



Glycerol: A green solvent for synthetic chemistry

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ABSTRACT

Glycerol is a biobased, biodegradable liquid known for its non-toxic, non-hazardous, non-volatile, and water-soluble properties, making it valuable in various applications. Derived from biodiesel production, it constitutes about 10% of the weight alongside fatty acid alkyl esters. Its availability and unique properties make glycerol an economically attractive and safe solvent for organic syntheses. Solvents, critical in chemical processes, require recycling or disposal, often via incineration. Eco-friendly profile of glycerol offers significant advantages over traditional solvents. Research has highlighted the role of glycerol as a hydrogen donor in metal-catalyzed transfer hydrogenation reactions, reducing compounds and aiding in metal nanoparticle preparation. Since 2010, glycerol has been recognized for its solvent capabilities in key organic reactions, such as C–C bond formations (e.g., Suzuki-Miyaura, Heck-Mizoroki), C–N, and C–P bond formations, among others. It also facilitates multicomponent reactions, showing high yields with various catalyst systems. The potential of glycerol extends to catalyst recyclability and

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sustainability in chemical processes. However, more systematic studies and modeling are needed to fully leverage its benefits. Exploring the use of crude glycerol could enhance cost-effectiveness and sustainability, and transitioning to continuous flow systems could improve productivity. Addressing these aspects can lead to broader and more sustainable glycerol utilization in the future.

1. Introduction

The utilization of biomass, particularly waste and non-food vegetable oils, as a carbon-neutral source for biofuel in thermal engines is undergoing further advancement due to the implementation of the circular economy concept (Lenardão et al., 2017; da Costa et al., 2022). When compared to fossil-based fuels, the use of biofuel derived from renewable feedstocks has a positive impact on overall CO₂ emissions. The continuous release of CO₂ into the environment from the combustion of fossil fuels, which is generated at a significantly slower rate than their consumption, contributes to the environmental burden (Lenardão et al., 2017). Biofuels offer additional advantages, such as a favorable energy balance and reduced levels of sulfur and nitrogen contaminants. These contaminants, when released during combustion, can generate harmful gases like SO₂, and NO_x (Yusoff et al., 2021; Galadima and Muraza, 2020; Valladares-Diestra et al., 2020). Biodiesel, among various biofuels, is considered a genuine alternative to petrodiesel. Its global production has increased from 20 billion liters in 2010 to 55 billion liters in 2021, with a stable production forecast for the coming years (Fig. 1) (OECD/FAO OECD-FAO, 2022).

Biodiesel holds a prominent position in the international market, with a well-established presence. When considering global production in 2021, the European Union emerged as the leading producer, manufacturing 19.72 billion liters, a figure that is expected to remain stable until the end of 2031. Following closely is the United States of America, which produced 11.1 billion liters. In the same year, Brazil and Argentina produced 6.62 and 0.640 billion liters of biodiesel, respectively. Additionally, Asian countries such as Thailand, Indonesia, and China contributed 9.2, 1.95, and 0.54 billion liters, respectively.⁶ Regarding, feedstocks, both current and projected biodiesel production heavily relies on conventional raw materials like vegetable oils and waste cooking oils (Table 1) (Kong et al., 2016; Kong et al., 2016).

Biodiesel production involves the transesterification of triglycerides using short-chain alcohol such as methanol or ethanol). The process can be enhanced by employing various types of catalysts, such as strong Brønsted bases or Lewis acids. The choice of catalyst depends on the properties of the feedstock, such as the content of free fatty acids (Scheme 1) (Melchiorre et al., 2022; Chilakamarry et al., 2022; Abdullah et al., 2022; Fattah et al., 2020). However, since glycerol is produced as a co-product in stoichiometric amounts (approximately 10% by weight), its availability and proper utilization pose new challenges for both academia and industries. Otherwise, the disposal of this by-product could create a bottleneck in biodiesel production (Cristino et al., 2020).

Glycerol is a tri-alcohol consisting of 3 carbon atoms, known as propan-1,2,3-triol. It is a viscous, odorless, transparent, and sweet liquid. Glycerol can be classified as a polar protic solvent and is considered an environmentally friendly substitute for traditional solvents. It possesses noteworthy characteristics such as biodegradability, biocompatibility, low toxicity, and a minimal risk profile. Glycerol is commercially available in crude, purified, and refined forms, each with distinct properties and compositions (Table 2).

Recent reviews have shed light on the wide range of technological and industrial applications of glycerol as a solvent across various

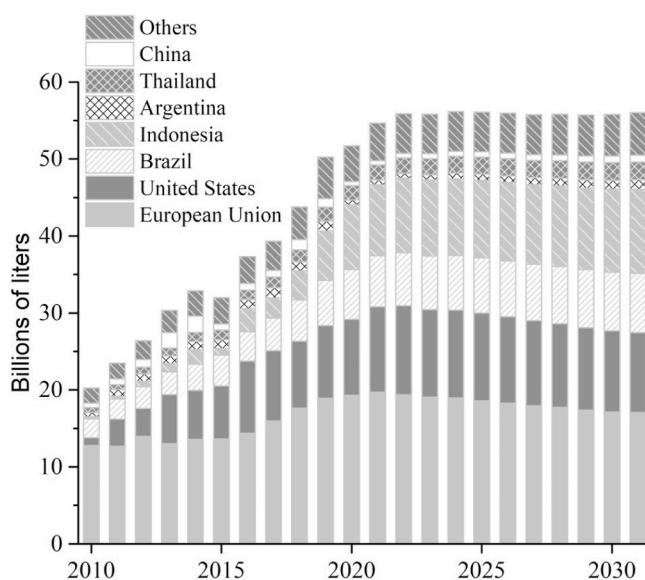


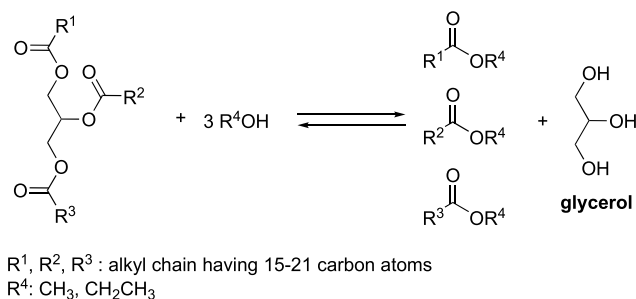
Fig. 1. Development of the world biodiesel production (OECD/FAO OECD-FAO).

Table 1
Biodiesel production ranking and major feedstock (OECD/FAO OECD-FAO).^{a,b}

	Production ranking (base period, 2021)	Major feedstock
European Union	1 (30.7%)	Rapeseed oil/Palm oil/used cooking oils
United States	2 (18.4%)	Soybean oil, used cooking oils
Indonesia	3 (17.5%)	Palm oil
Brazil	4 (13.1%)	Soybean oil
Argentina	5 (3.6%)	Soybean oil
Thailand	7 (3.0%)	Palm oil
China	8 (2.8%)	Used cooking oils

^a Numbers refer to country ranking in global production; percentages refer to the production share of countries in the base period.

^b In the OECD-FAO Agricultural Outlook 2022–2031, biodiesel includes renewable diesel (also known as Hydrotreated Vegetable Oil or HVO), although these are different products.

**Scheme 1.** General reaction involved in the production of biodiesel from triglycerides.**Table 2**
Chemical composition of *crude, purified, and commercial* glycerol (Chilakamarry et al., 2022; Nda-Umar et al., 2019).

Chemical composition	Crude glycerol	Purified glycerol	Refined glycerol
Glycerol (%)	60 to 80	99.1 to 99.8	99.2 to 99.98
Ash (%)	1.5 to 2.5	0.054	<0.002
Acidity content (mequiv/100 g)	0.7 to 1.3	0.10 to 0.16	0.04 to 0.07
Chloride content (ppm)	Below detection limit	1.0	0.6–9.5
Moisture content (%)	1.5 to 6.5	0.11 to 0.8	0.14 to 0.29
Soap (%)	3 to 5	0.1 to 0.16	–

sectors, including pharmaceuticals, food and beverages, surface coatings (such as varnishes, paints, and adhesives), as well as niche applications in material synthesis and explosives manufacturing (Fig. 2) (Lenardão et al., 2017; Ravichandiran and Gu, 2017; Luo et al., 2016; Kaur et al., 2020; Lima et al., 2021). However, despite its numerous applications, the production of crude glycerol currently exceeds its demand, resulting in its stockpiling without a clear purpose and subsequent depreciation (da Costa et al., 2022; da Costa et al., 2023). To prevent this situation, which adversely affects the entire biodiesel production process, it is crucial to explore alternative applications that can accommodate large quantities of glycerol.

Due to its high degree of functionality (possessing three hydroxyl groups for every three carbon atoms), glycerol has emerged as a promising platform molecule with the potential to be converted into various high-value chemicals for numerous applications. Processes such as hydrogenolysis, transesterification, etherification, and fermentation have been investigated for the transformation of glycerol into valuable compounds (da Costa et al., 2022; Kong et al., 2016; Ravichandiran and Gu, 2017; Goyal et al., 2021; Gokhale et al., 2022). However, there remain many unexplored avenues where glycerol can serve as a reagent for synthesizing high-added-value products or as a reactive solvent.

In any chemical process, whether conducted in a laboratory or on an industrial scale, a substantial quantity of solvents is typically required as reaction media and for product purifications (e.g. liquid extraction, chromatography). Due to the intricate nature of solvent-solute interactions, adopting greener alternatives necessitates a comprehensive approach (Pinto et al., 2019; Santoro et al., 2018; Gandeepan et al., 2019; Quaglia et al., 2022; Morelli Venturi et al., 2020). Consequently, the careful selection of a solvent for a specific step directly impacts the overall cost, hazard profile, and environmental footprint of the entire process (Lenardão et al., 2011, 2017; Díaz-Álvarez et al., 2014). Within this framework, reducing the usage of hazardous and petroleum-derived solvents, or substituting them entirely with less toxic and biobased solvents derived from biomass, significantly contributes to the development of a more sustainable chemical industry (Lenardão et al., 2017; Cristino et al., 2020; Tagliapietra et al., 2015; Gu and Jérôme, 2010; Cabrera et al., 2012). Research in Green Chemistry has been experiencing rapid growth, with increasing efforts focused on identifying sustainable processes that minimize environmental impact (Beatriz et al., 2011). This approach involves exploring innovative methods for synthesizing, processing, and utilizing chemical substances, aiming to prevent or mitigate pollution resulting from these activities (Oliveira et al., 2014; Nascimento et al., 2015).

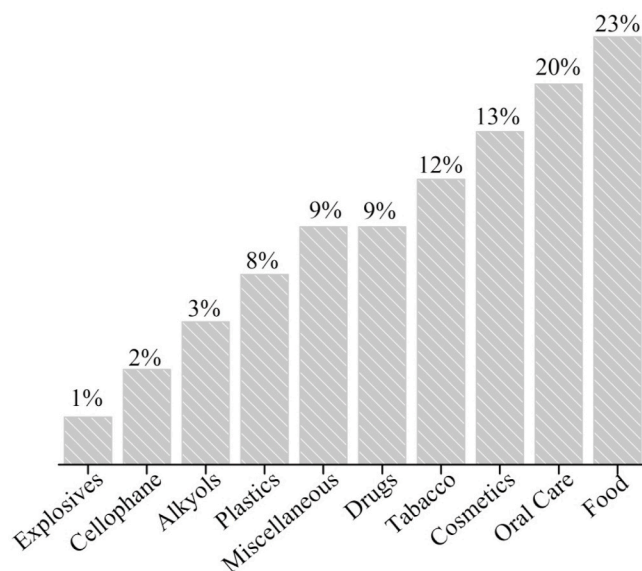


Fig. 2. Commercial consumption of glycerol (industrial sectors and volumes) (Ravichandiran and Gu, 2017).

In this regard, the utilization of glycerol as a reaction medium aligns with the principles of Green Chemistry, including safer chemical synthesis, the use of renewable raw materials, and the employment of safe solvents, thereby garnering the attention of researchers (Lenardão et al., 2017; Oliveira et al., 2014). Glycerol possesses three hydroxyl groups (-OH), which account for its hygroscopic nature and water solubility, facilitated by its ability to form hydrogen bonds. The property also aids in the dissolution of various inorganic compounds, including salts, acids, bases, and transition metals catalysts (Cristino et al., 2020; Chahdoura et al., 2013a; Chahdoura et al., 2013b; Chahdoura et al., 2014a; Chahdoura et al., 2014b; Chahdoura et al., 2015). Pertinent physicochemical properties and toxicity data of glycerol sourced from different studies are presented (Table 3) (Lenardão et al., 2017; Kong et al., 2016; Ravichandiran and Gu, 2017; Oliveira et al., 2014; Perin et al., 2010). Furthermore, when compared to other promising protic green solvents like protic ionic liquids (PILs), glycerol stands out as easily obtainable, harmless, cost-effective, and biodegradable (Beatriz et al., 2011). Moreover, the characteristics of glycerol render it suitable for the preparation of natural deep eutectic solvents (NADES). This solvent system comprises two or more compounds with hydrogen-bond acceptor (HBD) and hydrogen-bond donor (HBD)

Table 3

Physicochemical properties and toxicity data of glycerol (Kong et al., 2016; Ravichandiran and Y. Gu, 2017).

Description	Value
Molecular formula	C ₃ H ₅ (OH) ₃
Boiling point (°C)	290
Melting point (°C)	17.8
Vapor pressure at 25 °C (mmHg)	<1
LD50 (oral, rat) (mg kg ⁻¹) ^a	12 600
LD50 (dermal, rabbit) (mg kg ⁻¹)	>10 000
LD50 (rat, 1 h) (mg m ⁻³)	570
Auto ignition temperature (°C)	400
Critical temperature (°C)	492.2
Critical pressure (atm)	42.5
Flashpoint (°C)	160 (closed cup)
Dielectric constant at 25 °C	44.38
Dipole moment at 30–50 °C (D)	2.68
Viscosity at 20 °C (cP)	1410
Heat capacity at 25 °C (J mol ⁻¹ K ⁻¹)	221.9
Heat of vaporization (kJ mol ⁻¹)	91.7
The heat of fusion at 18.07 °C (cal g ⁻¹)	47.49
Density at 25 °C (g mL ⁻¹)	1.4746
Ethylene glycol and diethylene glycol limit (mg mL ⁻¹)	≤0.050
Residue on ignition	<0.001%
Chloride	≤0.001%
Sulfate	≤0.002%
Heavy metals (µg g ⁻¹)	<5
Chlorinated compounds	≤0.003%
Fatty acids and esters	Not more than 1 mL of 0.5 N sodium hydroxide is consumed

^a Lethal Dose (LD50) referring to the degree of acute toxicity of glycerol.

Table 4
Solubility of glycerol in various organic solvents (Kong et al., 2016).

Solubility	Solvents
Miscible	Water; methanol; ethanol; isopropanol; n-butanol; isobutanol; butan-2-ol; tert-amyl alcohol; o-cresol; diethylenetriamine; diethylformamide; diisopropylamine; triethylenetetramine; α -methylbenzylamine; α -methylbenzyl-diethanolamine; α -methylbenzylethanolamine; 2-methyl-5-ethylpyridine; 2-phenylethylamine; isopropanolamine; pyridine
5 wt%	Acetone
9 wt%	Ethyl acetate
Slightly soluble	Dioxane
Partially insoluble	Fatty acids, hydrocarbonate, hexane, benzene, chloroform; di-n-amylamine; di-n-butylamine
Insoluble	Ether; hydrocarbon; isoamyl acetate; n-amyl cyanide; anisaldehyde; benzyl ether; cinnamaldehyde; α -methylbenzyl-dimethylamine; o-phenetidine; diisobutyl ketone; diethyl acetic acid; di-2-ethylhexyl amine; ethyl chloroacetate; ethyl cinnamate; ethyl ether; ethyl phenylacetate; 3-heptanol; n-heptyl acetate; n-hexyl ether; methyl isopropyl ketone; 4-methyl-n-valeric acid; o-phenetidine; salicylaldehyde; tetradecanol; tri-n-butyl phosphate

properties, resulting in a mixture with a lower melting point compared to the individual compounds used. This approach allows for the utilization of solid biobased compounds (e.g. choline chloride, proline, betaine, glucose) at room temperature, optimizing the extraction performance of the solvent system. Glycerol-based NADES have recently found applications in ultrasound-assisted extraction systems as well (Hilali et al., 2022; Hikmawanti et al., 2021).

The solubility of glycerol in different organic solvents serves as a valuable reference for azeotropic distillation and analytical investigations of glycerol derivatives (Beatriz et al., 2011). A summary of glycerol's solubility in various organic solvents, highlighting its suitability as a reaction medium in organic synthesis is provided (Table 4) (Kong et al., 2016).

Glycerol has demonstrated successful application in unconventional heating and mixing techniques, including ultrasound- and microwave-assisted reactions, highlighting its promising performance as a reaction medium beyond conventional heating methods (Ravichandiran and Gu, 2017). Additionally, glycerol's presence as a solvent has been found to enhance both the yield and selectivity of the product in numerous reactions, enabling the recycling of both the catalyst and the glycerol or glycerol/catalyst system (Lenardão et al., 2017; da Costa et al., 2022; Gu and Jérôme, 2010).

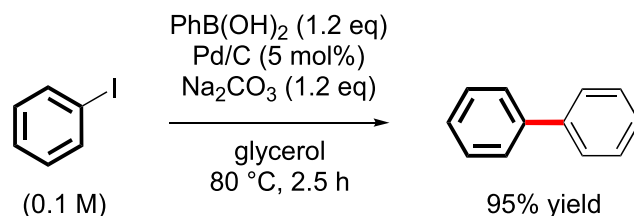
The interest in exploring new applications for glycerol surplus, arising from biodiesel production, has driven significant scientific and economic attention towards the field in recent years. This review offers a comprehensive analysis of the progress made in employing glycerol as a solvent in organic synthesis. It covers various aspects, including C–C bond formation, C–N and C–P bond formation, C–O, C–S, C–Se, and C–Te bond formation, as well as C–H, O–H, and N–H bond formation. Additionally, it explores reactions that involve the combination of multiple distinct bond formation processes including multicomponent reactions. Specifically, the review focuses on studies conducted between January 2010 and December 2022, presenting updated knowledge beyond previous literature reviews (Lenardão et al., 2017; Cristino et al., 2020; Ravichandiran and Gu, 2017; Goyal et al., 2021; Díaz-Álvarez et al., 2014; Tagliapietra et al., 2015; Chahdoura et al., 2014a; Favier and Pla, 2018; Mišan et al., 2019). Throughout the review, schematic representations of the described approaches are included, along with mechanistic representations in selected examples. For the sake of clarity, glycerol combined with another compound to form a eutectic solvent is not considered in this review.

2. Glycerol as reaction medium

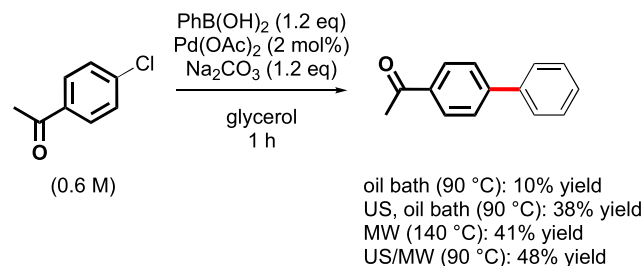
This section presents an overview of the studies exploring the utilization of glycerol as a solvent in organic syntheses. To facilitate a comprehensive discussion of the extensive body of research, the part is divided according to the different bonds created. These encompass the formation of C–C, C–N, and C–P bonds, as well as C–O, C–S, C–Se, and C–Te bonds. Additionally, they encompass the formation of C–H, O–H, and N–H bonds, as well as multicomponent reactions that entail the formation of C–C, C–N, and C–O bonds.

2.1. The C–C bond formation

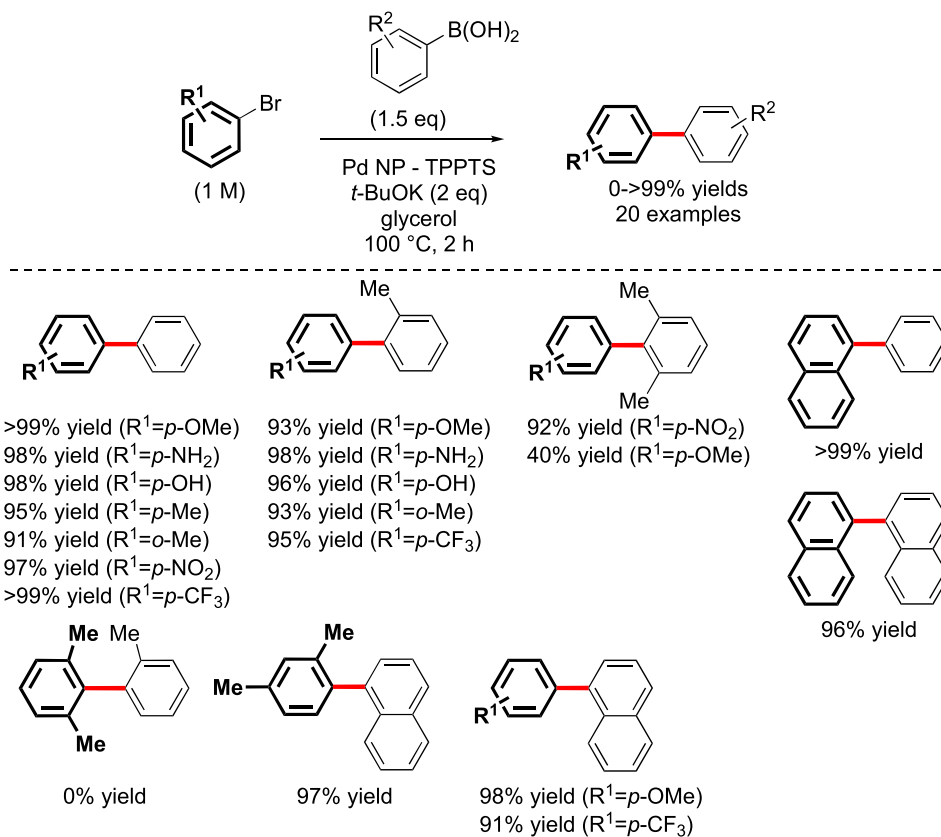
During recent decades the transition metal-catalyzed homo/cross-coupling reactions of organic substrates have become indispensable tools in the construction of a variety of molecules via the formation of C–C bonds (Lakshmidivi et al., 2021; Venkateswarlu, 2021; Appa et al., 2021). Examples of C–C bond-forming reactions in glycerol as a solvent are described in the literature. These include the Suzuki-Miyaura coupling, Heck-Mizoroki coupling, Sonogashira coupling, Barbier reaction, condensation reaction, metathesis, and the Pauson-Khand carbocyclization reaction. These reactions have found extensive utility within the pharmaceutical industry, facilitating the synthesis of crucial bioactive structures. Traditionally, these protocols have relied on the use of conventional polar solvents like DMSO, DMF, and MeCN, all of which pose environmental hazards (Farhang et al., 2022; Len et al., 2017; Beletskaya and Cheprakov, 2000; Chinchilla and Najera, 2007; Cordovilla et al., 2015; del Pozo et al., 2016). However, recent years have witnessed a noteworthy surge in the adoption of solvents derived from biomass, serving as environmentally benign reaction media in cross-coupling reactions catalyzed by palladium, copper, and nickel. Among C–C cross-coupling reactions, the Suzuki-Miyaura reaction stands out as a renowned method for synthesizing high-value chemicals. A notable application of this reaction involves the use of glycerol and its analogous solvents in the cross-coupling of iodobenzene and phenylboronic acid, yielding the desired 1,1'-biphenyl in an impressive 95% yield within a 2.5-h period at 80 °C (Scheme 2) (Wolfson et al., 2012). The effects of various solvents: glycerol, 1, 2-propanediol, diacetin, and triacetin were examined in this study. Both homogeneous and heterogeneous palladium catalysts, Pd(OAc)₂ and Pd/C, were employed in this investigation. The findings underscored the considerable influence of the reaction media's



Scheme 2. C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction catalyzed by Pd/C for the synthesis of 1,1'-diphenyl in glycerol (Wolfson et al., 2012).



Scheme 3. C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction catalyzed by Pd(OAc)₂ for the synthesis of 1,1'-diphenyl using different modes of activation in glycerol (Cravotto et al., 2011).



Scheme 4. C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction catalyzed by Pd NP - TPPTS for the synthesis of 1,1'-diphenyl derivatives in glycerol (Chahdoura et al., 2013b).

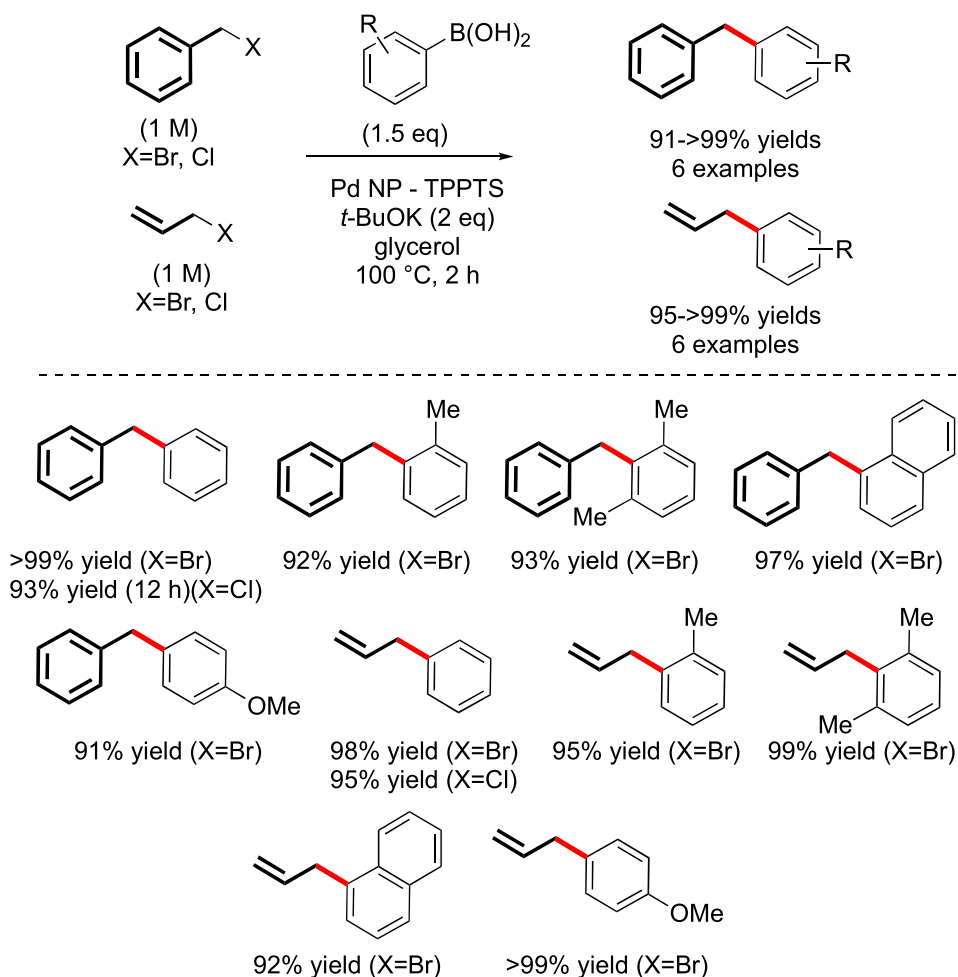
polarity (expressed as logP) on the reaction's outcome. Remarkably, the highest yield (100%) was attained with 1,2-propanediol as the solvent, attributed to its intermediate polarity (logP -0.92), which was well-suited for the specific reaction conditions ($80\text{ }^\circ\text{C}$ for 2.5 h). Intriguingly, even when glycerol was utilized as the solvent, the overall yield remained excellent at 95%, despite its markedly higher

polarity ($\log P -4.15$) – over three orders of magnitude lower than that of propane-1,2-diol. Furthermore, the article emphasized the connection between the product's solubility in the reaction solvent and its effectiveness in extraction using petroleum ether. Notably, glycerol exhibited superior extraction efficiency (100% yield) in comparison to propane-1,2-diol (81%).

