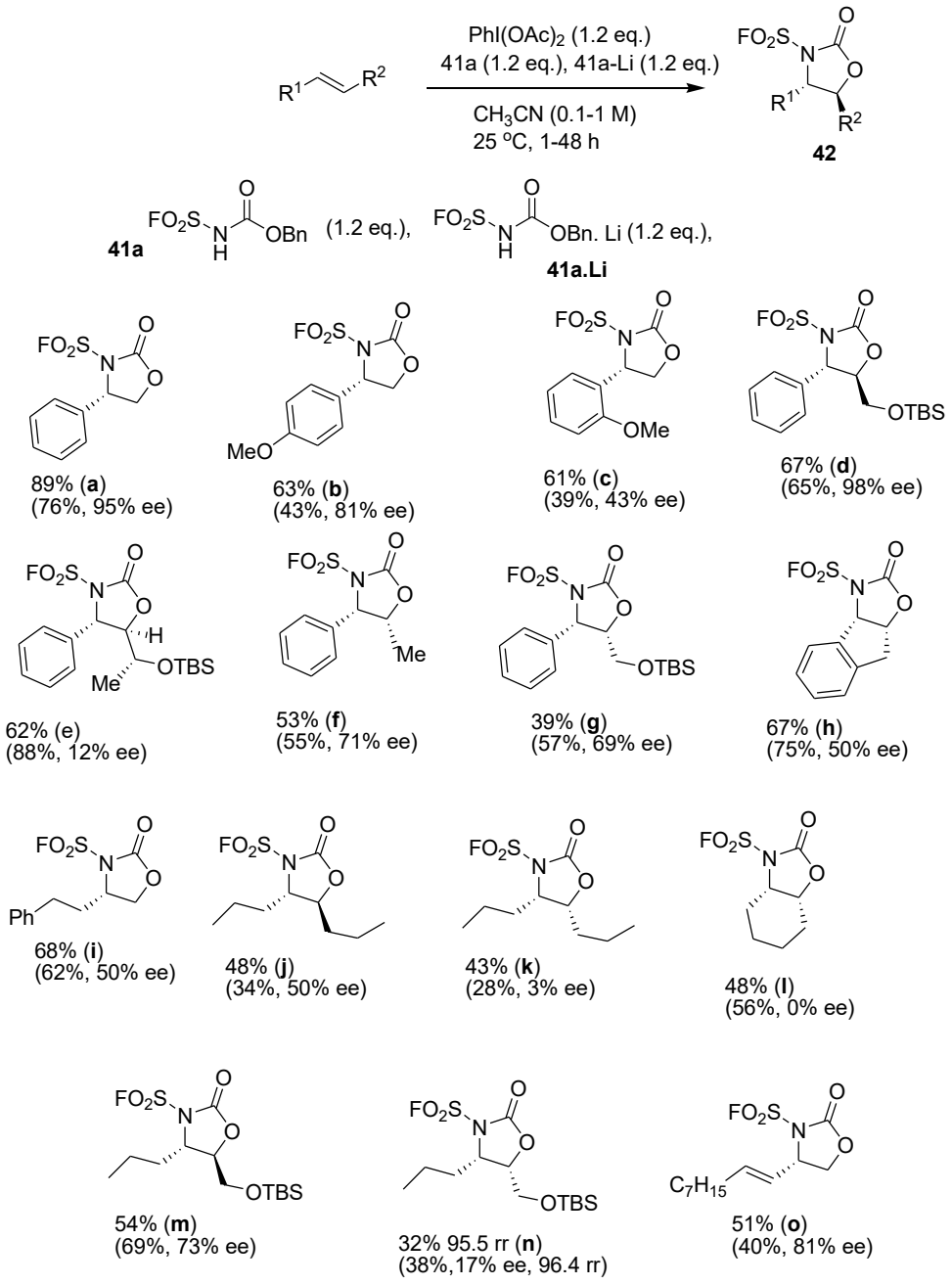
distinct diastereomers, but the yields varied. The study noted that trisubstituted and tetrasubstituted alkenes did not yield the desired oxazolidine products but instead produced alkene-containing byproducts, suggesting that increased steric hindrance may hinder the cyclization process.[83]



Y: CH_2(4-OMe)Ph. [a]de-Boc starting material recovered.

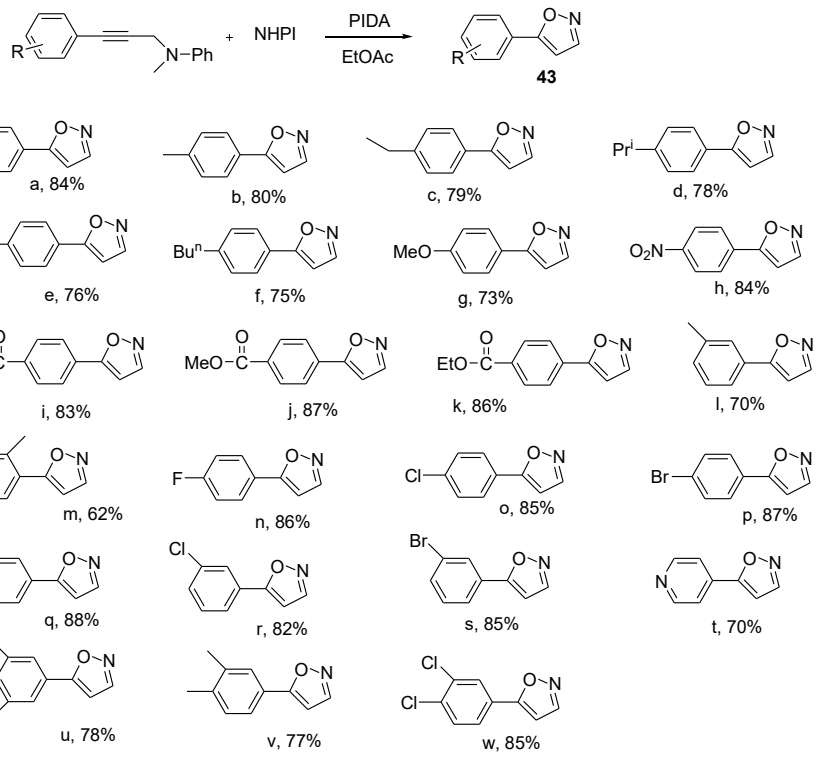
Scheme 25: PIDA in the oxidative cyclization of acrylamide N-carbamates to 5,5-disubstituted oxazolidine-2,4-diones

Wata and Hashimoto in 2021 have developed an enantioselective intermolecular oxyamination of alkenes. The aryl- and alkyl-substituted alkenes were treated with PIDA (1.2 equivalent), benzyl N-(fluorosulfonyl)- carbamate (1.2 equivalent), Li salt of benzyl N-(fluorosulfonyl)- carbamate (1.2 equivalent) in acetonitrile at 25 °C for 1-48h to synthesize the corresponding β-amino alcohols **42** in 39-89% yields (Scheme 26).[84]



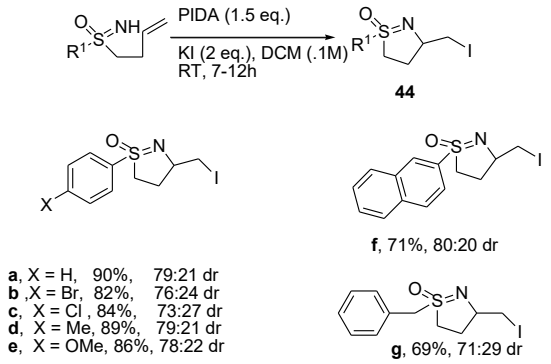
Scheme 26: PIDA mediated enantioselective intermolecular oxyamination of alkenes

Zhang and coworkers (2018) reported the synthesis of 5-substituted isoxazole derivatives. The reaction occurred through PIDA (3 equiv.) mediated cyclization of propargylic amines with N-hydroxyphthalimide (NHPI) in ethyl acetate at room temperature for 12h and the cyclized isoxazoles **43** were reported in 50-84% yield. During optimisation studies it was found that electronic factors (both electron donating and electron withdrawing substituents) had no significant effect on the products yield (Scheme 27).[85]



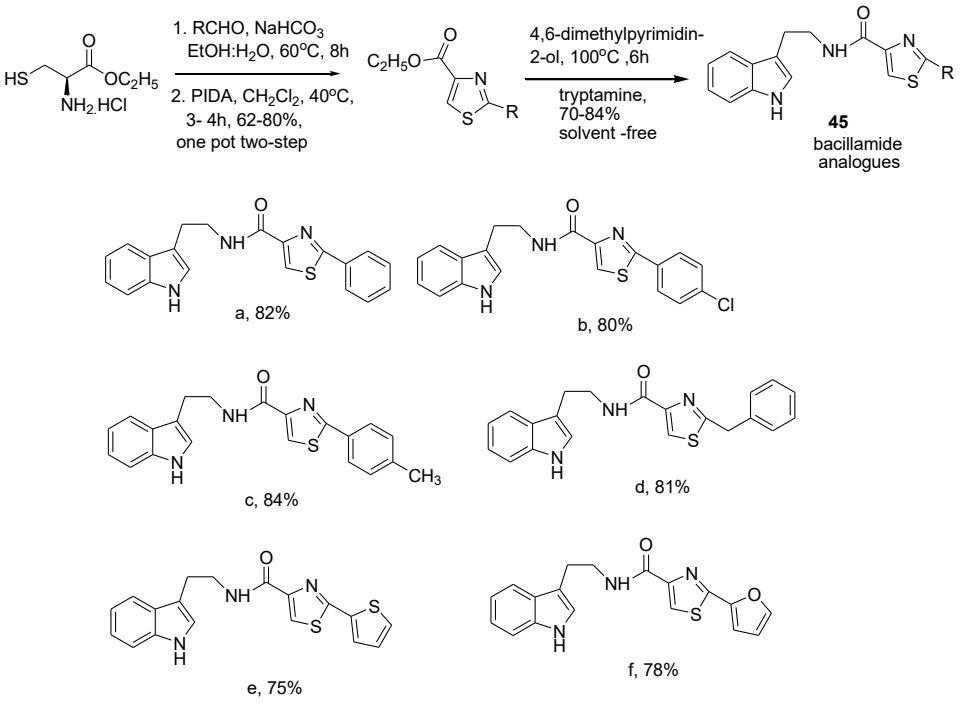
Scheme 27: Synthesis of 5-substituted isoxazoles from propargylic amines and N-hydroxyphthalimide facilitated by PIDA

2.3.2.3 With one nitrogen and one sulphur. The halocyclizations of S-alkenylsulfoximines in PIDA and potassium iodide was explored by Wang and coworkers in 2016. The reaction of S-(but-3-en-1-yl)sulfoximines in dichloromethane with KI (2 eq) and PIDA (1.5 eq) for 12 h gave the corresponding 3-substituted 3H-1λ^4-4,5-dihydroisothiazole 1-oxides **44** in 69-90% yields and good diastereomeric ratio (71:29–80:20). The reaction was unaffected by electron donating and withdrawing substituents, however, the yields obtained in nonhalogenated solvents were low (Scheme 28).[86]



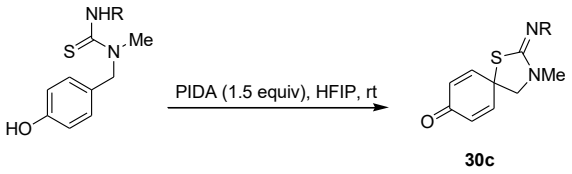
Scheme 28: Synthesis of dihydroisothiazole oxides

Kumar and Aggarwal developed the synthesis of bacillamide A and its analogues under solvent free conditions in the presence of 4,6-dimethylpyrimidin-2-ol in 75-84% yields. Bacillamides **45** were obtained by one pot synthesis of ethyl 2-acetyl-1,3-thiazole-4-carboxylate from the pyruvaldehyde, L-cysteine ethyl ester hydrochloride and sodium bicarbonate via [4+1] approach in aqueous ethanol at 60°C followed by oxidation with PIDA by aminolysis of ester in dichloromethane. The final step required aminolysis of ethyl 2-acetyl-1,3-thiazole-4-carboxylate with tryptamine (Scheme 29).[87]

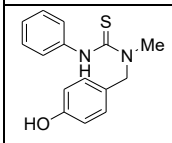
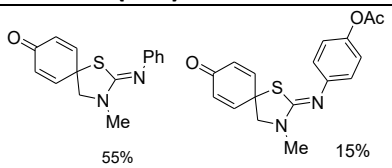
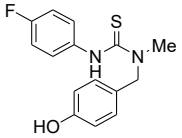
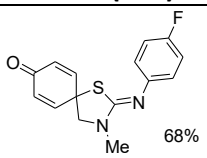
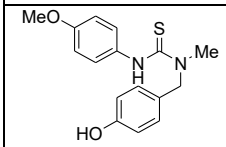
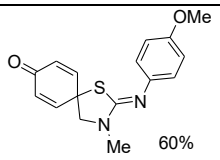
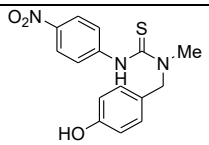
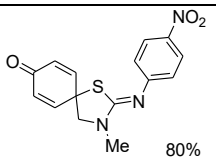
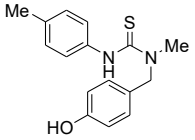
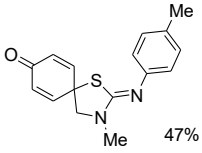


Scheme 29: Synthesis of bacillamide A and its analogues

The oxidative dearomatization of benzylthioureas with 1.5 equivalent of PIDA in hexafluoroisopropanol (HFIP) at room temperature gave the spirathiazolines **30** in 47-80% yield, as mentioned in Scheme 30. Studies showed that spirocyclization with thiourea lacking the N-methyl substituent did not give the desired spiro derivative instead thiadiazole was obtained. Initially, attempts with benzyl thioureas under standard conditions led predominantly to electrophilic aromatic substitution, forming products like benzothiazoles, rather than the desired dearomatized spiro compounds. To achieve dearomatization, inverted the approach by oxidizing the phenol derivatives instead of methyl aryl ethers linked to thioureas, gave moderate to good yields of spirocyclic heterocycles . Mechanistically, the process involves oxidation of the thiourea sulfur to generate reactive intermediates that can undergo intramolecular cyclization forming spiro fused heterocycles. [77]



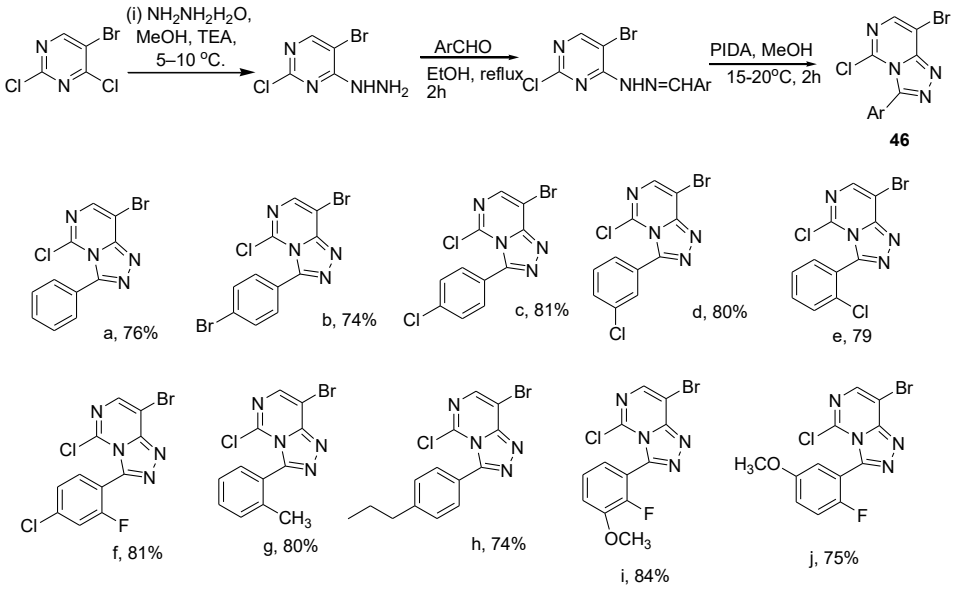
30c

Oxidative dearomatization of thiourea			
Substrate	**Product (30c)**	**Substrate**	**Product (30c)**
	 55% 15%		 68%
	 60%		 80%
	 47%		

