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Chapter 10: Sustainable catalytic protocol for the synthesis of biologically active heterocyclic compounds

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Abstract: Advancement of sustainable catalytic protocols in the synthesis of heterocyclic compound has transformed modern chemistry, offering efficient, environmental friendly alternatives to conventional synthetic methodologies. This chapter delves into the principles of sustainable chemistry as applied to synthesis of heterocycle compounds, focusing on catalytic developments that reduce waste, improve atom economy, and minimize reliance on hazardous reagents. Heterogeneous catalytic protocols enhance recyclability and operational efficiency. Enzymatic catalysis presented unique opportunities for development of high stereo- and regioselectivity under normal conditions, advancement of the field toward more sustainable and biocompatible synthetic protocols. Additionally, mechanochemical and solvent-free reaction protocols provide promising strategy for reducing environmental toxicity and energy consumption, followed by green chemistry principles, highlight the role of sustainable catalysis in the synthesis of heterocyclic compounds. The convergence of experimental development further redefines catalytic design and reaction optimization, ensuring the sustainable evolution for the synthesis of heterocyclic compounds. This chapter will continue the exploration of sustainable synthetic protocols, emphasizing their vital contributions to heterocyclic chemistry and the broader pharmaceutical industry. Through interdisciplinary collaborations and technological innovations, sustainable catalytic protocols will continue to enhance the efficiency, cost-effectiveness, and ecological viability for the synthesis of heterocyclic compounds, paving the way for greener pharmaceuticals and a more sustainable future.

Keywords: Atom economy, enzymatic catalysis, green chemistry, heterogeneous catalysis, mechanochemical, solvent-free protocols.

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1 Introduction

Field of pharmaceutical chemistry has long relied on the advancement of heterocyclic chemistry, which forms the main structural skeleton of numerous biologically active molecules, including antibiotics, antivirals, anticancer agents, and neuroactive drugs (P. Brown et al., 2018). As the high requirement for effective therapeutics grows, the need of efficient, selective, and environmentally sustainable synthetic protocols for the synthesis of heterocyclic compound becomes more pressing. Traditional synthetic protocols have enabled remarkable advancement in pharmaceutical chemistry, yet they often suffer from inherent drawbacks, like extensive use of toxic reagents, high-energy reaction processes, and single-use catalysts and that contribute to environmental toxin contamination. These challenges integrating sustainability into the synthesis of heterocyclic compounds, a transformation that is being driven by the development in catalytic reaction protocols. Sustainable organic synthesis revolves around minimizing waste, reducing the reliance on hazardous substances, and optimizing reaction conditions to improve efficiency and atom economy (R. Kumar et al., 2020). In the modern time, the catalytic protocols have emerged as a powerful tool for sustainable synthesis, offering solutions that normal reaction temperatures, eliminate hazardous chemicals, and enhance the overall sustainability. It is a philosophical reconsideration that redefines the way organic synthetic protocols, particularly for the synthesis of heterocyclic compounds. The application of catalysis in heterocycle synthesis encompasses a diverse array of reaction protocol, including heterogeneous, enzymatic, and organocatalytic approaches (Nguyen, P. H., et al. 2022). Heterogeneous catalytic protocols, often mediated by transition metals such as Pd and Cu, has transformed key reactions like cross-coupling and cyclization, allowing for streamlined for the synthesis of heterocyclic compounds. By fine-tuning ligand design and reaction protocols, researchers have developed selective and catalytic turnover, increasing environmental sustainability of the processes (M. Hernandez et al., 2020). Additionally, heterogeneous catalytic protocol provides unique advantages, particularly in terms of recyclability of the catalyst and industrial application (S. Kumar et al. 2022).

Over transition metal catalysed reaction protocols, organocatalysis has gained preference as an effective, sustainable reaction methodology for the synthesis of heterocyclic compounds. Metal-free catalytic reaction methodologies used organic molecules, facilitate stereoselective transformations, eliminating the risk of metal contamination with high efficiency. Enzymatic catalytic protocols further expand the scope of sustainability for the synthesis of heterocyclic compounds, replicating natural biochemical transformations to enhance the selectivity under normal reaction conditions (N. Ahmed et al., 2021). Mechanochemical reaction techniques offer yet another sustainable approach for the synthesis of heterocyclic compounds, applying mechanical force to drive the solvent-free chemical transformations. This technique

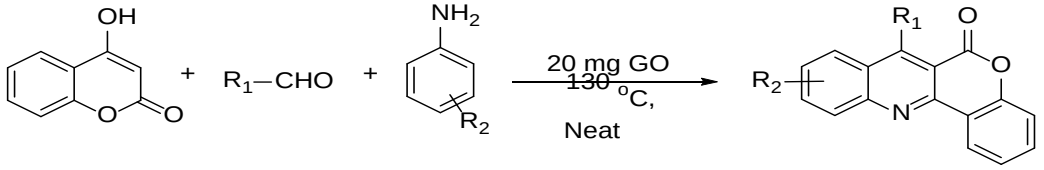
aligns with green chemistry principles. Mechanochemical reaction protocols have been successfully employed in the synthesis of heterocyclic compounds, which is an alternative to traditional solvent-based reaction methodologies while reducing the overall environmental pollution (D. Kumar et al., 2021). The continued exploration of mechanochemical, solvent-free reaction protocols holds promise for future pharmaceutical applications, particularly as an environmental friendly approach (G. Lopez et al., 2022). The growing demand for sustainable protocols in synthetic chemistry highlights the need for continued development in catalytic methodologies (J. Anderson et al., 2023). While a significant reaction protocol has been established, there remains vast potential for further refinement, mainly in expanding the utility of recyclable catalysts, bio-inspired transformative reactions, and mild-energy synthetic protocols. By combining traditional synthetic protocols with the innovative sustainable catalysis, the next generation of heterocyclic compounds can be developed in a manner that prioritizes both therapeutic efficacy and environmental responsibility (F. Gomez et al., 2023).

This chapter will delve into the reaction protocols and future directions of sustainable catalytic strategies for the synthesis of heterocyclic compounds, exploring their profound impact on heterocyclic chemistry. Through detailed discussions on reaction pathways and the following sections will illustrate how sustainable catalysis is redefining the synthesis of heterocyclic compounds while fostering a more environmentally conscious approach to drug discovery and development (M. Becker et al., 2023).

2. Metal-free sustainable protocols for the synthesis of heterocyclic compounds

The sustainable catalytic protocols have introduced organocatalysis as an alternative for the formation of heterocyclic compounds. Organocatalysts have small organic molecules to catalyzed stereoselective and regioselective transformative reactions, without any heavy metal contamination and toxicity. Among the most widely studied organocatalysts are secondary amines, which facilitate enamine catalysis for constructing functionalized heterocycles under normal reaction conditions. These reaction protocols have been effectively employed in asymmetric cyclization and annulation reactions, providing efficient and sustainable methodologies for the synthesis of heterocyclic compounds (R. Sarkar et al., 2021). Acid-base catalysis within organocatalytic frameworks has also advanced sustainable protocols for the synthesis of heterocyclic compounds. The use of bio-derived transformations has further reinforced the sustainability of catalytic strategies.

