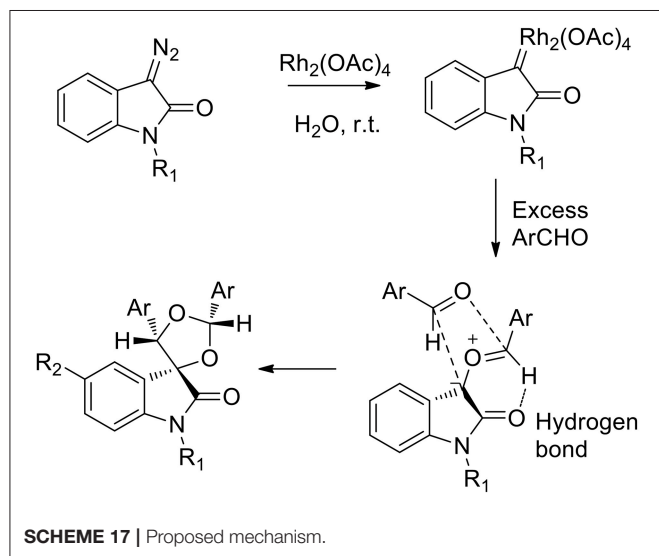


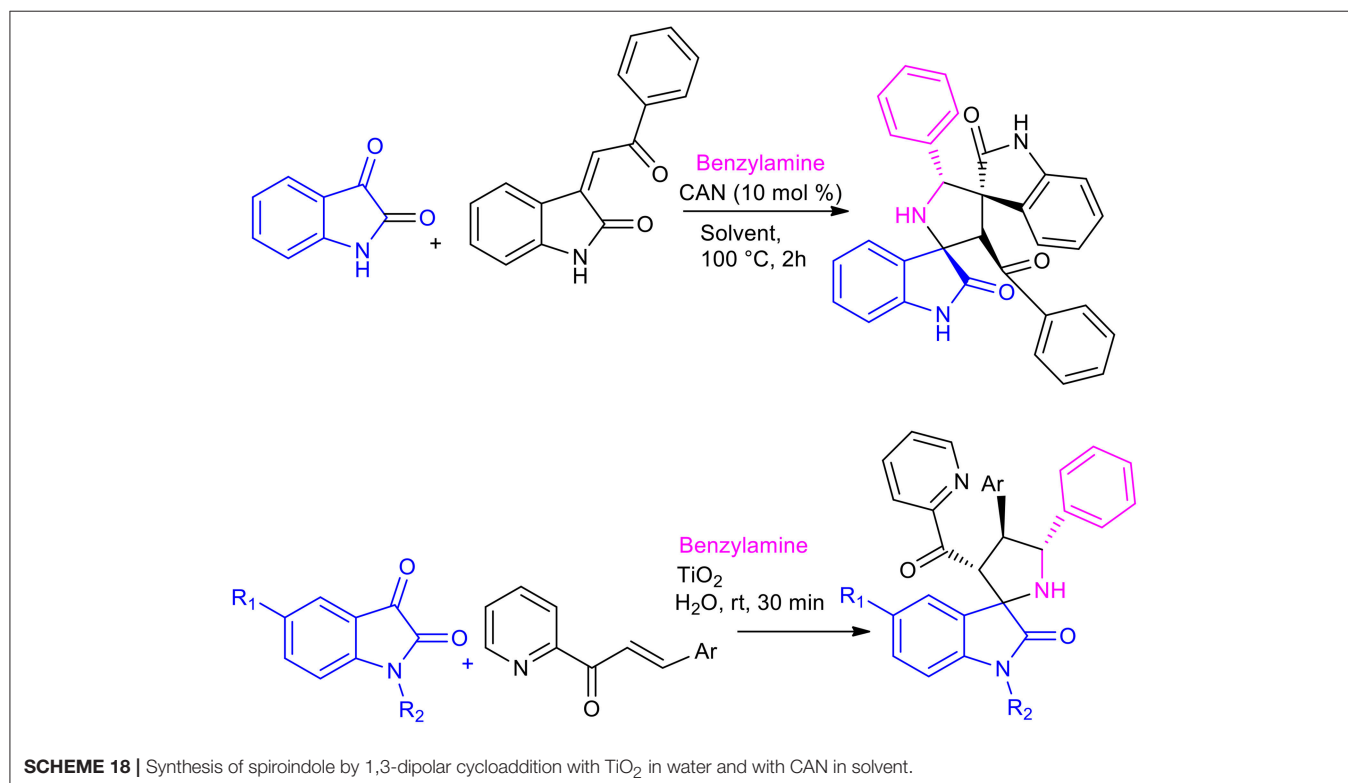
(Ramesh et al., 2016, 2018). The 1,3-dipolar cycloaddition was performed with 1 mol% of CAN in 2 h, while the reaction was complete after 30 min when heterogeneous  $\text{TiO}_2$  nanoparticles were used. Both reactions showed excellent regioselectivity and stereoselectivity, and the  $\text{TiO}_2$  nanocatalyst was reused 5 times without losing catalytic activity. 20 different spirooxindole-pyrrolidines were obtained, in 65–90% yields with CAN and the reaction showed increased average yield in the presence of  $\text{TiO}_2$ .