Scheme 30: Role of PIDA in the dearomatization of benzylthiourea

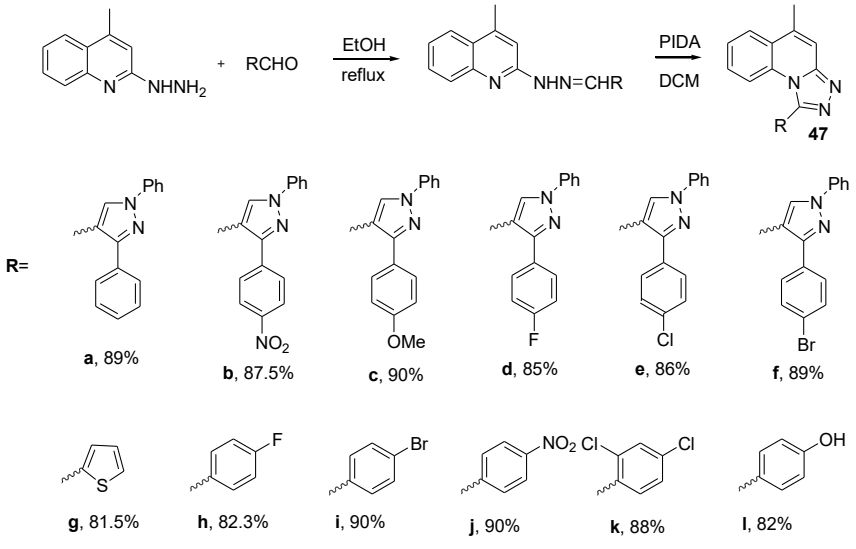
2.3.3. 5-membered compounds with three heteroatoms

2.3.3.1. With three nitrogens. 2-Benzylidene-1-(5-bromo-2-chloropyrimidin-4-yl)hydrazones were treated with PIDA in methanol for 2h at 15-20°C to synthesize 5-chloro-8-bromo-3-aryl-1,2,4-triazolo[4,3-c]pyrimidines **46** in 74-84% yields (Kumara et al., 2014). The reaction tolerated different substituents (Ar= Ph, 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 2-F,4-ClC_6H_3, 2-$CH_3C_6H_4$, 4-$C_3H_7C_6H_4$, 2-F,3-OCH_3-C_6H_3, 2-F,4-$OCH_3C_6H_3$) and good yields (75-84%) were isolated. The SAR studies showed that phenyl ring substituent was responsible for antimicrobial activity. The evaluation of antibacterial (against Bacillus subtilis MTCC 121, Staphylococcus aureus MTCC 7443, Xanthomonas campestris MTCC 7908 and Escherichia coli MTCC 7410) and antifungal (against Fusarium oxysporum MTCC 2480) studies revealed that the inhibitory activity followed the order 2-F,4-ClC_6H_3> 2-F,3-OCH_3-C_6H_3 >2-F,4-ClC_6H_3> 4-BrC_6H_4 >2-ClC_6H_4>3-ClC_6H_4>4-ClC_6H_4>4-$C_3H_7C_6H4$>2-$CH_3C_6H_4$>Ph against the tested microorganisms (Scheme 31)[88]



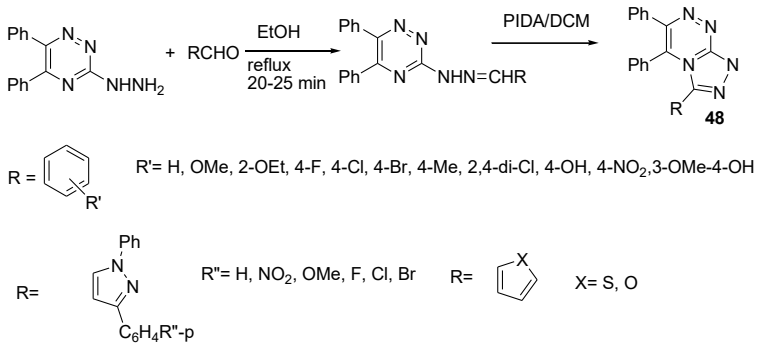
Scheme 31: Utility of PIDA in the synthesis of 5-chloro-8-bromo-3-aryl-1,2,4-triazolo[4,3-c]pyrimidines from 2-benzylidene-1-(5-bromo-2-chloropyrimidin-4-yl)hydrazones

Kumar et al. (2014) focused on the synthesis of triazolo[4,3-a]quinoline derivatives by the treatment of quinolin-2-yl linked hydrazones of various aryl/heteroaryl aldehydes with PIDA in dichloromethane. The triazoloquinolines **47** were evaluated for in vitro antibacterial activity against Enterococcus, Bacillus subtilis, Staphylococcus aureus, Psuedomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae. Among all the synthesized compounds, 3-(1',3'-diphenylpyrazol-4'-yl)-9-methyl-[1,2,4]triazolo[4,3- a]quinoline and 9-methyl-3-(3'-(4'-nitrophenyl)-10-phenylpyrazol-4-yl)-[1,2,4]triazolo[4,3-a]quinoline have been most potent against S. aureus and B. subtilis (Scheme 32).[89]



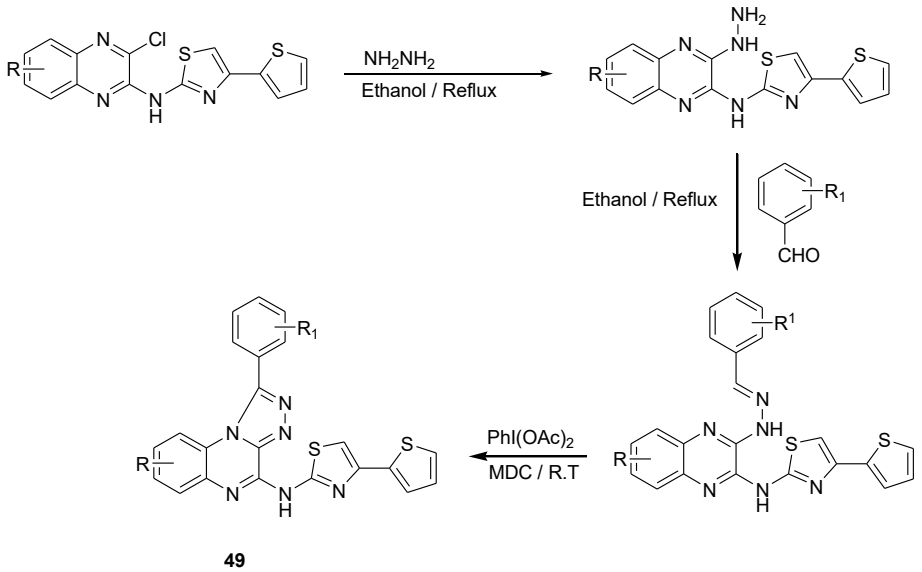
Scheme 32: Synthesis of triazolo[4,3-a]quinolones driven by PIDA

Kumar and coworkers (2014) isolated triazolotriazine derivatives **48** via oxidative cyclization of triazinylhydrazones with PIDA in DCM for 1h stirring. Biological studies using agarose gel electrophoresis on plasmid DNA showed that the derivatives containing nitro, methoxy, chloro, bromo, thiophene and furan groups exhibited good photocleaving activity. In case of triazolotriazines, the para substitution on phenyl ring attached to pyrazole moiety with electron-releasing group increases the DNA photocleavage ability whereas electron withdrawing group decreases but to a lesser extent. It was also found from these studies that triazinylhydrazones containing phenyl ring attached to pyrazole moiety having electron-releasing group also enhanced the DNA photocleavage potential (Scheme 33).[90]



Scheme 33: Synthesis of triazolotriazine derivatives via PIDA-promoted oxidative cyclization of triazinylhydrazones

Dehydrogenative cyclisation of 3-((E)-2-benzylidenehydrazinyl)-N-(4-(thiophen-2-yl)thiazol-2-yl)quinoxalin-2-amine derivatives with PIDA in dichloromethane at room temperature by stirring for 45-55 minutes led to the isolation of triazolo quinoxaline derivatives **49 (**Kathortiya et al., 2015). The quinoooxalin-2-amines were obtained in 70-90% (Scheme 34).[91]



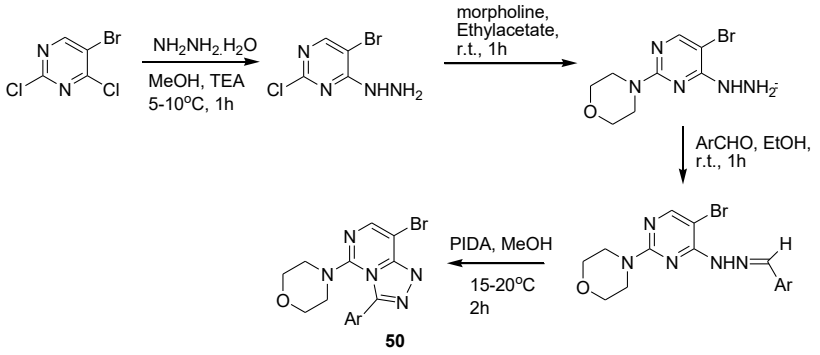
49

R = H, CH_3
R^1 = H, CH_3, OCH_3, F, Cl, Br, NO_2, OH

Compounds	R	R^1	Yield %	Compounds	R	R^1	Yield %
49a	H	H	89	**49k**	CH_3	H	87
49b	H	4-CH_3	90	**49l**	CH_3	4-CH_3	86
49c	H	4-OCH_3	88	**49m**	CH_3	4-OCH_3	88
49d	H	4-F	82	**49n**	CH_3	4-F	82
49e	H	4-Cl	80	**49o**	CH_3	4-Cl	83
49f	H	4-Br	81	**49p**	CH_3	Br	80
49g	H	4-NO_2	84	**49q**	CH_3	4-NO_2	86
49h	H	4-OH	82	**49r**	CH_3	4-OH	81
49i	H	3-NO_2	73	**49s**	CH_3	3-NO_2	74
49j	H	3-OH	71	**49t**	CH_3	3-OH	70

Scheme 34: $PhI(OAc)_2$ enabled synthesis of thiophenyl-thiazole containing triazolo quinoxaline derivatives

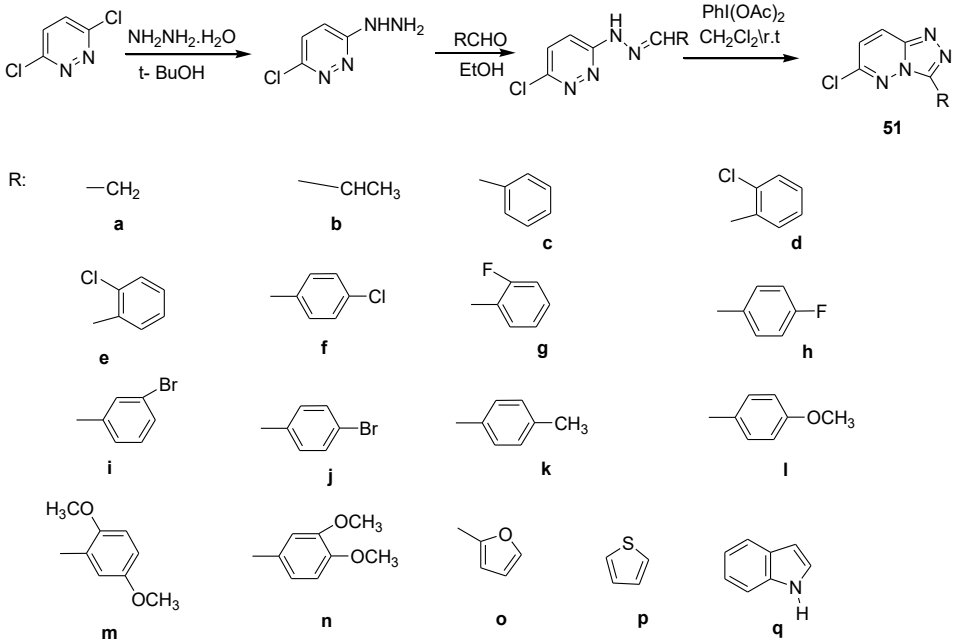
Vinay et. al. (2018) reported the synthesis of 8-bromo-5-morpholino-3-aryl-[1,2,4]triazolo[4,3-f]pyrimidine compounds **50** from the reaction of 2-arylidene-1-(5-bromo-2-morpholinopyrimidin-4-yl)hydrazines with PIDA when stirred in methanol at 15-20°C for 2 h. The triazolopyrimidines (Ar= Ph, 4-BrC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 2-F,4-ClC_6H_3, 4-$CH_3C_6H_4$) were obtained in good yields (74-81%). The screening of these triazolopyrimidines for anticonvulsant activity (maximum electroshock seizure model) and neurotoxicity revealed 8-bromo-3-(4-chloro-2-fluorophenyl)-5-morpholino- [1,2,4]triazolo[4,3-f]pyrimidine to possess good anticonvulsant activity without the significant neurological toxicity (Scheme 35).[92]



Ar= C_6H_5 (76%); p-Br-C_6H_4 (74%); p-Cl-C_6H_4 (81%); m-Cl-C_6H_4 (80%); o-Cl-C_6H_4 (79%); o-F,p-Cl-C_6H_3 (81%); o-CH_3-C_6H_4 (80%);

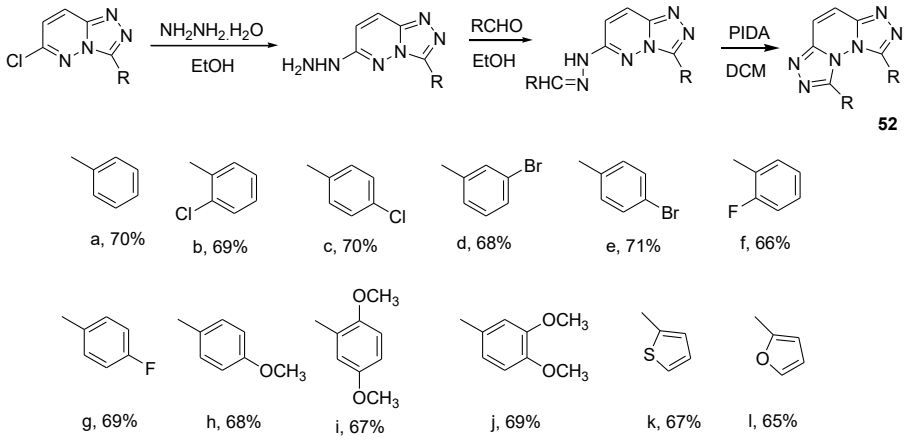
Scheme 35: Synthesis of 8-bromo-5-morpholino-3-aryl-[1,2,4]triazolo[4,3-f]pyrimidines from 2-arylidene-1-(5-bromo-2-morpholinopyrimidin-4-yl)hydrazines through PIDA

Intramolecular oxidative cyclization of 6-chloropyridazin-3-yl hydrazones was studied by Mamta et al., isolation of 6-chloro-3-substituted-[1,2,4]triazolo[4,3-b]pyridazines **51** was reported after stirring the reaction mixture in DCM with PIDA for 2-3 h. The anticancer activity of hydrazones and triazolopyridazines against three different human cancer viz., two acute lymphoblastic leukemia (ALL) cell lines, SB-ALL and NALM-6, and a human breast adenocarcinoma cell lines, MCF-7 was evaluated in vitro. It was found that pyridazines showed better cytotoxicity than their hydrazone precursors. Among the title compounds, 6-chloro-3-(4'-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine, 6-chloro-3-(4'-bromophenyl)-[1,2,4]triazolo[4,3-b]pyridazine and 6-chloro-3-(1H-indole-3'-yl)-[1,2,4]triazolo[4,3-b]pyridazine revealed potent cytotoxic activity against SB-ALL and NALM-6 compared with standard, doxorubicin (Scheme 36)[93]



