1

Glycerol as Eco-Efficient Solvent for Organic Transformations

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1.1 Introduction

Organic solvents are used in the chemical and pharmaceutical industries [1]. The global demand for these solvents has reached 20 million metric tons annually [2]. Solvents are unreactive supplementary fluids that can dissolve starting materials and facilitate product separation through recrystallization or chromatographic techniques. In a reaction mixture, the solvent is involved in intermolecular interactions and performs the following: (i) stabilization of solutes, (ii) promoting the preferred equilibrium position, (iii) changing the kinetic profile of the reaction, and (iv) influencing the product selectivity [3]. Selection of appropriate solvents for organic transformations is important to develop green synthesis pathways using renewable feedstock. In the past two decades, green methodologies and solvents have gained increasing attention because of their excellent physical and chemical properties [4–6]. Green solvents should be non-flammable, biodegradable and widely available from renewable sources [7].
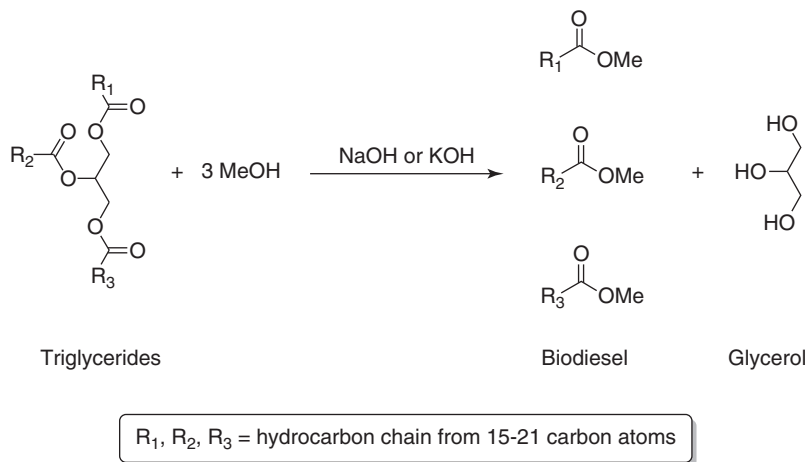
Figure 1.1 Reaction for biodiesel production.

Biodiesel production involves simple catalytic transesterification of triglycerides under basic conditions (Figure 1.1) [8]. This process generates glycerol as a by-product (approximately 10% by weight). The amount of glycerol produced globally has reached 1.2 million tons and will continue to increase in the future because of increasing demand for biodiesel [9]. Glycerol has more than 2000 applications, and its derivatives are highly valued starting materials for the preparation of drugs, food, beverages, chemicals and synthetic materials (Figure 1.2) [10].

The biodiesel industries generate large amounts of glycerol as a by-product. As such, the price of glycerol is low, leading to its imbalanced supply. Currently, a significant proportion of this renewable chemical is wasted. This phenomenon has resulted in a negative feedback on the future economic viability of the biodiesel industry and adversely affects the environment because of improper disposal [11]. In this regard, the application of glycerol as a sustainable and green solvent has been investigated in a number of organic transformations (Table 1.1). Glycerol is a colourless, odourless, relatively safe, inexpensive, viscous, hydroscopic polyol, and a widely available green solvent. Glycerol acts as an active hydrogen donor in several organic reactions. Glycerol exhibits a high boiling point, polarity and non-flammability and is a suitable substitute for organic solvents, such as water, dimethylformamide (DMF) and dimethylsulfoxide (DMSO). Thus, glycerol is considered a green solvent and an important subject of research on green chemistry. This review provides new perspectives for minimizing glycerol wastes produced by biomass industries.

Our research group has contributed a comprehensive review on green and unconventional bio-based solvents for organic reactions [12]. However, enthusiasm for using glycerol as a green solvent for organic transformations in particular continues to increase. The present paper thus summarizes recent developments
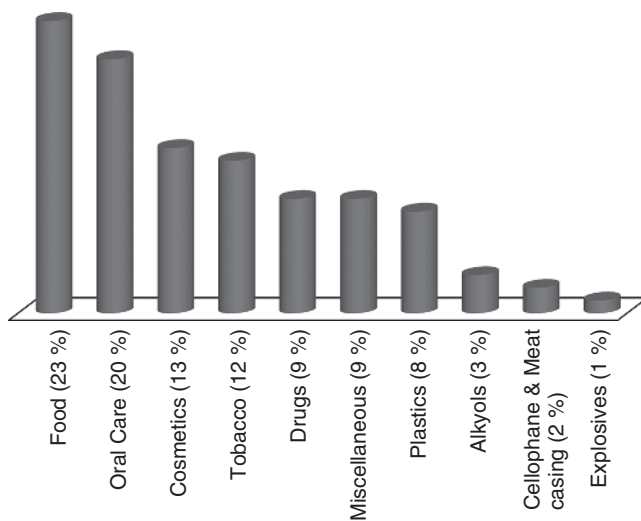
Figure 1.2 Commercial consumption of glycerol (industrial sectors and volumes). (A colour version of this figure appears in the plate section.)

Table 1.1 *Physical, chemical and toxicity properties of glycerol.*

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Melting point	17.8°C
Boiling point	290°C
Viscosity (20°C)	1200 cP
Vapour pressure (20°C)	<1 mm Hg
Density (20°C)	1.26 g cm^{-3}
Flash point	160°C (closed cup)
Auto-ignition temperature	400°C
Critical temperature	492.2°C
Critical pressure	42.5 atm
Dielectric constant (25°C)	44.38
Dipole moment (30–50°C)	2.68 D
LD$_{50}$ (oral, rat)	12600 mg kg^{-1}
LD$_{50}$ (dermal, rabbit)	>10 000 mg kg^{-1}
LD$_{50}$ (rat, 1 h)	570 mg m^{-3}

on metal-free and metal-promoted organic reactions in glycerol between 2002 and 2016.

## 1.2   Metal-Free Organic Transformations in Glycerol

The synthesis of complex organic molecules utilizes harsh reaction conditions, expensive reagents and toxic organic solvents. Most organic transformations use expensive metal catalysts, such as Pd(OAc)$_2$, PdCl$_2$, PtCl$_2$ and AuCl$_2$.

The drawbacks of metal-promoted organic reactions are categorized into the following: (i) isolation and reuse of catalysts, (ii) lack of catalytic efficiency in the second usage, and (iii) disposal of metal catalysts. Over the past three decades, both industrial and academic chemists have continuously explored suitable methodologies, such as the use of green solvents. The chemical synthesis of glycerol as a sustainable solvent has gained wide attention because it provides valuable chemical scaffolds. Sugar fermentation produces glycerol either directly or as a by-product of the conversion of lignocelluloses into ethanol. Glycerol promotes this reaction without requiring any metal catalysts because of its excellent physical properties. Moreover, glycerol is widely available from renewable feedstock and is thus an appropriate green solvent for various reactions [13].

Quinoxaline, benzoxazole and benzimidazole derivatives can be synthesized using different methods; these molecules are commonly prepared through the condensation reaction of aryl 1,2-diamine with 1,2-dicarbonyl compounds [14, 15]. Bachhav *et al.* [16] developed an efficient, catalyst-free and straightforward method for synthesis of quinoxaline, benzoxazole and benzimidazole ring systems in glycerol; the yield is higher than those of conventional methods. The substrates 2-aminophenol and benzaldehyde are used as counter-reagents for the preparation of 2-arylbenzoxazoles (**1**). This reaction was tested in different solvent systems, but the desired products were not obtained and only glycerol efficiently promoted the reaction (Scheme 1.1). Radatz *et al.* [17] reported the same condensation reaction between 1,2-diamine and 1,2-dicarbonyl compound for the synthesis of benzodiazepines and benzimidazoles; the catalyst-free condensation reaction between *o*-phenylenediamine and benzaldehyde in glycerol produces benzimidazoles (**2**). The reaction between *o*-phenylenediamine and ketones produces benzodiazepines (**3**) when using glycerol as solvent. Furthermore, glycerol can be easily recovered and reused for condensation. However, at the fourth time of using glycerol, it starts to lose its activity (Scheme 1.2).
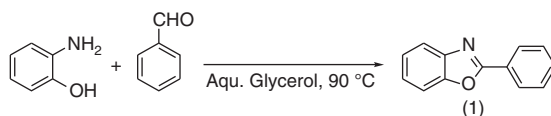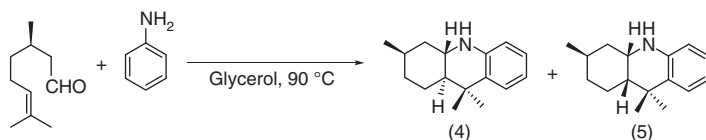

**Scheme 1.1**   Catalyst-free selective synthesis of 2-phenylbenzoxazole.
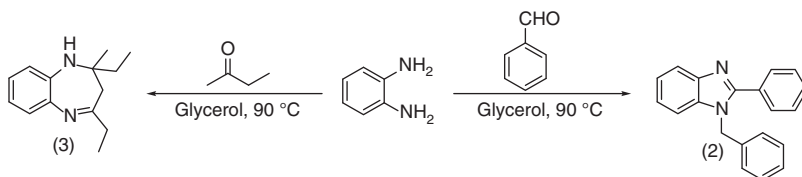
Scheme 1.2   Green synthesis of benzimidazoles and benzodiazepines in glycerol.

