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# Recent applications of Rose Bengal catalysis in N-heterocycles: a short review

Arjita Srivastava,<sup>a</sup> Pravin K. Singh,<sup>a</sup> Akram Ali,<sup>a</sup> Praveen P. Singh<sup>b</sup> and Vishal Srivastava<sup>\*a</sup>

The visible light harnessing ability of Rose Bengal, an organic dye, has been extensively employed in organic chemistry over the last few years. In visible light mediated reactions, this photoredox catalyst operates through multiple pathways and has the ability to provide distinctly different and valuable results. The most significant of these results are bond creation, bond functionalization, particularly for C–H and C–heteroatom bonds, and cross couplings. It is crucial to study these cases whenever these bond formations and couplings lead to the formation of heterocyclic compounds or their functionalization. The diverse biological activity and medicinal applications of heterocyclic compounds is an extensively explored area. This review primarily attempts to demonstrate the synthetic potential of Rose Bengal for synthesis and site selective functionalization of nitrogen containing heterocycles.

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## 1. Introduction

The applications of heterocyclic compounds are widely spread across medicinal chemistry, industry and applied chemistry. Most of the commercially available drugs use some derivative of or a functionalized heterocyclic moiety. Nitrogen containing heterocycles such as indoles, imidazoles, pyrrolidines, indolizine, quinolines *etc.* constitute a myriad of such biologically active compounds. This makes their functionalization strategies as significant as their synthesis. There has been extensive research

regarding the applications of nitrogen containing heterocyclic compound libraries.<sup>1–5</sup> The development of sustainable chemical strategies for synthesizing organic compound libraries is currently the field evoking the most interest in organic chemistry research. Visible light, the most sustainable reaction inducer, has been increasingly used to promote many synthetic transformations in organic chemistry.<sup>6–15</sup> There have been numerous efforts to mimic the ease with which plants use visible light to carry out photosynthesis. Scientists have faced multiple challenges to devise practical and diverse applications of visible light in synthesis, the biggest limitation in this progress being the incapability of most organic molecules to absorb light in visible spectrum. Ever since Ciamician documented the application of visible light as a sustainable energy source for chemical transformations in laboratory,<sup>16</sup> this research field has grown tremendously. With the

<sup>a</sup>Department of Chemistry, CMP Degree College, Prayagraj, India. E-mail: vishalgreenchem@gmail.com

<sup>b</sup>Department of Chemistry, United College of Engineering and Research, Prayagraj, India


Arjita Srivastava is working as Assistant Professor in Department of Chemistry, CMP Degree College, Prayagraj. She has completed her B.Sc. from Ewing Christian College, University of Allahabad and her M.Sc. in Organic Chemistry, D.Phil. from Department of Chemistry, University of Allahabad, India. Her current research interest is mainly focused on utilizing visible light and efficient photocatalysts as green tools for the synthesis of bio-active compounds.



Pravin K. Singh is working as Assistant Professor, Department of Chemistry, CMP College, Allahabad, India (Constituent P.G. College of Central University of Allahabad). Dr Singh is actively engaged in advanced research work for the development of environmentally benign, new synthetic routes for various bioactive heterocyclic compounds. He has completed his B.Sc., M.Sc., Doctorate (D.Phil.) and Post-Doctorate (D.Sc.) from University of Allahabad, India.



combination of wavelength specific LEDs and light absorbing photocatalysts, it has become possible to apply visible light as a “green energy source” for many reactions.<sup>17–19</sup> “Photocatalysts”, which basically act as intermediaries between visible light and organic substrates, have made possible for scientists to harness the energy of visible light to achieve chemical transformations.

The pioneers of photocatalysis were Honda–Fujishima who applied visible light for splitting of water using a titania semiconductor.<sup>20</sup> Ever since, a plethora of transition metal complexes<sup>21–33</sup> and organic dyes<sup>34–42</sup> have been used as photocatalysts. The most commonly used catalysts for such reactions are photoredox catalysts which induce SET pathways – single electron transfer to or from substrates and EnT pathways (light induced energy transfer pathways).<sup>43–45</sup> Most of the photoredox catalysts, however, are metallophotocatalysts. The application of transition metal complexes as photocatalysts somehow contradicts the purpose of sustainability. This is why, organo-catalysts are gaining a lot of popularity as they are excellent

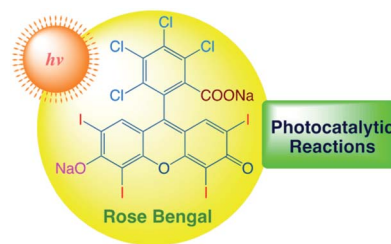


Fig. 1 Rose Bengal as photocatalyst.

photoredox catalysts, are environmentally friendly and are inexpensive. Photocatalysed synthesis, particularly organic dye catalyzed synthesis, is a relatively novel area which is still being explored. Rose Bengal (RB) is one such versatile photocatalyst which is being extensively employed in a variety of organic transformations (Fig. 1). This versatile photocatalytic nature of Rose Bengal is primarily the result of its redox potential values (Table 1).<sup>46</sup> It has emerged as an excellent photocatalyst for both synthesis and directed functionalization of heterocycles.<sup>47–59</sup>

RB is generally supplied and used as its disodium salt RB- $\text{Na}_2$  ( $\text{RB}^{2-}$ ), yet most of the reports depict the disodium salt itself as RB only. Rose Bengal excited by a light source is depicted generally as  $\text{RB}^*$ . This excited photocatalyst  $\text{RB}^*$  can influence a reaction either by energy transfer (EnT) pathway or single electron transfer (SET) pathway, the latter being the most common mode of action. The excited state photocatalyst  $\text{RB}^*$  is capable of acting both as an oxidant and a reductant and hence it can undergo either a reductive quenching or an oxidative quenching photoredox cycle via a single electron transfer (SET) pathway. The type of cycle RB will follow depends upon the redox potentials of  $\text{RB}^*$  and the reagents/substrates/intermediates being used/formed in the reaction. In the oxidative quenching cycle, excited state  $\text{RB}^*$  first gets converted to  $\text{RB}^{+}$  by a reagent or molecular oxygen from air and later on gets quenched to ground state RB by another reagent or reaction intermediate. In the reductive quenching cycle,  $\text{RB}^*$  first gets converted to its radical anion  $\text{RB}^{\cdot-}$  by a substrate or intermediate



Akram Ali is working as Assistant Professor in Department of Chemistry, CMP Degree College, Prayagraj. He has completed his Graduation (B.Sc.) from Kisan PG College, CCS University, Meerut and his Post-Graduation (M.Sc.) in Organic Chemistry, from SSV PG College, CCS University, Meerut. He has completed his Doctoral Degree (Ph.D) from Department of Chemistry, Indian Institute of

Technology Kanpur, India. His doctoral research work was focused on transition metal complexes of aminophenol-based non-innocent ligands. His current research interest is mainly focused on reactivity and catalytic aspects of transition metal complexes with redox-active ligands.



Praveen P. Singh is working as Assistant Professor in the Department of Chemistry at the United College of Engineering and Research, Prayagraj, India. He obtained his B.Sc., M.Sc. in Organic Chemistry from T. D. P. G. College (V. B. S Purvanchal University) Jaunpur and D.Phil. from Department of Chemistry, University of Allahabad, India. His current research interests include the development of

synthetic receptors for the recognition of biological target structures and the application of visible light chemical photocatalysis towards organic synthesis.



Vishal Srivastava is working as Assistant Professor, Department of Chemistry, CMP College, (Constituent P.G. College of Central University of Allahabad) Prayagraj, India. He has completed Graduation (B.Sc.), Post-Graduation (M.Sc.) in Organic Chemistry and Doctoral Degree (D.Phil.) from Department of Chemistry, University of Allahabad, India. His current research work involves the

designing of novel biologically active photoredox catalysed synthetic organic compounds.



## Review

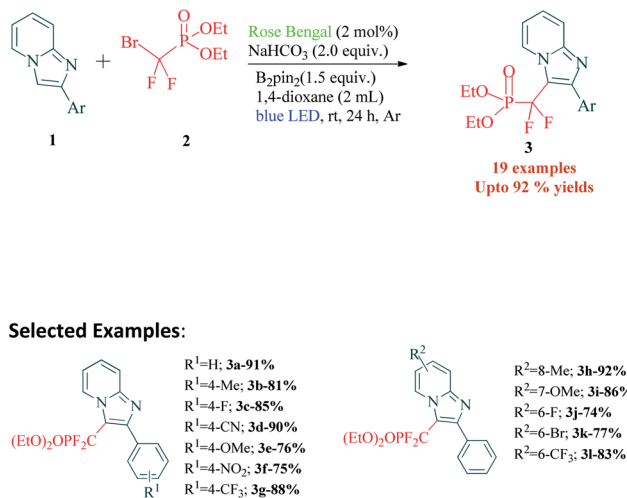
**Table 1** Physical properties of Rose Bengal (reproduced with permission from ref. 46 – "N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166". Copyright 2016 American Chemical Society)

$\lambda_{\text{max}}$ (nm)	549
$\tau_f$ (ns)	0.50
$\phi_f$	0.09
$\Phi_{\text{ISC}}$	0.77
Excited state energy (eV)	$E_{0,0}^{S_1}$ 2.17
	$E_{0,0}^{T_1}$ 1.8
Ground state reduction potential (V vs. SCE)	$E_{1/2}^{\text{red}}$ -0.99
	$E_{1/2}^{\text{ox}}$ +0.84
Excited state reduction potential (V vs. SCE): $S_1$	$E_{\text{red}}^{S_1}$ +1.18
	$E_{\text{ox}}^{S_1}$ -1.33
Excited state reduction potential (V vs. SCE): $T_1$	$E_{\text{red}}^{T_1}$ +0.81
	$E_{\text{ox}}^{T_1}$ -0.96