In 2021, R. Singha et al. reported a solvent-free, efficient, one-pot, multi-component reaction for the synthesis of chromeno[4,3-b]quinolin-6-one derivatives (R. Singha et al., 2021). This protocol, catalyzed by graphene oxide (GO), enables the reaction between 4-hydroxycoumarin, aldehydes, and aromatic amines, providing an efficient and environmentally friendly synthetic pathway. Graphene oxide (GO) has emerged as an innovative heterogeneous carbocatalyst, demonstrating remarkable reusability, retaining its catalytic efficiency even after five consecutive runs (Scheme 1).



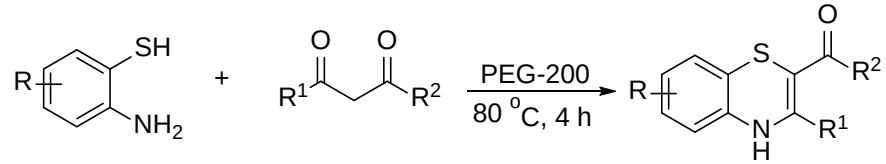
52-95% yield

R_1= C_6H_5, *p*-$CH_3C_6H_5$, *o*-$CH_3C_6H_5$, *p*-$OCH_3C_6H_5$, *p*-$NO_2C_6H_5$, *p*-FC_6H_5, *p*-ClC_6H_5, *p*-BrC_6H_5, C_3H_7, C_6H_{13}

R_2= H, CH_3

Scheme 1. Synthesis of chromeno[4,3-b]quinolin-6-one derivatives catalyzed by GO

In 2023, A. Islam et al. introduced an innovative, one-pot, two-component greener protocol for synthesized biologically significant 1,4-benzothiazine derivatives. This protocol, catalyzed by PEG-200, facilitates by the reaction of 2-aminobenzothiols and 1,3-dicarbonyl compounds, providing a sustainable and metal-free alternative for organic synthesis as shown in Scheme 2 (A. Islam et al., 2023).



R= H, Cl, CF_3

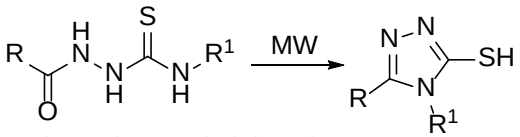
R^1= CH_3, $CH_2CH_2CH_2$, $CH_2C(CH_3)_2CH_2$, Ph

R^2= CH_3, Ph, OCH_2CH_3

76-95% yield

Scheme 2. Metal-free synthetic methodology was developed for the efficient preparation of functionalized 1,4-benzothiazines

In 2006, Zamani et al. reported the synthesis of various 4,5-disubstituted 1,2,4-triazole-3-thiones using both microwave irradiation and conventional heating (K. Zamani et asl., 2006). Their work demonstrates that microwave-assisted dehydrative cyclization of thiosemicarbazides across different media dramatically shortens reaction times from 2-9 hours to just 2-4 minutes, while only slightly reducing yields by 1-4% (Scheme 3).

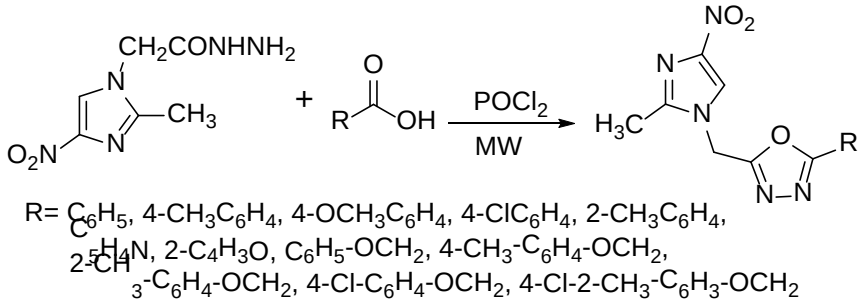


R= benzyl, 2-methylphenyl

R^1= 2-pyridyl, 3-pyridyl, 4-pyridyl

Scheme 3. Microwave-assisted protocol was developed for the synthesis of 4,5-disubstituted 1,2,4-triazole-3-thiones

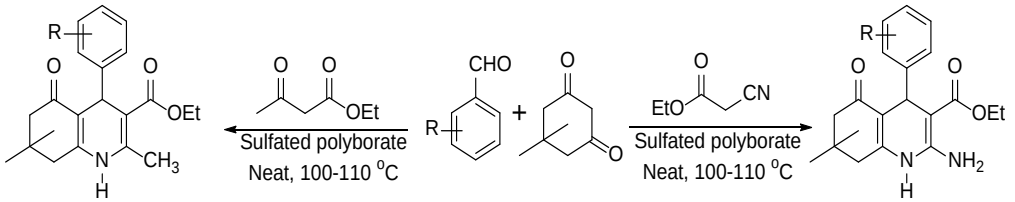
In 2007, P. V. Frank et al. reported both microwave-assisted and conventional syntheses of 5-substituted 2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles bearing a nitroimidazole moiety, and evaluated their antibacterial, antifungal, and anti-inflammatory activities shown in Scheme 4 (P. V. Frank et al., 2007).



R= C_6H_5, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-ClC_6H_4, 2-$CH_3C_6H_4$, 2-C_5H_4N, 2-C_4H_3O, C_6H_5-OCH_2, 4-CH_3-C_6H_4-OCH_2, 2-CH_3-C_6H_4-OCH_2, 4-Cl-C_6H_4-OCH_2, 4-Cl-2-CH_3-C_6H_3-OCH_2

Scheme 4. Microwave-assisted protocol for the efficient synthesis of 5-substituted 2-(2-methyl-4-nitro-1-imidazomethyl)-1,3,4-oxadiazoles

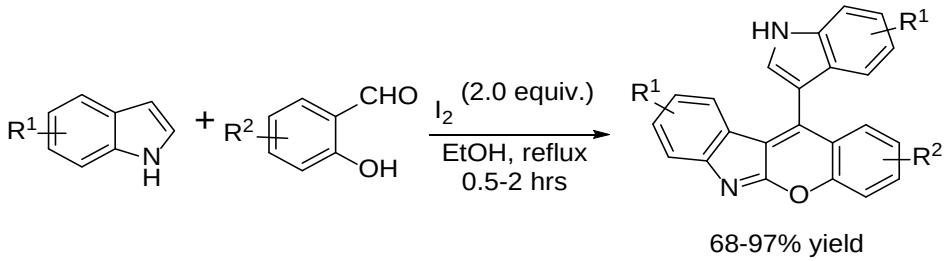
In 2020, Aute et al. disclosed an eco-friendly; efficient protocol for the synthesis of polyhydroquinolines via a Hantzsch four-component condensation of aromatic aldehydes, dimedone, ammonium acetate, and either ethyl acetoacetate or ethyl cyanoacetate (D. Aute et al., 2020). The reaction, catalyzed by sulfated polyborate under solvent-free conditions at 100 °C (Scheme 5), leveraged the catalyst's mild Brønsted acidity to deliver 85-94 % yields in just 18-30 minutes.



