2

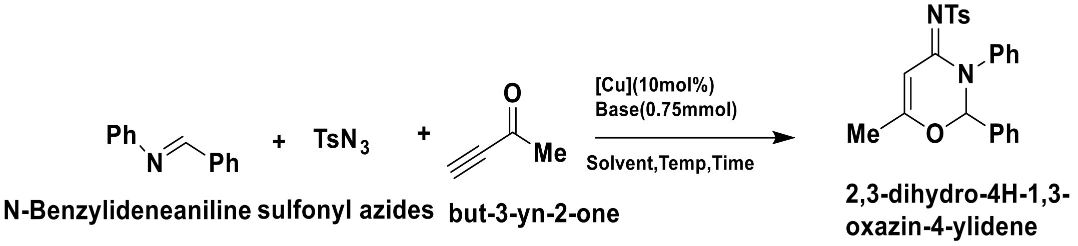
Review of literature

2.1 The Review of IEDDA Reactions is discussed under the following headings:

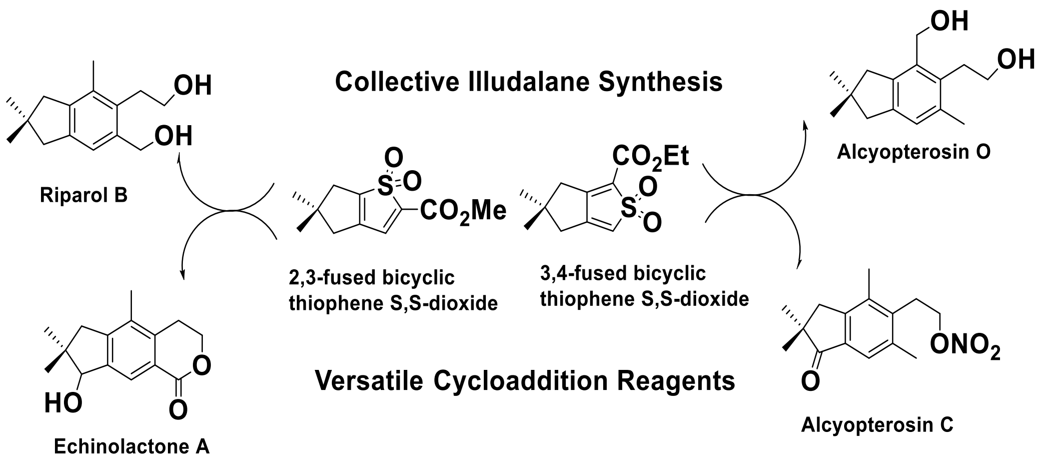
i. IEDDA reaction with Lewis acid catalyst
ii. IEDDA reaction with enamines
iii. Computational Chemistry of IEDDA Reaction
iv. Application of IEDDA reaction

2.1.1 IEDDA reaction with Lewis acid catalyst

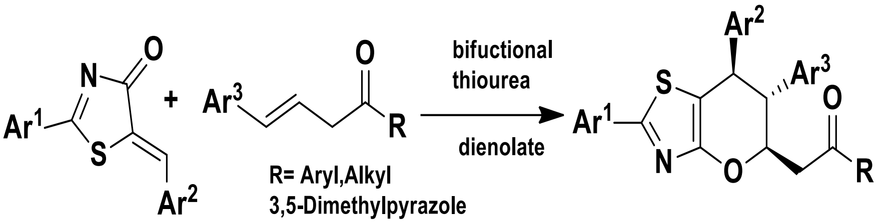
Yang *et al.*, (2022) developed an operationally simple and effective method for preparing 2,3-dihydro-4*H*-1,3-oxazin-4-ylidenes from a mixture of the corresponding imines, sulfonyl azides, and terminal ynones in presence of base with stirring at room temperature, using the Copper-catalyzed azide-alkyne-cycloaddition/ring cleavage/[4+2] annulation process. The intermediate N-sulfonyl acylketenimines, in particular, undergo cycloaddition under IEDDA reactions involving imines and a range of 1, 3-oxazine derivatives were successfully carried out in high yields**.**



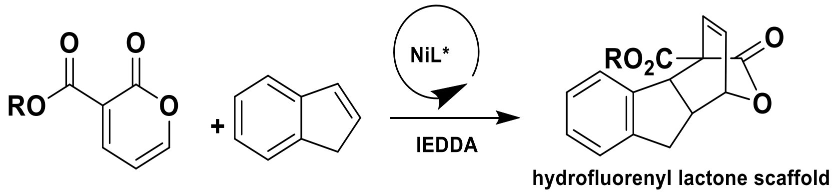
Park *et al.*, (2022) described a group synthesis of nine illudalane sesquiterpenes employing bicyclic thiophene S, S-dioxides as generic precursors to the indane core of the natural products. Furans with IEDDA cascades were used as uncommon dienophiles. The interaction of thiophene S, S-dioxides with both electron-poor and electron-rich dienophiles showed reaction pathways involving either nonpolar pericyclic or bifurcating ambimodal cycloadditions, which were rationalised by theoretical investigations. The study highlighted thiophene S, S-dioxides' broader potential as convenient and adaptable precursors to polysubstituted arenes.



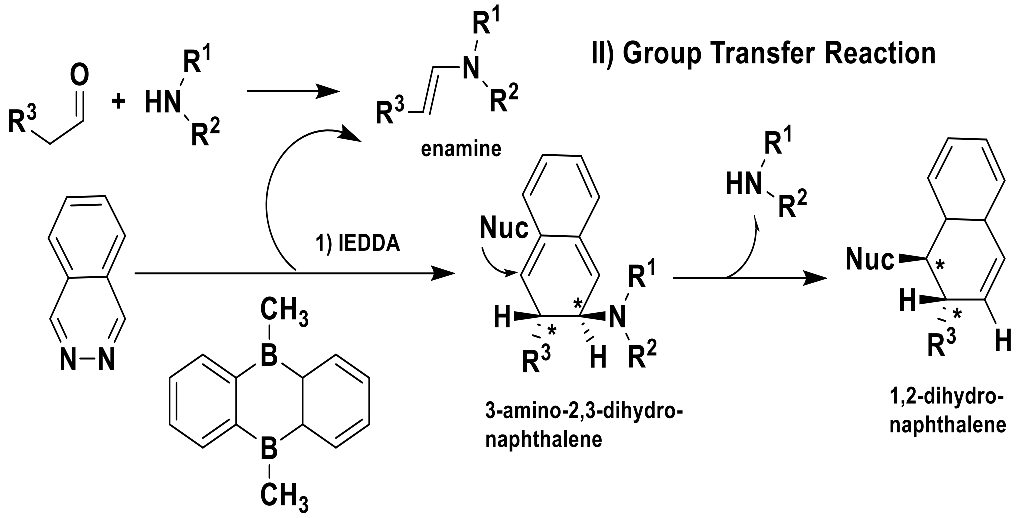
Yang ***et al.*****, (2022)** studied a quinine thiourea-enabled oxo-IEDDA reaction of 5-alkenyl thiazolones with, unsaturated carbonyl compounds. This enabled the enantioselective synthesis of a diverse set of highly functionalized pyranthiazoles with three continuous stereocenters. The methodology was applicable to a wide range of substrates and had a high potential for scale-up synthesis and easy transformation.



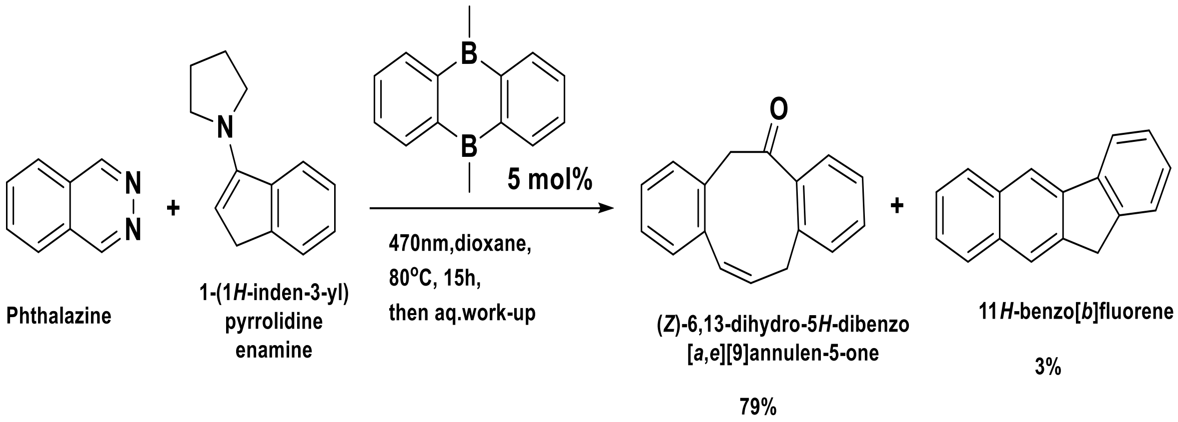
An asymmetric (IEDDA) reaction of electron-deficient 2-pyrones with electrically unbiased indenes catalysed by a chiral N,N′-dioxide/Ni(OTf)$_2$ complex was reported by **Zhang** ***et al.*****, (2022)** . Under moderate circumstances, a range of substituted hexahydrofluorenyl lactone scaffolds were produced with acceptable to exceptional yields (up to 98% yield) and enantioselectivities (up to 93% ee).



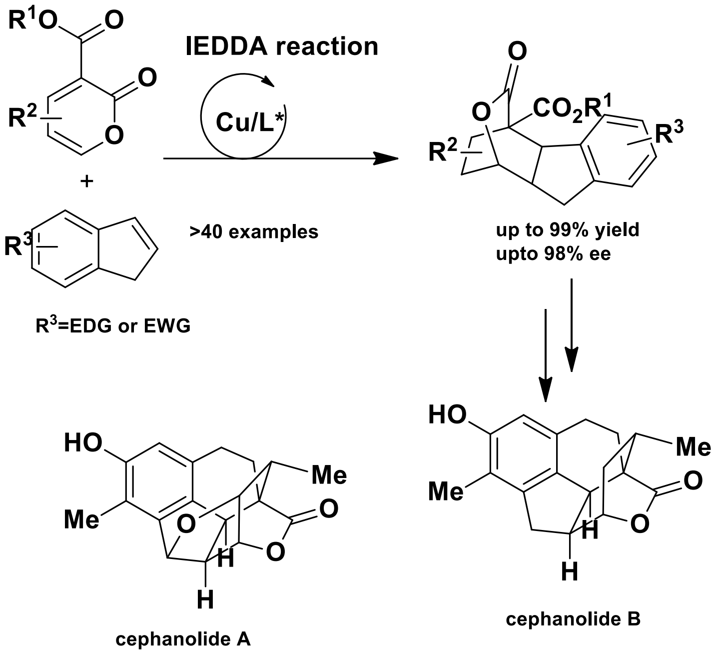
Beeck & Wegner, (2022) successfully coupled the notion of bidentate Lewis acid activation of phthalazine with asymmetric organocatalysis to launch a new enantioselective IEDDA/group transfer domino technique. An enamine was created in situ by reacting an aldehyde with a chiral secondary amine catalyst, which was activated by coordination to a bidentate Lewis acid catalyst. This technique resulted in 91:1 enantiomeric ratio.



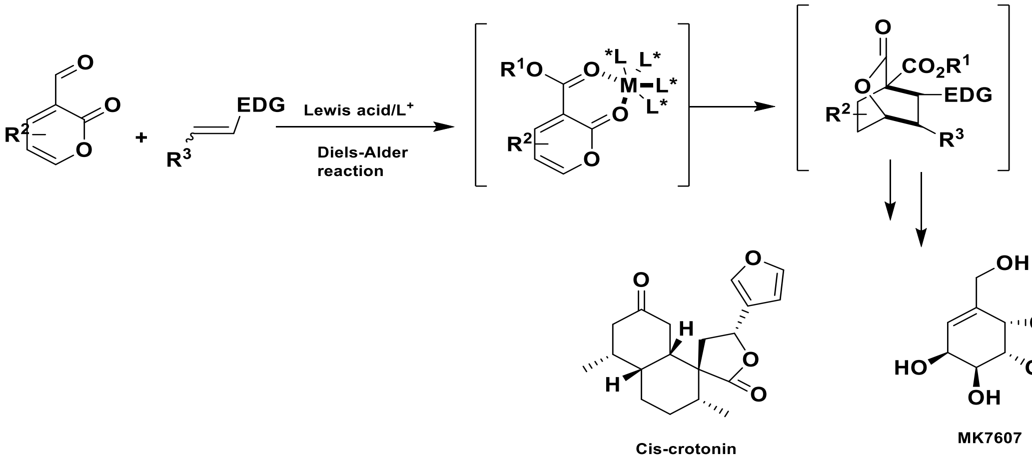
Strauss *et al.*, (2021) had computed and performed synthetic experiments to analyse the whole mechanism for all conceivable routes of the domino processes launched by the bidentate Lewis acid-catalyzed IEDDA reaction of diazenes. The essential structure was discovered as a quinodimethane intermediate, which served as the foundation for all subsequent transformations: elimination to aromatic naphthalene, rearrangement to dihydroaminonaphthalene, and photo-induced ring opening. These findings revealed precise information about the bidentate Lewis acid-catalyzed domino IEDDA reaction, which will be used in the future to create new reactions and build innovative catalysts.



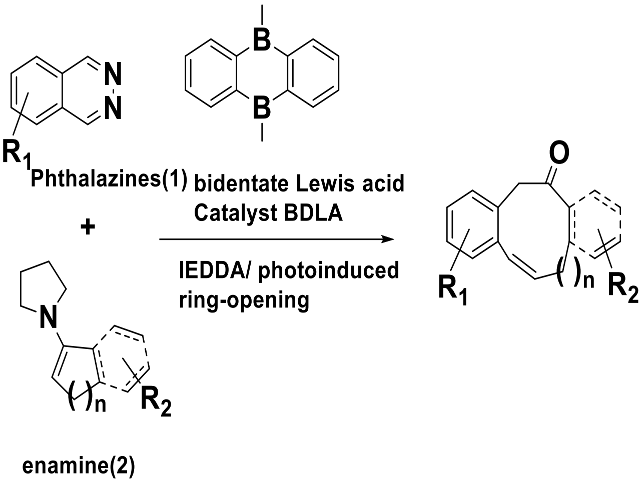
Lu *et al.*, (2021) reported an asymmetric IEDDA reaction catalysed by copper employing electron-deficient 3-carboalkoxyl-2-pyrones and electrically unbiased indenes as reactants. This approach allowed the quick and enantioselective synthesis of a wide variety of hexahydrofluorenyl bridged-lactone scaffolds. Asymmetric complete syntheses of cephanolides A and B were achieved using this approach.