Subsequently, noteworthy progress has been achieved in the application of glycerol as a reaction medium through the incorporation of high-intensity ultrasound (US) and/or microwave (MW) techniques. In this context, an extensive investigation into the palladium-catalyzed Suzuki coupling reaction in glycerol was conducted, encompassing the use of US, MW, or a combination of both techniques (Cravotto et al., 2011). Among these alternative approaches, the combination of MW and US exhibited the most favorable outcomes due to heightened heat and mass transfer effects.

By commencing with 4-chloroacetophenone and boronic acid in the presence of $\text{Pd}(\text{OAc})_2$ (2 mol%) under MW/US irradiation, the desired target was successfully synthesized with an impressive 48% yield after a 1-h reaction at 90 °C (Scheme 3). Similar reaction conditions were applied for the synthesis of other 1,1'-biphenyl derivatives, utilizing palladium-cross-linked chitosan as a heterogeneous catalyst (Pd content: 5 wt%). This involved the conversion of 3-bromoanisole and 4-chloroacetophenone to their respective 1,1'-biphenyl products.

A fascinating investigation centered on the synthesis of palladium nanoparticles (Pd NPs) within glycerol and their subsequent application in $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^2)$ and $\text{C}(\text{sp}^3)\text{-C}(\text{sp}^2)$ bond formations via Suzuki-Miyaura cross-coupling reactions has been documented. The process began with $\text{Pd}(\text{OAc})_2$ and tris(3-sulfophenyl)phosphine trisodium salt (TPPTS) employed as a stabilizer in glycerol, and was conducted under hydrogen pressure (3 bar) at 80 °C for a duration of 12 h, resulting in the formation of Pd NPs with a yield of 35%. Next, a combination of aryl, benzyl, or allyl halides, arylboronic acid, and *t*-BuOK, alongside Pd NPs within glycerol, were subjected to heating at 100 °C for 2 h, yielding the anticipated diaryl compounds (Schemes 4 and 5) (Chahdoura et al., 2013b). As anticipated, substrates containing chloro substituents produced the desired chemicals, albeit with a prolonged reaction time of 12 h compared to 2 h for other substrates. Intriguingly, when initiating the reaction with 4-bromoaniline possessing an available NH_2 group, no Buchwald-Hartwig amination was observed. Furthermore, the Pd NP catalyst demonstrated remarkable recyclability, maintaining its



Scheme 5. $\text{C}(\text{sp}^2)\text{-C}(\text{sp}^3)$ Suzuki-Miyaura cross-coupling reaction catalyzed by Pd NP - TPPTS for the synthesis of benzyl aryl and allyl aryl derivatives in glycerol (Chahdoura et al., 2013b).

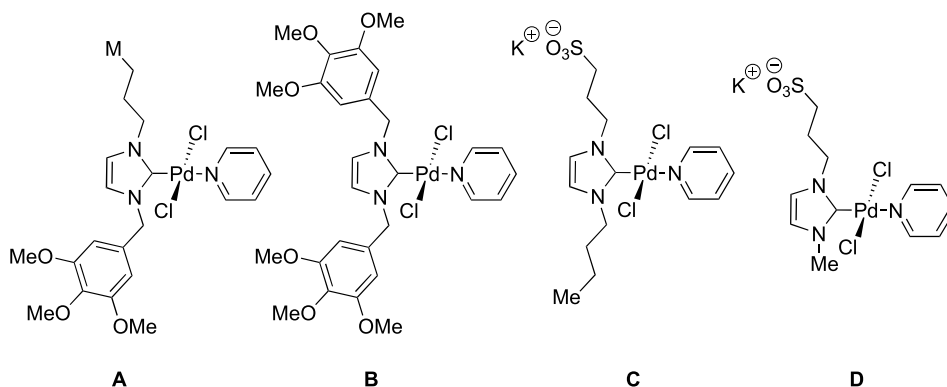
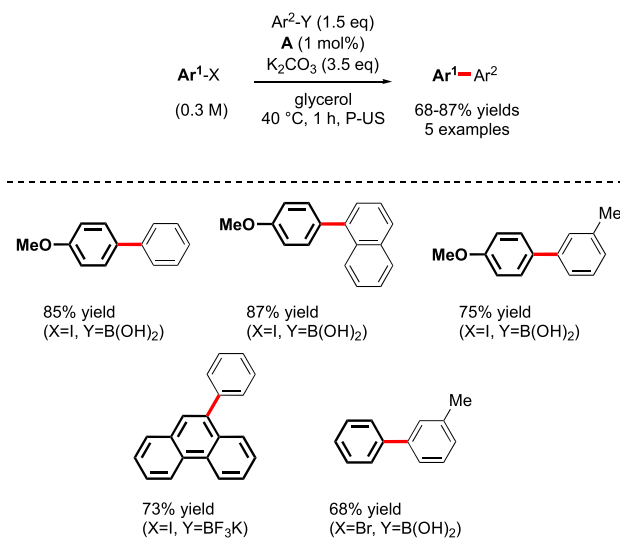


Fig. 3. Palladium(II)–NHC based complexes A–D (Azua et al., 2013).

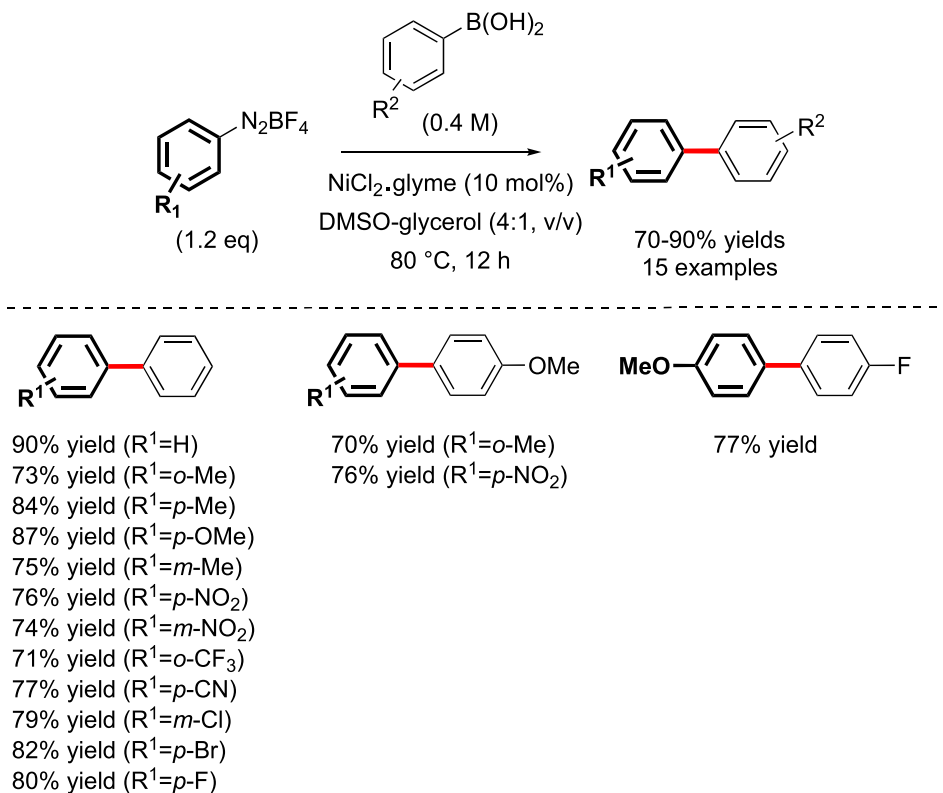


Scheme 6. C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction catalyzed by palladium(II)–NHC based complexes A for the synthesis of 1,1'-diaryl derivatives using P-US irradiation mode (Azua et al., 2013).

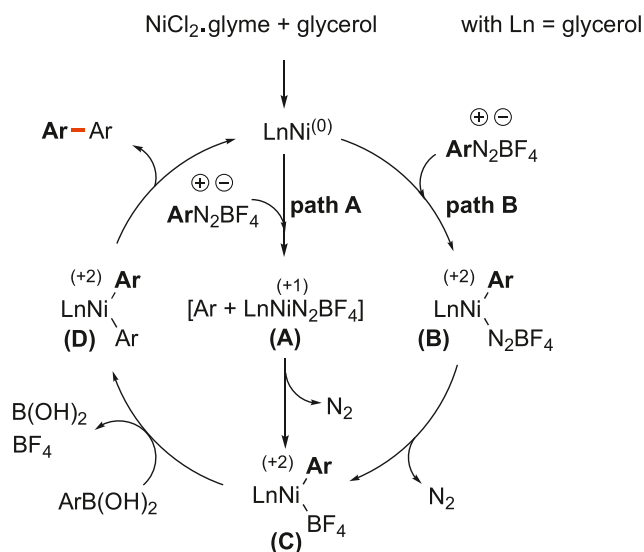
activity and selectivity across ten successive cycles (synthesis of 1-phenylnaphthalene). Investigation into the organic products, isolated and analyzed through ICP-MS, unveiled minimal palladium leaching.

Pulsed ultrasound (P-US) conditions were harnessed for the Suzuki-Miyaura cross-coupling reaction, employing Pd *N*-heterocyclic-carbene (NHC) precursors A–D (Fig. 3) (Azua et al., 2013). Within this framework, a solution comprising iodo (or bromo) arenes and boronic acid (or trifluoroboronate), in the presence of a palladium(II)–NHC complex A, in glycerol, yielded the desired 1,1'-biphenyl derivatives 68–87% yields at 40 °C for 1 h under P-US conditions (40% amplitude, with the probe activated for 10 s followed by a 10-s probe deactivation period) (Scheme 6). Although the authors did not detail a comprehensive methodology, they did highlight that irrespective of the chosen catalyst A–D, substrate variations (aryl iodide and aryl bromide), and boron source alternatives (B(OH)₂ and BF₃K), the efficiency of the C–C cross-coupling reaction remained consistently high. Transmission electron microscopy (TEM) and X-ray photoelectron spectroscopy (XPS) analyses performed on the reaction mixtures obtained during the catalytic sequences unveiled the emergence of palladium nanoparticles (Pd NPs) under P-US conditions within glycerol. As for the catalyst-solvent system's recyclability, a decrease in catalytic activity was noted after the initial cycle. Inductively coupled plasma mass spectrometry (ICP-MS) analysis corroborated the release of palladium and the presence of inorganic salts detected in the filtrate following each run, which likely contributed to the observed activity reduction.

In a green chemistry approach, the substitution of noble metals such as palladium by non-noble metals such as nickel is a recent challenge. A homogeneous and reusable catalytic system involving nickel-glycerol has been documented for the Suzuki-Miyaura cross-coupling reaction utilizing aryl diazonium salts. The procedure entailed stirring a mixture of diazonium salt and phenyl boronic acid in the presence of NiCl₂-glyme (10 mol%) within a blend of DMSO and glycerol at 80 °C for a duration of 12 h. This methodology yielded 1,1'-biphenyl in an impressive 90% yield (Scheme 7) (Bhojane et al., 2016). Expanding the reaction's scope, the study encompassed 15 distinct 1,1'-biphenyl derivatives, each obtained within a 12-h timeframe at 80 °C. The catalytic system demonstrated its compatibility with both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs), leading to the formation of diaryl products

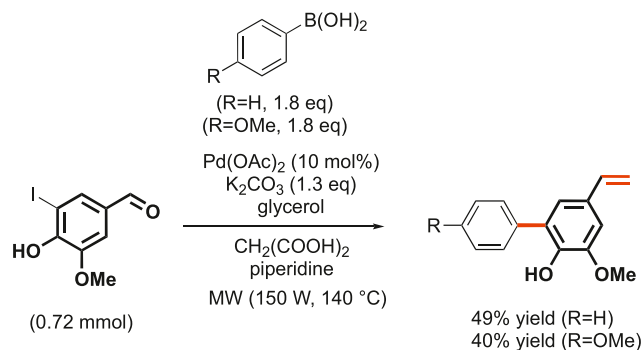


Scheme 7. C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction with arenediazonium catalyzed by NiCl₂·glyme for the synthesis of 1,1'-diphenyl (Bhojane et al., 2016).

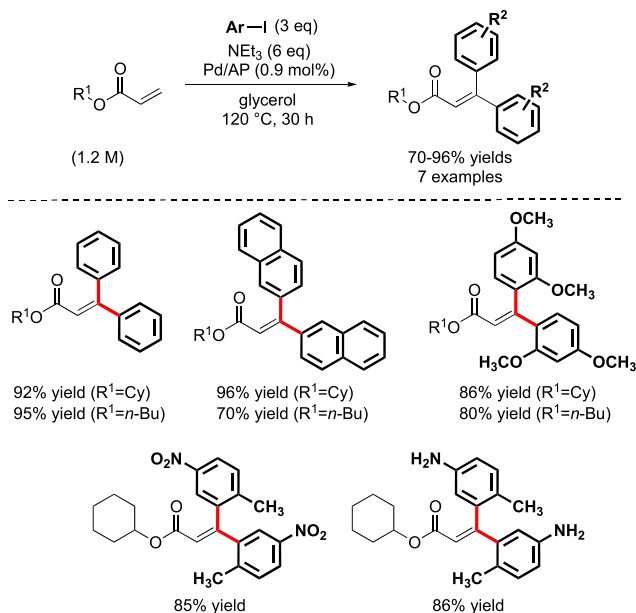


Scheme 8. Plausible mechanism for the C(sp²)-C(sp²) Suzuki-Miyaura cross-coupling reaction with arenediazonium catalyzed by NiCl₂·glyme in glycerol (Bhojane et al., 2016).

exhibiting yields ranging from good to excellent (70–90%). Notably, the catalyst-solvent system displayed successful recyclability over 6 consecutive runs, consistently maintaining yields between 90% and 80%. The heightened polarity and elevated boiling point of glycerol proved instrumental in enabling efficient reuse of the NiCl₂·glyme catalyst/solvent system, thereby accentuating glycerol's effectiveness as a sustainable and reusable solvent option. The authors proposed a mechanism where glycerol was used as ligand. Initially, an *in situ* generation of Ni⁽⁰⁾ species occurs due to glycerol. The reaction can proceed through either a single electron transfer



Scheme 9. Direct synthesis of hydroxy-biarylstyrenes and by one-pot tandem Suzuki-Miyaura/Knoevenagel-Doebner reaction using MW irradiation modes in glycerol (Sharma et al., 2011).



Scheme 10. C(sp²)-C(sp²) Heck-Mizoroki cross-coupling reaction catalyzed by Pd NPs stabilized by an aminopolysaccharide for the synthesis of β,β-diaryl compounds in glycerol (Delamplé et al., 2010).

(SET) or an oxidative addition mechanism. In path A, the process follows a SET mechanism, where Ni⁽⁰⁾ is transformed into the Ni⁽⁺¹⁾ intermediate **A** through the oxidative addition of an aryl diazonium salt, which then rapidly converts into intermediate **C**. In path B, the oxidative addition of an aryl diazonium salt changes Ni⁽⁰⁾ to Ni⁽⁺²⁾, which subsequently transforms into intermediate **C**. Intermediate **C** complexes with aryl boronic acid, facilitating the subsequent transfer of the phenyl group to the nickel complex (transmetalation), resulting in intermediate **D**. The final step involves the formation of a C–C bond through reductive elimination, ultimately regenerating the Ni⁽⁰⁾ catalyst (Scheme 8).

To synthesize hydroxy-biarylstyrene compounds relevant in both biological and industrial contexts, researchers have introduced a novel tandem reaction, combining the Suzuki-Miyaura and Knoevenagel-Doebner reactions (Sharma et al., 2011). Initially, *N,N*-dimethylformamide (DMF) was the chosen solvent, though without success. The researchers then experimented with glycerol. Beginning with 4-hydroxy-5-iodo-3-methoxybenzaldehyde, a sequential one-pot reaction involving phenylboronic acid and K₂CO₃, catalyzed by Pd(OAc)₂ (10 mol%) in glycerol, yielded the corresponding biarylbenzaldehyde. Subsequently, the introduction of malonic acid, facilitated by piperidine, accomplished the homologation. Employing microwave conditions, the styrene derivative was obtained with a 49% yield. When utilizing 4-methoxyphenylboronic acid, the desired compound was obtained with a 40% yield (Scheme 9). This approach exhibited enhanced yields compared to reactions conducted in DMF (10%) and PEG-200 (15%) as reaction solvents. The authors highlighted that their study marks the pioneering use of such a versatile strategy for the direct conversion of unprotected hydroxybenzaldehydes.

Among the other C–C cross-coupling reactions, the Heck-Mizoroki reaction is certainly the most common method to introduce an acrylate moiety. A convenient method for regioselective symmetrical and asymmetrical β,β-diarylation of acrylate derivatives in

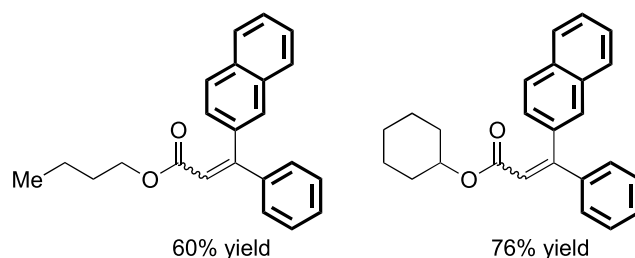
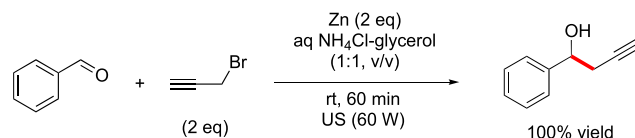


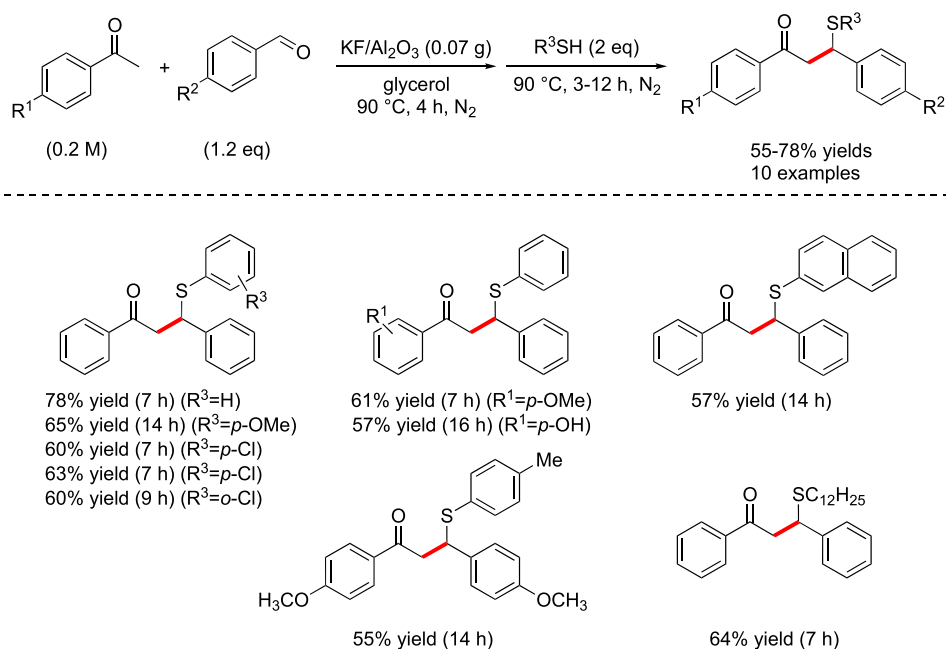
Fig. 4. Two successive Heck-Mizoroki cross-coupling reactions for the synthesis of asymmetrical β,β -diaryl compounds in the presence of Pd NPs stabilized by an aminopolysaccharide (AP) surfactant in glycerol (Delample et al., 2010).



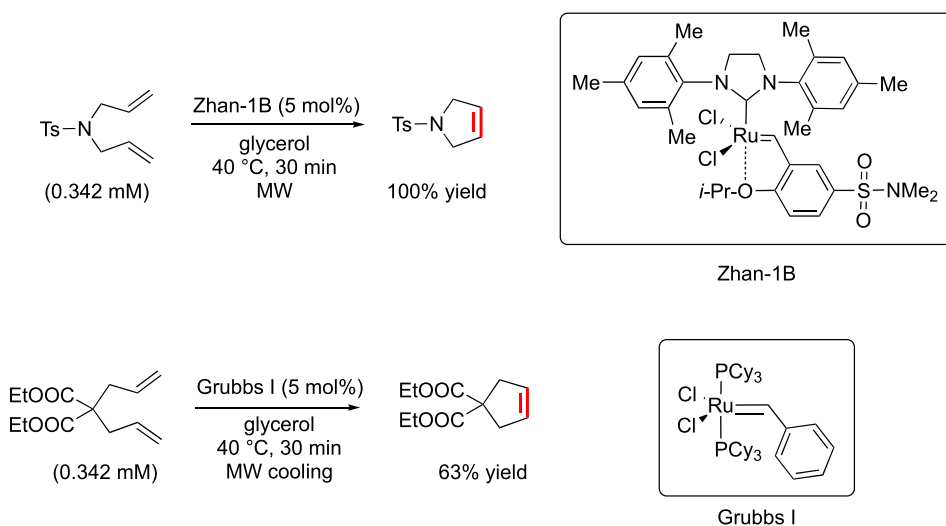
Scheme 11. Barbier reaction catalyzed by Zn for the synthesis of racemic 1-phenylbut-3-yn-1-ol catalyzed by Zn in glycerol (Cravotto et al., 2011).

glycerol using air-stable palladium nanoparticles (Pd NPs) was reported (Scheme 10) (Delample et al., 2010). The study demonstrated that the costly and air-sensitive palladium complexes typically required for this reaction could be substituted with easily prepared Pd NPs stabilized by an aminopolysaccharide (AP) surfactant derived from sugar. Starting from iodobenzene, cyclohexylacrylate, and triethylamine in the presence of Pd/AP (0.9 mol%) in glycerol at 120 °C for 30 h, the corresponding β,β -diaryl derivative was obtained in 92% yield (Scheme 10). Application of the above strategy with a range of various acrylate and aryl iodide permitted to give the symmetrical β,β -diaryl derivatives in 70–96% yield.

Importantly, it should be highlighted that solely the monoarylated product was achieved at a lower temperature (90 °C as opposed to 120 °C). Armed with these findings, the synthesis of asymmetrical β,β -diarylated alkenes was accomplished using a two-step Heck-Mizoroki process, performed at both 90 °C and 120 °C. Notably, purification steps were omitted following the initial cross-coupling reaction. The resulting (*E/Z*) isomers were attained with yields of 60% and 76% correspondingly (Fig. 4). This strategy established an economical, secure, and environmentally conscious pathway to valuable products within a span of 30 h (Delample et al., 2010). Following product extraction using supercritical CO₂, the researchers endeavored to recycle the Pd/AP-glycerol phase for successive reactions; however, they noted a gradual decline in yield over multiple cycles. Intriguingly, they also uncovered that the catalytic activity could be fully regenerated by extracting the Pd nanoparticles using dichloromethane and then recombining them with fresh



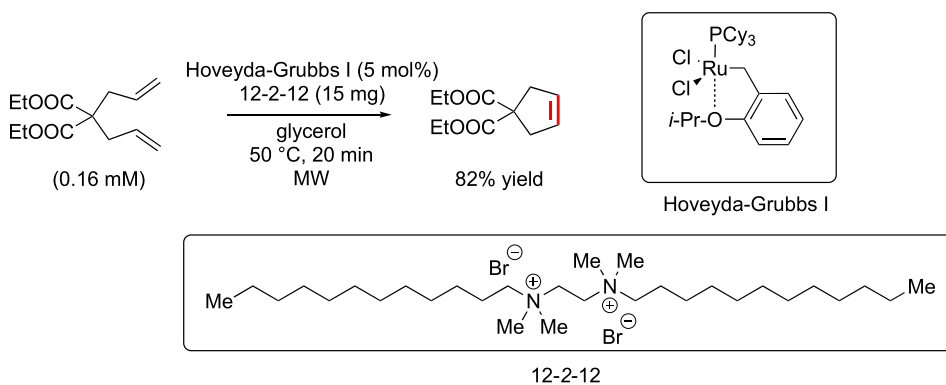
Scheme 12. Sequential one-pot reaction catalyzed by KF/Al₂O₃ for the synthesis of β -aryl- β -sulfanyl ketones in glycerol (Perin et al., 2014).



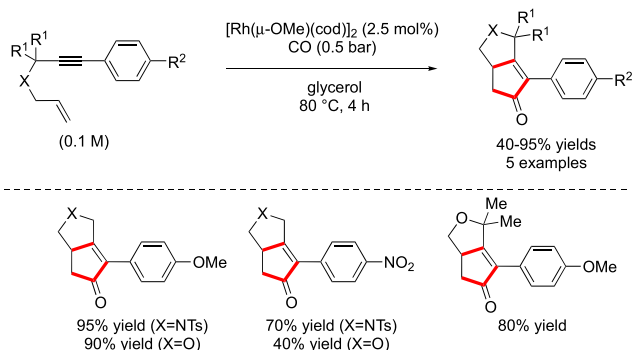
Scheme 13. Ring-closing metathesis of *N,N*-diallyltosylamine and diethyl diallylmalonate catalyzed by Ru(II) catalysts: Zhan-1B and Grubbs I under microwave irradiation in glycerol (Bakhrou et al., 2010).

glycerol. As a result, they concluded that the decline in performance observed across cycles was attributed to the accumulation of salts in the glycerol phase, rather than catalyst deactivation.

Notably, Pd nanoparticles synthesized from Pd(OAc)₂ and tris(3-sulfoxyphenyl)phosphinetrisodium salt (TPPTS) demonstrated remarkable efficiency in the Heck-Mizoroki cross-coupling reaction, Sonogashira cross-coupling reaction, C–H bond activation and the hydrogenation of various unsaturated C–C bonds (Chahdoura et al., 2013b). These included mono-substituted CH=CH₂, di-*gem*-substituted CH=CH₂, 1,2-disubstituted CH=CH, as well as endocyclic C=C bonds found in compounds like cyclohexene,



Scheme 14. Ring-closing metathesis of diethyl diallylmalonate catalyzed by Hoveyda-Grubbs I as catalysts and surfactant 12-2-12 under microwave irradiation in glycerol (Hamel et al., 2014).