R= H, 2-Cl, 2-NO_2, 3-NO_2, 3-Cl , 3-OMe, 4-OMe, 4-Me, 4-Br, 4-NO$_2$, 4-Cl, 4-OH, 4-F, 3,4-$(OMe)_2$, 2-Thiophene, 2-Furan, 2-OH, 3-Br, 3-OH, 4-$(NMe)_2$

Scheme 5. One-pot, multicomponent protocol for the efficient synthesis of polyhydroquinoline derivatives

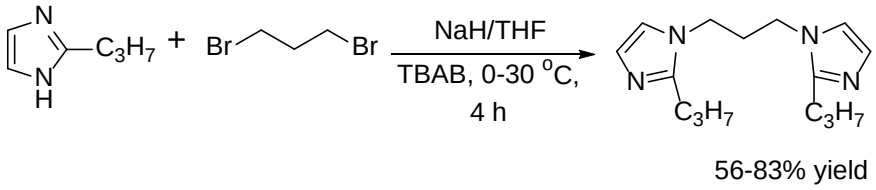
In 2018, G. Q. Rong and co-workers delineated an efficient synthetic route to indolylchromeno [2,3-*b*]indoles, in which molecular iodine functions as a catalytic mediator. The approach comprises a Friedel-Crafts alkylation between indole derivatives and salicylaldehydes, followed by an oxidative coupling step. Execution in ethanol under reflux conditions enables molecular iodine to facilitate transformations, thereby streamlining the reaction sequence and significantly enhancing its overall efficiency shown in Scheme 6 (G. -Q. Rong et al., 2018).



Scheme 6. I_2-mediated protocol for the synthesis of indolylchromeno[2,3-b]indoles

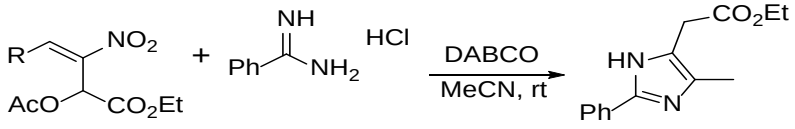
3. Synthesis of heterocyclic compounds using enzymatic reactions

In 2009, J. Pandey and co-workers delineated a concise synthetic route to 1,3-bis(2-propylimidazol-1-yl)propane *via* the base-mediated alkylation of 2-propylimidazole with 1,3-dibromopropane (J. Pandey et al., 2009). Employing sodium hydride in a polar aprotic medium at 0-30 °C over a four-hour interval, this protocol proved readily adaptable to the assembly of diverse substituted imidazoles and their multi-coupled analogues. Among the resultant library, the title bis-imidazolylpropane derivative exhibited the most pronounced antitubercular efficacy (Scheme 7).



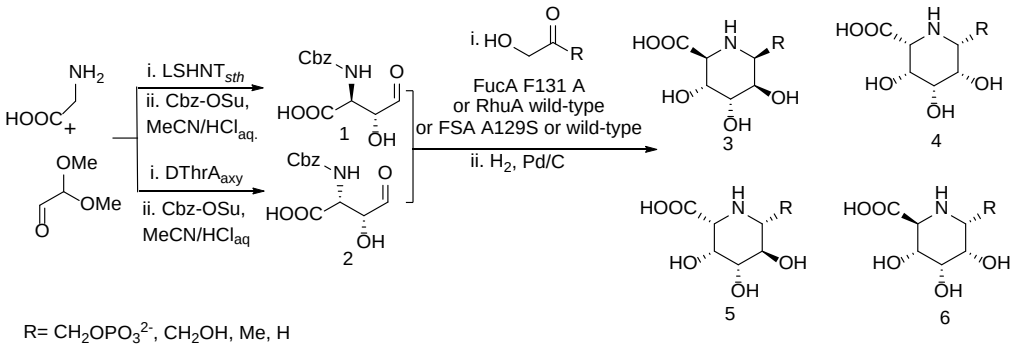
Scheme 7. Synthetic methodology for the preparation of an antitubercular active compound from 2-propylimidazole

In 2015, Irishi N. N. Namboothiri and co-workers conceptualized a one-pot synthesis of highly substituted, bioactive imidazole derivatives *via* the coupling of Morita-Baylis-Hillman (MBH) acetates of nitroalkenes with amidines under mild conditions (T. Kumar et al., 2015). The pronounced 1,2- and 1,3-bielectrophilic character of the nitroallylic acetates, in concert with the 1,3-binucleophilicity of amidines, orchestrates a cascade sequence culminating in imidazole ring formation. Employing DABCO as a base at ambient temperature, this protocol achieves efficient conversion to substituted imidazole frameworks in a single operation (Scheme 8).

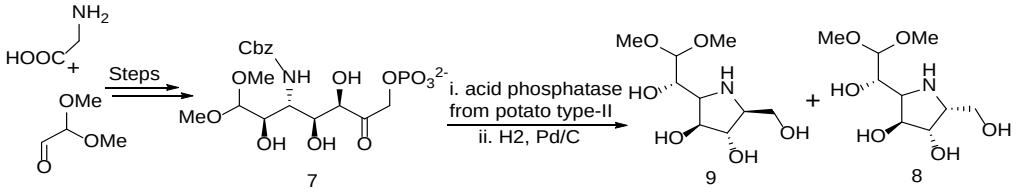


Scheme 8 Synthesis of trypanocidal active substituted imidazoles from Morita-Baylis-Hillman acetates

In 2014, Clapés and co-workers devised a chemoenzymatic, multistep strategy for the synthesis of five- and six-membered pyrrolidine and piperidine derivatives as *N*-heterocyclic analogues of pipecolic acid shown in Scheme 9a (A. Soler et al., 2014). The sequence initiates with the enzymatic conversion of glycine and 2,2-dimethoxyacetaldehyde into α-hydroxyamino acid intermediates (2S,3R)-2-(((benzyloxy)carbonyl) amino)-3-hydroxy-4-oxobutanoic acid, **1** and (2R,3R)-2-(((benzyloxy)carbonyl)amino)-3-hydroxy-4-oxobutanoic acid, **2** mediated respectively by L-serine hydroxymethyltransferase from Streptococcus thermophilus (LSHMTsth) or D-threonine aldolase from Achromobacter xylosoxidans (DThrAaxy), affording conversions of 54-80 %. These intermediates then undergo a second aldol reaction with dihydroxyacetone phosphate, dihydroxyacetone, hydroxyacetone or glycolaldehyde as electrophilic donors, catalyzed by L-fuculose-1-phosphate aldolase F131A (Fuc F131A), L-rhamnulose-1-phosphate aldolase (RhuA), or wild-type and variant FSA enzymes. Dephosphorylation followed by catalytic hydrogenation of the resulting aldol adducts furnishes the six-membered pipecolic acid derivatives **3-6**, with stereochemical outcomes ranging from single diastereoisomers to separable epimeric mixtures as resolved by cation-exchange chromatography. Employing an analogous enzyme-catalyzed cascade, the corresponding five-membered pyrrolidine analogues **8** and **9** are likewise accessed in a one-pot operation shown in Scheme 9b (A. Soler et al., 2014).