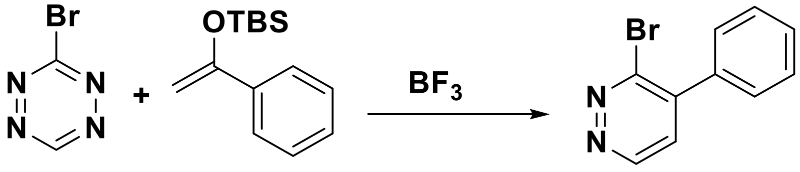
IEDDA reaction of diene 3-alkoxycarbonyl-2-pyrones with electron-rich alkenes dienophiles in the presence of Lewis acid catalyst have been successfully utilized for the synthesis of natural products like *Cis*-crotonin and MK7607 **Si *et al.*, (2021).**



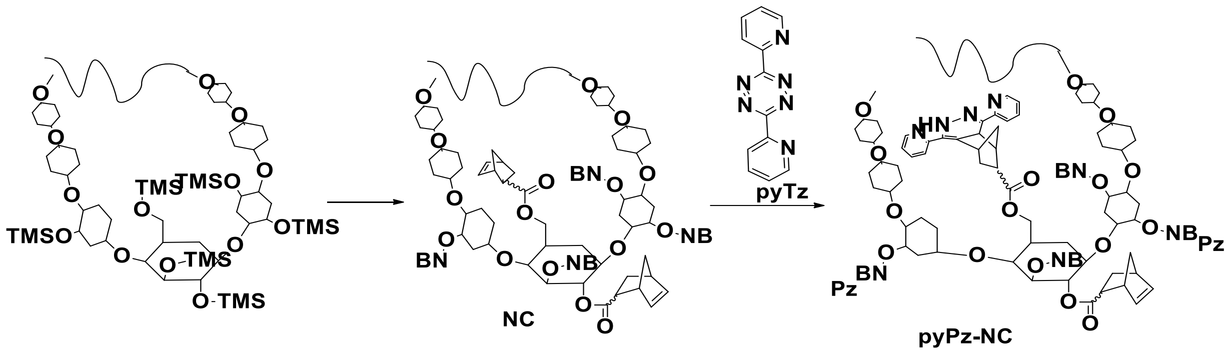
Ruhl *et al.*, (2021) demonstrated that the Lewis acid-catalyzed (IEDDA) reaction combined with a photoinduced ring-opening (PIRO) reaction of phthalazines and cyclic enamines was a strong tool for the synthesis of medium-sized carbocycles. The electron-rich enamines, 1-(6- methoxy-3H-inden-1-yl)pyrrolidine and 1-(6-methly-3Hinden-1-yl)pyrrolidine, and electron-deficient 5,8-difluorophthalazine, good yields of the respective medium-sized carbocycles. The electron-rich 6-methoxyphthalazine and electron-deficient 5-bromo-substituted enamine, on the other hand, only interacted slowly, and utilising enamines with varied ring widths revealed sterics for the IEDDA/PIRO process. Overall, the IEDDA/PIRO reaction provided a novel transition metal-free and stereoselective synthesis technique for 9- and 11-membered carbocycles, which will help to expand the molecular space for biological and materials applications.



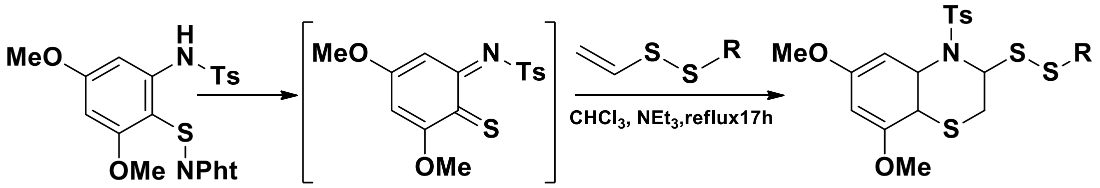
Schnell *et al.*, (2021) performed the Lewis acid-mediated IEDDA reaction between 3-monosubstituted s-tetrazine and silyl enol ethers and obtained pyridazines. Exclusive regioselectivity was reported for 1-monosubstituted silyl enol ethers. Downstream functionalization of the resultant 3-bromo-pyridazines was demonstrated using multiple cross-coupling techniques to synthesis 3, 4-disubstituted pyridazines with excellent control over the substitution pattern.



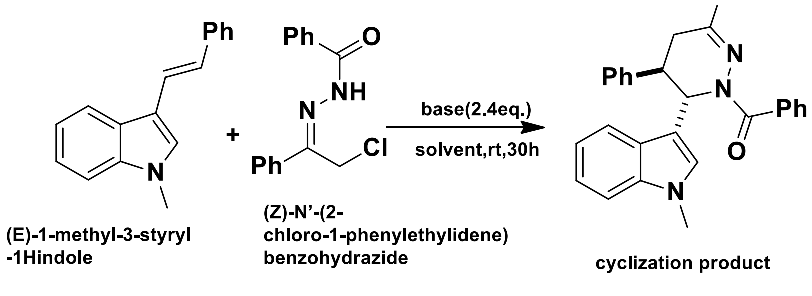
The direct reaction of trimethylsilyl cellulose with norbornene acid chloride resulted in a simple, catalyst-free synthesis of a norbornylated cellulosic substance norbornylated cellulosic material with a high degree of substitution. The reaction kinetics were equivalent to the Huisgen type 1,3-dipolar cycloaddition of azide with alkynes while avoiding hazardous catalysts **Wappl *et al.*, (2021).**



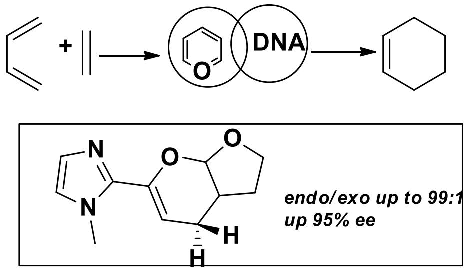
Jędrzejewski *et al.*, (2021) discovered a facile and practically viable approach for producing unsymmetrical vinyl disulfides with added functionalities such as hydroxy, carboxy, protected amino, or ester groups. Functionalized unsymmetrical vinyl disulfides interacted with transient o-iminothioquinones in an IEDDA reaction to form benzo[b][1,4]thiazine derivatives.



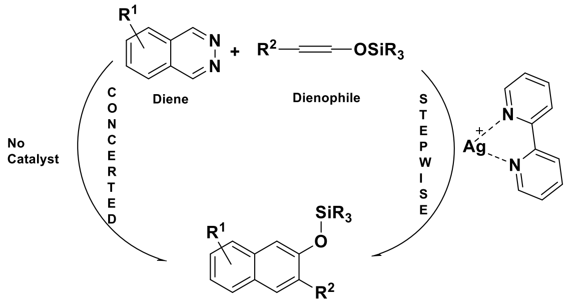
A catalyst-free and base-promoted aza- IEDDA reaction between readily accessible, in situ-generated azoalkenes and 3-vinylindoles was developed by **Chen *et al.*, (2021)**. As single diastereoisomer, this approach yielded highly substituted 3-(2, 3, 4, 5-tetrahydropyridazin-3-yl)-1*H*-indoles with good to high yields (72%-89% yields, >20:1 dr). Furthermore, a Cu (OTf) $_2$/(S, S)-^{i}Pr-box catalyst system was used to catalyse the asymmetric form of this reaction, yielding the required chiral product with 81% yield, >20:1 dr, and 93% ee. The cyclization products were highly functionalized, allowing easy transformations to access other valuable organic compounds.



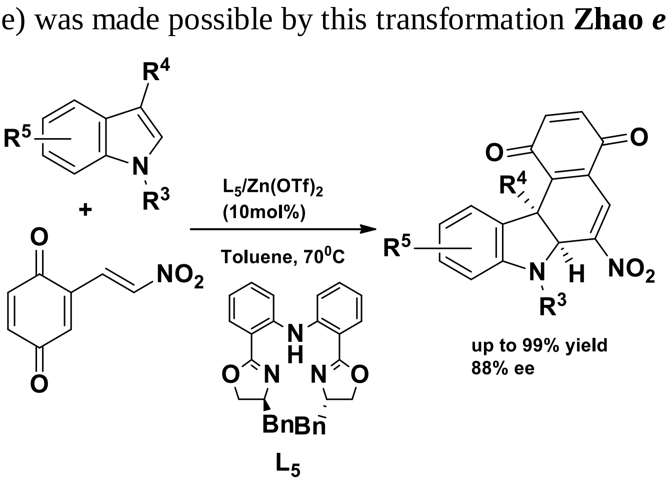
The first example of a DNA-catalyzed IEDHDA reaction involving dihydrofuran and various,unsaturated acyl imidazoles was presented by **Mansot *et al.*, (2020)**. With a minimal catalyst loading, the resultant fused bicyclic O,O-acetals with three contiguous stereogenic centres was produced in high yields (up to 99%) and excellent diastereo- (up to >99:1 dr) and enantioselectivities (up to 95% ee). These findings demonstrated that the theory of DNA-based asymmetric catalysis may be extended to novel synthetic transformations, providing an efficient, sustainable, and highly selective tool for the synthesis of chiral building blocks.



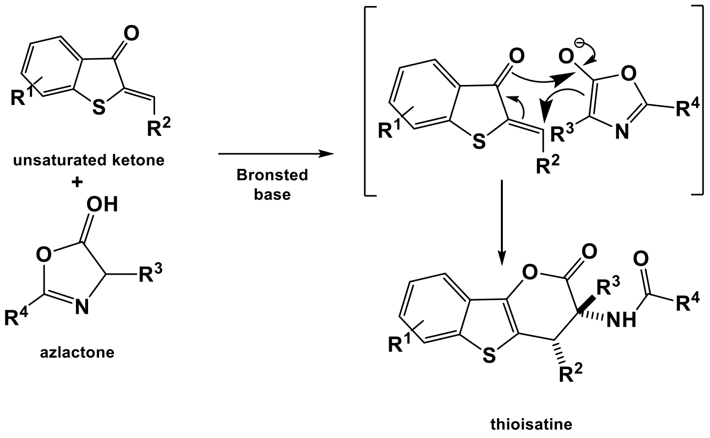
The inverse IEDDA reaction of phthalazines with siloxy alkynes was effectively enhanced by the silver catalyst, according to DFT calculations. Lowering the reaction barrier significantly changed the reaction from a concerted [4+2] cycloaddition to a stepwise ionic mechanism **Avcı *et al.*, (2020)**.



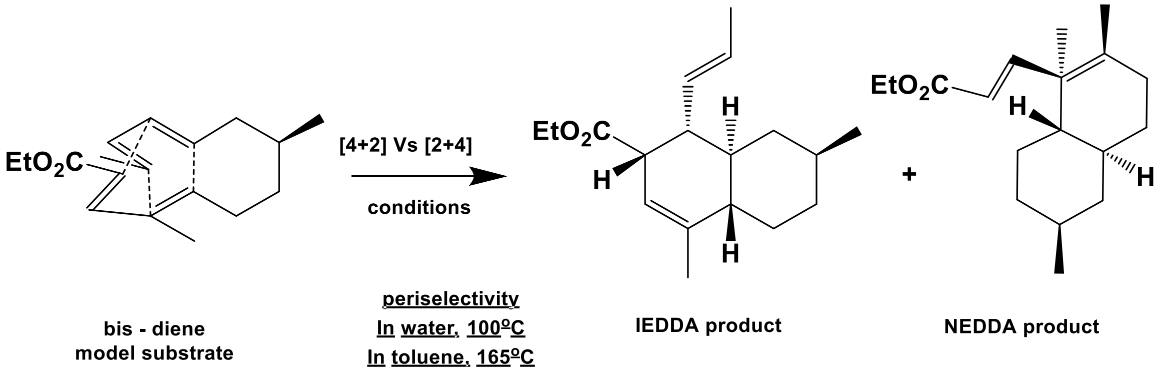
Dearomaitization with enantioselectivity using a chiral bisoxazoline/zinc complex as a catalyst, an IEDDA reaction/oxidation of indoles with 2-(2-nitrovinyl)-1, 4-benzoquinone was achieved. The synthesis of enantioenriched six-membered [2, 3]-fused indolines (up to 99% yield and 88% ee) was made possible by this transformation **Zhao *et al.*, (2020).**



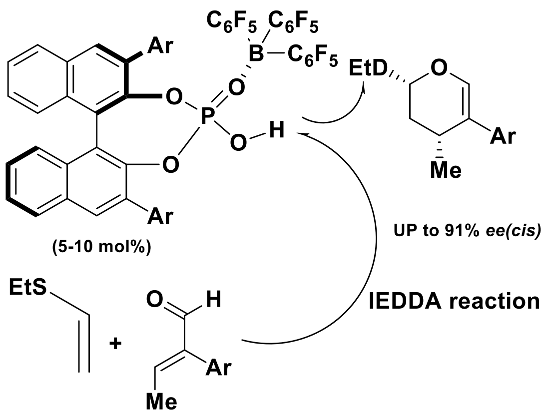
Saktura *et al.*, (2019) discovered an intriguing IEDHDA cycloaddition between azlactones and, α,β -unsaturated ketones derived from thioisatine. The reaction had been realised under basic conditions and benefited from its aromatic character, with the formation of the benzothiophene moiety being the driving force of the cascade. An enantioselective variant of the cycloaddition had also been developed with moderate enantioselectivity.



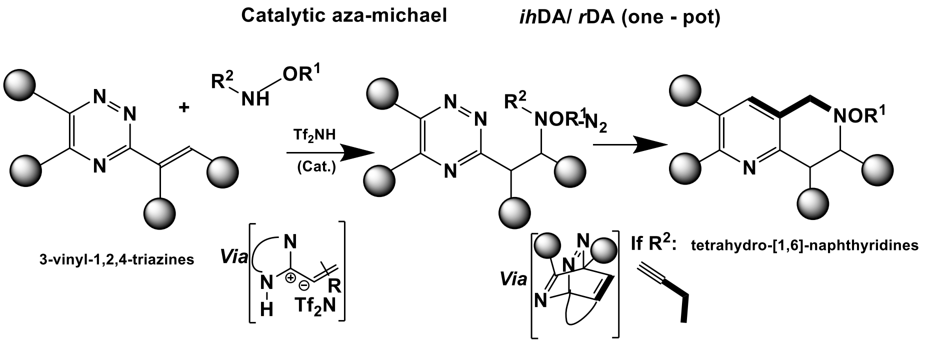
Zhang *et al.*, (2019) reported that a pericyclase IccD could be used to catalyse an inverse-electron demand Diels–Alder (IEDDA) reaction with a rate acceleration of 3x10^5 fold in the biosynthesis of the fungal natural product ilicicolin H. Pericyclase IccD was highly periselective towards the IEDDA cycloaddition over a competing normal electron demand Diels-Alder (NEDDA) reaction from an ambimodal transition state.



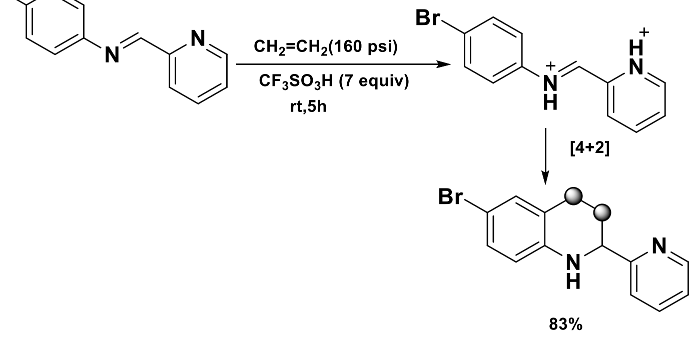
The bulky tris(pentafluorophenyl)borane-assisted chiral phosphoric acid catalysts were used to establish the enantioselective IEDHDA reaction of acroleins with ethyl vinyl sulphide. The multiselectivity reaction was controlled by the chiral cavity of the supramolecular Bronsted acid catalysts, and optically active 3,4-dihydro-2*H*-pyrans were produced in high yields **Hatano *et al.*, (2019).**



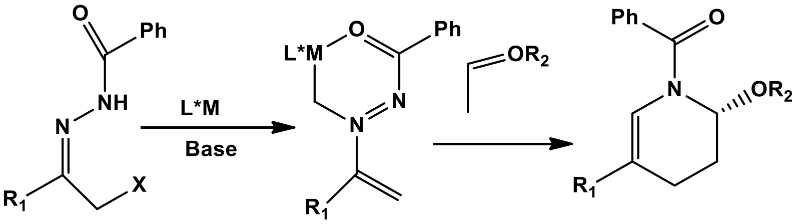
Buttard *et al.,* (2019) used the extremely acidic triflimide as an organocatalyst to achieve an unparalleled catalytic aza-Michael addition of substituted 3-vinyl-1, 2, 4-triazines with alkoxyamine nucleophiles by one-pot domino conjugate addition-IEDHDA/rDA reactions. The sequence using alkoxyamine nucleophiles, not only highlights an uncommon instance of the catalytic aza-Michael reaction of alkenylazaarenes but also showed promising way for the synthesis of a variety of biorelevant tetrahydro-[1,6]-naphthyridines.