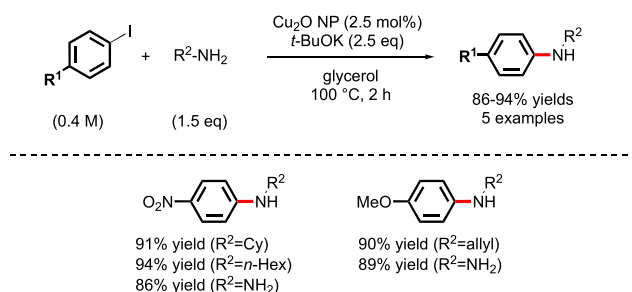


Scheme 15. Rh-catalyzed Pauson-Khand carbocyclisation reaction of enynes catalyzed by [Rh(μ-OMe)(cod)]₂ in glycerol (Chahdoura et al., 2013a).

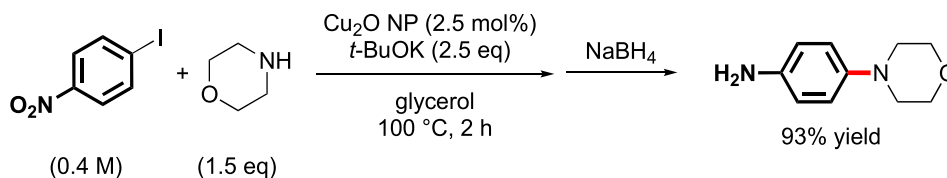
cyclopentene, coumarin lactone, and nitro groups. High yields of the corresponding saturated compounds were obtained through these processes. However, it's worth noting that indole and furan derivatives did not yield satisfactory results, achieving yields below 5%. Building upon the success observed in C–C cross-coupling reactions and the reduction of unsaturated C–C bonds, investigations were carried out to explore the application of Pd nanoparticle catalysts in one-pot C–C cross-coupling/hydrogenation sequential processes. Remarkably, this study successfully accomplished the synthesis of 4-(4-methoxyphenyl)-butan-2-one, a compound of industrial importance due to its association with the raspberry fragrance. This synthesis was achieved through a sequential one-pot Heck-hydrogenation process. Impressively, the target ketone was obtained with an outstanding overall yield of 95%. The dual catalytic behavior of the Pd nanoparticle catalyst in the glycerol phase, along with its unique characteristics of functioning both on a molecular level and at the surface, has enabled the facilitation of compelling applications in one-pot multi-step transformations catalyzed by palladium.

Barbier reaction in glycerol was studied in the presence of Zn dust and NH_4Cl starting from benzaldehyde (Cravotto et al., 2011). At room temperature for 1 h under sonication, the target 1-phenylbut-3-yn-1-ol was obtained in 100% yield (Scheme 11). It was notable that the use of ultrasound cleaning bath was negligible on the reaction rate whereas an ultrasound horn was efficient.

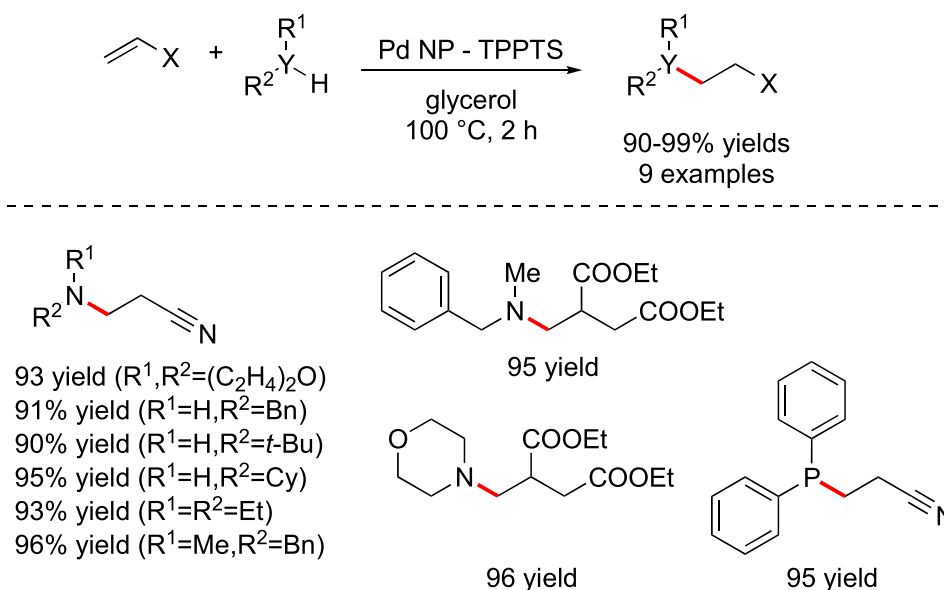
Running alongside addition reactions on alkynes, there have been documented cases of addition reactions occurring on alkenes



Scheme 16. C–N bond formation catalyzed by Cu_2O NP for the synthesis of the aniline derivatives in glycerol (Chahdoura et al., 2014b).



Scheme 17. One-pot sequential C–N cross-coupling reaction followed by chemical reduction for the synthesis of aniline derivative catalyzed by Cu_2O NP in glycerol (Chahdoura et al., 2014b).



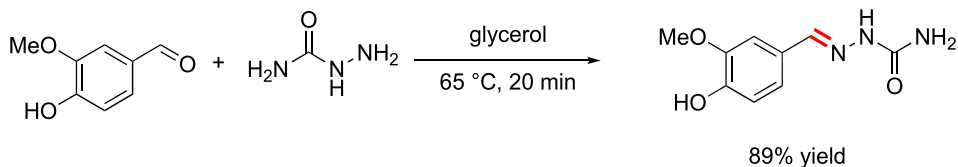
Scheme 18. C–N and C–P Bond formation catalyzed by Pd NPs TPPTS in glycerol (Chahdoura et al., 2013b).

when glycerol is utilized as the solvent. An illustrative instance involves a sequential procedure that encompasses aldol condensation, followed by thia-Michael addition, to achieve the synthesis of β -sulfanylketones using both liquid and solid reagents (Perin et al., 2014). This cascade process leverages glycerol as the solvent and employs $\text{KF}/\text{Al}_2\text{O}_3$ as a pivotal catalyst, operating at a temperature of 90°C (Scheme 12). The presence of electron-withdrawing and electron-donating groups in the aryl thiols was noted to result in a slight reduction in the yield of β -sulfanyl ketones. The condensation reaction between acetophenone and benzaldehyde within the $\text{KF}/\text{Al}_2\text{O}_3/\text{glycerol}$ system emerged as the rate-determining step, resulting in the formation of the chalcone product with an efficiency level of 45%.

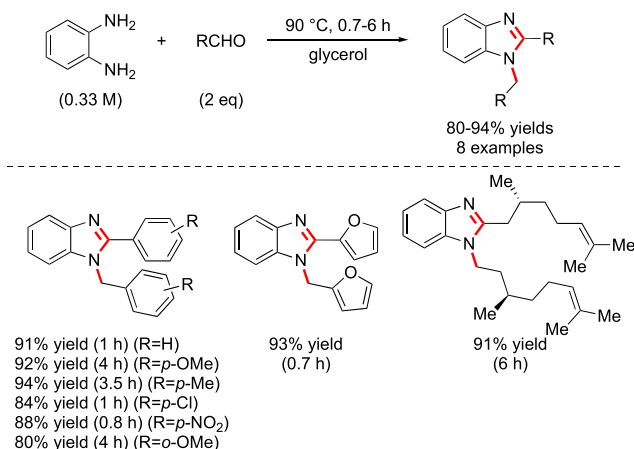
Olefin metathesis reactions have exerted a profound influence on organic synthesis in recent decades. Amongst these transformative reactions, the process of alkene ring-closing metathesis (RCM) has risen to prominence as a widely employed technique in synthetic procedures. An exploration into the utilization of microwave-assisted activation for ring-closing metathesis (RCM) reactions, using either *N,N*-diallyltosylamine or diethyl diallylmalonate as starting materials, in the presence of Ru(II) catalysts within a glycerol medium, was conducted (Bakhrou et al., 2010). When commencing from *N,N*-diallyltosylamine within glycerol, the most effective catalyst was identified as the commercially available Zhan-1B. This catalyst facilitated the formation of the desired cyclic product in a quantitative yield within just 30 min at 40°C under microwave irradiation (Scheme 13). For the RCM transformation of diethyl diallylmalonate, optimal results were achieved using the Grubbs I catalyst after 1 h at 40°C , while concurrently maintaining reactor cooling. Notably, under the same conditions but without vessel cooling, the RCM adduct yield was reduced (49% compared to 63%). This decrement was attributed by the authors to the potential formation of byproducts, stemming from the glycerolysis of the ester groups within diethyl diallylmalonate.

The same research group also documented the utilization of micellar catalysis for the RCM of diethylmalonate under microwave irradiation (Hamel et al., 2014). By employing the bis(*N,N*-dimethyl-*N*-dodecyl)ethylene-1,2-diammonium dibromide: 12-2-12 surfactant and the Hoveyda-Grubbs I catalyst in a glycerol medium, the cyclic alkene was obtained in an 82% yield within just 20 min at 50°C under microwave irradiation. In contrast, when glycerol was used as the sole solvent, a yield of only 52% was achieved after 1 h at 50°C (Scheme 14). It is worth highlighting that in the absence of the surfactant, PEG-3400 resulted in a quantitative yield, while with the introduction of the surfactant, water yielded only a trace amount of the desired compound. The investigation suggested that the formation of byproducts was primarily linked to glycerolysis, and the incorporation of surfactants led to enhanced solubility and improved diffusion of organic substrates and catalysts. This, in turn, expedited the primary reaction rate and suppressed undesired side processes.

Multi-step syntheses, such as the Rh-catalyzed Pauson-Khand reaction (PKR), offer invaluable means of cost reduction and environmental impact mitigation. Within a one-pot PKR reaction, the concurrent formation of multiple C–C bonds is achieved, alongside the incorporation of a carbonyl functionality derived from carbon monoxide. This study delved into the feasibility of Rh-catalyzed PKR carbocyclization within a glycerol medium (Chahdoura et al., 2013a). Commencing from 1,6-enynes, catalyzed by ligand-free $[\text{Rh}(\mu\text{-OMe})(\text{cod})_2]$ at 80°C and CO (0.5 bar) in glycerol, bicyclo[3.3.0]octenones were generated with yields reaching up to 40%. The efficacy of this reaction was attributed to glycerol's Brønsted acid behavior, a proposition substantiated by extensive NMR



Scheme 19. Catalyst-free green protocol for the synthesis of vanillin semicarbazone in crude glycerol (Jovanović et al., 2013).

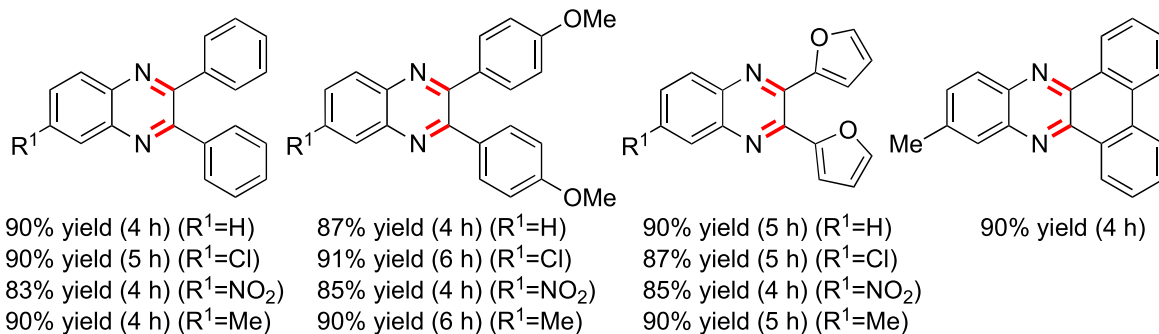
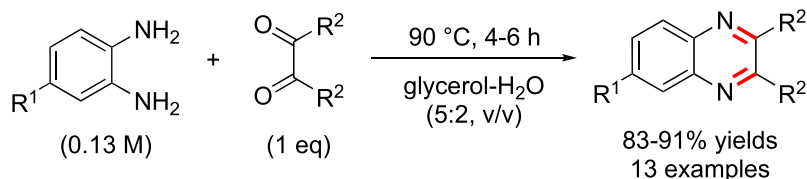


Scheme 20. Catalyst-free synthesis of benzimidazole derivatives in glycerol (Radatz et al., 2011).

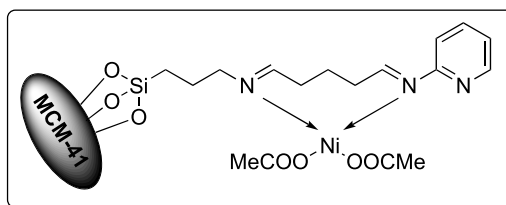
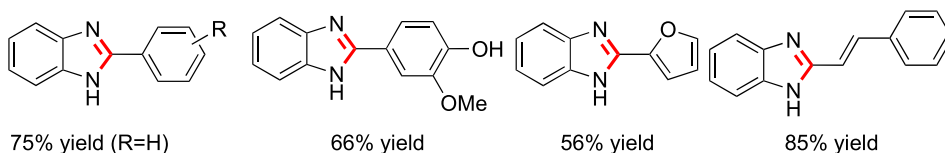
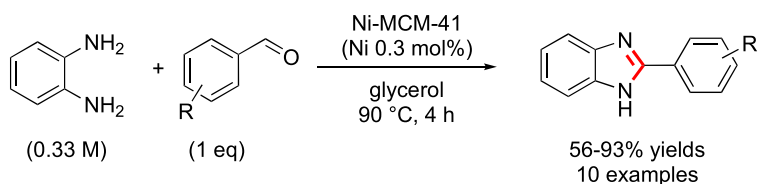
investigations affirming its catalytic role in the process. Notably, substrates containing electron-donating groups within the aryl moiety exhibited heightened reactivity, further underscoring the effectiveness of this catalytic system (Scheme 15). These findings illuminate glycerol's non-innocent function in the context of PKR. Its coordination properties facilitate the destabilization of alkoxide groups, thereby promoting the formation of coordinatively unsaturated intermediates crucial for enyne coordination. Moreover, glycerol contributes to intermediate stabilization through its coordinating behavior. However, it's important to note that this study did not evaluate the reusability of both glycerol and the catalyst.

2.2. The C–N and C–P bond formation

Nitrogen-containing compounds have a ubiquitous presence, spanning from natural products to synthetic compounds. In parallel with C–C cross-coupling reactions, the cross-coupling of amines, aryl halides, and pseudohalides to establish C–N bonds has emerged as a remarkably versatile technique for synthesizing aromatic amines, covering a broad spectrum of both fundamental and applied research domains (Ruiz-Castillo and Buchwald, 2016). Instances of C–N bond-forming reactions taking place in glycerol as a solvent are documented in the literature. Notable examples encompass the Buchwald-Hartwig reaction, C–H-bond activation, condensation

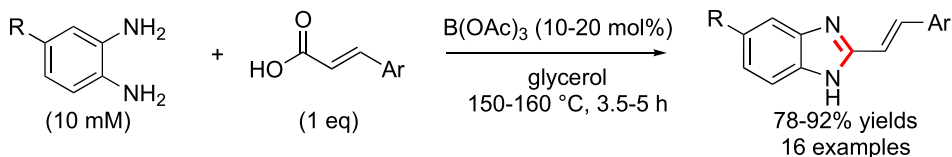
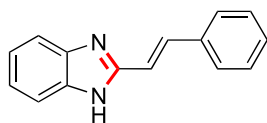
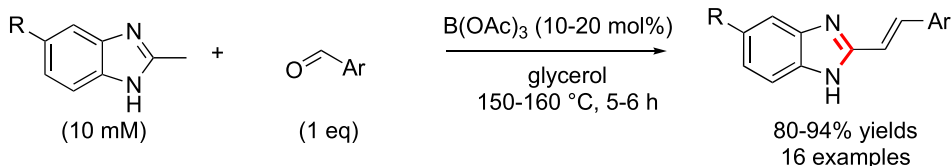


Scheme 21. Catalyst-free synthesis of quinoxalines in glycerol (Bachhav et al., 2011).

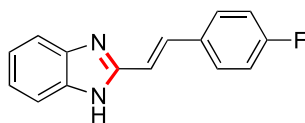


Ni-MCM-41

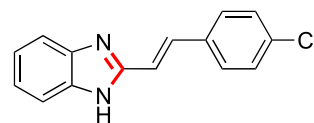
Scheme 22. Synthesis of benzimidazole derivatives catalyzed by Ni-MCM-41 in glycerol (Bharathi et al., 2019).

Method A**Method B**

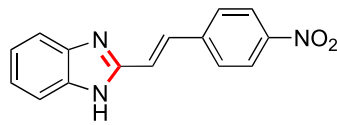
Method A: 90% yield (160 °C, 4 h)
 Method B: 88% yield (160 °C, 6 h)



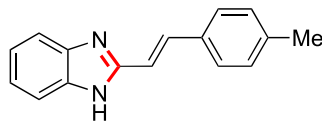
Method A: 86% yield (150 °C, 3.5 h)
 Method B: 92% yield (160 °C, 6 h)



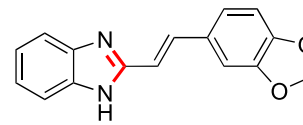
Method A: 90% yield (160 °C, 3.5 h)
 Method B: 90% yield (160 °C, 6 h)



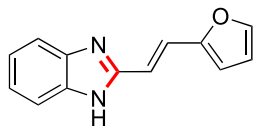
Method A: 90% yield (150 °C, 4 h)
 Method B: 92% yield (160 °C, 6 h)



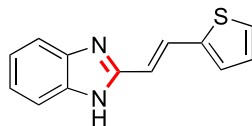
Method A: 85% yield (160 °C, 5 h)
 Method B: 88% yield (160 °C, 6 h)



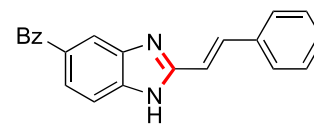
Method A: 78% yield (160 °C, 5 h)
 Method B: 85% yield (150 °C, 6 h)



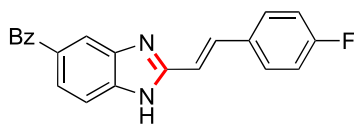
Method A: 92% yield (150 °C, 5 h)
 Method B: 94% yield (150 °C, 5 h)



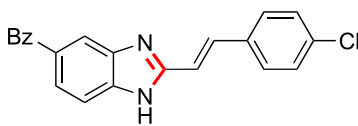
Method A: 92% yield (160 °C, 5 h)
 Method B: 90% yield (150 °C, 5 h)



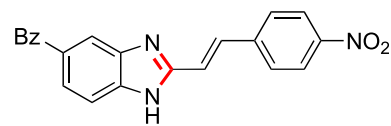
Method A: 90% yield (160 °C, 5 h)
 Method B: 88% yield (160 °C, 6 h)



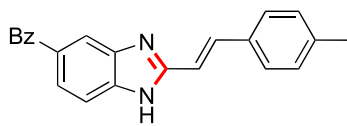
Method A: 84% yield (160 °C, 5 h)
 Method B: 90% yield (160 °C, 6 h)



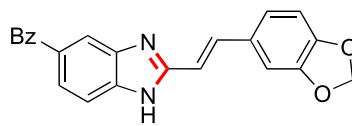
Method A: 90% yield (160 °C, 5 h)
 Method B: 90% yield (160 °C, 6 h)



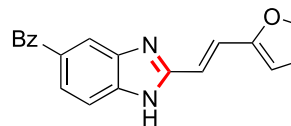
Method A: 92% yield (150 °C, 5 h)
 Method B: 86% yield (160 °C, 6 h)



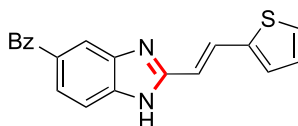
Method A: 88% yield (150 °C, 5 h)
 Method B: 86% yield (160 °C, 6 h)



Method A: 84% yield (160 °C, 5 h)
 Method B: 88% yield (160 °C, 5 h)

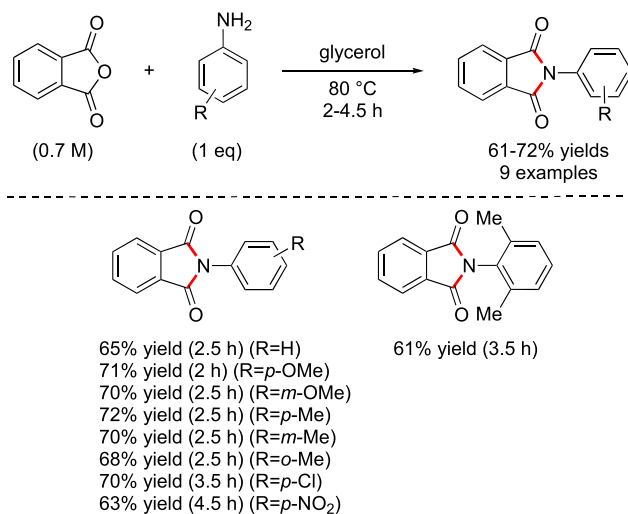
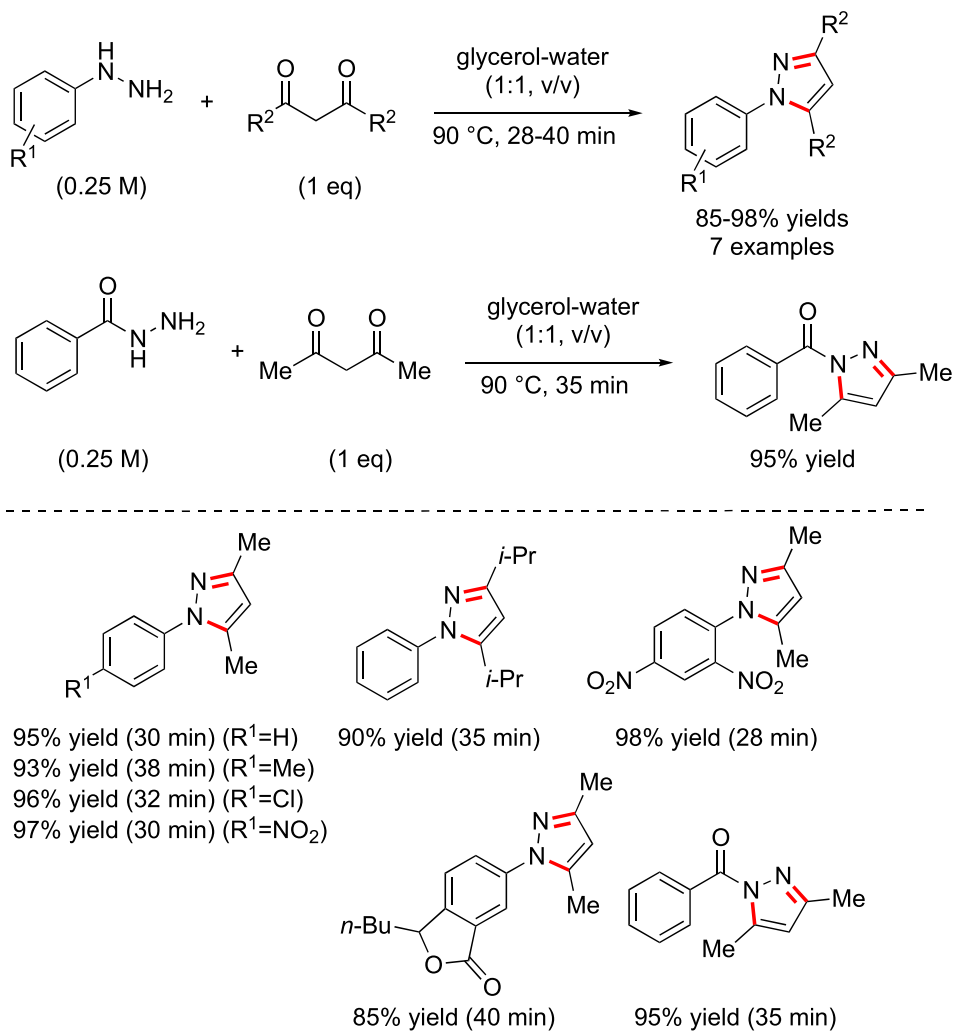


Method A: 80% yield (160 °C, 5 h)
 Method B: 82% yield (150 °C, 5 h)

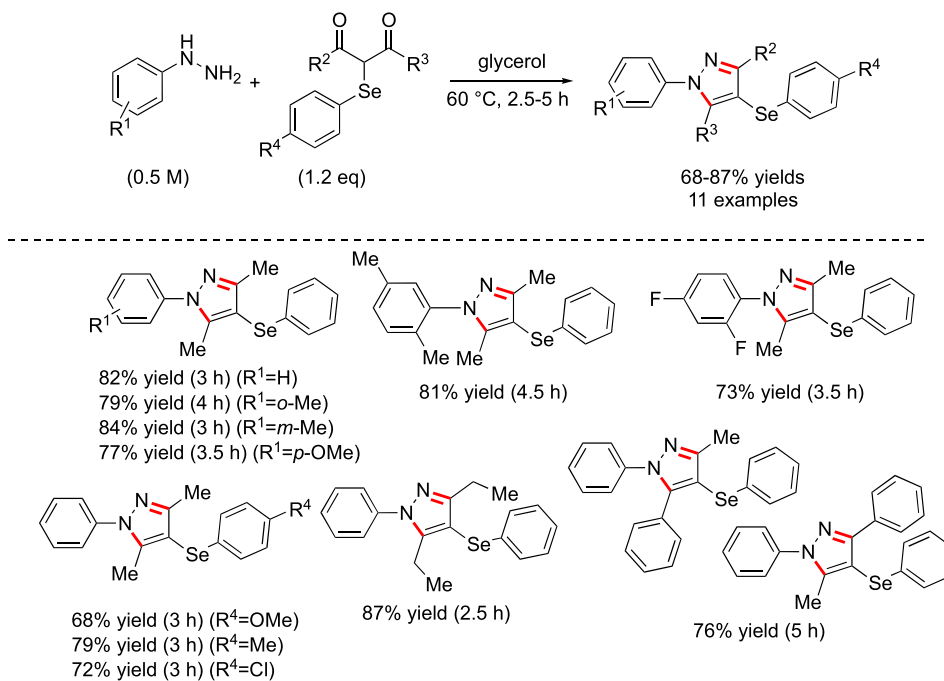


Method A: 78% yield (150 °C, 5 h)
 Method B: 80% yield (150 °C, 5 h)

Scheme 23. Synthesis of 2-styrylbenzimidazoles from either *o*-aminoanilines and cinnamic acids (method A) or 2-methylbenzimidazoles and aromatic aldehydes (method B) catalyzed by triacetylborate in glycerol (Taduri et al., 2014).

Scheme 24. Synthesis of *N*-aryphthalimides in glycerol (Lobo et al., 2012).

Scheme 25. Catalyst-free synthesis of pyrazoles in aqueous glycerol (Min et al., 2015).



Scheme 26. Catalyst-free synthesis of 4-arylselenylpyrazoles in glycerol (Nascimento et al., 2015).

reactions involving aryl amines and carbonyl compounds, the condensation of nitroarenes and benzyl alcohol, and the Huisgen azide-alkyne cycloaddition.