Nascimento *et al.* [18] used a similar kind of methodology for one-pot hetero-Diels–Alder reaction between (*R*)-citronellal and substituted arylamines; glycerol was used as a green, sustainable and recyclable solvent for the catalyst-free reaction and functioned as a model substrate to produce octahy-droacridines (**4,5**) at high percentage yields with an isomeric product ratio of 46 : 54. The reactions proceeded without using acid catalysts (Scheme 1.3). Somwanshi *et al.* [19] developed a catalyst-free one-pot imino Diels–Alder reaction, with aldehydes, amines and cyclic enol ethers as model substrates to prepare the desired furano- and pyranoquinolines (**6**). 3,4-Dihydro-2*H*-pyran was used to prepare pyranoquinolines, and the mixture was obtained as endo-isomers, exo-isomers and errandendo-diastereomers; when furans were used as reagents, a single isomeric product is produced. Glycerol can be used as a sustainable solvent and leads to more efficient reactions than those using other organic solvents (Scheme 1.4).

Cabrera *et al.* [20] confirmed that glycerol is an efficient solvent for the oxidation of aromatic, aliphatic and functionalized thiols under microwave conditions. The oxidation reactions proceeded quickly, and the preferred disulfides (**7**) were obtained in good to excellent yields. Thiophenol, a strong nucleophile, was used as model substrate, and sodium carbonate, an inorganic base, was used as catalyst. Glycerol was easily recovered and used for further oxidation of thiols (Scheme 1.5). Zhou *et al.* [21] reported the condensation reaction between
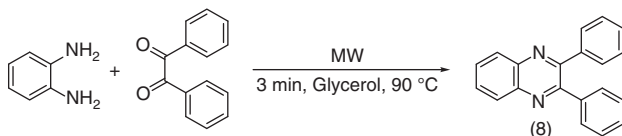

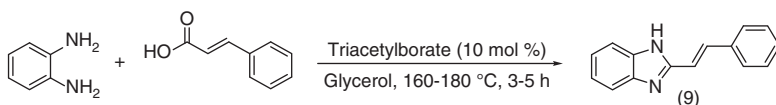**Scheme 1.3**   Catalyst-free synthesis of isomeric mixtures of octahydroacridines.
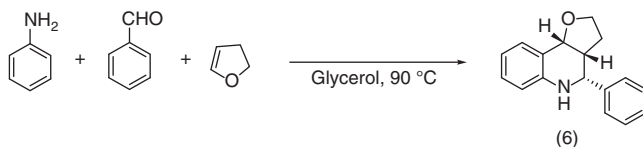
Scheme 1.4   One-pot synthesis of furanoquinolines by green method.
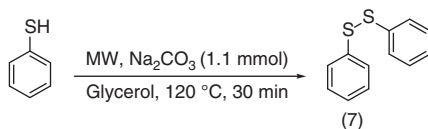
Scheme 1.5   Microwave-assisted synthesis of phenyl disulfide.

Scheme 1.6   Green synthesis of 2,3-diphenyl-quinoxaline in glycerol.


**Scheme 1.7**   Triacetylborate-catalysed green synthesis of 2-styryl-1*H*-benzimidazole.

1,2-diamines and 1,2-dicarbonyl compounds for synthesis of quinoxaline derivatives in glycerol at 90°C for 3 minutes without adding inorganic salts; the desired product (**8**) exhibited a high degree of purity (Scheme 1.6).

The synthesis of benzimidazole scaffolds has attracted wide interest because of their biological activities. Taduri *et al.* [22] performed a green synthesis of 2-heterostyrylbenzimidazole derivatives. The condensation reaction between *o*-phenylenediamine and 3-phenylacrylic acid in glycerol was catalysed by 10 mol.% triacetylborate and produced the desired bicyclic benzimidazoles (**9**) (Scheme 1.7). The mechanism of condensation involves the reaction between triacetylborate and glycerol to form an intermediate by trailing two acetate units; the intermediate accepts electrons from the oxygen atom of cinnamic acid and reacts with *o*-phenylenediamine, which undergoes intramolecular cyclization to form the final product (**8**).

N-Aryl phthalimide derivatives are important organic skeletons applied in biology and electronics because of their structural arrangements. Lobo *et al.* [23] reported that glycerol promoted the synthesis of *N*-aryl phthalimide; the model reaction was conducted with dehydrative condensation of phthalic anhydride and aryl nucleophile in glycerol to produce the desired *N*-aryl phthalimides (**10**) with high yield. Deep eutectic solvents, such as choline chloride : malonic acid/urea (1 : 1, v/v), were also efficient solvents and catalysts for this reaction system (Scheme 1.8).
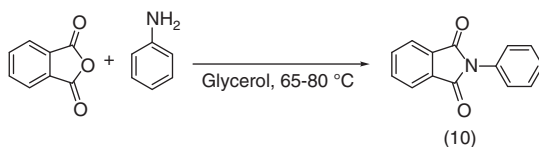
Scheme 1.8   Glycerol-mediated synthesis of *N*-aryl phthalimides.
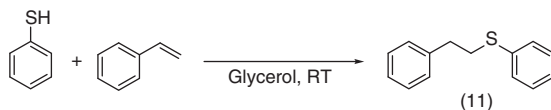
Scheme 1.9   Metal-free synthesis of thioethers at room temperature.
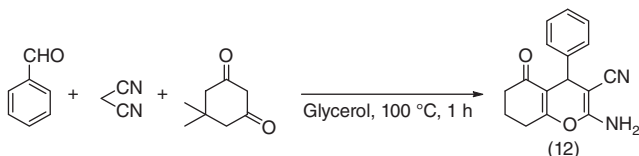

Scheme 1.10   Green synthesis of 4*H*-pyrans.

In the synthesis of linear thioethers, glycerol was used as an efficient and recyclable solvent for addition of thiols to non-activated alkenes [24]; the mock-up reaction was performed with styrene and thiophenol in glycerol at room temperature or under heating conditions to produce the desired thioethers (**11**) with 94% yield. Glycerol is considered a renewable and non-toxic solvent because of its excellent physical and chemical properties. This solvent can be utilized in green methods to effectively synthesize novel thioeugenols with antioxidant activities (Scheme 1.9).

Safaei *et al.* [25] used glycerol, a biodegradable and reusable medium, as solvent for one-pot three-component synthesis of 4*H*-pyrans under catalyst-free conditions, with benzaldehyde, dimedone and malononitrile as model substrates; the reaction follows the tandem Knoevenagel condensation and Michael-like addition in glycerol to produce the desired product 4*H*-pyrans (**12**). Solvents such as poly(ethylene glycol) 400 (PEG400), ethylene glycol and water also exhibited high product yields (83%, 80% and 71%, respectively) (Scheme 1.10). Shekouhy and co-workers [26] used the same reaction to synthesize simple urazole derivatives within a short reaction period; the model multi-component reaction utilized benzaldehyde condensed with *N*-phenyl urazole and an active methylene compound (dimedone) in glycerol to produce 94% of the desired urazole derivative (**13**). Glycerol plays an important role, that is, its polar amphoteric hydroxyl groups easily react with weakly acidic and basic components in the reaction because hydrogen bonds stabilize the intermediates (Scheme 1.11).

Thurow *et al.* [27] synthesized arylselanylanilines, which are important medicinal scaffolds and molecular skeletons. This synthesis was realized by the reaction between *N,N*-dimethylaniline and phenylselanyl chloride in glycerol, resulting in 99% yield of the desired product (**14**). In this Mannich-type reaction, *N,N*-dimethylaniline as nucleophile attacks phenylselanyl chloride at the *para*-position to form the intermediate aryliminium, which undergoes proton
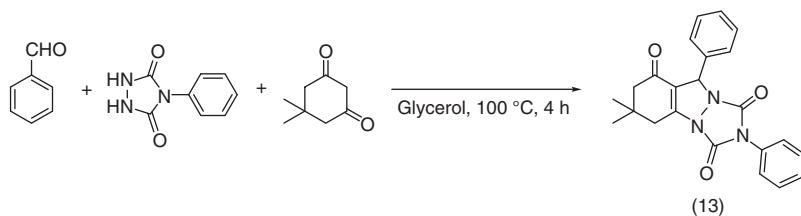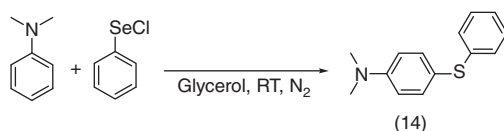
Scheme 1.11   Glycerol-promoted synthesis of triazolo[1,2-*a*]indazole-triones.

elimination to produce the desired compound (**14**). Glycerol plays a unique role in the reaction because it stabilizes the hydrogen bonds with the iminium intermediate (Scheme 1.12).

Vanillin semicarbazone derivatives are potent molecules for the treatment of antimicrobial diseases and are abundant in natural products [28, 29]. Jovanović *et al.* [30] synthesized vanillin and semicarbazone derivatives through green carbonyl–amine condensation; the reaction used vanillin and semicarbazone in glycerol solvent and was performed at 65°C for 20 minutes to produce the desired Schiff base (**15**). The same reaction conducted in ethanol provided high yield, that is, 72% of the desired vanillin semicarbazone, but required strong acid catalysts, such as sulfuric acid (Scheme 1.13).