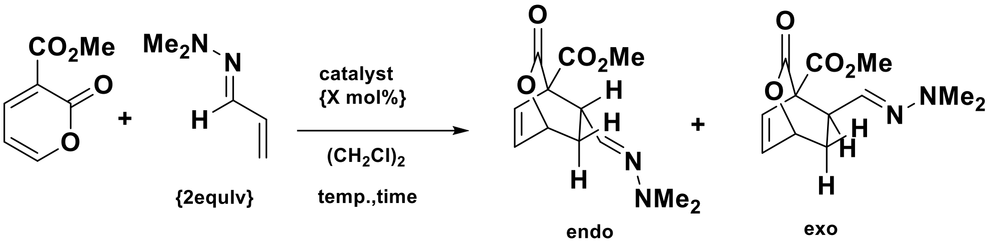
IEDDA reaction of superelectrophilic iminium ions with ethylene has been discovered. This was employed to develop a sequence of tetrahydroquinoline products, marking the initial application of superelectrophilic activation in a cycloaddition reactions as well as a new approach of using ethylene as a C_2 building block **(Vuong *et al.,* 2018).**



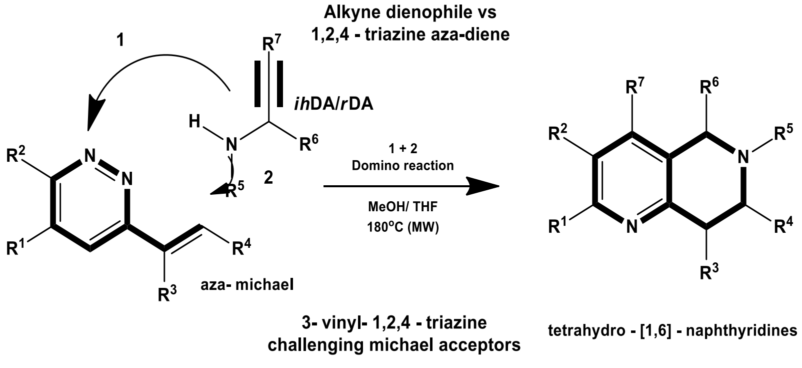
Wei ***et al.,*** **(2018)** generated a CuOTf/bisoxazoline complex that catalysed an asymmetric IEDDA reaction of azoalkenes with fulvenes in situ**.** The methodology provided a direct entry point for the synthesis of bicyclic tetrapyridazine derivatives with exclusive regioselectivity, excellent stereoselectivity, and a high yield.



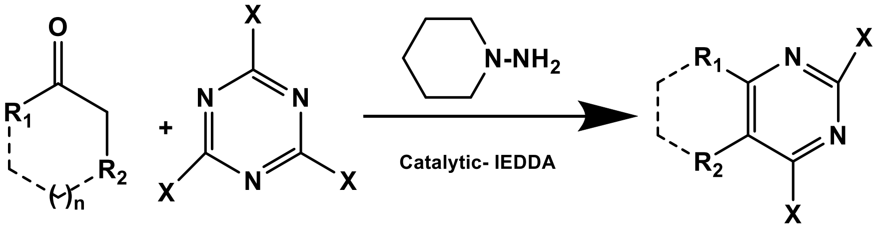
By mixing pyrones with a 3-electron-withdrawing group and α, β-unsaturated hydrazones in an IEDDA reaction catalysed by the oxophilic lanthanide complex Eu(hfc)$_3$,**Hashimoto** ***et al.,*** **(2018)** generated a novel form of electron-rich olefin. This approach was used to create a cycloadduct containing hydrazone that can perform hydrazone-specific reactions. Dehydrazonation was also accomplished, generating the equivalent aldehyde, which was difficult to get by cycloaddition of pyrone and enal**.**



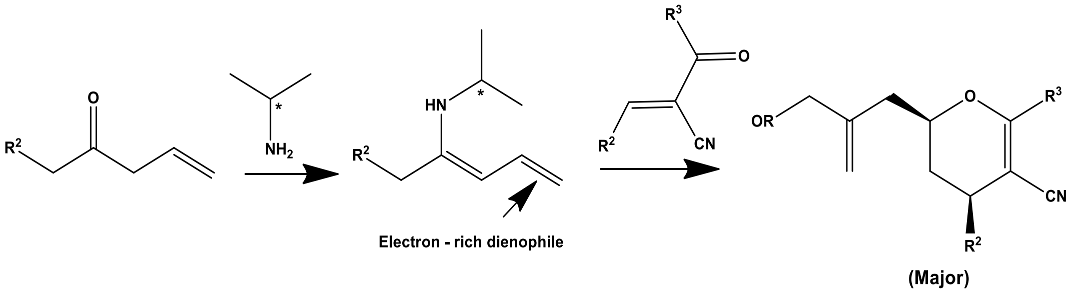
Between propargylamine derivatives (1° and 2°) and 3-vinyl-1,2,4-triazines, a facile domino aza-Michael IEDHDA/rDA reaction were studied by **Jouha** ***et al.,*** **(2017).** A novel route to synthesize polysubstituted tetrahydro1,6-naphthyridine scaffolds was developed besides the distinctiveness of this dual-heterocyclic platform..



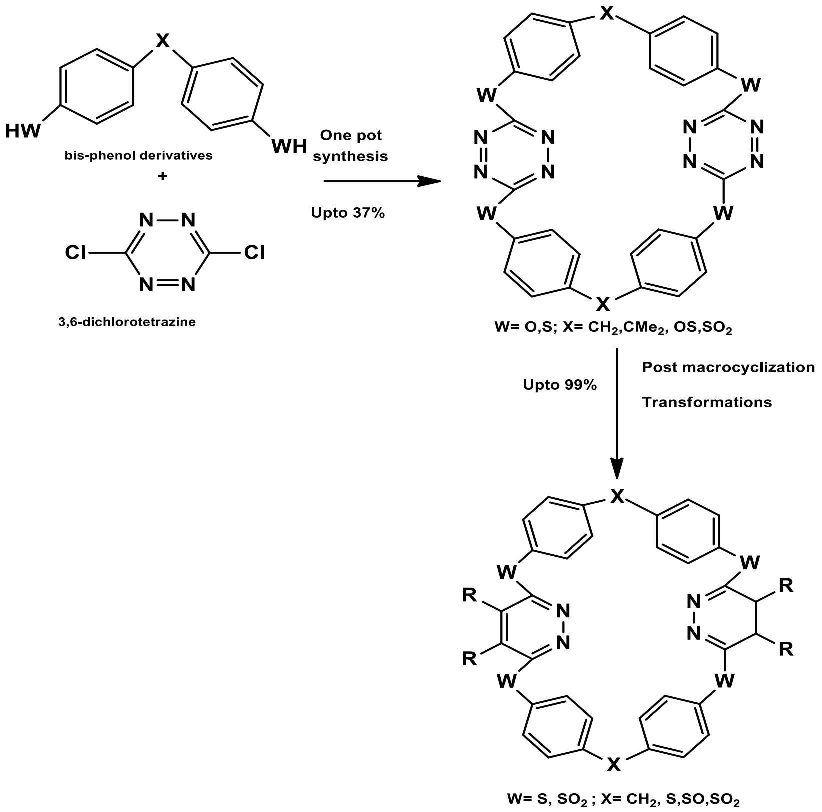
An organocatalytic version of the IEDDA reaction of 1,3,5-triazines was successfully developed by **K. Yang *et al.*, (2017).** Hydrazine was used as an effective organo-catalyst for the direct IEDDA reaction of ketones with 1, 3, 5-triazines.1, 3, 5-triazine. The reaction was simple, economical, and a green approach for the preparation of highly functionalized pyrimidines from readily available ketones.



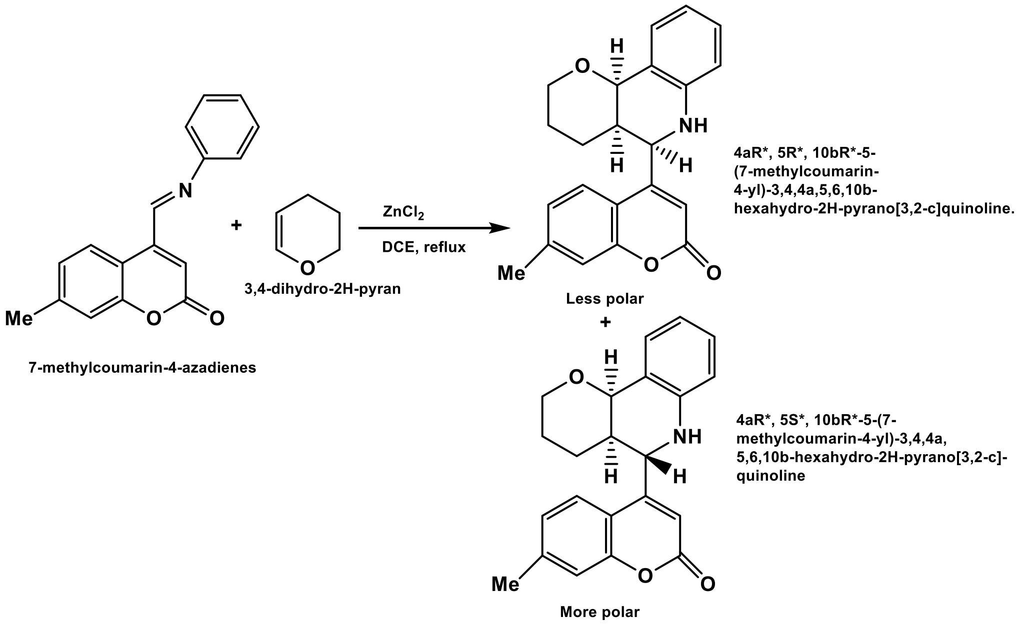
A fascinating IEDDA reaction of linear deconjugated enones catalyzed by a readily available quinine-derived primary amine and benzoic acid was explored by **Maity and Pan (2017)** . Electron-poor oxadienes with a cyano group was found to be suitable in this reaction. With a 20 mol% loading of a quinine-derived primary amine catalyst, high yields and excellent enantioselectivities were attained for a variety of 2, 4-stereogenic 3, 4-dihydropyran products under mild reaction conditions. This two stereogenic centers dihydropyran products were important frameworks and could be applied in the synthesis of pharmaceuticals and bioactive natural products.



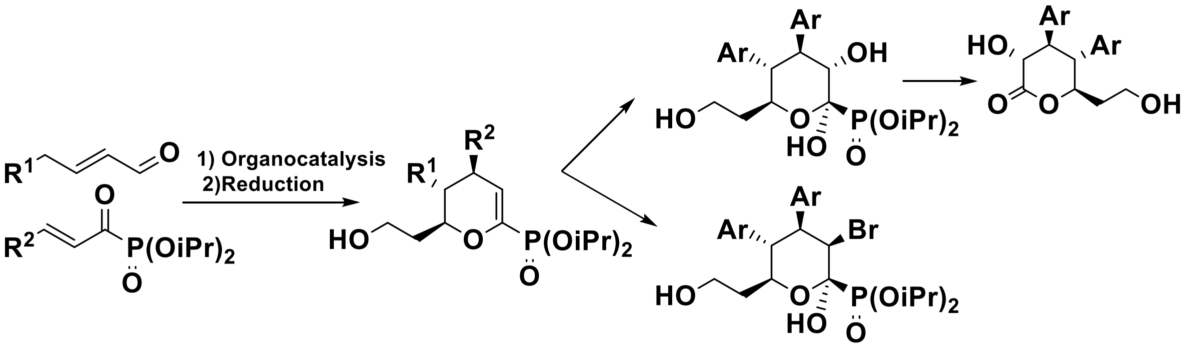
Based on nucleophilic aromatic substitution processes ,**Fu *et al.*, (2016)** had created an operationally straightforward one-pot reaction technique for the synthesis of corona[4]arene[2]-tetrazines that included various bridging units, such as oxygen, sulphide, methylene, and sulfone. Different corona [4] arene[2]pyridazines were produced by macrocyclic ring transformations using an IEDDA reaction of tetrazine moieties with enamines and the following sulphide oxidation process. These new synthesised macrocycles might be helpful in the study of supramolecular chemistry due to their accessibility and intriguing structural behaviours.



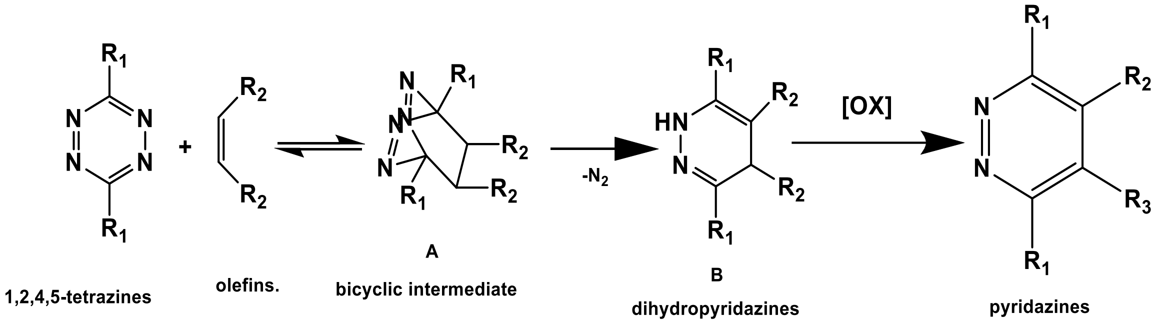
Sanap & Samant, (2015) highlighted regiospecific IEDDA of 7-methyl coumarin-4-azadienes. Reaction between 7–methyl-4-carbaldeyde and aniline derivatives offered 7-methyl coumarin-4-azadienes. In IEDDA reaction, 7-methyl coumarin-4-azadienes reacted with dihydrofuran, dihydropyran and styrene. This reaction was catalysed by anhydrous $ZnCl_2$ which provided two diasteroisomers but cis-configuration was the major product.



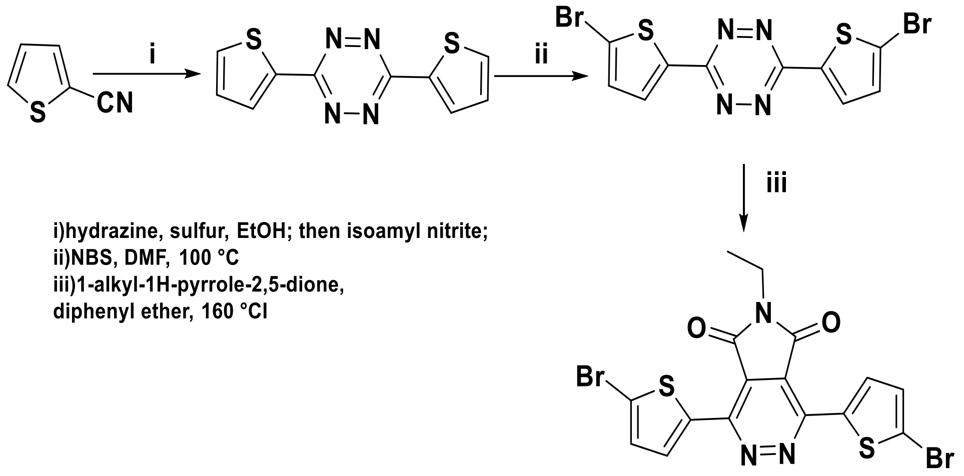
The simultaneous activation of α, β-unsaturated aldehydes and acyl phosphonates resulted in the enantioselective IEDHDA reaction of the distant olefin functionality in dienamines. The enantioselective reaction produced dihydropyran frameworks with three contiguous stereogenic centres. Various substitution sequences for both the heterodiene and the dienophile was feasible, and the target products was produced with high yields and up to 92% ee. **Weise *et al.*, (2014).**



Knall *et al.*, (2014) studied pseudo-first-order reactions rates of norbornene-based compounds by UV-Vis measurements with unsubstituted norbornene and other alkenes. This study discovered that, exo, exo-5-norbornene-2, 3-dimethanol the most one, as reactive as then the unsubstituted norbornene. But (±)-*endo, exo*-dimethyl 5-norbornene-2, 3-dicarboxylate reacted just marginally quicker than unstrained alkenes.