To promote environmentally friendly reactions, the utilization of copper as a non-noble catalyst was explored as an alternative to the more prevalent palladium for C–N bond formation in glycerol (Chahdoura et al., 2014b). The process involved the synthesis of copper oxide nanoparticles (Cu_2O NPs) through the reduction of copper acetate within glycerol, employing polyvinylpyrrolidone (PVP) as a stabilizer under a hydrogen atmosphere at 100 °C. Starting from iodoarenes, primary amines, and *t*-BuOK in the presence of Cu_2O NP (2.5 mol%), the corresponding aniline derivatives were obtained in yields ranging from 86% to 94% after a 2-h reaction at 100 °C (Scheme 16). This investigation underscored glycerol's capability to effectively stabilize and immobilize metal oxide nanoparticles. This characteristic enhances the efficiency of catalyst recycling, making it particularly advantageous for optimizing processes aimed at synthesizing multifunctional molecules using a one-pot approach.

Having achieved favorable outcomes when commencing with the nitro derivative, the researchers proceeded to investigate the transition-metal catalyzed reduction of the intermediate that arose during the C–N coupling reaction between 1-iodo-4-nitrobenzene and morpholine. They employed sodium borohydride to accomplish this and successfully obtained the 4-aminoaniline derivative in a remarkable 93% yield (Scheme 17) (Chahdoura et al., 2014b). This study effectively showcased that copper catalyzed the reduction of the nitroarene derivative, as no reaction occurred in its absence.

C–N and C–P bond formations were examined catalyzed by Pd NPs – TPPTS, the same catalyst used for the Suzuki-Miyaura cross-coupling reaction (Chahdoura et al., 2013b). Reaction between either primary and secondary amines, or secondary phosphines and acrylonitrile in glycerol at 100 °C for 2 h gave the corresponding secondary, tertiary amines and tertiary phosphines, respectively (Scheme 18).

Condensation reactions occur when two or more reagents, or active sites within the same molecule undergoing intramolecular reactivity, combine to generate a primary product. This process is accompanied by the liberation of a small molecule such as water, ammonia, ethanol, acetic acid, or other compounds. Extensive research has been dedicated to condensation reactions in glycerol, particularly for synthesizing cyclic molecules of interest. Nevertheless, documentation of glycerol-mediated condensation for acyclic molecule synthesis remains limited. By employing vanillin as the carbonyl component and semicarbazide as the amino component, a catalyst-free synthesis of vanillin-semicarbazone was achieved starting from crude glycerol at 65 °C for 20 min, yielding an impressive 89% (Scheme 19) (Jovanović et al., 2013). In contrast, substituting glycerol with ethanol or methanol necessitated the use of a robust acid catalyst, such as sulfuric acid, and an extended reaction time of 45 min to achieve a 72% yield.

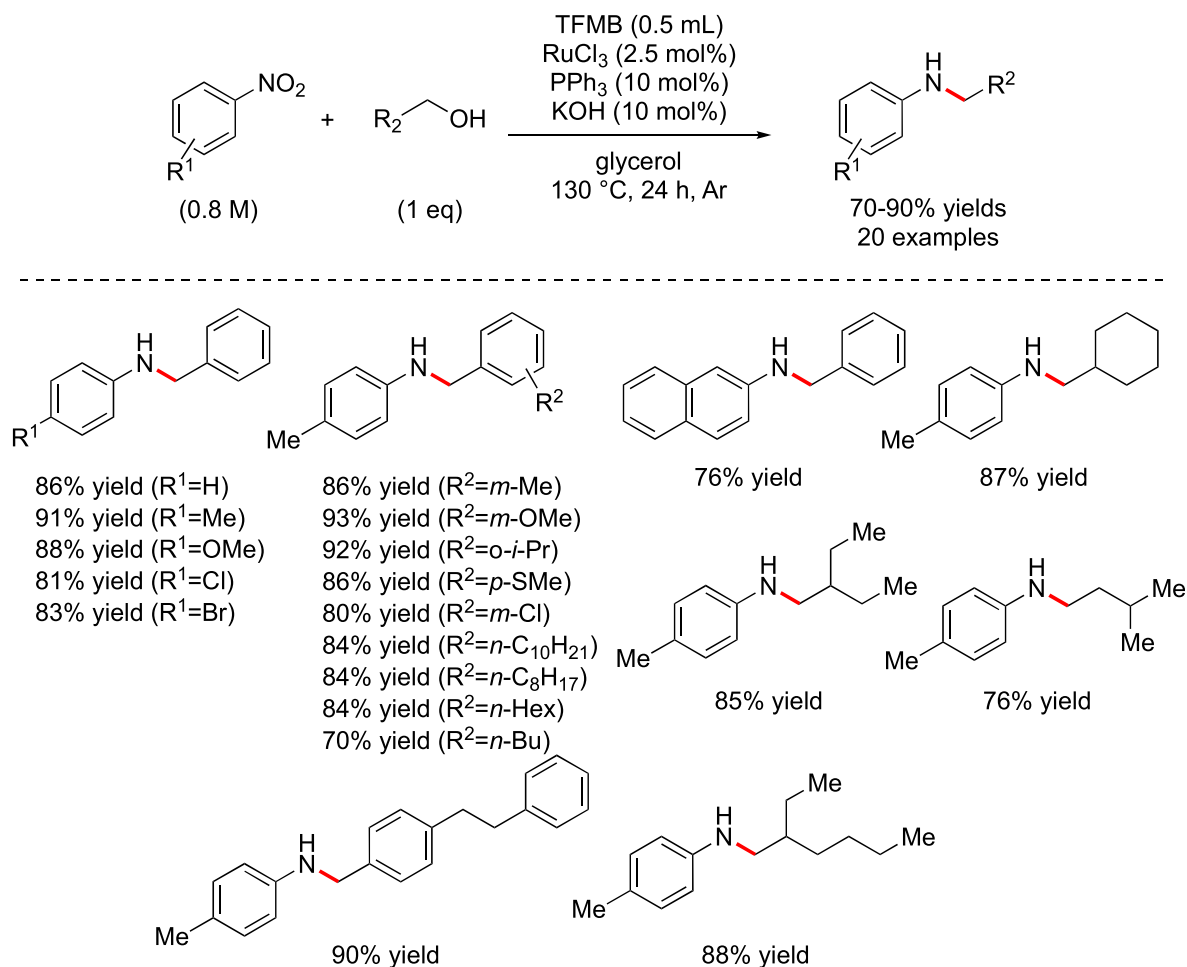
Cyclization reactions provide a rapid and efficient avenue for the generation of molecular complexity. In fact, a substantial portion of complex molecule synthesis involves one or more cyclization steps. In this domain, the synthesis of quinoxaline, benzoxazole, benzimidazole, quinoline, phthalimide, and oxazoline has been extensively documented. A notable example is the catalyst-free synthesis of benzimidazole, achieved through the condensation of *o*-aminoaniline with various aldehydes in glycerol at 90 °C (Scheme 20) (Radatz et al., 2011). Strikingly, even when employing naturally occurring and functionalized aldehydes, such as (*R*)-citronellal, the resulting chiral benzimidazole was obtained in an impressive 91% yield after 6 h. The study also explored glycerol's potential for reuse, demonstrating its effectiveness in five consecutive reactions for the synthesis of 1-benzyl-2-phenyl-1H-benzo[*d*]imidazole. Starting

from acetophenone, the same procedure gave the corresponding benzodiazepines in 45–96% yields after 4–8 h.

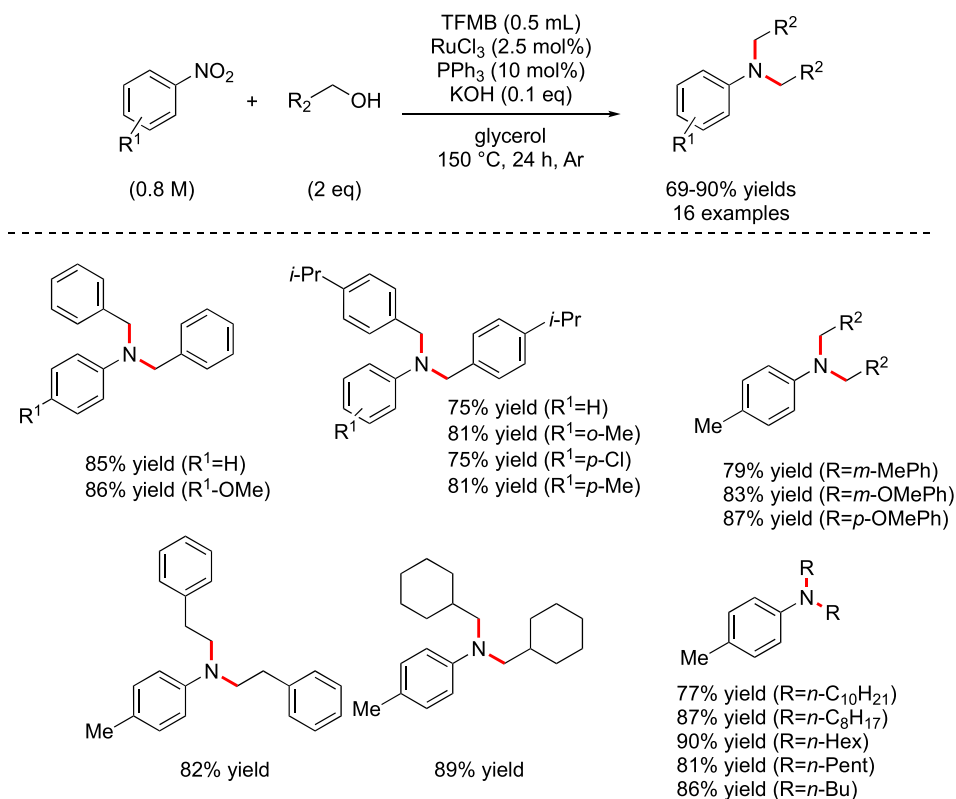
Employing a similar catalyst-free strategy, benzimidazoles were successfully generated using a reduced quantity of aldehyde (1 eq) and starting from *o*-phenylenediamine in a mixture of glycerol and water (5:2, v/v) (Bachhav et al., 2011). Following the reaction's completion, the glycerol phase was efficiently recovered and employed for subsequent reactions, maintaining consistent yields. By employing the optimized conditions, the synthesis of quinoxaline derivatives was achieved starting from *o*-phenylenediamines and 1, 2-diketones without the need for a catalyst. This reaction occurred in a mixture of glycerol and water (5:2, v/v) at 90 °C (Scheme 21) (Bachhav et al., 2011). Another study detailed the synthesis of quinoxalines under microwave irradiation at 90 °C for 3–8 min, yielding similar results without the addition of water (Zhou et al., 2013). However, while efficiency remained at 84% after two successive cycles, it significantly dropped to 24% after three cycles, highlighting the limited recyclability of glycerol. Overall, this approach offers a green, straightforward, and effective technique for synthesizing quinoxaline derivatives.

Further research efforts have focused on the synthesis of benzimidazole derivatives utilizing heterogeneous catalysts. Employing a homemade Ni/MCM-41 solid catalyst within a glycerol medium, a mixture of *o*-aminoaniline and aldehyde underwent reaction at 90 °C for 4 h, yielding the corresponding benzimidazoles in yields ranging from 56% to 93% (Scheme 22) (Bharathi et al., 2019). Among the various aldehydes tested in combination with *o*-aminoaniline, anisaldehyde exhibited a higher turnover frequency (TOF) value of 71 h⁻¹, signifying enhanced catalytic activity compared to the others. This investigation revealed that both the catalyst and glycerol were readily recoverable and reusable for up to four reaction cycles, maintaining 80% of their catalytic efficacy. Furthermore, the authors noted that the performance of the optimized catalyst was on par with those reported in the existing literature (Rajabi et al., 2015; Chari et al., 2010, 2011; Khan et al., 2009; Mahdavinia et al., 2012; Gadekar et al., 2010).

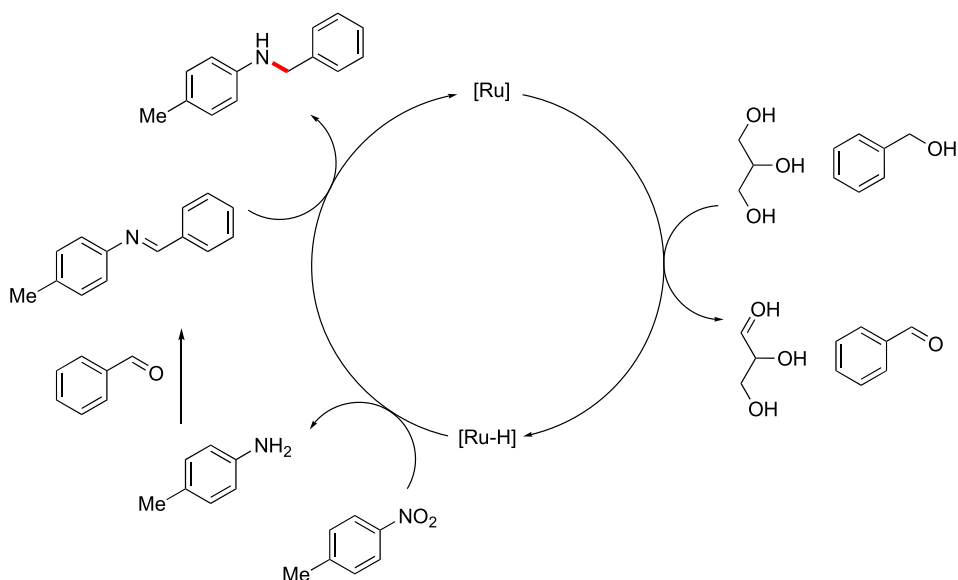
To synthesize diverse 2-styrylbenzimidazoles intended as MAO-B inhibitors, two distinct strategies were devised: the initial approach commenced with *o*-aminoanilines and cinnamic acids, employing triacetylborate at temperatures ranging from 160 to 180 °C for a duration of 3–5 h. The second strategy involved commencing with 2-methylbenzimidazoles and aromatic aldehydes, also utilizing triacetylborate, albeit at slightly lower temperatures ranging from 150 to 180 °C and extended reaction times of 5–6 h (Scheme 23) (Taduri et al., 2014). It's worth noting that, in this particular study, carboxylic acids were chosen over aldehydes and ketones as



Scheme 27. RuCl₃-Assisted catalytic transfer hydrogenation of nitrobenzenes using primary alcohol in a mixture of glycerol and TFMB for the synthesis of *N*-monosubstituted amines (Cui et al., 2013).



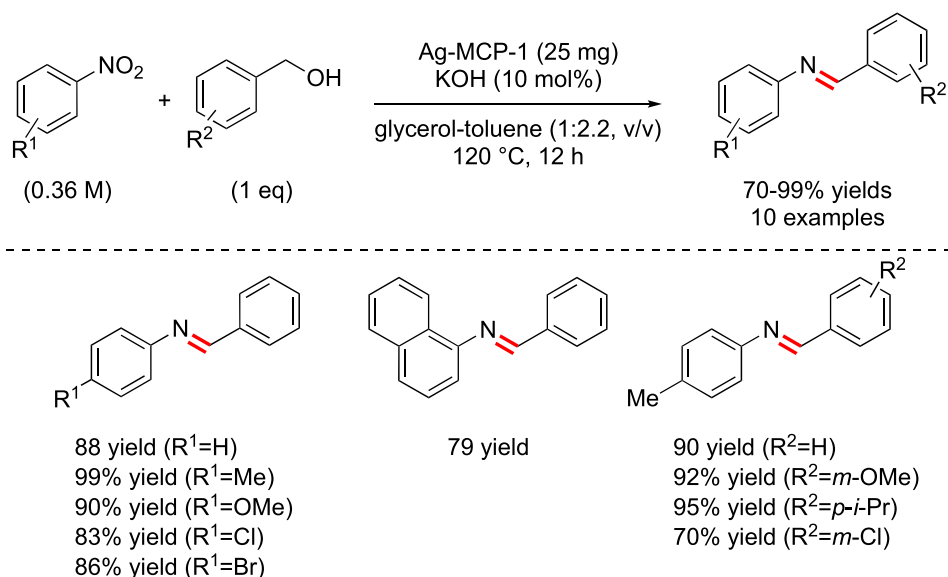
Scheme 28. RuCl₃-Assisted catalytic transfer hydrogenation of nitrobenzenes using primary alcohol in a mixture of glycerol and TFMB for the synthesis of *N,N*-disubstituted amines (Cui et al., 2012).



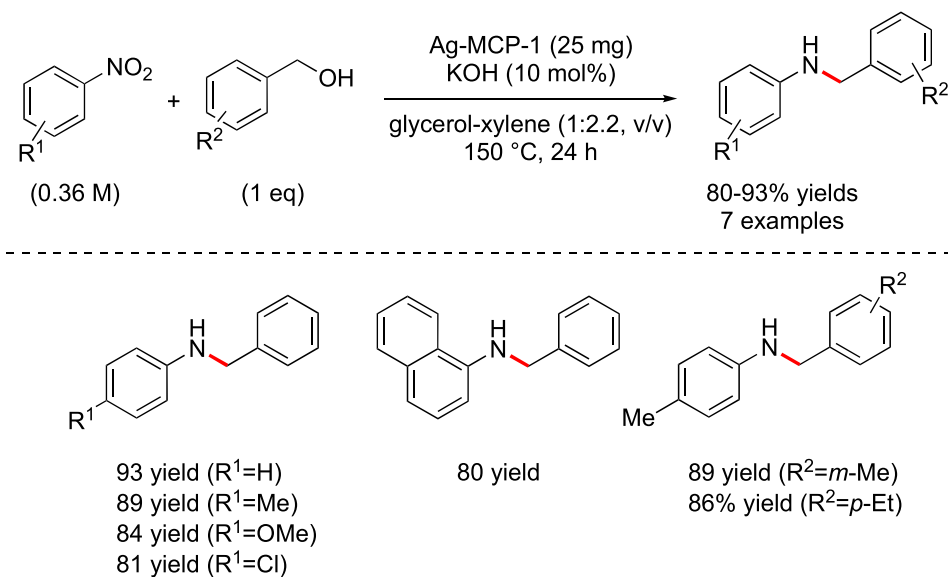
Scheme 29. Plausible pathway of the *N*-alkylation of 4-methylnitrobenzene into *N*-benzyl amine catalyzed by RuCl₃ PPh₃ in a mixture of glycerol and TFMB (Cui et al., 2012, 2013).

reactants.

The process of condensation to create C–N bonds holds the capability to interlink amines with aldehydes, ketones, and carboxylic acids. Taking this concept, a step further, the exploration of anhydrides as starting materials has been undertaken. Of particular interest are *N*-phenylphthalimide and its derivatives, which offer promising pharmacological attributes. Consequently, the development



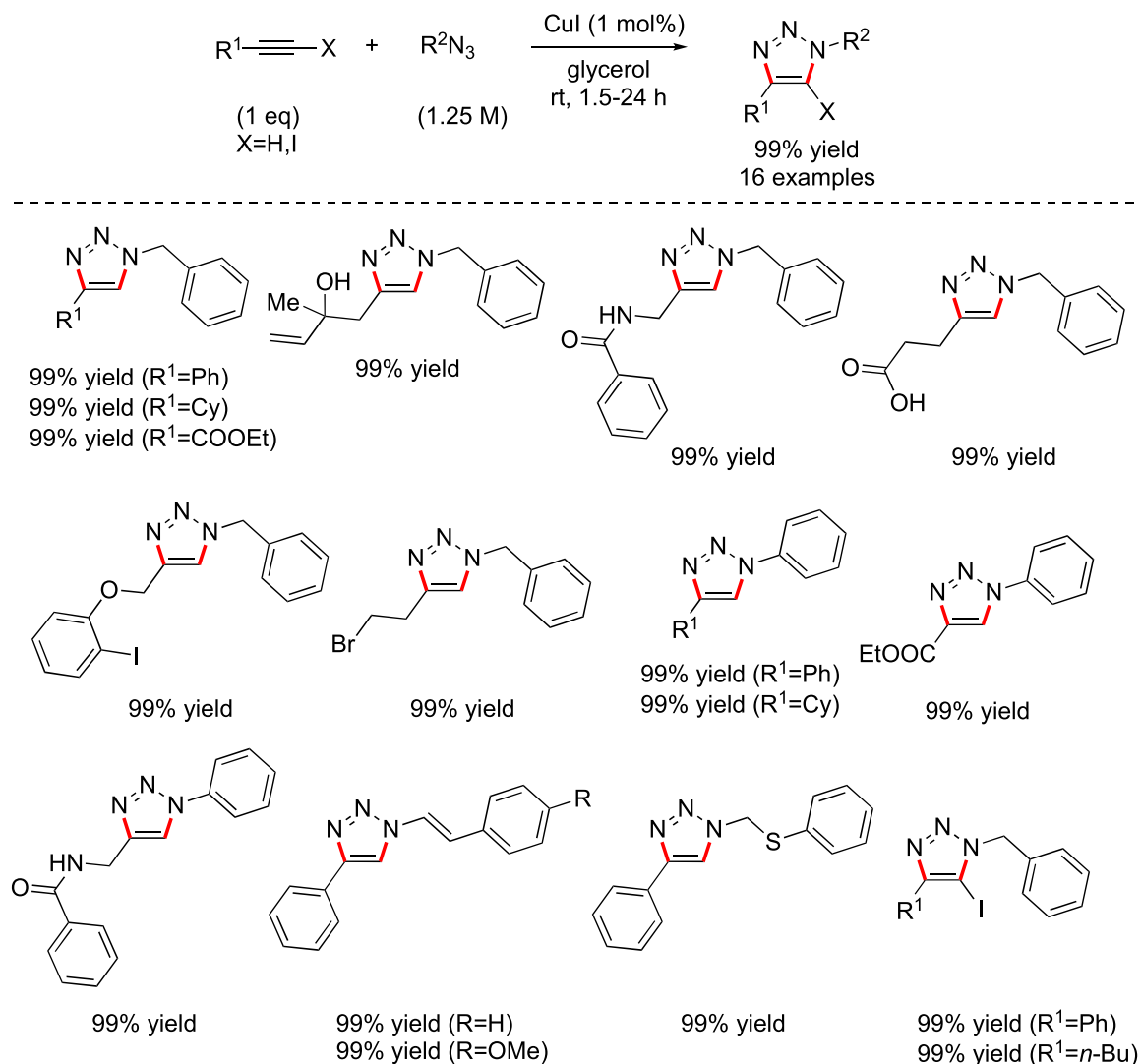
Scheme 30. Ag-MCP-1-Assisted catalytic transfer hydrogenation of nitroarenes using primary alcohol for the synthesis of imines in a mixture of glycerol and toluene (Mandi et al., 2016).



Scheme 31. Ag-MCP-1-Assisted catalytic transfer hydrogenation of nitroarenes using primary alcohol for the synthesis of primary amines in a mixture of glycerol and xylene (Mandi et al., 2016).

of more sustainable synthetic routes for these compounds is of paramount importance. In this context, glycerol has emerged as a potent solvent, effectively catalyzing the synthesis of *N*-aryl phthalimides from the combination of phthalic anhydride and aniline. This approach has exhibited favorable outcomes across an array of functional groups, encompassing both electron-donating and electron-withdrawing moieties (Lobo et al., 2012). Notably, the reaction displayed heightened reactivity in the presence of electron-donating substituents, translating to comparatively higher yields (Scheme 24). A pivotal aspect emphasized in the report is the remarkable atomic efficiency inherent in this reaction. Indeed, almost all the atoms present in the initial reactants were seamlessly incorporated into the final compounds, with the exception of one oxygen atom and two hydrogen atoms forming the water generated. Additionally, glycerol showcased impressive recyclability, with its repeated use in subsequent cycles yielding minimal impact on the yields, even after undergoing five consecutive runs. It's worth noting that a comparative investigation involving deep eutectic solvents such as choline chloride-urea and choline chloride-malonic acid was conducted. For all substrates, the reaction yields were found to be superior when employing deep eutectic solvents compared to glycerol.

Pyrazole, a five-membered heterocycle having two adjacent nitrogen atoms, is often used as a scaffold to form compounds with

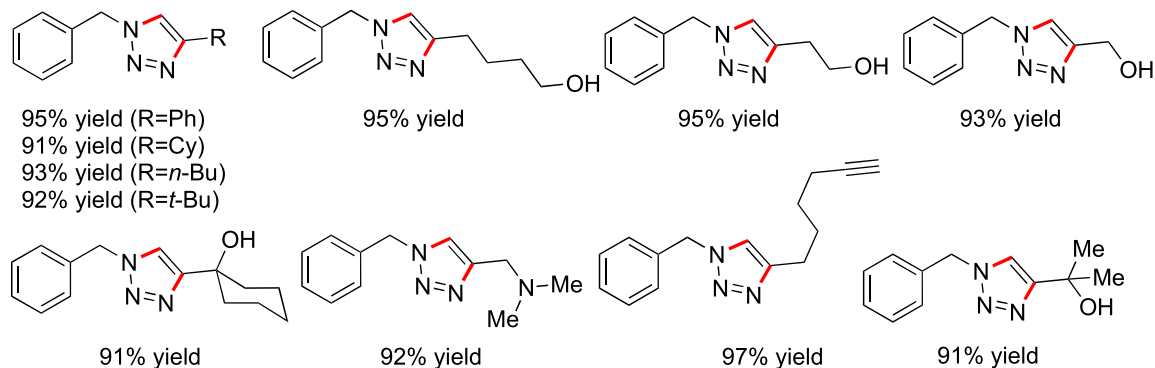
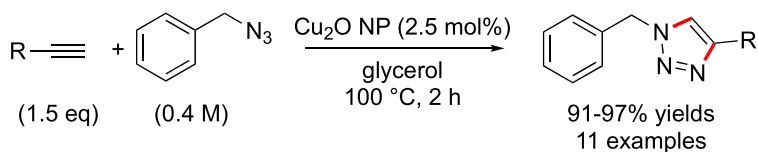


Scheme 32. CuI-catalyzed synthesis of 1-benzyl-4-phenyl-1H-[1-3]triazole at room temperature in glycerol (Vidal et al., 2014).