A recent study elaborated a well-organized, green synthesis of 1-amidoalkyl-2-naphthols (**16**) through one-pot three-component condensation of aromatic aldehydes, acetamide and 2-naphthol, in glycerol solvent, with glycerosulfonic acid as catalyst (Scheme 1.14). The interaction of glycerosulfonic
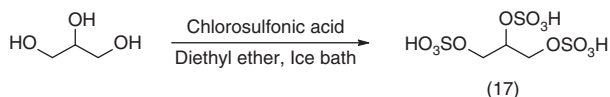

Scheme 1.12   Synthesis of dimethyl-(4-phenylsulfanyl-phenyl)-amine.
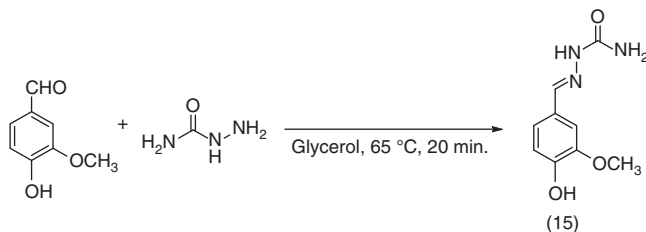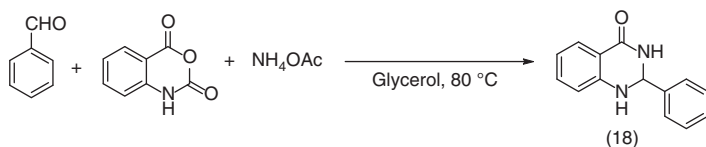

Scheme 1.13   Catalyst-free green protocol for synthesis of vanillin semicarbazone.
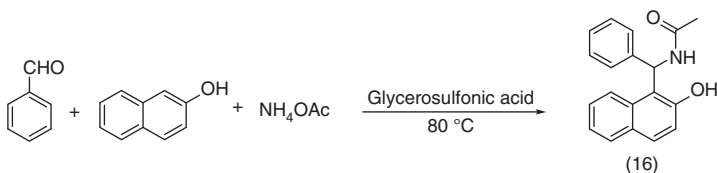
Scheme 1.14 Glycerosulfonic acid-promoted synthesis of 1-amidoalkyl-2-naphthol.

***Scheme 1.15*** Preparation of glycerosulfonic acid.

Scheme 1.16 Synthesis of 2,3-dihydroquinazoline-4(1*H*)-one.

acid with chlorosulfonic acid in diethyl ether produced compound (**17**) (Scheme 1.15). A simple method for one-pot three-component synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones (**18**) has also been established using isatoic anhydride, aldehydes and ammonium acetate as model substrates in glycerol as green catalyst and solvent (Scheme 1.16). Thus, glycerol can be used as an effective and valuable solvent for synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones and 1-amidoalkyl-2-naphthols [31].

He *et al.* [32] reported the glycerol-promoted synthesis of di(indolyl)methanes, xanthene-1,8(2*H*)-diones and 1-oxo-hexahydroxanthenes through catalyst-free electrophilic activation of aldehydes. The model reaction was carried out with 4-nitrobenzaldehyde and 2-methylindole in glycerol solvent to produce the desired compound, namely, di(indolyl)methanes (**19**). The glycerol-mediated reactions obtained 95% yield, and 2.0 ml of glycerol was required to proceed the reaction (Scheme 1.17). Glycerol is used as solvent in organic reactions because its hydrophilic nature facilitates the isolation of the product. The same protocol was used to isolate the product by adding water containing glycerol to the reaction mixture; the product settled down in water and was separated by vacuum filtration (Figure 1.3).

Nascimento *et al.* [33] developed a simple direct cyclocondensation reaction with model substrates α-arylselanyl-1,3-diketones and arylhydrazines, which
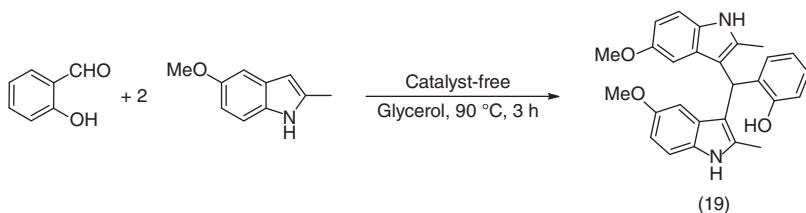
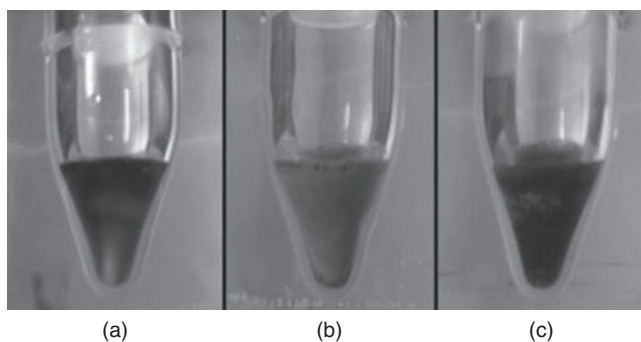**Scheme 1.17**   Catalyst-free green synthesis of di(indolyl)methane.

Figure 1.3   Development of the model reaction in glycerol [32]: (a) beginning of the reaction as an identical mixture; (b) partial precipitation of the reaction; (c) the end of the precipitation of the reaction. From He *et al.* (2009) *Green Chem.*, **11**, 1767–1773. Reproduced by permission of RSC. (A colour version of this figure appears in the plate section.)
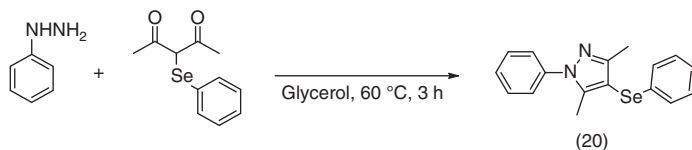
Scheme 1.18   Metal-free synthesis of 4-arylselanylpyrazoles.

possess both electron-withdrawing and electron-donating groups, to obtain high yields of 4-arylselanylpyrazoles (**20**) (Scheme 1.18). Similarly, Min *et al.* [34] demonstrated the same cyclocondensation reaction, which can be promoted using an economical and environment-friendly solvent, namely, glycerol–water system. Phenylhydrazine and 1,3-dicarbonyl compounds were used as benchmark partners to prepare the desired pyrazoles (**21**) (Scheme 1.19).

Rodriguez *et al.* [35] developed an intermolecular azide–alkyne Huisgen cycloaddition reaction between diphenylacetylene and benzylazide to produce
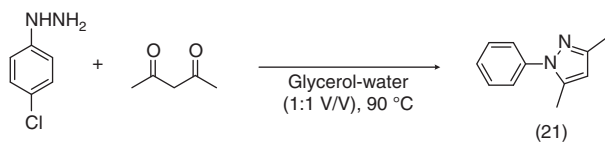
Scheme 1.19 Direct cyclocondensation reaction between phenylhydrazine and pentane-2,4-dione in glycerol–water system.

high yields of 1,2,3-triazole (**22**). Non-activated internal alkynes have been converted in neat glycerol under thermal and microwave dielectric heating. The important role of glycerol in the reaction has been confirmed by theoretical density functional theory (DFT) calculations. The DFT results revealed that the BnN_3/glycerol adduct promotes the reaction and stabilizes the corresponding lowest unoccupied molecular orbital (LUMO), thereby increasing the reactivity with alkyne in the first case (Scheme 1.20).

The multi-component Petasis borono–Mannich (PBM) reaction is a useful tool for preparing complex tertiary morpholine derivatives (**23**). Boronic acids, aldehydes/ketones and amines can be used as promoters in the reaction. Glycerol provided high product yield, and crude glycerol was considered an appropriate solvent for successful PBM reaction (Scheme 1.21) [36].

Ganesan *et al.* [37] developed a three-component Betti reaction with non-toxic and inexpensive glycerol as solvent. A reaction without catalyst was also performed, and the desired Betti bases (**24**) were isolated, providing up to 91% yield. The reaction in glycerol works well for all kinds of amines and aldehydes. The reaction in 20 mol.% methanesulfonic acid as catalyst also produced 93% benzoxanthene (Scheme 1.22).
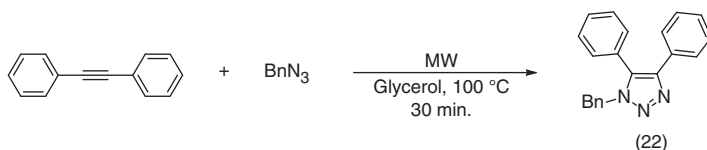
Scheme 1.20   Huisgen cycloaddition reaction for preparing 1,2,3-triazoles.
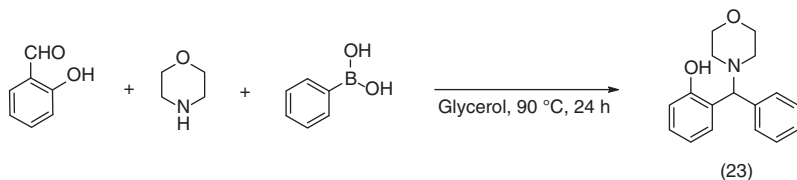
Scheme 1.21   PBM reaction for preparing complex tertiary morpholine derivatives.
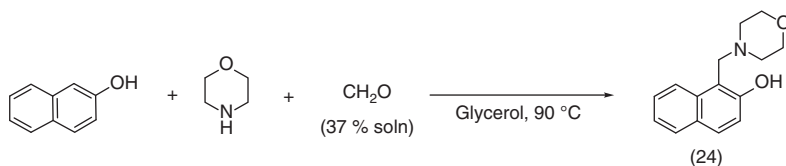
Scheme 1.22 Preparation of 1-(morpholinomethyl)naphthalen-2-ol through the Betti reaction.
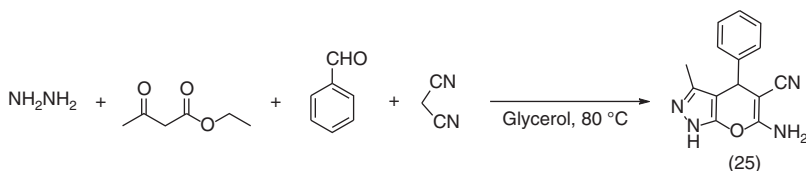

Scheme 1.23 Glycerol-mediated, one-pot synthesis of dihydropyrano[2,3-c]pyrazoles.

Sohal *et al.* [38] proposed a multi-component, one-pot synthesis of various pyrazole derivatives through the condensation of ethyl acetoacetate, hydrazine, aromatic aldehyde and malononitrile, with glycerol as solvent. The reaction involved the condensation between hydrazine and ethylacetoacetate; the Knoevenagel condensation occurred between malononitrile and aldehyde to form arylidenepropanedinitrile as intermediate; and the Michael-like addition to produce the desired pyrazole derivative (**25**) at high yield (Scheme 1.23).