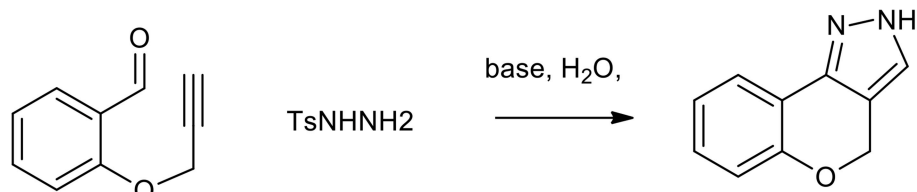


Diazoalkanes can be generated from the decomposition of tosylhydrazones and are efficient 1,3-dipoles exploitable for the synthesis of several nitrogen containing heterocycles (Munro and Sharp, 1984). An intramolecular 1,3-dipolar cycloaddition strategy for rapid access to pyrazoles or triazoles makes use of the *in situ* generated diazomethanes, in a two-step sequence, in which diazomethanes undergo smooth cycloaddition with alkyne or nitrile moieties (Padwa and Ku, 1980). As described in **Scheme 19**, this process can be used as a step-economical route to benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazone. This reaction, which is usually performed in DMF, can be performed in water with  $\text{K}_2\text{CO}_3$ , providing excellent yields (more than 80%).

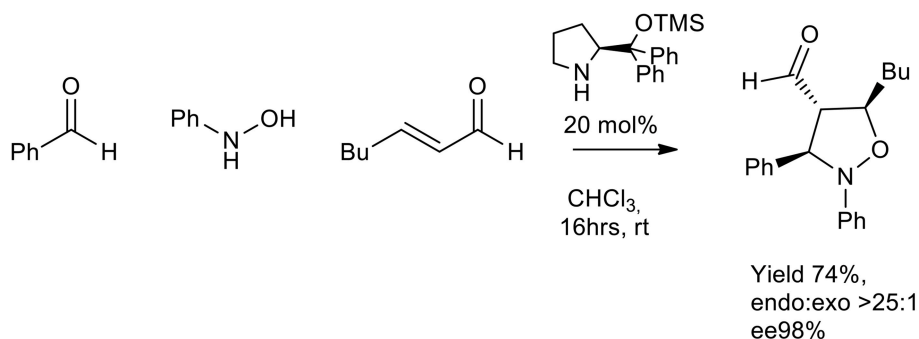
## ORGANO-CATALYZED AND CATALYST-FREE 1,3-DIPOLAR-CYCLOADDITION

A novel organocatalytic asymmetric 1,3-dipolar addition has been proposed by MacMillan, that explored the synthesis of oxazolidine starting from nitrones and  $\alpha,\beta$ -unsaturated aldehydes (Jen et al., 2000). In the presence of different chiral imidazolidinone-HCl the reaction between crotonaldehyde and *N*-benzyl phenyl nitron showed moderate to high yield (45–77%) and *ee* (42–93%); when a Brønsted acid was added as co-catalyst, the efficient iminium activation could increase yield (98%) and *ee* (94%).