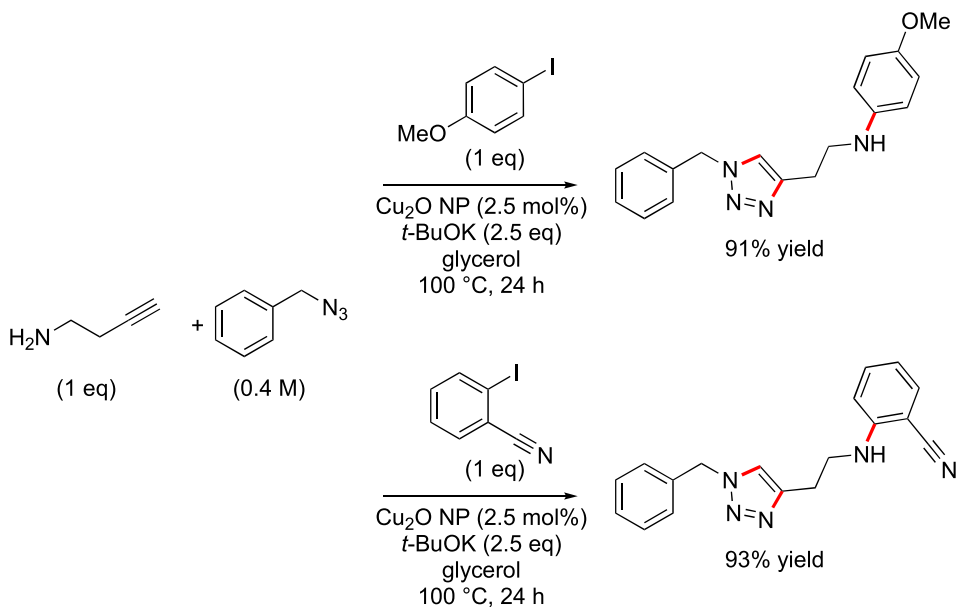
medicinal properties. Through a catalyst-free cyclization reaction, the fusion of phenylhydrazine derivatives and acetylacetone was achieved at 90 °C for 45 min within glycerol, yielding the corresponding pyrazole at an 85% rate. Alternatively, a blend of glycerol and water in a 1:1 ratio (v/v) produced the desired compounds at an enhanced yield of 95% after a condensed 30-min reaction period (Scheme 25) (Min et al., 2015). Evidently, the adoption of a glycerol-water mixture instead of pure glycerol not only resulted in an improved yield (from 85% to 95%) but also expedited the reaction time (from 45 min to 30 min). The reaction's scope encompassed the synthesis of diverse pyrazoles containing both electron-donating and electron-withdrawing groups, all achieved with yields surpassing 85%.

Another type of pyrazoles, specifically 4-aryl selenylpyrazoles, were synthesized by reacting phenylhydrazines with α -phenyl-selenylacetylacetone in glycerol. These compounds, containing both electron-donating and electron-withdrawing groups, were obtained with moderate to good yields (Scheme 26) (Nascimento et al., 2015). The reaction took place at 60 °C under a nitrogen atmosphere for a duration of 3 h. Glycerol exhibited superior efficiency in comparison to water, PEG-400, bioethanol, and even a solvent-free medium, although the latter required an extended reaction time of 5 h. The remarkable speed of this cyclization reaction in the absence of a catalyst can be attributed to glycerol itself, which facilitates the electrophilic activation of carbonyl compounds.

Carbon-nitrogen bonds constitute crucial structural elements found in medicinal compounds and natural products. The traditional method for the preparation of N-substituted amines revolves around alkylating amines with alkyl halides. In the pursuit of more environmentally conscious options, a greener alternative emerged: the Pd-catalyzed one-pot synthesis of N-substituted amines. This method involves employing either nitrobenzene and aldehyde or amine and aldehyde, all under the influence of hydrogen pressure in glycerol (Reina et al., 2016). In order to remove the use of hydrogen, numerous studies have demonstrated that propan-2-ol or formic acid/triethylamine mixtures have been used as hydrogen sources in transfer hydrogenation (TH) reactions catalyzed by metals. TH is



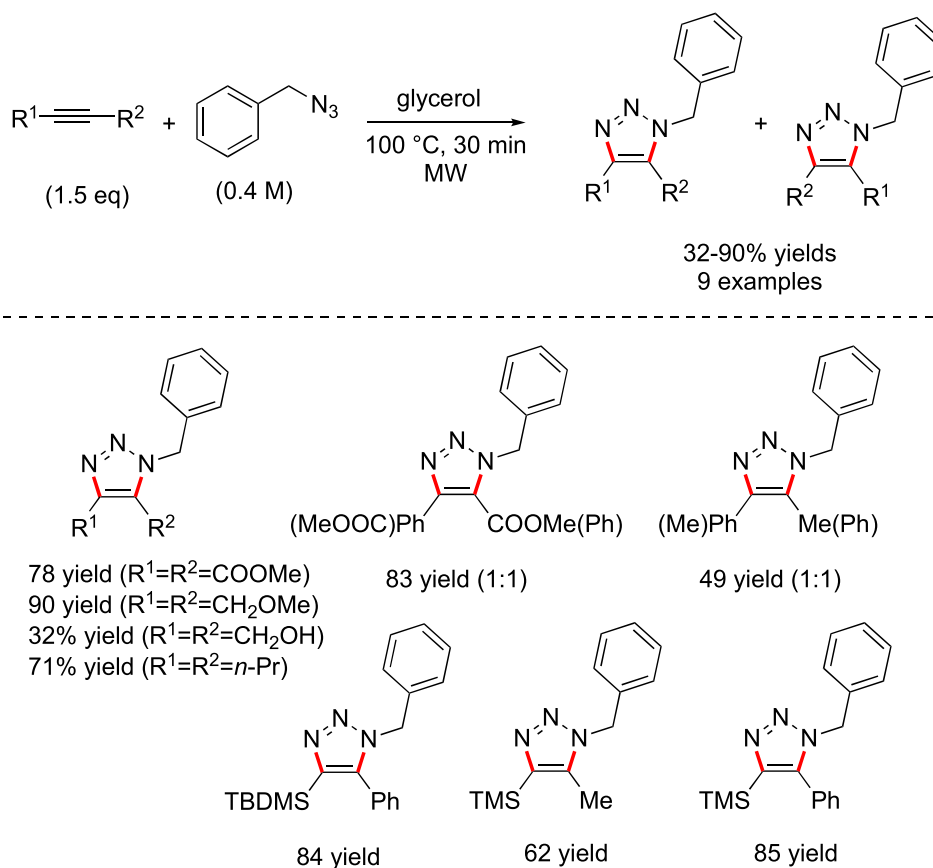
Scheme 33. Cu-catalyzed Huisgen azide-alkyne cycloaddition at 100 °C in glycerol (Chahdoura et al., 2014b).



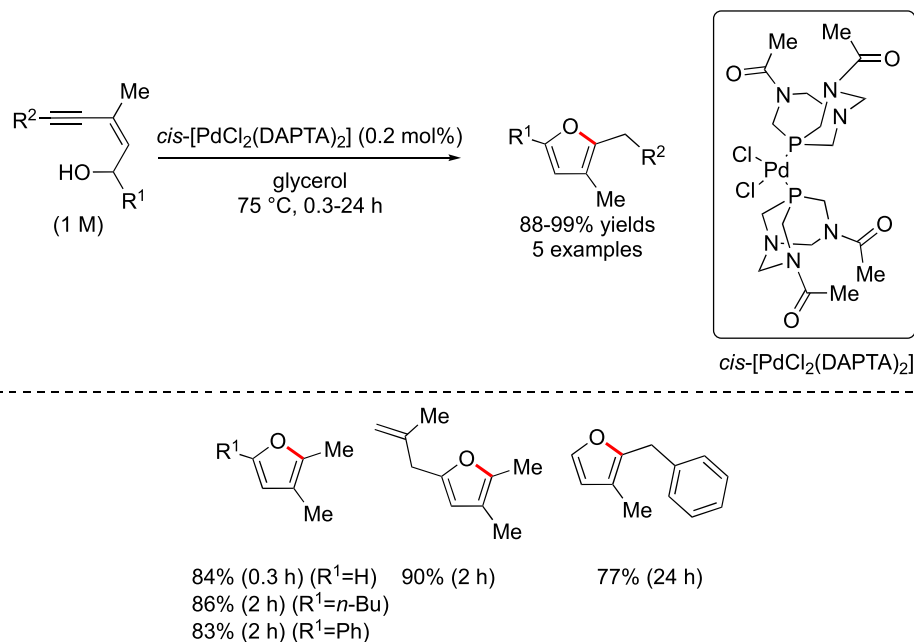
Scheme 34. Cu(I)-catalyzed Huisgen azide-alkyne cycloaddition in glycerol (Chahdoura et al., 2014b).

recognized as an efficient method for reducing unsaturated organic compounds such as ketones, aldehydes, and olefins. However, replacing them with glycerol both as a solvent and a reducing agent offers economic advantages and greater environmental friendliness. This technique enables the synthesis of secondary and tertiary amines through the reaction between nitroarenes and primary alcohols. Furthermore, the amination of alcohols with diverse structures was accomplished under stoichiometric conditions. The combination of RuCl_3 with PPh_3 as catalysts in a mixture of glycerol and (trifluoromethyl)benzene (TFMB) facilitated the synthesis of mono- or disubstituted amines with exceptional yields (Scheme 27) (Cui et al., 2013). For *N,N*-dialkylation, a higher temperature of 150 °C was employed compared to 130 °C, while maintaining the same reaction duration (Scheme 28). However, the catalytic system's recyclability was not explored in this study. Nevertheless, it is noteworthy that the Ru(III)/glycerol catalytic system demonstrated improved performance compared to the previously reported Au/Ag-Mo (nanorods - NRs) catalyst (Cui et al., 2012).

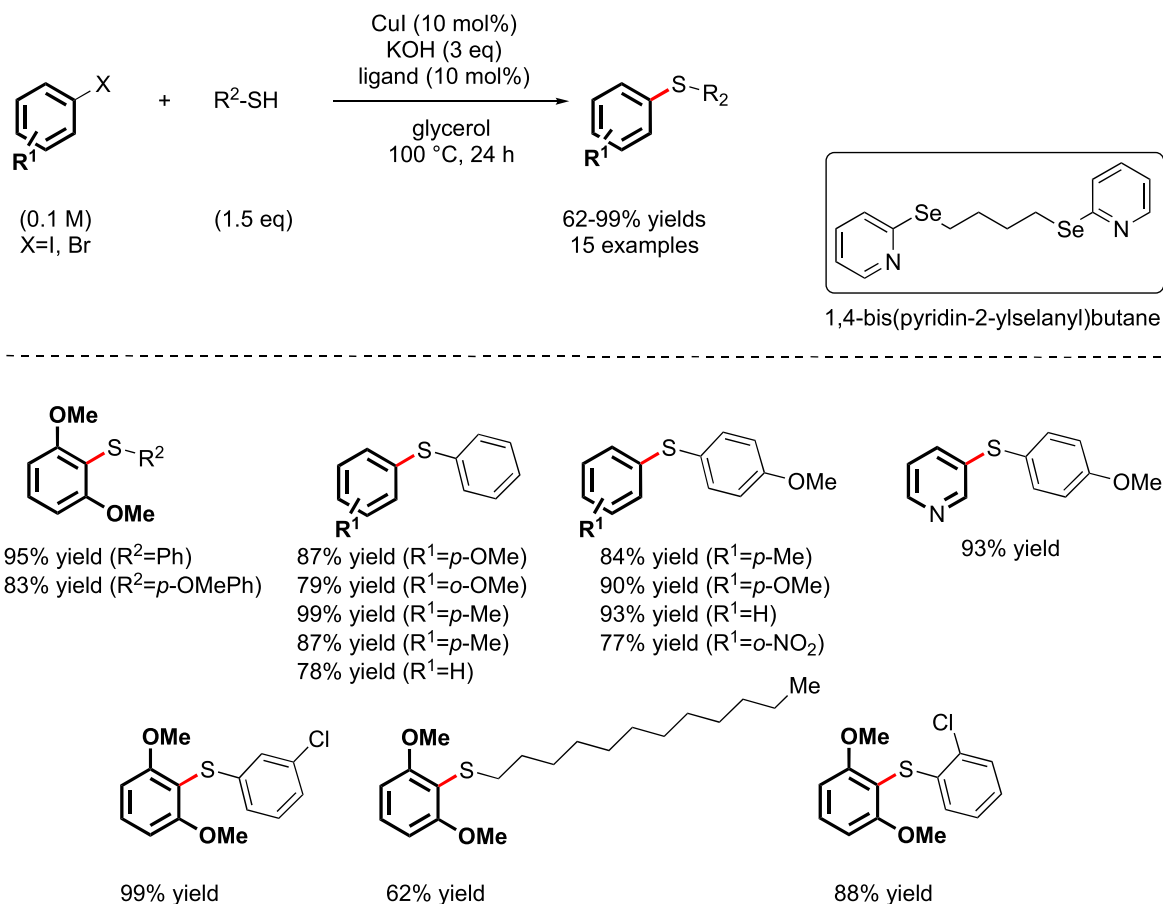
The authors provide a plausible pathway for the reductive *N*-alkylation of nitro compounds into *N*-alkyl and *N,N*-dialkyl amines using glycerol (Scheme 29). In the presence of ruthenium, glycerol and benzylic alcohol undergo transformation into glyceraldehyde and benzaldehyde, respectively. Subsequently, 4-methylnitrobenzene is reduced to its corresponding aniline, which then forms an



Scheme 35. Catalyst-free Huisgen azide-alkyne cycloaddition of internal alkynes under microwave irradiation in glycerol (Rodríguez-Rodríguez et al., 2015).



Scheme 36. Pd-catalyzed cycloisomerization of (Z)-2-en-4-yn-1-ols for the synthesis of furans in glycerol (Franco and Cadierno, 2010).



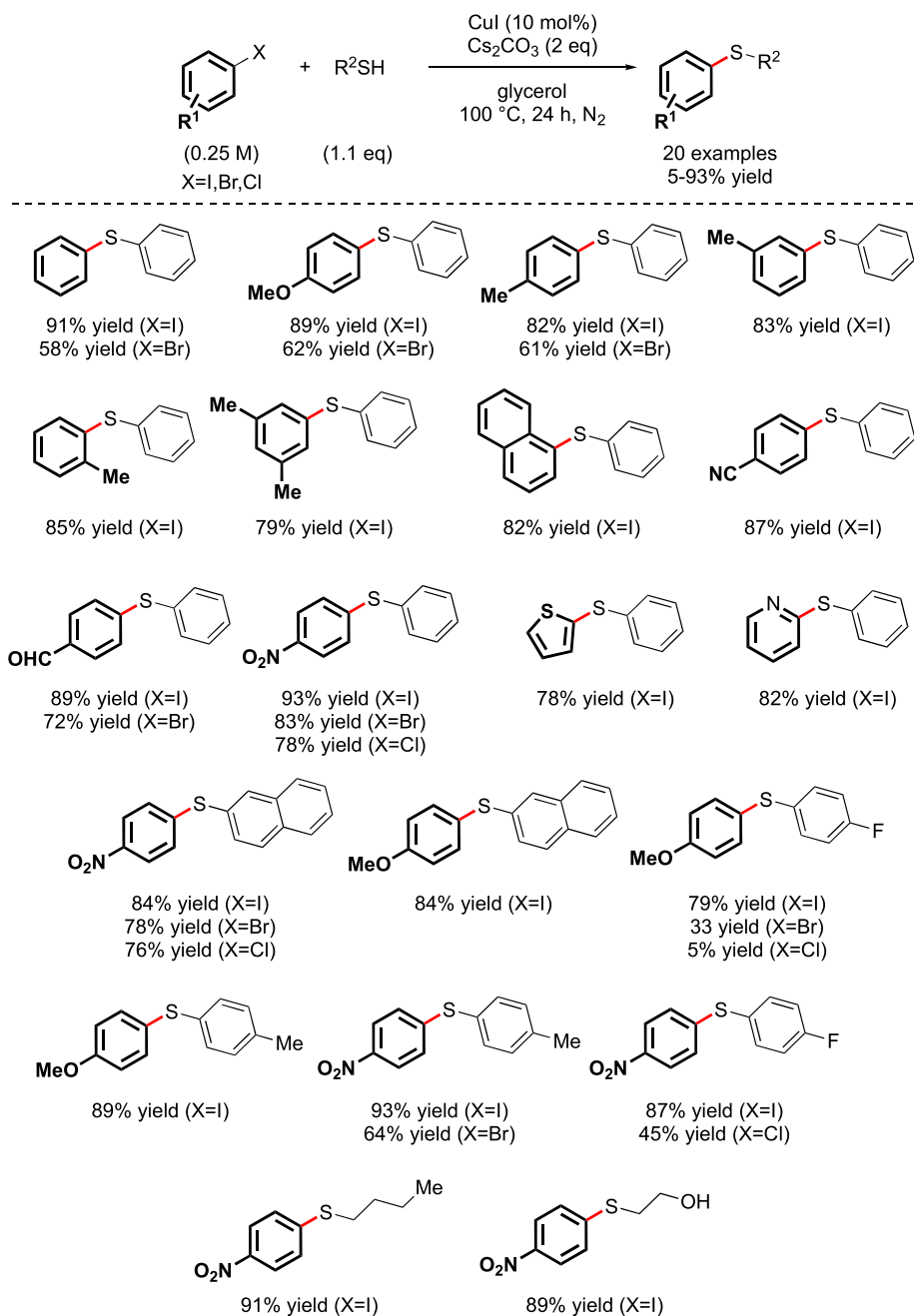
Scheme 37. C–S cross-coupling reaction for the synthesis of arylthioethers using CuI-1,4-bis(pyridine-2-ylselanyl)butane catalyst (Cargnelutti et al., 2015b).

imine followed by an amine.

An alternative catalyst type was investigated for the reductive coupling of nitrobenzenes and benzyl alcohols, utilizing silver nanoparticle-immobilized mesoporous cross-linked polyacrylic acid, known as Ag-MCP-1, as a proficient heterogeneous catalyst in glycerol (Mandi et al., 2016). Under similar conditions, except for the solvent nature, temperature, and reaction time, two types of target compounds were synthesized: imines and primary amines (reductive imination employed toluene at 120 °C for 12 h, while reductive amination used xylene at 150 °C for 24 h). The catalytic activity was assessed using a 1:1 M ratio, and the catalytic system displayed its suitability across a broad spectrum of substituted and unsubstituted organic substrates, yielding products ranging from good to excellent (70–99%) (Schemes 30 and 31). Upon completion of the reaction, the catalyst was isolated from the reaction mixture, meticulously washed with water and acetone. The fabricated nanocomposite exhibited remarkable recovery rates and sustained its catalytic efficiency consistently, even after undergoing five consecutive runs. Additionally, a leaching test confirmed the heterogeneous nature of the Ag-MCP-1 nanocatalyst. The article highlights the superiority of their catalytic system, which achieved higher yields of the desired products compared to recent literature data.

The Cu(I)-catalyzed Huisgen azide-alkyne cycloaddition stands as a widely recognized methodology for synthesizing 1,2,3-triazoles, and its applicability spans various domains within the field of chemistry. An investigation into the 1,3-dipolar Huisgen cycloaddition reaction involving azides and terminal alkynes or 1-iodoalkynes, facilitated by a CuI catalyst at room temperature for 1.5–24 h in glycerol as the solvent, was undertaken (Scheme 32) (Vidal and García-Álvarez, 2014). The methodology was applied across a diverse range of functionalized alkynes and benzyl azides, yielding 1,2,3-triazoles with remarkable selectivity and quantitative yields. Exploring water as an alternative solvent also achieved excellent product yields, albeit with extended reaction times. The CuI/glycerol system displayed successful recyclability for up to six runs, although a partial decline in activity surfaced after the third ones (1.5–2 h, 97–99% yield), necessitating prolonged reaction times to attain complete conversion (3–24 h, 97–99% yield). The authors attributed the reduction in reaction rate post the third run to a blend of catalyst leaching during processing and catalyst deactivation.

The research team responsible for developing copper oxide nanoparticles (Cu₂O NPs) from copper acetate for cross-coupling reactions also examined the catalyst's applicability in synthesizing various triazoles (Chahdoura et al., 2014b). Commencing with terminal alkynes featuring diverse alkyl, aryl, and amine substituents, along with benzyl azide, and utilizing Cu₂O NPs (2.5 mol%) at 100 °C for 2 h, the Huisgen cycloaddition yielded 1,4-disubstituted triazoles with exceptional selectivity (Scheme 33). Building on this foundation, the utilization of the same Cu₂O NPs catalyst enabled the creation of more intricate structures, containing two or three

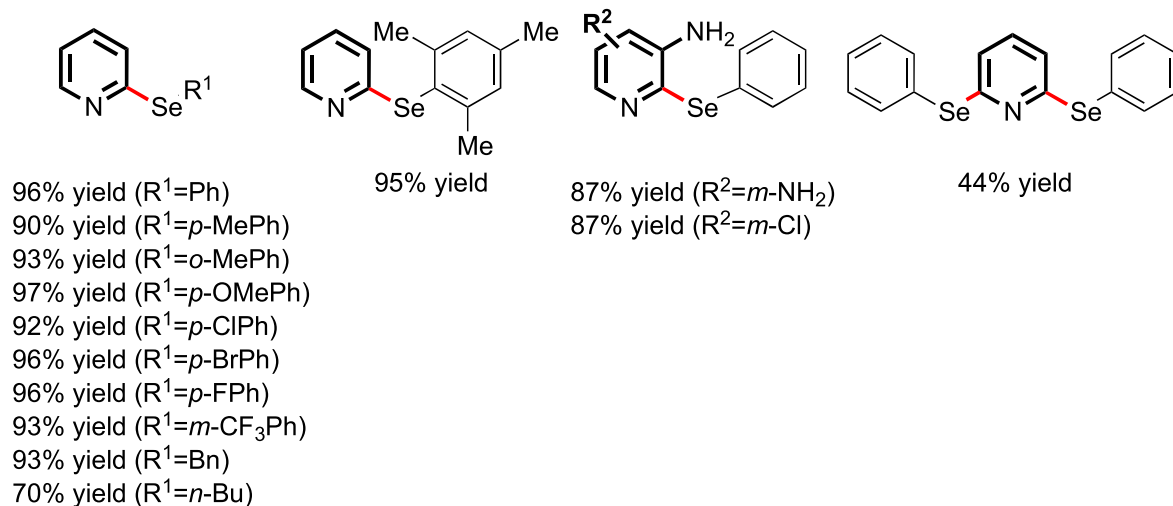
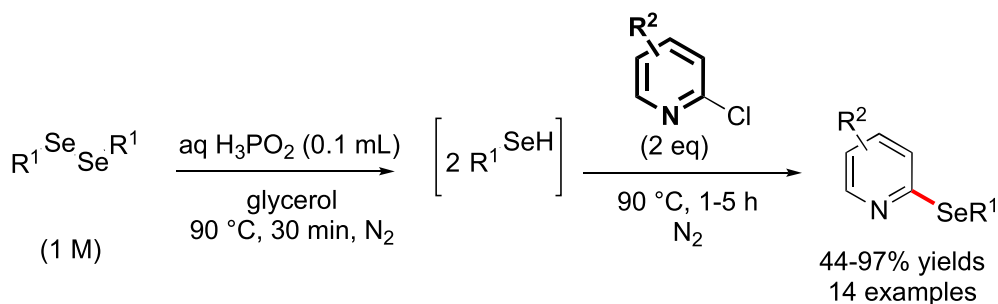


Scheme 38. C-S cross-coupling reaction for the synthesis of arylthioethers using ligand-free CuI catalyst in glycerol (Dubey et al., 2017).

triazole units, originating from dialkyne derivatives or triazide derivatives. Noteworthy is the Cu₂O NPs catalyst's remarkable recyclability, sustaining its high efficiency for up to ten cycles without any loss of activity. The triazole products consistently achieved yields ranging between 94% and 97%. Analysis through Transmission Electron Microscopy (TEM) following five consecutive runs revealed the presence of small, well-dispersed nanoparticles.

Employing Cu₂O NPs as the catalyst, the research team documented a Cu(I)-catalyzed azide-alkyne cycloaddition/cross-coupling tandem process. This integrated approach facilitated the one-pot creation of 2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethan-1-amine through a cycloaddition step, succeeded by the establishment of a C-N bond with diverse iodoarenes. This synthesis yielded the respective secondary amines with exceptional efficiency, exceeding 90% yields (Scheme 34) (Chahdoura et al., 2014b).

In a distinct investigation, the same research team detailed the azide-alkyne cycloaddition reaction involving diphenylacetylenes and benzyl azide within a glycerol medium. This approach hinged on a catalyst-free methodology, accelerated by microwave irradiation (Rodríguez-Rodríguez et al., 2015). The adoption of this alternative technique heightened reactivity, leading to the rapid



Scheme 39. Synthesis of 2-selenylpyridines by selenol in glycerol (Thurow et al., 2013).

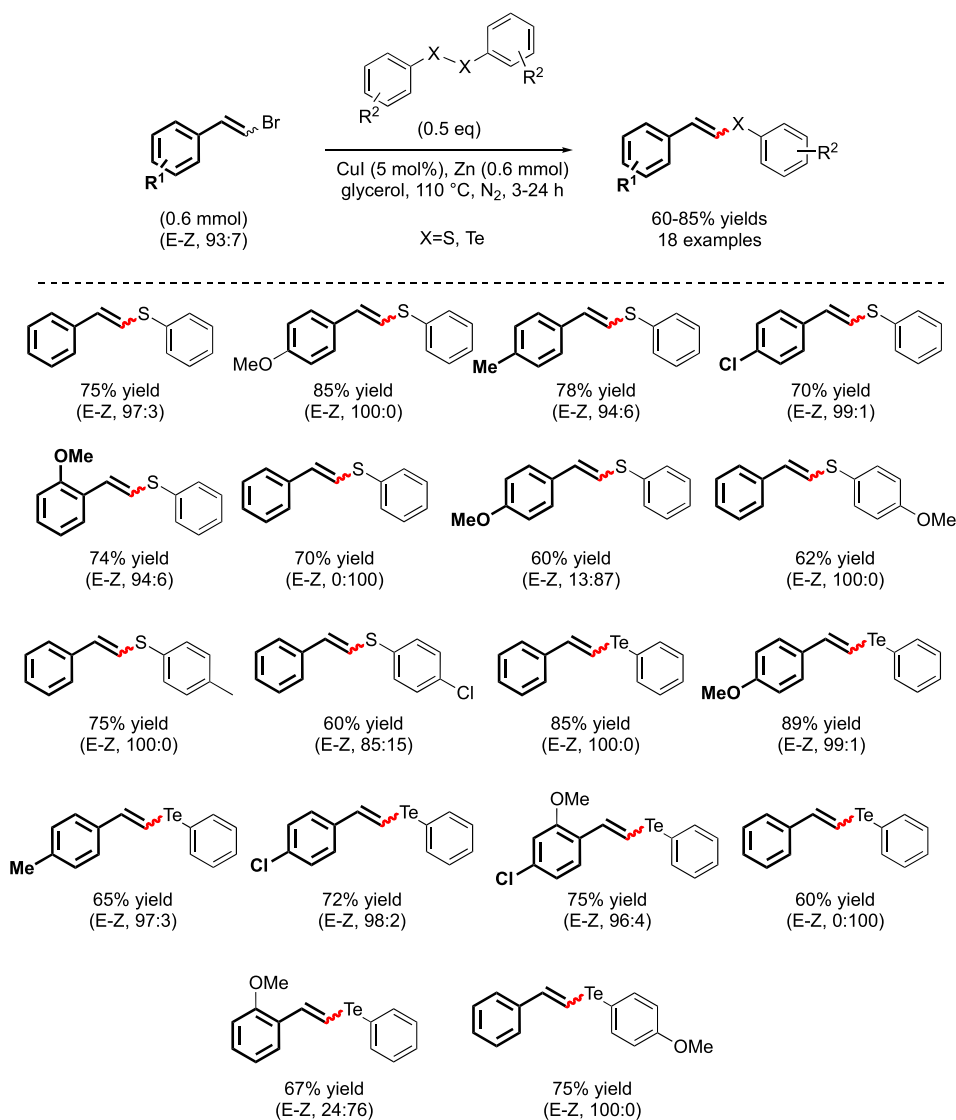
formation of diverse triazole regioisomers. When silylated alkynes were used the major regioisomers having the silyl group in position 4 of the triazoles were obtained. In the case of *t*-butyldimethylsilyl group, only one regioisomer was produced (Scheme 35). Notably, no discernible reaction occurred when employing other protic solvents such as water, ethanol, or diols. By employing Density Functional Theory calculations for theoretical analysis, the authors elucidated that the BnN_3 -glycerol adduct exhibited more pronounced stabilization of the LUMO frontier orbital in comparison to analogous BnN_3 -alcohol adducts. This distinctive attribute lent support to its heightened reactivity with the alkyne.