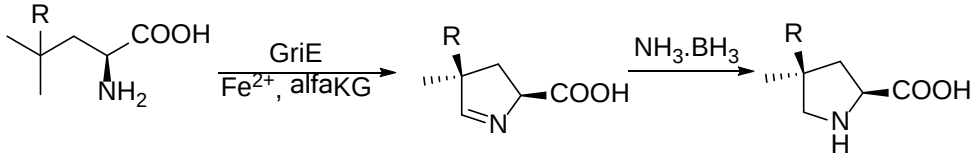


Scheme 9a. Synthetic methodology for the preparation of six-membered pipecolic acid analogues



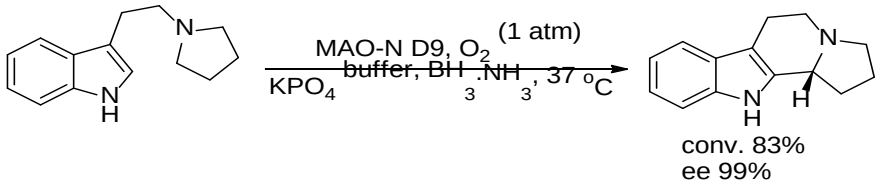
Scheme 9b. Synthetic methodology for the preparation of five-membered pipecolic acid analogues

In 2018, Zwick and Renata unveiled a streamlined chemo-enzymatic route to proline analogues (Scheme 10), exploiting the α-ketoglutarate-dependent dioxygenase GriE for direct C–H hydroxylation of leucine derivatives. At elevated enzyme loading, GriE converts substrates into hydroxylated intermediates that undergo an *in situ* oxidation/condensation sequence to forge imines. A subsequent, mild $NH_3{\cdot}BH_3$ reduction then cleanly delivers the target prolines in 75-88 % yield. Crucially, GriE's active site desymmetrize leucine's two methyl termini to lock in full stereo control at C4, yet remains flexible enough to accommodate diverse γ-substituents during oxidation (C. R. Zwick et al., 2018).



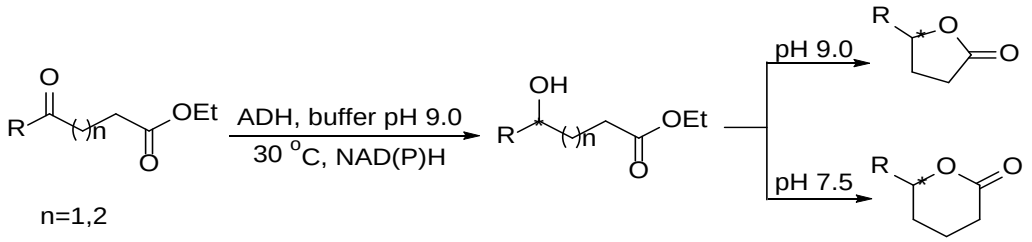
Scheme 10. Chemo-enzymatic method for the synthesis of proline analogues *via* enzymatic C–H hydroxylation of leucine derivatives

In 2013, Ghislieri et al. showed that the monoamine oxidase variant MAO-N D9 can directly forge the tetracyclic core of (R)-harmicine from indole in a concise biocatalytic cascade (D. Ghislieri et al., 2013). MAO-N D9 first oxidizes the pyrrolidine ring of indole to generate iminium, which then cyclizes non-stereo selectively to give racemic tetracycle. A second MAO-N D9-catalyzed oxidation in the presence of $NH_3{\cdot}BH_3$ triggers dynamic deracemization, delivering (R)-harmicine in 83 % conversion with 99 % ee. This elegant sequence effectively represents a biocatalytic enantioselective Pictet-Spengler reaction (Scheme 11).



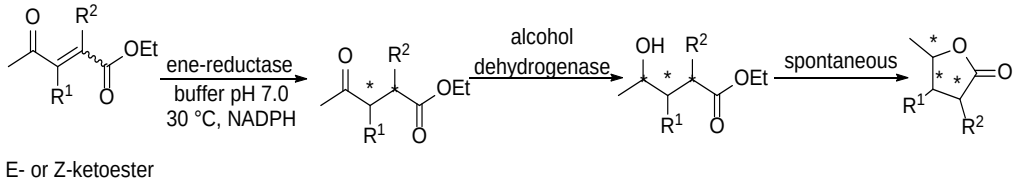
Scheme 11. Biocatalytic Pictet-Spengler reaction, MAO-N as the catalyst, for the enantioselective assembly of tetrahydro-β-carboline frameworks

In 2014, Gotor et al. unveiled a concise, one-pot alcohol dehydrogenase (ADH)–catalyzed synthesis of γ- and δ-lactones shown in Scheme 12 (A. Díaz-Rodríguez et al., 2014). By reducing γ- and δ-keto esters at pH 9 with a panel of ADHs, they achieved hydroxy-ester intermediates in 97-99 % ee. Under those same conditions, γ-hydroxy esters cyclized spontaneously to afford γ-lactones, whereas δ-lactone formation required a simple pH drop to 7.5.



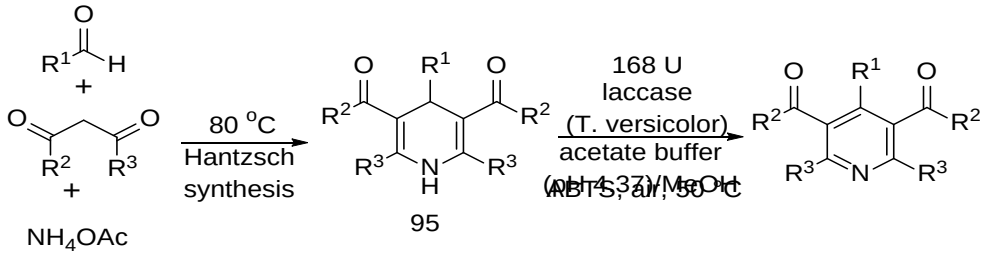
Scheme 12. Chemoenzymatic protocol for the synthesis of lactones using alcohol dehydrogenases (ADHs) and ene-reductases

In 2014, Pietruszka unveiled a concise biocatalytic cascade to convert ethyl 4-oxopent-2-enoate substrates into substituted γ-butyrolactones (T. Classen et al., 2014). An ene-reductase first hydrates the C=C bond, setting the stereochemistry to furnish γ-hydroxyesters. Without isolation, an alcohol dehydrogenase then reduces the ketone, and the resulting hydroxy ester cyclizes spontaneously to deliver γ-butyrolactones with exceptional stereo control up to 99 % ee and de (Scheme 13).



Scheme 13. Chemoenzymatic protocol for the synthesis of lactones from alcohol dehydrogenases (ADHs) and ene-reductases

In 2012, the Beifuss et al. achieved the first enzymatic aromatization of 1,4-dihydropyridines (DHPs) prepared *via* Hantzsch synthesis into pyridine derivatives (H. T. Abdel-Mohsen et al., 2012). They screened Trametes versicolor laccase with various mediators (ABTS, HOBt, TEMPO and its derivatives), identifying ABTS (1.25 mol %) as optimal. Employing 168 U of laccase, DHP 95 was converted to pyridine 96 in 78 % yield over 7 h at room temperature; raising the temperature to 50-55 °C boosted the yield to 90 % in just 4 h. Building on these findings, they developed a one-pot protocol, a Hantzsch condensation of aldehydes, diketones (or keto esters) and NH_4OAc at 80 °C furnished DHP substrates, then dilution into acetate buffer/MeOH with 168 U laccase and ABTS under air at 50 °C for 5–26 h delivered various substituted pyridines in up to 74 % yield (Scheme 14).