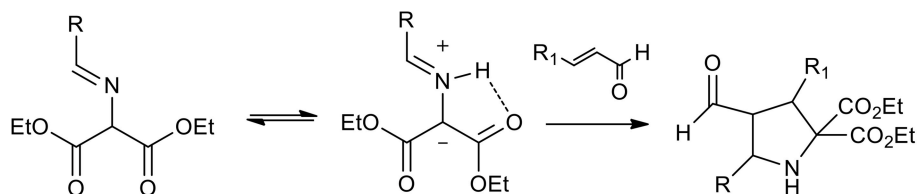




**SCHEME 19** | Synthesis of benzopyranopyrazole from propargylated salicylaldehydes and tosyl hydrazine.



**SCHEME 20** | Enantioselective synthesis of substituted isoxazolidine.



**SCHEME 21** | Schematic representation of iminoesters as the precursors of stabilized azomethine ylides.

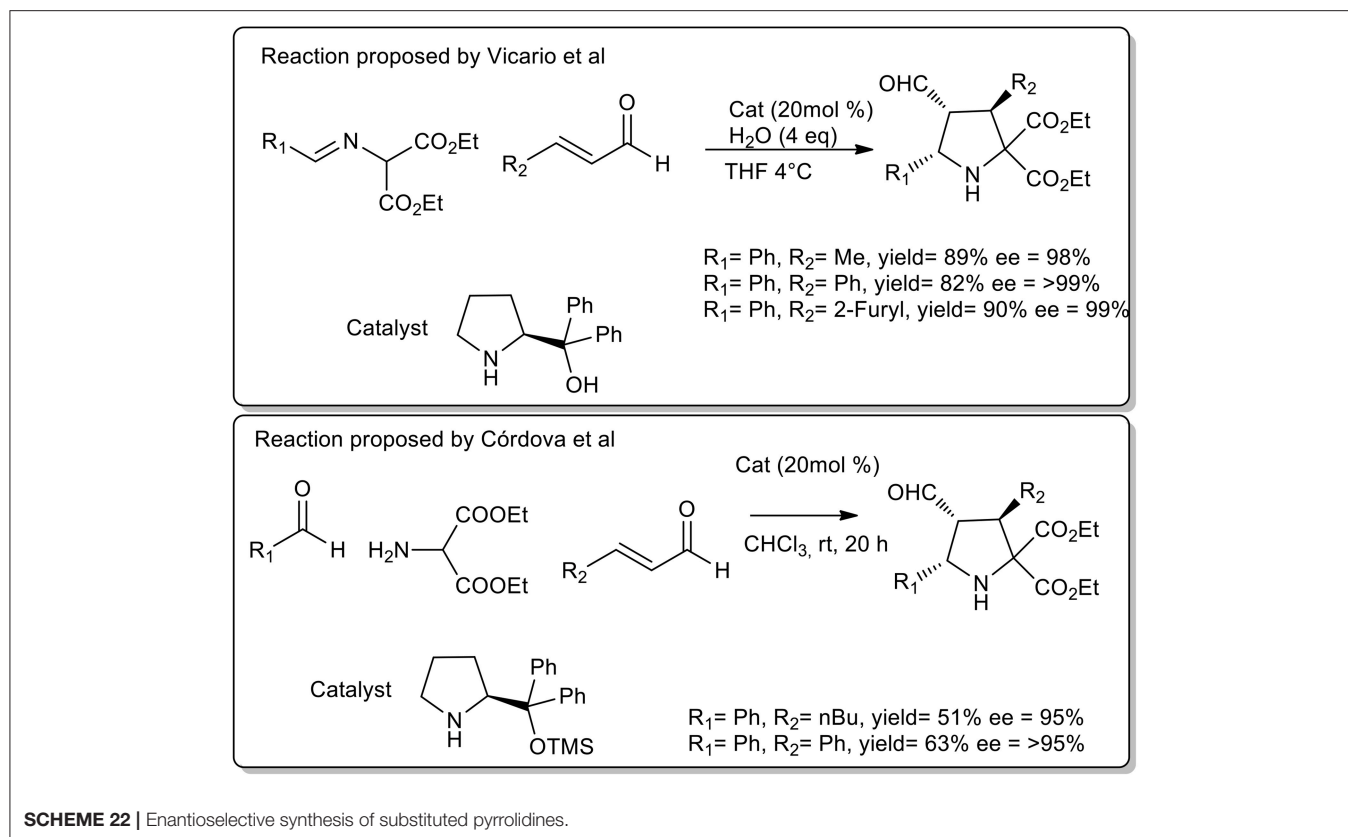
In 2007 Córdova et al. proposed an enantioselective organocatalyzed synthesis of substituted oxazolidine. *N*-arylhydroxylamines, aldehydes, and  $\alpha,\beta$ -unsaturated aldehydes were reacted in the presence of a chiral organic catalyst. The *in-situ* generated nitron reacted with activated enal, in chloroform or THF at room temperature (16 h) to give the isoxazolidine as a single diastereomer (>25:1 *endo:exo*). TMS protected diarylprolinol gave *ee* % up to 98% (**Scheme 20**) (Rios et al., 2007).

Organo-catalyzed (3+2) dipolar cycloadditions of azomethineylide with various dipolarophiles has been the object of intense investigation. Several publications studied iminoesters as the precursors of stabilized azomethine ylides, because, as described in the scheme, they can undergo thermal tautomerism to produce azomethine ylides (**Scheme 21**).

Vicario et al. observed that cycloaddition of imine and crotonaldehyde catalyzed diphenylprolinol provided a single *endo* isomer with excellent enantioselectivity (Vicario et al., 2007). The authors highlighted the fundamental role of free OH groups on the catalyst and the acceleration rate by water addition.

The optimized protocol was performed at 4°C in THF. Similarly, Cordoba et al. proposed the synthesis of pyrrolidine in CHCl<sub>3</sub>, at room temperature with protected prolinol. As described in **Scheme 22**, a slightly lower yield and selectivity were observed (Ibrahim et al., 2007).

An elegant example of 1,3-dipolar cycloaddition in asymmetric catalysis has been published by the Córdova group, which proved that a hydrogen bond donating network with a co-catalyst was to direct the cycloaddition by locking the conformation of the intermediate so to achieve a highly selective reaction (Lin et al., 2011). This dynamic one pot reaction was directed to cycloaddition in THF or DMF and the presence of hydrogen bond donating molecules such as oximes was favorable for the acceleration of the reaction when the substrate was cyanoacetate or  $\alpha$ -cyanoglycine. Compared to the previously described approach, this one pot reaction generated four contiguous chiral centers including a quaternary carbon. As described in the scheme, the proposed mechanism involves the prototropy of the imine cyanoglycine so that the H bond activate the iminium salt and lock its conformation as **1** (see **Scheme 23**)



stereoselective cycloaddition from the *Re* face of intermediate **3** by an *endo* mechanism.

Another recent approach to activate different dipolarophiles other than unsaturated aldehydes was pursued by Chen et al. and chiral phosphoric acids were successfully exploited to obtain pyrrolidine or spirooxindole (Chen et al., 2009; Chang et al., 2016). Excellent yield and enantioselectivity were obtained in DCM at room temperature with chiral sterically hindered phosphoric acids for the imine activation (see **Scheme 24**).