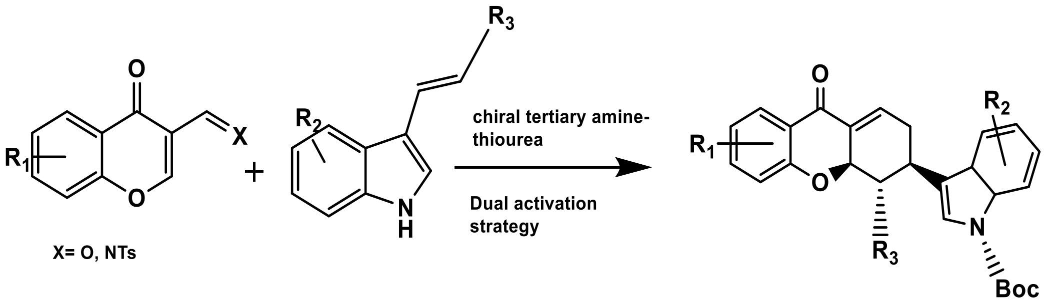


6-alkylpyrrolo [3, 4-*d*] pyridazine-5, 7-dione (PPD) with a low LUMO level was produced using the IEDDA reaction between thiophene and furan-decorated tetrazine substrates and an electron-deficient 1-alkyl-1*H*pyrrole-2, 5-dione unit. It has been included in a number of donor-acceptor-type polymers that have outstanding optical contrast, quick switching times, and high colouring efficiencies **Ye et al., (2014).**



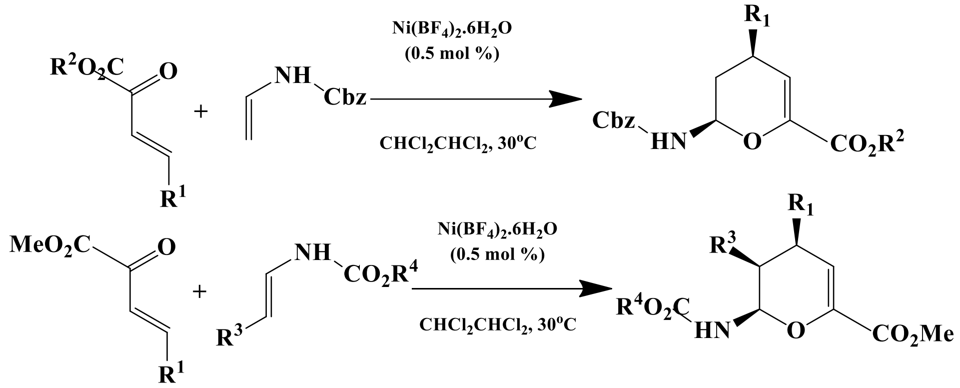
i)hydrazine, sulfur, EtOH; then isoamyl nitrite;
ii)NBS, DMF, 100 °C
iii)1-alkyl-1H-pyrrole-2,5-dione,
diphenyl ether, 160 °Cl

Pharmocologically active flavonoids based chromanone, dihydropyran and indole had been constructed through catalytic asymmetric IEDDA reaction of chromone oxadienes and 3-vinylindoles which were used as dienophiles by **Chen *et al.*, (2015).** The reaction proceeded smoothly to afford the IEDDA adducts with good to high yields and enantioselectivities (up to 91% total yield, up to 94% ee for *endo* product). Although the *endo/exo* ratios of the product were moderate, the two diastereoselectivities could be easily separated by flash chromatography.

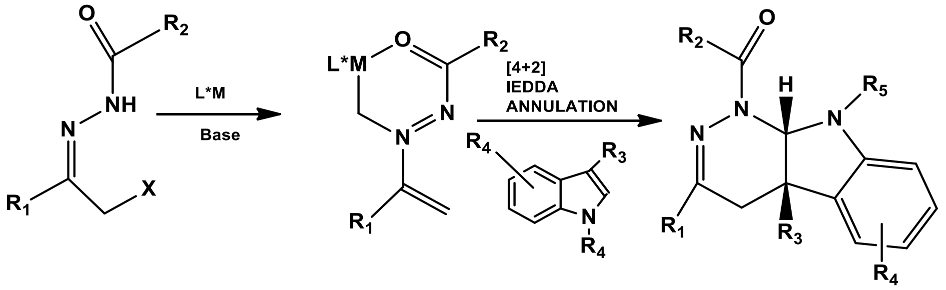


3 (endol)
16 example, up to 91% yield,
up to 3,8/1 endoexo, up to 94% ee gram-scale

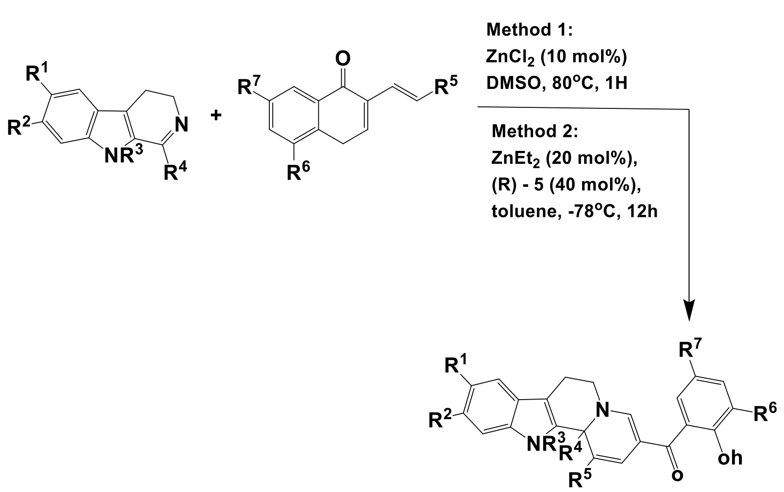
Zhou *et al.*, (2014) had developed N, N′-dioxide/Ni (II) complexes as efficient catalysts for the enantioselective IEDHDA reaction of methyleneindolinones with mono- and disubstituted acyclic vinyl ethers, 3, 4-dihydro-2*H*-pyran, as well as enecarbamates. In the presence of 0.5–10 mol% catalysts, a variety of optically active dihydropyran-fused indoles were obtained in up to 99% yields with up to >95 : 5 dr and up to 99% ee under mild reaction conditions.



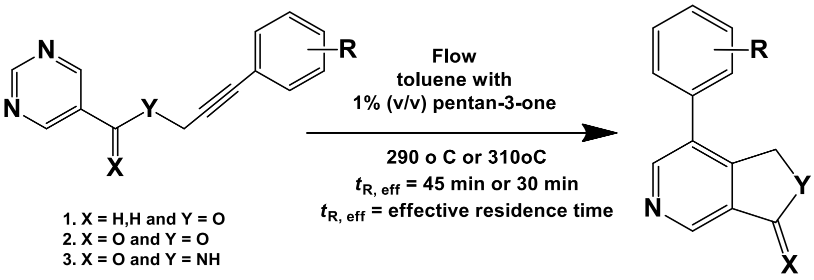
Tong *et al.*, (2014) had successfully developed the first catalytic asymmetric IEDDA reaction of indoles with in situ formed azoalkenes catalyzed by CuI /tBu-Phosferrox complex. This method provided facile access to a diverse set of biologically important [2, 3]-fused indoline tetrahydropyridazine heterocycles in good yields (up to 97%) with high regioselectivity and diastereoselectivity (> 20:1 d.r.), and excellent enantioselectivity (up to 99% ee).



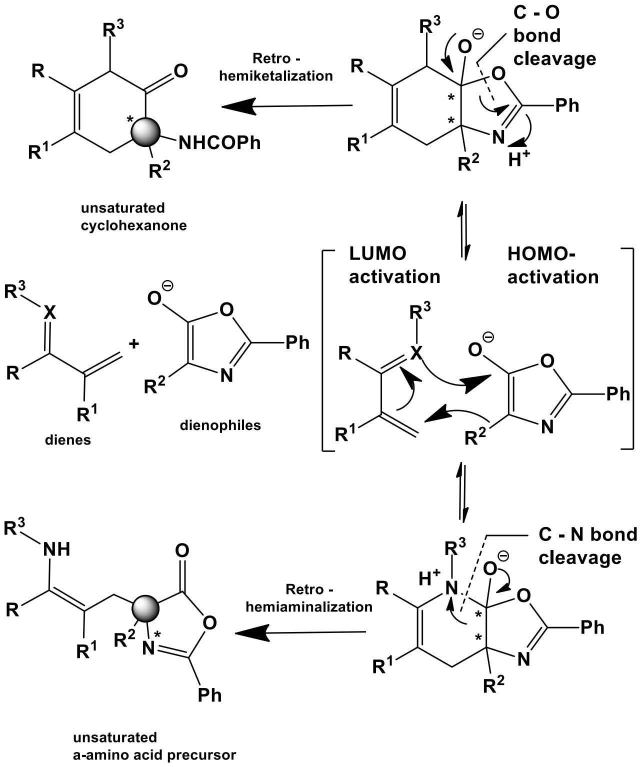
A catalytic and asymmetric IEDIDA reaction between various cyclic imines and chromone-derived dienes was developed by **Eschenbrenner-Lux, Kumar, and Waldmann (2014)**. The reaction was catalyzed by zinc/binol complexes. This novel reaction provided a facile entry to a natural product inspired collection of ring-fused quinolizines.



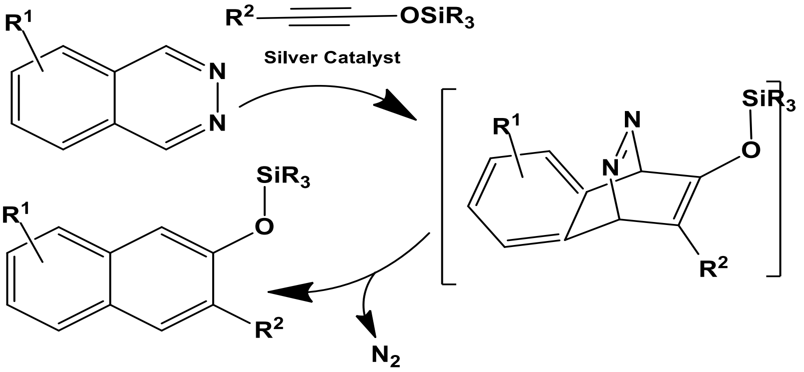
Martin *et al.,* (2013) had developed a new advantageous process that allowed the controlled continuous flow synthesis of a number of fused bicyclic 5-aryl substituted pyridine derivatives through an intramolecular IEDDA/ rDA reaction cascade. This served as a useful building block in medicinal chemistry with good to excellent yields and short processing times (<45 min).



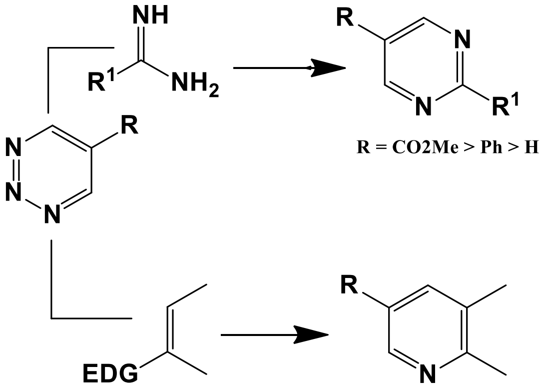
Jiang *et al.,* (2013) disclosed a bifunctional catalytic, chemo-, regio- and enantioselective IEDDA reaction cascade of a variety of methylene but-3-enoates with azlactones proceeding at high levels of yield and enantioselectivity (up to 99% yield, and >99% ee) via a dual HOMO dienophiles and LUMO dienes activated pathway in a heterogeneous catalytic system. The immobilized catalyst can be conveniently recycled and reused for 10 runs with only a slight loss in activity.



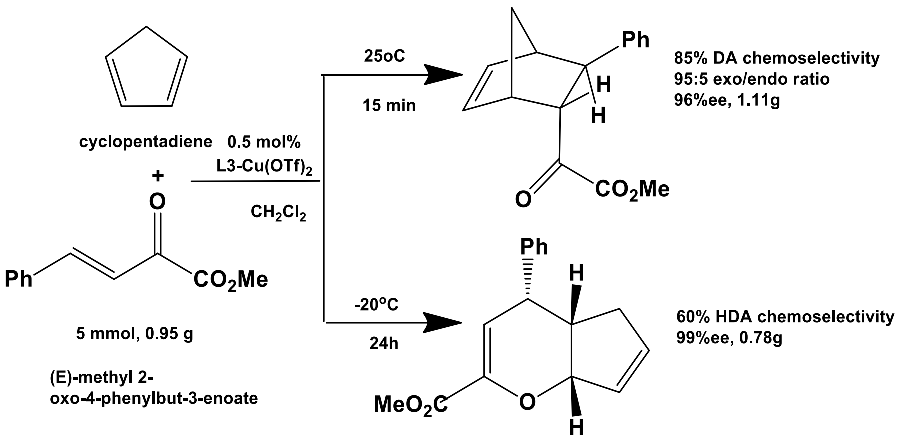
A highly effective silver catalyzed formal IEDDA reaction of phthalazines with siloxy alkynes to afforded a broad range of silyl protected 2- naphthols **(Türkmen et al., 2012).** The cycloadditions of siloxy naphthalenes and anthracenes under mild reaction condition and in presence of low amount of catalyst produced good to high yields of the product.



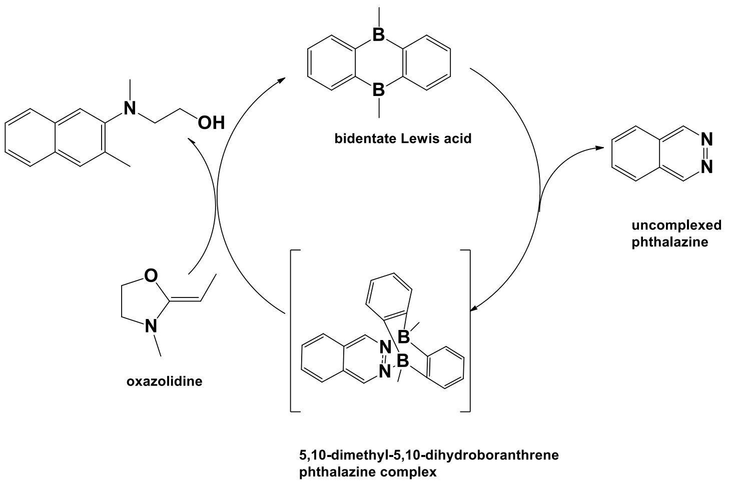
Anderson & Boger, (2011) studied IEDDA reactions of 1, 2, 3-triazines, and the impact of its C_5 substituent on cycloaddition. An enhancement in the intrinsic cycloaddition regioselectivity was observed in the reaction. Hence it concluded, C5 substituents were not only impacting the reactivity and regioselectivity of 1, 2, 3-triazines, but also expanding the range of participating dienophiles and also portending extensive synthetic utility. This study also revealed that 1, 2, 3-triazines can be used as a powerful dienophile like 1, 2, 4-triazines and 1, 3, 5-triazines in IEDDA reactions.



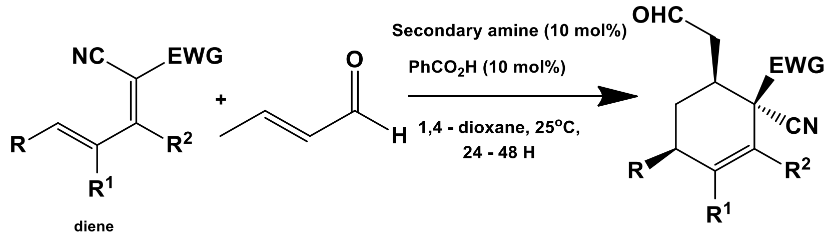
Zhu *et al.*, (2010) had developed a catalytic asymmetric enantioselective DA and IEDHDA reactions between β,γ-unsaturated α-ketoesters and cyclopentadiene promoted by N,N′-dioxide-Cu$(OTf)_2$ complex. Quantitative conversion of β,γ-unsaturated α-ketoesters and excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to >99% ee) were observed for a broad range of substrates. Both aromatic and aliphatic β,γ-unsaturated α-ketoesters were found to be suitable substrates for this reactions. Moreover, the chemoselectivity of the IEDHDA adducts were improved by regulating the reaction temperature. In contrast, low temperature was favorable for the chemoselective formation of the IEDHDA adducts (208^{o}C), up to 65%). The reaction also featured mild reaction conditions, a simple procedure, and required remarkably low catalyst loading (0.1–1.5 mol %).