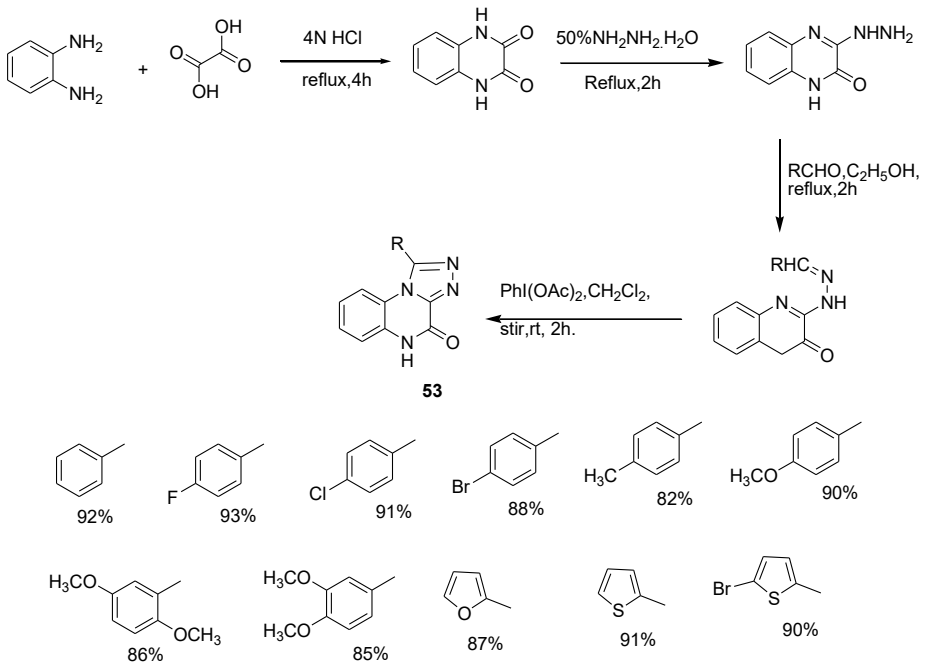
Scheme 36: PIDA-mediated oxidative cyclization of 6 - chloropyridazine-3-yl hydrazones to [1,2,4] triazolo [4,3-b]pyridazines

3,6-Disubstituted-bis-1,2,4-triazolo-[4,3-b][3' ,4'-f]pyridazines **52** were obtained by Aggarwal et al., 2019 by intramolecular cyclization of 6-arylidenehydrazino-3-aryl-1,2,4-triazolo[4,3-b]pyridazine using PIDA in DCM at room temperature in 70-82% yield; the crystal structure of 3,6-di-(2' -fluorophenyl)-bis-1,2,4-triazolo-[4,3-b][3',4'-f] pyridazine; 3,6-di-(4'-fluorophenyl)-bis-1,2,4-triazolo-[4,3-b][3',4'-f] pyridazine was reported (Scheme 37).[94]



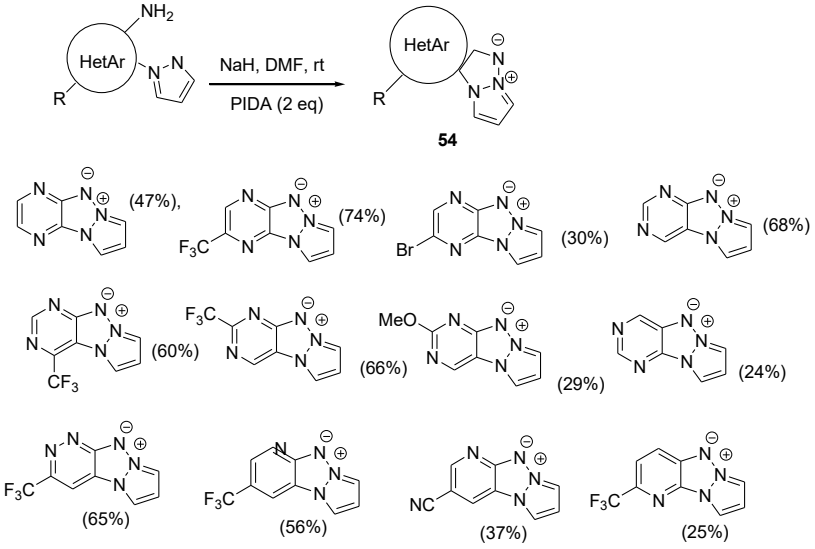
Scheme 37: PIDA-enabled synthesis of 3,6-disubstituted-bis-1,2,4-triazolo-[4,3-b][3' ,4'-f]pyridazines

Iodobenzene diacetate mediated oxidative intramolecular cyclization of 3-(2-(aryl/ heteroarylidene)hydrazinyl)-quinoxalin-2(1H)-ones led to the isolation of 1-aryl/heteroaryl-[1,2,4]-triazolo[4,3-a]quinoxalin-4(5H)-ones **53** with promising DNA cleaving abilities which was dependent on photoirradiation time, structure and concentration. It was found that photocleavage process was mainly due to the formation of superoxide anion radicals. The photobiological studies revealed that 1-(5'-bromothiophen-2'-yl)-[1,2,4]-triazolo[4,3-a]quinoxaline-4(5H)-one could serve as potential chemotherapeutic agent (Scheme 38).[95]



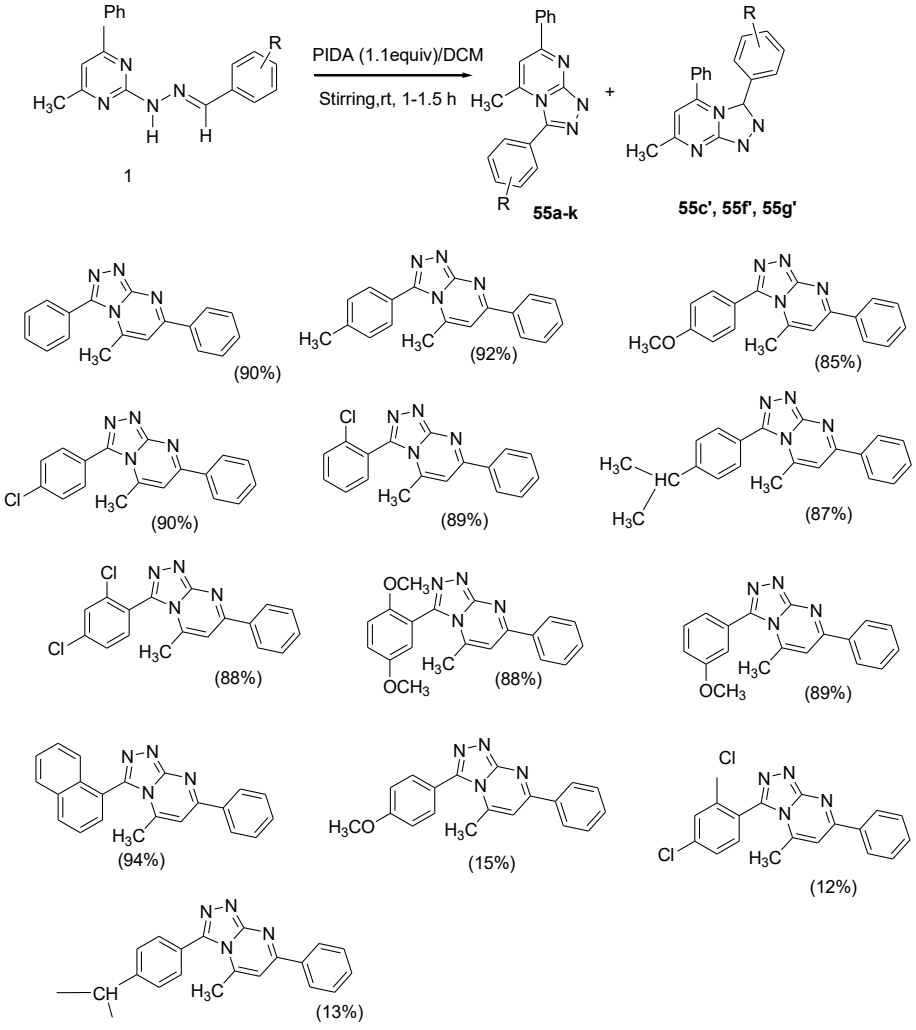
Scheme 38: Synthesis of 1-aryl/heteroaryl derivatives of [1,2,4]-triazolo[4,3-a]quinoxalin-4(5H)-ones

Daniel et al (2019) focussed on exploring the utility of PIDA in a direct intramolecular N-N oxidative bond formation approach with pyridine, pyrazine, pyrimidine and pyridazine containing heteroaromatic amines and pyrazoles in DMF with base at room temperature for 24 h. In case of pyrazine or pyrimidine, there was a decrease in the yields in the presence of electron withdrawing groups (CF_3) while electron donating groups (Me, OMe) showed mild effect. It is to note that there is no utility of adding electron donating group on the pyrazole and an electron withdrawing group on the diazine. Further, the fluorescence studies showed the pyrazine series **54** to have the quantum yield from 0.41 to 0.47. The nature of the substituents, on the azole or the azine parts, had no impact on the excitation and emission wavelengths but a strong impact was found on the molar absorption coefficient and the quantum yields (Scheme 39)[96]



Scheme 39: Iodine (III) reagent in a direct intramolecular N-N oxidative bond formation

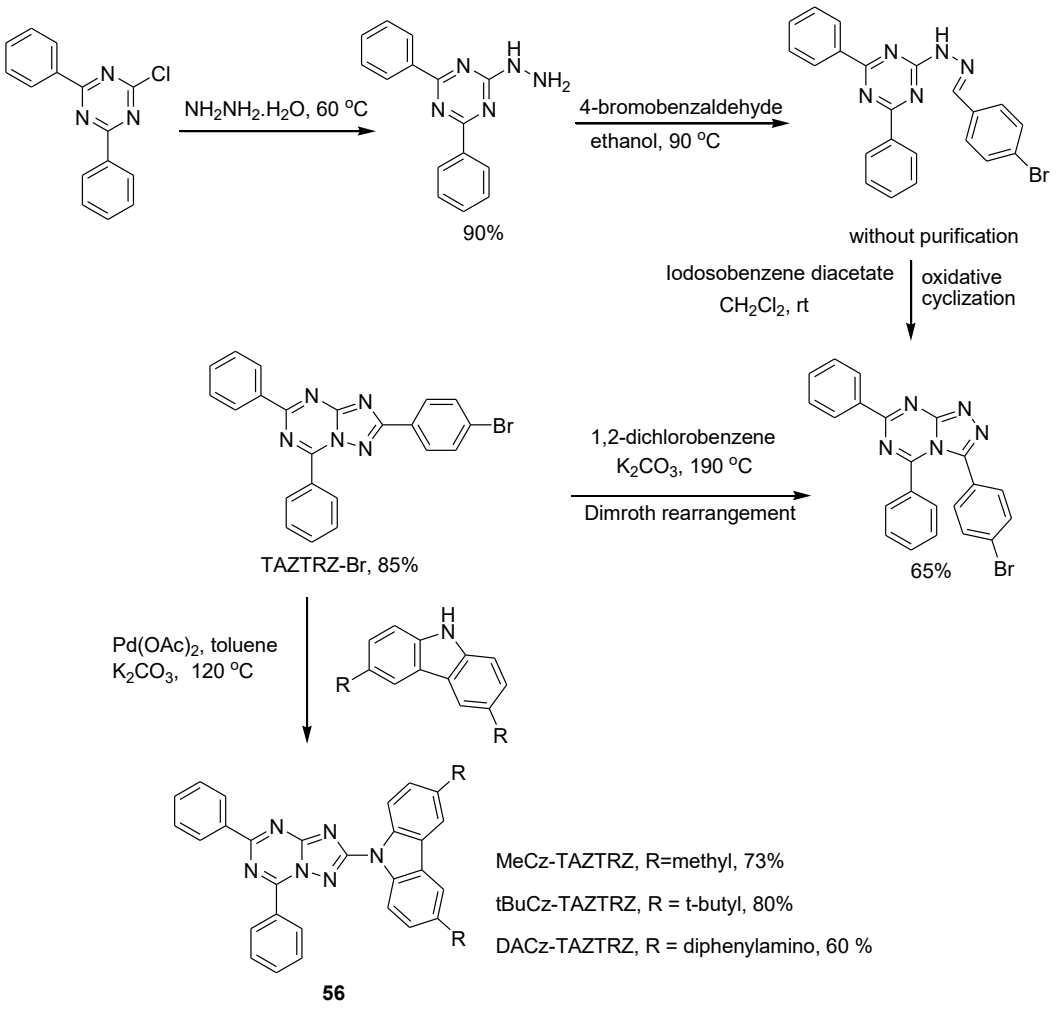
Kamal and coworkers focussed their studies on PIDA (1.1equivalent) mediated oxidative-cyclization of 2-(2-arylidenehydrazinyl)-4-methyl-6-phenylpyrimidine derivatives. A mild and regioselective PIDA (1.1equivalent) mediated reaction of 2-(2-arylidenehydrazinyl)-4-methyl-6-phenylpyrimidines in DCM at room temperature gave the expected [1,2,4]triazolo[4,3-a]pyrimidine derivatives **55**. The screening of the title compounds for anticancer activity using MTT assay for bone cancer and breast cancer using MG-63 and MCF-7 cell lines and also for the testicular germ cells showed significant biological activity. 3-(2,4-Dichlorophenyl)-5-methyl-7-phenyl-[1,2,4]triazolo[4,3-a]pyrimidine was found to be most significant apoptotic inducing molecule against bone cancer (MG-63) and breast cancer (MCF-7) cell lines with GI50 value 148.96 mM and 114.3 mM respectively (Scheme 40).[97]



Scheme 40: Oxidative-cyclization of 2-(2-arylidenehydrazinyl)-4-methyl-6-phenylpyrimidines to [1,2,4]triazolo[4,3-a]pyrimidines

A facile method for the synthesis of triazolotriazine-based thermally activated delayed fluorescence materials for fluorescent organic light-emitting diodes (TSF-OLEDs) have been highlighted by Su and

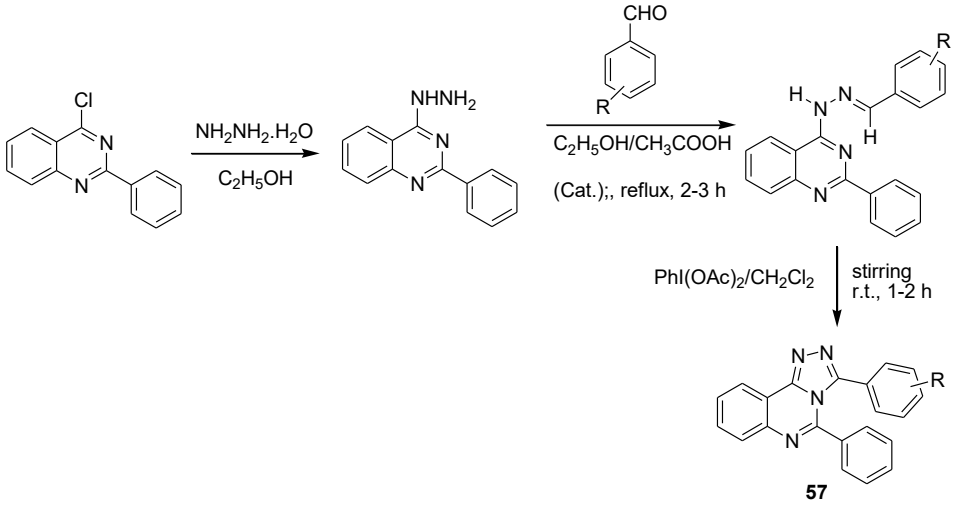
coworkers. In this context, the authors carried out the reaction starting with the amination of 2-chloro-4,6-diphenyl-1,3,5-triazine, with hydrazine hydrate and condensation with 4-bromobenzaldehyde followed by intramolecular oxidative cyclization with PIDA accomplished the fusion of the pentagonal framework with the hexagonal TRZ moiety. The desired products were obtained by the Dimroth rearrangement reaction to transform [1,2,4]triazolo[4,3-a] [1,3,5]triazine to [1,2,4]triazolo[1,5-a][1,3,5]triazine (TAZTRZ) **56** in 85% yield. These TAZTRZ-based luminogens have applications as the TADF emitters to realize highly efficient TADF-OLEDs and utilised as the TADF sensitizer (Scheme 41).[98]