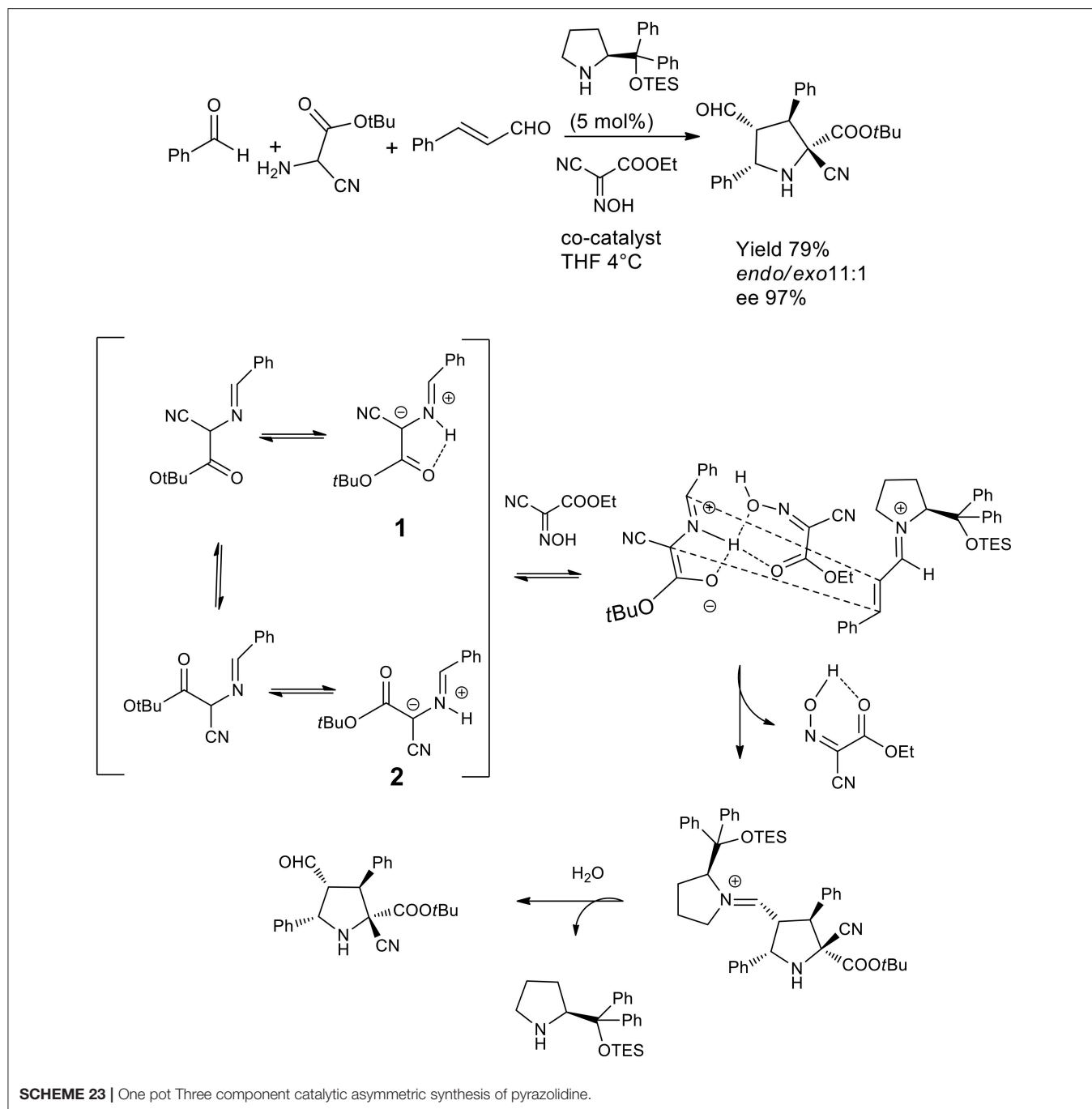
Pyrazoles are known to be potent insecticides and herbicides, and have been also studied for their anti-tumor, anti-inflammatory, anti-microbial and anti-psychotic properties. Diazo compounds may react with alkynes to provide efficient synthesis of pyrazole via 1,3-dipolar cycloaddition. The 1,3-dipolar cycloaddition of alkynes to electron-rich diazo compounds has been described, whereas the intermolecular 1,3-dipolar cycloaddition of alkynes with electron-poor diazocarbonyl compounds is much less often reported because of the high HOMO–LUMO energy difference between alkynes and diazocarbonyl compounds. In presence of Lewis acid or transition metals LUMO of the alkyne dipolarophiles is lowered. Wang et al. (2013) developed an organocatalytic inverse-electron-demand [4+2] cycloaddition between diazoacetates and various carbonyl compounds. Secondary amines were employed as “green promoters,” to catalyze the cycloaddition reaction and produce the target pyrazole ring

(**Scheme 25**). Pyrrolidine was selected as the most effective catalyst and DMSO as best solvent for this transformation. The optimized protocol was performed in DMSO at room temperature with 10 mol% of pyrrolidine and a 1:2 ratio of diazoacetates and carbonyl compounds.

When the reaction was performed with unsymmetrical cyclic ketones, high levels of regioselectivity were achieved. Nonetheless, the authors discovered that in the reaction between diazoacetates and aldehydes, it performed better in presence of acyclic secondary diethyl amine catalysis. Moderate-to-excellent yields of the corresponding adducts were obtained also varying the side-chain of the carbonyl group.

The hypothesis of selective C–H<sub>1</sub> bond-breaking was confirmed by a deuterium labeling experiment. The enamine-promoted cycloaddition reaction with  $\alpha$ -deuterated benzyl diazoacetate yielded the final compound without any deuterium being incorporated into the pyrazole ring, which supports the hypothesis of a selective C–H<sub>1</sub> bond breaking. The authors supposed that the C–H<sub>1</sub> bond is activated by the adjacent electron-withdrawing ester group, toward the selective cleavage over the C–H<sub>2</sub> bond. The final product derived from an elimination step followed by tautomerization (**Scheme 26**).