Singh *et al.* [39] developed the first glycerol-promoted green synthesis of spirooxindole-indazolones and spirooxindole-pyrazolines; this multi-component tandem reaction used isatin, phenyl hydrazine and dimedone as substrates. Glycerol was used as solvent to promote the formation of the dimedone anion (Scheme 1.24). Singh *et al.* [40] described the catalyst-free facile synthesis of pyrido[2,3-*d*]pyrimidines using glycerol as promoting medium. Benzaldehyde, malononitrile and uracil used as substrates were condensed through sequential reaction, involving Knoevenagel condensation, Michael-type addition and air
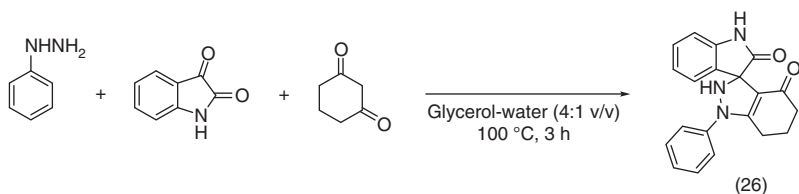
Scheme 1.24 Catalyst-free synthesis of spirooxindole-indazolones.
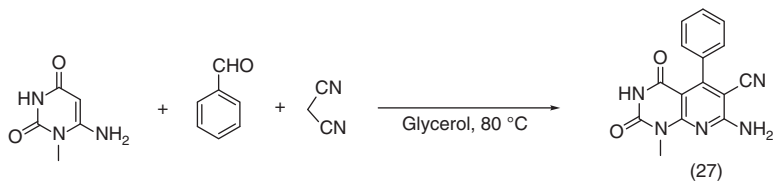
Scheme 1.25 Multi-component tandem synthesis of pyrido[2,3-*d*]pyrimidine.
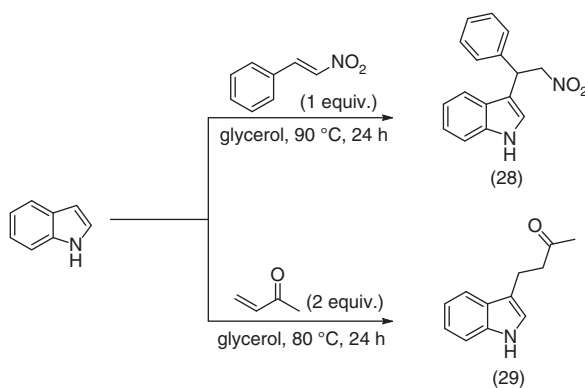
Scheme 1.26 Friedel–Crafts alkylation of indoles in glycerol.

oxidation, to produce a high yield of the desired pyrido[2,3-*d*]pyrimidine (**27**) (Scheme 1.25).

For the Michael-type reaction of indole to the α,β-unsaturated compound, conventional organic solvents, such as DMSO, toluene, 1,2-dichloroethane or DMF, are ineffective under catalyst-free conditions. Low amounts of products (**28,29**) were formed in the Michael addition of indoles to β-nitrostyrene and 3-buten-2-one in water. However, the reaction in glycerol produced high yields of the desired products (**28,29**) without using any Brønsted or Lewis acid catalysts (Scheme 1.26) [41].

Glycerol is also an exceptional supporting medium for the ring-opening reaction of styrene oxide with *p*-anisidine. The reaction did not use any catalysts but showed good selectivity. In aqueous medium the selectivity of the reaction products **30** : **31** was in the ratio 76 : 24, and that in glycerol was 93 : 7 under identical conditions (Scheme 1.27) [42].

Tan *et al.* [43] developed a coupling reaction of phenylhydrazine, β-keto ester, formaldehyde and 1-ethyl-2-phenylindole in glycerol solvent to form a highly functionalized indole derivative (**32**; 42% yield) (Scheme 1.28).
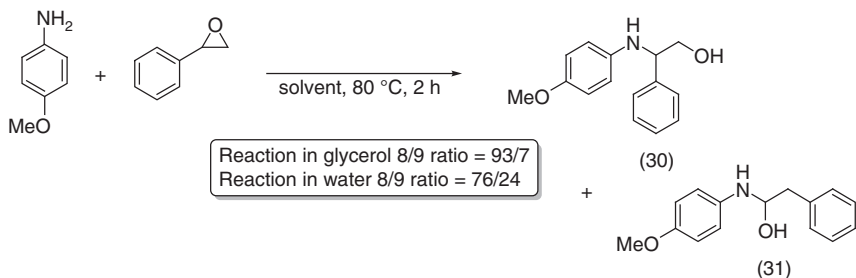
Scheme 1.27   Catalyst-free ring-opening reaction of styrene oxide with *p*-anisidine.
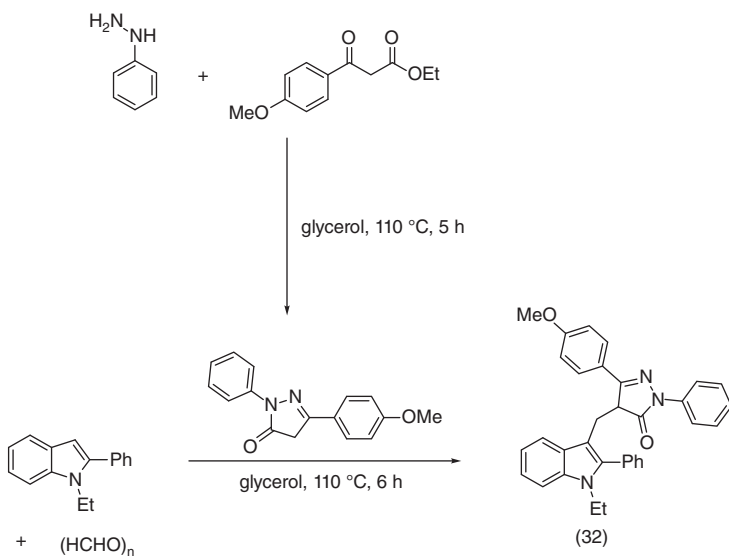
Scheme 1.28   Coupling reaction for synthesis of the functionalized indoles.

The multi-component reactions with three or more reactants are combined in a single-step reaction to facilitate diverse complex molecules. Therefore, glycerol was established to be a convenient medium for multi-component reactions. Styrene, primary amines, 2-naphthol, 4-hydroxy-6-methyl-2-pyrone and 4-hydroxy-1-methyl-2-quinolone are readily available molecules for use as target partners accumulated with 1,3-cyclohexadiones and formaldehyde in glycerol to obtain complex polycyclic compounds (**33–37**) under catalyst-free conditions (Scheme 1.29). In these multi-component reactions, glycerol not only provided efficient reaction but also allowed simple separation of the products (**33–37**) through extraction because of its strong hydrophilic nature [44].
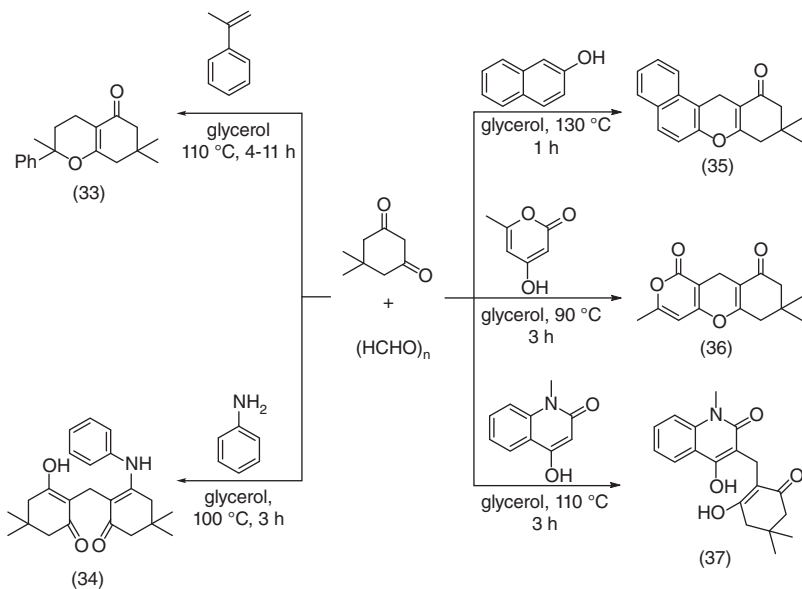
Scheme 1.29 Multi-component reactions of 1,3-cyclohexanediones and formaldehyde in glycerol.

1.3   Metal-Promoted Organic Transformations in Glycerol

Metal-free organic reactions in glycerol are commonly used because of their green properties, despite the fact that complex molecular skeletons can be synthesized through metal-catalysed organic reactions. Catalysis plays a prominent role in this type of green organic synthesis because it allows economical and environment-friendly efficient preparation of chemicals and materials [45]. New selective catalysts can provide short-cuts in the total synthesis but remain inefficient. Currently, metal-promoted green organic synthesis is attracting considerable attention and is documented through published books [46] and articles [47]. Over the past decades, chemical industries have applied a number of homogeneous catalysts to prepare bulk chemicals. The important and versatile property of these homogeneous catalysts is attributed to the tunability of transition metal complexes by changing the ligands coordinated with the metal [48]. Homogeneous catalysts cannot be reused because they are difficult to isolate from the reaction mixture. By contrast, heterogeneous catalysts can be easily separated from the reaction and are thus commonly used in organic preparations. Metal catalysts embedded with nanoparticles can be efficient catalysts for a number of organic transformations. These metal catalysts in green solvents, such as water, glycerol, poly(ethylene glycol) and gluconic acid, also provide interesting medicinal scaffolds. In particular, metal-catalysed organic reactions

with glycerol as solvent medium show interesting chemical properties, such as low toxicity, biodegradability, polarity and non-flammability, resulting in high reaction efficiency. Thus, metal-promoted green synthesis with glycerol as solvent must be further investigated.

