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REVIEW

Sustainable Solvent-Free Diels–Alder Approaches in the Development of Constructive Heterocycles and Functionalized Materials: A Review

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Abstract

The Diels–Alder reaction (DAR) is found in myriad applications in organic synthesis and medicinal chemistry for drug development, as it is the method of choice for the expedient synthesis of complex natural compounds and innovative materials including nanomaterials, graphene expanses, and polymeric nanofibers. Furthermore, the greatest focus of attention of DARs is on the consistent reaction procedure with stimulus yields by highly stereo- and regioselective mechanistic pathways. Therefore, the present review is intended to summarize conventional solvent-free (SF) DARs for the expedient synthesis of heterocyclic compounds and materials. In particular, this review deals with the DARs of mechanochemical grinding, catalysis (including stereoselective catalysts), thermal, and electromagnetic radiation (such as microwave [MW], infrared [IR], and ultraviolet [UV] irradiation) in SF procedures. Therefore, this comprehensive review validates the application of DARs to pharmaceutical innovations and biorenewable materials through consistent synthetic approaches.

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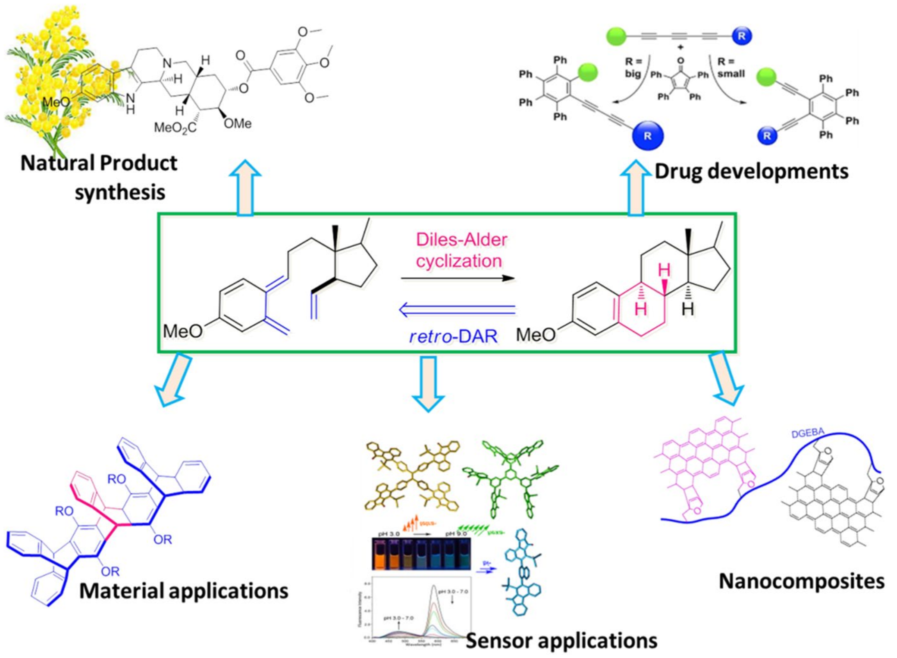
Graphical Abstract



Keywords Cycloaddition · Diels–Alder reaction (DAR) · Stereoselectivity · Solvent-free (SF) · Thermal reaction

1 Introduction

Diels–Alder reactions (DAR) are of great prominence in the synthesis of biologically potent therapeutic leads such as natural compounds and functionalized materials [1]. The overall principle of the DAR is that the reaction of a diene (4π) electron system with a dienophile (2π) forms a cyclic six-membered adduct of a ($4+2\pi$) electron system. On the other hand, the reverse reaction (or) retrosynthetic approach for DAR, i.e. cyclic adduct must be formed into a diene and a dienophile, is called a *retro*-DAR (*r*DAR) reaction. However, the stability, regio- and stereoselectivity, and enantiomeric ratio of the cyclic product(s) depend on the criteria of the reaction process either in normal electron demand DAR (NEDDA) or inverse electron demand DAR (IEDDA) [2–4]. In the IEDDA approach, the electron interactions between diene and dienophiles are inversely proportional to the NEDDA, as presented in Fig. 1. According to the classical frontier molecular orbital (FMO) theory, the electron-rich diene highest occupied molecular orbital (HOMO) orbital ($\boldsymbol{\Psi_2}$) interacts with the lowest unoccupied molecular orbital (LUMO) ($\boldsymbol{\Psi_3}$) of the electron-poor dienophile in NEDDA reactions. However, in the IEDDA, the electron-withdrawing

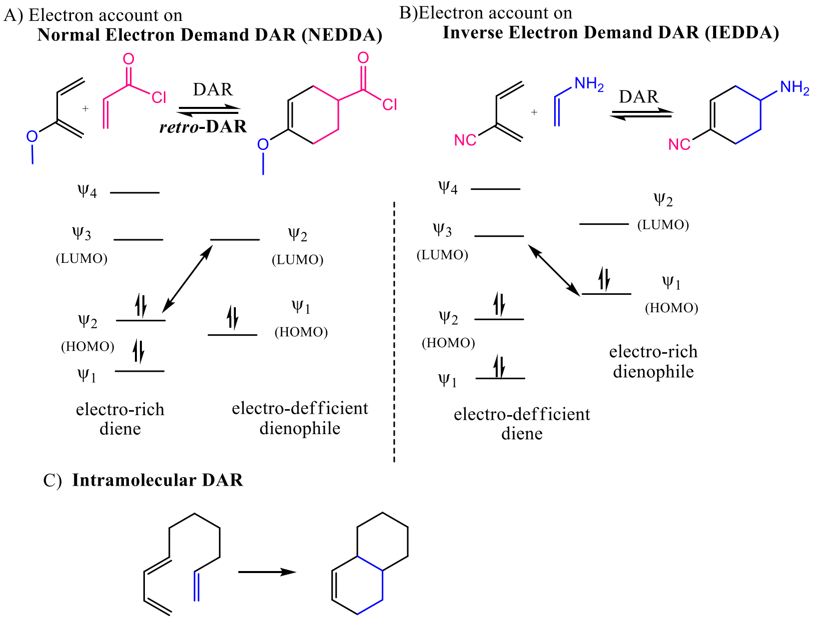


Fig. 1 Electronic account of HUMO/LUMO interactions in DAR system

groups (EWG) on diene decrease the energy of the LUMO $\boldsymbol{\Psi_3}$, giving rise to interactions with the energetically increased HOMO orbital $\boldsymbol{\Psi 2}$ of dienophiles [5]. Thus, the HUMO/LUMO interaction is substantial in DARs, which triggers the formation of more energetically stabilized product(s). Further, the DARs are classified into various groups based on reactant/catalyst selection, including (1) homo-DAR, (2) hetero-DAR, (3) Lewis acid-catalyzed DAR, (4) asymmetric-DAR and (5) hexadehydro-DAR (Fig. 2). In addition, hetero-DARs involving one or more heteroatoms (O, N) are categorized into different groups including *oxo*-DAR, *aza*-DAR, and *imine*-DAR. Consequently, DARs have a wide range of applications in the development of various heterocyclic scaffolds due to the large selection of reactants, including heteroatom relieving substances.

The DAR is a creative way to construct complex organic molecules without tedious synthetic strategies. Thus far, various enrichment methods including enantioselective, metal-catalyzed, enzyme-catalyzed, and asymmetric DA cycloaddition have been introduced [6–8]. In addition, various DA reactions of solvent-free (SF) and aqueous conditions have been reported [9]. Over the past decade, the application of DA cycloaddition has been expanded into various fields such as biomaterials applications, polymerization reactions, drug delivery systems, and biomedical engineering [10, 11]. In particular, DARs play a dynamic role in the synthesis of functionalized nanomaterials such as block-polymers, cell-adhesive peptides, crosslinked hydrogels, dendrimers, and drug -delivery systems [10, 12, 13]. Therefore, the current review focuses on SF-DA cycloaddition reactions and their applications on classified grounds. Additionally, recent developments in organic synthesis and

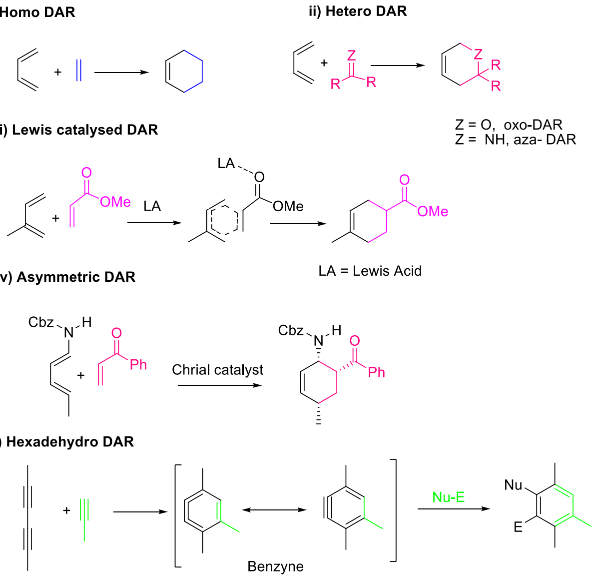
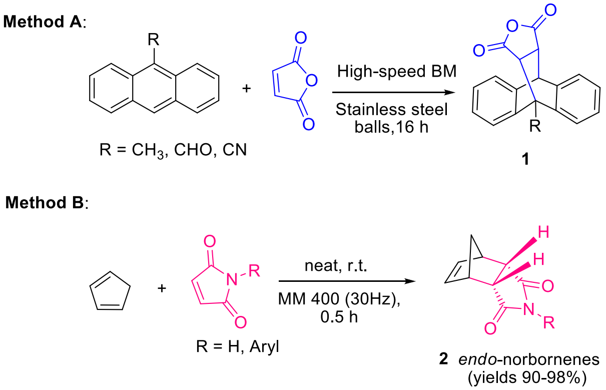


Fig. 2 Classification of Diels–Alder reactions based on the reactants

materials science have led to the emergence of eco-friendly approaches such as SF reactions, mechanochemistry (ball-milling approach) and green chemistry [14–16]. These approaches have multiple advantages including low cost, simple procedures, superior yields, and environmentally friendly operation. Therefore, over recent decades, considerable attention has been focused on the development of new PASE (pot, atom, and step economy)-based methods in the fields of organic synthesis, medicinal chemistry, materials science and drug development [17–19]. As an example, the ball-milling technique has been identified as an important synthetic route for the development of numerous organic molecules with outstanding yields [14, 15, 20].