Kessler & Wegner, (2010) described a systematic approach toward a bidentate Lewis acid, 5, 10-dimethyl-5, 10-dihydroboranthrene catalyzed IEDDA reactions of an unsubstituted phthalazine.

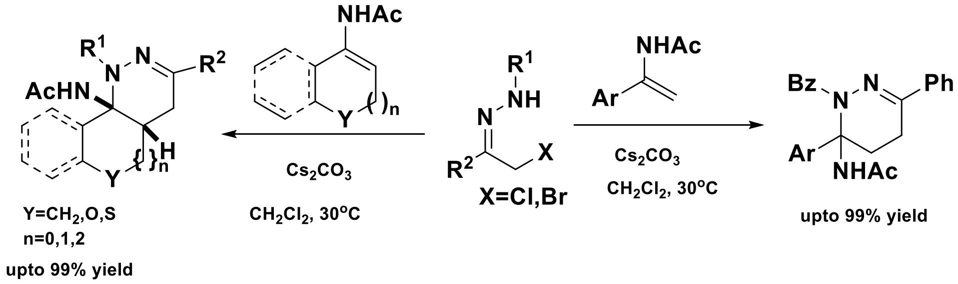


First organocatalytic asymmetric all-carbon-based IEDDA reaction of electron-deficient dienes and crotonaldehyde through a HOMO-activation strategy was developed by **Han *et al.*, (2009)**. Highly diastereo- and enantioenriched cyclohexene derivatives with substantial substitution diversity were smoothly delivered (up to 99% ee, d.r. up to 95:5).

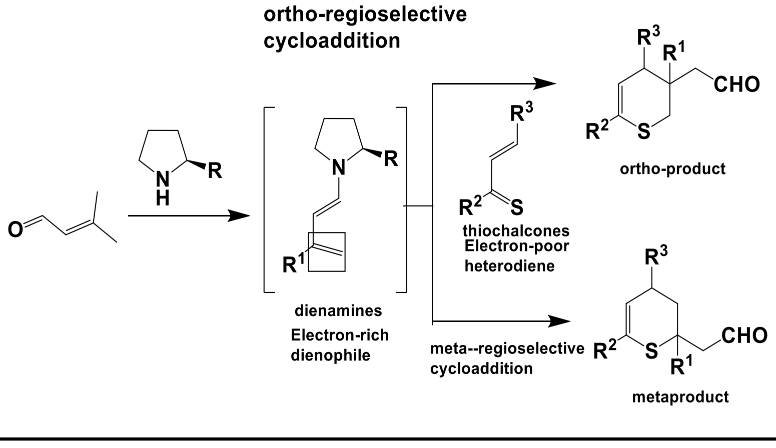


2.1.2 IEDDA reaction with enamines

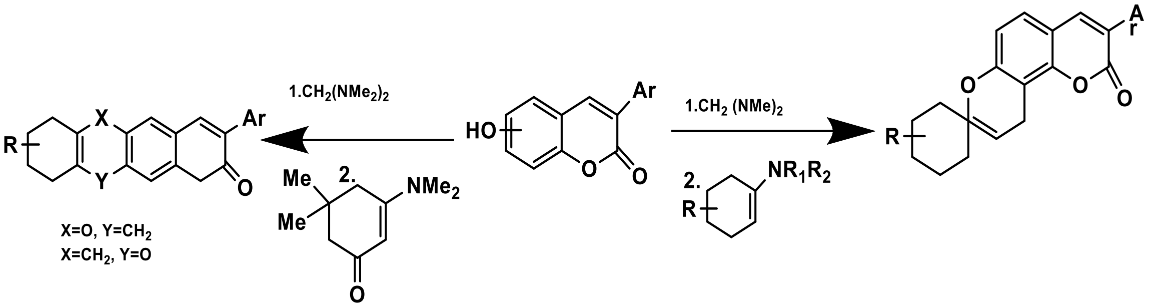
***Shen et al.*, (2021)** discovered an effective inverse electron-demand aza-Diels-Alder cycloaddition of cyclic enamides to in situ produced 1,2-diaza1,3-dienes from cesium carbonate and halogeno hydrazones. Under moderate reaction conditions, a wide range of fused polycyclic tetrahydropyridazines were produced in up to 99% isolated yield using the described methodology. Furthermore, the treatment of acyclic enamides with 1,2-diaza-1,3-dienes resulted in 85.99% yield of 1,4,5,6-tetrahydropyridazine compounds.



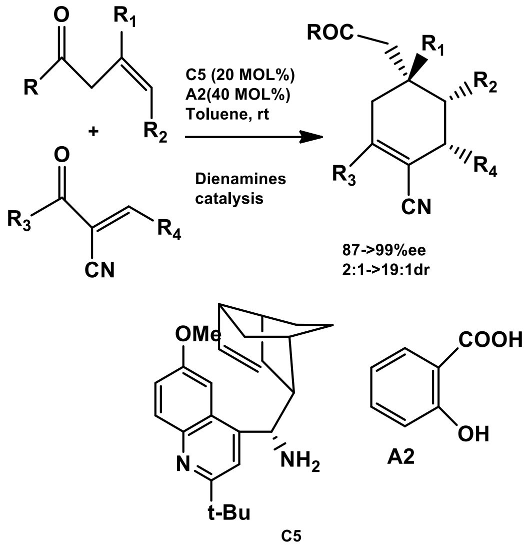
Hejmanowska *et al.*, (2017) described that (IEDHDA) reaction with thiochalcones as unique heterodienes can proceed with unprecedented ortho-regioselectivity product, thus opening a new and exciting area of research. It had been demonstrated that, with the proper choice of reactants and conditions, IEDHDA cycloaddition can be realised with unique regioselectivity arising from the reaction between the terminal carbon atom of the dienamines and the heteroatom of the 3-methylbut-2-enal.



Use Mannich bases of 6- and 7-hydroxy-3-arylcoumarins as precursors of o-quinone methides,for IEDDA reaction was proved by **Mrug *et al.*, (2016).** It was determined that the structure of enamines and their aminomethyl derivatives affected the structure of adducts with enamines.

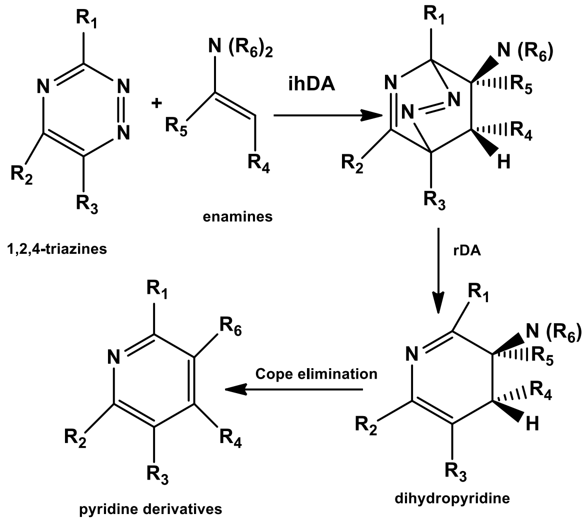


Asymmetric inverse-electron-demand oxa-Diels-Alder cycloaddition reactions of allylic ketones and -cyano-,unsaturated ketones were studied by **Shi *et al.*, (2016)** using an dienamine from cinchona. The reactions showed distinct, β, γ-regioselectivity, and a range of densely substituted dihydropyran derivatives with outstanding enantioselectivity and fair to excellent diastereoselectivity. This catalytic method was also extended to enone substrates with a α-ester or -nitro group, increasing the heterocyclic products that are potentially useful in medicinal chemistry.

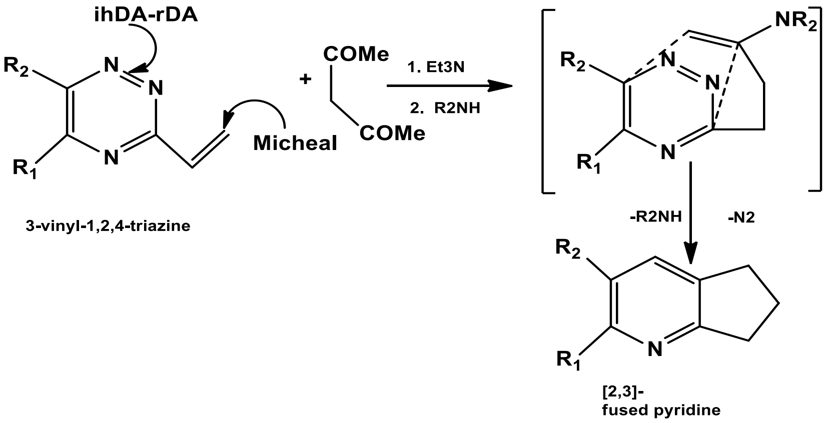


Fershtat *et al.*, (2016) developed convenient, simple, regioselective, and highly effective one-pot method for the synthesis of previously unrecognized hybrid heterocyclic systems, (1, 2, 4-triazin-3-yl)furoxans by tandem IEDHDA followed by rDA reactions. The cycloaddition of enamine or norbornadiene to the 1,2,4-triazine ring of (1,2,4-triazin-3-

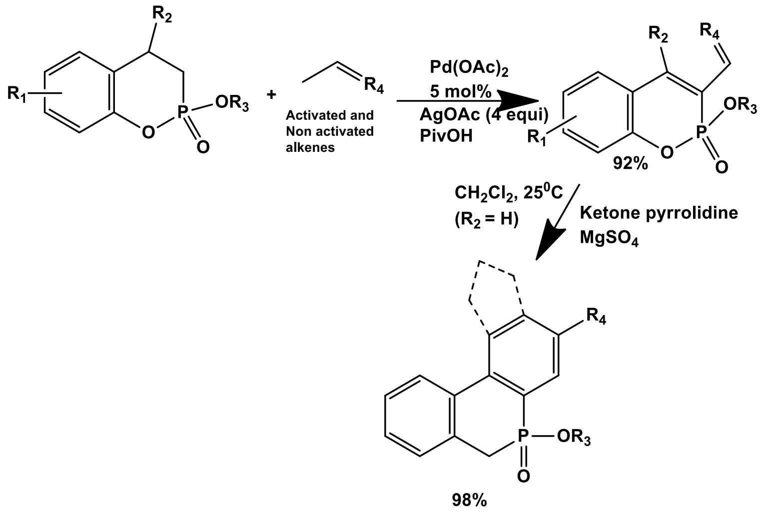
yl)furoxans, followed by one-pot transformation of the formed intermediates, yielded an extensive series of polyheterocyclic ensembles combining furoxan and pyridine rings in one molecule via a C-C bond in good to excellent yields.



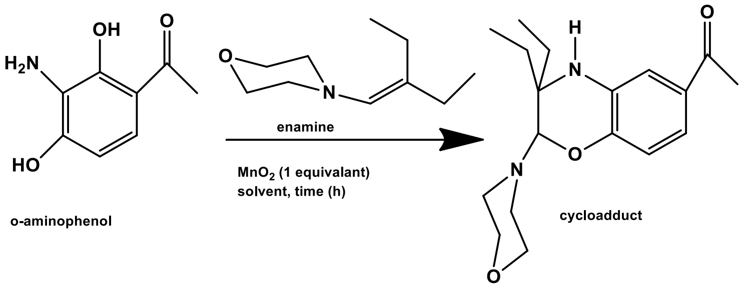
A one-pot sequential domino Michael-IEDDA/rDA reaction was reported by **Lorion *et al.*, (2015),** employing 3-vinyl-1,2,4-triazine as an unusual Michael acceptor. This sequence opened up a new pathway for functionalized [2, 3]-fused pyridine derivatives via a novel intramolecular ihDA reaction of 1, 2, 4-triazines aided by enamine intermediates.



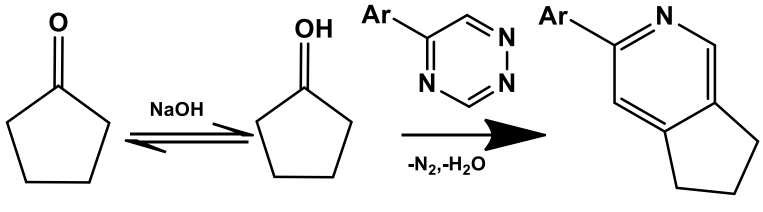
Kim *et al.*, (2015) discovered an alkenylation process using phosphacoumarins and a wide spectrum of activated and nonactivated alkenes via aerobic oxidative Heck reactions. Furthermore, 3-alkenylphosphacoumarins was gone through IEDDA reactions with enamines in situ generated from ketone and pyrrolidine followed by 1,2- elimination and a dehydrogenation, provided fluorescent benzophosphacoumarins



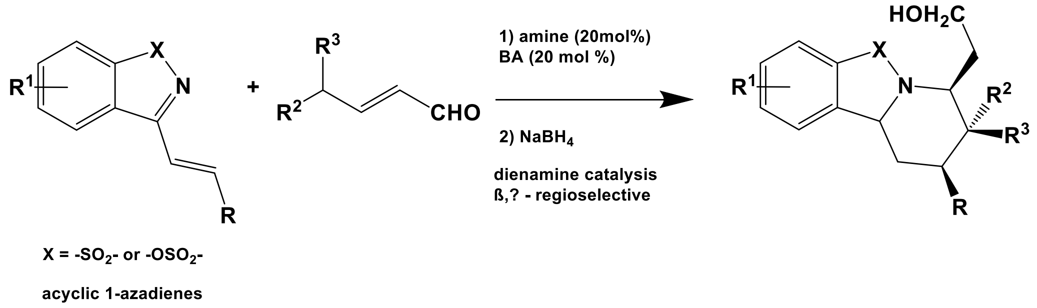
A stoichiometric amount of manganese dioxide was used as the oxidant in a tandem oxidation-IEDDA reaction of o-aminophenol derivatives and enamines at room temperature to produce highly substituted 1,4-benzoxazine cycloadducts with complete regiochemical control was reported by **Nguyen *et al.*, (2015)** .



Wang *et al.*, (2014) effectively established a simple and efficient IEDDA synthesis employing methyl ketones and 1, 2, 4-triazines. The use of methyl ketones as a possible dienophile without the development of an enamine intermediate was a standout feature of the reaction, which was complimentary to the conventional Boger reaction.

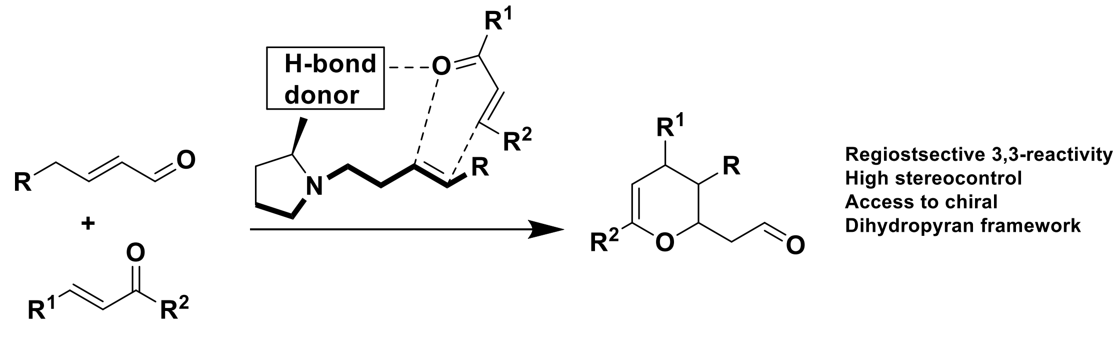


Gu *et al.*, (2014) studied aza-Diels-Alder cycloadditions of cyclic 1-azadienes with α, β-unsaturated aldehydes bearing a motif of 1, 2-benzoisothiazole-1, 1-dioxide or 1, 2, 3-benzoxathiazine-2, 2-dioxide. This reaction catalysed by chiral secondary amine,dienamine exhibited greater regioselectivity for enal substrates with substantial structural variety and wide functionalities, resulting in highly enantioenriched fused piperidine derivatives and allowing for the efficient sequential building of complex polycyclic frameworks.