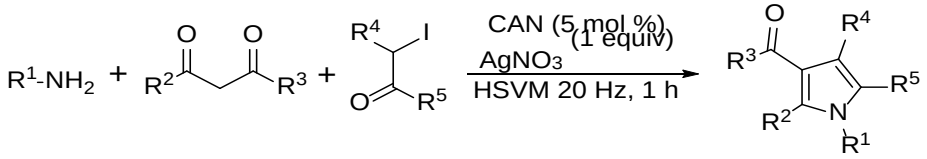


Scheme 14. Chemoenzymatic protocol utilizing laccase catalysis was developed for the efficient synthesis of pyridine derivatives

4. Mechanochemistry: solvent-free heterocycle formation

Mechanochemistry has gained attention as a solvent-free approach to green catalysis, relying on mechanical force to drive chemical transformations. By employing ball milling and grinding techniques, mechanochemical methods eliminate solvent-related waste, reducing the overall environmental footprint of heterocycle synthesis. Mechanochemical reactions have been effectively employed in cyclization and annulation processes, demonstrating efficiency in constructing nitrogen-containing heterocycles under low-energy conditions, these methods align with green chemistry principles (M. Rashid et al., 2025). Mechanochemistry continues as an alternative pathway for sustainable catalytic systems for heterocycle formation without the drawbacks of conventional liquid-phase reactions.

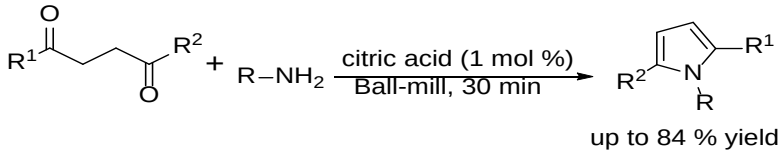
In 2013, Menendez et al. introduced a mechanochemical, three-component Hantzsch pyrrole synthesis under ball-milling conditions (V. Estévez et al., 2013). First, milling a ketone with *N*-iodosuccinimide (NIS) and *p*-toluenesulfonic acid for one hour generates the corresponding α-iodoketone. Without isolation, the crude mixture is then combined in the mill with a primary amine, a β-dicarbonyl compound, 5 mol % Ceric Ammonium Nitrate (CAN) and 1 equiv. silver nitrate. This sequence forms a β-enaminone intermediate, which couples with the α-iodoketone and cyclo-condenses to furnish the substituted pyrroles shown in Scheme 15.



Scheme 15. Mechanochemical protocol for the efficient Hantzsch-type synthesis of pyrrole derivatives

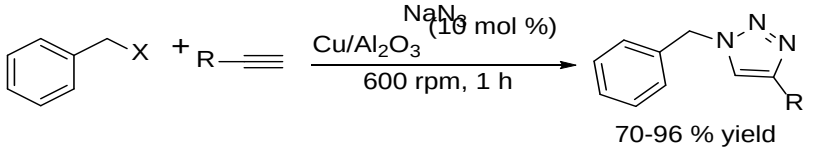
In 2016, Rousseau and co-workers reported a solvent-free mechanochemical Paal-Knorr pyrrole synthesis using a solid, bio-sourced acid-citric acid (Scheme 16). Milling

substituted anilines, benzyl or aliphatic amines with 1,4-diketones in the presence of just 1 mol % citric acid furnished the corresponding *N*-substituted pyrroles in quantitative yield (L. Akelis et al., 2016).

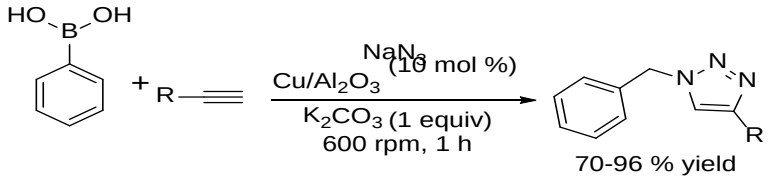


Scheme 16. Mechanochemical protocol for the efficient Paal-Knorr synthesis of pyrrole derivatives

In 2013, Ranu and co-workers harnessed a Cu/Al_2O_3 catalyst (10 mol% Cu on alumina) under mechanochemical conditions to assemble triazoles from benzyl halides, sodium azide, and terminal alkynes (Scheme 17a) (N. Mukherjee et al., 2013). Substituted phenyl acetylenes and aliphatic alkynes smoothly furnished triazoles in 70-96 % yield. Extending the methodology, phenyl boronic acids were also engaged alongside 1 equiv. K_2CO_3 to deliver triazole products in over 85 % yield (Scheme 17b) (N. Mukherjee et al., 2013).

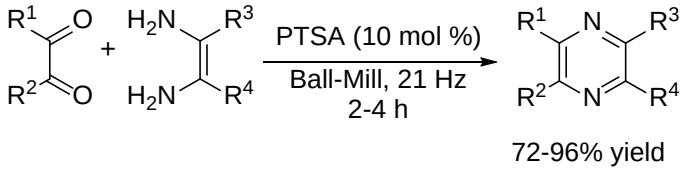


Scheme 17a. Mechanochemical protocol for the click reaction employing an alumina-supported copper catalyst



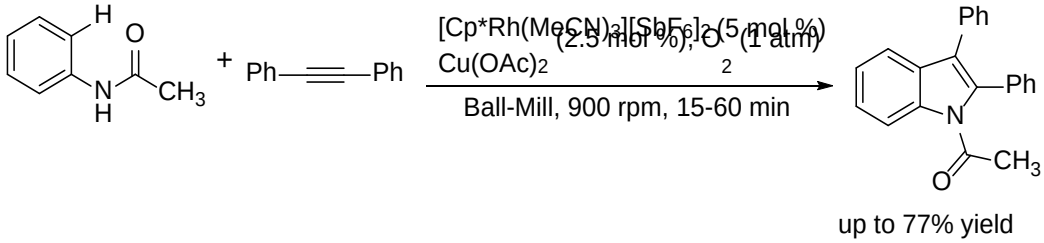
Scheme 17b. Mechanochemical protocol for the click reaction employing an alumina-supported copper catalyst

In 2016, Mal et al. harnessed mechanochemistry to assemble hetero-acenes by milling 1,2-dicarbonyl compounds with 1,2-diaminoarenes in the presence of just 10 mol% *p*-toluenesulfonic acid (Scheme 18). This solvent-free, room-temperature process forges pyrazaacene, phenazine, bis(phenazine) and bis(quinoxaline) scaffolds in 72-96% yield within 2-4 h. Workup is trivial, a simple wash with a polar solvent and no harsh conditions are required. By contrast, analogous solution-phase syntheses demand 3 days of reflux to reach only 30-40% yield, underscoring the speed, efficiency and sustainability of the mechanochemical route (P. K. Sahoo et al., 2016).