Scheme 41: Construction of triazolotriazines by utilizing PIDA-DCM

PIDA-mediated strategy for the synthesis of 3-aryl-5-phenyl-[1,2,4]triazolo[4,3-c]quinazoline derivatives **57** via intramolecular oxidative cyclization of (E)-4-(2-benzylidenehydrazineyl)-2-phenylquinazoline precursors is implemented. Biological evaluation of the products **57** revealed that 5-phenyl-3-(2,3,4-trimethoxyphenyl)-[1,2,4]triazolo[4,3-c]quinazoline and 3-(2,3-dichlorophenyl)-5-phenyl-[1,2,4]triazolo[4,3-c]quinazoline were the most potent derivatives displaying pronounced cytotoxic activity against the MCF-7 breast cancer cell line with IC_{50} values of 1.14 and 1.39 mM, respectively. These compounds also showed significant antiproliferative

effects against the MDA-MB-231 cell line, with IC_{50} values of 2.79 mM and 1.95 mM. Furthermore, ABTS radical-scavenging assays demonstrated that 3-(4-fluorophenyl)-5-phenyl-[1,2,4]triazolo[4,3-c]quinazoline exhibited the highest antioxidant activity, with an IC_{50} value of 11.2 ± 0.14 µg/mL. The antioxidant efficacy of the entire compound series was further substantiated through density functional theory (DFT) calculations. (Scheme 42)[99]



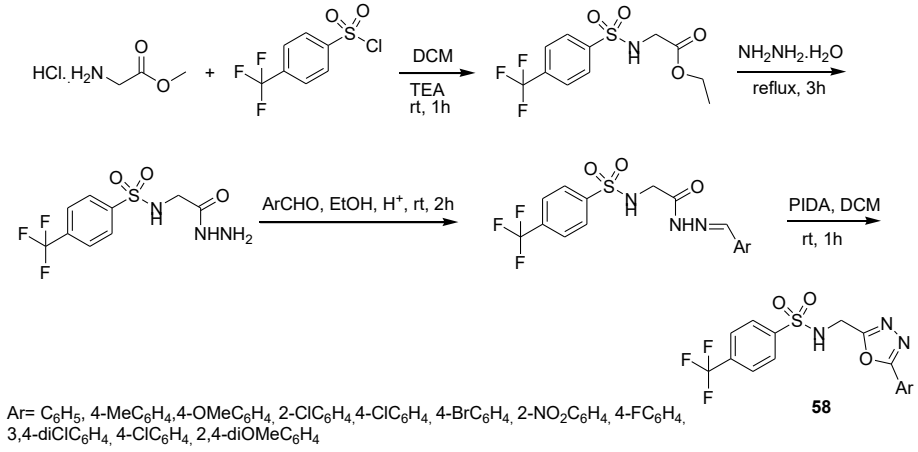
57

Compound	R	Yield	Compound	R	Yield
57a	2-CH_3	55%	**57h**	4-F	68%
57b	3-CH_3	54%	**57i**	4-Cl	75%
57c	4-CH_3	58%	**57j**	2,3-Cl	76%
57d	4-$CH(CH_3)_2$	77%	**57k**	Naphthyl	80%
57e	4-OH	56%	**57l**	4-CF_3	81%
57f	4-OCH_3	60%	**5m**	3-NO_2	86%
57g	2,3,4-OCH_3	82%	**57n**	4-NO_2	88%

Scheme 42: Synthesis of 3-aryl-5-phenyl-[1,2,4]triazolo[4,3-c]quinazolines

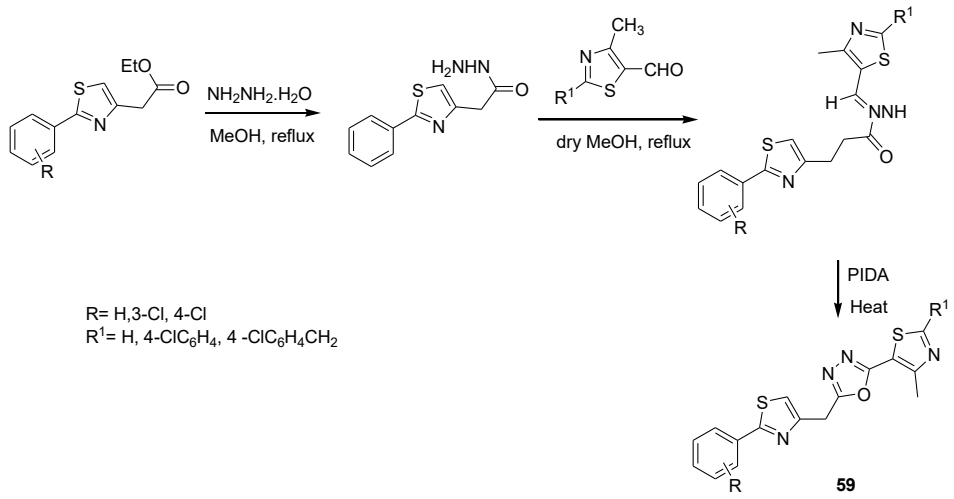
2.3.3.2 With two nitrogens one oxygen. A number of studies have been reported for PIDA mediated synthesis of oxadiazoles. The biological importance of 1,3,4-oxadiazoles promoted Kumar et al., 2014 to carry their studies on PIDA mediated synthesis of 2,5-disubstituted-1,3,4-oxadiazoles **58** from (E)-2-(arylbenzylidene)-2-[(4-methoxyphenyl)amino]acetohydrazides. Ethyl((4-trifluoromethyl)phenyl)sulfonylglycinate was obtained by stirring glycine ethylester hydrochloride, triethylamine in dichloromethane with 4-(trifluoromethyl)benzenesulfonyl chloride. Refluxing the mixture of this glycinate with hydrazine hydrate afforded N-(2-hydrazinyl-2-oxoethyl)-4-(trifluoromethyl)benzenesulfonamide. These benzenesulphonamides on refluxing with substituted benzaldehydes in ethanol gave corresponding (E)-N-(2-(2-benzylidenhydrazinyl)-2-oxoethyl)-4-(trifluoromethyl)benzenesulfonamide. (E)-N-(2-(2-benzylidenhydrazinyl)-2-oxoethyl)-4-(trifluoromethyl)benzenesulfonamide and PIDA at room temperature for 1h afforded the corresponding N-((5-

phenyl-1,3,4-oxadiazole-2-yl)methyl)-4- (trifluoromethyl)benzenesulfonamide in 74% yield. Similarly, the reaction was carried out on different derivatives (Ar=4-tolyl, 4-methoxyphenyl, 2-chlorophenyl, 4-chlorophenyl, 4-bromophenyl, 2-nitrophenyl, 4-fluorophenyl, 3,4-dichlorophenyl, 2,4-dimethoxyphenyl) to get their respective oxadiazoles in 72-92% yields. Screening of the synthesised oxadiazoles against four cell lines viz., MDA-MB 231, K562, Colo-205, and IMR32 cells revealed that the oxadiazoles with electron withdrawing groups viz., fluoro and chloro groups were active against all the tested four cell lines. (Scheme 43)[100]



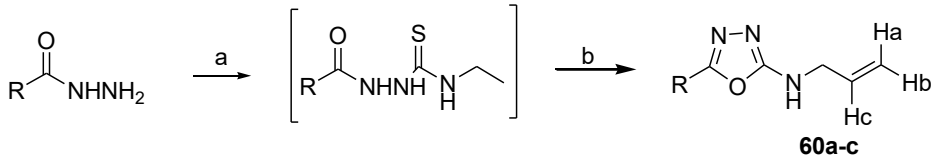
Scheme 43: Role of PIDA in the construction of 2,5-disubstituted-1,3,4-oxadiazole derivatives

Mhaske et al.,(2015) focused on the preparation of Schiff's bases viz., N'-((4-methyl-2-arylthiazol-5-yl)methylene)-2-(2-aryl/benzylthiazol-4-yl)acetohydrazide by refluxing 2-(2-aryl/ benzylthiazol-4-yl)acetohydrazide with 4-methyl-2-arylthiazole-5-carbaldehyde in methanol for 4h. Next, oxidative cyclo-condensation of the Schiff's bases with iodobenzenediacetate afforded the 2-(2-aryl-4-methyl-thiazol-5-yl)-5-((2-aryl/ benzylthiazol-4-yl)methyl)-1,3,4-oxadiazole derivatives **59**. The biological activity screening studies showed that all the compounds (particularly R= 3-Cl, R^1 = 4-Cl-C_6H_4; R = 4-Cl, R^1= 4-Cl-C_6H_4; R= 4-Cl , R^1 = 4-Cl-$C_6H_4CH_2$) with acetohydrazide group exhibited good antifungal activity against Candida albicans, Candida tropicalis, Aspergillus flavus and Aspergillus niger compared to oxidised products i.e. oxadiazoles (Scheme 44).[101]



Scheme 44: Synthesis of 2-(2-Aryl-4-methyl-thiazol-5-yl)-5- ((2-aryl/benzylthiazol-4-yl)methyl)-1,3,4-oxadiazole derivatives

Hassan and Rauf (2016) discussed the cyclization of 1-substituted-5-propenylthiosemicarbazides via iodobenzene diacetate in dry THF for 6-8 h and isolated the 5-substituted-N-propenyl-1,3,4-oxadiazole-2-amines **60** in 70-80% yields (Scheme 45).[102]



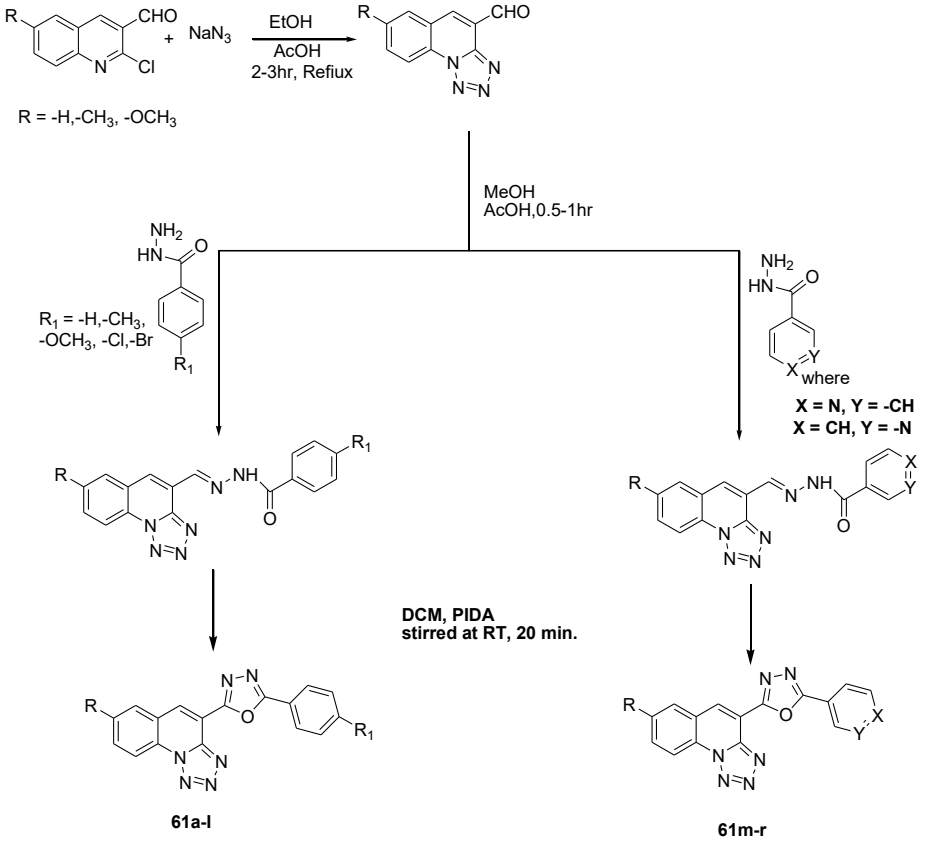
Reagents and conditions : (a) $CH_2 = CHCH_2NCS$, absolute EtOH, Reflux, 8 h (b) $PhI(OAc)_2$, THF, stir, RT, 6-8h

Compound	R
60a	H_3C–(n)–CH_2 (n=11)
60b	H_3C–n^1–n^2–CH_2 n^1= 6, n^2= 5
60c	H_3C–n^1–n^2–CH_2 n^1= 3, n^2= 6

Scheme 45: Oxidative cyclization of 1-substituted-5-propenylthiosemicarbazides to 5-substituted-N-propenyl-1,3,4-oxadiazole-2- amines

Sapariya and coworkers (2017) carried out the reaction of 7-substituted tetrazolo[1,5-a]quinoline-4-carbaldehydes and 4-substituted benzohydrazide (nicotinohydrazide and isonicotinohydrazide) in glacial acetic

acid/methanol (reflux) for one hour, to obtain (E)-4-substituted-N'-((7-substitutedtetrazolo[1,5-a]quinolin-4-yl)methylene)benzohydrazide and (E)-N'-((7-substitutedtetrazolo[1,5-a]quinolin-4-yl)methylene)nicotinohydrazide/isonicotinohydrazide when R =H,CH_3, OCH_3 and R^1= H, CH_3, OCH_3, Cl, which served as precursors for IBD-mediated cyclization yielding the corresponding 1,3,4-oxadiazoles **61**. During the biological activity studies, it was found that oxadiazoles with R= OCH_3, X=N, Y=CH showed good antimicrobial, antitubercular, antimalarial and antioxidant activities (Scheme 46).[103]

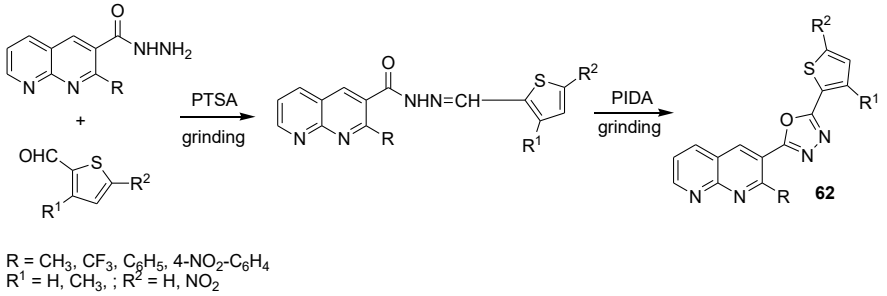


Compound	R	R^1	Yield (%)	Compound	R	X	Y	Yield (%)
61a	H	H	93	**61m**	H	N	CH	84
61b	H	CH_3	73	**61n**	H	CH	N	77
61c	H	OCH_3	81	**61o**	CH_3	N	CH	86
61d	H	Cl	80	**61p**	CH_3	CH	N	81
61e	H	Br	86	**61q**	OCH_3	N	CH	85
61f	CH_3	H	83	**61r**	OCH_3	CH	N	83
61g	CH_3	CH_3	79					
61h	CH_3	OCH_3	74					
61i	CH_3	Cl	89					
61j	OCH_3	H	76					

61k	OCH_3	CH_3	84					
61l	OCH_3	OCH_3	80					

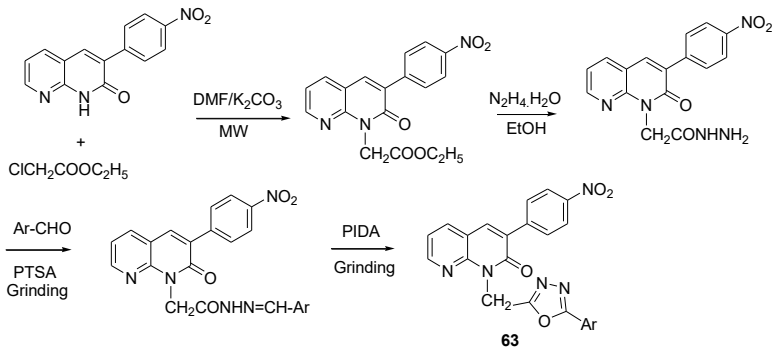
Scheme 46. Synthesis of 7-substituted tetrazolo [1,5-α] quinolines incorporating oxadiazole nucleus