2.3. The C–O, C–S, C–Se and C–Te bond formation

Concurrently with the formation of C–C, C–N, and C–P bonds, the creation of C–O, C–S, C–Se, and C–Te bonds represents an exceptionally valuable approach for synthesizing a wide variety of compounds in the domain of biology, pharmaceuticals, and materials science. Depending on the specific type of bond being considered, noteworthy examples include O-alkylation, thiol addition to alkynes, coupling reactions, cycloisomerization, C–H bond activation, and condensation reactions involving aryl thiol and carbonyl compounds, as well as electrophilic aromatic substitution. The oligomerization of glycerol is typically an important reaction using glycerol both as solvent and starting material. In this context, different works have been reported in batch and continuous flow processes using conventional and microwave activation (Galy et al., 2017; Nguyen et al., 2017, 2021). Since glycerol is considered both a starting material and a solvent, its oligomerization is not discussed in the manuscript.

The metal-catalyzed cyclization of derivatives of (*Z*)-2-en-4-in-1-ol presents an economically viable route to furans, which serve as pivotal structural elements in biologically active compounds, pharmaceutical agents, and synthetic organic chemistry. The intramolecular catalytic cyclization of (*Z*)-2-en-4-in-1-ols, leading to the formation of 2,3-dimethylfuran, has been documented in the presence of the *cis*-[$\text{PdCl}_2(\text{DAPTA})_2$] complex, which incorporates hydrophilic 1,3,5-triaza-7-phosphaadamantane ligands (Scheme 36) (Francos and Cadierno, 2010). This investigation disclosed that the reactions proceeded effectively in all examples, with notably swifter kinetics evident in aqueous environments compared to glycerol, when employing the *cis*-[$\text{PdCl}_2(\text{DAPTA})_2$] complex at a temperature of 75 °C. However, the recycling of the palladium/glycerol system demonstrated superior efficiency, maintaining high activity over five successive runs (providing 96–99% yields within 20 min). In contrast, the effectiveness of the aqueous solution considerably declined after each recycling cycle, necessitating 24 h of heating in the fifth cycle to achieve a 91% conversion rate. These findings underscore the potential of glycerol, a renewable and cost-effective raw material, in tandem with the observed efficient catalytic recycling, to facilitate the development of sustainable processes in organic synthesis.

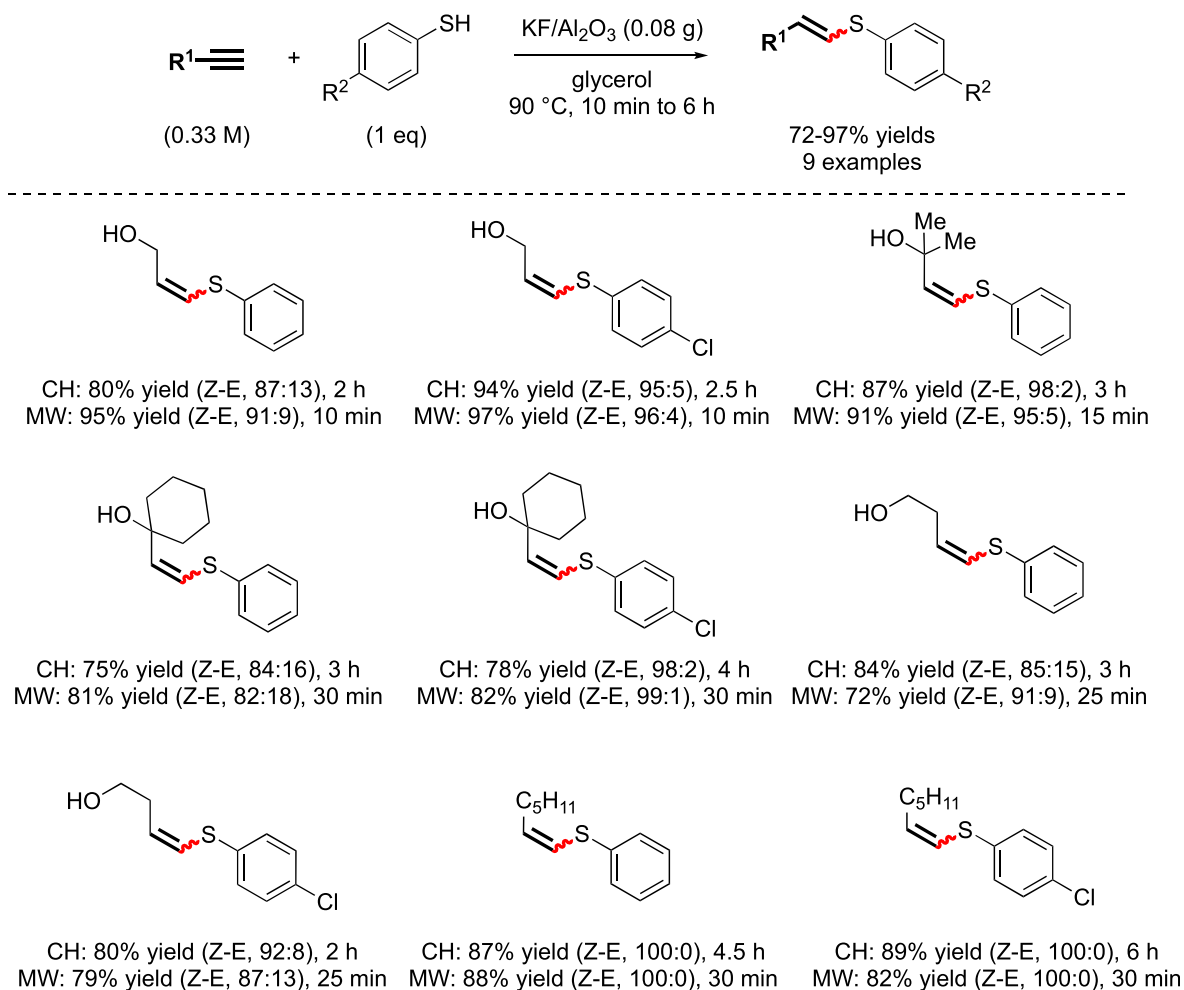
The C–S bond formation was examined using different strategies. A CuI complex promoted cross-coupling reaction utilizing the Se-



Scheme 40. Synthesis of (*E/Z*)-phenylstyryl sulfides and tellurides from (*E/Z*)- β -bromo styrene in glycerol (Goncalves et al., 2010).

bidentate ligand 1,4-bis(pyridine-2-ylselanyl)butane was reported (Cargnelutti et al., 2015b). In this study, iodo- and bromoarene, along with thiophenol derivatives, were employed as substrates. The reaction was conducted using KOH as an inorganic base in glycerol solvent at 100 °C for 24 h (Scheme 37). The resulting diphenylthioethers were achieved in yields ranging from 77% to 99%, except for when dodecan-1-thiol was used, which led to a 62% yield of the thioether product. Interestingly, employing the same conditions along with ultrasound irradiation yielded compound in an 88% yield in just 1.5 h. In the same year, the same research group presented a similar procedure with a variation in the ligand (Cargnelutti et al., 2015a). The outcomes showcased the efficient coupling of aryl halides containing electron-donating and electron-withdrawing groups (EDG and EWG). This reaction was carried out under the specified conditions, yielding bis(aryl) sulfide products with yields ranging from good to excellent. The article points out the efficacy of their approach in comparison to previously reported methods in the literature. However, it was noted that the catalyst was not reusable due to decomposition. As a result, the CuI-ligand-glycerol system proposed in this work is effective for conducting C-S cross-coupling reactions without the necessity of using toxic organic solvents or costly metals. Additionally, the application of ultrasound as an energy source is a notable aspect of this method.

An innovative approach involving a copper-glycerol combination without the need for a ligand was introduced for the efficient, recyclable, and environmentally conscious synthesis of bis(aryl) sulfides (Scheme 38) (Dubey et al., 2017). The investigation encompassed a range of reactions utilizing aryl iodide, arylthiol (and alkylthiol), and Cs₂CO₃ in the presence of CuI (10 mol%) within glycerol at 110 °C under a nitrogen atmosphere for 24 h. This methodology provided the corresponding thioethers in yields ranging from 78% to 93%. In comparison to the aforementioned research, the ligand-free process represents a notable advancement. As anticipated, the reactivity of aryl halides in the oxidative addition step followed the sequence: aryl iodide > aryl bromide > aryl

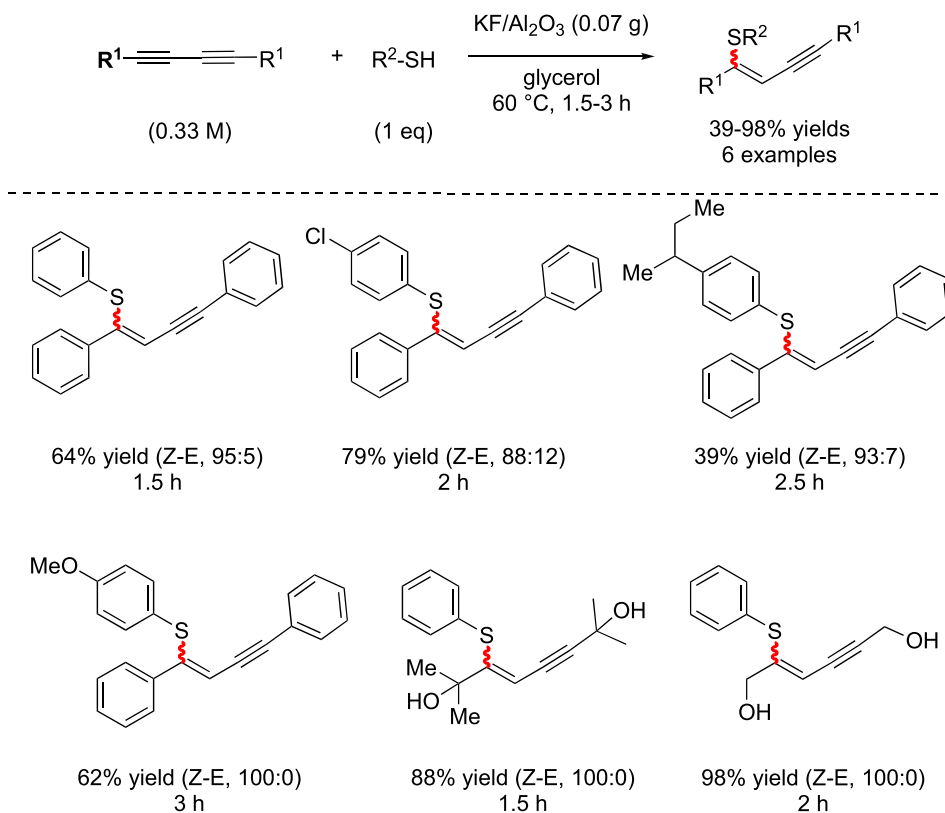


Scheme 41. Hydrothiolation of alkynes using KF/Al₂O₃ in glycerol (Lenardão et al., 2011).

chloride. Furthermore, an assessment of the recyclability of the glycerol-CuI system in the reaction between iodobenzene and thio-phenol was conducted. This study highlighted the system's stability over 5 consecutive runs, yielding results ranging from 84% to 62%. The outlined protocol demonstrated an extensive range of substrates for synthesizing aryl sulfides from aryl halogens and thiols, showcasing its adaptability for scaling up to gram-scale synthesis. Notably, an 85% yield of 2-(4-chlorophenylthio)benzaldehyde was achieved, which serves as a precursor to Gemmacin and Gemmacin B. This underlines the method's potential significance in practical applications.

The formation of C–Se bonds was documented in the context of a one-pot, two-step synthesis to produce 2-organoselenyl pyridines. This synthesis occurs within glycerol and involves a reaction between 2-chloropyridines and organoselenol, which is generated *in situ* by the reaction between various diselenides (both aromatic and aliphatic) and hypophosphorous acid (H₃PO₂), serving as a reducing agent (Scheme 39) (Thurow et al., 2013). Notably, diaryl diselenides featuring both electron-withdrawing and electron-donating groups yielded the corresponding arylselenyl pyridines in commendable yields. Furthermore, the glycerol/H₃PO₂ system exhibited recyclability without the requirement for pre-treatment. Specifically, a yield of 99% was attained for producing 2-phenylselenyl pyridine in a reused system. This efficiency was maintained at 90% for up to the fourth cycle but experienced a significant drop to 60% after the sixth cycle. As per the report, the solvent/reducing agent system can be recovered and employed for subsequent reactions without necessitating any preparatory treatment.

Continuing from the research conducted in 2010 (Goncalves et al., 2013), which investigated the cross-coupling reaction involving (*E/Z*)-β-bromo styrene and diphenyl diselenide, catalyzed by CuI with metallic Zn as an additive in glycerol, the exploration extended to the utilization of diaryl disulfide and diaryl ditellurides for the synthesis of (*E/Z*)-phenylstyryl sulfides and tellurides (Scheme 40) (Goncalves et al., 2010). The central outcomes of this study encompassed the successful formation of (*E/Z*)-aryl(styryl) sulfides and tellurides, attaining yields ranging from 60% to 85%. Importantly, the method exhibited a remarkable selectivity in preserving the specific configuration. The methodology exhibited a favorable tolerance towards both electron-donating and electron-withdrawing groups present in the diphenyl sulfides and tellurides, as well as in the vinyl bromide substrates. The recovery of the reactive mixture (CuI–Zn–glycerol) was effective in the diphenyl disulfide reaction pathway, maintaining stable yields for up to five cycles



Scheme 42. Selective hydrothiolation of 1,4-diorganylbutadi-1,3-ynes using KF/Al₂O₃ in glycerol (Alves et al., 2011).

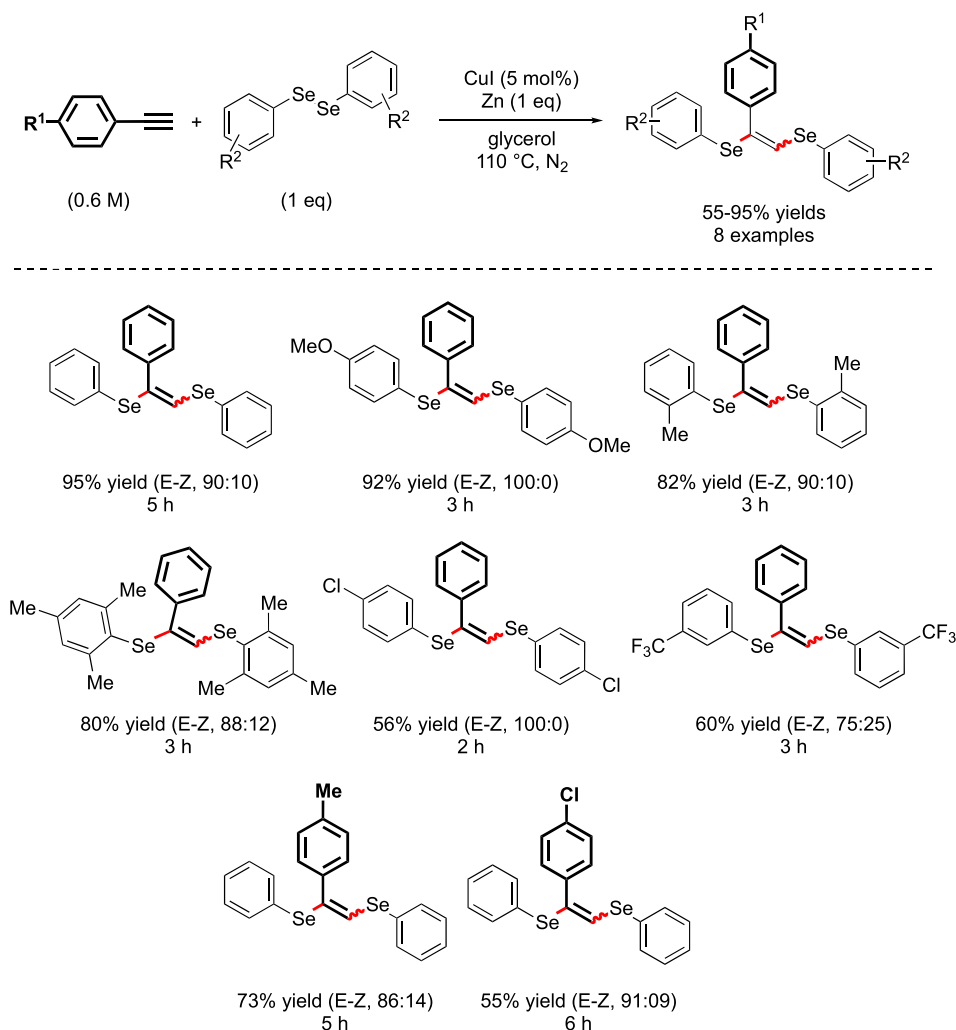
(yields: 75%, 73%, 72%, 70%, 64%, 56%).

A parallel approach was adopted utilizing a CuI-glycerol system to synthesize diaryl chalcogenides. The starting materials encompassed respective diaryl chalcogenides, accompanied by boronic acid, with the addition of DMSO as a reactive enhancer (Ricordi et al., 2012). The assessment of electron-donating and electron-withdrawing effects underscored the versatility of the methodology, which demonstrated sensitivity to electronic influences. The synthesis of diaryl selenides yielded satisfactory results, with yields ranging from 73% to 90%. Furthermore, the technique proved effective in producing diphenyl telluride and diphenyl sulfide, yielding 93% and 25%, respectively. The authors acknowledged ongoing research endeavors aimed at elucidating the mechanism and role of DMSO within this reaction. In consonance with the earlier study, the CuI-glycerol catalytic system was effortlessly recoverable. Notably, the addition of DMSO (1 eq) in each reaction led to an improved recycling efficiency, with a reported rate of 86% in the 4th cycle.

A study presented the hydrothiolation of alkynes utilizing KF/Al₂O₃ catalyst at 90 °C in glycerol. The reaction involved terminal alkynes and thiophenol derivatives, yielding the desired vinyl sulfides in noteworthy yields ranging from 75% to 94% (Scheme 41) (Lenardão et al., 2011). As anticipated, the application of microwave irradiation facilitated a reduction in reaction time, with resulting yields in these conditions remaining comparable at 72–97%. In terms of the reaction's scope, the *E/Z* ratio was contingent on the specific terminal alkyne utilized. Intriguingly, the anti-Markovnikov adduct was obtained in higher quantities than the Markovnikov counterpart. The synthetic route and underlying reaction mechanism were thoroughly elucidated. Furthermore, the study showcased the recycling efficiency of the glycerol/KF/Al₂O₃ system. Notably, during the reaction between propargylic alcohol and thiophenol, an 80% recycling efficiency was observed in the 5th run.

The same research group had previously reported a comparable strategy for the targeted synthesis of (*Z*)-organythioenynes through hydrothiolation (Alves et al., 2011). This approach involved initiating the reaction from 1,4-diorganylbutadi-1,3-ynes in glycerol, albeit at a lower temperature of 60 °C, in contrast to the prior 90 °C temperature. Notably, in contrast to their earlier results, the authors noted a pronounced tendency towards the formation of the *Z* isomer. Depending on the specific substrates employed, the desired compounds were achieved with yields spanning from 39% to 98% (Scheme 42). It's worth highlighting that the utilization of PEG instead of glycerol resulted in improved yields. Furthermore, the research team showcased the sustained efficiency of the approach, which persisted even across three successive reaction runs. This was substantiated by the direct reutilization of the residual mixture containing glycerol/KF/Al₂O₃.

The synthesis of a diverse array of (*E*)-1,2-bis(arylselane)alkenes was achieved through the reaction between symmetric diaryl diselenides and primary aryl alkynes using the same strategy developed starting from alkenes (Goncalves et al., 2010, 2013). This transformation was facilitated using a CuI/Zn/glycerol catalytic system at 110 °C, which proved to be a recyclable setup (Scheme 43)

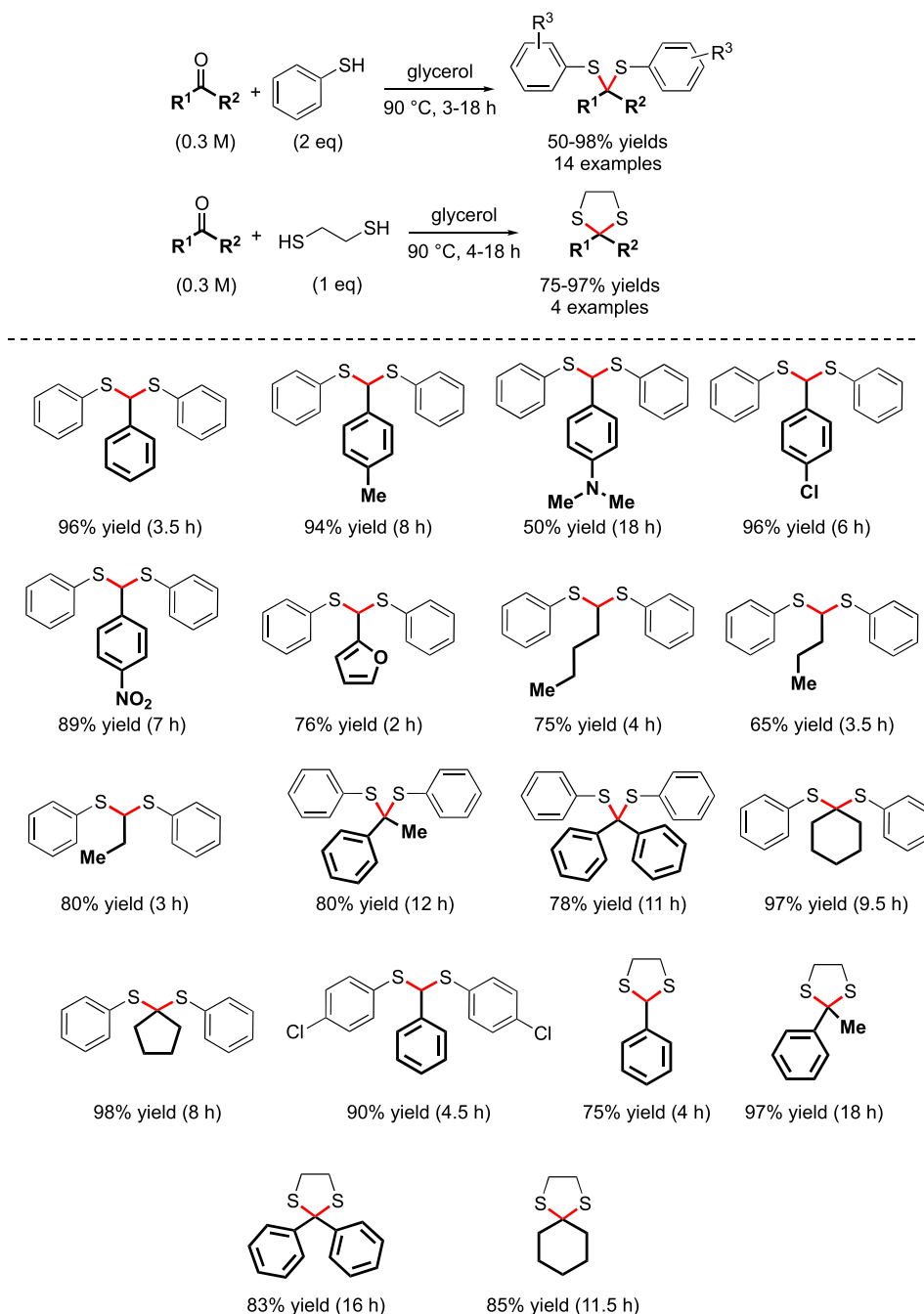


Scheme 43. CuI/Zn-assisted vicinal diselenylation of alkynes in glycerol (Goncalves et al., 2014).

(Goncalves et al., 2014). The method demonstrated heightened efficacy when electron-rich diaryl diselenides were employed, with electron-withdrawing groups yielding less favorable results. The study delved into the system's recyclability, revealing consistent yields over six consecutive runs for producing (*E*)-(1-phenylethene-1,2-diyl)bis(phenylselenane): 95%, 94%, 91%, 88%, 84%, and 76%, respectively. Moreover, considering the significance of the pyrazolic moiety in bioactive heterocycles, the methodology's scope was broadened to encompass *N*-propynylpyrazoles. This extension enabled the synthesis of a blend of bis- and mono-chalcogen alkenes, albeit with moderate selectivity. Among these targeted alkenes, (*E*)-1,2-bis[(4-methoxyphenyl)seleno]styrene emerged as the most potent in terms of antioxidant activity, even in the prevention of linoleic acid oxidation. The authors suggested that the presence of electron-donating groups within this compound possibly accounted for its heightened antioxidant performance.

The protection of carbonyl groups as thioacetals stands as a widely employed and firmly established synthetic technique within organic chemistry. It finds frequent application in the synthesis of various significant natural and synthetic organic compounds. Thioacetals demonstrate their efficacy as carbonyl-protecting groups owing to their inherent stability under both acidic and basic conditions. Exploring glycerol's potential as a selective solvent, the study delved into catalyst-free thioacetalization reactions involving aldehydes and ketones alongside benzenethiol or ethane-1,2-dithiol (Scheme 44) (Perin et al., 2010). Within a reaction time of 12 h at 90 °C, the reactions smoothly progressed, rendering the sought-after products in satisfactory yields. Impressively, glycerol could be readily recovered and reused for subsequent thioacetalization reactions, maintaining a high efficiency with yields of 90% even after four consecutive cycles, despite extended reaction times. This approach not only reduces costs but also minimizes waste production, aligning harmoniously with the principles of green chemistry.