**Fig. 2** General scheme involving Rose Bengal (RB).

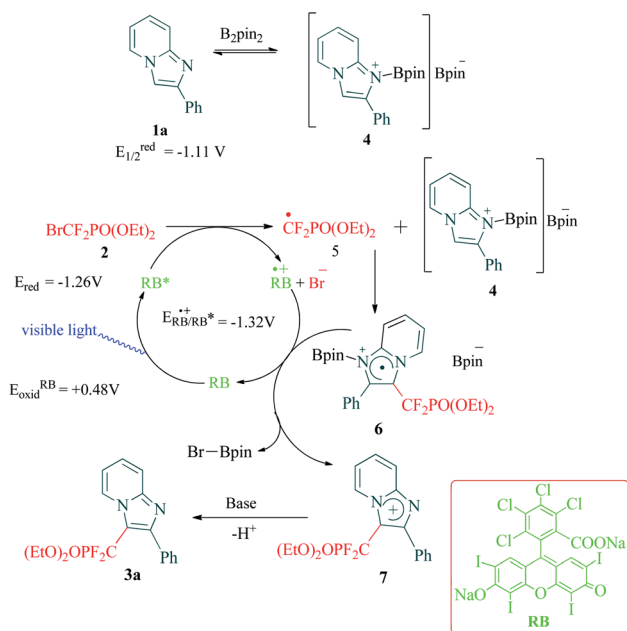
of the reaction. In most of the reactions, radical anion  $\text{RB}^{\bullet-}$  later gets quenched by molecular oxygen from air to produce ground state RB and superoxide radical anion  $\text{O}_2^{\bullet-}$ , which often takes part in further reaction mechanism (Fig. 2). However, in some cases, reaction may occur through energy transfer (EnT) pathway, either by energy transfer from excited state  $\text{RB}^*$  to a substrate or intersystem crossing (ISC) of singlet excited state  $^1\text{RB}^*$  to triplet excited state  $^3\text{RB}^*$  and subsequent energy transfer from  $^3\text{RB}^*$  to a substrate. There might be variations to the general mechanism in different reactions, especially in cases where a different terminal oxidant is employed.<sup>60,61</sup>

A detailed comprehensive insight into the mechanistic pathways and recent manipulations in the mode of action of Rose Bengal was reported by Sharma *et al.*<sup>62</sup> in 2019. This review, however, aims to present the synthetic applications of RB, in particular for N-heterocyclic rings, with a basic discussion of its mechanism in such syntheses. In continuation of our work on development of photocatalysed synthesis<sup>63a-n</sup> this review might be particularly useful for those who are already involved in the area of heterocycles and interested in the use of visible light and photocatalysts for heterocyclic synthesis. Since this is a short review, only a selected number of published reports on this topic have been covered.

**Scheme 1** Visible light promoted difluoromethylene-phosphonation of imidazoheterocycles.

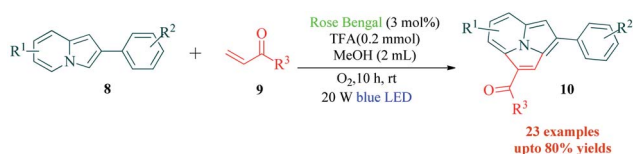
## 2. $\text{C}(\text{sp}^2)\text{-H}$ functionalization of imidazoles

Functionalized imidazoles are versatile in their applications and are utilized in various areas of chemistry and industry. Besides being key pharmacophores in a wide range of commercial drugs, they find their applications in co-ordination chemistry, as catalysts, in material sciences and for natural product synthesis.<sup>64–67</sup> Singsardar *et al.*<sup>68</sup> recently reported  $\text{C}(\text{sp}^2)\text{-H}$  difluoromethylenephosphonation of imidazoheterocycles catalyzed by RB *via* a single electron transfer pathway

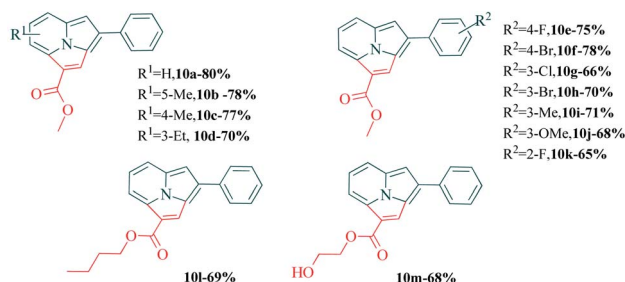
**Scheme 2** Rose Bengal catalyzed  $\text{C}(\text{sp}^2)\text{-H}$  difluoromethylene-phosphonation of imidazopyridines.



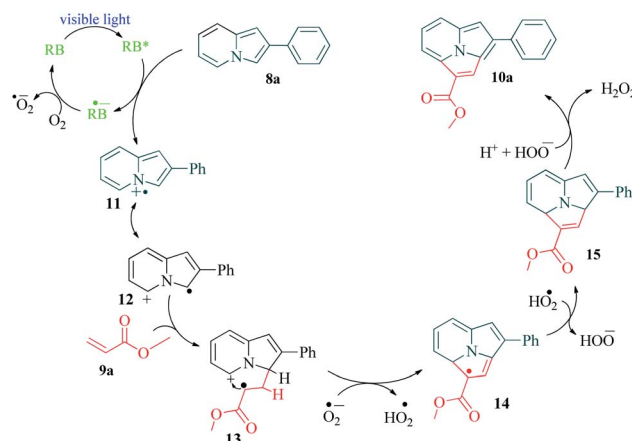
(Scheme 1). The reaction required bis(pinacolato)diboron ( $B_2pin_2$ ) as an additive, for the activation and stabilization of the heterocyclic system. In the absence of additive  $B_2pin_2$ , the authors observed decomposition of imidazopyridine and no desired coupling product. The reaction was carried out under argon atmosphere in 34 W blue LED for 24 h. Their optimizations revealed 1,4-dioxane as solvent, 2 mol% of Rose Bengal, 2.0 equiv. of  $NaHCO_3$  and 1.5 equiv. of  $B_2pin_2$  at room temperature as the optimum conditions. In their control experiments, they found out that the reaction did not yield any products in the presence of radical scavengers like TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl), BHT (2,6-di-*tert*-butyl-4-methyl phenol) *etc.* The reaction was found to be completely suppressed on addition of 1,3-diphenylethylene. Both these observations suggest a radical pathway for the mechanism. In their cyclic voltammetry measurements, authors probably obtained reversible response for **1a** ( $E_{1/2}^{red} = -1.11$  V) and irreversible response for  $RB^*$  ( $E_{oxid} = +0.48$  V) and compound **2** ( $E_{red} = -1.26$  V). Their cyclic voltammetry results clearly showed that  $BrCF_2PO(OEt)_2$  (**2**) has the potential to oxidize the excited state of photocatalyst  $RB^*$  to generate  $RB^{*+}$  and radical intermediate **5**. This radical intermediate **5** reacts with  $B_2pin_2$  activated 2-phenylimidazo[1,2-*a*]pyridine **4** to produce radical intermediate **6**. This intermediate **6** gets converted to intermediate **7** in the photoredox cycle completion process simultaneously generating ground state  $RB$ . The final product **3a** is eventually obtained by a proton abstraction from intermediate **7** by the base (Scheme 2). To demonstrate the substrate scope and generality of the reaction, the authors also explored the reaction with other heterocycles such as indoles, imidazo[2,1-*b*]thiazoles and benzo[*d*]imidazo[2,1-*b*]thiazoles, and obtained good to excellent yields.



#### Selected Examples:



Scheme 3 Rose Bengal catalyzed intermolecular [3 + 2] alkenylation-cyclization.



Scheme 4 Postulated mechanism for the intermolecular [3 + 2] alkenylation-cyclization.

### 3. Synthesis of pyrrolo[2,1,5-*cd*]indolizines

The synthesis of fused heterocyclic rings has always been an attractive area for synthetic chemists. The combination and modification of activities of two heterocyclic rings opens up new arenas for drug discovery. Fused indolizines have found applications in pharmaceutical industry, agrochemical industry and cell functional studies.<sup>69–73</sup> In a recent report published by Liang *et al.*,<sup>74</sup> Rose Bengal was used as a photosensitiser for an intermolecular [3 + 2] alkenylation-cyclization strategy for the synthesis of pyrrolo[2,1,5-*cd*]indolizine derivatives (Scheme 3). The authors report that other photocatalysts also provided product of the reaction, but with lower yields. Their fluorescence quenching experiments revealed that the fluorescence intensity of Rose Bengal decreased on interaction with **8**. Based on this fact, the postulated mechanism shows energy transfer *via* activated Rose Bengal  $RB^*$  to **8a**, resulting in the formation of radical intermediate **11** and  $RB^{\cdot-}$ . The completion of photoredox cycle by  $O_2$  results in the formation of ground state photocatalyst  $RB$  and superoxide radical anion  $O_2^{\cdot-}$ . Intermediate **11** transforms to its resonance structure **12**, which then undergoes addition with **9a** to produce radical intermediate **13**. A sequential dehydrogenation oxidation of **13** with the superoxide radical anion  $O_2^{\cdot-}$ , then produces intermediate **15** *via* radical intermediate **14**. This finally undergoes an electron transfer to produce product **10a** (Scheme 4). The authors were able to synthesize 23 different variants of fused indolizine derivatives.