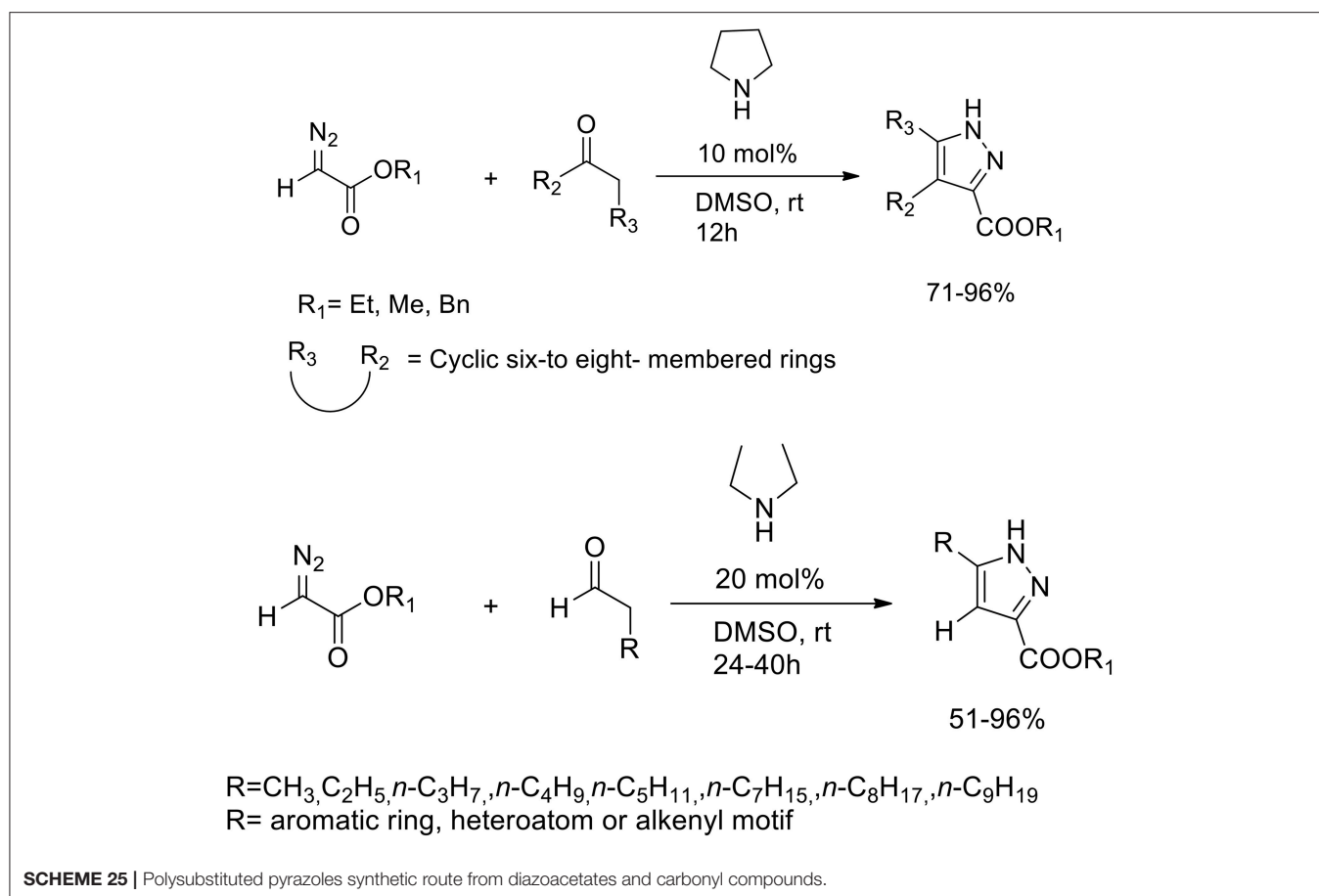
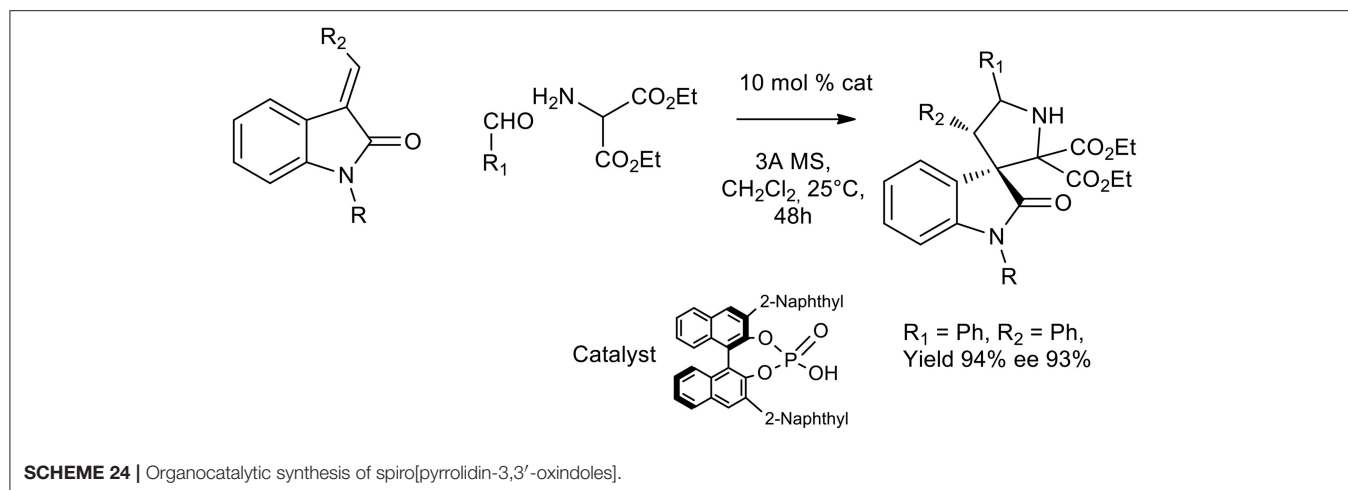
Liu et al. (2017) have presented the first catalyst-free 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines and 3-nitroindoles to prepare highly functionalised, five-ring-fused tetrahydroisoquinolines, which feature an indoline scaffold with excellent diastereoselectivity. The reaction performed the