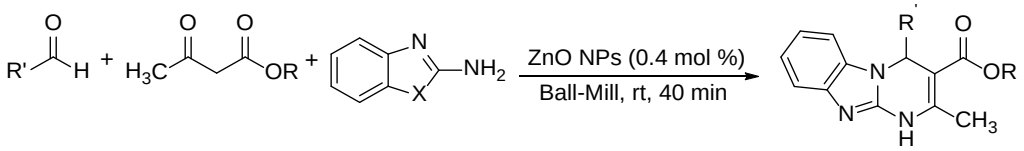
Scheme 18. Mechanochemical protocol for the efficient synthesis of azacene derivatives

In 2017, Bolm and co-workers reported a mechanochemical Rh-catalyzed C-H functionalization to forge indole cores under planetary ball-milling conditions (Scheme 19) (G. N. Hermann et al., 2017). Milling acetanilide with diphenylacetylene in the presence of 5 mol % Rh-catalyst, 2.5 mol % $Cu(OAc)_2$ and O_2 (1 atm) delivered a variety of substituted indoles in yields up to 77 %.



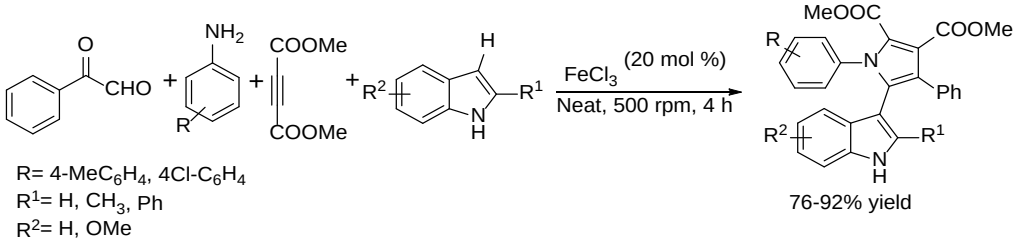
Scheme 19. Mechanochemical, Rh-catalyzed protocol for the efficient synthesis of indole derivatives

In 2017, Tilak Raj et al. synthesized aromatic-capped ZnO nanoparticles *via* a sol-gel route to furnish the NS-5 catalyst for a solvent-free, one-pot multicomponent ball-milling synthesis of diverse pyrimidine derivatives (Scheme 20). The protocol's sustainability was quantified by Ecoscale and E-factor analyses. NS-5 proved highly efficient and recyclable, enabled straightforward multi gram-scale production, and allowed facile product isolation (T. Raj et al., 2017).



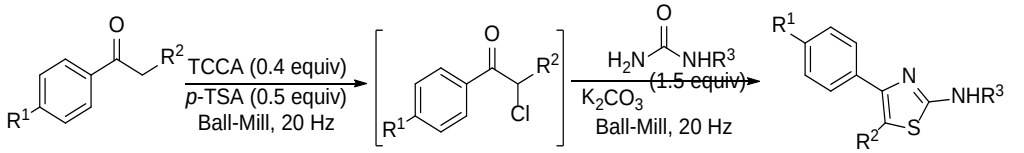
Scheme 20. ZnO NP-catalyzed one-pot MCR yields pyrimidine derivatives from 2-aminobenzimidazole, aromatic aldehydes, and acetoacetate

In 2022, Chupakhin et al. unveiled an Fe(III)-catalyzed, solvent-free, four-component mechanochemical cascade (Scheme 21) to assemble highly substituted 3-(1*H*-pyrrol-2-yl)-1*H*-indoles. This single-pot ball-milling protocol tolerates a broad array of starting materials, delivering diverse polysubstituted pyrrolo-indoles in high to excellent yields (A. Mukherjee et al., 2022).



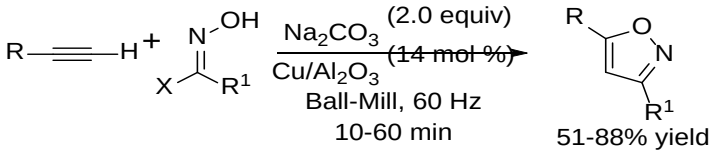
Scheme 21. Mechanochemical Fe(III)-catalyzed cascade multicomponent protocol *via* C-H activation yields functionalized heterocycles in one pot

In 2016, Nagarajaiah and Moorthy reported a metal- and solvent-free mechanochemical route to 2-aminothiazoles and 2-amino-8*H*-indeno[1,2-*d*]thiazoles *via* a one-pot, sequential acid- and base-mediated cascade (Scheme 22). The sequence begins with atom-efficient *in situ* chlorination of ketones using trichloroisocyanuric acid (TCCA) and *p*-toluenesulfonic acid (*p*-TSA) to furnish α-chloroketones. These intermediates then undergo base-promoted condensation with thiourea or thiosemicarbazides, delivering the target 2-aminothiazole frameworks in high yields (H. Nagarajaiah et al., 2016).



Scheme 22. Mechanochemical, greener one-pot acid-base sequence yields 2-aminothiazoles from ketones

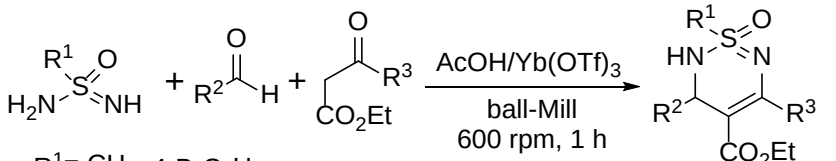
In 2022, Rafael A. Hernández R. et al. reported a scalable, solvent-free ball-milling route to 3,5-isoxazoles (Scheme 23). Terminal alkynes and hydroxyimidoyl chlorides are coupled in the presence of a recyclable Cu/Al_2O_3 nanocomposite catalyst, delivering 3,5-isoxazoles in moderate to excellent yields. Remarkably, the conditions translate directly to a 1.0-gram scale without any adjustment to milling time (R. A. Hernandez R. et al., 2022).



R= $SiMe_3$, CO_2Me, CH_2Br, C_2H_4Br, C_6H_5, p-$MeO_2CC_6H_4$
R^1= Br, 4-OMe-C_6H_4, 4-NO_2-C_6H_4,CO_2Et

Scheme 23. Catalyst-free mechanochemical one-pot protocol yields 3,5-isoxazole derivatives

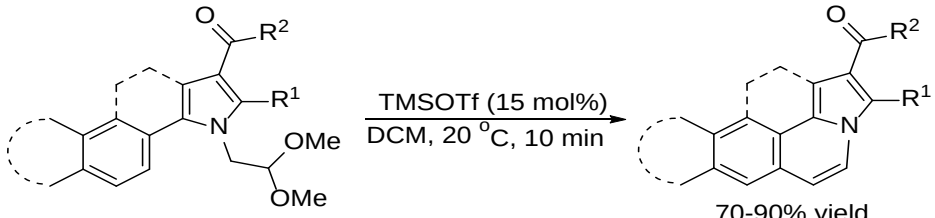
In 2021, Felix Krauskopf and co-workers harnessed NH-free sulfonimidamides in Biginelli-type multicomponent reactions to access 2,3-dihydro-1,2,6-thiadiazine 1-oxides in excellent yields (Scheme 24). The ball-mill process employs either acetic acid or ytterbium triflate as catalyst, enabling rapid assembly of the highly functionalized heterocycle. A representative product was unambiguously characterized by single-crystal X-ray analysis, revealing its intricate three-dimensional framework. Further post-MCR modifications expanded the scaffold diversity, underlining the method's versatility (F. Krauskopf et al., 2021).