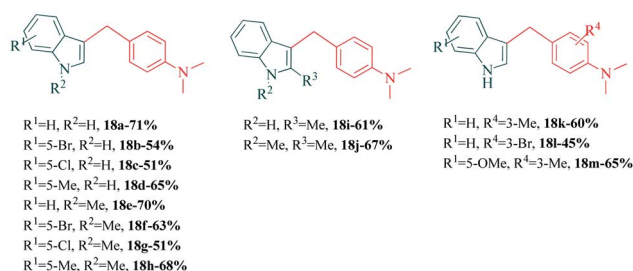
### 4. C3-Functionalization of indoles

The indole skeleton and its functionalized derivatives are one of the most extensively studied heterocyclic skeletons because of their presence in a large number of drugs and its capability to be utilized as a versatile building block. The modifications of this ring, has therefore warranted a lot of attention.<sup>75–80</sup> In 2018, Dai *et al.*<sup>81</sup> reported an efficient visible light promoted, Rose Bengal catalysed synthesis of C3-alkylated indoles by Friedel–





## Selected Examples:

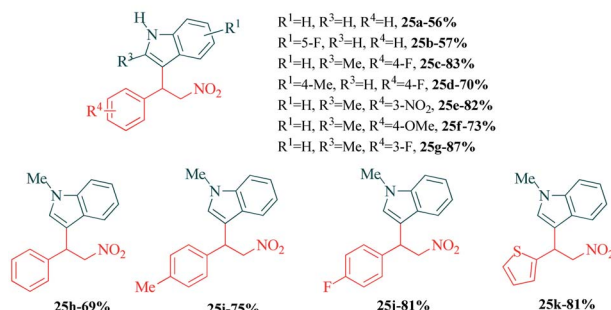


Scheme 5 Visible light promoted synthesis of C3-alkylated indoles.

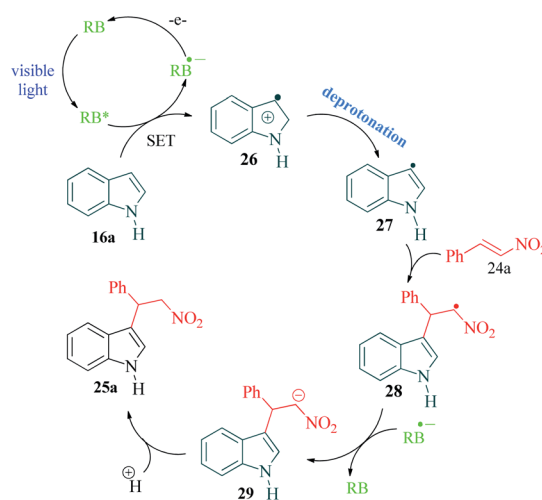
Crafts alkylation using *N,N*-dimethylanilines as the carbon source (Scheme 5). Although the authors obtained considerable yields in CH<sub>3</sub>CN as solvent, mixed CH<sub>3</sub>CN/H<sub>2</sub>O solvents were employed to obtain fast demethylation of tertiary amines. According to the mechanism postulated by the authors, visible light activated Rose Bengal undergoes reductive quenching by *N,N*-dimethylaniline **17a** to give radical cation **19** and RB<sup>•−</sup>. The oxidation of RB<sup>•−</sup> with O<sub>2</sub> produces ground state RB and superoxide radical anion O<sub>2</sub><sup>•−</sup>. The radical cation **19** loses a proton to superoxide radical anion O<sub>2</sub><sup>•−</sup> to produce iminium ion **20**, which gets oxidized or hydrolyzed and gets decomposed in the process to give compounds **21** and **22**. The decomposition product **21**, obtained as a by-product of the reaction, was isolated from the reaction mixture. The other decomposition product **22**, undergoes condensation with indole **16a** to produce intermediate cation **23**. This intermediate finally reacts with



## Selected Examples:



Scheme 7 Friedel–Crafts alkylation of indoles with nitroalkenes in water.



Scheme 8 Rose Bengal catalysed Friedel–Crafts alkylation of indoles.

*N,N*-dimethylaniline **17a** to produce the desired product **18a** (Scheme 6). To support the mechanism, the authors carried out a Rose Bengal catalyzed three component reaction of indole **16a** (1 eq.), *N,N*-dimethylaniline **17a** (2 eq.) and formaldehyde **22** (3 eq.) under their standard reaction conditions and obtained the desired product **18a**.

## 5. Rose Bengal as photocatalyst for Friedel–Crafts alkylation of indoles with nitroalkenes in water

In another interesting methodology for functionalization of indoles, Yu *et al.*<sup>82</sup> reported a metal free photocatalyzed Friedel–

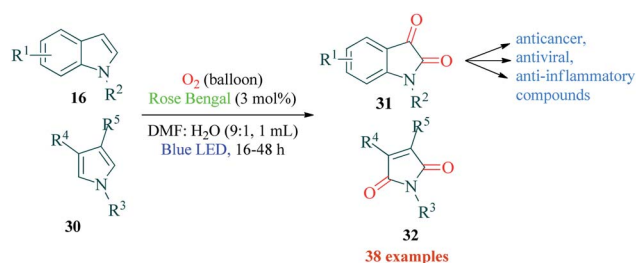
Scheme 6 Postulated mechanism for the Friedel–Crafts alkylation of indoles.



Crafts alkylation of indole ring with nitroalkenes using water as the reaction medium (Scheme 7). The strategy is highly efficient and it is noteworthy that good to excellent yields of the desired product were obtained without the use of any external oxidant. The authors performed control experiments under oxygen and nitrogen atmosphere to establish that external oxidant was unnecessary in this protocol. Their cyclic voltammetry experiments further proved that  $\text{RB}^*$  and indole **16** could react spontaneously with each other. Based on their data, the proposed mechanism by the authors involves SET between  $\text{RB}^*$  and indole **16a** to produce  $\text{RB}^{\bullet-}$  and radical cation **26**. This radical cation **26** undergoes deprotonation to radical **27**, which undergoes Michael addition with nitroethenyl benzene **24a** to produce intermediate **28**. The intermediate **28**, after undergoing another SET cycle with  $\text{RB}^{\bullet-}$  and protonation, yields the desired product **25a** (Scheme 8).

## 6. Visible light mediated dearomatisation of indoles and pyrroles

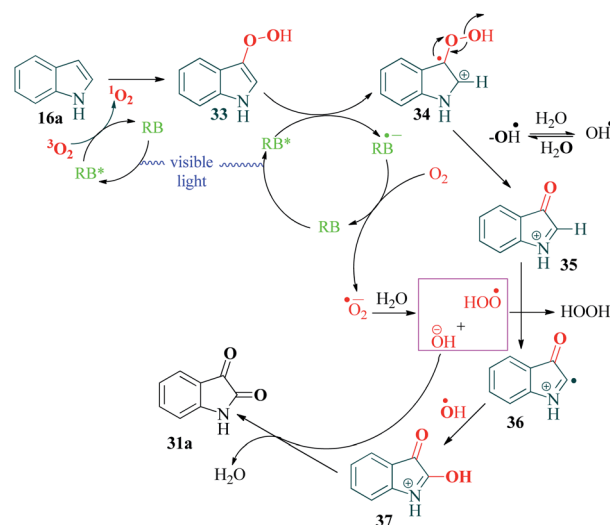
The dearomatisation of indoles to isatin derivatives and pyrroles to imides was reported by Schilling *et al.*<sup>83</sup> in 2019 (Scheme 9). The structural modification of any heterocyclic ring is a highly promising area and continues to be explored for synthesis of potential pharmacologically active compounds. Isatin is one of the privileged building blocks of heterocyclic chemistry and numerous structural modifications are possible. In a considerable improvement over the already reported methods, the authors devised an atom efficient, mild, metal free



### Selected Examples:



Scheme 9 Visible light mediated dearomatisation of indoles and pyrroles.



Scheme 10 Rose Bengal catalyzed dearomatisation of indoles.

single step protocol for dearomatisation of indoles and pyrroles. Their optimization studies revealed Rose Bengal to be the best catalyst for the reaction. The reaction could tolerate a wide range of substitutions in the aromatic ring, even C2- and C3-substituted indole carboxylic acids provided good to excellent yields. From their dearomatised product, the authors also successfully synthesized different pharmaceuticals exhibiting anticancer, anticonvulsant, antitumor, antiviral and anti-inflammatory activities. The radical pathway of the reaction was confirmed by the authors by addition of  $\text{CuCl}_2$ , benzoquinone, sodium azide and Stern–Volmer quenching experiments. In the mechanism postulated by the authors, the excited state of Rose Bengal  $\text{RB}^*$  is quenched by oxygen to form singlet oxygen, which then reacts with indole **16a** to form peroxo species **33**. This peroxo species **33** gets oxidized by  $\text{RB}^*$  to form peroxindole intermediate **34** and  $\text{RB}^{\bullet-}$ . While the intermediate **34** cleaves to form cation **35** and hydroxyl radical,  $\text{RB}^{\bullet-}$  reduces molecular oxygen to produce superoxide radical anion ( $\text{O}_2^{\bullet-}$ ), which then reacts with water to form hydroxide ion and peroxide radical. The peroxide radical formed probably abstracts a proton from cation **35** to form intermediate **36**. The reaction between intermediate **36** and hydroxyl radical produces **37**, which loses a proton to hydroxide ion formed earlier to finally give the product **31a** (Scheme 10). Apart from the various differently substituted indole derivatives, the reaction conditions were also optimal for dearomatisation *via* decarboxylation of C-2 and C-3 carboxylated indoles. The authors also synthesized significant pharmaceuticals from specific substituted indoles.