Variously substituted 2-(2-substituted[1,8]naphthpyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles **62** were isolated by the oxidation of N'3{1-(substituted-2-thienyl)methylidene]-2-substituted[1,8]naphthyridine with PIDA. At room temperature solvent free grinding of 2-substituted [1,8]naphthyridine-3-carboxylic acid hydrazides and thiophene-2-aldehydes using catalytic amount of PTSA afforded corresponding substituted products viz., N'3{1-(substituted-2-thienyl)methylidene]-2-substituted[1,8]naphthyridine. All the synthesized compounds showed antibacterial as well as anti-inflammatory activities. Antibacterial activity was comparable to standard gentamycin when R= CF_3, R^1 = CH_3, R^2 = H and promising antinflammatory activity was reported when R = R^1= CH_3, R^2 = H; R =CF_3, R^1=R^2=H; R= CF_3, R^1 = CH_3, R^2 = H; R= 4-$NO_2C_6H_4$, R^1=CH_3, R^2=H (Mogilaiah et al., 2017).(Scheme 47)[104]



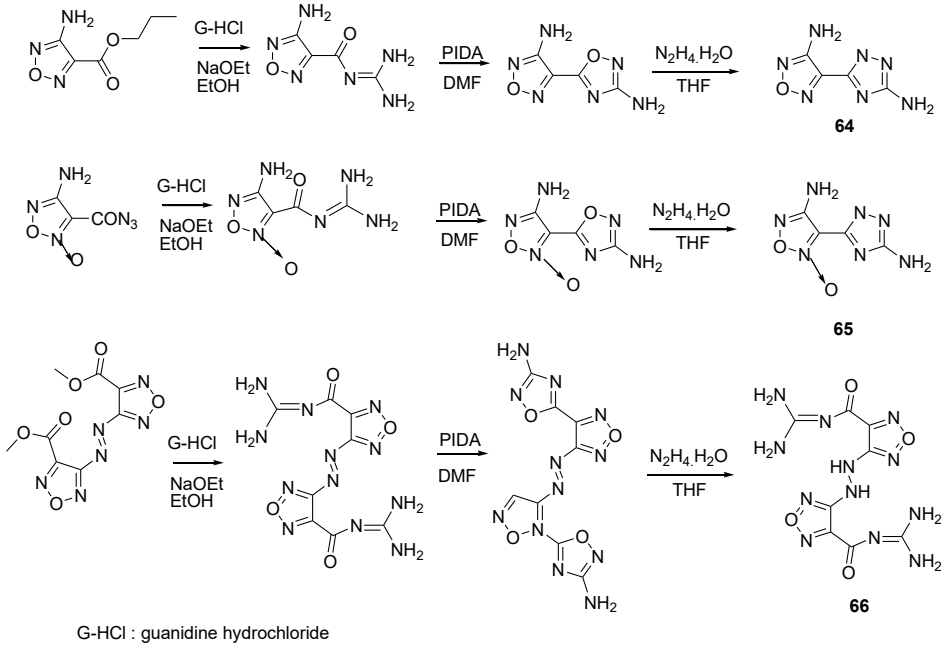
Scheme 47: Synthesis of 2-(2-substituted[1,8]naphthpyridin-3-yl)-5-(substituted-2-thienyl)-1,3,4-oxadiazoles employing PIDA under grinding conditions

Mogilaiah and coworkers (2017) explored the synthetic utility of iodobenzene diacetate in the oxidative cyclization of N'3-[1-(substituted-2-thienyl)methylidene]-2-substitued[1,8]naphthyridine-3-carbohydrazides with PIDA in solid state. The reaction occurred at room temperature by simple grinding and 1-[(5-aryl-1,3,4-oxadiazol-2-yl)-methyl]-3-(4-nitrophenyl)-1,2-dihydro[1,8]-naphthyridin-2-ones **63** were isolated in 85-96% yields. All the synthesised compounds were screened for antibacterial and anti-inflammatory activity. It was found that 1-[(5-(2-chlorophenyl)-1,3,4-oxadiazol-2-yl)-methyl]-3-(4-nitrophenyl)-1,2-dihydro [1,8]-naphthyridin-2-ones showed both the antibacterial and anti-inflammatory activities. In addition, compounds (4-Me-phenyl, 2-Cl-phenyl, 4-F-phenyl) also showed good anti-inflammatory activity.(Scheme 48)[105]



Scheme 48: PIDA mediated oxidative cyclization of N'3-[1-(substituted-2-thienyl)methylidene]-2-substitued[1,8]naphthyridine-3-carbohydrazides through grinding

Furazan substituted 3-amino-5-R-1,2,4-oxadiazoles were synthesized through PIDA by Tang et al., 2018. The reaction of N-carbamimidoyl derivatives with IBD (1.5 eq.) in DMF at room temperature for 24 h afforded the oxadiazoles **64, 65** and **66** in moderate yields. (Scheme 49)[106]



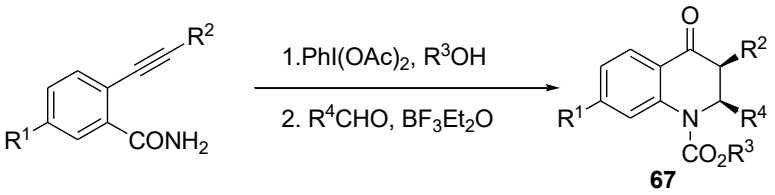
Scheme 49: PIDA enabled synthesis of furazan substituted 3-amino-5-R-1,2,4-oxadiazoles

2.4. 6-membered compounds with one/two/three heteroatoms

2.4.1. 6-membered compounds with one heteroatom

2.4.1.1. With one nitrogen. The synthesis of quinolones from the PIDA promoted Hofmann-type rearrangement of 2-alkynylbenzamides showed high *trans*-selectivities. The substituent effect (R^1) on the aromatic ring showed that either electron-donating or moderately electron-withdrawing substituents R^1 of 2-

alkynylbenzamides, the yields of the quinolones **67** were 72-80%. Aromatic ring bearing strongly electron-withdrawing nitro group hinders the reaction and higher temperature 90 °C is needed in *p*-cyanobenzaldehyde or *p*-nitrobenzaldehyde. Further, the reaction could also tolerate aliphatic aldehydes and terminal alkyne. While, benzophenone failed to give quinolones under similar conditions. (Okamoto et al., 2014). (Scheme 50)[66]

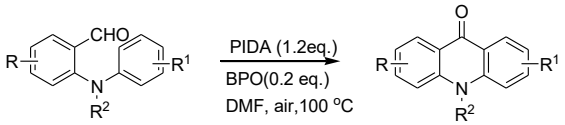


67

R^1 = H, F, NO_2, OMe ; R^2 = H, Ph, n-Bu ; R^3 = Et, Me; R^4 = p-Tol, Ph, p-CNC_6H_4, p-$NO_2C_6H_4$, hexyl, cylohexyl

Scheme 50: Synthesis of quinolones from the PIDA promoted Hofmann-type rearrangement of 2-alkynylbenzamides

In view of the classical Friedel-Crafts reaction for C-C bond formation, Zheng et al studied a recent PIDA mediated approach for cross-dehydrogenative coupling of different 2-(N-arylamino)aldehydes with benzoyl peroxide (BPO) in DMF at 100°C to form acridone derivatives **68**. The reaction tolerated both electron releasing and electron withdrawing groups equally well. (Scheme 51)[107]

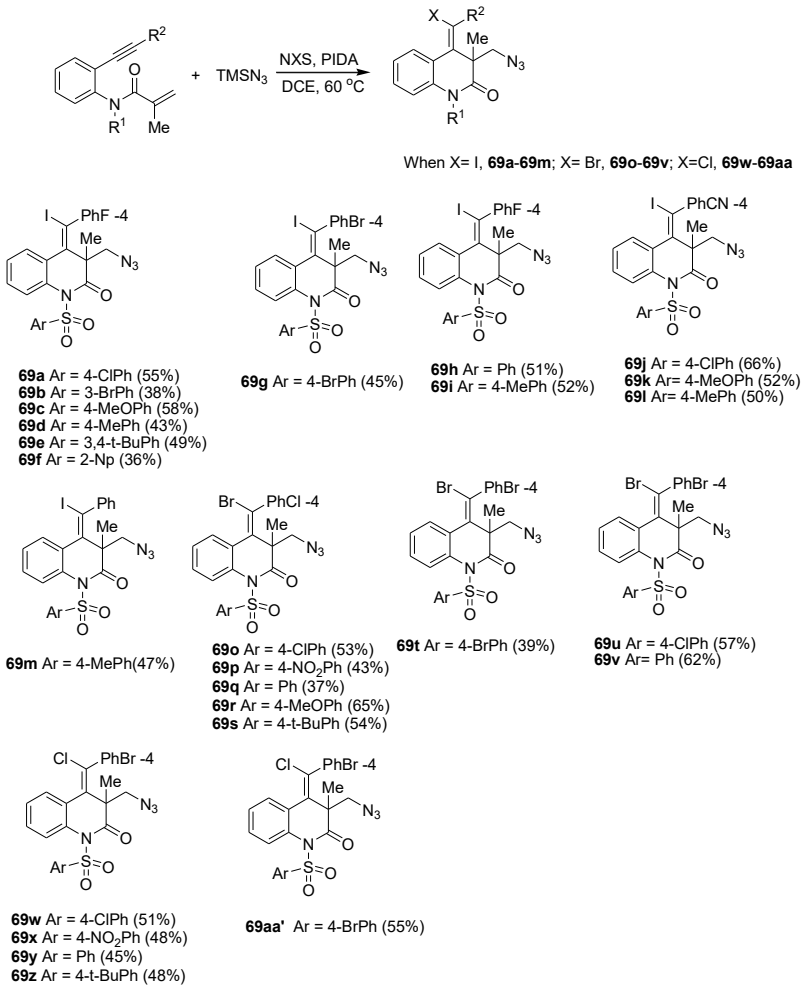


68

R = H, 3-Cl, 4-F, 4-OMe, 4-Me
R^1 = H, 3'-CF_3, 3'-Br, 4'-OMe, 4'-Me, 2'-Me, naphthalenyl
R^2 = Me, Bn

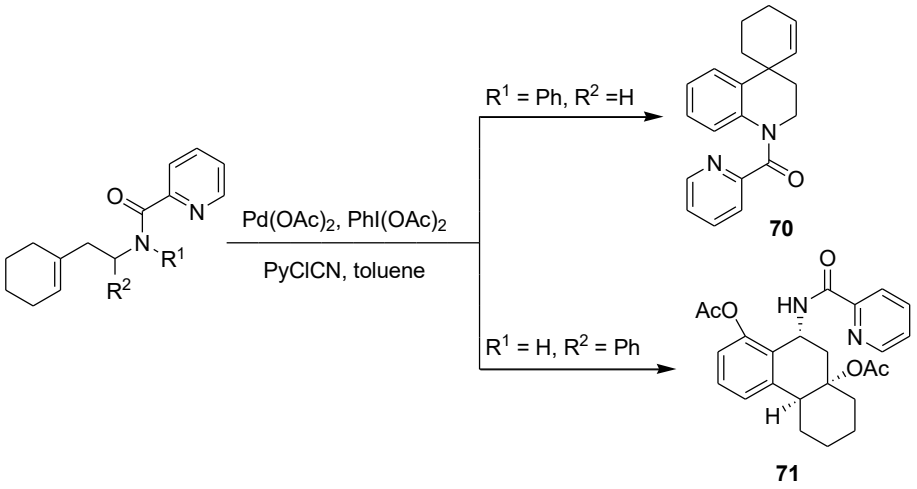
Scheme 51: Synthesis of acridones facilitated by PIDA

Wang and coworkers (2016) reported the PIDA promoted synthesis of polyfunctionalized 3,4-dihydroquinolin-2(1H)ones **69** via radical haloazidation of benzene-tethered 1,7-enynes. The reaction was carried out with $TMSN_3$ as a source of azidyl radicals in the presence of N-halosuccinimide (Scheme 52).[108]



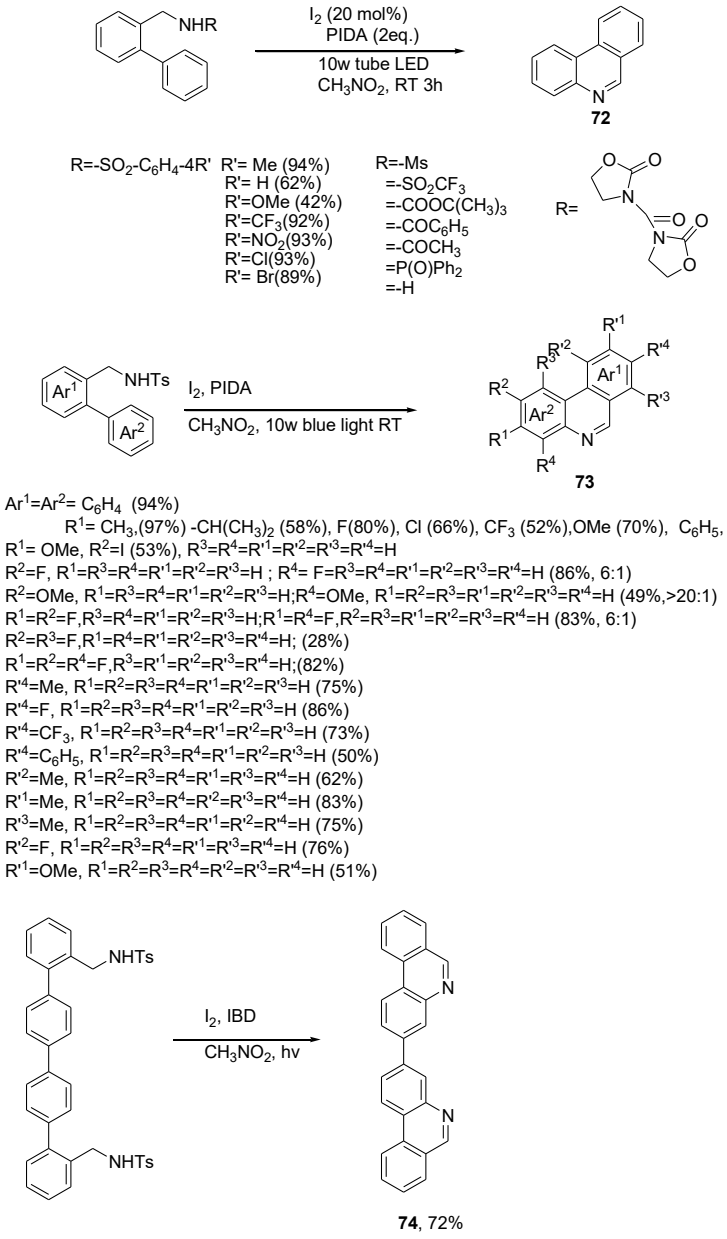
Scheme 52: PIDA in the three-component iodo/bromo/chloro-azidation of 1,7- enynes to synthesize polyfunctionalized 3,4-dihydroquinolin-2(1H)ones

Zang et al. (2017) explored the direct oxidative arylation of the alkenyl anilines, with picolinamide as a directing group, which undergo cyclization to afford spiro-dihydroquinolines **70**, **71**. Additionally, the sequential oxidative arylation and double acetoxylation of the alkenyl benzylamines revealed the isolation of the octahydrophenanthrene derivatives. It was found from a number of experiments that $Pd(OAc)_2$ and $PhI(OAc)_2$ are important for this conversion. Different Pd(II) catalysts $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, or $PdCl_2$(dppf) were found to give lesser yields (38-55%); metal catalysts viz., $FeCl_3$, $RuCl_3$, $Sc(OTf)_3$ when tried failed to initiate the reaction. Further, poor yields were reported in the absence of PyClCN or presence of various additives such as PhCN. The study also reported that changing the solvent or reducing temperature has no effect in improving the yields (Scheme 53).[109]