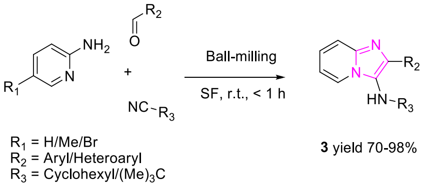
2 Mechanochemical Procedures

Mechanochemistry is a key tool for the development of C–C/C–N/C–O/C–X bond reactions of cycloadditions, oxidation and reductions, supramolecular chemistry, and nanomaterial synthesis [18, 21]. Mechanochemistry is reported as a more promising approach for high-throughput DARs than other conventional procedures [22, 23]. Therefore, recent green-chemistry advances in organic synthesis include the versatile tool mechanochemistry approach, as it offers a high-potency translation that can prime reactions more effectively than a solution phase [24]. Indeed, the principle of mechanochemical synthesis is largely based on the efficiency of particle mixing and surface stimulation procedures, but also prioritizes all functional parameters as in conventional procedures. Mechanochemical reactions also have the advantages of low-cost procedures, easy maintenance, and eco-friendly processes. In this respect, McKissic et al. [25] demonstrated an efficient SF ball-milling-assisted



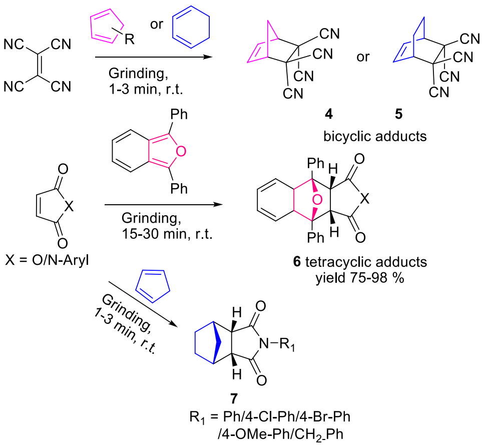
Scheme 1 Solvent-free Diels–Alder cyclization over mechanochemical milling procedures

Scheme 2 Solvent-free Ugi-MC-DA ball-milling conditions for the synthesis of imidazo[1,2-a] pyridines

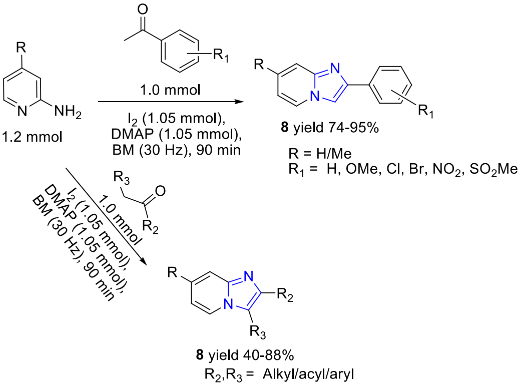


DAR of maleic anhydride with substituted anthracenes over 95–112 kJ mol^{-1} activation energy as illustrated in Scheme 1, Method A, while equivalent reactions require 90 °C ambient conditions in the solution phase using a conventional procedure. , the tabulated studies have revealed that the kinetic-energy factors of a mechanical reaction depend on the mass and velocity of the balls. Then, the number of collisions generated by the mechanical force of the balls is translated into reaction energies. Zhang et al. [23] reported a quantitative yield of 90–98% *endo*-norbornenes **2** through a DA cycloaddition of cyclopentadiene with maleimide derivatives in SF mechanochemical milling conditions, as shown in Scheme 1, Method B. The same solvent phase (1:4 v/v THF-hexane) cycloaddition reaction resulted in 65–78% moderate yields of cyclic adducts with trace quantities of other diastereomers in overnight room temperature stirring condition. Also, a postulation is that the SF mechanochemical reactions may precede through second-order reaction dynamics. In addition, the high concentration of reactants under SF conditions that experience extreme mechanical energy in the form of molecular friction and high pressure initiatives the reactions with high product yields [23, 26].

Similarly, Maleki et al. [27] portended the 3-aminoimidazo[1,2-*a*]pyridines **3** series with the best yields of 70–98% over multicomponent ball-milling reaction conditions, as depicted in Scheme 2. The listed mechanochemical synthesis is the competent one-pot-three-component SF condensation reaction of assorted 2-aminopyridines, aldehydes, and isocyanides under ball-milling conditions, with a rapid reaction time of 15–45 min. Thus, the SF Ugi-multicomponent reaction (Ugi-MCR) reaction is highly efficient for the synthesis of imidazo[1,2-a]pyridines **3** as it



Scheme 3 Mechanochemical grinding DA approach for the quantitative yields of bi-, tri-, and tetracyclic heterocycles



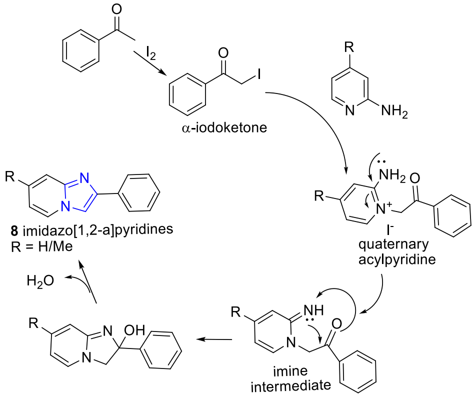
Scheme 4 Solvent-free-DA reactions of I_2 catalyzed ball-milling condensation procedure for imidazo[1,2-a] pyridines

provides facile synthesis processes, excellent yields, short-reaction time, and a high atom economy. Likewise, Agarwal et al. [28] described the most efficient mechanochemical grinding method for quantitative yields of bi-, tri- and tetracyclic heterocycles **4**–**7** by DARs of different dienes and dienophiles at ambient temperatures, as categorized in Scheme 3. The exceeding DA reactions under SF and catalyst-free conditions are highly economical because they yield quantitative products up to 98% in short-reaction procedures.

3 Catalysis-Induced

The effects of various catalysts on the development of high-output SF-DARs are well demonstrated. The SF mechanochemical DARs promoted by Lewis acid and metal catalysts are also well reported [6]. For example, Wang et al. [29] proposed a series of imidazo[1,2-a]pyridines **8** through I_2-catalyzed SF ball-milling condensation reaction of different acetophenones and 2-aminopyridines (Scheme 4).

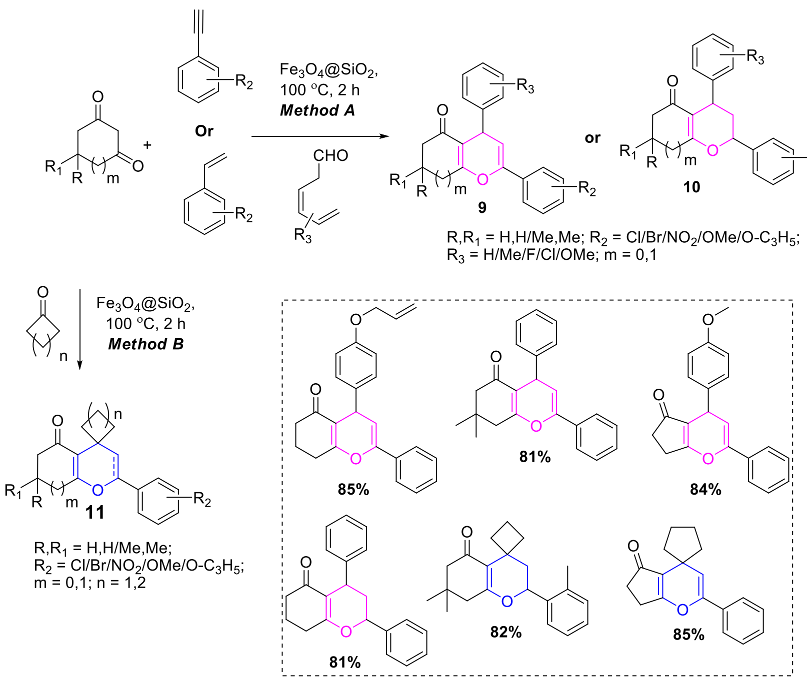
Scheme 5 Plausible mechanistic pathway for I_2 catalyzed DAR of highly functionalized imidazo[1,2-*a*]pyridines



Optimization studies revealed that due to the important role of DMAP in tolerating the HI conversion to I_2, the low product yields have gradually improved to 93%, and the mechanistic investigation has shown that the initial reaction of I_2 with acetophenone leads to *α*-iodoketones, and then reaction with 2-aminopyridine produced quaternary acyl-pyridines. Subsequently, the formation of imines and then dehydration of cyclized products led to imidazo[1,2-a]pyridines **8** as described in Scheme 5. This quantified ball-milling procedure is the most effective and facile procedure for the synthesis of highly functionalized imidazo[1,2-a]pyridines.