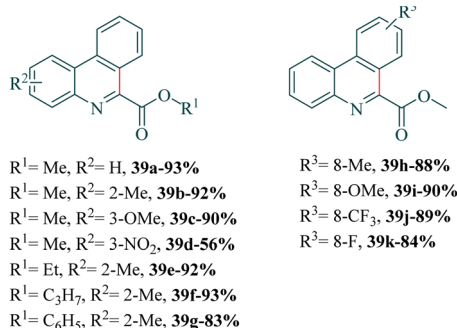
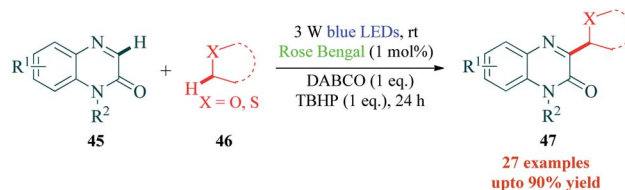
## 7. Oxidative radical cyclization for synthesis of phenanthridines

Phenanthridine are core heterocycles in many anticancer, antibacterial, antiprotozoal, antifungal, antiviral and other biologically active compounds. There are also a number of natural products constituted of phenanthridine ring.<sup>84–88</sup> In

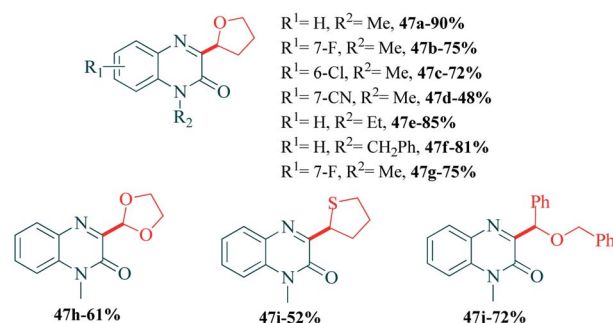




## Selected Examples:

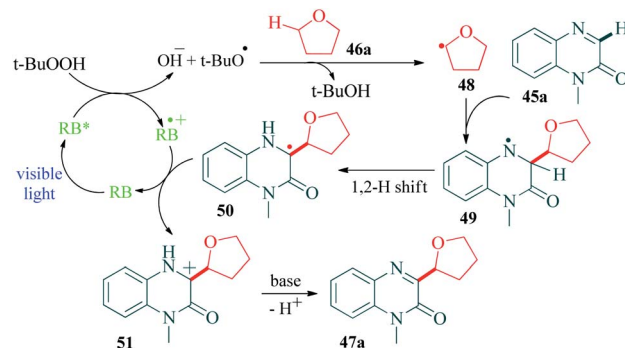
Scheme 11 Oxidative radical cyclization of *N*-biaryl glycine esters to phenanthridines.

## Selected Examples:

Scheme 13 Visible light promoted 3-oxyalkylation of quinoxalin-2(1*H*)-ones.Scheme 12 Photocatalysed conversion of *N*-biaryl glycine esters to phenanthridines.

a first ever attempt for visible light photocatalysed conversion of biocompatible *N*-biaryl glycine esters to phenanthridines, Natarajan *et al.*<sup>89</sup> recently published a report which involves a Rose Bengal catalyzed intramolecular cyclization–dehydrogenation to provide excellent yields of the desired products (Scheme 11). The authors demonstrated the requirement of oxygen in the reaction, since the replacement of oxygen with nitrogen, inferior yields of the product was obtained. Based on the mechanism postulated by the authors (Scheme 12), the

reductive quenching of RB by glycine ester **38a** leads to the formation of RB<sup>•+</sup>, which further produces superoxide radical anion O<sub>2</sub><sup>•-</sup> from molecular oxygen. This superoxide anion radical O<sub>2</sub><sup>•-</sup> and the amine radical cation **40** react to afford biaryl glycine ester radical **41** and peroxide radical. The biaryl glycine ester **41** undergoes C–H aromatic coupling to yield another radical **42**, which on reaction with the peroxide radical, produces the phenanthridine derivative **43**. Another photoredox cycle between excited state photocatalyst RB\*, molecular oxygen and phenanthridine derivative **43** results in the formation of radical cation **44**, which loses a H<sup>+</sup> and a H<sup>•</sup> to yield the final product **39a**. An additional experiment was conducted by the authors to confirm the mechanism where effective conversion of compound **43** to methyl phenanthridine-6-carboxylate **39a** was achieved under optimized reaction conditions.



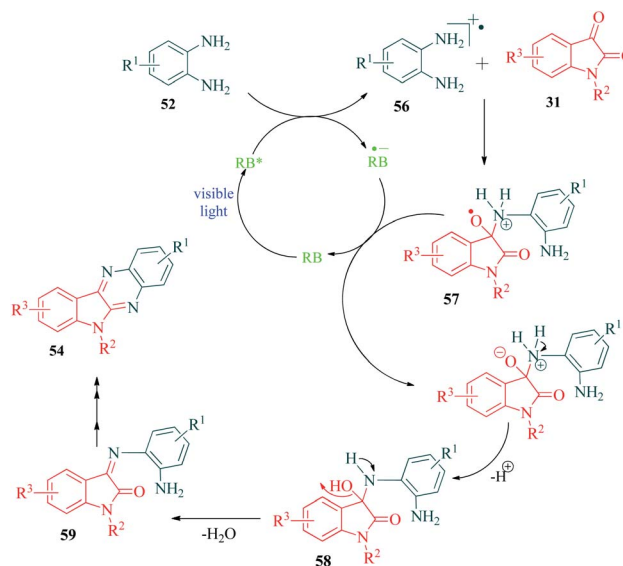
Scheme 14 Rose Bengal catalysed C–H/C–C cross-dehydrogenative-coupling.





## 8. Functionalization of quinoxalin-2(*H*)-ones

Quinoxalines and their derivatives, particularly C-3 functionalized, are one of the most extensively studied moieties of heterocyclic chemistry. They exhibit a remarkable range of biological activities such as anticancer, antimicrobial, anti-inflammatory, benzodiazepine receptor agonist, DNA cleaving agents and protein kinase inhibitory activities.<sup>90–95</sup> Wei *et al.*<sup>96</sup> reported a visible light promoted synthesis of 3-oxyalkylated quinoxalin-2(*H*)-ones at room temperature (Scheme 13). The C3-functionalization of quinoxalin-2-ones is one of the significant merits of this method. Their control experiment with TEMPO completely suppressed the reaction and TEMPO-THF complex was also detected, suggesting a radical pathway for the mechanism. The reaction proceeded through Rose Bengal catalyzed C–H/C–H cross-dehydrogenative-coupling (CDC) of quinoxalin-2(*H*)-ones with simple ethers. TBHP (*tert*-butyl hydroperoxide) used in the reaction causes oxidative quenching of RB to produce hydroxide ion and *t*-butoxy radical. The next step is  $\alpha$ -C–H bond cleavage of furan **46a** in the presence of *t*-butoxy radical, to generate radical intermediate **48**, which on reaction with **45a** produces radical intermediate **49**. A 1,2-hydrogen shift from **49** generates radical intermediate **50**. The photoredox cycle is completed by a SET between this radical intermediate **50** and RB<sup>•+</sup> providing cation intermediate **51**. Finally, a  $\beta$ -H abstraction from **51** yields the desired product **47a** (Scheme 14).



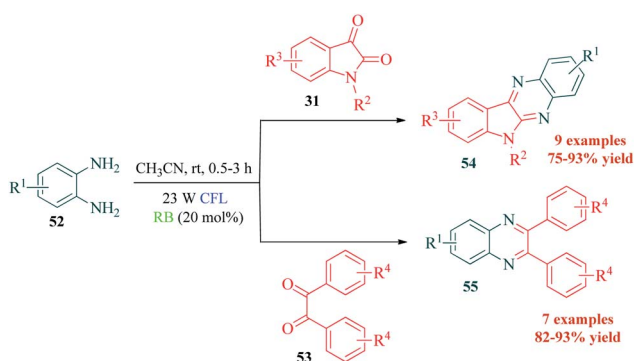
Scheme 16 Visible light promoted Rose Bengal catalyzed formation of C–N bond in quinoxalines.

## 9. Rose Bengal catalysed synthesis of quinoxalines

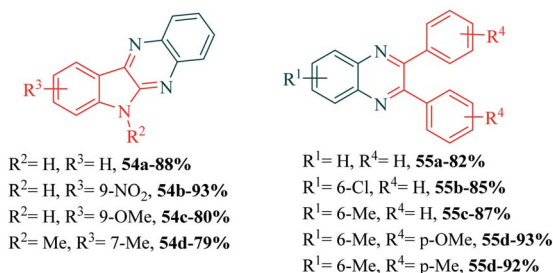
Jaiswal *et al.*<sup>97</sup> reported a novel protocol for photocatalyzed coupling of phenylene 1,2-diamines and 1,2-dicarbonyls for the synthesis of quinoxaline derivatives (Scheme 15). The protocol is an improvement over the already reported conventional methods, is sustainable and exhibits excellent atom economy. Rose Bengal is reported to have good catalytic performance in many organic solvents, yet CH<sub>3</sub>CN seems to be the optimum choice for most reactions. The authors propose that photoexcited singlet state photocatalyst RB\* (S<sub>1</sub>) undergoes ISC to more stable triplet state RB\* (T<sub>1</sub>), which then acts as the photocatalyst to produce radical cation **56** from 1,2-phenylenediamine **52** (Scheme 16). This radical cation **56**, on reaction with isatin **31**, produces **57**, which through a series of single electron transfer, deprotonation and dehydration produces intermediate **59**. This intermediate undergoes cyclization to finally yield the target compound **54**.

## 10. C–H oxidation of tryptoline and tetrahydroisoquinoline substrates to corresponding $\delta$ -lactams

Guryev *et al.*<sup>98</sup> reported a highly efficient Rose Bengal catalyzed protocol for the synthesis of amide derivatives of tetrahydroisoquinoline and tryptoline (Scheme 17). The lactams of these heterocyclic rings are frameworks of many biologically active compounds. The authors were able to synthesize antiviral activity exhibiting derivatives a plant alkaloid strychnocarpine<sup>99</sup> (a dihydrocarbolinone compound), which is otherwise used as a muscle relaxant and 5-hydroxytryptamine receptor stimulant.<sup>100–103</sup> This is the first ever report on facile access of such



### Selected Examples:

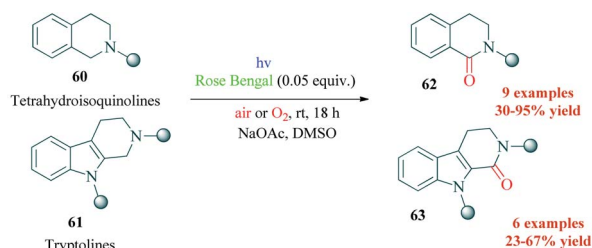


Scheme 15 Rose Bengal catalyzed synthesis of quinoxalines.