use of catalysts or additives and more than 95% yield was obtained in EtOAc (**Scheme 27**). In the presence of 20 mol%  $\text{Cu}(\text{OTf})_2$  in  $\text{CHCl}_3$  the cycloaddition reaction afforded the corresponding product with only 23% conversion after 24 h at room temperature. When  $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  was used in  $\text{CHCl}_3$ , the conversion was enhanced to 89%. *N*-tosyl and *N*-alkoxycarbonylated protected, 3-nitroindoles performed very well giving in high yields the corresponding cycloadducts. Because of its reduced electrophilicity *N*-Methyl-protected 3-nitroindole failed to undergo the transformation. The versatility

of this method was demonstrated with a list of structurally different C,N-cyclic azomethine imines.

1,2,3-triazoles have a wide range of applications as potential bioactive compounds and are often used in drugs synthesis. A general and efficient method for their fabrication came in the early 2000s with the novel concept of “click” chemistry and the Cu-catalyzed alkyne–azide cycloaddition reaction provides the regioselective formation of 1,4-disubstituted 1,2,3-triazoles. The metallo-catalyzed alkyne–azide cycloaddition reaction for the formation of 1,5-disubstituted 1,2,3-triazoles

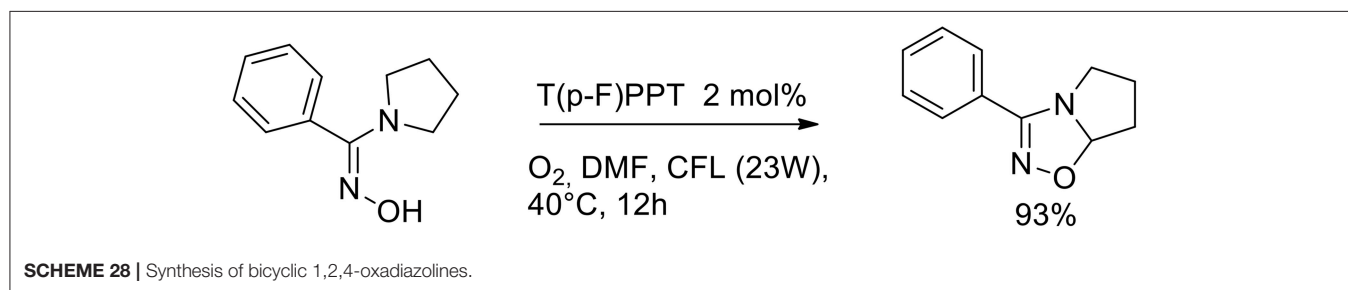
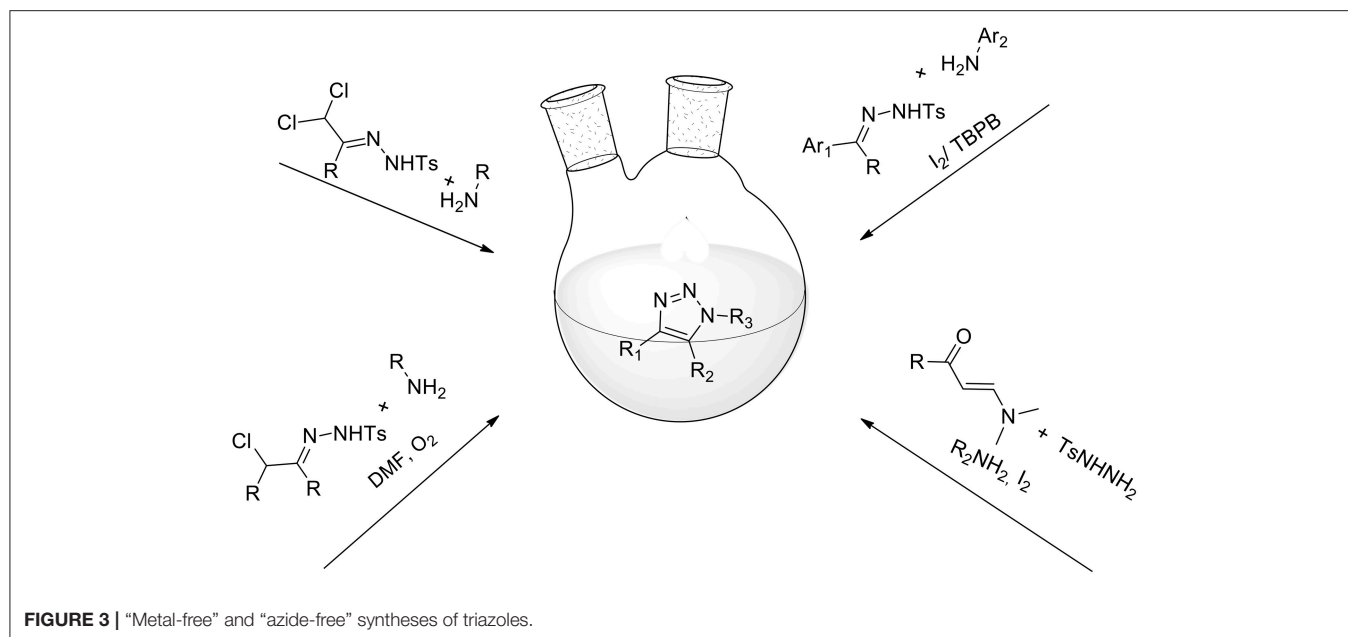