R^1= CH_3, 4-BrC_6H_4
R^2= Et, *i*-Pr, *t*-Bu, Cyclohexyl, PhC_2H_4
R^3= CH_3, Et

Scheme 24. Mechanochemical Biginelli-type one-pot synthesis of 2,3-dihydro-1,2,6-thiadiazine 1-oxides from sulfonimidamides

In 2017, Marco Leonardi and co-workers combined a three-component pyrrole synthesis under mechanochemical conditions with a TMSOTf-catalyzed oxonium-mediated cyclization to access pyrrolo[2,1-*a*]isoquinoline derivatives under exceptionally mild conditions (Scheme 25). This tandem approach not only streamlined the assembly of the core heterocycle but also paved the way to six additional, structurally unique polyheterocyclic frameworks, highlighting the platform's remarkable scope and versatility (M. Leonardi et al., 2017).

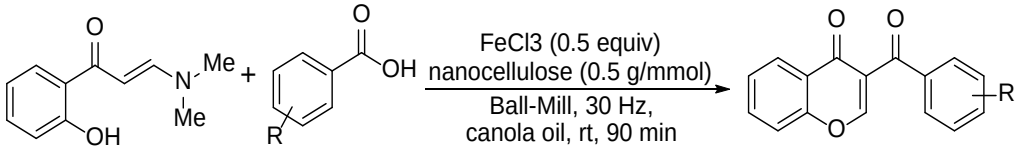


R^1= CH_3, CH_2COCH_3
R^2= CH_3, OCH_3, OEt

Scheme 25. Mechanochemical multicomponent pyrrole reaction yields pyrrolo[2,1-*a*]isoquinolines under mild conditions

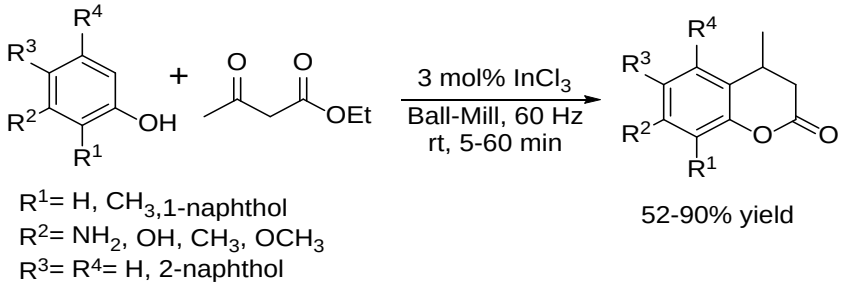
In 2023, Mkrtchyan and co-workers devised mechanochemical route to 3-acylchromones *via* $FeCl_3$ nanocellulose-mediated dehydrative coupling of ortho-

hydroxy arylenaminones with carboxylic acids (Scheme 26). Under ball-milling, the arylenaminones undergo electrophilic domino cyclization followed by an unconventional acylation using inexpensive, readily available carboxylic acids as acyl donors. Nanocellulose serves as the biodegradable reaction medium while $FeCl_3$ catalyzes the sequence, delivering a broad scope of 3-acylchromones in high yields under mild conditions (S. Mkrtchyan et al., 2023).



Scheme 26. Synthesis of 3-acylchromones using ball-mill catalyzed by $FeCl_3$ in nanocellulose

In 2023, Becerra-Anaya et al. reported a streamlined and highly efficient protocol for the synthesis of 4-methylcoumarins *via* the mechanochemical Pechmann condensation. The approach employs phenolic substrates (or naphthols) and ethyl acetoacetate in the presence of 3 mol % indium(III) chloride to afford coumarin (7-amino-4-methylcoumarin) and its analogues (Scheme 27). Conducted at ambient temperature in a high-speed ball-mill mixer, the solvent-free reaction proceeds rapidly and reproducibly, delivering coumarin derivatives in 52–92 % yield. Systematic investigation of critical operational variables including milling duration, ball diameter and composition, reactor material, and vibration frequency as well as catalyst loading, identified optimal conditions. A cost-effective Zenith amalgamator operating at 60 Hz (3600 rpm) was employed with a single 5 mm stainless-steel ball in a Duralon jar to suppress secondary reactions and ensure maximal conversion under entirely solvent less conditions (S. J. Becerra-Anaya et al., 2023).

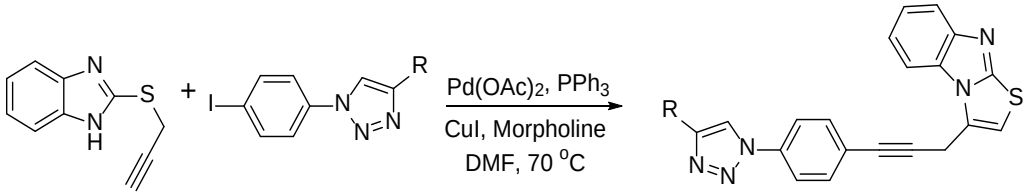


Scheme 27. Ball-Milling Pechmann condensation yielding 4-methylcoumarins under solvent-free condition

5. Synthesis of heterocyclic compounds catalyzed by Pd-Cu dual catalysts

Modern sustainable chemistry explored for the synthesis of heterocyclic compounds catalyzed by Pd-Cu dual catalyst. The researchers used a dual catalyst system that employed recyclable Pd and Cu, for higher conversion rates while maximizing catalytic efficiency. The reaction proceeded efficiently in water-ethanol medium, avoiding the use of toxic organic reaction medium. This dual catalyzed protocols enabled the ring formation without extra additive oxidants, preserving a high level of selectivity while ensuring optimal product yield. Additionally, the Pd-Cu dual catalyst successfully reused over multiple cycles, demonstrating remarkable sustainability. Using these dual catalysts increase the ability to synthesized heterocyclic compounds under mild, environmentally friendly reaction conditions provides a greener pathway (X. Tang et al., 2016).

In 2014, Falahatkar et al. introduced an efficient, one-pot synthesis of hybrid 1,2,3-triazole scaffolds incorporating benzimidazole and thiazolo[3,2-a]benzimidazole moieties (Scheme 28). Acetylenic benzimidazoles and substituted iodoaryl triazoles were subjected to Sonogashira coupling followed by intramolecular heteroannulation in DMF at 70 °C, employing $Pd(OAc)_2$/CuI catalysis and morpholine as base. This protocol afforded the targeted triazoles derivatives in 75-90 % yield. The protocol's key advantages include operational simplicity, high isolated yields, and a telescoped reaction design under mild conditions (H. Falahatkar et al., 2024).