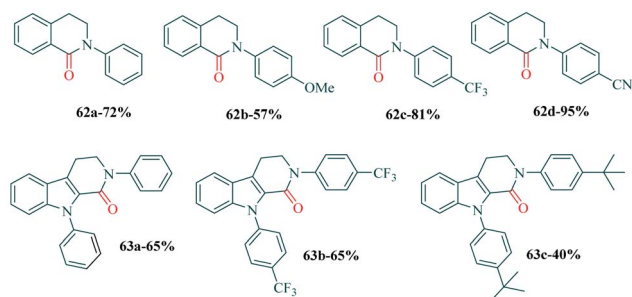




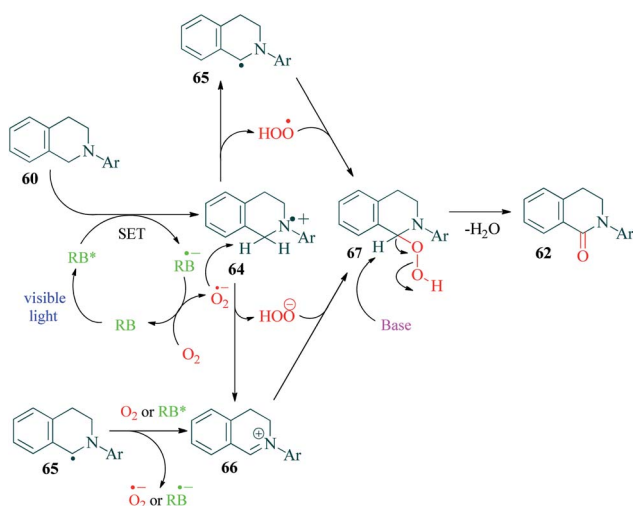
## Review



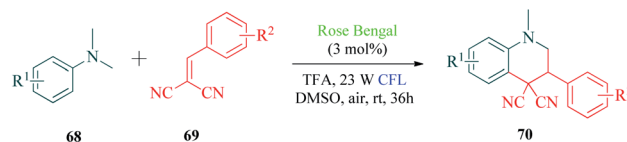
## Selected Examples:

Scheme 17 Photocatalyzed synthesis of  $\delta$ -lactams.

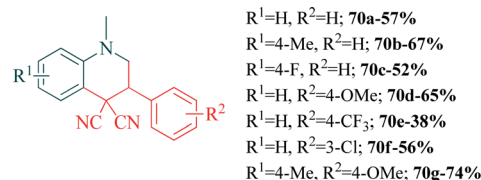
selective derivatives of *Strychnos* alkaloid. The biological activity investigation of all synthesized  $\delta$ -lactams is underway according to the authors. This environmentally friendly protocol represents an excellent example of metal free C–H photooxidation of cyclic amines. NaOAc was required as a base in the reaction in an attempt to accelerate the formation of  $\alpha$ -amine radical. The mechanism proposed by the authors successfully explains the requirement of oxygen as the terminal oxidant (Scheme 18). The usual photoredox cycle between RB, substrate **60** and molecular oxygen results in the formation of superoxide radical anion and radical cation **64**. The superoxide radical anion can react with **64** to form either  $\alpha$ -aminoradical **65** or iminium ion **66**, both of



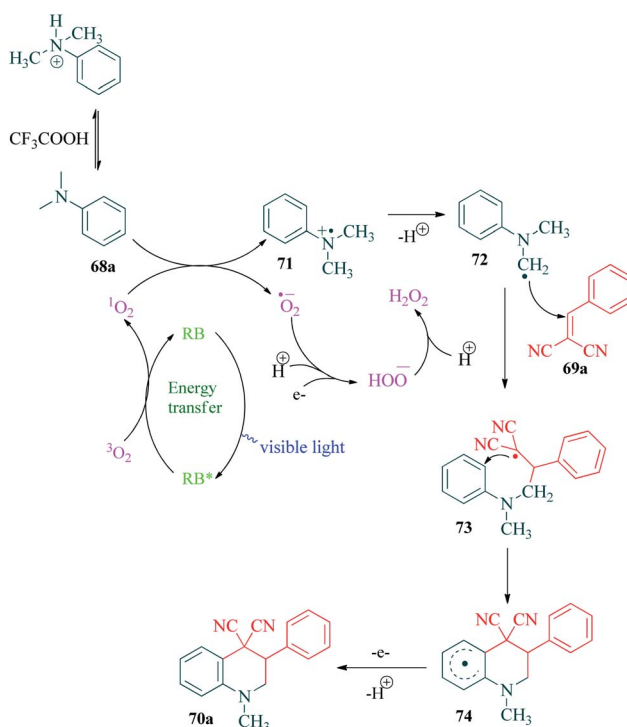
Scheme 18 Rose Bengal catalyzed C–H oxidation of tryptoline and tetrahydroisoquinoline substrates.



## Selected Examples:



Scheme 19 Visible light promoted synthesis of tetrahydroquinoline.



Scheme 20 Visible light promoted synthesis of tetrahydroquinolines.

which pathways ultimately result in the final product **62**, via intermediate **67**.

## 11. Visible light promoted synthesis of tetrahydroquinoline derivatives

Quinoline and its derivatives have a ubiquitous presence in medicinal agents and natural products. The quinoline ring is one of the most researched heterocycles with regards to drug discovery. There is a long list of therapeutic agents that are constituted of this compound.<sup>104–108</sup> In 2017, Xin *et al.*<sup>109</sup> reported the synthesis of tetrahydroquinoline derivatives via



visible light promoted reaction of *N,N*-dimethylanilines and 2-benzylidenemalononitriles using Rose Bengal as the photosensitizer (Scheme 19). The authors performed different control experiments to establish the reaction mechanism (Scheme 20). They observed complete inhibition of the reaction on addition of TEMPO and addition of DABCO provided only trace amounts of product. The collective interpretation was that the reaction involved a radical pathway and singlet oxygen participation. TFA was added to the reaction in an attempt to regulate the balance between free amine **68a** and its unreactive ammonium salt. The  $^1\text{O}_2$  generated by interaction of excited Rose Bengal  $\text{RB}^*$  and  $^3\text{O}_2$ , reacts with free amine **68a** to produce amine radical cation **71**. This radical **71** undergoes deprotonation to produce radical **72**, which on reaction with 2-benzylidenepropanedinitrile **69a**, provides radical intermediate **73**. This radical intermediate undergoes a series of intramolecular cyclization (through intermediate **74**) and proton elimination to finally produce desired product **70a**.

## 12. Rose Bengal catalyzed oxidative dehydrogenation of N-heterocycles

Sahoo *et al.*<sup>110</sup> reported Rose Bengal catalyzed synthesis of different medicinally significant N-heteroarenes such as quinoxaline, quinoxaline, quinazoline and acridine (Scheme 21). This strategy was further utilized for oxidative dehydrogenation of indolines. They obtained excellent yields of desired dehydrogenated heterocycles using a catalytic amount of Rose Bengal.



### Selected Examples:



Scheme 21 Rose Bengal catalyzed oxidative dehydrogenation of N-heterocycles.



Scheme 22 Rose Bengal catalyzed oxidative dehydrogenation mechanism.

The authors emphasize the fact that this organic dye catalyzed process provided good yields of dehydrogenated products even from halogen-substituted tetrahydroisoquinolines, which is generally difficult to achieve by conventional transition metal catalysts because of unwanted side reactions. It is significant to note that their control experiments proved that N-H motif in cycloalkane was a prime requirement for the reaction. The mechanism postulated by the authors shows reaction initiation by ISC from singlet state excited photocatalyst  $\text{RB}^{2*} (\text{S}_1)$  to triplet state photoexcited catalyst  $\text{RB}^{2*} (\text{T}_1)$ . This triplet state photocatalyst oxidizes the amine **75a** to radical cation **78**, and the reduced photocatalyst  $[\text{RB}^{2-}]^{\bullet-}$  thus generated, reduces  $\text{O}_2$  to superoxide radical anion  $\text{O}_2^{\bullet-}$ . This superoxide radical anion helps in the oxidation of radical cation **78** to imine **80**, through a hydrogen atom transfer (HAT) step. Under the reaction conditions, imine **80** isomerizes to provide imine **81**, which then undergoes a similar dehydrogenation step to finally provide the desired product **76a** (Scheme 22).