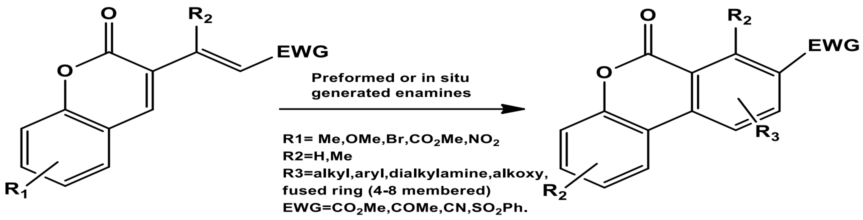
Albrecht *et al.*, (2012) discovered the first H-bond-directed IEDHDA reaction through a dienamine intermediate. The resultant dienamine species underwent regio- and stereoselective functionalization at the distant double bond, five bonds away from the stereogenic centre of the catalyst, to yield dihydropyran derivatives with three contiguous stereogenic centres under optimised reaction conditions. High stereoselectivities were produced by using a bifunctional squaramide-containing aminocatalyst, and the stereochemical result of the process was rationalised. Furthermore, the introduced chiral framework was shown to be capable of being used in the synthesis of tetrahydropyrans as well as polycyclic compounds.

H-Bond-directing approach via dienamine intermediate

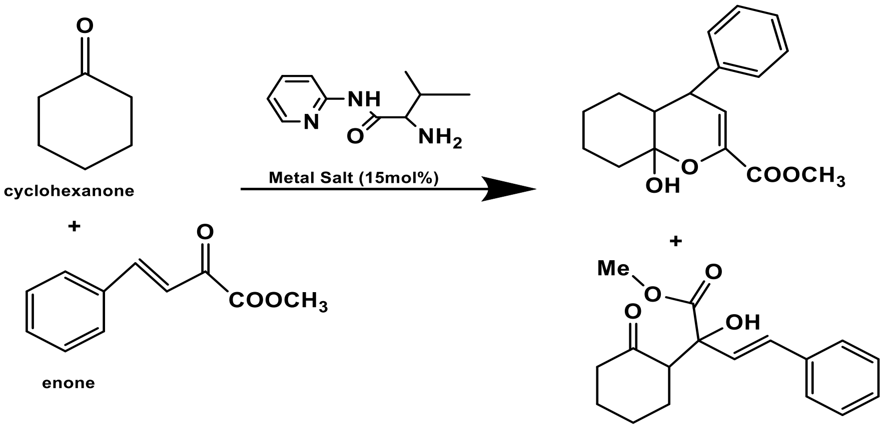


Pottie *et al.*, (2011) had synthesized a set of coumarin-fused electron-deficient 1,3-dienes , which differed in their position of substituents and the nature of the electron withdrawing group (EWG) at the terminus of the diene unit. The enamine derived from cyclopentanone and pyrrolidine reacted with these dienes to yield the corresponding cyclopenteno-fused 6*H*-dibenzo [*b,d*]pyran-6-ones, most likely via a domino

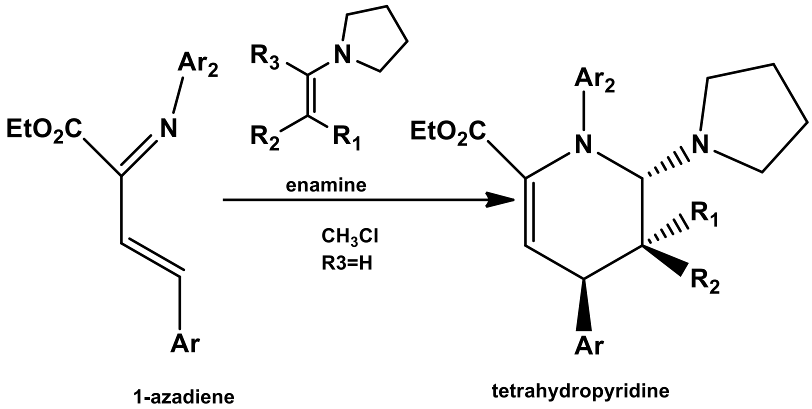
(IEDDA)/elimination/transfer hydrogenation sequence. A range of electron-rich dienophiles (mostly enamines) reacted with the parent diene (EWG = CO_2Me, no substituent) to give the corresponding 6*H*-dibenzo*[b,d]*pyran-6-ones or their nondehydrogenated precursors, which were aromatized upon treatment with a suitable oxidant. The enamines could either be synthesized prior to the reaction or generated in situ.



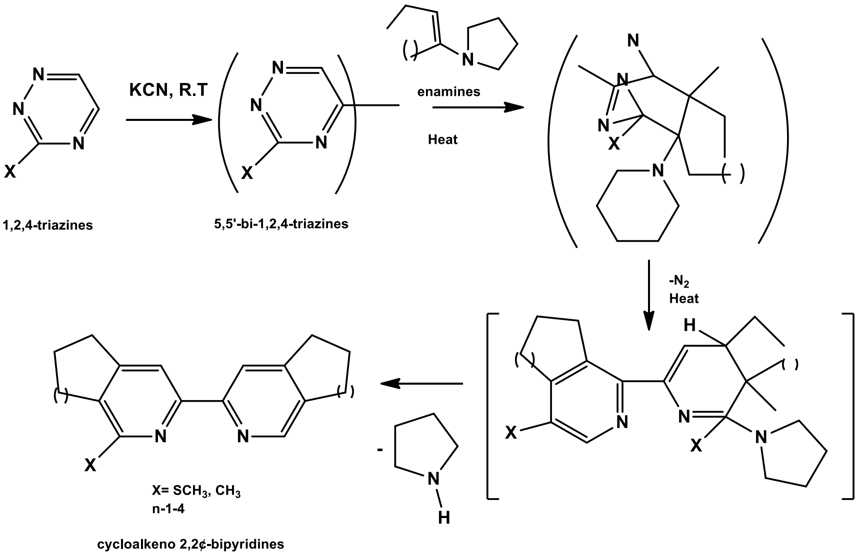
Xu *et al.*, (2011) performed efficient, atom-economic, and highly enantioselective IED-HDA reaction of six-membered cyclic ketones using enamine-metal Lewis acid bifunctional catalysis. The remarkable activity and stereoselectivity of this reaction were attributed to the robust activation of the enone through metal chelation and the bifunctional catalyst's intramolecular nature.



Vicario *et al.*, (2011) used the inverse electron demand aza-Diels-Alder reaction [ADA] of N-aryl-1-azadienes and enamine dienophiles to create a regio- and diastereoselective of 1, 4, 5, 6-tetrahydropyridines from α-amino acids. The all-*trans* structures of tetrahydropyridines were consistent with the process *endo* transition state. N-aryl-1-azadienes, on the other hand, dimerize through an ADA reaction in the presence of a Lewis acid, Yb(OTf)$_3$, resulting in the regio- and stereoselective production of tetrahydropyridines. An optically active enamine was used in the asymmetric synthesis of functionalized 1, 4, 5, 6-tetrahydropyridine compounds obtained from α-amino acids.

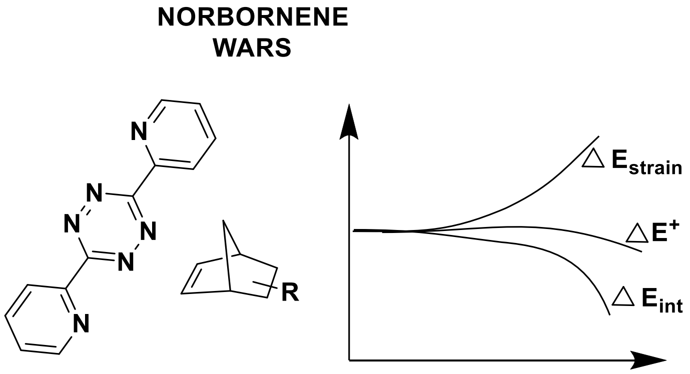


Branowska (2003) utilised the IEDDA reaction to synthesise a new class of bisfunctionalized symmetrical and unsymmetrical cycloalkeno[c]fused 2, 2’-bipyridines from widely accessible bisfunctionalized 5, 5’-bi-1, 2, 4-triazine derivatives. The regioselective reaction of 1-vinylimidazole with 5,5’-bi-1,2,4-triazines produced 5-(2-pyridyl)-1,2,4-triazine , which then underwent IEDDA reaction with cyclic enamines to produce unsymmetrical 2,2’-bipyridines with one cycloalkene ring attached.

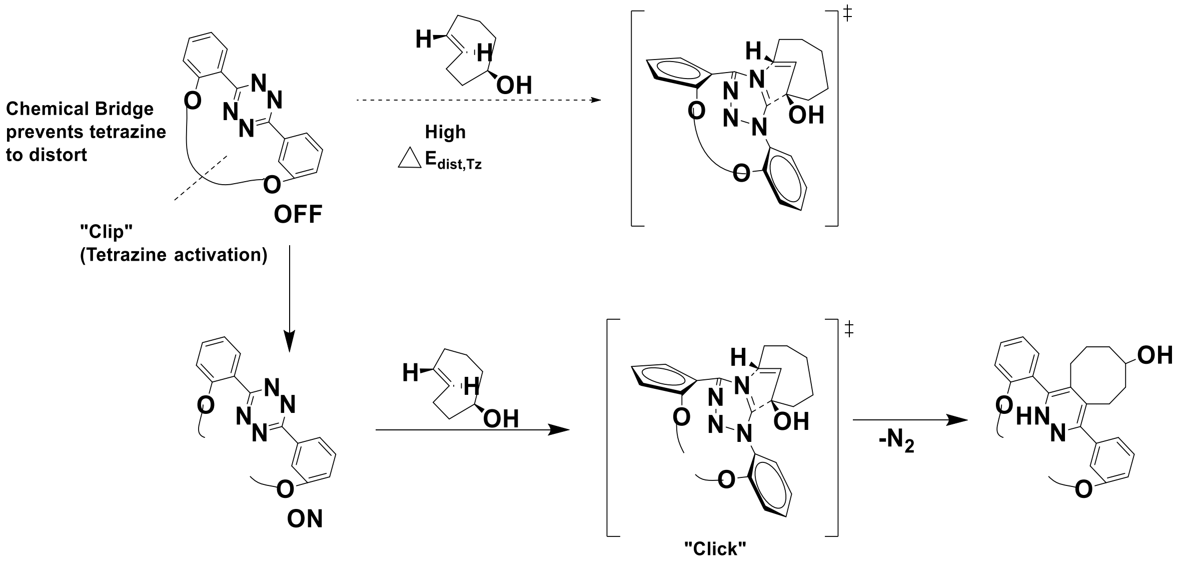


2.1.3 Computational Chemistry of IEDDA reaction

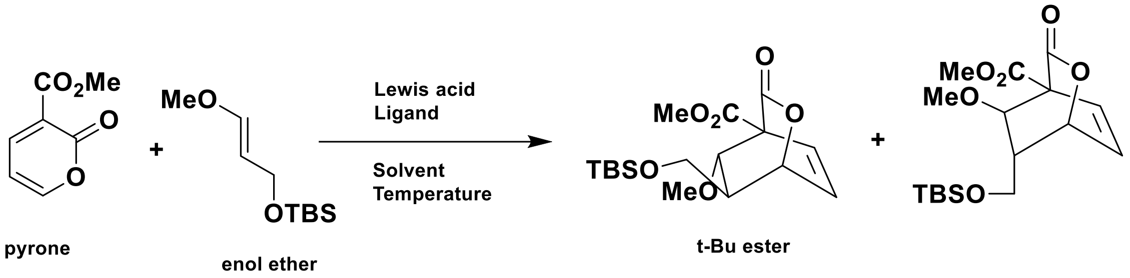
García-Azna *et al.*, (2022) investigated the IEDDA reaction of 3,6-dipyridin-2-yl-1,2,4,5-tetrazine with a series of norbornene derivatives using quantum mechanical calculations at the M06-2X/6-311+G(d,p) level of theory. The experimental findings supported the theoretical predictions, which were subsequently examined with the distortion and interaction model.



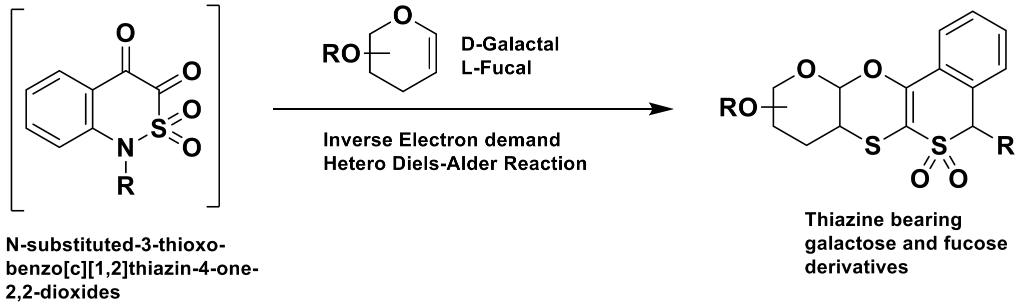
Novianti ***et al.*****, (2022)** created "Clip to click," a universal technique for controlling tetrazine reactivity in the IEDDA process. The addition of a chemical bridge to 3, 6-diphenyl-1, 2, 4, 5-tetrazine (macrocyclic tetrazine) rendered it inactive against trans-cyclooctene. According to the computational study, the unreactive feature of macrocyclic tetrazines was mostly owing to tetrazine's large distortion energy. The results showed that the macrocyclic linker cleavage ("Clip") can activate the tetrazine moiety for the IEDDA reaction.



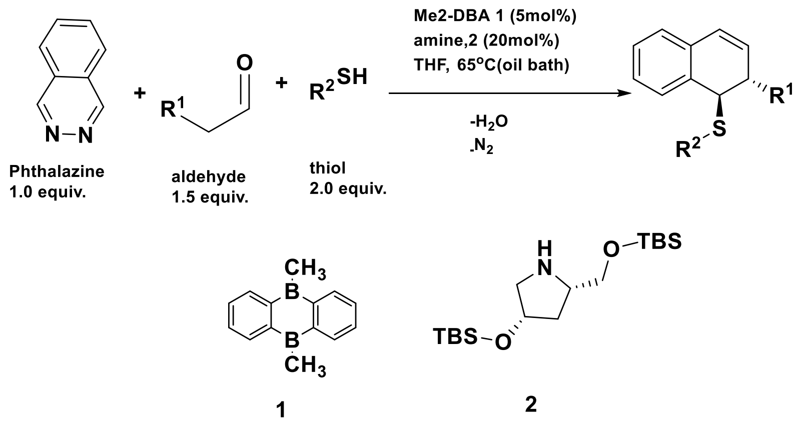
Huang ***et al.*****, (2022)** presented a generally applicable diastereo- and enantioselective IEDDA reaction of substituted 2-pyrones and acyclic enol ethers using a copper (II) *bis* (oxazoline) catalytic system. A bridging bicyclic lactone was synthesised in extremely high yields (up to 99%) and enantioselectivities (up to 99% ee). Mechanistic investigations and DFT simulations both supported the existence of a sequential process. The enantioselective synthesis of polyfunctional cyclohexenes and cyclohexadienes, as well as a carbasugar unit, demonstrated the synthetic potential of bridging bicyclic lactones.