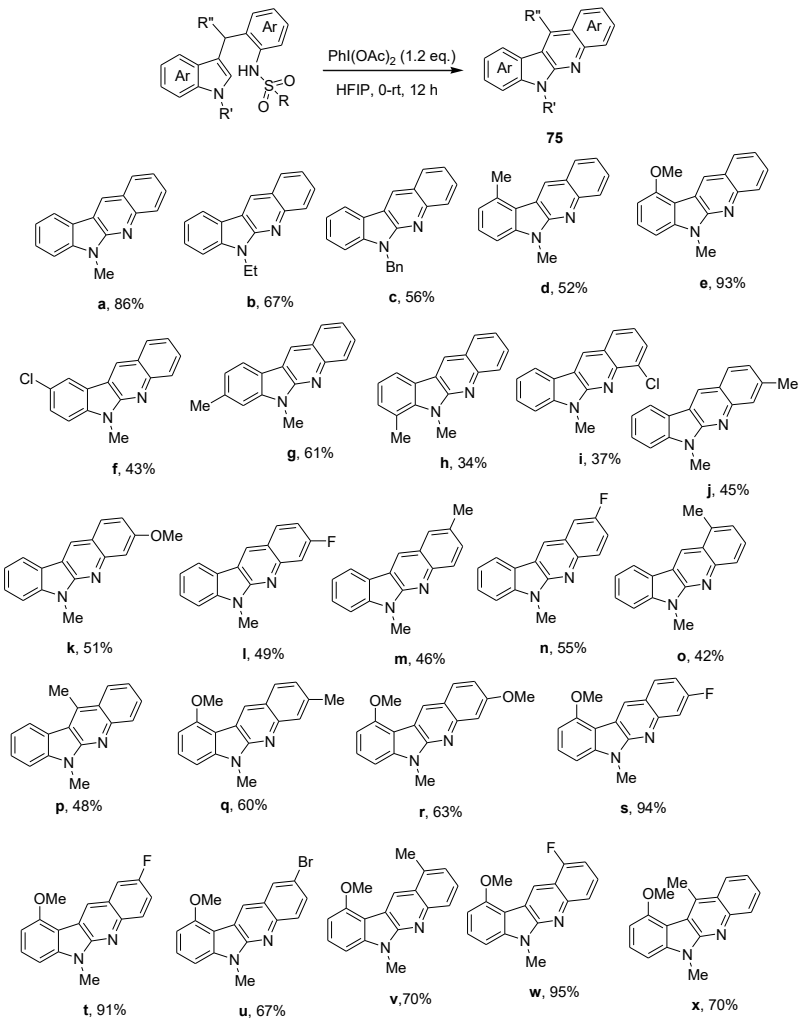
Scheme 53: Oxidative arylation of alkenyl anilines to spiro-dihydroquinolines

Iodobenzene diacetate supported one pot intramolecular C-H amination followed by oxidation of the cyclic intermediate using molecular oxygen under blue light for the synthesis of phenanthridines was explored. Gao et al studied the reaction of N-([1,1'-biphenyl] -2-ylmethyl)-4-methylbenzenesulfonamide, I_2, $PhI(OAc)_2$ in CH_3CN under 10 W blue light at room temperature and the phenanthridine **72** was isolated in 75% yield. The effects of N-substituents on the rate of the reaction were also explored. The expected products were obtained in moderate to good yields in N-sulfonyl-containing aryl, methyl and trifluoromethyl substrates as well as N-Boc substituted substrate could also gave the product in 33% yield. The N-phosphoryl substituted substrates gave moderate to good yields of phenanthridine **73**, **74**. While, no product was isolated in N-acyl-protected substrates such as N- ([1,1'-biphenyl] -2-ylmethyl)benzamide and N- ([1,1'-biphenyl] -2-ylmethyl)acetamide. Oxidation of methanamine to cyano group was observed when N free [1,1'-biphenyl] -2-ylmethanamine was tried. The detailed mechanistic aspects revealed that the N-I bond undergoes photolytic homolysis, giving an iodine radical and an N-centered radical from N-protected-2-biarylmethanamine and its derivatives. The transformation from the intermediate N-tosyl-5,6-dihydrophenanthridine to phenanthridine occurs through a radical mechanism and was confirmed by the fact that the reaction was completely inhibited in the presence of free radical scavengers (like TEMPO and BHT) (Scheme 54).[110]



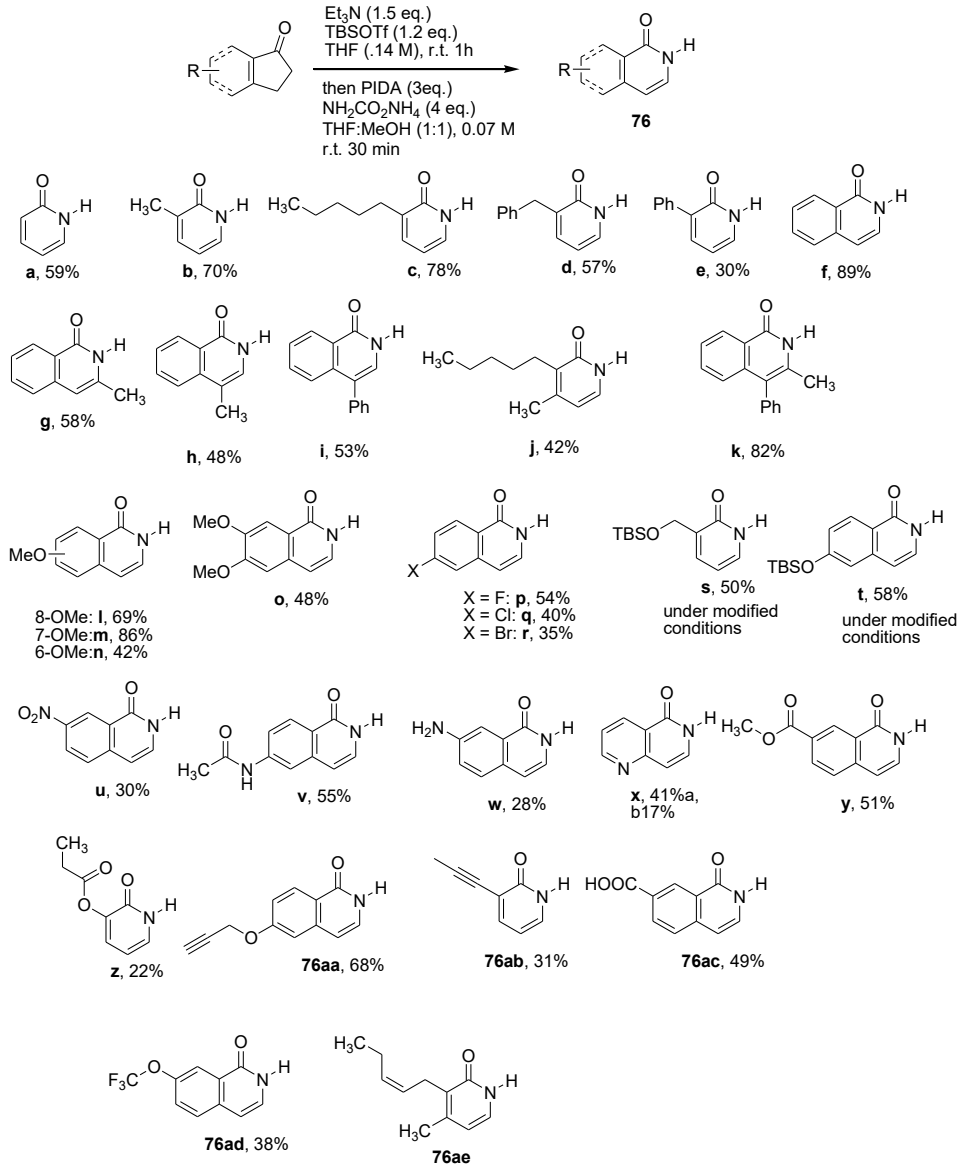
Scheme 54: Iodine-supported amination and oxidation under visible light to synthesise phenanthridines

Wang et al., (2021) developed an efficient synthetic approach to access a series of indolo[2,3-b]quinoline derivatives. PIDA was utilized as oxidising agent in the intramolecular oxidative C–N coupling followed by detosylative aromatization. The reaction of indole derivatives with PIDA (1.2 equivalent) under argon atmosphere in HFIP at 0^{o}C followed by stirring for 12 h yielded the corresponding products **75** in 34-94% yield. It was also reported that both steric hindrance as well as electronic factors influenced the product yields (Scheme 55).[111]



Scheme 55: PIDA mediated intramolecular cyclization for preparing indolo[2,3-b]quinolones

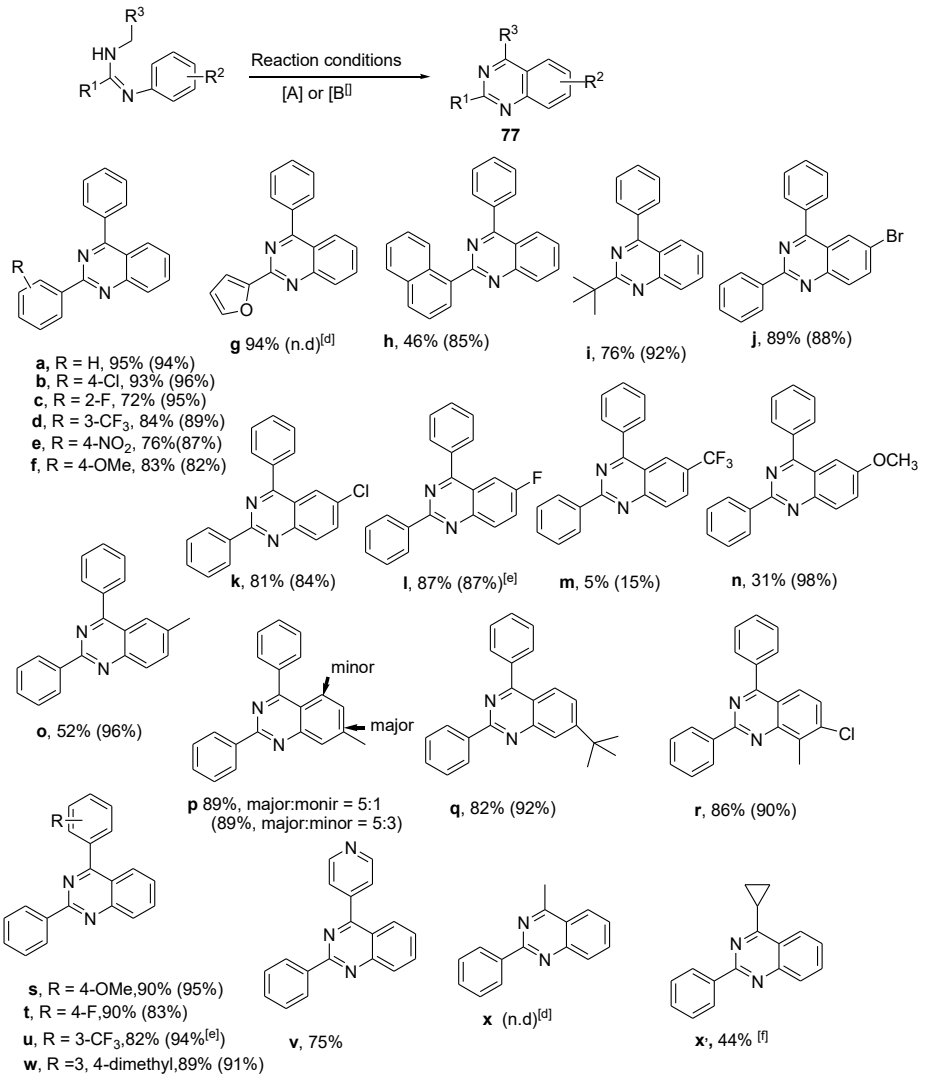
One-pot oxidative amination process for the synthesis of pyridones from readily available cyclopentenones is reported by Botlik et al. The reaction sequence involves the *in situ* formation of silyl enol ethers from the cyclopentenone building blocks, followed by the introduction of a nitrogen atom into the carbon skeleton and successive aromatisation to yield the desired pyridone **76** products. The transformation exhibits broad functional group tolerance, complete regioselectivity, and is well scalable, providing facile access to both industrially relevant pyridone products and their derivatives, including 15N-labelled targets (Scheme 56).[112]



Scheme 56: IBD mediated synthesis of pyridones from cyclopentenones

2.4.2. 6-membered compounds with two heteroatoms

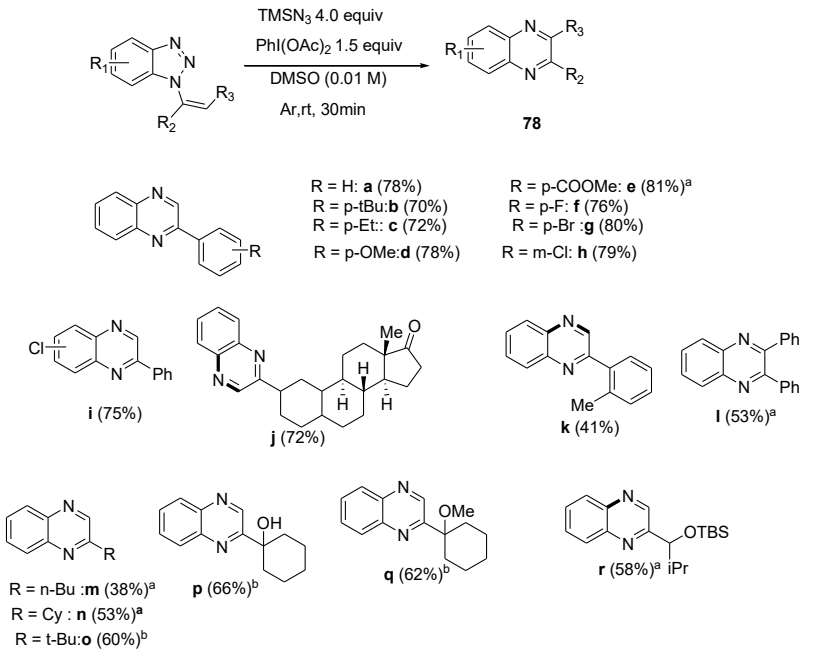
2.4.2.1. With two nitrogens. A large range of variously substituted quinazolines **77** have been synthesised under metal- and base-free conditions by Lin et al., 2014. It was reported that PIDA-promoted reaction with solvents of different polarity yielded 6-membered rings. It was further found that quinazoline was formed using $K_2S_2O_8$ and TEMPO (0.2 equiv) in CH_3CN at 120 °C for 3 h. The effect of different substituents was also studied. (Scheme 57)[113]



Reaction conditions [A]: 3 (0.4 mmol), $PhI(OAc)_2$ (1.6 mmol), toluene (40 mL), 120 °C, 1 h.
Reaction conditions [B]: 3 (0.2 mmol), $K_2S_2O_8$ (0.6 mmol), TEMPO (0.04 mmol), MeCN (4 mL), 120 °C, 3h.