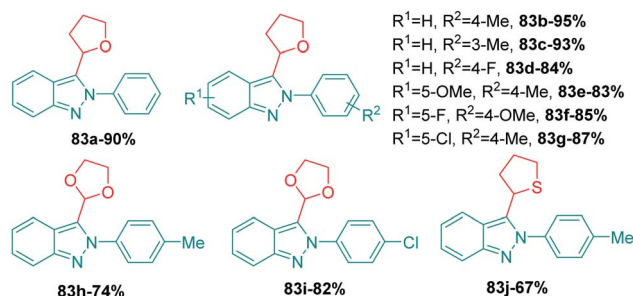
## 13. Ether functionalization of 2H-indazoles

The bicyclic fused indazole ring is one of the most significant N-heterocycle and has widespread applications in medicinal chemistry. Indazole and its derivatives are well known to be exhibit multiple biological activities, particularly against different types of cancers, including inducer of tumor regression, selective CRAF inhibitor activity against melanoma cell lines, inhibition of hepatocellular carcinoma proliferation, multikinase inhibitor activity, and many more.<sup>111-117</sup> The spectrum of biological activities that can be obtained by targeted functionalization of the ring is very interesting and has great potential for drug discovery. In 2019, Singardar *et al.*<sup>118</sup> developed a method for Rose Bengal catalyzed regioselective  $\text{C}(\text{sp}^2)\text{-H}/\text{C}(\text{sp}^3)\text{-H}$  cross-dehydrogenative coupling of indazoles with ethers (Scheme 23). The authors used THF as the oxyalkylating agent in this Rose Bengal catalyzed protocol and obtained excellent yields with TBHP as an additive and DABCO (1,4-diazabicyclo[2.2.2]octane) as a base. The reaction conditions were thoroughly optimized by the authors and they performed a series of control experiments using radical

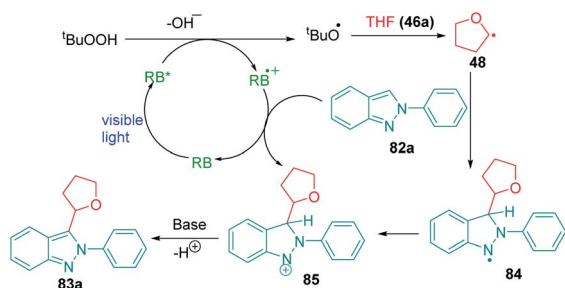




## Selected Examples:



Scheme 23 Rose Bengal catalyzed cross-dehydrogenative-coupling of indazoles.



Scheme 24 Rose Bengal catalyzed coupling of indazoles.

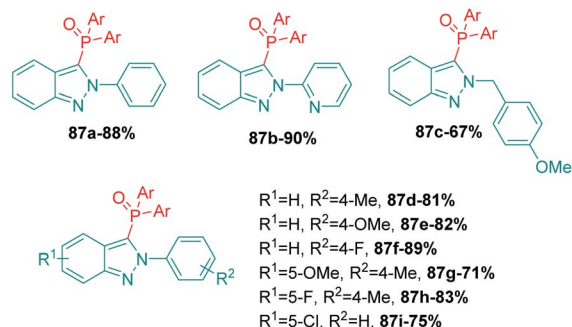
scavengers like TEMPO and BHT to establish the radical pathway of the reaction mechanism. According to the mechanism proposed by the authors, a single electron transfer between excited Rose Bengal  $RB^*$  and TBHP produces  $RB^{+\bullet}$ , hydroxide ion and *t*-butyloxy radical. The *t*-butyloxy radical deprotonates the  $\alpha$ -C(sp<sup>3</sup>)-H of THF **46a** to produce alkoxyalkyl radical **48** which then reacts with indazole **82a** to provide radical intermediate **84**. This radical intermediate **84**, on reaction with  $RB^{+\bullet}$ , furnishes a cationic intermediate **85** which finally undergoes deprotonation to produce the desired 3-oxyalkylated indazole **83a** (Scheme 24).

## 14. Phosphonylation of indazoles using diphenylphosphine oxide

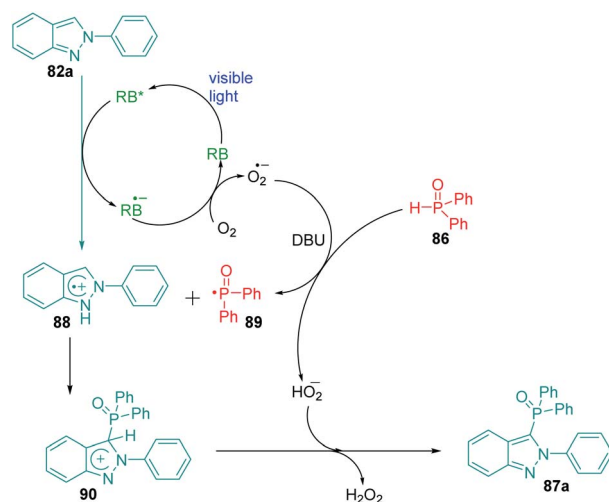
Phosphines containing organic compounds have found various applications in organic synthesis and material sciences. The functionalization of indazole ring with phosphines has the potential to generate derivatives with interesting applications.



## Selected Examples:



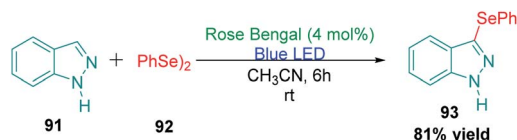
Scheme 25 Rose Bengal catalyzed phosphonylation of indazoles.



Scheme 26 Rose Bengal catalyzed phosphonylation of indazole.

The introduction of phosphine to indazole has the potential to cause interesting modifications in the properties and activities of the ring owing to the formation of N-C-P bond.<sup>119,120</sup> In 2018, Singardar *et al.*<sup>121</sup> reported an excellent method for Rose Bengal catalysed C(sp<sup>2</sup>)-H functionalization of indazoles using diphenylphosphine oxide at room temperature (Scheme 25). The authors were able to achieve excellent substrate scope with this protocol. Based on the mechanism proposed by the authors, excited state  $RB^*$  undergoes a single electron transfer process (SET) with indazole **82a** to produce radical cation intermediate **88** and  $RB^{\bullet-}$ . The photoredox cycle then gets completed by reduction of molecular oxygen by  $RB^{\bullet-}$  to produce ground state RB and superoxide radical anion  $O_2^{\bullet-}$ . A hydrogen atom transfer process (HAT) then occurs between superoxide





Scheme 27 Rose Bengal catalyzed selenylation of indazoles.

radical anion  $O_2^{\cdot-}$  and diphenylphosphine oxide **86** in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), to produce diphenylphosphinoyl radical **89** and  $HO_2^-$ . This radical **89** now undergoes coupling with radical cation intermediate **88** to produce cation intermediate **90**, which undergoes deprotonation by  $HO_2^-$  to finally produce  $H_2O_2$  and the desired product **87a** (Scheme 26). The authors also report that no phosphorylation of DBU was observed during the reaction suggesting that it only acts as a base in this protocol.

## 15. Rose Bengal catalysed selenylation of indazoles

Organoselenium compounds are becoming more prominent in the area of medicinal chemistry because of their pharmacological activities and their applications in material science.<sup>122,123</sup> The selenylation of indazole ring to produce a potentially bioactive compound is a highly promising area. One such highly efficient protocol was developed by Saba *et al.*<sup>124</sup> in 2018. The authors achieved effective Rose Bengal catalysed selenylation of various heterocyclic rings, including indazole, using diorganoyl diselenides (Scheme 27).

## 16. Conclusion

Nitrogen containing heterocycles are ubiquitous in pharmaceutical industry and their synthesis and site selective targeted functionalization has always held a significant place in the area of drug discovery. Synthetic chemists continue to explore and develop novel, sustainable methods for synthesis of potentially bioactive N-heterocycles. With the boom of visible light promoted synthesis using organic dyes as photoredox catalysts, the area of sustainable synthesis is being utilized like never before and holds vast potential. Rose Bengal has emerged as an excellent photoredox catalyst for a variety of organic syntheses and has been the catalyst of choice for many protocols involving synthesis and functionalization of nitrogen containing heterocycles. Further developments in the site selective functionalization of heterocycles would prove extremely beneficial for synthetic and medicinal chemistry. Rose Bengal catalysed synthetic strategies would prove as viable tools for construction of potentially bioactive N-heterocycles and other heterocyclic moieties. Rose Bengal could also be employed as a better alternative to metal based catalysts in a variety of organic transformations. In conclusion, the harnessing of visible light using Rose Bengal is a highly promising area for pharmaceutical industry and needs to be explored to a much greater extent in the future.

## Conflicts of interest

There are no conflicts to declare.

## References

- 1 Y. Wang, B. Xu, R. Sun, Y. J. Xu and J. F. Ge, *J. Mater. Chem. B*, 2020, **8**, 7466–7474.
- 2 D. Didier, A. N. Baumann and M. Eisold, *Tetrahedron Lett.*, 2018, **59**(45), 3975–638.
- 3 M. T. El-Sayed, N. A. Hamdy, D. A. Osman and K. M. Ahmed, *Adv. Mod. Oncol. Res.*, 2015, **1**, 20–638.
- 4 L. Wang, Y. Tian, W. Chen, H. Liu, P. Zhan, D. Li, H. Liu, E. D. Clercq, C. Pannecouque and X. Liu, *Eur. J. Med. Chem.*, 2014, **85**, 293–638.
- 5 N. Siddiqui, N. Andalip, S. Bawa, R. Ali, O. Afzal, M. J. Akhtar, B. Azad and R. Kumar, *J. Pharm. BioAllied Sci.*, 2011, **3**(2), 194–638.
- 6 Y. Yasu, T. Koike and M. Akita, *Chem. Commun.*, 2013, **49**, 2037–638.
- 7 T. Chatterjee, G. Roh, M. A. Shoaib, C. H. Suhl, J. S. Kim, C. G. Cho and E. J. Cho, *Org. Lett.*, 2017, **19**(7), 1906–638.
- 8 Y. Z. Chen, D. H. Wang, B. Chen, J. J. Zhong, C. H. Tung and L. Z. Wu, *J. Org. Chem.*, 2012, **77**(16), 6773–638.
- 9 Q. Liu, F. Liu, H. Yue, X. Zhao, J. Li and W. Wei, *Adv. Synth. Catal.*, 2019, **361**(22), 5277–638.
- 10 Z. Li, H. Song, R. Guo, M. Zuo, C. Hou, S. Sun, X. He, Z. Sun and W. Chu, *Green Chem.*, 2019, **21**, 3602–638.
- 11 A. N. Nadaf and K. Shivashankar, *J. Heterocycl. Chem.*, 2018, **55**(6), 1375–638.
- 12 X. F. Xia, G. W. Zhang and S. L. Zhu, *Tetrahedron*, 2017, **73**(19), 2727–638.
- 13 J. Sun, Y. He, X. D. An, X. Zhang, L. Yu and S. Yu, *Org. Chem. Front.*, 2018, **5**, 977–638.
- 14 M. Parasrama and V. Gevorgyan, *Chem. Soc. Rev.*, 2017, **46**, 6227–638.
- 15 G. Zhao and T. Wang, *Angew. Chem.*, 2018, **57**(21), 6120–638.
- 16 G. Ciamician, *Science*, 1912, **36**, 385–638.
- 17 J. Chen, J. Cen, X. Xu and X. Li, *Catal. Sci. Technol.*, 2016, **6**, 349–638.
- 18 L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem.*, 2018, **57**(32), 10034–638.
- 19 B. König, *Eur. J. Org. Chem.*, 2017, **15**, 1979–638.
- 20 A. Fujishima and K. Honda, *Nature*, 1972, **238**, 37–638.
- 21 C. K. Prier, D. A. Rankic and D. W. C. Macmillan, *Chem. Rev.*, 2013, **113**(7), 5322–638.
- 22 J. Twilton, C. Le and P. Zhang, *Nat. Rev. Chem.*, 2017, **1**, 0052–638.
- 23 B. L. Toth, O. Tischler and Z. Novak, *Tetrahedron Lett.*, 2016, **57**(41), 4505–638.
- 24 Y. Wang, A. Liu, D. Ma, S. Li, C. Lu, T. Li and C. Chen, *Catalysts*, 2018, **8**, 355–638.
- 25 H. M. Yang, M. L. Liu, J. W. Tu, E. M. Stempel, M. G. Campbell and G. J. Chuang, *J. Org. Chem.*, 2020, **85**(4), 2040–638.