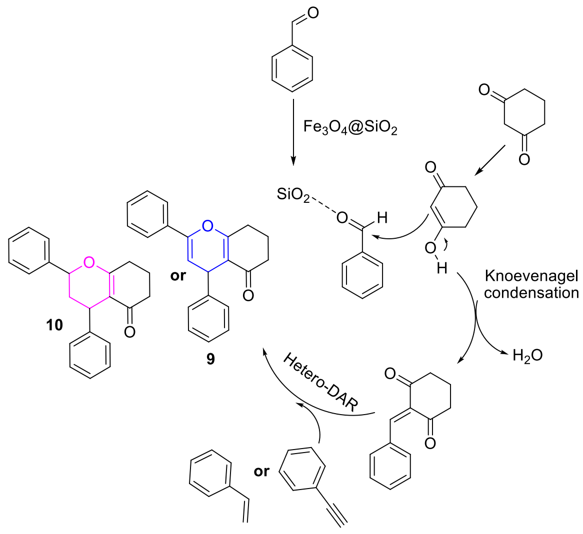
Similarly, Suri et al. [30] reported the facile multicomponent domino Knoevenagel-hetero-DA (DKHDA) procedure for the synthesis of diverse chromenones/dihydrochemenones and spirochromenes (**9–11**) under SF conditions. Initially, the $Fe_3O_4@SiO_2$ catalyst promoted DKHDA reaction of the assorted cyclic-1,3-diketones, and aldehydes with diverse aryl-alkenyls driven to the corresponding chromenones **9** in 72–80% best yields (Scheme 6, Method A). The treatment of styrenes in place of aryl-alkenyls in the identical reaction has afforded the respective dihydrochromenone derivatives **10** with good yields of 75–81%. In addition, the mechanistic study revealed that Fe_3O_4 supported SiO_2 plays an important role in facilitating the Knoevenagel condensation between the enol-form of cyclicketones with aldehydes. Subsequently, the twisted new exocyclic enone-intermediate experienced a thermal [4+2] cycloaddition reaction with aryl-alkenyls or styrenes induced the target chromenones/dihydrochromenones as depicted in Scheme 7. Likewise, the parallel multicomponent SF-DA reaction of various 1,3-diketones, cyclobutanone/cyclopentanones with aryl-alkenyl/styrene derivatives produced the spirochromenes **11** in 73–85% outstanding yields at 100 °C as shown in Scheme 6, Method B. Also, this SF-DA reaction is more advantageous due to its facile synthesis, high-atom economy, short-reaction period, and multicomponent and ecological properties of the catalytic cycles. Therefore, methods similar to the described multicomponent reactions are very advantageous for the synthesis of heterocyclic compounds because they give rise to high regio- and stereoselective products under SF conditions.

Similarly, Ando et al. [31] established an efficient Aerosil® silica (AS®) supported $FeCl_3$ (4 or 10 mol%) catalyzed SF-DA protocol for the cycloaddition of various *p*-benzoquinones with dienes as shown in Scheme 8. Initially, the optimization

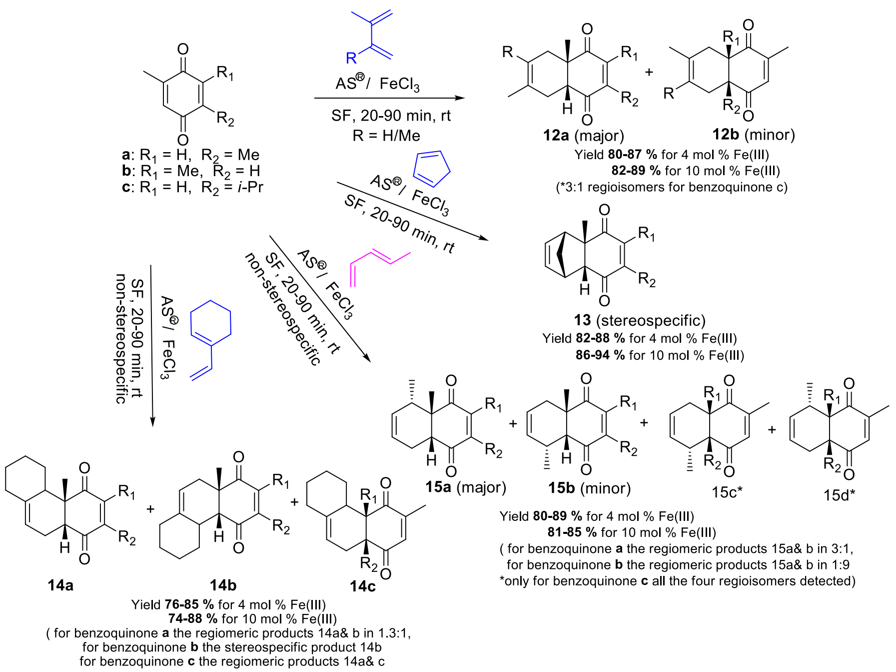


Scheme 6 Solvent-free expedited multicomponent domino Knoevenagel-hetero-Diels–Alder (DKHDA) synthesis of diverse chromenones/dihydrochemenones and spirochromenes

Scheme 7 The thermal Knoevenagel-hetero-[4+2] cycloaddition mechanism for the expedient synthesis of various chromenones/spirochromenes



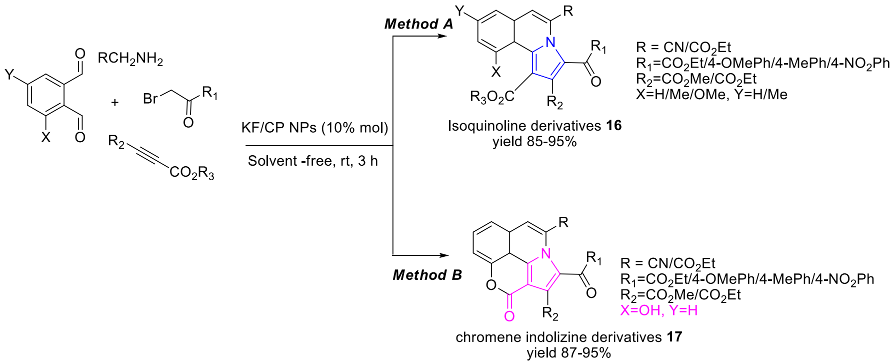
of cycloaddition reactions of *p*-benzoquinones with substituted isoprenes produced a mixture of regioisomers of **12** with satisfactory yields. Optimization studies showed that the catalytic ratio AS®/10 mol% of FeCl$_3$ was significant for enriched yields



Scheme 8 AS®/$FeCl_3$ supported SF-DA protocol for the cycloaddition of various *p*-benzoquinones with dienes.

and reduced reaction time from 96 to 20 h. Subsequently, the reactions of selected *p*-benzoquinones with cyclopentadiene stimulated the stereoselective products **13** in 82–88% yields with AS®/4 mol% Fe(III), and in 86–94% with AS®/10 mol% Fe(III) catalytic cycles. Further, the SF-DA cycloaddition of benzoquinones with 1-vinyl-cyclohexene resulted in non-rational regioisomers with different diastereoselectivity ratios, as shown in Scheme 8. Likewise, the cycloaddition of simple alkyl-substituted benzophenone with *trans*-piperylene yielded the regioselective products **15a&b**, whereas the same reaction with isopropyl-relieved benzophenone furnished four regioselective isomers **15a–d** in the ratio 16:1.5:1.5:1. Thus, the quantified study revealed that the Lewis acid catalyst (AS®/$FeCl_3$) did not have a significant effect on the stereoselectivity of the products, though it demonstrated a reasonable effect on the enriched yields and reaction time with the catalytic load of the Fe(III) molar ratio. Therefore, the AS®/$FeCl_3$-promoted SF-DA cycloaddition method is beneficial and convenient for the synthesis of a variety of molecules due to the wide choice of starting materials and operative yields at room temperature.