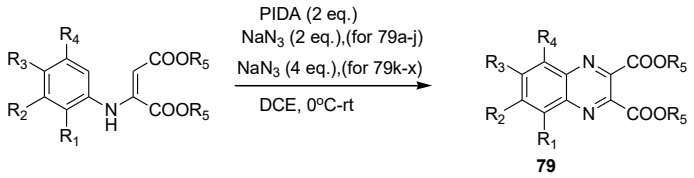
Scheme 57: Application of PIDA in the synthesis of quinazoline derivatives

Su et al., 2015, have introduced an approach for 1,2,3-triazole ring opening via intermolecular azide radical addition to vinyltriazole providing excellent chemoselectivity to yield quinoxaline under mild, reagent-controlled conditions. The quinoxaline product (**78**) was synthesized through metal-free denitrogenative transannulation by using $TMSN_3$ and employing much higher dilution (0.01 M in DMSO) to suppress competing intermolecular pathways, resulting in good yields and demonstrating a viable alternative synthesis for substituted quinoxalines.(Scheme 58)[114]



Scheme 58: Synthesis of quinoxaline products through denitrogenative transannulation

PIDA facilitated N incorporation in intermolecular cyclization was reported by Sagar et al. in 2016. Synthesis of diethyl quinoxaline-2,3-dicarboxylates **79** starting from diethyl 2-(phenylamino)maleate and azides using NaN_3 (2eq.)/PIDA (2eq.) in DCE promoted the workers to study the scope of the reaction with differently substituted substrates (Scheme 59). It was concluded that synthesis of various 1,4,5,8-tetraazaphenanthrene derivatives **80** was assisted using PIDA, NaN_3 in DCE . Further studies were conducted to unfold the isolation of tetramethyl pyrazino[2,3-f]-quinoxaline-2,3,8,9-tetracarboxylates from bis N-aryl vinylogous carbamates using PIDA (4 equiv)/NaN_3 (8 equiv) (Scheme 60).[115]



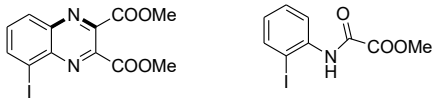
Nitrogenation reaction of N-aryl vinylogous carbamates bearing electronic donating groups

a R^1= H, R^2= H, R^3= H, R^4=H, R^5=Et (78%); **b** R^1= H, R^2= H, R^3= H, R^4=H, R^5=Me (72%)
c R^1= H, R^2= H, R^3= OMe, R^4=H, R^5=Me (67%); **d** R^1= H, R^2= Me, R^3= OMe, R^4=H, R^5=Et (80%)
e R^1= H, R^2= Me, R^3= OMe, R^4=H, R^5=Me (75%); **f** R^1= Me, R^2= H, R^3= H, R^4=Me, R^5=Me (65%)
g R^1= Me, R^2= H, R^3= Me, R^4=H, R^5=Me (68%); **h** R^1= Me, R^2= H, R^3= Me, R^4=H, R^5=Et (64%)[c]
i R^1= Me, R^2= H, R^3= H, R^4=H, R^5=Et (62%); **j** R^1= Me, R^2= H, R^3=H, R^4=H, R^5=Me (61%)

Nitrogenation reaction of N-aryl vinylogous carbamates bearing halogens

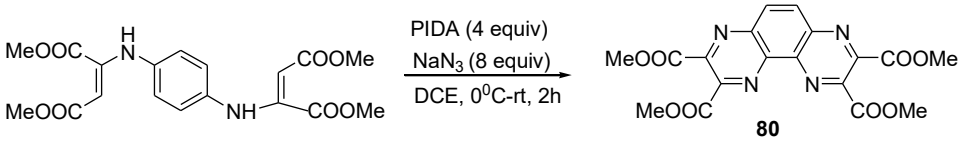
When R^1= I, Br, H, Cl, F; R2= H; R3=Me, I, Br, H, Cl, F; R4=H, Br; R5=Me, Et,

k, R^1= I, R^2= H, R^3= H, R^4=H, R^5= Et (58%, 0%), **l**: R^1= I, R^2= H, R^3= H, R^4=H, R^5= Me (59%);
m: R^1= Br, R^2= H, R^3= H, R^4=H, R^5= Et (61%), **n** R^1= Br, R^2= H, R^3= H, R^4=H, R^5= Me (58%);
o R^1= F, R^2= H, R^3= H, R^4=H, R^5= Et (57%); **p** R^1= H, R^2= H, R^3= I, R^4=H, R^5= Et (61%);
q R^1= H, R^2= H, R^3= Br, R^4=H, R^5= Et (64%); **r** R^1= H, R^2= H, R^3= Br, R^4=H, R^5= Me (51c%, 4c%);
s, R^1= H, R^2= H, R^3= Cl, R^4=H, R^5= Et (64%); **t** R^1= Cl, R^2= H, R^3= H, R^4=H, R^5= Me (60%, 10%);
u R^1= H, R^2= H, R^3= F, R^4=H, R^5= Et (62%); **v** R^1= H, R^2= H, R^3= F, R^4=H, R^5= Me (64%);
w-1, 2 R^1= Br, R^2= H, R^3= H, R^4=Br, R^5= Me (64%, 3%c);
x-1, 2 R^1= Br, R^2= H, R^3= Me, R^4=H, R^5= Et (48%, 5%c);



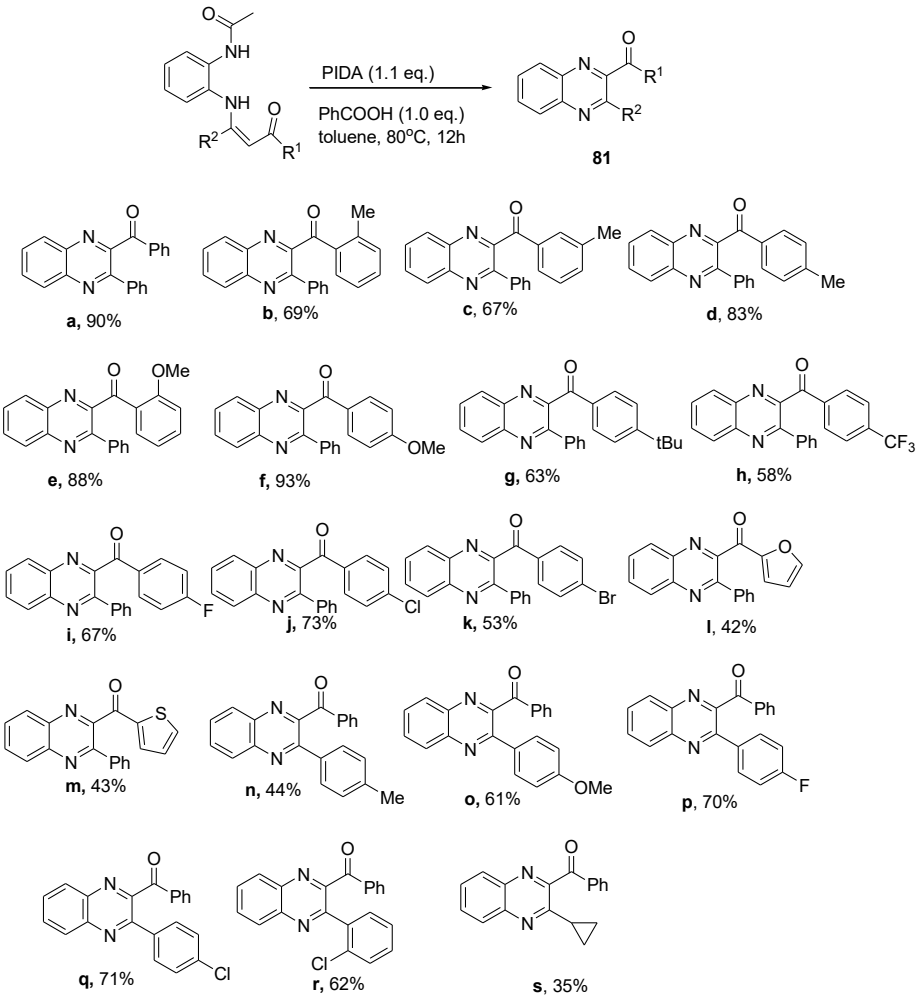
79k-1 (58%) **79k-2** (0%)

Scheme 59: Synthesis of diethyl quinoxaline-2,3-dicarboxylates using PIDA (4 equiv)/NaN_3



Scheme 60: PIDA in the synthesis of tetramethyl pyrazino [2,3-*f*] quinoxaline-2,3,8,9-tetracarboxylate

Substituted N-(2-acetaminophenyl)enaminones were used as precursors for the synthesis of quinoxalines **81** in toluene with PIDA (1.1 equiv.) and PhCOOH (1.0 equiv.) as the additive at 80º C in 44-93% yields by Zhang et al 2019. The reaction could tolerate very well, both electron releasing as well as electron withdrawing substituents. Further, it was reported that the reactants with electron donating substituents at para position gave good yields compared to ortho or meta positions. (Scheme 61)[116]



Scheme 61: PIDA-mediated intramolecular oxidative synthesis of quinoxalines from enaminones

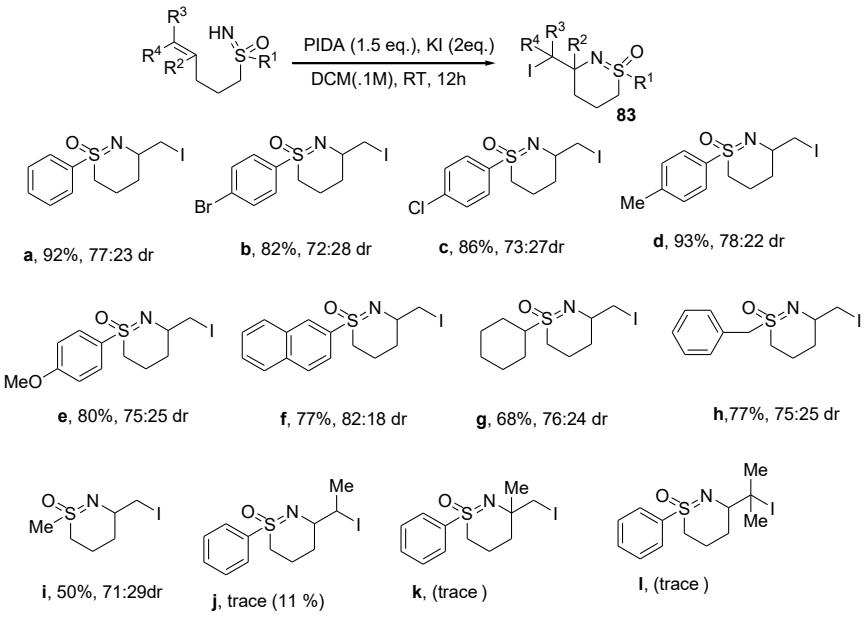
Visible-light and PIDA promoted reaction for the synthesis of 1,2,3-triazolo[1,5-a]quinazolin-5(4H)-ones **82** was reported (Du et al., 2020). The reaction involves intramolecular C–H amination of N-phenyl-2-(1,2,3-triazol-1-yl)benzamides using catalytic iodine I_2 (activated under visible light blue LEDs) at room temperature. The radical intermediate generated from iodine initiated reaction undergoes coupling with the azole moiety leading to formation of 1,2,3-triazolo[1,5-a]quinazolin-5(4H)-one product. The study showed that various groups on the phenyl ring linked to the amide nitrogen atom both electron-donating and electron-withdrawing groups, as well as N-alkyl substituted 2-(1,2,3- triazol-1-yl)benzamides were also tolerated in the reaction . Further, the presence of an iodo substituent was shown to survive the reaction conditions, allowing for further functionalization (Scheme 62).[117]

82

R^1=H, R^3=p-tolyl, R^2=-C_6H_5 (90%)
R^1=H, R^3=p-tolyl, R^2=2-Me-C_6H_4 (73%)
R^1=H, R^3=p-tolyl, R^2=3Me-C_6H_4 (87%)
R^1=H, R^3=p-tolyl, R^2=4-Me-C_6H_4 (65%)
R^1=H, R^3=p-tolyl, R^2=2-OMe-C_6H_4 (98%)
R^1=H, R^3=p-tolyl, R^2=2-iPr-C_6H_4 (47%)
R^1=H, R^3=p-tolyl, R^2=2-Cl-C_6H_4 (77%)
R^1=H, R^3=p-tolyl, R^2=3-Cl-C_6H_4 (64%)
R^1=H, R^3=p-tolyl, R^2=4-Cl-C_6H_4 (96%)
R^1=H, R^3=p-tolyl, R^2=4-I-C_6H_4 (89%)
R^1=H, R^3=p-tolyl, R^2=-CH2$(C_6H_4)_3CH_3$ (51%)
R^1=H, R^3=p-tolyl, R^2=-CH2-C_6H_5 (48%)
R^1=Me, R^2=Ph, R^3=p-tolyl (88%)
R^1=Cl, R^2=Ph, R^3=p-tolyl (37%)
R^1=Me-N(1),phenyl ring of substratr, R^2=Ph, R^3=p-tolyl (88%)
R^1=Cl-N(1),phenyl ring of substratr R^2=Ph, R^3=p-tolyl (87%)
R^1=Me-N(1),phenyl ring of substratr R^2=Ph, R^3=p-tolyl (29%)
R^1=H, R^2=Ph, R^3=p-anisyl (98%)
R^1=H, R^2=Ph, R^3=o-anisyl (81%)
R^1=H, R^2=Ph, R^3=p-chlorophenyl (75%)
R^1=H, R^2=Ph, R^3=m-chlorophenyl (64%)
R^1=H, R^2=Ph, R^3=o-chlorophenyl (55%)
R^1=H, R^2=Ph, R^3=cyclopropyl (68%)
R^1=H, R^2=Ph, R^3=2-thienyl (60%)

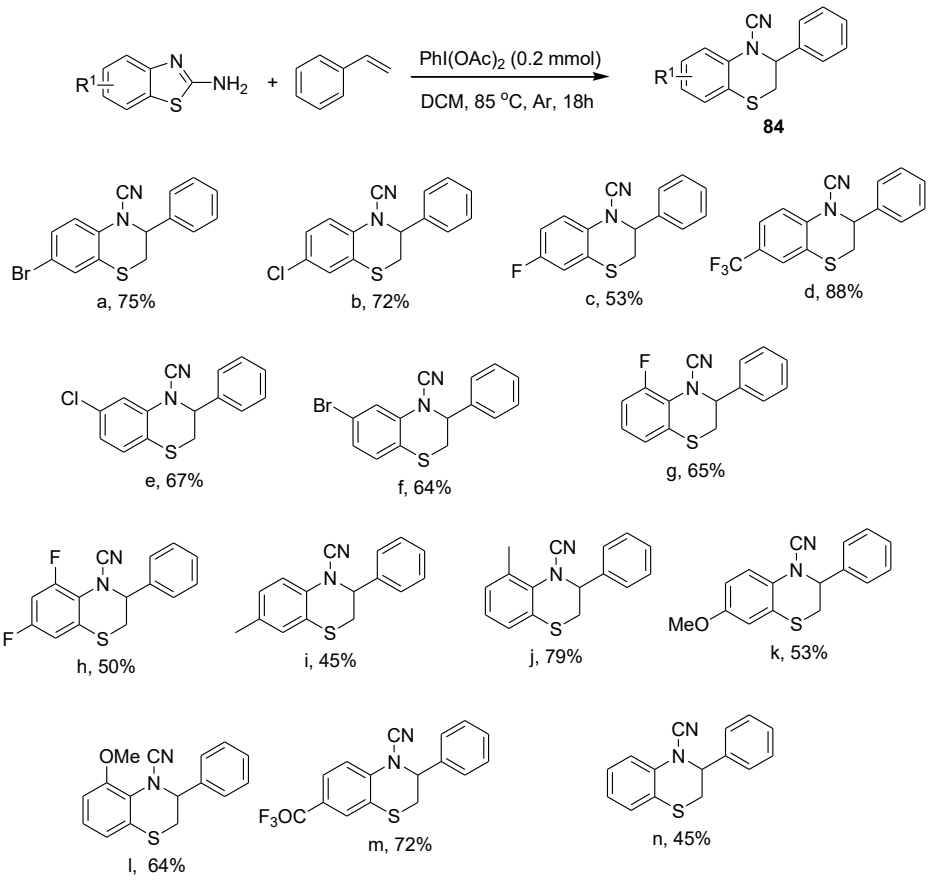
Scheme 62: Visible-light and PIDA promoted synthesis of 1,2,3-triazolo[1,5-a]quinazolin-5(4H)-ones

2.4.2.2 With one nitrogen and one sulphur. Halocyclization of S-alkenylsulfoximines was explored by Wang et al. in 2016. The treatment of S-(pent-4-en-1-yl)-S-arylsulfoximines in DCM with KI (2 equiv.) and PIDA (1.5 equiv.) for 12 h gave the corresponding cyclized products i.e. S-oxides of dihydro isothiazoles **83** and tetrahydro-1,2- thiazines in 77% to 93% yields. The diastereoselectivity ratios were reported to be dr (72:28 to 82:18) when R^1 = C_6H_5, 4-Br-C_6H_4, 4-ClC_6H_4, 4CH_3-C_6H_4, 4-OCH_3-C_6H_4, $C_{10}H_7$ (2-naphthyl) and dr (up to 76:24) when R^1 = C_6H_{11}, C_7H_7, CH_3 and the exo products were obtained with excellent regioselectivity. While studying the electronic effects it was observed that electron donating or electron withdrawing substituents did not have much effect on the output of the reaction. Further, S-alkenyl-S-alkylsulfoximines also afforded the respective products in 50-77% yields and dr (up to 76:24). However, in the case of trisubstituted alkenes, due to steric factors induced by the additional methyl substituents, the reaction failed with trisubstituted double bonds under similar reaction conditions.(Scheme 63)[118]