- 26 A. Graml, I. Ghosh and B. Konig, *J. Org. Chem.*, 2017, **82**(7), 3552–638.
- 27 X. Zhang, P. Zhu, R. Zhang, X. Li and T. Yao, *J. Org. Chem.*, 2020, **85**(15), 9503–9513.
- 28 W. M. Cheng and R. Shang, *ACS Catal.*, 2020, **10**(16), 9170–9196.
- 29 J. Tang, G. Grampp, Y. Liu, B. X. Wang, F. F. Tao, L. J. Wang, X. Z. Liang, H. Q. Xiao and Y. M. Shen, *J. Org. Chem.*, 2015, **80**(5), 2724–638.
- 30 R. Kancherla, K. Muralirajan, A. Sagadevan and M. Rueping, *Trends Chem.*, 2019, **1**(5), 510–638.
- 31 Y. Z. Chen, D. H. Wang, B. Chen, J. J. Zhong, C. H. Tung and L. Z. Wu, *J. Org. Chem.*, 2012, **77**(16), 6773–638.
- 32 M. Parasram and V. Gevorgyan, *Chem. Soc. Rev.*, 2017, **46**, 6227–638.
- 33 Y. Yasu, T. Koike and M. Akita, *Chem. Commun.*, 2013, **49**, 2037–638.
- 34 X. Z. Fan, J. W. Rong, H. L. Wu, Q. Zhou, H. P. Deng, J. D. Tan, C. W. Xue, L. Z. Wu, H. R. Tao and J. Wu, *Angew. Chem.*, 2018, **57**(28), 8514–638.
- 35 V. Srivastava and P. P. Singh, *RSC Adv.*, 2017, **50**, 31377–638.
- 36 X. Li, X. Gu, Y. Li and P. Li, *ACS Catal.*, 2014, **4**(6), 1897–638.
- 37 W. Fan, Q. Yang, F. Xu and P. Li, *J. Org. Chem.*, 2014, **79**(21), 10588–638.
- 38 S. Kaur, G. Zhao, E. Busch and T. Wang, *Org. Biomol. Chem.*, 2019, **17**, 1955–638.
- 39 C. Ni, W. Chen, C. Jiang and H. Lu, *New J. Chem.*, 2020, **44**, 313–638.
- 40 W. Zhang, X. X. Xiang, J. Chen, C. Yang, Y. L. Pan, J. P. Cheng, Q. Meng and X. Li, *Nat. Commun.*, 2020, **11**.
- 41 L. Teng, X. Liu, P. Guo, Y. Yu and H. Cao, *Org. Lett.*, 2020, **22**(10), 3841–638.
- 42 Y. Zhang, C. Ye, S. Li, A. Ding, G. Gu and H. Guo, *RSC Adv.*, 2017, **7**, 13240–638.
- 43 F. S. Kalthoff, M. J. James, M. Teders, L. Pitzer and F. Glorius, *Chem. Soc. Rev.*, 2018, **47**, 7190–638.
- 44 D. Staveness, I. Bosque and C. R. J. Stephenson, *Acc. Chem. Res.*, 2016, **49**(10), 2295–638.
- 45 Q. Q. Zhou, Y. Q. Zou, L. Q. Lu and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2019, **58**(6), 1586–638.
- 46 N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–638.
- 47 G. Kibriya, S. Samanta, S. Jana, S. Mondal and A. Hajra, *J. Org. Chem.*, 2017, **82**, 13722–638.
- 48 Q. Yu, Y. Zhang and J. P. Wan, *Green Chem.*, 2019, **21**, 3436–638.
- 49 W. Z. Weng, H. Liang and B. Zhang, *Org. Lett.*, 2018, **20**, 4979–638.
- 50 H. Cui, W. Wei, D. Yang, Y. Zhang, H. Zhao, L. Wang and H. Wang, *Green Chem.*, 2017, **19**, 3520–638.
- 51 W. Guo, W. Tan, M. Zhao, K. Tao, L. Y. Zheng, Y. Wu, D. Chen and X. L. Fan, *RSC Adv.*, 2017, **7**, 37739–638.
- 52 H. Cui, W. Wei, D. Yang, Y. Zhang, H. Zhao, L. Wang and H. Wang, *Green Chem.*, 2018, **20**, 141–638.
- 53 W. Wei, P. Bao, H. Yue, S. Liu, L. Wang, Y. Li and D. Yang, *Org. Lett.*, 2018, **20**, 5291–638.
- 54 H. F. Qian, C. K. Li, Z. H. Zhou, Z. K. Tao, A. Shoberu and J. P. Zou, *Org. Lett.*, 2018, **20**, 5947–638.
- 55 L. Tang, X. M. Li, J. H. Matuska, Y. H. He and Z. Guan, *Org. Lett.*, 2018, **20**, 5618–638.
- 56 W. Wei, H. Cui, H. Yue and D. Yang, *Green Chem.*, 2018, **20**, 3197–638.
- 57 J. Kovvuri, B. Nagaraju, A. Kamal and A. K. Srivastava, *ACS Comb. Sci.*, 2016, **18**, 644–638.
- 58 S. S. Shah and N. P. Singh, *Tetrahedron Lett.*, 2018, **59**, 247–638.
- 59 J. G. Sun, H. Yang, P. Li and B. Zhang, *Org. Lett.*, 2016, **18**, 5114–638.
- 60 Z. C. Shen, P. Yang and Y. Tang, *J. Org. Chem.*, 2016, **81**(1), 309–638.
- 61 R. R. Mondal, S. Khamarui and D. K. Maiti, *Org. Lett.*, 2017, **19**, 5964–638.
- 62 S. Sharma and A. Sharma, *Org. Biomol. Chem.*, 2019, **17**, 4384–638.
- 63 (a) V. Srivastava, P. K. Singh and P. P. Singh, *Croat. Chem. Acta*, 2014, **87**(2), 91–638; (b) V. Srivastava, P. K. Singh and P. P. Singh, *Croat. Chem. Acta*, 2015, **88**(1), 59–638; (c) V. Srivastava, P. K. Singh and P. P. Singh, *Croat. Chem. Acta*, 2015, **88**(3), 227–638; (d) V. Srivastava, P. K. Singh and P. P. Singh, *Asian J. Chem.*, 2016, **28**(10), 2159–638; (e) V. Srivastava, P. K. Singh and P. P. Singh, *Rev. Roum. Chim.*, 2016, **61**(10), 755–638; (f) V. Srivastava, P. K. Singh and P. P. Singh, *Croat. Chem. Acta*, 2017, **90**(3), 435–638; (g) V. Srivastava, P. K. Singh, S. Kanaujia and P. P. Singh, *New J. Chem.*, 2018, **42**, 688–638; (h) P. K. Singh, P. P. Singh and V. Srivastava, *Croat. Chem. Acta*, 2018, **91**(3), 383–638; (i) V. Srivastava, P. K. Singh and P. P. Singh, *Tetrahedron Lett.*, 2019, **60**, 40–638; (j) V. Srivastava, P. K. Singh and P. P. Singh, *Tetrahedron Lett.*, 2019, **60**, 1333–638; (k) V. Srivastava, P. K. Singh and P. P. Singh, *Tetrahedron Lett.*, 2019, **60**, 151041–638; (l) V. Srivastava, P. K. Singh, A. Srivastava and P. P. Singh, *RSC Adv.*, 2020, **10**, 20046–638; (m) V. Srivastava, P. K. Singh and P. P. Singh, *Rev. Roum. Chim.*, 2020, **65**(3), 221–638, DOI: 10.33224/rch.2020.65.3.01; (n) A. Verma, A. Srivastava, S. K. Tiwari, N. Yadav, M. D. Ansari, V. B. Yadav, H. Sagir and I. R. Siddiqui, *J. Heterocycl. Chem.*, 2020, **57**(9), 3493–638.
- 64 B. Kuzu, M. Tan, P. Taslimi, I. Gülçin, M. Taşpınar and N. Menges, *Bioorg. Chem.*, 2019, **86**, 187–638.
- 65 M. S. Roy, X. Meg, K. Koda, S. Rasapalli, D. Gout and C. J. Lovely, *Tetrahedron Lett.*, 2019, **60**, 979–638.
- 66 J. Muñoz and M. Köck, *J. Nat. Prod.*, 2016, **79**, 434–638.
- 67 L. Zhang, X. M. Peng, G. L. V. Damu, R. X. Geng and C. H. Zhou, *Med. Res. Rev.*, 2014, **34**, 340–638.
- 68 M. Singsardar, S. Mondal, S. Laru and A. Hajra, *Org. Lett.*, 2019, **21**(14), 5606–638.
- 69 A. S. Jorgensen, P. Jacobsen, L. B. Christiansen, P. S. Bury, A. Kanstrup, S. M. Thorpe, S. Bain, L. Nerum and K. Wassermann, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 399–638.
- 70 A. Shemet and E. M. Carreira, *Org. Lett.*, 2017, **19**, 5529–638.
- 71 K. C. Majumdar and S. K. Chattopadhyay, *Heterocycles in Natural Product Synthesis*, Wiley-VCH, United States, 2011.