was published later. However, the reactions mentioned above have made use of heavy metals, which has limited their practical applications.

Alternative synthetic pathways for 1,2,3-triazoles have also been developed and 1,2,3 triazoles have freely been obtained from a combination of azides with a range of reaction partners:

e.g., cycloadditions of either  $\beta$ -keto esters or nitriles to azides catalyzed by secondary amines (Costa et al., 2017), cycloaddition of a triple domino sequence of reactions between azide, amine, and 5-bromo-2-furylcarbinol (Yang et al., 2015), the reaction of enols and enamines with azides (Blastik et al., 2018), nitro methylene-based three-component synthesis (Thomas et al.,





## LIGHT INDUCED

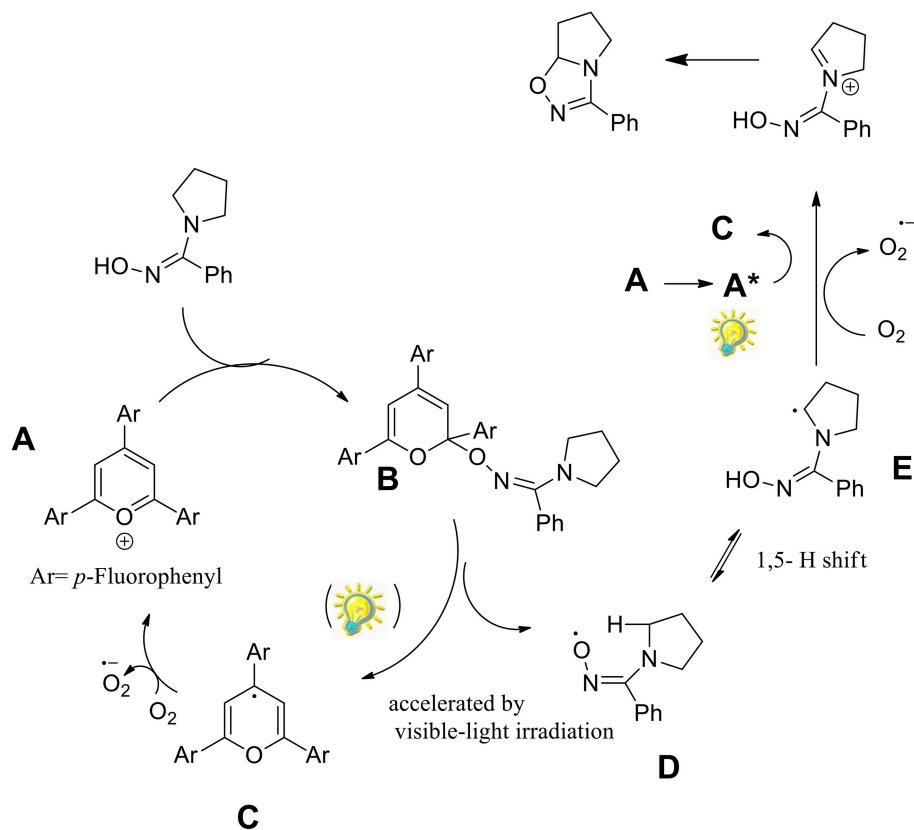
The importance of aza-heterocycles relates to their presence as natural products, drugs and biologically relevant compounds. A variety of methods have been developed for the synthesis of 1,2,4-oxadiazolines, and these are typically carried out via the [4+2] cycloaddition of an imine with a nitrile oxide (generated *in situ* from hydroxamoyl chloride or nitroalkane). The design of a new synthetic path of 1,2,4-oxadiazolines, especially greener methods, is highly desirable because many of these methods suffer from one or more drawbacks. Soni et al. (2018) have very recently presented a greener method for the synthesis of 1,2,4-oxadiazolines via an intramolecular oxidative cyclisations of amidoximes in the presence of an organocatalyst and molecular oxygen. The authors optimized the reaction conditions to give 3-phenyl-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole from phenyl(pyrrolidin-1-yl)methanone oxime, which was used as a model substrate. The optimized conditions involved 2 mol% of an organophotocatalyst, 2,4,6-tris(4-fluorophenyl)pyrylium tetrafluoroborate [T(p-F)PPT] at a 0.2M concentration in DMF under an atmosphere of molecular oxygen. Visible-light irradiation was provided by a

compact fluorescent lamp (CFL, 23 W). Organophotocatalyst can reduce the drawbacks of transition metals related to toxicity and the low residues admitted in pharmaceutical products (**Scheme 28**).