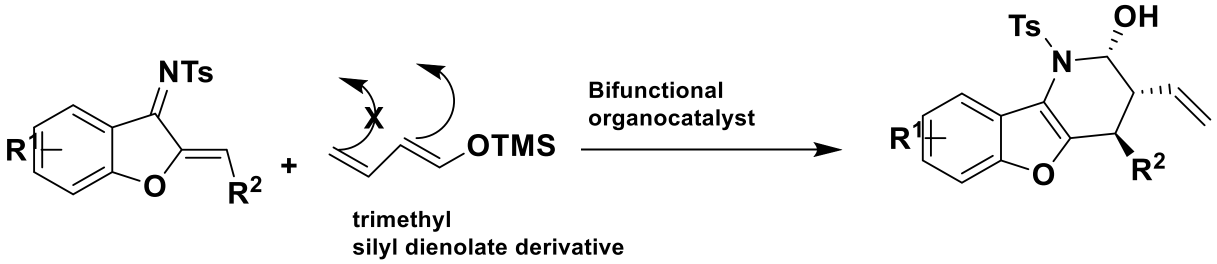
In a [4+2] IEDHDA reaction **Biagiotti *et al.*, (2022)** reported the synthesis and reactivity of an innovative class of electron-poor heterodienes, the N-substituted-1*H*benzo[*c*][1,2]thiazin-4-one-2,2-dioxides. In this reaction the extremely reactive electrophiles provided surprisingly selective access to undiscovered benzo-thiazine glyco-fused derivatives, even when utilising acetylated glycals. DFT simulations backed up the experimental evidence.



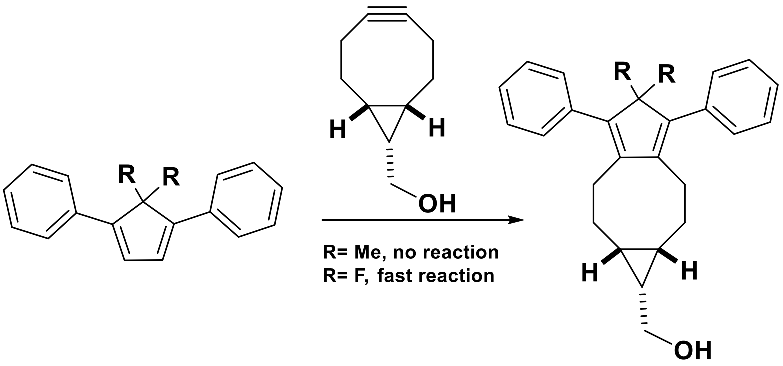
A novel enantioselective multicomponent reaction of phthalazines, aldehydes, and thiolsthioether-substituted 1,2-dihydronaphthalenes was reported by **Beeck & Wegner (2022)**. The mechanism of this domino IEDDA/thiol transfer reaction was thoroughly investigated. NMR studies identified a competing reaction route, resulting in N, S-acetals. DFT calculation illuminated the mechanism of the group transfer process and enabled an explanation for the formation of the most dominant byproduct.



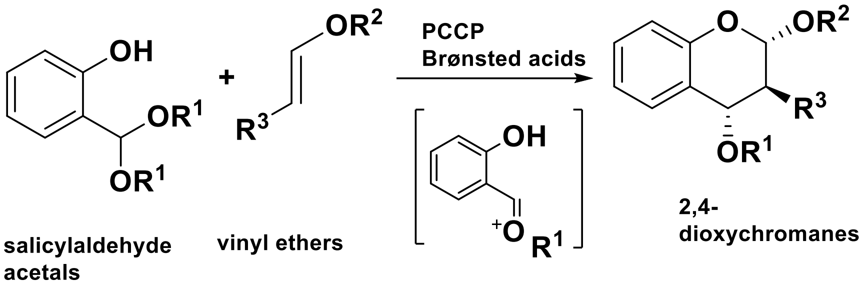
Asymmetric aza-IEDDA reaction of aza-sulfonyl-1-aza-1,3-butadienes and silyl dienol ethers was described by **Laina-Martín *et al.*, (2021).** Unlike the reactivity reported for dienolates formed in situ from unsaturated derivatives, which was validated by density functional theory (DFT), the hydrogen-bond donor-based bifunctional organocatalyst selectively activated the reaction via the dienophile's ipso, α-position. which had highlighted the reaction process as well as the capacity of the hydrogen-bond donor core to selectively hydrolyze the dienol ether's E isomer The results proved the use of silyl enol ethers as nucleophiles in the asymmetric synthesis of intriguing benzofuran-fused derivatives; the catalytic system was also employed to install an aromatic ring in piperidine adducts.



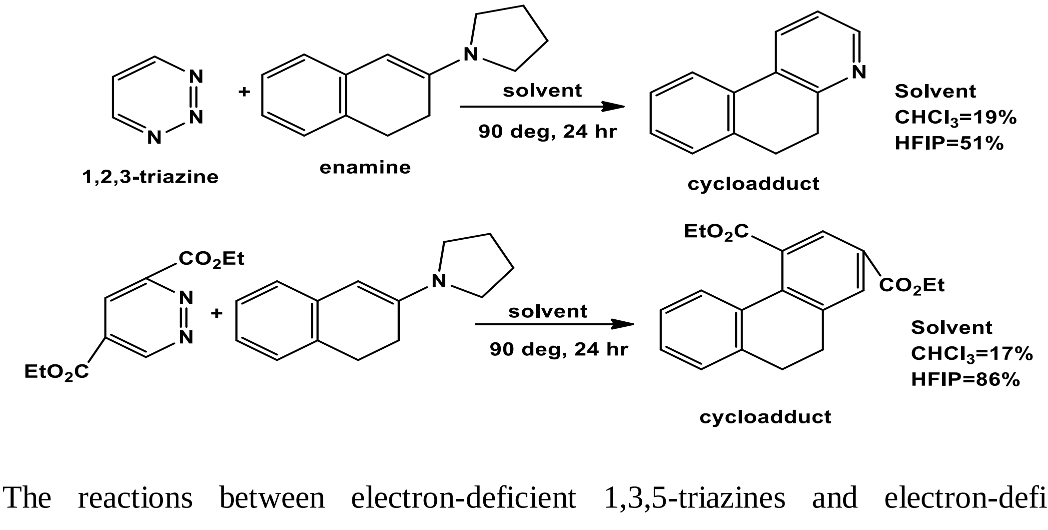
The IEDDA reactivity of 4,4-difluoro-3,5-diphenyl-4*H*-pyrazole with *endo*-bicyclo [6.1.0]non-4-yne was explored experimentally and computationally by **Levandowski *et al.*, (2019)**.



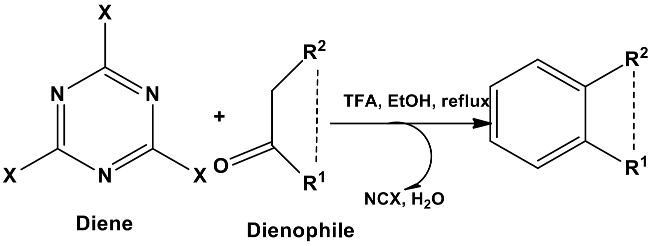
An enantioselective catalytic IEDDA reaction of salicylaldehyde acetal-derived oxocarbenium ions with vinyl ethers to form 2,4-dioxychromanes was discussed by **Gheewala *et al.*, (2018).** Chiral pentacarboxycyclopentadienes(PCCP) bronsted acids was proved to be effective for a wide range of substrates. Computational and x-ray crystallographic investigations confirmed that the absolute sense of stereochemistry in the reaction was governed by point chirality-induced, helically chiral anion



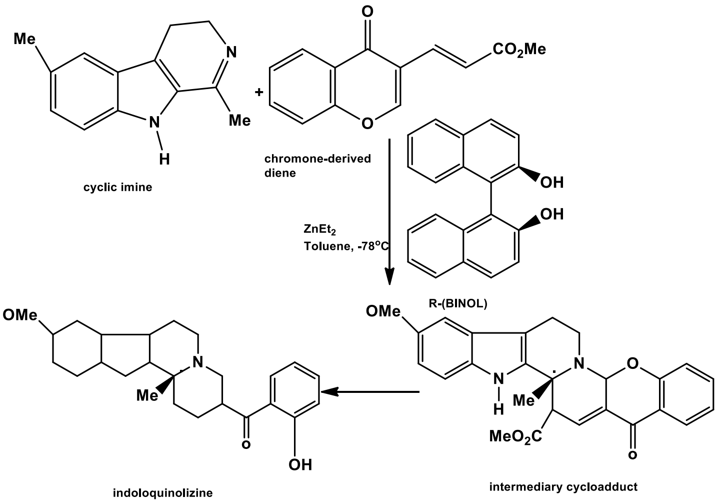
Y. F. Yang *et al.*, (2017) utilized DFT calculations to examine the processes of Diels-Alder reactions using 1, 2, 3-triazines and enamine and studied the causes of the various reactivities brought on by substituents or the solvent hexafluoroisopropanol. IEDDA reactions of Triazines' had several uses in the synthesis of natural products and bioorthogonal chemistry. In accordance with the kind of substituents and solvents, both concerted and stepwise cycloadditions were expected. The zwitterionic intermediate and the effect of hexafluoroisopropanol in speeding up cycloadditions with enamines were studied. The findings demonstrated the sensitivity of concerted versus stepwise processes of IEDDA reactions of 1, 2, 3-triazines and that the effect of solvents in changing the path of mechanisms by promoting hydrogen bonds and electron-withdrawing substituents.



The reactions between electron-deficient 1,3,5-triazines and electron-deficient aldehydes and ketones producing highly functionalized pyrimidines in moderate to good yields was shown by **K. Yang, *et al.*, (2017).** The reaction process was extensively examined by experimental and computational research. The reactions included a series of stepwise IEDHDA, rDA, and water elimination. Both IEDHDA and rDA reactions proceeded under acidic condition. By contrasting the relative reactivity of aldehydes, ketones, and their equivalent vinyl ethers in the present reaction system, this mechanism was further confirmed.

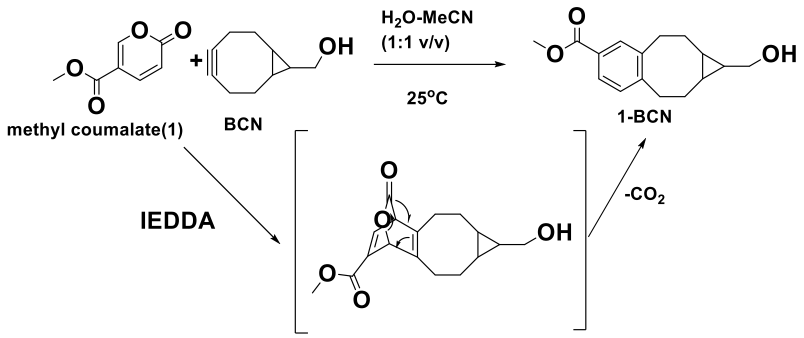


The mechanism and stereochemistry of an inverse electron-demand imino Diels–Alder (IEDIDA) reaction between a cyclic imine and an electron-poor chromone-derived diene catalyzed by a chiral BINOL–zinc complex have been studied using the. combination of DFT calculations, chemical reactivity indices and distortion/interaction analyses by **Li *et al.*, (2015).** The calculations revealed that the coordination of Lewis acid zinc catalyst to the ester C=O group of the electrophilic diene significantly lowered the energy barriers of the cycloaddition reaction by an increase of the electrophilic character of the diene. The electrophilic/nucleophilic interaction defined the most favored alignment between the dienophile and the diene–catalyst complex, which overwhelms the distortion of these fragments and realized the exo-selectivity of the cycloadduct.

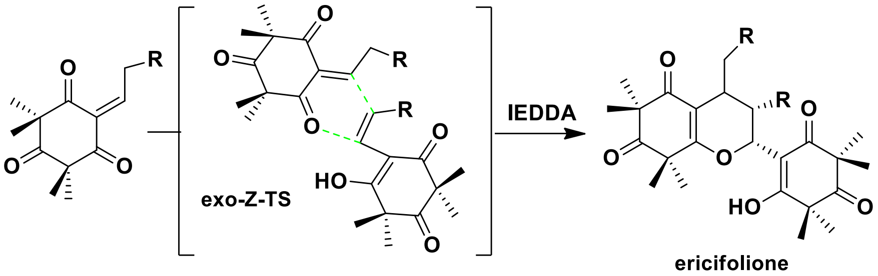


2.1.4 Application of IEDDA reaction

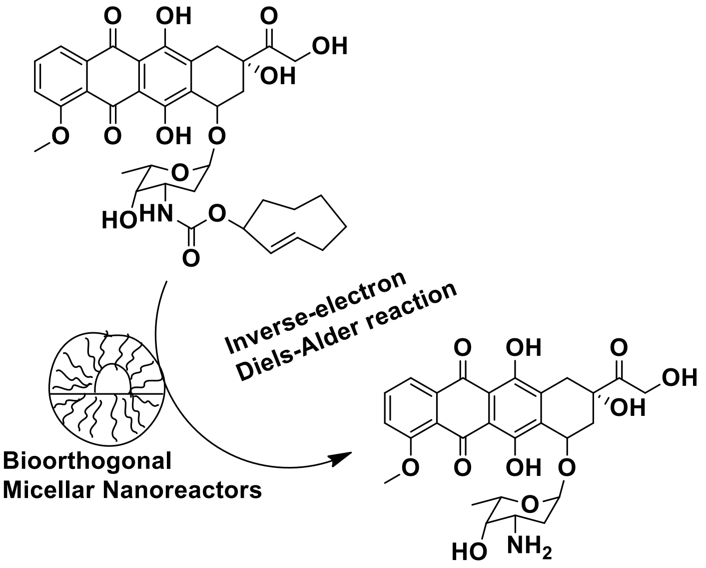
Cserép *et al.*, 2022 investigated the 2-pyrone moiety's potential in bioorthogonal reaction schemes in conjunction with cyclooctyne through IEDDA reactions. Under physiological parameters, the pyrones were shown to be appropriate for IEDDA reactions. Furthermore, the stable pyrone moiety might be used to create conveniently accessible fluorogenic probes. The mutual orthogonality of the 2-pyrone IEDDA reaction and the strain-promoted azide-alkyne cycloaddition (SAAC) reaction was also investigated.



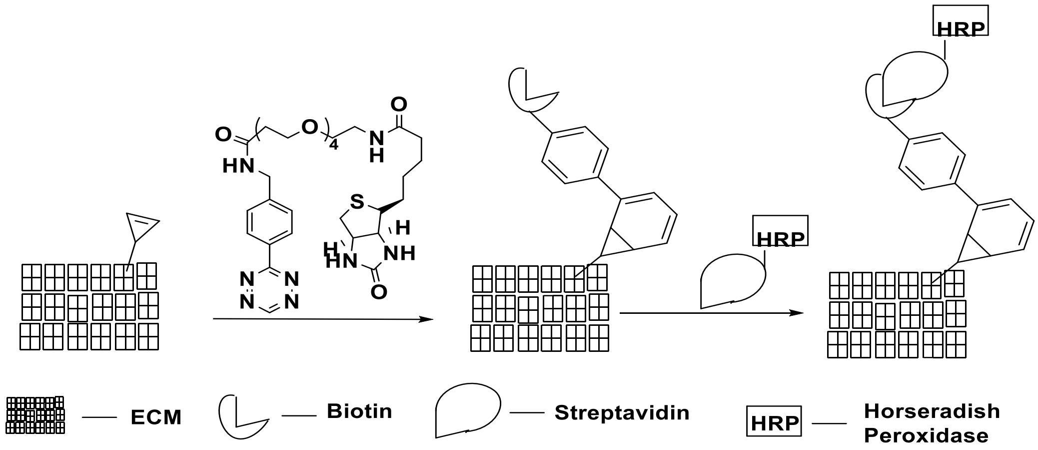
A biomimetic tautomerization/intermolecular IEDHDA reaction cascade sequence promoted by sodium acetate was established by **Zhou *et al.*, (2022)** to rapidly construct sterically hindered dihydropyran scaffolds. This allowed for the first simple biomimetic complete synthesis of ericifolione and its equivalents. The technique paved the way for the creation of relevant natural products or derivatives.