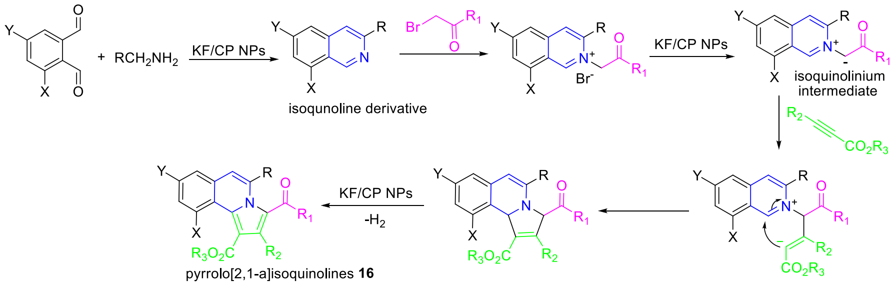
Similarly, Soleimani Amiri et al. [32] proposed an efficient multicomponent one-pot reaction for the expedient synthesis of pyrrolo[2,1-a]isoquinoline **16** and 10-oxo-10*H*-chromeno-[5,4,3-ghi] indolizine-1,4-dicarboxylates **17** under SF conditions, as described in method A, Scheme 9. Primarily, a four-component reaction of phthalaldehyde derivative, primary amine, alkyl bromide and activated acetylenic compounds afforded pyrrolo[2,1-a]isoquinoline derivatives **16** in the presence



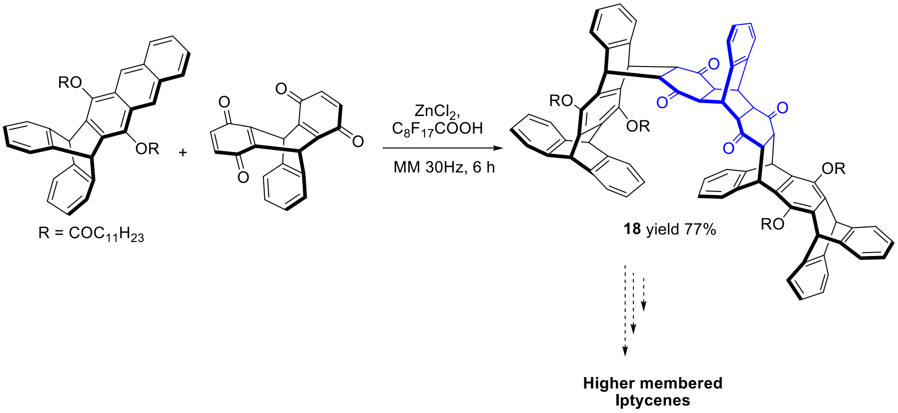
Scheme 9 An efficient one-pot multicomponent reaction for the synthesis of pyrrolo[2,1-a]isoquinoline and 10-oxo-10*H*-chromeno-[5,4,3-ghi] indolizine-1,4-dicarboxylates under solvent-free conditions

of potassium fluoride/clinoptilolite nanoparticles (KF/CN NPs). According to the mechanistic optimization reaction, it was revealed that the reaction proceeded with the formation of a stable isoquinolinium intermediate, followed by imine DA cyclization and dehydrogenation procedures, respectively **16**, as illustrated in Scheme 10. Another four-component reaction of 2-hydroxyphthalaldehyde, primary amine, alkyl bromide, and electron-deficient acetylenic analogues produced the corresponding chromene indolizine derivatives **17** under SF and KF/CN NP catalytic conditions, as shown in method B, Scheme 9, In addition, the synthesized pyrrolo[2,1-a]isoquinolines **16** exhibited excellent antioxidant and catalytic reduction properties against free radicals/metal concentrations.

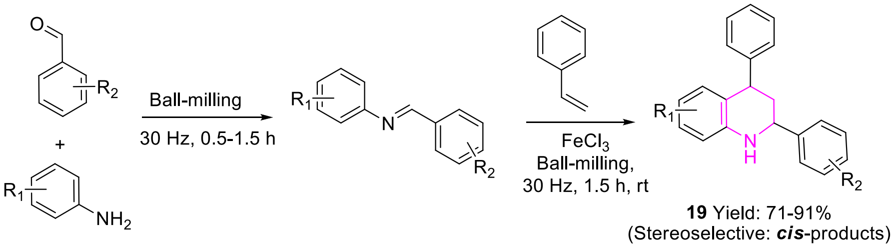
SF mechanochemical DARs are also becoming an efficient approach for the synthesis of highly functionalized molecular structures including iptycenes, polymers, sustainable polyesters, and functionalized nanomaterials. The iptycenes are highly rigid nonlinear three-dimensional frame molecules, and are widely used in purposeful materials such as superconductive polymer films, chemical sensors, molecular machines, supramolecular chemistry, and materials science applications [33, 34]. Zhao et al. [35] reported mechanochemical double-DARs for the generation



Scheme 10 Plausible mechanistic pathway for the expedient synthesis of pyrrolo[2,1-a]isoquinoline analogues



Scheme 11 Solvent-free mechanochemical double-Diels–Alder reactions for the expansion of highly ordered iptycenes

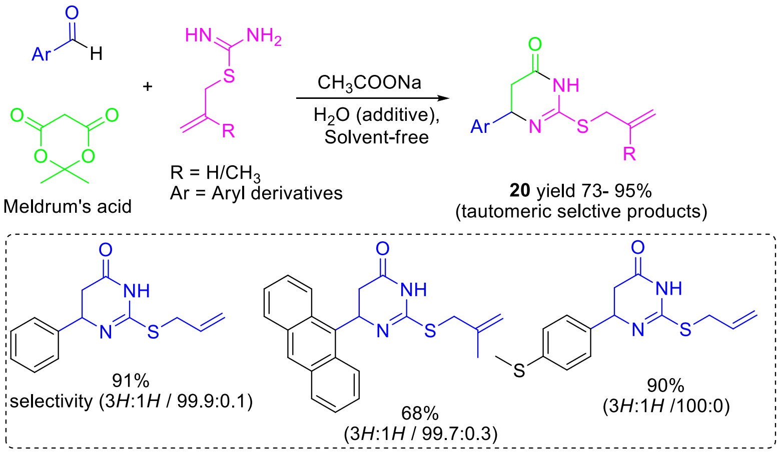


Scheme 12 FeCl$_3$ promoted SF-ball-milling DA-cyclization for stereoselective *cis*-(2e,4e)-diphenyl-1,2,3,4-tetrahydroquinolines

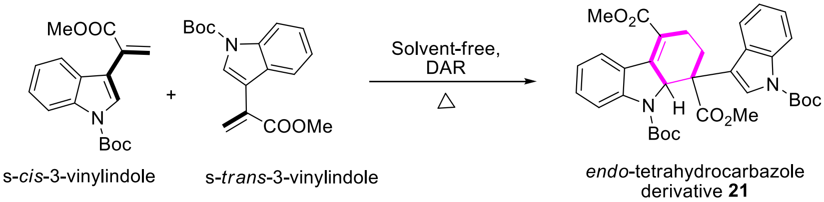
of high-ordered iptycenes **18** under SF conditions with regulatory yields as shown in Scheme 11. This specified mechanochemical synthesis of iptycene is more feasible than other reported methods, as the double-DA anthracene-1,4-diesters with a bifunctional triptycene-diquinone (dienophile) result in highly stereoselective product(s) in 70% good yields with the presence of catalyst ZnCl$_2$ (10 eq.) and an additive C$_8$F$_{17}$COOH (4 eq.). Therefore, the enriched synthesis demonstrated a more efficient path by avoiding the repetitive reaction steps in the assembly of higher members of iptycene-molecular cage structures.

3.1 Stereoselective Catalysis

Tan et al. [36] developed a series of *cis*-2,4-tetrahydroquinolines **19** in 71–91% yields by a FeCl$_3$ promoted SF-ball-milling cyclization of in situ generated *N*-aryl-imidines with styrene at room temperature. Optimization studies revealed that the *cis*-(2e,4e)-diphenyl-1,2,3,4-tetrahydroquinolines **19** (Scheme 12) was achieved in high diastereoselectivity as the reaction continued through the second-order kinetics under SF mechanochemical conditions. While the same



Scheme 13 One-pot tandem solvent-free synthesis of the 5,6-dihydropyrimidin-4(3*H*)-ones as tautomer-selective products

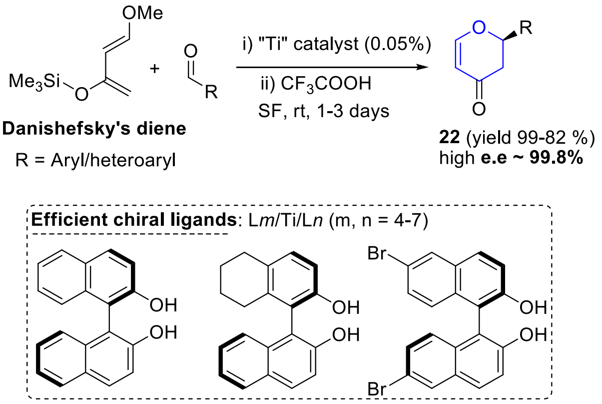


Scheme 14 Stereoselective Diels–Alder dimerization procedure for the synthesis of *endo*-tetrahydrocarbazole

reaction takes place in organic solvents (CH_2Cl_2, THF), the tracer quantities of *trans*-isomer also occur along with major *cis*-products. Therefore, the listed ball-milling procedure is highly efficient and facilities the potent yields of *syn*-substituted tetrahydroquinolines.

Jankovic et al. [37] demonstrated an interesting SF approach to the expedient synthesis of 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones **20** as shown in Scheme 13. The one-pot reaction of Meldrum's acid with various aryl aldehydes and isothiourea derivatives gave rise to the respective dihydropyrimidinones **20** through tandem Knoevenagel, aza-Michael, and retro-DAR procedures. The strategic advantages of this procedure include high tautomeric selectivity (3H ≥ 99.9%) with excellent yields of ~ 95% in SF conditions. Also, optimized isotope (D_2O) labeling studies revealed that the function of water was a proton source in the proposed synthesis.