- 72 B. Sadowski, J. Klajn and D. T. Gryko, *Org. Biomol. Chem.*, 2016, **14**, 7804–638.
- 73 A. S. Jorgensen, P. Jacobsen, L. B. Christiansen, P. S. Bury, A. Kanstrup, S. M. Thorpe, S. Bain, L. Nerum and K. Wassermann, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 2383–638.
- 74 Y. Liang, L. Teng, Y. Wang, H. Qiuxing and H. Cao, *Green Chem.*, 2019, **21**, 4025–638.
- 75 G. Martinez-Ariza, B. T. Mehari, L. A. G. Pinho, C. Foley, K. Day, J. C. Jewett and C. Hulme, *Org. Biomol. Chem.*, 2017, **15**, 6076–638.
- 76 V. Sharma, P. Kumar and D. Pathak, *J. Heterocycl. Chem.*, 2010, **47**, 491–638.
- 77 G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–638.
- 78 V. K. Outlaw, J. W. Zhou, A. E. Bragg and C. A. Townsend, *RSC Adv.*, 2016, **6**, 61249–638.
- 79 J. Wang, J. Wang, Y. Zhu, P. Lu and Y. Wang, *Chem. Commun.*, 2011, **47**(11), 3275–638.
- 80 D. A. Vargas, A. Tinoco, V. Tyagi and R. Fasan, *Angew. Chem., Int. Ed.*, 2018, **57**(31), 9911–638.
- 81 X. Q. Dai, W. X. Xu, Y. L. Wen, X. H. Liu and J. Q. Weng, *Tetrahedron Lett.*, 2018, **59**, 2945–638.
- 82 Z. Y. Yu, J. N. Zhao, F. Yang, X. F. Tang, Y. F. Wu, C. F. Ma, B. Song, L. Yun and Q. W. Meng, *RSC Adv.*, 2020, **10**, 4825–638.
- 83 W. Schilling, Y. Zhang, D. Reimer and S. Das, *Chem.–Eur. J.*, 2020, **26**(2), 390–638.
- 84 Y. Wu, S. M. Wong, F. Mao, T. L. Chan and F. Y. Kwong, *Org. Lett.*, 2012, **14**, 5306–638.
- 85 R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. Yu and J. C. Walton, *Chem. Commun.*, 2011, **47**, 7974–638.
- 86 T. Nakanishi and M. Suzuki, *J. Nat. Prod.*, 1998, **61**, 1263–638.
- 87 T. Ishikawa, *Med. Res. Rev.*, 2001, **21**, 61–638.
- 88 W. A. Denny, *Curr. Med. Chem.*, 2002, **9**, 1655–638.
- 89 P. Natarajan, D. Chuskit and Priya, *Green Chem.*, 2019, **21**, 4406–638.
- 90 A. Carta, S. Piras, G. Loriga and G. Paglietti, *Mini-Rev. Med. Chem.*, 2006, **6**, 1179–638.
- 91 T. Kazunobu, T. Ryusuke, O. Tomohiro and S. Matsumura, *Chem. Commun.*, 2002, 212–638.
- 92 H. M. Refaat, A. A. Moneer and O. M. Khalil, *Arch. Pharmacol. Res.*, 2004, **27**, 1093–638.
- 93 S. L. Mangold, L. R. Prost and L. L. Kiessling, *Chem. Sci.*, 2012, **3**, 772–638.
- 94 A. A. Hashem, M. A. Gouda and F. A. Badria, *Eur. J. Med. Chem.*, 2010, **45**, 1976–638.
- 95 D. A. E. Issa, N. S. Habib and A. E. Abdel Wahab, *Med. Chem. Commun.*, 2015, **6**, 202–638.
- 96 W. Wei, L. Wang, H. Yue, P. Bao, W. Liu, C. Hu, D. Yang and H. Wang, *ACS Sustainable Chem. Eng.*, 2018, **6**(12), 17252–638.
- 97 D. Jaiswal, J. Tiwari, S. Singh, A. K. Sharma, J. Singh and J. Singh, *ChemistrySelect*, 2019, **4**, 8713–638.
- 98 A. A. Guryev, F. Hahn, M. Marschall and S. B. Tsogoeva, *Chem.–Eur. J.*, 2019, **25**(16), 4062–638.
- 99 R. Jokela and M. Lounasmaa, *Tetrahedron*, 1987, **43**, 6001–638.
- 100 A. Putey, F. Popowycz, Q.-T. Do, P. Bernard, S. K. Talapatra, F. Kozielski, C. M. Galmarini and B. Joseph, *J. Med. Chem.*, 2009, **52**, 5916–638.
- 101 H. Rommelspacher, H. Kauffmann, C. H. Cohnitz and H. Coper, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 1977, **298**, 83–638.
- 102 E. Lukevics, I. Segal, A. Zablotzkaya and S. Germane, *Molecules*, 1997, **2**, 180–638.
- 103 J. M. Harris and A. Padwa, *Org. Lett.*, 2003, **5**, 4195–638.
- 104 V. I. Nikulin, I. M. Rakov, J. E. De Los Angeles, R. C. Mehta, L. Y. Boyd, D. R. Feller and D. D. Miller, *Bioorg. Med. Chem.*, 2006, **14**, 1684–638.
- 105 T. Nagatsu, *Neurosci. Res.*, 1997, **29**, 99–638.
- 106 J. D. Scott and R. M. Williams, *Chem. Rev.*, 2002, **102**(5), 1669–638.
- 107 A. E. Wright, D. A. Forleo, G. P. Gunawardana, S. P. Gunasekera, F. E. Koehn and O. J. McConell, *J. Org. Chem.*, 1990, **55**(15), 4508–638.
- 108 A. C. Collins, J. L. Cashaw and V. E. Davis, *Biochem. Pharmacol.*, 1973, **22**(18), 2337–638.
- 109 J. R. Xin, J. T. Guo, D. Vigliaturo, Y. H. He and Z. Guan, *Tetrahedron*, 2017, **73**, 4627–638.
- 110 M. K. Sahoo, G. Jaiswal, J. Rana and E. Balaraman, *Chem.–Eur. J.*, 2017, **23**(57), 14167–638.
- 111 S. P. Govek, J. Y. Nagasawa, K. L. Douglas, A. G. Lai, M. Kahraman, C. Bonnefous, A. M. Aparicio, B. D. Darimont, K. L. Grillot, J. D. Joseph, J. A. Kaufman, K.-J. Lee, N. Lu, M. J. Moon, R. Y. Prudente, J. Sensintaffar, P. J. Rix, J. H. Hager and N. D. Smith, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 5163–638.
- 112 W. Aman, J. Lee, M. Kim, S. Yang, H. Jung and J.-M. Hah, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 1188–638.
- 113 W. Yichao, H. Shengzhuo, L. Wei and T. Zilong, *Anti-Cancer Agents Med. Chem.*, 2018, **18**, 1228–638.
- 114 Y.-Y. Lu, J.-J. Wang, X.-K. Zhang, W.-B. Li and X.-L. Guo, *J. Pharm. Pharmacol.*, 2015, **67**, 1393–638.
- 115 A. Thangadurai, M. Minu, S. Wakode, S. Agrawal and B. Narasimhan, *Med. Chem. Res.*, 2012, **21**, 1509–638.
- 116 D. J. Dong, D. Q. Zhang, Z. Wang, D. G. Huang and P. S. Li, *ChemMedChem*, 2018, **13**(15), 1490–638.
- 117 T. Yakaiah, B. P. V. Lingaiah, B. Narsaiah, B. Shireesha, B. A. Kumar, S. Gururaj, T. Parthasarathy and B. Sridhar, *Bioorg. Med. Chem. Lett.*, 2007, **17**(12), 3445–638.
- 118 M. Singsardar, S. Laru, S. Mondal and A. Hajra, *J. Org. Chem.*, 2019, **84**, 4543–638.
- 119 A. Mucha, P. Kafarski and L. Berlicki, *J. Med. Chem.*, 2011, **54**, 5955–638.
- 120 A. George and A. Veis, *Chem. Rev.*, 2008, **208**, 1670–638.
- 121 M. Singsardar, A. Dey, R. Sarkar and A. Hajra, *J. Org. Chem.*, 2018, **83**(20), 12694–638.
- 122 H. J. Reich and R. J. Hondal, *ACS Chem. Biol.*, 2016, **11**, 821–638.
- 123 J. Trenner, C. Depken, T. Weber and A. Breder, *Angew. Chem., Int. Ed.*, 2013, **125**, 9121–638.
- 124 S. Saba, J. Rafique, M. S. Franco, A. R. Schneider, L. Espindola, D. O. Silva and A. L. Braga, *Org. Biomol. Chem.*, 2018, **16**, 880–638.