Khatri *et al.* [49] used aryl halides in glycerol for *N*-arylation of amines. Copper acetate (5 mol.%) and KOH (2 mmol) were dissolved in glycerol at 100°C to obtain the desired product (**38**) with 96% yield. In this reaction, glycerol acts as ligand and coordinates with the metal catalyst to accelerate the reaction (Scheme 1.30).

Lenardão *et al.* [50] used glycerol as a promoting medium for the cross-coupling reaction of diaryldiselenides with (*Z*) or (*E*) vinyl bromides, which contain electron-withdrawing and electron-donating groups. The mock cross-coupling reaction was carried out with (*E*)-β-bromostyrene and diphenyldiselenide in glycerol and catalysed by the combined system of copper iodide CuI (5 mol.%) and Zn dust (0.6 mmol) at 110°C in the absence of oxygen atmosphere to produce the desired product (**39**) with 98% yield (Scheme 1.31). Lenardão *et al.* [51] also reported the synthesis of 2-organylselanyl pyridines. The reaction was promoted by glycerol under nitrogen atmosphere. Interestingly, this reaction did not use any metal catalysts for cross-coupling of diphenyldiselenide. The reaction was carried out with diphenyldiselenide and 2-chloropyridinein glycerol with H_3PO_4 (1.0 ml) as reducing agent to produce the targeted product, 2-phenylselanyl-pyridine (**40**), with 99% yield (Scheme 1.32). The same research group [52] reported that PEG400 and glycerol promoted the green synthesis of organylthioenynes at high yields and high selectivity with KF/Al_2O_3 as catalytic system. The catalytic mixture KF/Al_2O_3 (0.7 g) was used to promote the reaction and produce the *Z* and *E* mixture of organylthioenynes (**41,42**) (Scheme 1.33). The same group used a green solvent and catalytic system for one-pot synthesis of β-aryl-β-sulfanyl
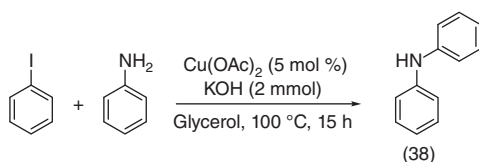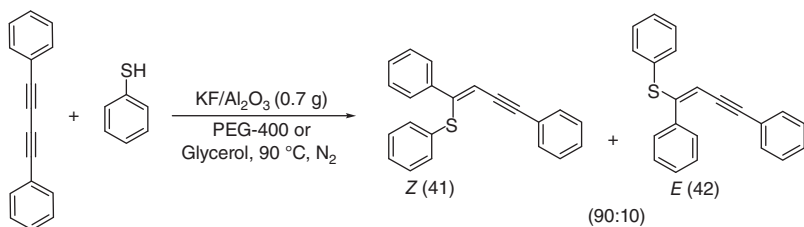

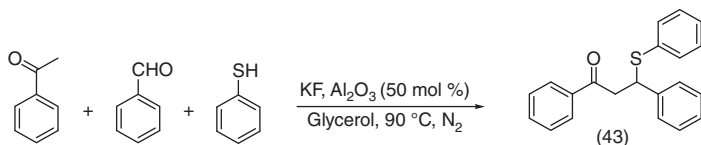**Scheme 1.30**   Copper acetate-promoted *N*-arylation of aromatic amine.
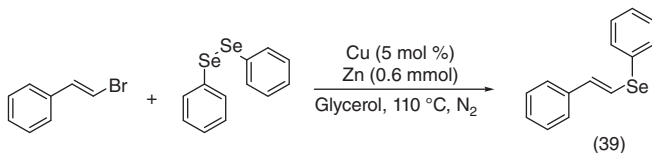
Scheme 1.31   CuI-promoted green synthesis of phenyl selenide derivatives.
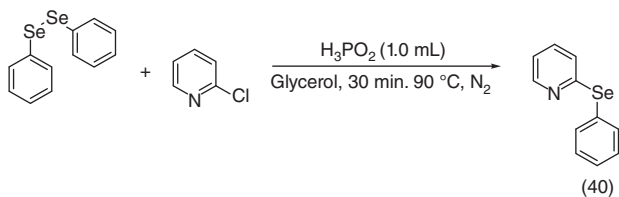
Scheme 1.32 Synthesis of 2-phenylselanyl-pyridine.

Scheme 1.33 Green solvent and catalyst promoted the synthesis of a *Z* and *E* mixture of organylthioenynes.

Scheme 1.34 Green synthesis of β-aryl-β-sulfanyl ketones.

ketones [53]. One-pot solid-supported green synthesis was carried out with acetophenone, active carbonyl compounds and nucleophile in glycerol. Notably, 50 mol.% KF/Al$_2$O$_3$ was needed to produce the desired β-aryl-β-sulfanyl ketones (**43**) (Scheme 1.34).

The mixture of CuI and glycerol displayed versatile catalytic activity in the Huisgen cycloaddition of azides and terminal or 1-iodoalkynes [54]. The base-free Cu(I)-catalysed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes were synthesized and reported by Vidal *et al.* [55] in 2014. The reaction started with benzyl azide and phenylacetylene in pure glycerol; it was catalysed by 1 mol.% of CuI to produce an enormous 1,3-dipolar cycloaddition product (**44**) with 99% yield (Scheme 1.35). In order to prove the efficiency of glycerol in the reaction, other solvents were also used to promote the reaction; however, they produced only marginal product yield.

Cross-coupling and azide–alkyne cycloaddition processes have been catalysed by copper oxide nanoparticles (Cu$_2$ONP), as reported by Chahdoura and
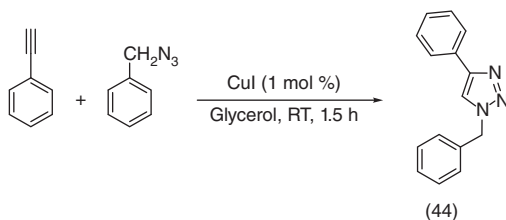
Scheme 1.35   Copper(I)-catalysed synthesis of 1-benzyl-4-phenyl-1*H*-[1–3]triazole.

co-workers [56] in 2014. The Cu$_2$ONP were synthesized under a dihydrogen atmosphere from copper acetate at 100°C; glycerol was used as a solvent and polyvinylpyrrolidone (PVP) as a stabilizer. Then the catalytic activities of these metal nanoparticles (MNPs) have been studied for carbon–heteroatom couplings and azide–alkyne cycloaddition with 4-nitro-iodobenzene and 4-methyl-thiophenolin, a base, *tert*-BuOK, and glycerol at 100°C for 24 hours to produce the desired polyfunctional product (**45**) with 89% yield without the isolation of intermediates. The scope of the catalyst and substrates were further extended and a library of organic scaffolds has been synthesized and reported (Scheme 1.36).

Catalysis by palladium nanoparticles (PdNP) in a green synthesis using glycerol has been reported by Chahdoura *et al.* [57]. The multi-step synthesis of heterocycles involved carbonylative couplings followed by intramolecular cyclization, which leads to the formation of *N*-substituted naphthalimides (**46**), isoindole-1-ones and tetrahydroisoquinolin-1,3-diones in better isolated yields. Apart from this synthesis, the PdNP were also employed to synthesize 2-benzofurans and dihydrobenzofurans via Sonogashira coupling/heterocyclisation tandem processes (Scheme 1.37).

Recently, the cross-coupling reactions were tested again for the catalytic system bis(2-pyridyl)diselenoethers [58]. Coupling reagents, such as 2-iodo-1,3-dimethoxy-benzene, and the strong counter-nucleophile, thiophenol, were used as model substrates, glycerol as a greener solvent, and an inorganic salt, KOH (3 equiv), as a base. The ligand, [Cu$_4$I$_4${(2-PySe)$_2$CH$_2$}$_2$], was used as the metal ligand in the reaction, and the desired product 1,3-dimethoxy-2-phenylsulfanyl-benzene (**47**) was isolated from the reaction with 63% yield. Other ligands, such as [CuCl$_2${(2-PySe)$_2$CH$_2$}]$_n$,
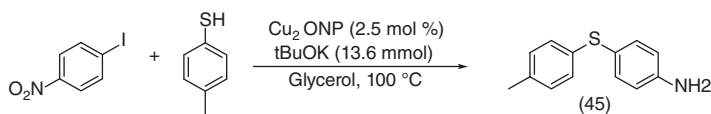
Scheme 1.36   Copper nanoparticle-promoted synthesis of 4-*p*-tolylsulfanyl-phenylamine.
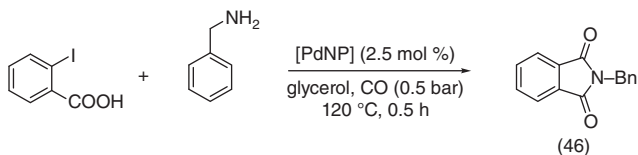
Scheme 1.37 Palladium nanoparticle-catalysed synthesis of *N*-substituted phthalimides.
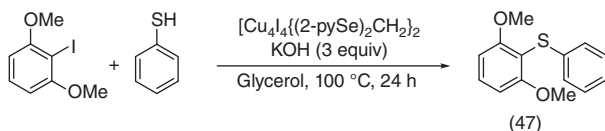
Scheme 1.38 Metal ligand-promoted green synthesis of bis(2-pyridyl)diselenoethers.

$[CuCl_2\{(2\text{-PySe})_2(CH_2)_3\}_2]$, were also used in the reaction to prepare the desired C–S coupling products (Scheme 1.38).