Valdez-Camacho et al. [38] developed an innovative one-step and second-order DA cyclization procedure for the exclusive *endo*-tetrahydrocarbazole derivative(s) **21** as illustrated in Scheme 14. The optimized DA dimerization between s-*cis* and s-*trans* conformations of 3-vinylindole derivatives gave rise to



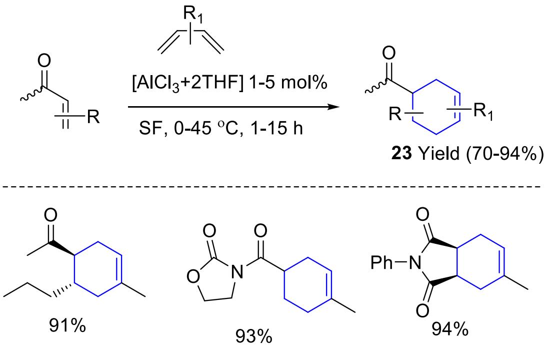
Scheme 15 Solvent-free *asymm*-HDA reaction with 0.05 mol% Lewis acid catalytic load for highly stereoselective dihydropyrones

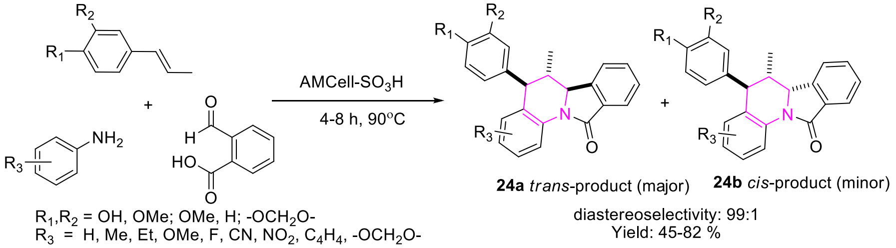
highly stereoselective *endo*-cyclic adducts **21**. The kinetic parameters and stereochemical analysis suggest that the reaction proceeds with a stereoselective single activated (complex) transition state for the *endo*-[4+2] cyclization process. Therefore, it is the most advantageous asynchronous procedure for the efficient total synthesis of various complex natural compounds.

Similarly, Long et al. [39] developed a series of dihydropyrones **22** with high enantioselectivity (~99.8%) using a combinatorial approach-based asymmetric 'Ti'-complex catalysis SF-DAR procedure at 20 °C as described in Scheme 15. Further, the optimized SF-asymmetric-hetero-DA reaction of Danishefsky's diene with assorted aldehydes produced the corresponding stereoselective dihydropyrones **22** in 82–99% yields with 90.8–99.8% enantioselectivity over a 0.05 mol% Lewis acid catalytic ratio. Therefore, the asymmetric-HRD in the presence of chiral-titanium ligands is highly ecological and beneficial for the synthesis of dihydropyrones in an SF state. Likewise, the Lewis acid, i.e., $AlCl_3$, has been acknowledged as an efficient catalyst for the cycloaddition of α,β-unsaturated carbonyl compounds, but affords polymerized products due to uncontrolled reactivity [40]. In this regard, Fringuelli et al. [41] have developed an efficient stoichiometric catalyst of $AlCl_3$/THF (1:2) for the DARs of various dienophiles with isoprene under SF conditions at room temperature. The quantified catalyst $AlCl_3$.2THF is highly selective for the controlled-DA of α,β-unsaturated carbonyl compounds with dienes, resulting in highly regio- and stereoselective products **23** in excellent yields 70–92% as described in Scheme 16.

Merchan Arenas and Kouznetsov [42] reported an efficient three-component-one-pot synthesis of diastereoselective isoindolo[2,1-*a*]quinolin-11-ones **24** in 45–82% yields through an amorphous-milled cellulose sulfonic acid (AMCell-SO_3H) catalyzed SF-DA cascade approach as described in Scheme 17. Mechanistic investigation suggested that an in situ-generated imine product and propenyl-phenols underwent hetero-DA/intramolecular amide cyclization through a *trans*-endo-favored transition state, as shown in Scheme 18. Thus, the AMCell-SO_3H-promoted SF-DA cascade approach promoted high regio- and diastereoselective *trans*-isoindolo[2,1-*a*]

Scheme 16 An efficient stoichiometric $AlCl_3 \cdot 2THF$ catalyzed SF-DA cyclization for regio- and stereoselective cyclohexene derivatives



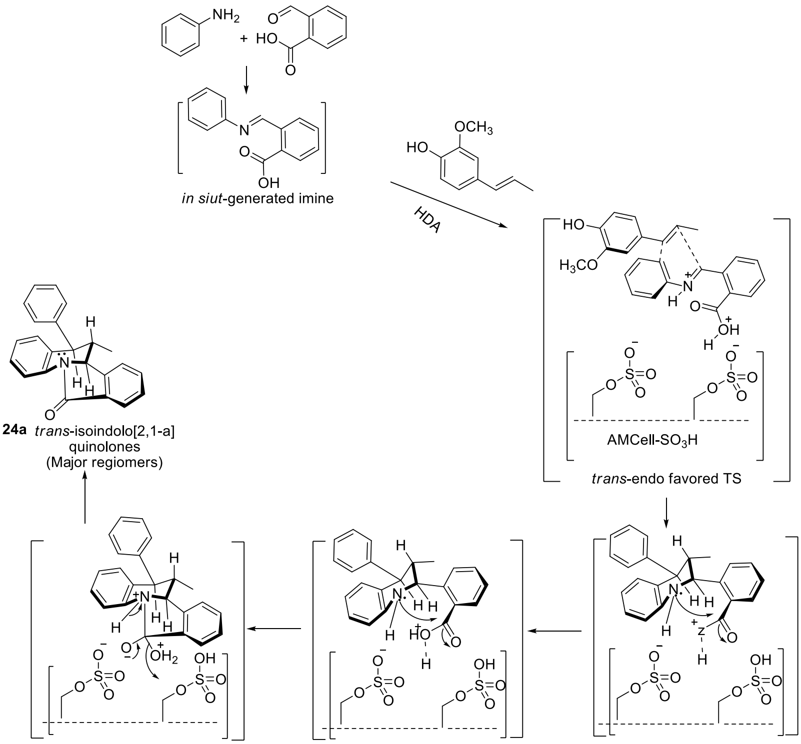


Scheme 17 An efficient one-pot three-component AMCell-SO_3H-catalyzed SF-DA cascade synthesis of diastereoselective isoindolo[2,1-a]quinolin-11-ones

quinolin-11-ones **24a** as major products with a short reaction period of 4–8 h at 90 °C. Thus, it is a striking green-synthesis template for the development of new chemical entities like bioactive natural compounds from lavishly accessible starting materials.

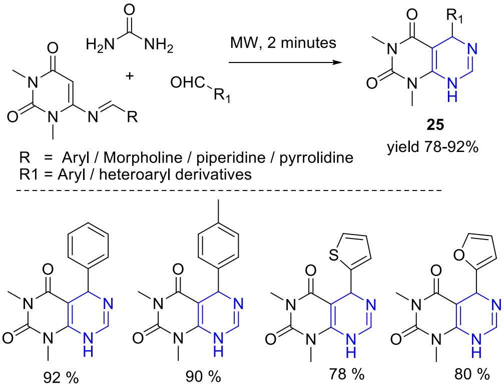
4 EMR Irradiation

In recent years, electromagnetic radiation (EMR) sources such as microwave (MW), infrared (IR), and ultraviolet (UV) irradiation have been widely used for industrial methods of organic synthesis and materials science due to their sustainable and facile-synthetic campaigns [43]. Although EMR practices have been a great success in the synthesis of heterocycles, there are still inadequate applications due to their limitations [44]. However, EMR is a great resource for conducting DA cycloadditions in SF conditions. In this regard, Sarma et al. [45] described an efficient *aza*-DA synthesis of dihydropyrido[4,3-*d*]pyrimidines **25** under SF MW reaction conditions. Optimization study revealed that the in situ generated aryl-imine experienced an *aza*-DA [4+2] cycloaddition with uracil derivatives, which stemmed dihydropyrido[4,3-*d*] pyrimidines **25** as described in Scheme 19. The key advantage of this reaction was that the catalyst- and solvent-free MW reaction procedure produced an optimal yield of 78–92% of the products **25** over a short reaction period of 2 min.

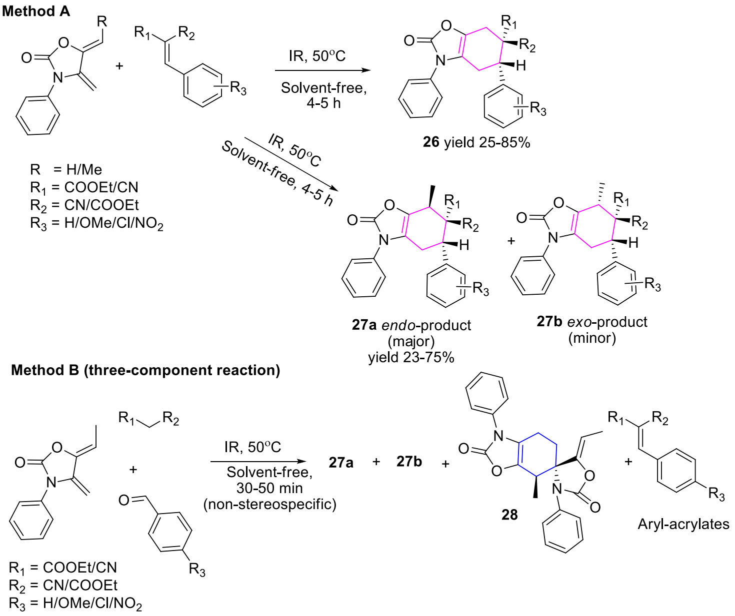


Scheme 18 The mechanistic investigation of *trans*-diastereoselective isoindolo[2,1-*a*]quinolin-11-ones achieved through a hetero-DA/intramolecular amide cyclization of in situ-generated imine with propenylphenols