A metal and base-free route for synthesizing arylselenylanilines was unveiled through a reaction involving *N,N*-disubstituted anilines and substituted phenylselenenyl chlorides. This process utilized glycerol as a solvent at room temperature (Scheme 45) (Thurrow et al., 2014). The study effectively yielded twelve products, spanning from good to excellent yields. The proposed mechanism for this Mannich-type reaction entails *N,N*-dimethyl aniline serving as a nucleophile, instigating an attack on phenylselenenyl chloride at the

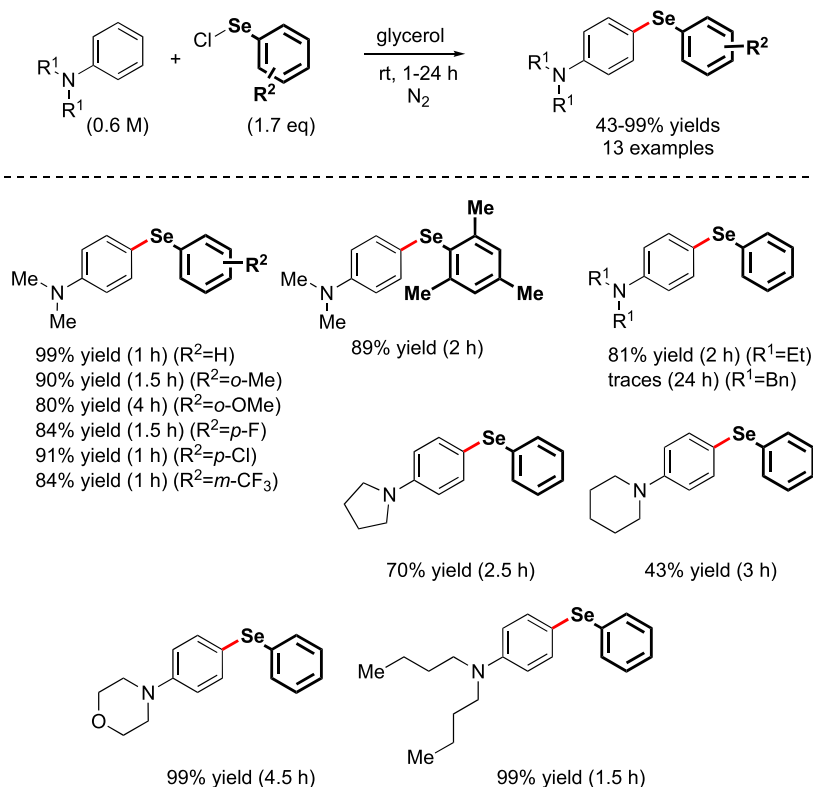


Scheme 44. Catalyst-free thioacetalization reactions in glycerol (Perin et al., 2010).

para position. This reaction leads to the formation of an aryliminium intermediate, which undergoes proton elimination, ultimately yielding the desired compound. In essence, this work underscores several merits. Firstly, the utilization of glycerol at room temperature stands out, particularly given that glycerol is conventionally employed at temperatures exceeding 60 °C. Furthermore, the remarkable selectivity in forming substitution products at the para position of the aromatic ring within anilines, coupled with the omission of any additives, renders this glycerol-facilitated procedure a captivating alternative to conventional methods for producing these functionalized anilines.

2.4. The C–H bond formation

The formation of C–H bonds through the reduction of alkenes and alkynes is a prevalent reaction in the domain of organic chemistry and catalysis. Illustrative instances encompass hydrogenation and catalytic transfer hydrogenation in glycerol has been

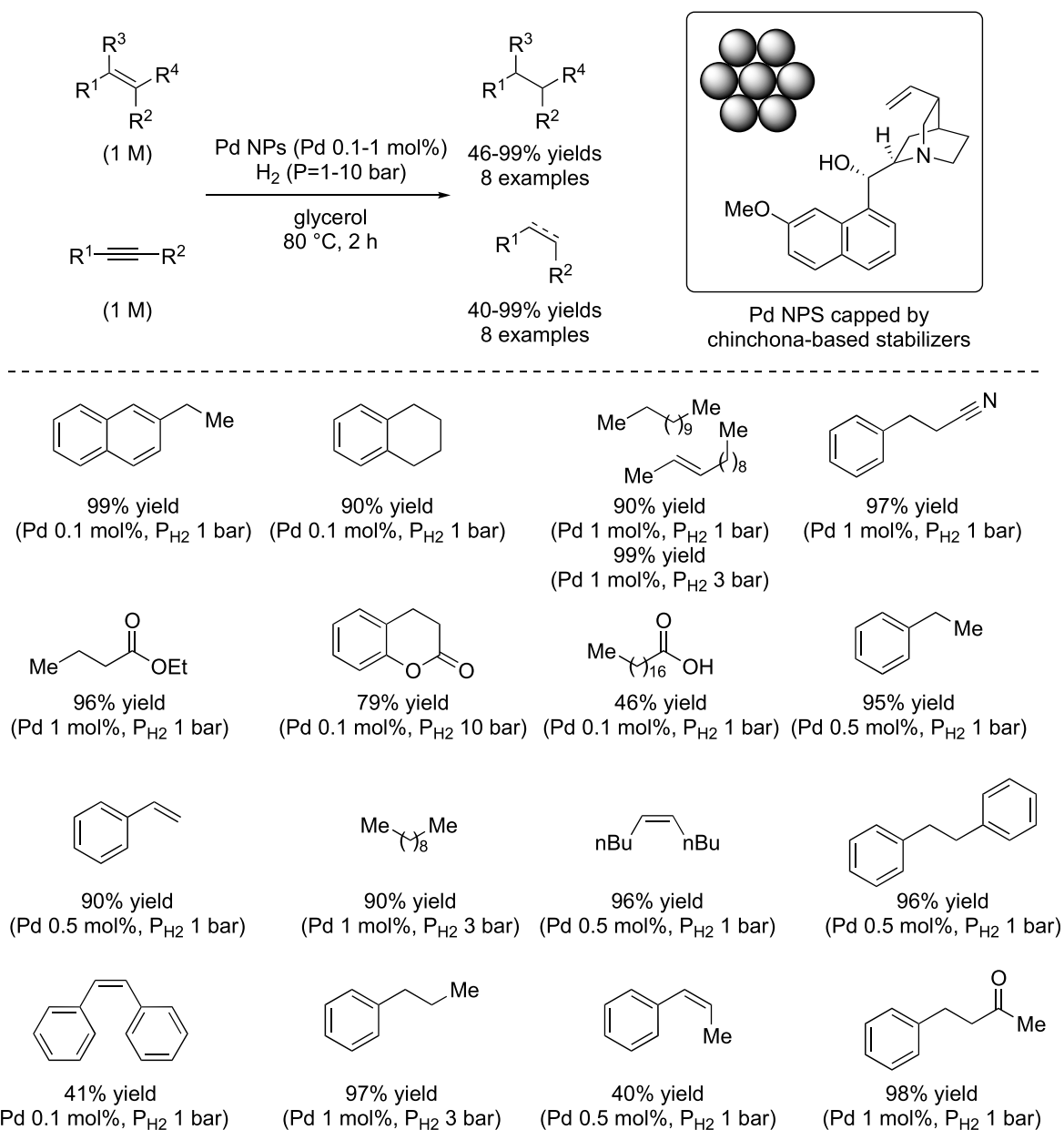


Scheme 45. Metal and base-free synthesis of arylselanyl anilines in glycerol (Thurow et al., 2014).

reported. Investigation into alkene and alkyne hydrogenation utilized a novel palladium catalyst featuring a quinidine ligand. This catalyst was synthesized from Pd(OAc)₂ and quinidine under H₂ pressure in glycerol (Scheme 46) (Reina et al., 2016). The resulting alkenes and alkynes yielded partially or completely reduced compounds in excess of 40% yield. Notably, isomerization of linear alkenes was also detected. The quinidine-stabilized colloidal palladium catalyst (II) exhibited remarkable efficiency in facilitating the hydrogenation of aromatic compounds under low dihydrogen pressure. When glycerol was employed as the solvent, the reactions consistently yielded good to excellent outcomes. The authors reported that the catalytic phase (glycerol/Pd NPs) underwent four cycles of recycling, maintaining consistent catalytic performance (yields of 95-94%) in the synthesis of 4-phenylbutan-2-one from 4-phenylbut-3-en-2-one. Importantly, no detectable palladium was found in the isolated ketone after multiple runs, with palladium loading measuring less than 0.01 ppm, falling below the detection limit of ICP-AES. The study underscored the critical role of glycerol as a solvent for nanoparticle-based catalysts. This role encompassed both the stabilization of nanocatalysts and the facile recycling of the catalytic phase.

A method for the preparation of palladium nanoparticles stabilized by choline-based ionic liquids in glycerol was reported (Garg et al., 2020). The synthesis procedure entailed heating uncomplicated Pd(II) precursors at 80 °C under an argon atmosphere. The participation of water within the ionic liquid was identified as the driving force behind the reduction of Pd(II) into zero-valent palladium species. The palladium nanoparticles generated through this process underwent comprehensive characterization in both liquid and solid phases, utilizing XRD, XPS, and TEM techniques. The metallic nanoparticles exhibited remarkable catalytic activity in hydrogenation processes encompassing a broad spectrum of functional groups including alkenes and alkynes (Scheme 47). Specifically, in the hydrogenation of 4-phenylbut-3-en-2-one as a benchmark reaction, the Pd NPs selectively yielded 4-phenylbutan-2-one with outstanding yields. The study substantiated the absence of Pd leaching through ICP-AES analysis following catalysis. Nevertheless, some nanoparticle aggregation was observed via TEM, while XPS verified the presence of zero-valent Pd NPs. The article highlighted that the formation of these aggregates could potentially account for the observed reduction in catalytic activity, thus posing a challenge to the effective recycling of the Pd NPs in this study.

The chemoselective 1,4 reduction of α,β -unsaturated ketones, such as (*E*)-chalcones, has been elucidated through the *in-situ* generation of benzeneselenol (Mesquita et al., 2014). This generation occurs via the reaction of diphenyl diselenide with H₃PO₂ at 90 °C in glycerol (Scheme 48). The corresponding reduced compounds were achieved with yields ranging from 70% to 89%, and these reactions exhibited consistent performance regardless of the electronic effects within the aromatic ring of the chalcone. Furthermore, the authors explored the potential reusability of the H₃PO₂/glycerol system by utilizing chalcone and diphenyl diselenide. Notably, a significantly enhanced recycling efficiency was accomplished, yielding a remarkable 74% yield of 1,3-diphenyl-1-propanone in the 5th cycle. This outcome underscores the pronounced effectiveness of this system for repetitive applications. Additionally, under analogous conditions, the natural product zingerone [4-(4-hydroxy-3-methoxyphenyl)-butan-2-one], derived from ginger, was synthesized with an



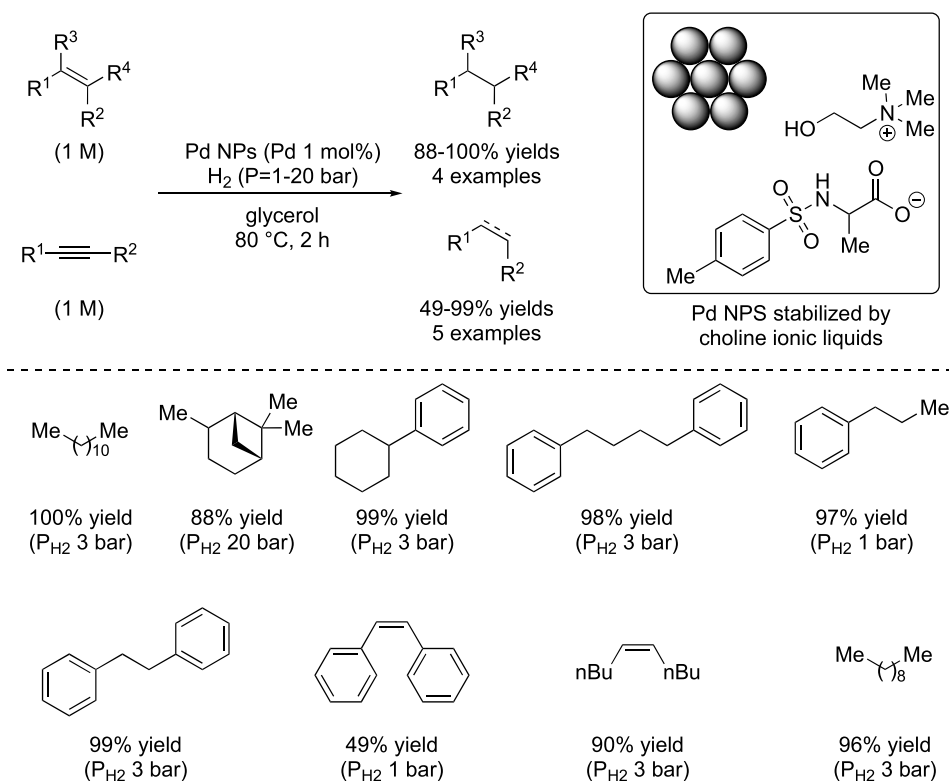
Scheme 46. Hydrogenation of alkenes and alkynes catalyzed by palladium nanoparticles stabilized by cinchona-based alkaloids in glycerol (Reina et al., 2016).

impressive yield of 68%.

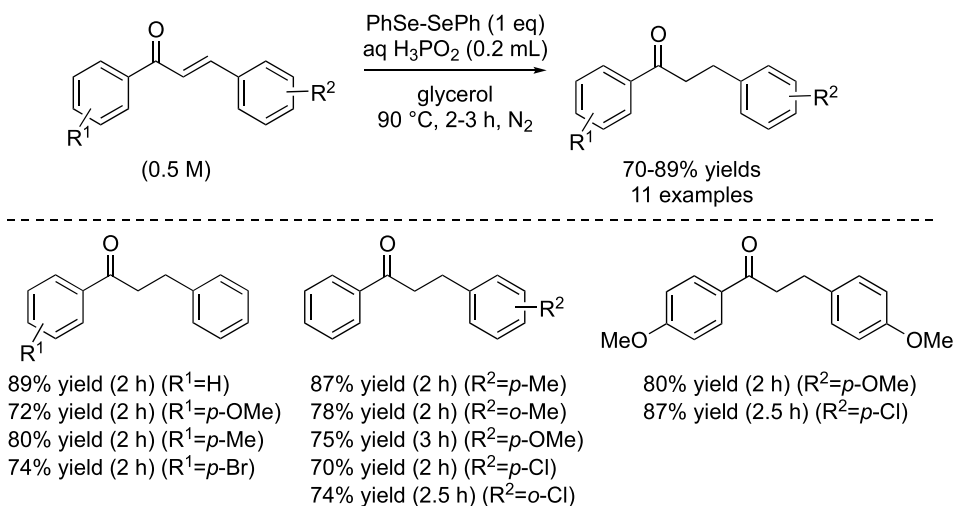
The efficacy of Ir(III) catalysts containing *N*-heterocyclic carbene (NHC) ligands, specifically [IrI₂(AcO)(bis-NHC)], was evaluated for the catalytic transfer hydrogenation of olefins and acetylenes. Glycerol was both employed as a solvent and served as the reducing agent (Azua et al., 2011). Among these catalysts, IrI₂(AcO)(bis-NHC)-2 and IrI₂(AcO)(bis-NHC)-4 exhibited limited activity in the reduction of phenylacetylene and styrene. In order to activate the olefins, allyl ketones were introduced as the starting materials. To assess the chemoselectivity of the catalytic transfer hydrogenation between enones or enals and glycerol, two sulfonated catalysts were employed under conditions of 100 °C (Schemes 49 and 50). In each experiment, two primary compounds were generated, with a notable preference for the reduction of the C–C double bond, except in the case of the enal.

According to the authors, the probable mechanism is as follows: (i) successive formation of a glycerolate in a basic medium followed by an iridium alkoxide; (ii) formation of an iridium hydride intermediate by β-hydrogen elimination from the glycerol forming the dihydroxyacetone; (iii) insertion of the carbonyl group of the starting ketone or aldehyde into the iridium-hydride bond to give an alkoxide; (iv) alkoxide exchange in which a second glycerol molecule enters the metal coordination sphere, regenerating the catalytic species (Scheme 51).

Extensive research has been conducted to explore an appealing alternative to conventional hydrogenation reactions for reducing

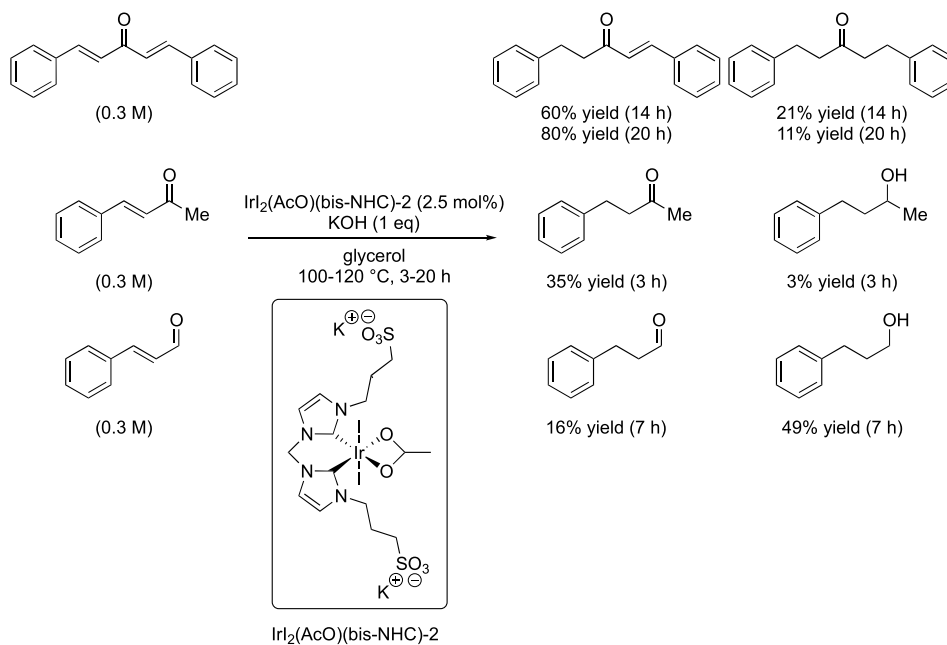


Scheme 47. Hydrogenation of alkenes and alkynes catalyzed by palladium nanoparticles stabilized by cinchona-based alkaloids in glycerol (Garg et al., 2020).

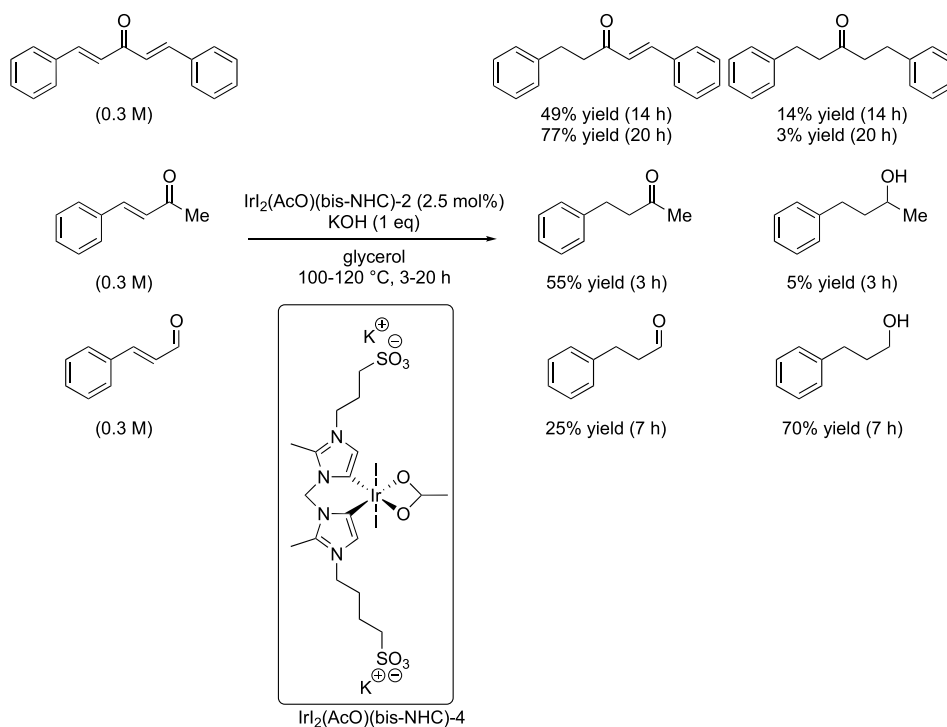


Scheme 48. Application of the H_3PO_2 -glycerol system in the reduction of (*E*)-chalcones by selenol in glycerol (Mesquita et al., 2014).

the C–C bond within allylic alcohols (Díaz-Álvarez et al., 2011). This catalytic process unfolds in a seamless one-pot fashion, employing ruthenium hydride intermediates along with the arene-Ru(II) complex $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)(\text{DAPTA})]$ (where DAPTA stands for 3,7-diacetyl-1,3,7-triaza-5-phospha-bicyclo[3.3.1]nonane) in conjunction with KOH. The mechanism entails a sequential series of two distinct reactions: initially, a redox isomerization of allylic alcohol to propionaldehyde, followed by a subsequent transfer hydrogenation of the resultant carbonyl compound. This leads to the formation of the corresponding saturated alcohol (Scheme 52). This catalyst system, when implemented in pharmaceutical-grade glycerol, expedites the conversion of allylic alcohols to saturated propan-1-ol with remarkable yields (reaching up to 97%) and nearly complete selectivity, all accomplished within a short span of 6 h. Importantly, the same reaction conducted using technical-grade glycerol (with a purity of 87%) also resulted in the quantitative generation of propan-1-ol within a similar 6-h timeframe. In terms of catalyst recycling, the researchers examined the reutilization of the

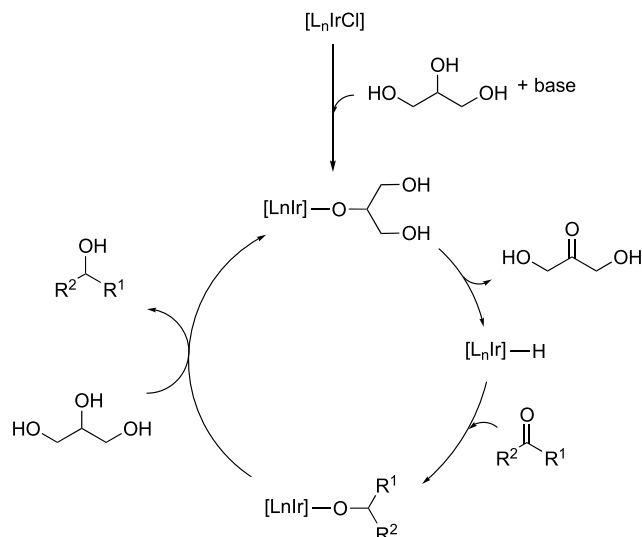


Scheme 49. Metal catalytic transfer hydrogenation of dibenzylidene ketone, benzylidene ketone and benzylidene aldehyde in glycerol as solvent and reducing agent (Azua et al., 2011).

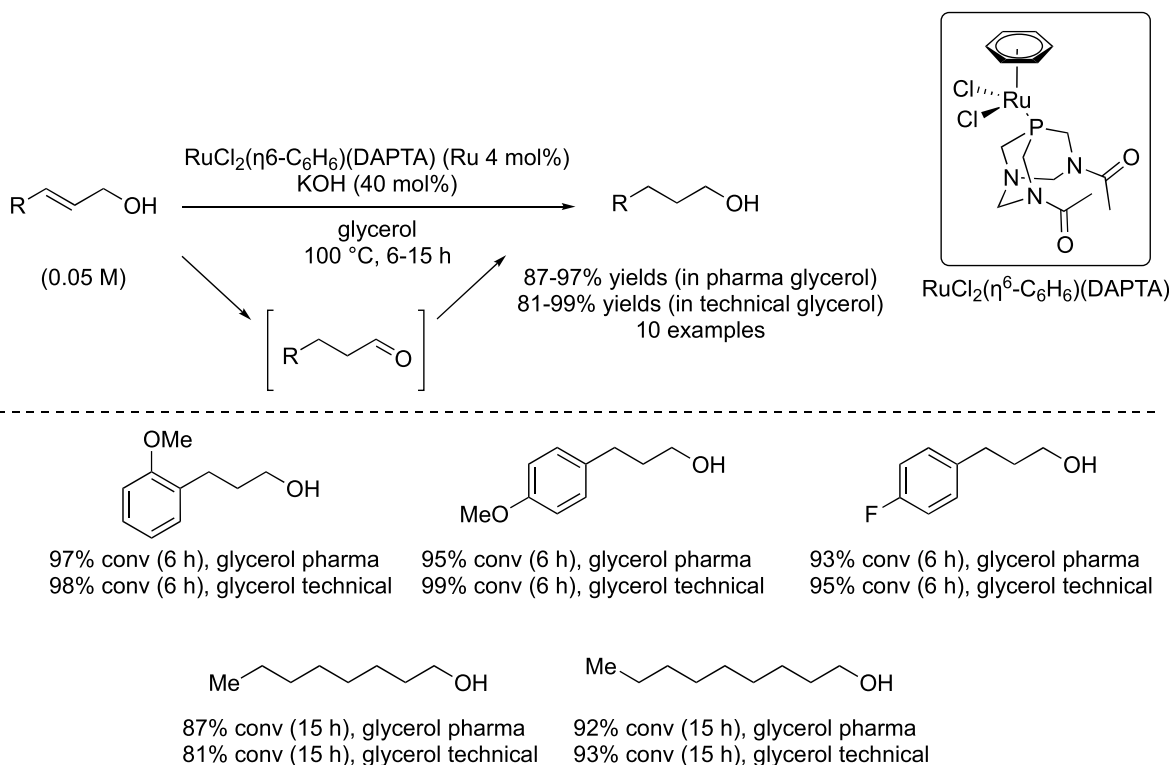


Scheme 50. Metal catalytic transfer hydrogenation of benzylidene ketone, dibenzylidene ketone and benzylidene aldehyde in glycerol as solvent and reducing agent (Azua et al., 2011).

[$\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)(\text{DAPTA})$] complex for the reduction of (*E*)-3-phenyl-2-propen-1-ol to 3-phenylpropan-1-ol in technical-grade glycerol, serving as a model reaction. However, they observed a gradual decrease in activity after each cycle due to the catalyst's partial decomposition. This decomposition was evidenced by the release of the aryl ligand (C_6H_6) into the solution during prolonged periods at 100 °C.

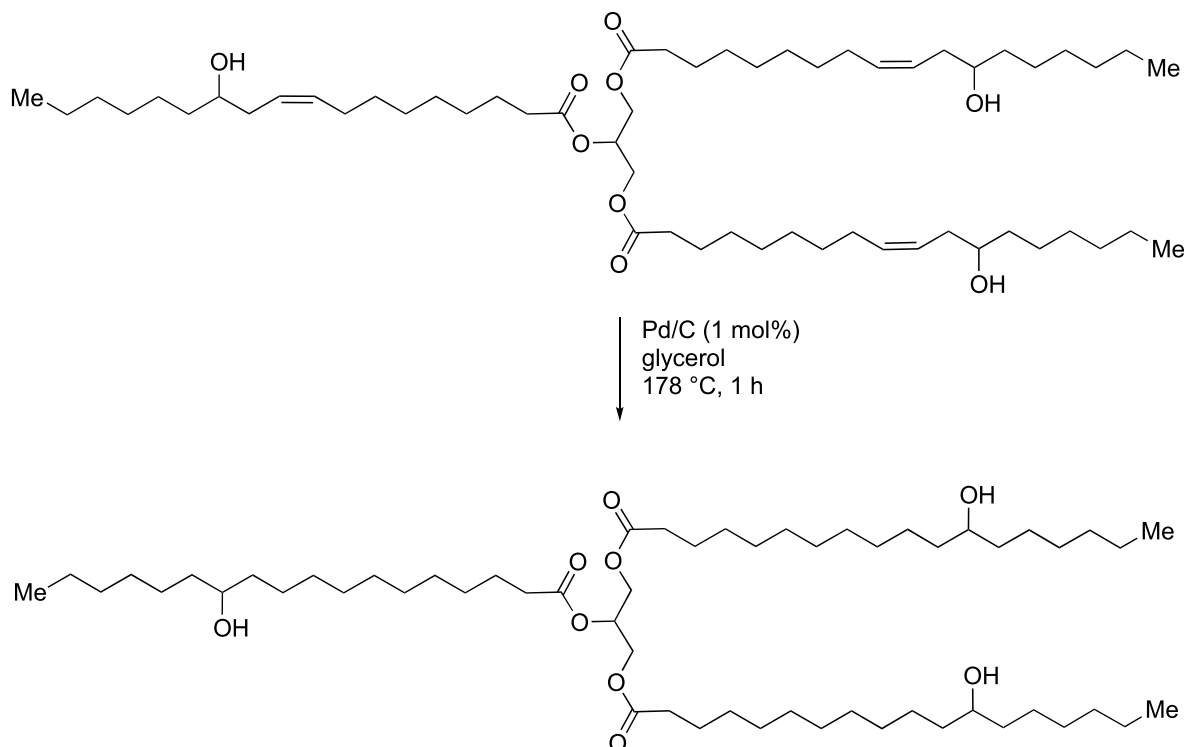


Scheme 51. Plausible mechanism for catalytic transfer hydrogenation of ketone in glycerol using iridium NHC based catalyst (Azua et al., 2011).