Glycerol is a sustainable green solvent for many organic transformations. Nevertheless, it has drawbacks, such as low solubility of gases, high viscosity and high hydrophobicity. These problems can be overcome by using some other new techniques in a stand-alone manner, such as microwaves (MW) [59] or high-intensity ultrasound (US) [60, 61], or in a combined manner [62, 63], which results in the enhancement of the reaction rates. A similar kind of reaction protocol has been demonstrated by Cravotto *et al.* [64]. They realized a transfer hydrogenation reaction of benzaldehyde using glycerol as dual solvent and hydrogen donor. By using Ru(*p*-cumene)Cl$_2$ as catalyst, the reaction proceeded with 100% conversion in the presence of bases (NaOH + KOH) under ultrasonic conditions, to give the desired product, phenyl-methanol (**48**) (Scheme 1.39).

The cross-coupling reactions for the construction of C–C and C–heteroatom bonds have attracted considerable attention because of their significance in medicinal chemistry [65, 66]. The formation of one C–N bond and one C–C bond on the identical carbenic centre has been developed and reported by Aziz *et al.* [67]. A hypothesis for this reaction was that it involves a copper acetate-catalysed cross-coupling reaction between 2′-bromo-biaryl-*N*-tosylhydrazones and different
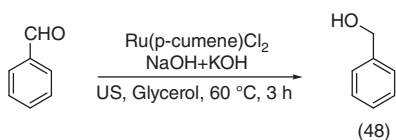
Scheme 1.39 Ultrasound-promoted green synthesis of phenyl-methanol.
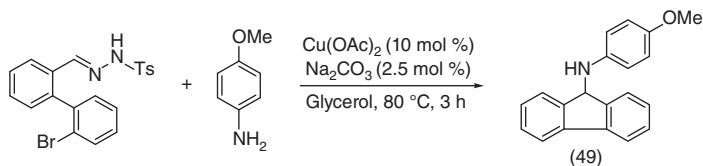
Scheme 1.40 Copper-catalysed cross-coupling between *N*-tosylhydrazones and 4-methoxyaniline.
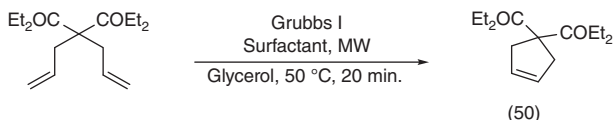
Scheme 1.41 Microwave-assisted ring-closing metathesis of diethyl diallylmalonate.

amines as benchmark partners, leading to the formation of 9*H*-fluoren-9-amine derivatives (**49**). This reaction proceeds under mild conditions with 2.5 mol.% sodium carbonate in glycerol, a cheap and environmentally gracious solvent, without external ligand (Scheme 1.40).

The microwave-assisted ring-closing metathesis has also been studied recently by Hamel and co-workers [68]. The reaction was started with diethyl diallylmalonate in glycerol under microwave irradiation. Catalysis with Grubbs I catalyst generates the desired five-membered cyclic product (**50**). The reaction proceeding without the catalyst generates by-products (Scheme 1.41).

Selective hydrogen transfer methodologies for the reduction of ketones or imines and oxidation of alcohols and amines, and the donation of protons (typically 2-propanol) or electrons (e.g. acetone) are easily conducted in green solvents like water or glycerol [69, 70]. The selective transfer of hydrogen from organic carbonyl compounds has also been studied recently by Azua *et al.* [71]. Ir(III) complexes, which possess chelating bis-NHC ligand and sulfonate groups, are efficient catalysts because of their excellent solubility in the reaction medium and the strong electron-donor nature of the bis-carbene ligands. KOH was used to accelerate the reaction and reduce acetophenone in glycerol to produce the desired hydrogen transferred product, 1-phenyl-ethanol (**51**), and by-product, 1,3-dihydroxy-propan-2-one (**52**) (Scheme 1.42).
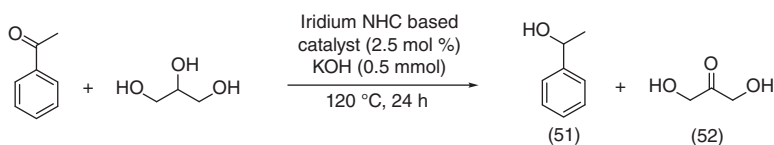
Scheme 1.42 Iridium-catalysed selective hydrogen transfer of acetophenone in glycerol.
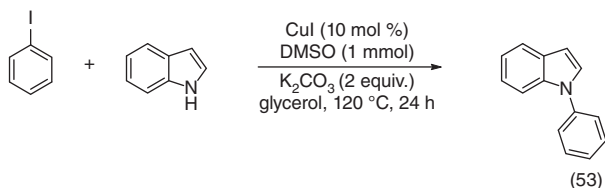
Scheme 1.43   Copper/glycerol catalytic system for the synthesis of *N*-aryl indoles.
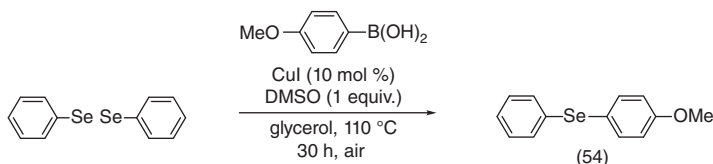
Scheme 1.44   Synthesis of diarylselenides using glycerol as solvent.

The copper-catalysed synthesis of different *N*-aryl indoles (**53**) has been developed by Yadav *et al.* [72]. The cross-coupling reaction of indoles with aryl halides used glycerol as a green sustainable solvent and DMSO as an additive to accelerate the reaction. The low catalytic amount of CuI (10 mol.%) in the reaction provided various *N*-aryl indoles in good to outstanding yield (Scheme 1.43). Similarly, the copper-catalysed cross-coupling reactions of diaryldiselenides with aryl boronic acids have been reported by Ricordi *et al.* [73]; glycerol promoted cross-coupling to produce the corresponding diarylselenides (**54**) (Scheme 1.44).

The reactions at the carbon–carbon double bond of (*E*)-chalcones have been described by Mesquita *et al.* [74]. The reaction of diphenyldiselenide in glycerol at 90°C with H_3PO_2 as a reducing agent with different (*E*)-chalcones produced chemoselective 1,4-reduction products (**55**). Moreover, under similar conditions, the natural product, zingerone, was synthesized and obtained in high yield (Scheme 1.45).

The combined catalytic system of glycerol and zinc(II) acetate for the synthesis of 2-pyridyl-2-oxazolines (**56**) was developed by Carmona *et al.* [75]. The reaction
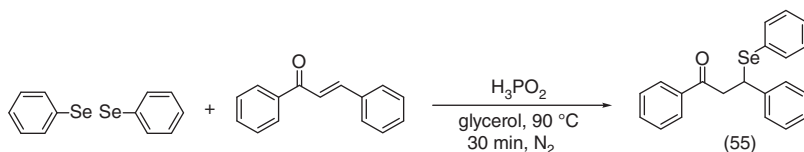
Scheme 1.45   Synthesis of 1,3-diphenyl-3-(phenylselanyl)propan-1-one under a green protocol.
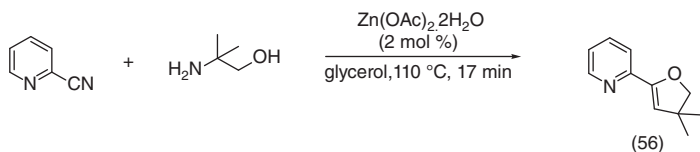
Scheme 1.46   Oxazoline synthesis using glycerol as solvent.

Scheme 1.47   Suzuki coupling of phenyl boronic acids in glycerol.
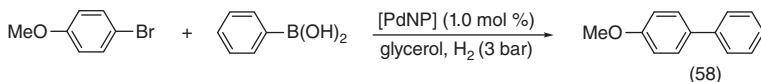
Scheme 1.48   Suzuki–Miyaura coupling reaction of aryl halides in glycerol.

started with amino alcohols and 2-cyanopyridines under microwave irradiation and resulted in the formation of the desired 2-pyridyl-2-oxazoline derivatives. Conventional heating did not significantly improve the reaction, and the catalytic system was recovered and reused for further synthesis (Scheme 1.46).

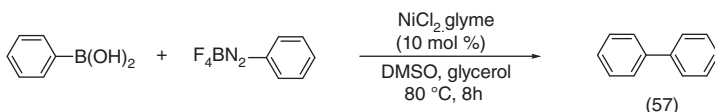The base-free nickel-catalysed Suzuki coupling reaction of phenyl boronic acids with aryl diazonium salts in glycerol has been described by Bhojane *et al.* [76]. Different aryl diazonium salts reacted with aryl boronic acids under the optimized conditions to obtain high yields of the corresponding diaryl compounds (**57**) (Scheme 1.47). Similarly, a Suzuki–Miyaura coupling reaction of aryl halides has been demonstrated by Chahdoura *et al.* [77]. Palladium nanoparticles catalysed the reaction efficiently to produce the desired coupling product (**58**). An interesting catalytic immobilization in glycerol was observed for C–C coupling (up to 10 runs without loss of any catalytic activity) (Scheme 1.48).

The aldoxime rearrangement to primary amides has been studied by González-Liste *et al.* [78]. Commercially available bis(allyl)-ruthenium(IV) complex [{RuCl(μ-Cl)(η^3:η^3-$C_{10}H_{16}$)}$_2$] ($C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) was used as a catalyst to promote the reaction under thermal and microwave heating. The reactions were carried out cleanly in a mixture of water/glycerol (1 : 1). Aromatic, heteroaromatic, aliphatic and α,β-unsaturated aldoximes served as benchmark partners to produce the desired amides (**59**) in moderate to high yields (Scheme 1.49).
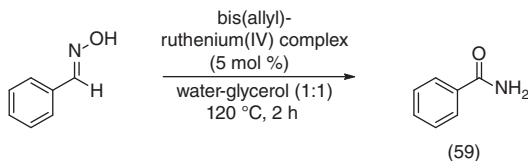
Scheme 1.49 Rearrangement of (*E*)-benzaldoxime into benzamide in glycerol.