Scheme 19 A facile SF-MW accustomed *aza*-DA cyclization for expedient synthesis of dihydropyrido[4,3-*d*]pyrimidines



Similarly, Flores-Conde et al. [46] proposed the IR-aided SF-DA cycloaddition of *exo*-2-oxazolidinones (1 equiv.) and aryl-acrylates (1.2 equiv.) for highly stereoselective 3,5-diphenyltetrahydrobenzo[*d*]oxazole-2-ones **26** in 25–85% yields at 50 °C as shown in Scheme 20, method A. However, the equivalent thermal

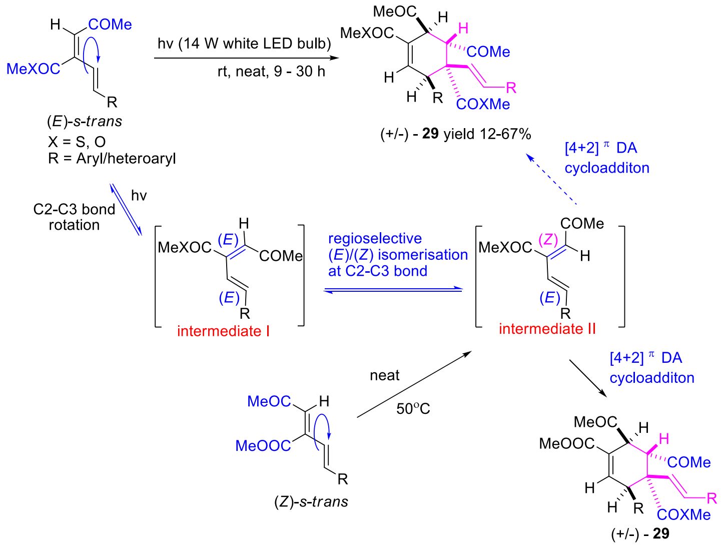


Scheme 20 Solvent-free-IR irradiation assisted DA cycloaddition reaction for 3,5-diphenyltetrahydrobenzo [*d*]oxazole-2-ones

cycloaddition reaction of acrylates with methyl-substituted *exo*-heterocyclic dienes results in a mixture of *endo* and *exo*-cyclo adducts **27a/b** in 55–88% optimal yields over a 4–5 h time period. Also, the substrate substitution patterns have been found to ensure greater influence on the formation of exclusive *para*-endo or *para*-exo cyclic adducts **27a/b**.

Further, the three-component Knoevenagel cascade reaction of aryl-aldehydes and active-methylene derivatives (1:1 molar-equivalence) induced in situ acrylates, to a consecutive DA cycloaddition with *exo*-2-oxazolidinones produced an equal diastereomeric mixture of tetrahydrobenzo[*d*]oxazole-2-ones **27a/b** beside the dimerized-oxazolidinones **28** as described in method B, Scheme 20. Extending the reaction time to 150–240 min produced only a mixture of aryl-acrylates and oxazolidinone dimers **28**. Therefore, optimization studies showed that IR-promoted multicomponent SF-DA reactions are inappropriate for the production of stereoselective tetrahydrobenzo[*d*]oxazole-2-ones, while its controlled reactions are constructive for the favored *para*-endo cyclo adducts **26** and **28**.

Likewise, Naskar et al. [47] anticipated a visible-light promoted cascade rearrangement of 2,4-dienone, which was then dimerized to stereoselective cyclohexenes **29** by SF-DA cycloaddition as illustrated in Scheme 21. However, optimization studies showed that (*E*)-*s*-*trans* on irradiation with visible light/thermal heat (50 °C) underwent (*E*)-*s*-*cis* isomerization via C3–C4 bond-rotation in neat conditions, and further underwent C2–C3 bond (*E*)/(*Z*)-regioselective isomerization to a highly reactive (*Z*)-*s*-*cis* dienone intermediate (II). Subsequently, dimerization of (*Z*)-*s*-*cis*-dienone through [4+2] DA cycloaddition stimulated yields of 12–67%

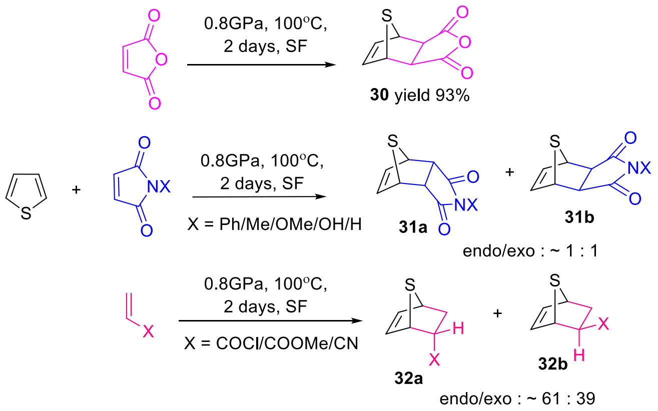


Scheme 21 Visible-light promoted 2,4-dienone regioselective isomerization and succeeding DA cycloaddition for stereoselective cyclohexenes under neat conditions

stereoselective cyclohexenes **29** over a reaction period of 9–30 h. However, the (*Z*)-*s-trans*-dienone also underwent (*E*)/(*Z*)-regioselective isomerization by C2–C3 bonding, resulting in a reactive (*Z*)-*s-cis* dienone intermediate (II) that underwent further dimerization to cyclic adducts **29** in quantifiable yields. The effect of substitutions on C-5 of 2,4-dienones was also observed, for instance, by replacing the aryl/heteroaryl with alicyclic or alkyl groups of substrates, which significantly reduced the yields of cyclic adducts. Therefore, this visible light-promoted dimerization reaction is a more facile and economical process as it entails stereoselective DA cycloaddition at ambient temperature.

5 Thermal-Induced

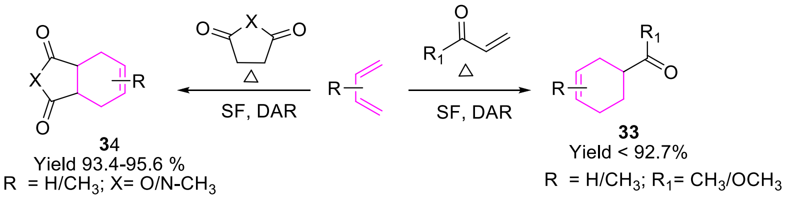
This section describes the applications of DARs under optimal conditions of temperature and pressure, i.e., reactions free from effects of catalyst and solvent interactions. Furthermore, various studies have reported the substantial effects of temperature and pressure on the progression of DARs under neat conditions. For instance, Kumamoto et al. [48] detailed an SF high-temperature- and high-pressure-facilitated DA reaction of thiophene with various dienophiles, as labeled in Scheme 22. The 4:1 ratio of thiophene and maleic anhydride at 0.8 high pressure (GPa) and 100 °C exclusively afforded the *exo*-DA adduct **30** at 93%, and demonstrated greater advantage than solvent medium reaction. However, optimization studies showed that pressure and temperature higher than 0.4–0.6 GPa and 80 °C have a significant effect on the implied yields of DAR products. Correspondingly, the same conditions also facilitate the reaction of thiophene with maleimides and acrylic dinophiles,



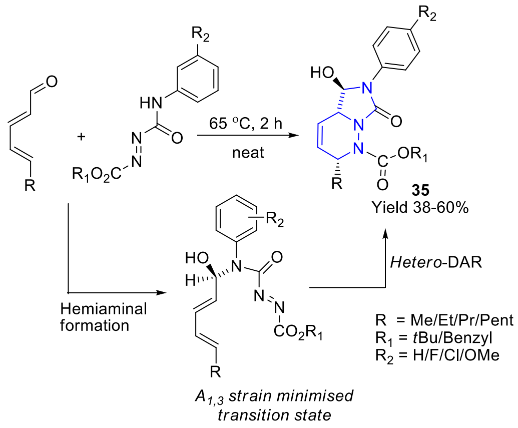
Scheme 22 High–temperature and pressure-assisted SF-DA reaction of thiophene with assorted dienophiles

respectively, to non-stereoselective (endo/exo) ratio products **31a-b** and **32a-b**, as shown in Scheme 22. The study also revealed the polymerization of acrylic dienophiles at high temperature and pressure. However, the quantified study is advantageous because the high pressure and temperature DA reaction facilitates significant yields of dienophiles, which do not react under solvent conditions.