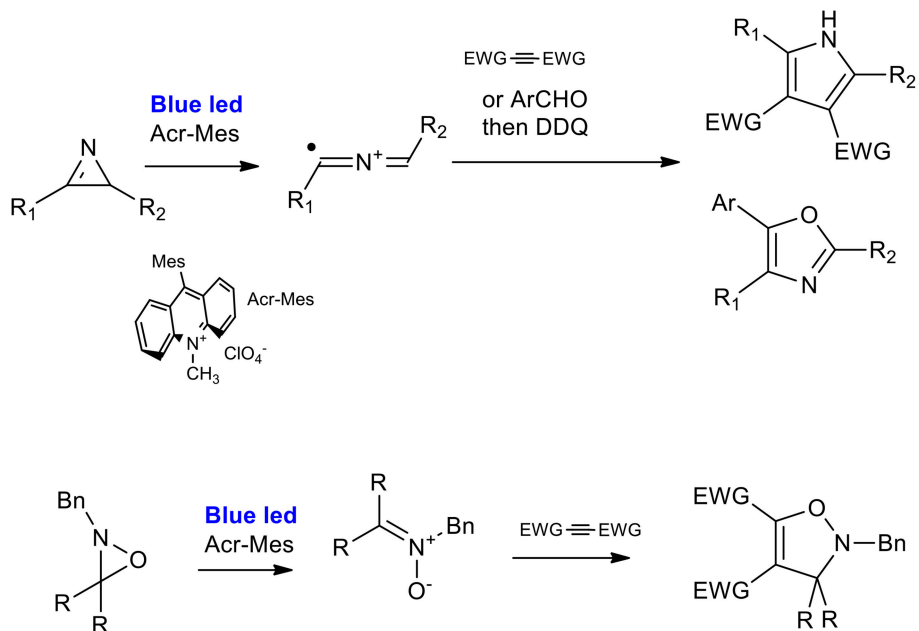
The authors investigated several pyrrolidinyl oxime derivatives both with electron-withdrawing and electron-donating substituents, for the oxidative cyclization to 1,2,4-oxadiazolines with a mechanism as proposed in **Scheme 29**.

It was observed that triphenylpyrylium (TPP) derivatives were the only effective photocatalysts among those examined, with conversion even in absence of light. As described in the **Scheme 29**, the reaction begins with the nucleophilic addition to the triphenylpyrylium ion (A) toward intermediate B. Molecular oxygen provides the oxidation of C by regenerates catalyst A. The iminyloxy radical D undergoes an intramolecular 1,5-hydrogen atom transfer (HAT) to the radical E, which is then oxidized to the iminium ion F. The final 1,2,4-oxadiazoline is generated by intramolecular cyclization of F.

Visible-light-driven photoredox catalysis is attracting interest because of its inherent features of green chemistry and sustainability. In addition to a number of radical reactions,



**SCHEME 29** | Plausible mechanism for the synthesis of 1,2,4-oxadiazolines.



**SCHEME 30** | Visible-light mediated synthesis of pyrroles and isozazoles from of 2H-azirines and 2H-oxazirine.



several [2+3] cycloaddition applications have been described in the existing literature (Narayanam and Stephenson, 2011; Nakajima et al., 2016; Staveness et al., 2016; Savateev and Antonietti, 2018).

2*H*-azirines can react with activated alkynes or aldehydes to produce polysubstituted pyrroles or 2,5-dihydrooxazole, respectively, under very mild reaction conditions (visible-light irradiation, metal-free, and room temperature). As described by Xuan et al., the optimized procedure is catalyzed by 9-mesityl-10-methyl-acridinium perchlorate in dichloroethane under irradiation from a 3 W white LED light. Excellent results were obtained when a range of substituted 2*H*-azirines were reacted with dimethyl but-2-yne-dioate (Xuan et al., 2014). 2*H*-Azirines reacted with aldehydes in the presence of Li<sub>2</sub>CO<sub>3</sub>. This was done to avoid the oxidation of aldehydes to carboxylic acids, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added to the reaction system in order to perform the one pot synthesis of oxazole. The applicability of the reactions was demonstrated using a panel of 12 2,4,5 trisubstituted oxazoles, giving yields in the 40–80% range (Scheme 30) (Zeng et al., 2015).

The ring-opening of 2*H*-oxazirine has been described as occurring via visible-light-mediated photoredox-catalyzed single-electron transfer (SET), giving nitron precursors. The 1,3-dipolar cycloaddition was therefore used for the synthesis of

4-isoxazolines. 9-mesityl-10-methyl-acridinium perchlorate was the strategic choice of catalyst because of its high oxidizing power (+2.06 V). The [3 + 2] cycloaddition reaction of oxaziridine with dimethyl acetylenedicarboxylate gave very good results when performed in CH<sub>3</sub>CN in the presence of water, used as an additive, and a large set of 4-isoxazolines was synthesized with a good average yield.

The first attempt to describe the mechanism of pyrrole cyclization focused on a radical cycloaddition of the intermediate 2-azaallenyl radical cation, which was in equilibrium with a 1,3-radical-cationic species. Subsequently, the publication mentioned the synthesis of the dihydroisoxazole by an hypothesis of a polar cycloaddition. In fact, the authors proposed the single-electron reduction of the nitron radical to a nitron species.

## AUTHOR CONTRIBUTIONS

All the authors contributed equally to the review preparation. GC supervised the work and edited the final version.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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