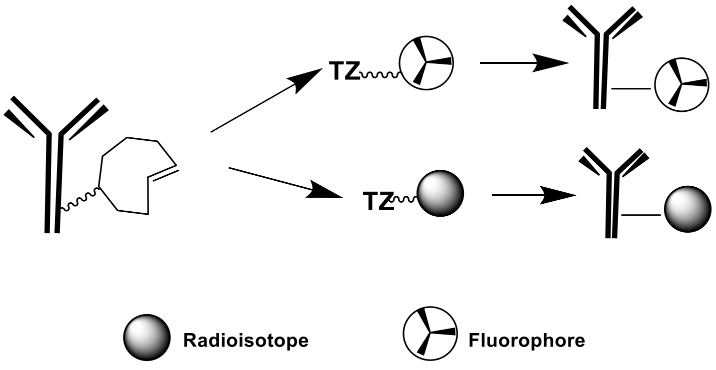
Block copolymer micelles functionalized with tetrazine groups can be used as nanoreactors to activate a trans-cyclooctene-functionalized prodrug for anticancer drug release through a bioorthogonal IEDDA reaction. **Suehiro *et al.*, (2022).**



Nellinger *et al.*, (2022) demonstrated the possible modification of a cell-derived extracellular matrix (ECM) with dienophiles as chemical reporter groups (functionalization) using metabolic glycoengineering (MGE). The outcome demonstrated dienophile modification of an ECM (terminal alkenes, cyclopropene), which may be handled by an (IEDDA) reaction. Because no cytotoxic catalysts were required, the ECM contained a bioactive molecule (an enzyme), and it had been established that the functional groups had no influence on cellular activity, this reaction was cell-friendly. As a result, the novel material had a high potential for usage as a biomaterial that can be uniquely tailored for a variety of purposes.

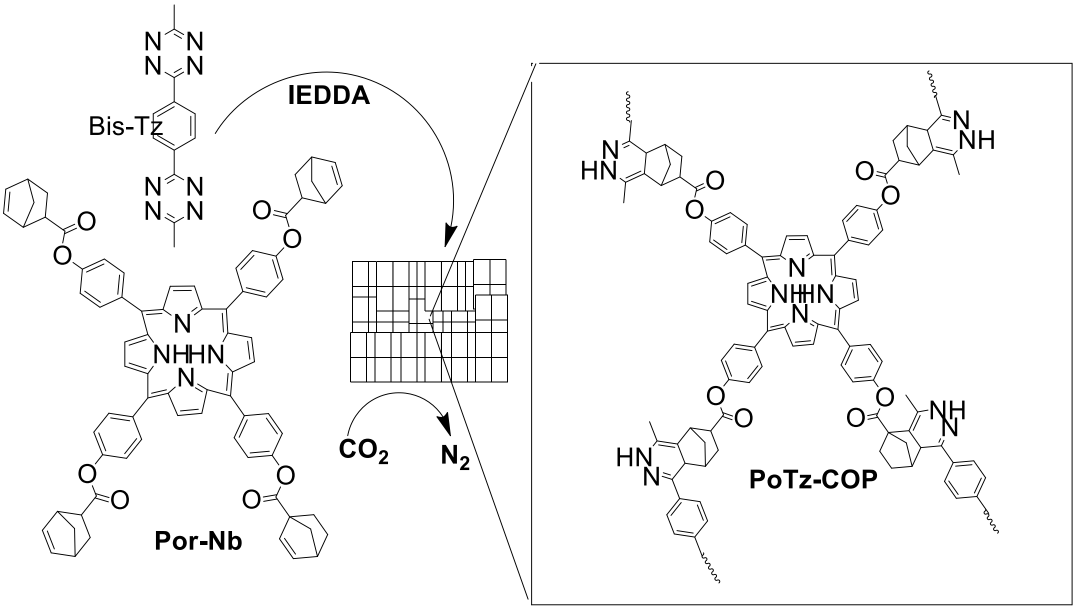


Fernanda García *et al.*, (2021) investigated the use of IEDDA as a modular conjugation platform for Rituximab labelling to identify CD20+ B cells. A conjugation method was evaluated against IEDDA *in vivo* conjugation utilising Cy7 as the tracer. The technique enabled the *in vitro* and *in vivo* production of conjugated Rituximab with fluorophores like the cyanines 5.5 and 7 (Cy 5.5 and Cy 7 respectively) as well as the gamma emmiter technetium-99m.

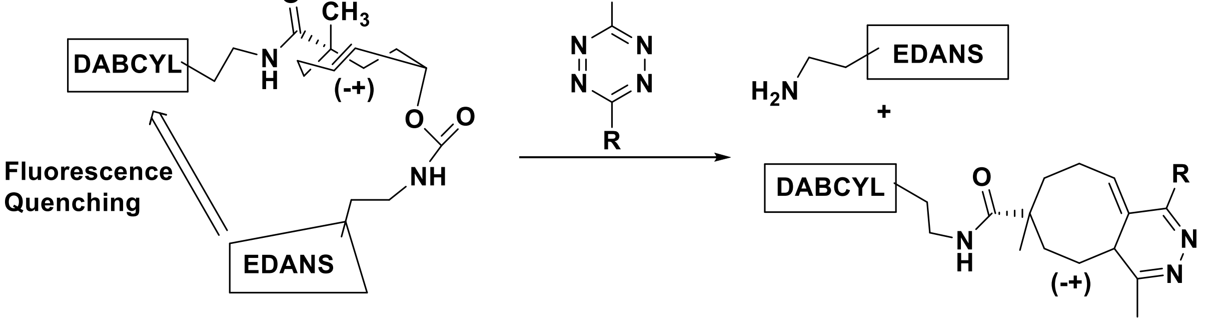


Modular conjugation strategy for *in vivo* and *in vitro* labelling of Rituximab, TZ=[1,2,4,5]tetrazinyl moiety

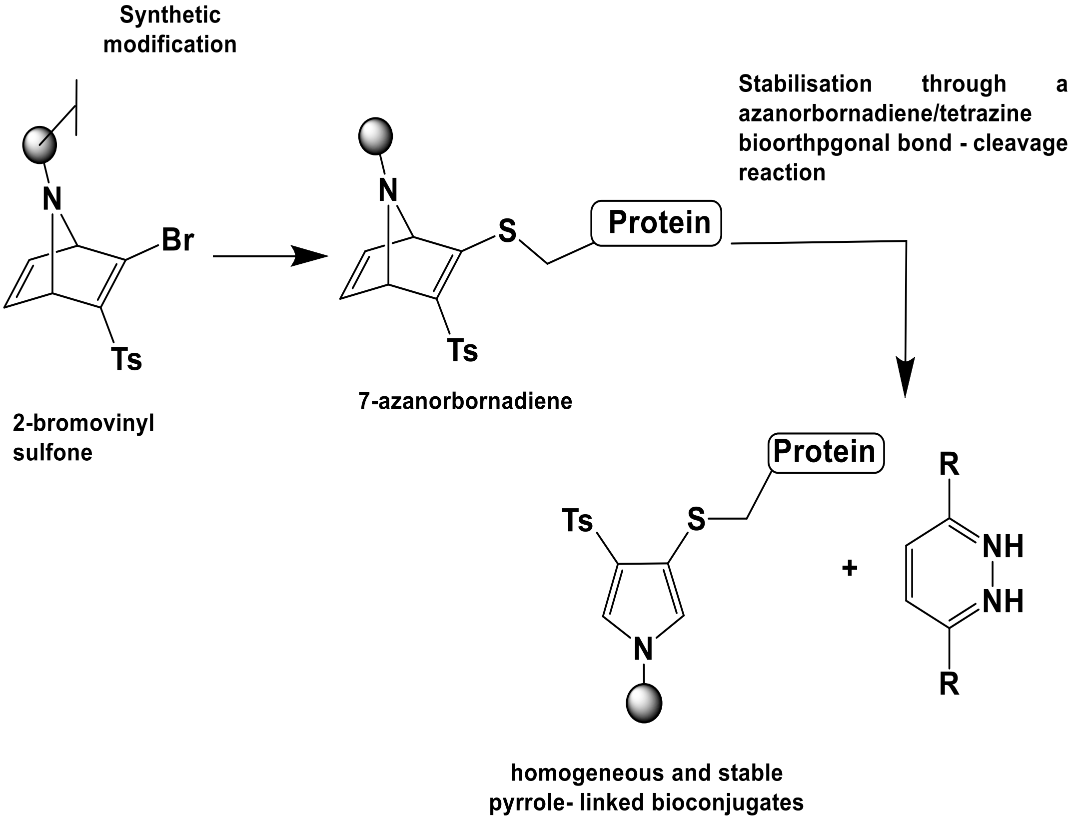
Ali *et al.*, (2021) designed a synthetic method based on the IEDDA reaction to create a porphyrin-based covalent organic polymer (PoTz-COP). A tetra-norbornene functional porphyrin served as the core, while a bis-tetrazole served as the linker. The PoTz-COP was easily synthesised by simply mixing the components together without the need of a catalyst and under moderate circumstances. PoTz-COP had a very high CO_2 adsorption selectivity over N_2 and a reasonably low optical band gap.



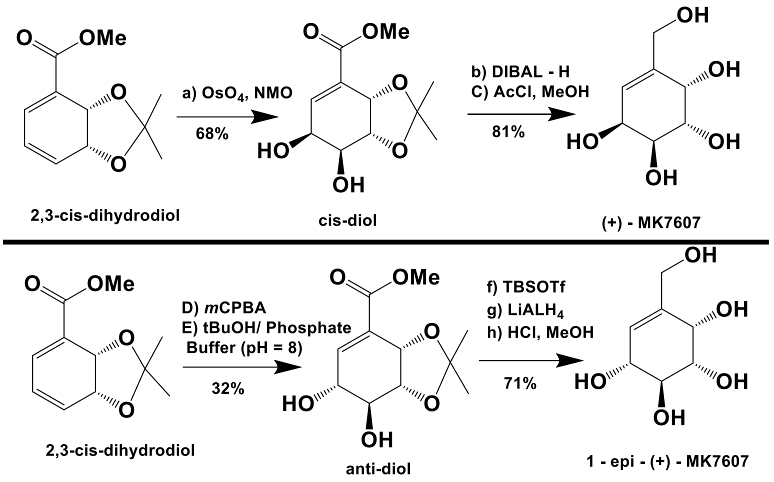
The IEDDA pyridazine elimination reaction between tetrazines and allylic substituted transcyclooctenes (TCOs) was an important participant in bioorthogonal bond cleavage processes **de Geus *et al.*, (2020)** described a fluorogenic instrument comprised of a TCO-linked 5-[(2-Aminoethyl) amino] naphthalene-1-sulfonic acid [EDANS] fluorophore and a 4-(4’-dimethylaminophenylazo)benzoicacid [DABCYL] quencher for reliable measurement of both the click and release rates of any tetrazine at physiologically appropriate concentrations.



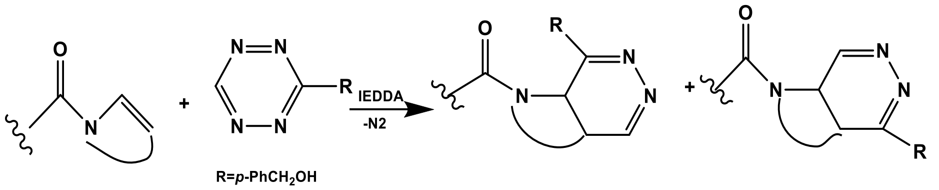
Gil de Montes *et al.*, (2020) had developed an azanorbornadiene bromovinylsulfones for cysteine-selective bioconjugation.Most synthetic modifications can be accommodated by this reagent, which had high reactivity and chemoselectivity towards cysteine residues on proteins. The corresponding conjugates, which feature an azanorbornadiene thio-vinyl sulfone linker, may be reacted with tetrazines through IEDDA cycloaddition with subsequent double retro-Diels–Alder (rDA) reactions to form pyrrole-linked protein conjugates that are stable in both human plasma and in the presence of high amounts of glutathione. The use of azanorbornadiene bromovinyl sulfones for cysteine-selective protein modification combined with the azanorbornadiene/tetrazine bond-cleavage reaction constituted a new and robust method for the preparation of stable and chemically defined bioconjugates.



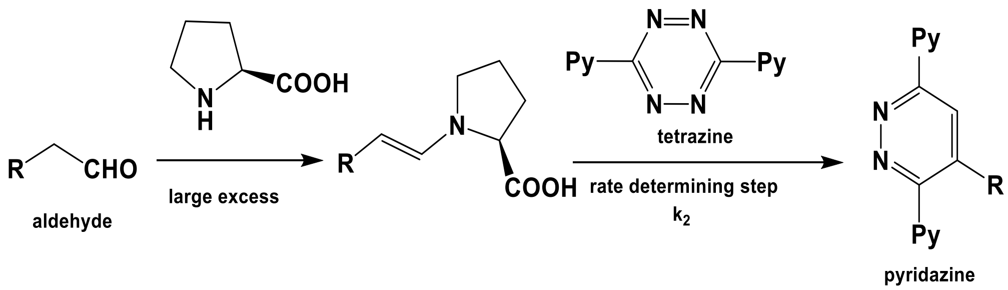
Liang *et al.*, (2019) used consecutive asymmetric (IEDDA) reactions of 2-pyrones and Retro-DA extrusion of CO_2 to achieve enantioselective chemical synthesis of arene cis-dihydrodiols from 2-pyrones .This method effectively produced a number of substituted arene cis-dihydrodiols with strong enantioselectivities (> 99% ee in several instances). This approach allowed quick and effective asymmetric total syntheses of epimers such as (+)-MK7607 and 1-epi-(+)-MK7607.



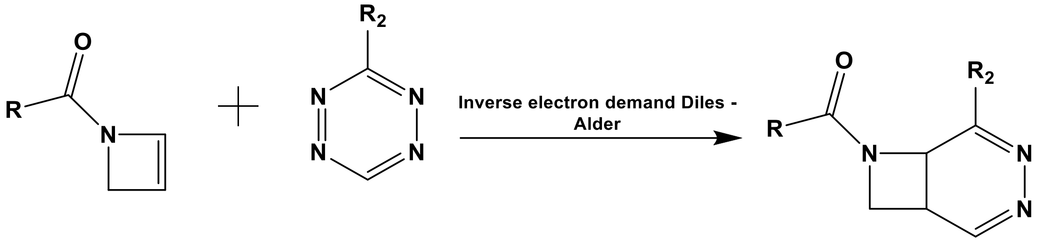
In light of the bioorthogonal (IEDDA) strategy, an extended investigation into the effects of ring-strain and electron inductive effects on the reactivity of the N-acylenamine core towards tetracycline had been carried out by **Engelsma *et al.*, (2018)**. Through a comparative study among N-acylazetines, N-vinylcarbamates, and N-vinylamide, it was shown that ring-strain had a more significant effect on reaction rate than electron donation. A significantly improved synthetic route was reported for the preparation of the N-acylazetine biorthogonal tag.



Lai *et al.*, (2016) had developed proline-accelerated IEDDA reaction of aldehydes and tetrazine, which exhibits an exceptionally high reaction rate and it was further employed in the *in vitro* labelling of a protein in aqueous medium. As all reagents had been proved to be of high biocompatibility, this method could potentially be employed as a bioorthogonal coupling reaction product formed.



Engelsma *et al.*, (2014) designed and synthesized a new bioorthogonal N-acylazetine tag, which was small and achiral, suitable for tetrazine mediated IEDDA conjugation. The performance of the new tetrazinophile in the labeling of catalytically active proteasome subunits was comparable to that of the more sterically demanding norbornene tag.



Schoch *et al.*, (2011) successfully established the IEDDA process for RNA labelling. RNAs that were chemically synthesised as well as enzymatically transcribed were effectively labelled with biotin or a fluorescent tag. The considerable labelling of RNA with only a 5-fold excess of the labelling reagent proceeded easily in neutral water with no any additions such as transition metal ions, organic solvents, and so on