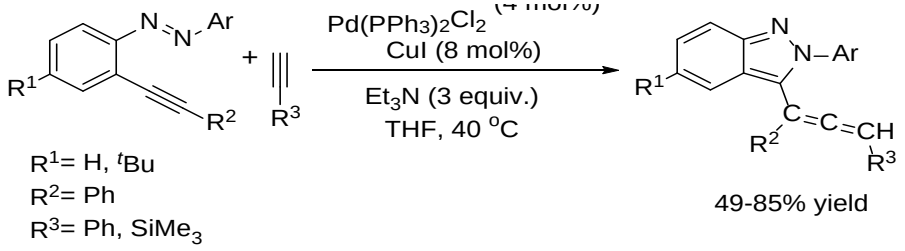


R= C_6H_5, -O-C_6H_4-4-CHO, -O-C_6H_4-2-CH_3'

Scheme 28. Synthesis of triazole-benzimidazole hybrids by the coupling of 1-(4-iodophenyl)-1*H*-1,2,3-triazoles with propargylated benzimidazoles catalyzed by Pd-Cu dual catalyst

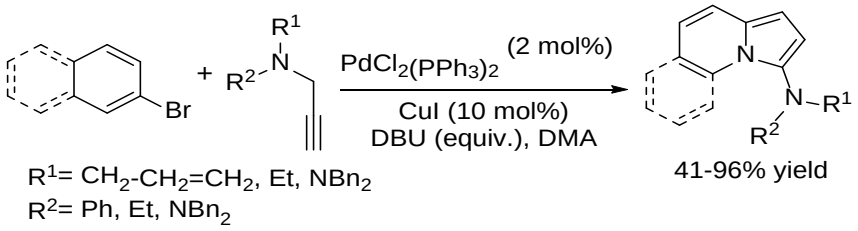
In 2017, Zhu and co-workers reported a tandem Pd/Cu-catalyzed assembly of (3-isoindazolyl)allenes via the coupling of 2-alkynyl-azobenzenes with terminal alkynes (Scheme 29). Under THF at 40 °C, employing $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (10 mol %), and excess Et_3N, the reaction proceeds through sequential Cu- and Pd-carbenoid intermediates to furnish the allenic heterocycles in 49-85 % yield. A broad array of electron-rich and -deficient aryl substituents on the azobenzene partner was well tolerated, whereas ortho-substitution led to diminished efficiency. Likewise, various

aryl acetylenes delivered the corresponding allenes smoothly, but sterically encumbered alkyl and $SiMe_3$-substituted alkynes failed, likely due to β-hydride elimination from the Pd^{II} intermediate. To demonstrate synthetic utility, heating one representative allene at 150 °C in NMP induced cyclization to afford a 5-benzyl-6-phenyl-indazolo[2,3-a]quinoline framework, a scaffold noted for its antitumor and intriguing optical properties (C. Zhu et al., 2017).



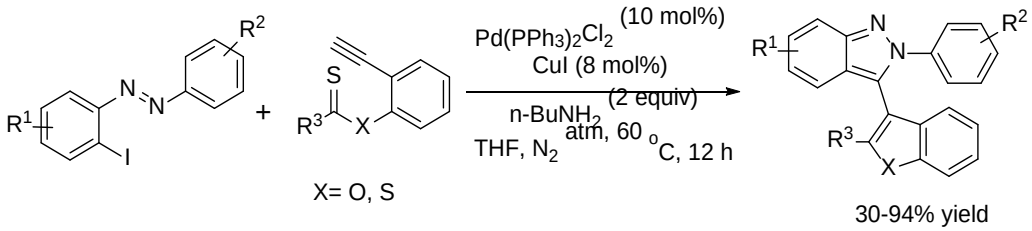
Scheme 29. Pd–Cu dual-catalyzed synthesis of (3-isoindazolyl)allene

In 2018, Liu and co-workers described a Pd/Cu dual-catalyzed protocol for the synthesis of indolizine derivatives via cross-coupling of 2-bromopyridines with propargylic amines (Scheme 30). Under the optimized conditions $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), and stoichiometric DBU in N,N-dimethylacetamide (DMA) at 80 °C, various indolizines were obtained in 41-96% yield. Notably, propargylic amines bearing N-aryl methyl, aryl, allyl, or diaryl substituents afforded superior yields relative to dialkyl analogues, a trend attributed to enhanced propargyl-allenyl isomerization efficiency in the former. Subsequent propargyl-allenyl rearrangement and intramolecular cycloisomerization furnish the indolizine core. This cascade sequence underscores the complementary roles of Pd and Cu catalysis in enabling C-C bond construction and skeletal reorganization under mild, operationally straightforward conditions (Y. Liu et al., 2007).



Scheme 30. Synthesis of indolizine derivatives catalyzed by Pd-Cu dual catalyst

In 2023, Ding et al. introduced a cascade reaction protocol for the assembly of indazole-containing biheteroaryls (Scheme 31). The reaction protocol commences with a Sonogashira coupling, which, although mechanistically multi-steps process, is most conveniently observed as a single, sequential operation. Upon formation of the alkynyl intermediate, an intermolecular aza-enyne cyclization, generating a metal-carbene species that subsequently engages in a Barton-Kellogg-type coupling to the formation of second heterocycle. Notably, while the reaction can proceed in the absence of copper, the inclusion of a CuI profoundly accelerates each transformative reaction. This dual catalyst use of an acetylene unit as a one-carbon synthons for two distinct five-membered rings affords rapid access to a diverse array of substituted indazole biheteroaryls under mild, scalable conditions (R. Ding et al., 2023).



Scheme 31. Synthesis of indazole-containing biheteroaryls using Sonogashira coupling azaenyne cycloisomerization-Barton-Kellogg

Conclusions

Development of sustainable catalytic protocols for the synthesis of heterocyclic compounds represents a significant evolution in pharmaceutical chemistry. As the demand for efficient, selective, and environmental friendly synthetic protocols, sustainable catalysis has emerged as a cornerstone for achieving more advancement for the synthesis of heterocyclic compounds. By integrating metal-free synthesis, biocatalysis and Pd-Cu dual catalysis, researchers have redefined heterocycle construction in ways that minimizing the use of environmental hazardous chemicals. Their diverse biological activities necessitate scalable and sustainable synthetic reaction protocol that can produce high-quality heterocyclic compounds with minimal waste generation. Sustainable catalytic reactions offer alternative pathways that reduce toxicity, eliminate use of excessive reagent, and improve reaction efficiency. Another transformative reaction methodology in sustainable catalysis has been mechanochemical solvent-free reaction technique, which has demonstrated remarkable efficiency in the formation of heterocyclic compounds. These reaction protocol

eliminate the need for traditional oxidants and toxic additive reagents, enabling mild and efficient protocol for the construction of heterocyclic compounds. The pharmaceutical industry is already adopting eco-friendly reaction frameworks, driven by regulatory incentives, environmental policies, and industrial sustainability goals. As researchers continue to innovate, sustainable catalytic reaction protocols will become the high standard for the synthesis of heterocyclic moiety, ensuring advancement of future sustainability, efficiency, and ethical pharmaceutical manufacturing. The next generation of heterocyclic compounds will be synthesized with minimal ecological impact, reinforcing the commitment to ethical, sustainable chemistry. As advancement of modern research in hybrid catalysis, mechanochemical protocol and bio-inspired reaction protocols ensuring that synthetic chemistry aligns with global sustainability imperatives.

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