Similarly, Sun et al. [49] reported high yields of cyclohexene adducts by a closed-batch SF-DAR of substituted diene with various dienophiles including methyl vinyl ketone, methyl acrylate, and maleic anhydride, as illustrated in Scheme 23. Further, optimization studies showed that SF reactions persist through exothermic energy synchronization, resulting in more cost-effective yields of cyclic adducts **33** and **34** than solvent-mediated reactions. Also, the study suggested that appropriate temperature and pressure facilitate the high selectivity of DA cyclization under SF conditions. Likewise, Crouillebois et al. [50] demonstrated a facile and SF procedure for tetrahydroimidazo[1,5-*b*]pyridazine-1(2*H*)-carboxylate hybrids **35** through hemiaminal formation and hetero-DAR route as depicted in Scheme 24. Optimization studies revealed that high diastereoselectivity of **35** was attained as the intramolecular-DA reactions continued through an allylic strain-minimized transition ($A_{1,3}$). Moreover, significant effects of alkyl chain lengths of both diene and dienophiles



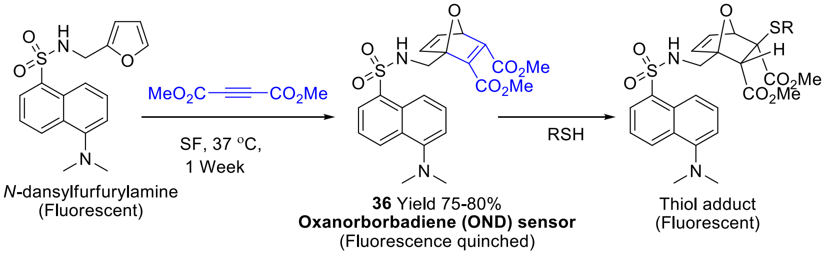
Scheme 23 Closed batch solvent-free DA reactions of assorted dienes and dienophiles for the accessible yields of cyclohexene derivatives



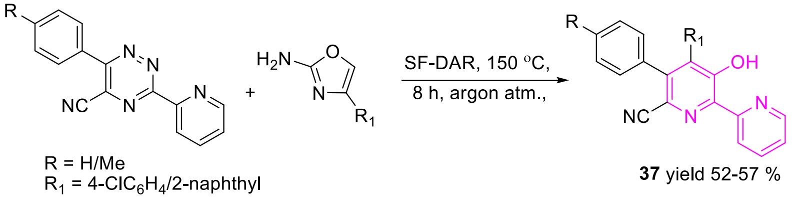
Scheme 24 A facile hetero-Diels–Alder reaction procedure for diastereoselective tetrahydroimidazo[1,5-b]pyridazine-1(2*H*)-carboxylate hybrids under neat condition

on the yields of bicyclic products **35** were also observed. Also, a key advantage of the proposed hetero-DA reaction is high-regio- and diastereoselective products **35** in efficient yields 10–67% over a catalyst-free and SF procedure. Further, Patterson et al. [51] developed the room-temperature SF-DA reaction mechanism for thiol-reactive fluorogenic sensor **36**, as presented in Scheme 25. The quantified oxanorbornadiene (OND) sensor is highly reactive with thiol-containing biomolecules and is therefore beneficial for protein labeling(s) like *N*-acetylcysteine, serum albumin, and human hair samples. Therefore, the foregoing synthesis route serves as a template for the development of imminent sensor(s) for real-time applications.

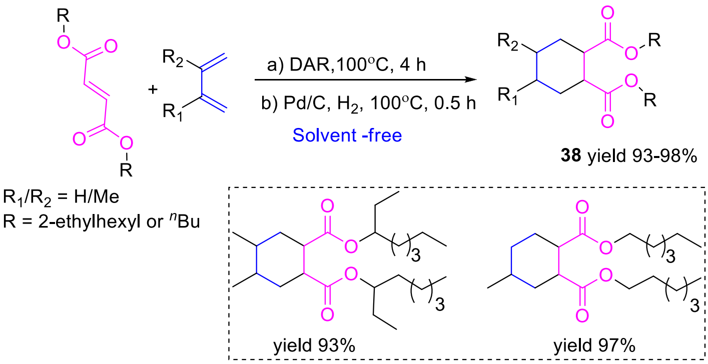
Likewise, Krinochkin et al. [52] demonstrated an SF inverse electron demand DAR (IEDDA) route for the expedient synthetic of 3-hydroxybipyridines over a neat



Scheme 25 A facile solvent-free DA reaction method for an expedient fluorogenic sensor

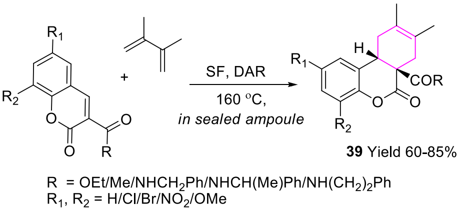


Scheme 26 A solvent-free inverse electron demand Diels–Alder reaction protocol for the expedient synthesis of 2,2′-bipyridine-3-ols



Scheme 27 One-pot tandem SF-DA cyclization and hydrogenation approach for the synthesis of 1,2-cyclohexenedicarboxylates as safe plasticizers

Scheme 28 A solvent-free thermal [4+2] DA cyclization procedure for tricyclic coumarene-carboxylates

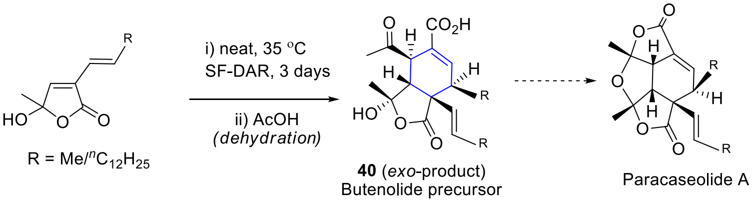


condition reaction, as demonstrated in Scheme 26. A high-temperature 150 °C striving coupling of 3-(pyridin-2-yl)-1,2,4-triazine-5-carbonitriles (diene) with 2-amino-4-aryoxazole (dienophile) afforded 3-hyroxy-2,2′-bipyridine-6-carbonitrile **37** in 52–57% efficient yields through the IEDDA reaction pathway. This documented protocol is very humble to produce the rare and pharmacologically essential 2,2′-bipyrine-3-ols over a controlled reaction procedure.

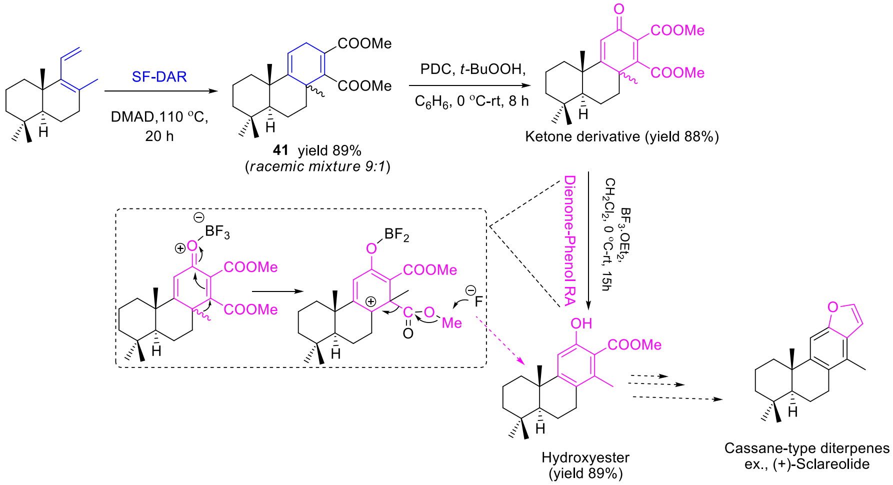
Hu et al. [53] also demonstrated an efficient one-pot DAR and Pd/C-catalyzed hydrogenation of bio-based fumarates and 1,3-dienes ensued 1,2-cyclohexanedicarboxylates with excellent yields in SF conditions as described in Scheme 27. Further, hydrogenated 1,2-cyclohexenedicarboxylates **38** have been found to be promising plasticizers for the polyvinylchloride (PVC)/polymer industry. Optimized biological experiments also showed that the analogues **38** are beneficial as safe/non-toxic plasticizers for human/environmental applications.

6 Natural Products

In addition, DA cyclization plays an increasing role in the synthesis of natural chromophores, including bicyclic, tricyclic, polycyclic, macrocyclic, and spirocyclic scaffolds and their hybrids [1]. The current review also presents some SF-DA examples to illustrate their importance. Flores-Larios et al. [54] demonstrated a facile SF-DA cyclization procedure for the synthesis of tricyclic coumarine-carboxylates



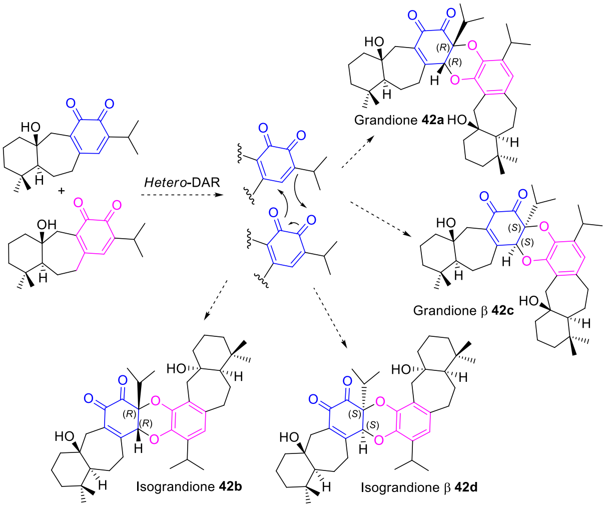
Scheme 29 A SF-DA cyclization method for the development of butenolide precursor **40** of paracaseolide A



Scheme 30 An efficient solvent-free DA cyclization route for the expansion of hydroxy ester, a precursor of cassane-type furan diterpenes

39 with convincing yields of 60–85%, as revealed in Scheme 28. Molecular and spectral optimization studies revealed that the cyclized DA adducts **39** were twisted through a *cis*-fusion pattern of diene and dienophiles. Similarly, Wang and Hoye [55], described a neat conditioned SF bis-pericyclic [4+2] dimerization route for the development of the butenolide precursor **40** of the natural scaffold paracaseolide A, as illustrated in Scheme 29. Therefore, the proposed synthesis is the simplest non-enzyme dimerization procedure that facilitates stereoselective precursor **40** exclusively by the ideal lowest energy *exo*-bis-pericyclic transition state.