Scheme 63: Synthesis of tetrahydro-1,2-thiazine 1-oxides

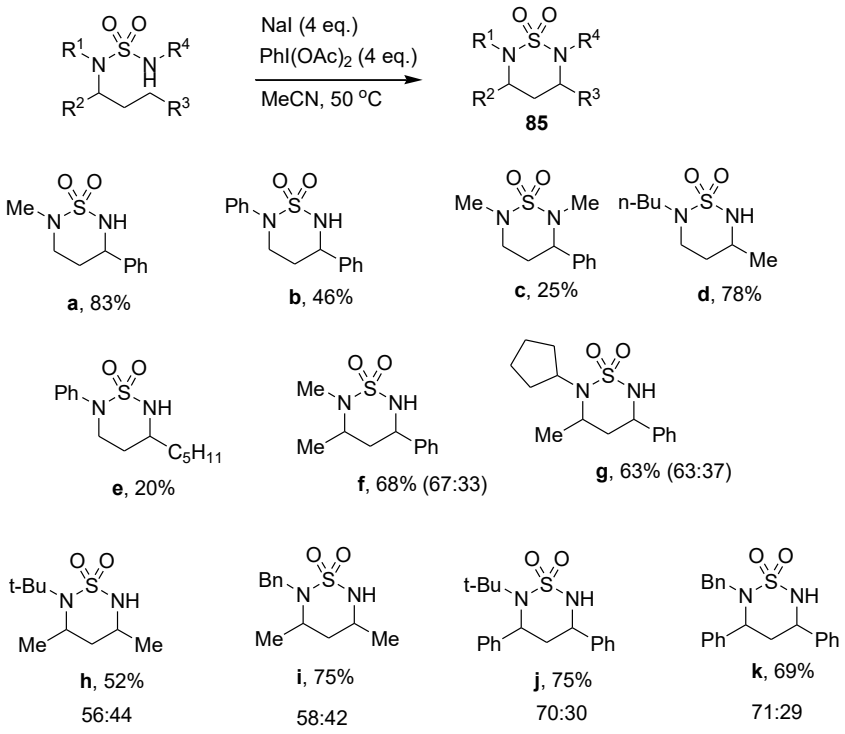
Sun and Bao (2022) reported the use of PIDA in (4+2) heteroannulation method in the oxidative ring expansion of 2-aminobenzothiazoles with olefins to give corresponding benzothiazines **84**. The reaction tolerated a range of olefins, including terminal and internal alkenes, as well as various substituted styrene derivatives, yielding moderate to excellent yields. The highest yield (92%) was obtained in reaction with 2-phenylpropylene with the desired product. The computational studies provided mechanistic details that the reaction occurs via a non-radical pathway, emphasizing the importance of the primary amino group in 2-aminobenzothiazoles including the formation of intermediates and transition states. Frontier molecular orbital (FMO) studies further gave an insight into the key [4+2] cycloaddition step. The alternative scenario for this reaction is mainly due to the presence of cyano electron-withdrawing group with the diene analogue. However, this [4+2] cycloaddition step is not favored for the dienophile with electron-withdrawing groups, which might account for the unsuccessful case with ethyl acrylate. (Scheme 64)[119]



Scheme 64: PIDA mediated synthesis of dihydro-1,4-benzothiazine derivatives via oxidative ring-expansion of 2-aminobenzothiazoles with olefins

2.4.3. 6-membered compounds with three heteroatoms

2.4.3.1 With two nitrogens and one sulphur. The work describes a method for the regioselective γ-C–H amination of the side-chain of saturated 2-alkyl nitrogen heterocycles, proceeding through a sulfamide-directed 1,6-radical translocation, thus providing rapid access to 1,3-diamines (Griggs et al., 2021). The reaction of differently substituted linear alkyl amines (non reacting N substituents and N-alkyl chain undergoing amination) using NaI (4eq.) in acetonitrile at 50 °C with 4 eq. $PhI(OAc)_2$ afforded cyclic sulfamides **85**. The higher selectivities for cyclisation to benzylic positions was considered due to faster interconversion of the iodides and/or an increased preference for the larger phenyl substituent (versus methyl) to be equatorial. The C-H amination reaction was explored with pyrrolidine and azepane ring systems, heteroatom containing rings, morpholine, and saturated and aromatic bicyclic structures, octahydrocyclopena[c]pyrrole and 1,2,3,4-tetrahydroisoquinoline and in all these reactions cis isomer was found to be the major diastereomer confirmed by X-ray analysis and/or NMR spectroscopy (Scheme 65). The practicality of this approach to 1,3-diamines is studied in a short synthesis of the alkaloid tetraponerine T8 and non-natural analogues.[120]

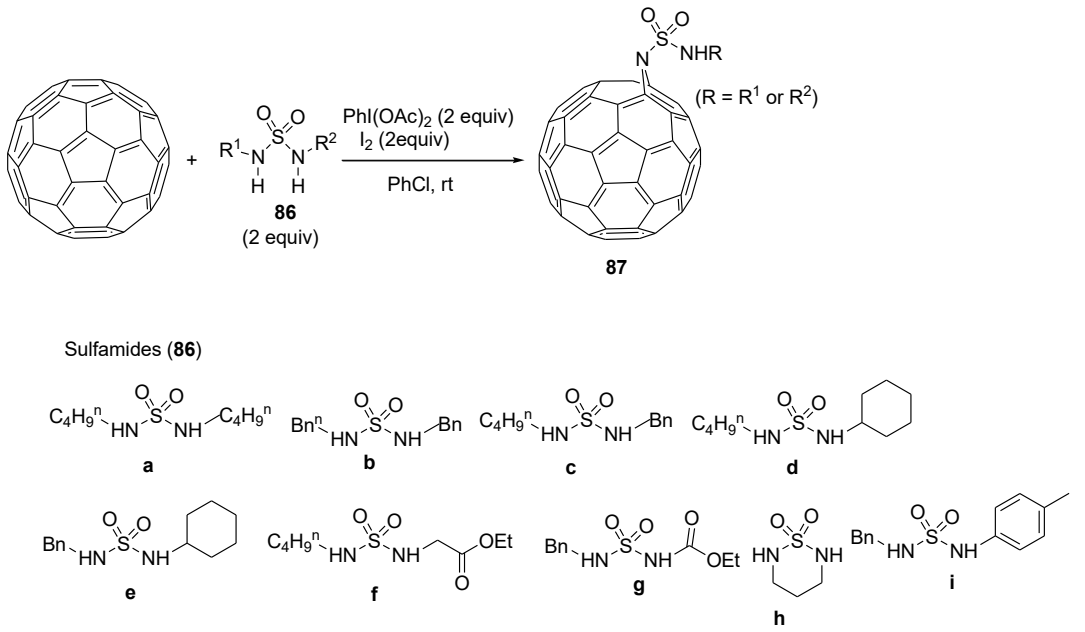


Scheme 65: PIDA mediated synthesis of 1,3-diamines by regioselective γ-C–H amination of the side-chain of saturated 2-alkyl nitrogen heterocycles

2.5 Miscellaneous

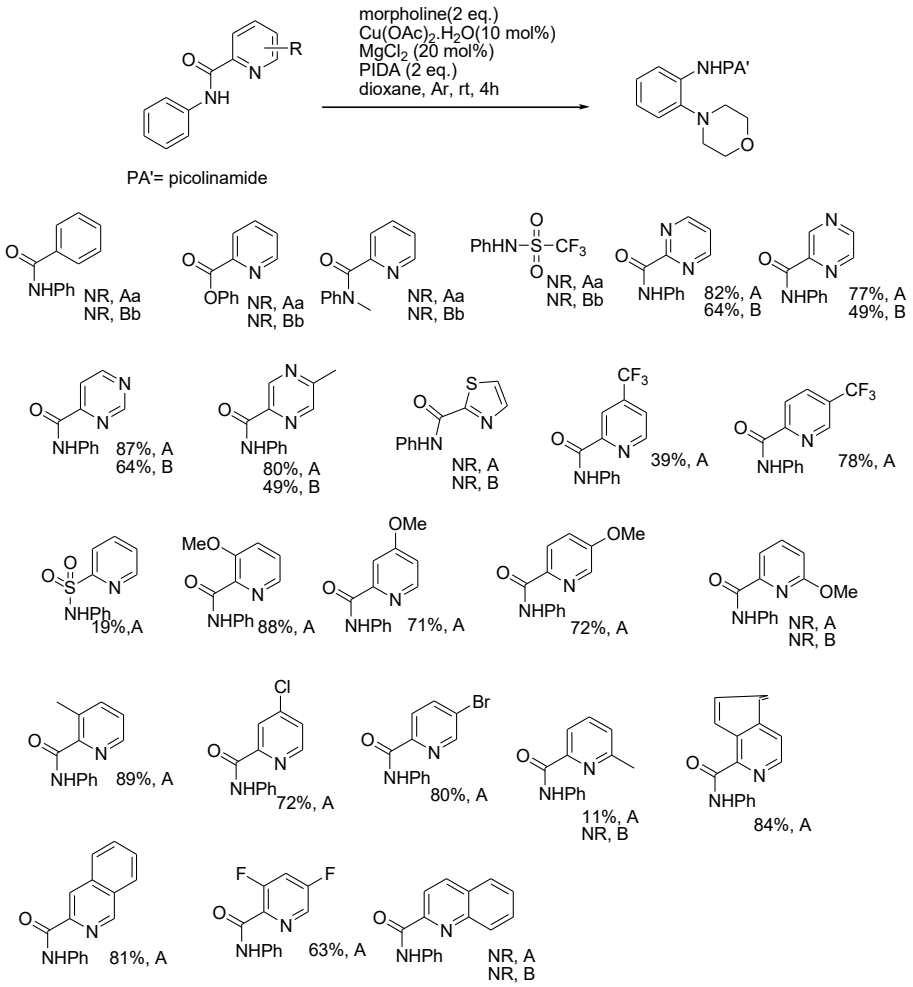
2.5.1 Azafullaenoids

Yang et al. explored the PIDA assisted synthesis of C60-fused cyclic sulfamide/ phosphoryl diamide derivatives **87**. The intermolecular diamination under $PhIO/I_2$ or $PhI(OAc)_2/I_2$ conditions of C60 and sulfamides/ phosphoryl diamides afforded the desired fullerenes in good yields. (Scheme 66)[121]

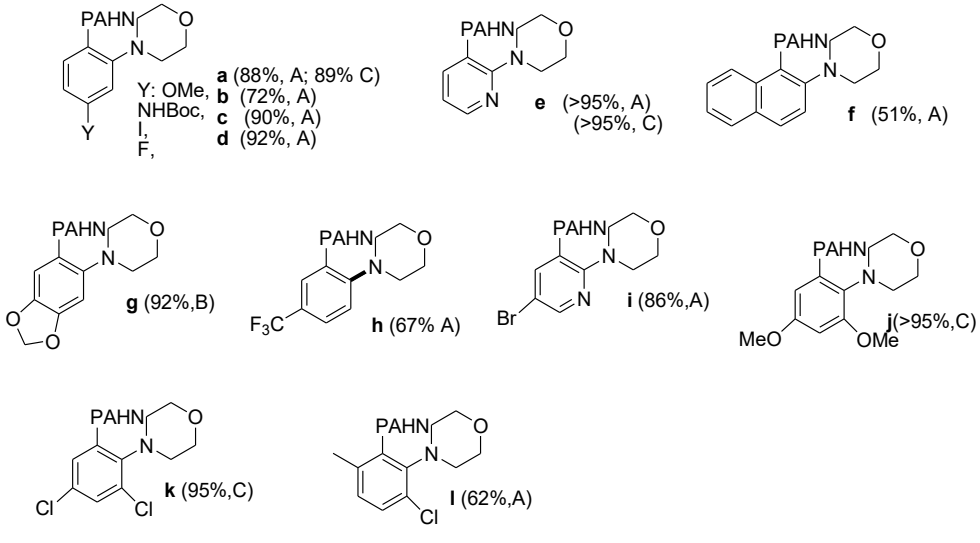


Scheme 66: Synthesis of different C60-fused cyclic sulfamide/ phosphoryl diamide derivatives using $PhI(OAc)_2/I_2$

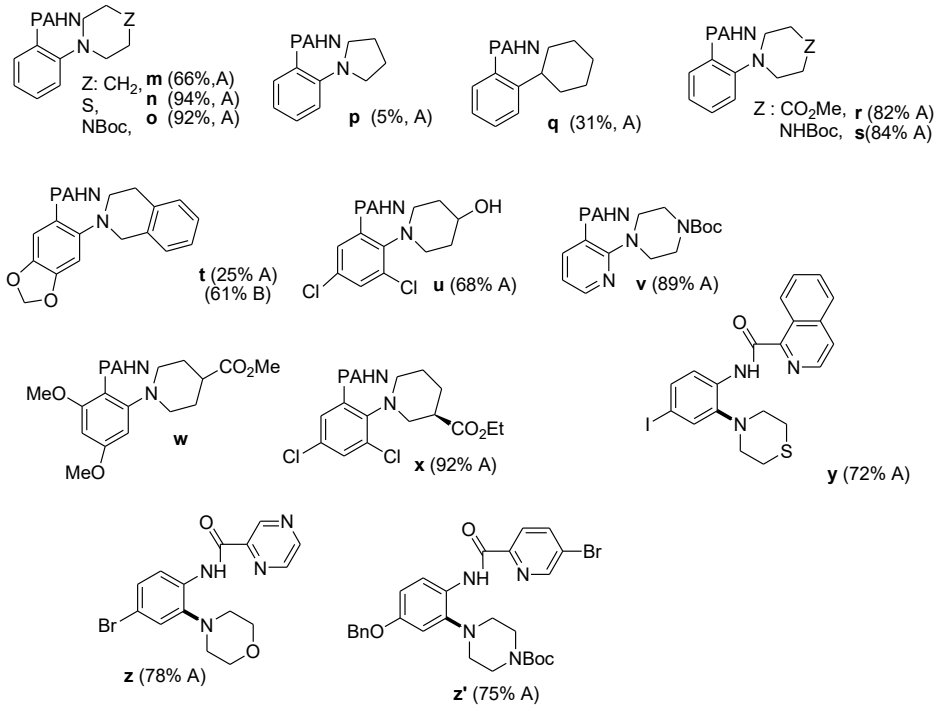
2.5.2 Arylamination of anilines. Copper catalysed ortho alkylamination of anilines with $MgCl_2$, PIDA (2 equiv.) in dioxane at room temperature was reported as shown in the (Scheme 67). The single electron transfer (SET)-mediated mechanism was suggested by Li and coworkers (2014).[122]



A) Substrate scope of anilines



B) Substrate scope of amines



[a] Isolated Yield on a 0.2mmol scale under the standard conditions. (A): rt, 4h. (B): 90 °C,4h. (C): rt, 5 min.

Scheme 67: Copper-catalyzed carboxamide-directed ortho amination of anilines with alkylamines

3. Conclusions

The review summarizes the significance of the iodine (III) reagent, PIDA in the construction of a diverse class of the nitrogen-containing heterocycles. The compilation in the critically important area will provide valuable insights for all the scientists working in synthetic organic chemistry, medicinal chemistry or material science and will inspire others to work with the environment-friendly organoiodine reagents.

Abbreviations

IBD- Iodobenzene diacetate
PIDA- Phenyliodine diacetate
DIB- (Diacetoxyiodo)benzene
TIPS- Triisopropylsilyl
Troc- Trichloroethoxycarbonyl
Teoc- 2-(Trimethylsilyl)ethoxycarbonyl
DDQ- *2,3-Dichloro-5,6-dicyano-1,4-benzoquinone*
MDC- Methylenedichloride
DCE- Dichloroethane

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