1.4 Conclusions and Perspectives

We have described the beginning and development of the uses of glycerol as a green solvent, reagent and hydrogen donor for synthetic organic chemistry to transform the waste by-product into a useful solvent and products. Glycerol is very useful for organic reactions because of its availability from renewable sources on a bulk scale at cheap price and its advantageous properties, such as non-flammability, non-toxicity and biodegradability. Apart from the organic transformations, a number of nanocatalysts and room-temperature ionic liquids have also been prepared from glycerol, as described in this review. Use of glycerol as a solvent has several advantages and very few disadvantages. One of the latter is its viscosity, which could mean poor substrate contact with the solvent. The extraction of highly functionalized reaction products from glycerol is, in addition, a difficulty that needs to be solved prior to practical uses. Nevertheless, the above few problems will be overcome by the wise use of glycerol as a solvent. Glycerol has attracted considerable interest among green and organic chemists, and the authors believe that this inclusive literature will direct the further development in the field of glycerol chemistry.

Acknowledgements

References

1. Ashcroft, C.P., Dunn, P., Hayler, J. and Wells, A.S. (2015) Survey of solvent usage in papers published in *Organic Process Research & Development* 1997–2012. *Org. Process Res. Dev.*, **19**, 740–747.

 2. DECHEMA (2012) *Press Release: New natural resource base in the chemical indus-try – only a matter of time*, June. http://www.achema.de/fileadmin/user_upload/Bilder/ Presse/ACHEMA2012/Trendberichte/Trendberichte_2012/tb19_en_Biobased_Chemicals .docx (accessed 4 May 2016).

 3. Reichardt, C. and Welton, T. (2010) *Solvents and Solvent Effects in Organic Chemistry*, 4th edn, Wiley-VCH, Weinheim.

 4. Handy, S.T. (2003) Greener solvents: room temperature ionic liquids from biorenewable sources. *Chem. Eur. J.*, **9**, 2938–2944.

 5. Leitner, W. (2007) Editorial: Green solvents for processes. *Green Chem.*, **9**, 923.

 6. Horváth, I.T. (2008) Solvents from nature. *Green Chem.*, **10**, 1024–1028.

 7. Nelson, W.M. (2003) *Green Solvents for Chemistry: Perspectives and Practice*, Oxford University Press, Oxford.

 8. Kemp, W.H. (2006) *Biodiesel: Basics and Beyond*, Azlext Press, Ontario.

 9. Zhou, C.-H., Beltramini, J.N., Fan, Y.-X. and Lu, C.Q. (2008) Chemoselective catalytic conversion of glycerol as a biorenewable source to valuable commodity chemicals. *Chem. Soc. Rev.*, **37**, 527–549.

10. Gu, Y. and Jérôme, F. (2010) Glycerol as a sustainable solvent for green chemistry. *Green Chem.*, **12**, 1127–1138.

11. Pagliaro, M. and Rossi, M. (2008) *The Future of Glycerol: New Usages for a Versatile Raw Material*, RSC Publishing, Cambridge.

12. Gu, Y. and Jérôme, F. (2013) Bio-based solvents: an emerging generation of fluids for the design of eco-efficient processes in catalysis and organic chemistry. *Chem. Soc. Rev.*, **42**, 9550–9570.

13. Díaz-Álvarez, A.E., Francos, J., Lastra-Barreira, B., et al. (2011) Glycerol and derived solvents: new sustainable reaction media for organic synthesis. *Chem. Commun.*, **47**, 6208–6227.

14. Liu, C., Zhou, L., Jiang, D. and Gu, Y. (2016) Multicomponent reactions of aldo-X bifunc-tional reagent α-oxoketene dithioacetals and indoles or amines: divergent synthesis of dihy-drocoumarins, quinolines, furans, and pyrroles. *Asian J. Org. Chem.*, **5**, 367–372.

15. Ravichandiran, P., Lai, B. and Gu, Y. (2017) Aldo-X bifunctional building blocks for the synthesis of heterocycles. *Chem. Rec.*, **17**, 142–183.

16. Bachhav, H.M., Bhagat, S.B. and Telvekar, V.N. (2011) Efficient protocol for the synthesis of quinoxaline, benzoxazole and benzimidazole derivatives using glycerol as green solvent. *Tetrahedron Lett.*, **52**, 5697–5701.

17. Radatz, C.S., Silva, R.B., Perin, G., et al. (2011) Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent. *Tetrahedron Lett.*, **52**, 4132–4136.

18. Nascimento, J.E.R., Barcellos, A.M., Sachini, M., et al. (2011) Catalyst-free synthesis of octahydroacridines using glycerol as recyclable solvent. *Tetrahedron Lett.*, **52**, 2571–2574.

19. Somwanshi, J.L., Shinde, N.D. and Faruqui, M. (2013) Catalyst-free synthesis of furano-and pyranoquinolines by using glycerol as recyclable solvent. *Heterocyclic Lett.*, **3**, 69–74.

20. Cabrera, D.M.L., Líbero, F.M., Alves, D., et al. (2012) Glycerol as a recyclable solvent in a microwave-assisted synthesis of disulfides. *Green Chem. Lett. Rev.*, **5**, 329–336.

21. Zhou, W.J., Zhang, X.Z., Sun, X.B., et al. (2013) Microwave-assisted synthesis of quinoxa-line derivatives using glycerol as a green solvent. *Russ. Chem. Bull.*, **62**, 1244–1247.

22. Taduri, A.K., Babu, P.N.K. and Devi, B.R. (2014) Glycerol containing triacetylborate medi-ated syntheses of novel 2-heterostyryl benzimidazole derivatives: a green approach. *Org. Chem. Int.*, **2014**, 260726.

23. Lobo, H.R., Singh, B.S. and Shankarling, G.S. (2012) Deep eutectic solvents and glycerol: a simple, environmentally benign and efficient catalyst/reaction media for synthesis of *N*-aryl phthalimide derivatives. *Green Chem. Lett. Rev.*, **5**, 487–533.

24. Lenardão, E.J., Jacob, R.G., Mesquita, K.D., et al. (2013) Glycerol as a promoting and recyclable medium for catalyst-free synthesis of linear thioethers: new antioxidants from eugenol. *Green Chem. Lett. Rev.*, **6**, 269–276.

25. Safaei, H.R., Shekouhy, M., Rahmanpur, S. and Shirinfeshan, A. (2012) Glycerol as a biodegradable and reusable promoting medium for the catalyst-free one-pot three component synthesis of 4*H*-pyrans. *Green Chem.*, **14**, 1696–1704.

26. Shekouhy, M., Sarvestani, A.M., Khajeh, S. and Nezhad, A.K. (2015) Glycerol: a more benign and biodegradable promoting medium for catalyst-free one-pot multi-component synthesis of triazolo[1,2-*a*]indazole-triones. *RSC Adv.*, **5**, 63705–63710.

27. Thurow, S., Penteado, F., Perin, G., et al. (2014) Metal and base-free synthesis of arylselanyl anilines using glycerol as a solvent. *Green Chem.*, **16**, 3854–3859.

28. Binil, P.S., Anoop, M.R., Jisha, K.R., et al. (2013) Growth, spectral and thermal characterization of vanillin semicarbazone (VNSC) single crystals. *J. Therm. Anal. Calorim.*, **111**, 575–581.

29. Ali, S.M.M., Azad, M.A.K., Jesmin, M., et al. (2012) *Asian Pac. J. Trop. Biomed.*, **2**, 438–442.

30. Jovanović, M.B., Konstantinović, S.S., Ilić, S.B. and Veljković, V.B. (2013) The synthesis of vanillin-semicarbazone in a crude glycerol as a green solvent. *Adv. Technol.*, **2**, 38–44.

31. Hajjami, M., Bakhti, F. and Ghiasbeygi, E. (2015) Incredible role of glycerol in multicomponent synthesis of 2,3-dihydroquinazoline-4(1*H*)-ones and 1-amidoalkyl-2-naphthols. *Croat. Chem. Acta*, **88**, 197–205.

32. He, F., Li, P., Gu, Y. and Li, G. (2009) Glycerol as a promoting medium for electrophilic activation of aldehydes: catalyst-free synthesis of di(indolyl)methanes, xanthene-1,8(2*H*)-diones and 1-oxo-hexahydroxanthenes. *Green Chem.*, **11**, 1767–1773.

33. Nascimento, J.E.R., de Oliveira, D.H., Abib, P.B., et al. (2015) Synthesis of 4-arylselanylpyrazoles through cyclocondensation reaction using glycerol as solvent. *J. Braz. Chem. Soc.*, **26**, 1533–1541.

34. Min, Z.-L., Zhang, Q., Hong, X., et al. (2015) A green protocol for catalyst-free syntheses of pyrazole in glycerol–water solution. *Asian J. Chem.*, **27**, 3205–3207.

35. Rodriguez-Rodriguez, M., Gras, E., Pericas, M.A. and Gomez, M. (2015) Metal-free intermolecular azide–alkyne cycloaddition promoted by glycerol. *Chemistry Eur. J.*, **21**, 18706–18710.

36. Rosholm, T., Gois, P.M.P., Franzen, R. and Candeias, N.R. (2015) Glycerol as an efficient medium for the Petasis borono–Mannich reaction. *ChemistryOPEN*, **4**, 39–46.

37. Ganesan, S.S., Rajendran, N., Sundarakumar, S.I., et al. (2013) β-Naphthol in glycerol: a versatile pair for efficient and convenient synthesis of aminonaphthols, naphtho-1,3-oxazines, and benzoxanthenes. *Synthesis*, **45**, 1564–1568.

38. Sohal, H.S., Goyal, A., Sharma, R., et al. (2013) Glycerol mediated, one pot, multicomponent synthesis of dihydropyrano[2,3-*c*]pyrazoles. *Eur. J. Chem.*, **4**, 450–453.