Likewise, Zentar et al. [56] demonstrated a competent route for the expansion of terpenoid precursor **41** of cassane-sort natural diterpene(s) through SF-DA cyclization and decarboxylative dienone-phenol procedures, as illustrated in Scheme 30. Compared with earlier approaches, this procedure was more effective, as the DAR of a diene with dimethyl acetylenedicarboxylate (DMAD) resulted in the desired cyclic adduct **41** (9:1 epimeric-mixture) under mild SF reaction conditions at 110 °C over a 20 h period. Subsequently, the cyclic adduct **41** was converted to a good yield of ketone derivative with a catalytic pyridinium dichromate

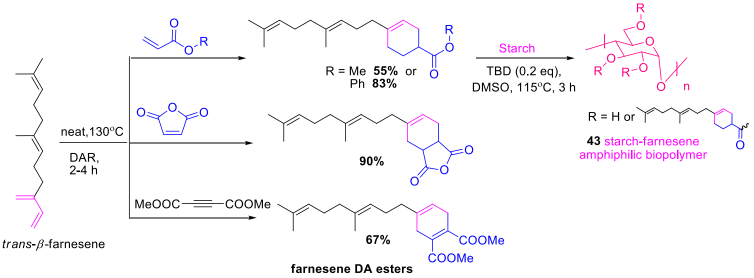


Scheme 31 A theoretical biosynthetic *hetero*-DA approach for the synthesis of icetexane diterpene-dimer grandione

(PDC)/*t*-BuOOH oxidation process. In addition, the treatment of dienone with Lewis acid (BF_3.OEt_2) promoted methyl-migration, followed by decarboxylation to afford the hydroxy ester product by a dienone-phenol rearrangement. Therefore, the quantified SF procedure of DA cyclization and dienone-phenol RA was an expedient route to access the hydroxy ester, which is an important precursor to cassane-type furan diterpene synthesis.

Quijano-Quinones et al. [57] demonstrated a tandem hetero-DA biosynthetic approach for the synthesis of icetexane diterpene-dimer grandione in a density functional theory (DFT) mechanistic theoretical study. The dynamic strategies of the proposed synthetic approach involve the establishment of a key bicyclic adduct via hetero-DAR and the subsequent *domino*-Claisen rearrangement for the stereo- and region-selective products **42a–d** as illustrated in Scheme 31. The premeditated transition-state energy barriers are also recommended for the viability of a tandem reaction mechanism for the expansion of the diterpene dimer grandione. Therefore, the quantified reactions like one-pot hetero-DAR/dominone-Clasien rearrangement are highly facile and economical for complex heterocycles/natural scaffold synthesis.

Similarly, Orzolek et al. [58] revealed a stimulating method for starch-farnesene amphiphilic biopolymer **43** synthesis, as illustrated in Scheme 32. Initially, the *trans*-*β*-farnesene was transformed into esterified products with assorted dienophiles by a high-yielding SF-DA procedure. Subsequently, the transesterification of farnesene DA esters with starch by the catalyst 1,5,6-triazabicyclo[4.4.0]dec-5-ene [TBD] induced amphiphilic biopolymers with high desirability. The key advantages of the this process are the SF state and strategic approach for new biorenewable materials like polysaccharide substrates. Moreover, optimization studies showed that the biopolymer **43** was thermally stable at 250 °C and mechanically nominal as biodegradable material.

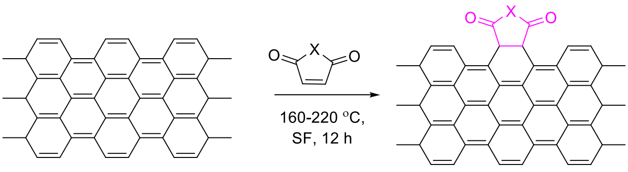


Scheme 32 Facile synthesis of starch-farnesene amphiphilic biopolymers as biorenewable materials through SF-DAR and transesterification approaches

7 Material Applications

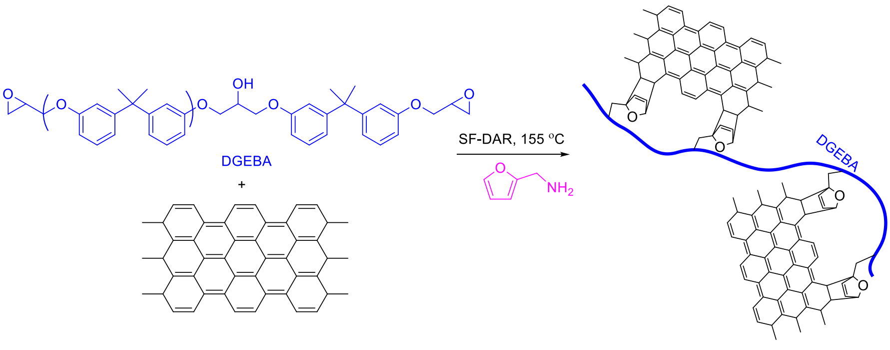
Over the past decade, the DAR under thermal conditions has evolved into a highly advantageous approach for the expansion of functionalized materials such as π-extended fullerenes [59, 60], nanomaterials (carbon nanotubes, nanofibers) [61–63], and graphene materials [64]. The π-extended materials have sluggish charge recombination strategies and enable efficient charge separation, and are thus promising materials for light to energy conversion (solar cells, thin films), fluorescent materials and conducting materials [65]. To this end, Seo and Baek [64] demonstrated a thermally driven SF approach to the development of graphite nanosheets with polar groups. The heating of a mixture of graphite and dienophile (maleic anhydride/maleimide) in an argonated sealed glass ampoule afforded the [4+2] cyclized stable product **44** as depicted in Scheme 33.

Oh et al. [62] also established a facile and SF-DA cyclization procedure for the development of enriched graphene-nanocomposite materials **45** as illustrated in Scheme 33. The graphene-epoxy-resin nanocomposite surface was attained through an in situ DA cyclization route by heating the graphene-nanoplate blend and furfurylamine of bisphenol A-based epoxy resin (DGEBA) in a Teflon mold at 70 °C as shown in Scheme 34. Therefore, the molded GNP/EP nanocomposite surface **45** was valuable and highly stable with enhanced mechanical and thermal characteristics. The same group of authors [63] has also proposed another identical in situ DA cyclization procedure for the development of graphene-nanoplate/polyurethane nanocomposite (GNP/PU) surface **45** under neat conditions.



44 X = O/NH

Scheme 33 Schematic SF-DA cyclization route for the expansion of covalent functionalized graphite nanosheets

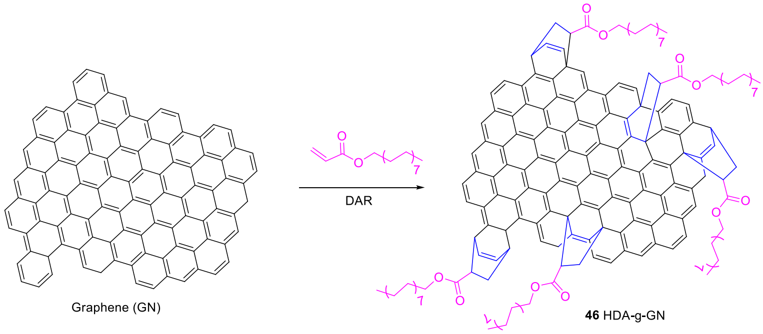


45 GNP/EP nanocomposite surfaces

Scheme 34 A solvent-free DA cyclization route for the development of graphene-nanoplate/epoxy nanocomposite surface composite surface

Additionally, the surface morphology and mechanical characterization studies have illustrated that the thermally self-healing nanocomposite surface materials are advantageous for latent polymer and conducting material applications.

Cao et al. [66] established a facile procedure for the hexadecyl acrylate-grafted-graphene (HAD-g-GN) **46** through SF-DA of HAD over graphene surface as described in Scheme 35. Optimization studies of the phase-change material HAD-g-GN **46** showed that it is thermally stable and had excellent electro-to-thermal conversion performance. Thus, it expands into real-time-resolved applications such as energy storage devices, thermal management systems, and biomedical devices.



46 HDA-g-GN

Scheme 35 A facile SF-DA cyclization method for the expedient synthesis of hexadecyl acrylate-grafted-graphene (HAD-g-GN) as multi-responsive phase-change material (PCM)

8 Conclusions

In summary, the DA cycloaddition has tremendous utility in the synthesis of stereo- and regioselective products confined in the SF state. In the absence of solvent interactions (solvent-free) under neat conditions, the effects of temperature and pressure on reactants are significant. Additionally, the formation of by-products and toxic waste is reduced in SF reactions owing to the high selectivity of SF-DARs. Thus, the expedient DA cyclization of natural and heterocyclic compounds provides the best yields with greater selectivity under SF conditions. In view of the importance of sustainable SF-DAR, it is a promising approach for the expanded development of functionalized materials such as nanomaterials, polymeric nanofibers, and graphene nanocomposites. Moreover, SF-DA cyclization shows a potential role in the synthesis of complex natural compounds for pharmacological applications. Thus, the materials highlighted in this review have stimulated the development of ecologically benign synthetic procedures in parallel with SF-DAR for practical drug development and material applications.

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Author Contributions The authors AR and APK conceived the study and collected the literature associated with the review. AR, APK, and AFK performed the manuscript writing and analysis of the data. DSK and GVZ supported with their attentive discussions and advice to fulfill this study. The final version of the manuscript was submitted after it had been read and approved by all authors.

Declarations

Conflict of interest The authors declare that they have no competing interests related to this article.

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