39. Singh, S., Saquib, M., Singh, S.B., et al. (2015) Catalyst free, multicomponent-tandem synthesis of spirooxindole-indazolones and spirooxindole-pyrazolines: a glycerol mediated green approach. *RSC Adv.*, **5**, 45152–45157.

40. Singh, S., Saquib, M., Singh, M., et al. (2016) A catalyst free, multicomponent-tandem, facile synthesis of pyrido[2,3-*d*]pyrimidines using glycerol as a recyclable promoting medium. *New J. Chem.*, **40**, 63–67.

41. Habib, P.M., Kavala, V., Kuo, C.-W. and Yao, C.-F. (2008) Catalyst-free aqueous-mediated conjugative addition of indoles to β-nitrostyrenes. *Tetrahedron Lett.*, **49**, 7005–7007.

42. Gu, Y., Barrault, J. and Jerome, F. (2008) Glycerol as an efficient promoting medium for organic reactions. *Adv. Synth. Catal.*, **350**, 2007–2012.

43. Tan, J.-N., Li, M. and Gu, Y. (2010) Multicomponent reactions of 1,3-disubstituted 5-pyrazolones and formaldehyde in environmentally benign solvent systems and their variations with more fundamental substrates. *Green Chem.*, **12**, 908–914.

44. Li, M., Chen, C., He, F. and Gu, Y. (2010) Multicomponent reactions of 1,3-cyclohexanediones and formaldehyde in glycerol: stabilization of paraformaldehyde in glycerol resulted from using dimedone as substrate. *Adv. Synth. Catal.*, **352**, 519–530.

45. Johansson Seechurn, C.C.C., Kitching, M.O., Colacot, T.J. and Snieckus, V. (2012) Palladium-catalyzed cross-coupling: a historical contextual perspective to the 2010 Nobel Prize. *Angew. Chem., Int. Edn*, **51**, 5062–5085.

46. Rylander, P.N. (1973) *Organic Syntheses with Noble Metal Catalysts*, Academic Press, New York.

47. Perin, G., Lenardão, E. J., Jacob, R.G. and Panatieri, R.B. (2009) Synthesis of vinyl selenides. *Chem. Rev.*, **109**, 1277–1301.

48. Leenders, S.H.A.M., Gramage-Doria, R., de Bruin, B. and Reek, J.N.H. (2015) Transition metal catalysis in confined spaces. *Chem. Soc. Rev.*, **44**, 433–448.

49. Khatri, P.K. and Jain, S.L. (2013) Glycerol ingrained copper: an efficient recyclable catalyst for the *N*-arylation of amines with aryl halides. *Tetrahedron Lett.*, **54**, 2740–2743.

50. Gonçalves, L.C., Fiss, G.F., Perin, G., et al. (2010) Glycerol as a promoting medium for cross-coupling reactions of diaryl diselenides with vinyl bromides. *Tetrahedron Lett.*, **51**, 6772–6775.

51. Thurow, S., Webber, R., Perin, G., et al. (2013) Glycerol/hypophosphorous acid: an efficient system solvent-reducing agent for the synthesis of 2-organylselanyl pyridines. *Tetrahedron Lett.*, **54**, 3215–3218.

52. Alves, D., Sachini, M., Jacob, R.G., et al. (2011) Synthesis of (*Z*)-organylthioenynes using KF/Al$_2$O$_3$/solvent as recyclable system. *Tetrahedron Lett.*, **52**, 133–135.

53. Perin, G., Mesquita, K., Calheiro, T.P., et al. (2014) Synthesis of β-aryl-β-sulfanyl ketones by a sequential one-pot reaction using KF/Al$_2$O$_3$ in glycerol. *Synth. Commun.*, **44**, 49–58.

54. Díaz-Álvarez, E., Francos, J., Crochet, P. and Cadierno, V. (2014) Recent advances in the use of glycerol as green solvent for synthetic organic chemistry. *Curr. Green Chem.*, **1**, 51–65.

55. Vidal, C. and García-Álvarez, J. (2014) Glycerol: a biorenewable solvent for base-free Cu(ɪ)-catalyzed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes. Highly efficient transformations and catalyst recycling. *Green Chem.*, **16**, 3515–3521.

56. Chahdoura, F., Pradel, C. and Gómez, M. (2014) Copper(ɪ) oxide nanoparticles in glycerol: a convenient catalyst for cross-coupling and azide–alkyne cycloaddition processes. *ChemCatChem*, **6**, 2929–2936.

57. Chahdoura, F., Mallet-Ladeira, S. and Gómez, M. (2015) Palladium nanoparticles in glycerol: a clear-cut catalyst for one-pot multi-step processes applied in the synthesis of heterocyclic compounds. *Org. Chem. Front.*, **2**, 312–318.

58. Cargnelutti, R., da Silva, F.D., Abram, U. and Lang, E.S. (2015) Metal complexes with bis(2-pyridyl)diselenoethers: structural chemistry and catalysis. *New J. Chem.*, **59**, 7948–7953.

59. Kappe, C.O. and Stadler, A. (2005) *Microwaves in Organic and Medicinal Chemistry*, Wiley-VCH, Weinheim.

60. Cravotto, G., Nano, G.M., Palmisano, G. and Tagliapietra, S. (2003) The reactivity of 4-hydroxycoumarin under heterogeneous high-intensity sonochemical conditions. *Synthesis*, **8**, 1286–1291.

61. Cravotto, G. and Cintas, P. (2006) Power ultrasound in organic synthesis: moving cavitational chemistry from academia to innovative and large-scale applications. *Chem. Soc. Rev.*, **35**, 180–196.

62. Cravotto, G., Garella, D., Calcio Gaudino, E. and Leveque, J.-M. (2008) Microwaves–ultrasound coupling: a tool for process intensification in organic synthesis. *Chim. Oggi*, **26** (2), 44–46.

63. Cravotto, G. and Cintas, P. (2007) The combined use of microwaves and ultrasound: improved tools in process chemistry and organic synthesis. *Chemistry, Eur. J.*, **13**, 1902–1909.

64. Cravotto, G., Orio, L., Calcio Gaudino, E., et al. (2011) Efficient synthetic protocols in glycerol under heterogeneous catalysis. *ChemSusChem*, **4**, 1130–1134.

65. Barluenga, J. and Valdés, C. (2011) Tosylhydrazones: new uses for classic reagents in palladium-catalyzed cross-coupling and metal-free reactions. *Angew. Chem., Int. Edn*, **50**, 7486–7500.

66. Fulton, J.R., Aggarwal, V.K. and de Vicente, J. (2005) The use of tosylhydrazone salts as a safe alternative for handling diazo compounds and their applications in organic synthesis. *Eur. J. Org. Chem.*, **2005**, 1479–1492.

67. Aziz, J., Frison, G., Gómez, M., et al. (2014) Copper-catalyzed coupling of *N*-tosylhydrazones with amines: synthesis of fluorene derivatives. *ACS Catal.*, **4**, 4498–4503.

68. Hamel, A., Sacco, M., Mnasri, N., et al. (2014) Micelles into glycerol solvent: overcoming side reactions of glycerol. *ACS Sustain. Chem. Eng.*, **2**, 1353–1358.

69. Hamid, M., Slatford, P.A. and Williams, J.M.J. (2007) Borrowing hydrogen in the activation of alcohols. *Adv. Synth. Catal.*, **349**, 1555–1575.

70. Dobereiner, G.E. and Crabtree, R.H. (2010) Dehydrogenation as a substrate-activating strategy in homogeneous transition-metal catalysis. *Chem. Rev.*, **110**, 681–703.

71. Azua, A., Mata, J.A. and Peris, E. (2011) Iridium NHC based catalysts for transfer hydrogenation processes using glycerol as solvent and hydrogen donor. *Organometallics*, **30**, 5532–5536.

72. Yadav, D.K.T., Rajak, S.S. and Bhanage, B.M. (2014) *N*-Arylation of indoles with aryl halides using copper/glycerol as a mild and highly efficient recyclable catalytic system. *Tetrahedron Lett.*, **55**, 931–935.

73. Ricordi, V.G., Freitas, C.S., Perin, G., et al. (2012) Glycerol as a recyclable solvent for copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids. *Green Chem.*, **14**, 1030–1034.

74. Mesquita, K.D., Waskow, B., Schumacher, R.F., et al. (2014) Glycerol/hypophosphorous acid and PhSeSePh: an efficient and selective system for reactions in the carbon–carbon double bond of (*E*)-chalcones. *J. Braz. Chem. Soc.*, **25**, 1261–1269.

75. Carmona, R.C., Schevciw, E.P., de Albuquerque, J.L.P., et al. (2013) Joint use of microwave and glycerol–zinc(II) acetate catalytic system in the synthesis of 2-pyridyl-2-oxazolines. *Green Process Synth.*, **2**, 35–42.

76. Bhojane, J.M., Sarode, S.A. and Nagarkar, J.M. (2016) Nickel–glycerol: an efficient, recyclable catalysis system for Suzuki cross coupling reactions using aryl diazonium salts. *New J. Chem.*, **40**, 1564–1570.

77. Chahdoura, F., Favier, I., Pradel, C., et al. (2015) Palladium nanoparticles stabilised by PTA derivatives in glycerol: synthesis and catalysis in a green wet phase. *Catal. Commun.*, **63**, 47–51.

78. González-Liste, P.J., Cadierno, V. and García-Garrido, S.E. (2015) Catalytic rearrangement of aldoximes to primary amides in environmentally friendly media under thermal and microwave heating: another application of the bis(allyl)-ruthenium(IV) dimer [{RuCl(μ-Cl)(η^3:η^3-C$_{10}$H$_{16}$)}$_2$]. *ACS Sustain. Chem. Eng.*, **3**, 3004–3011.