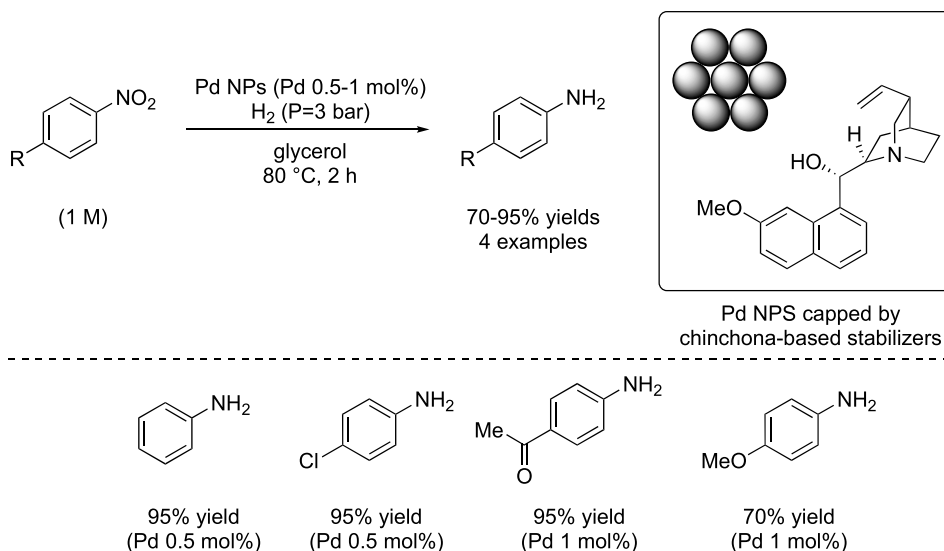


Scheme 52. Catalytic transfer hydrogenation of allylic alcohol to propan-1-ol in pharma grade and technical grade glycerol (Díaz-Álvarez et al., 2011).

The utilization of catalytic transfer hydrogenation was documented in the context of castor oil, aiming to synthesize a hydrogenated oil with reduced saturation (Mohd Amin et al., 2020). The investigation showed that the reaction occurred at 178 °C for a duration of 1 h, conducted under atmospheric pressure and employing a 10% Pd/C catalyst (Scheme 53). This hydrogenation process led to a noteworthy elevation in the melting point of the resultant oil derivative. Specifically, the melting point escalated from -7 °C for castor oil to 74.7 °C for the hydrogenated oil. This pronounced change is attributable to the increased level of saturation achieved through the hydrogenation process. This observation underscores the promising potential of crude glycerol as a hydrogen source within a tandem transesterification/reduction procedure. This approach offers a pathway for the on-site utilization of crude glycerol, which is generated during biodiesel production.



Scheme 53. Catalytic transfer hydrogenation of Castor oil to hydrogenated Castor oil in glycerol (Mohd Amin et al., 2020).⁹².

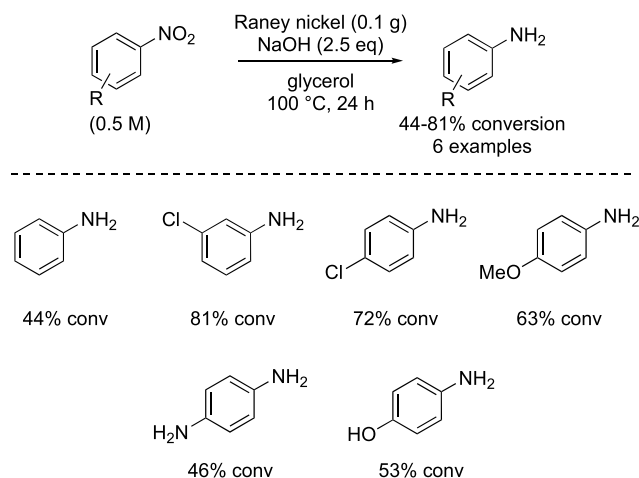


Scheme 54. Hydrogenation of nitroarene catalyzed by palladium nanoparticles stabilized by cinchona-based alkaloids in glycerol (Reina et al., 2016).

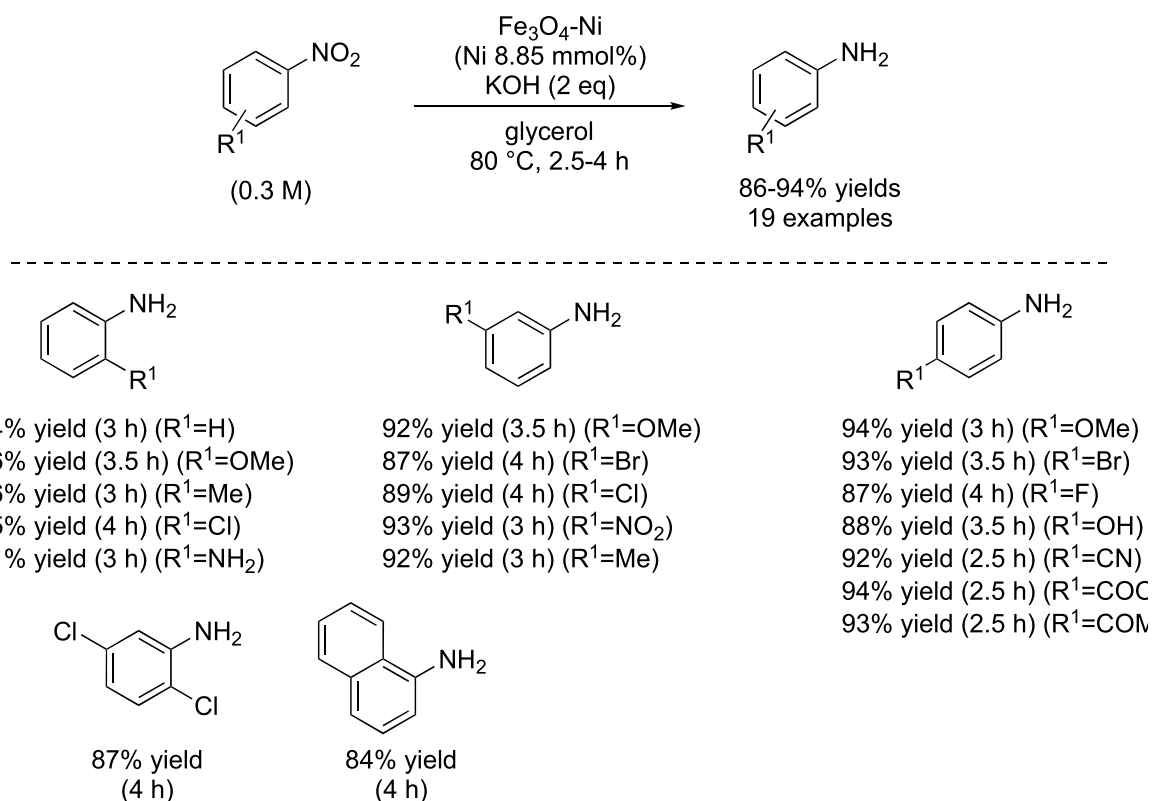
2.5. The N–H bond formation

The N–H bond formation can be done by cleavage of amides, carbamates, imides and by reduction of azides, imines, nitriles, nitro compounds and others. Using glycerol as a solvent, reduction of nitro aryl derivatives was examined. The catalyst reported for the reduction of alkenes and alkynes (Reina et al., 2016; Garg et al., 2020) was used for the reduction of nitroarene with hydrogen for the synthesis of anilines (Scheme 54).

Metal-catalyzed transfer hydrogenation was investigated for the reduction of nitroarenes to their corresponding aniline derivatives in glycerol (Tavor et al., 2011). A reaction mixture comprising nitrobenzene derivatives and NaOH, along with Raney nickel as the catalyst, was subjected to 100 °C for 24 h, resulting in the formation of the respective amines with a conversion rate exceeding 44%



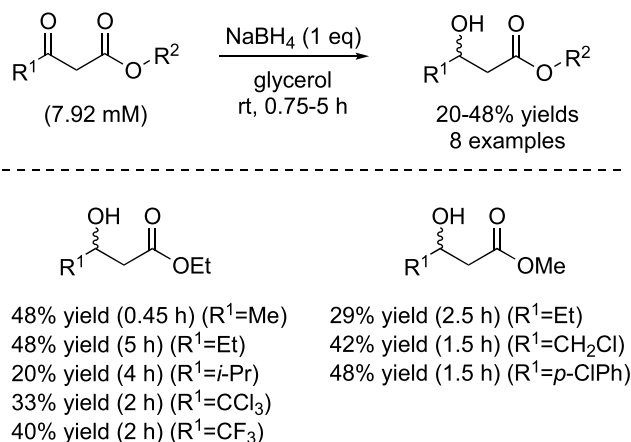
Scheme 55. Catalytic transfer hydrogenation of nitrobenzenes to anilines in glycerol (Tavor et al., 2011).



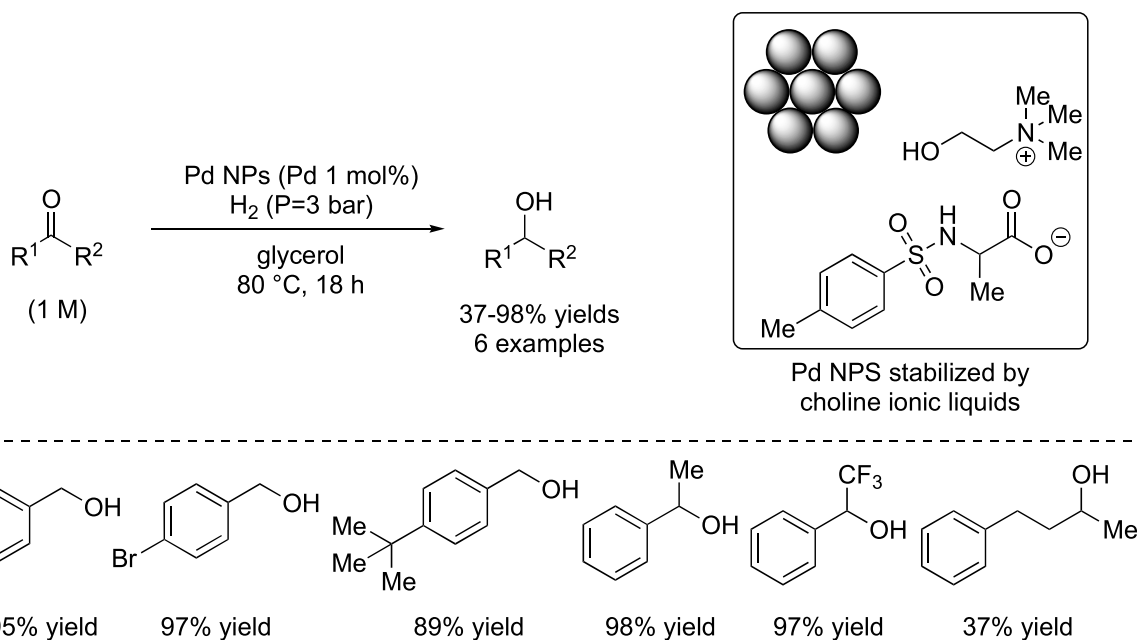
Scheme 56. Catalytic transfer hydrogenation between carbonyl compounds and glycerol in the presence of $\text{Fe}_3\text{O}_4\text{-Ni}$ (Gawande et al., 2012).

(Scheme 55). Notably, nitrobenzene derivatives containing electron-withdrawing substituents exhibited a higher propensity for reduction to anilines in contrast to those bearing electron-donating groups. Upon scaling up the reaction with an increased nitrobenzene ratio (2.5 g vs 0.25 g) and a reduced catalyst amount (0.4 g vs 1 g) over a 72-h span, nitrobenzene underwent a 56% conversion, leading to a 48% yield of aniline. The research also underscored that the reaction rate was primarily governed by the quantity of the base and by the operative temperature. The use of glycerol as a solvent facilitated the straightforward separation of products and allowed for efficient catalyst recycling. However, it was noted that the addition of fresh NaOH was required to achieve complete conversion for three consecutive cycles. Despite the necessity for supplemental base addition, this approach showcased the potential for recycling the catalytic system, which in turn contributed to reductions in costs and waste generation.

Building upon the prior research conducted on the reduction of carbonyl compounds utilizing $\text{Fe}_3\text{O}_4\text{-Ni}$ magnetic nanoparticles, an



Scheme 57. Synthesis of racemic β -hydroxy esters through reduction of β -keto esters using NaBH_4 in glycerol (de S. Oliveira et al., 2014).



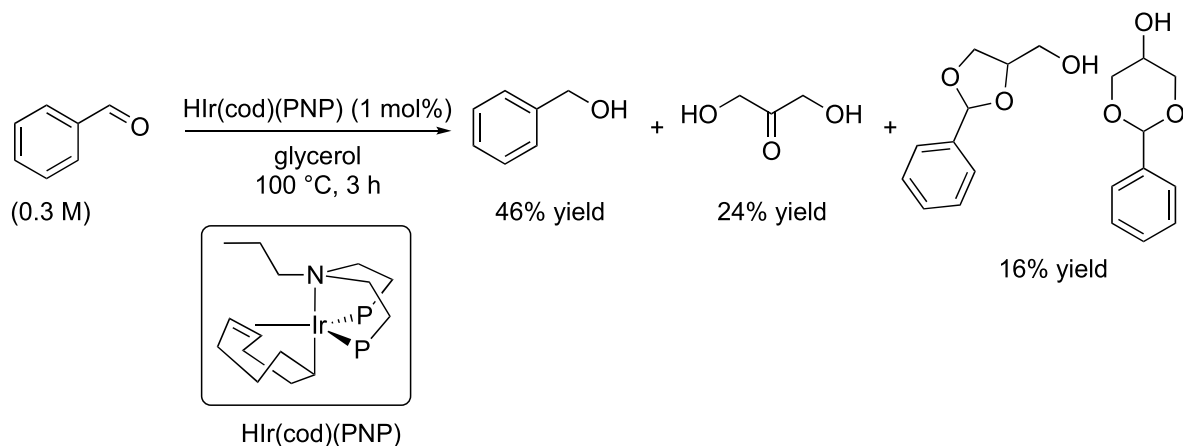
Scheme 58. Hydrogenation of carbonyl compounds catalyzed by Pd NPs stabilized by choline ionic liquid in glycerol (Garg et al., 2020).

expansion of this approach was explored for the catalytic transfer hydrogenation of nitroarenes (Scheme 56) (Gawande et al., 2012). This investigation demonstrated the versatility and resilience of the catalyst. Irrespective of the substituents present on the aromatic core, anilines were consistently obtained with yields exceeding 86%.

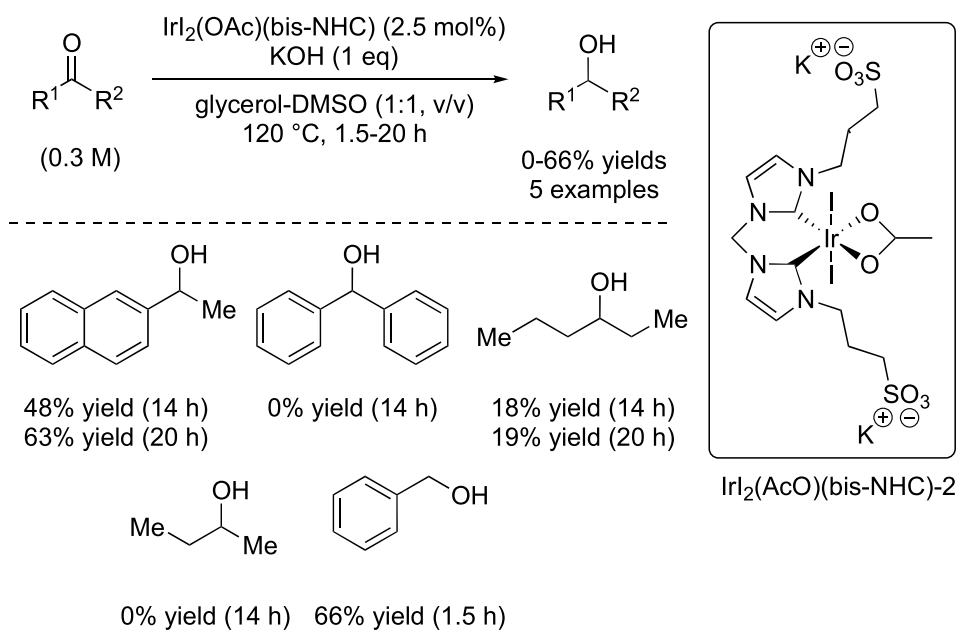
2.6. The O–H bond formation

O–H bond formation can be achieved through the cleavage of ethers, esters, carbonates, carbamates, acetals, and the reduction of carbonyl compounds, epoxides, and other relevant compounds. To the best of our knowledge, in cases where glycerol served as the solvent, only the reduction of carbonyl derivatives led to the formation of the corresponding O–H bond. The selective reduction of β -keto esters holds significant importance for synthesizing the corresponding β -hydroxy esters, a common synthon in natural molecules. The synthesis of β -hydroxy esters is accomplished through the chemical reduction of β -keto esters, utilizing NaBH_4 as the reducing agent in glycerol (Scheme 57) (de S. Oliveira et al., 2014). In contrast, when methanol was employed as the conventional solvent, the resulting yields were notably lower, ranging from 11% to 45%. Remarkably, the utilization of glycerol as a solvent proved to be notably more effective across a diverse array of substrates compared to the conventional methodology, all under the same reaction conditions.

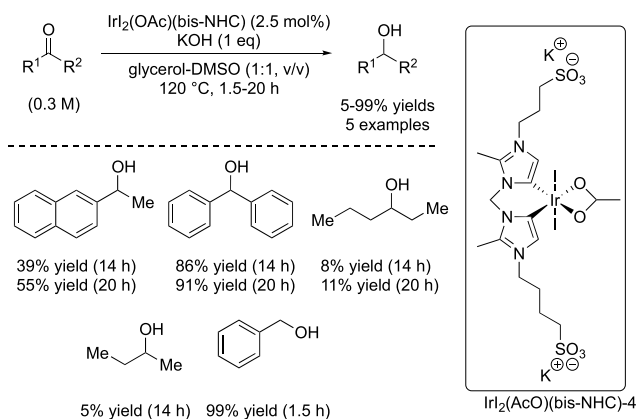
Hydrogenation of carbonyl compounds was examined in the presence of the same catalyst used for the reduction of alkynes, alkenes and nitro compounds (Garg et al., 2020). The reduction of aldehydes and ketones at 80 °C for 18 h furnished the primary alcohols and



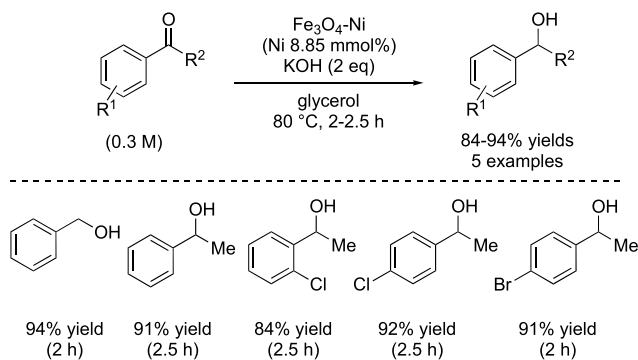
Scheme 59. Metal catalytic transfer hydrogenation between benzaldehyde and glycerol (Crotti et al., 2010).



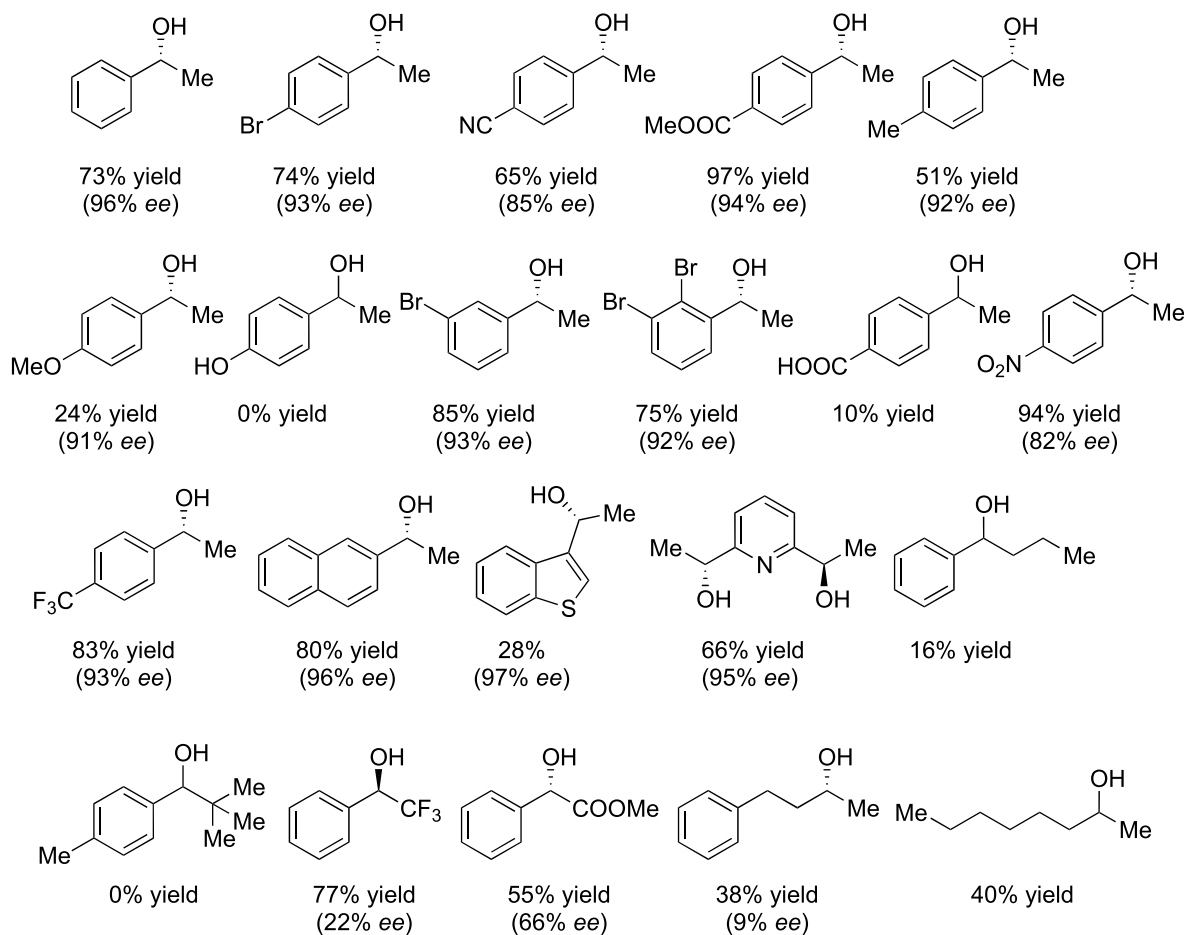
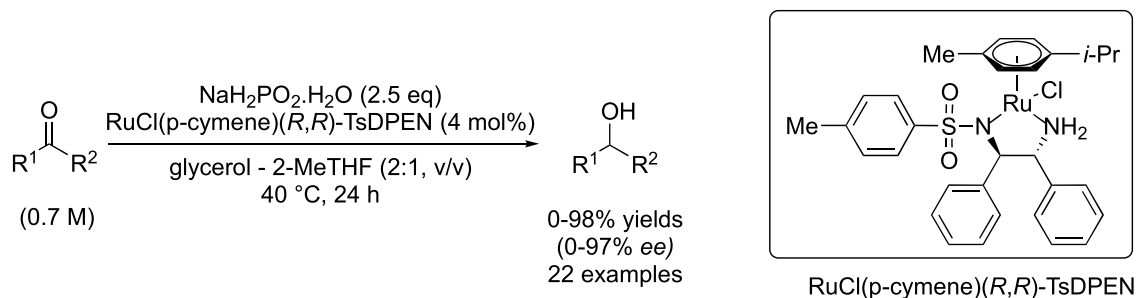
Scheme 60. Metal catalytic transfer hydrogenation between carbonyl compounds and glycerol (Azua et al., 2011).



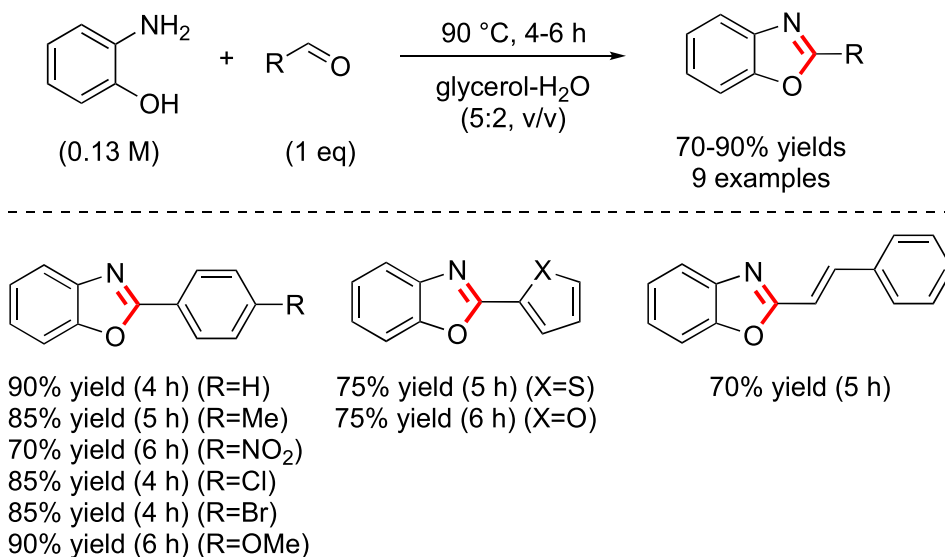
Scheme 61. Metal catalytic transfer hydrogenation between carbonyl compounds and glycerol (Azua et al., 2011).



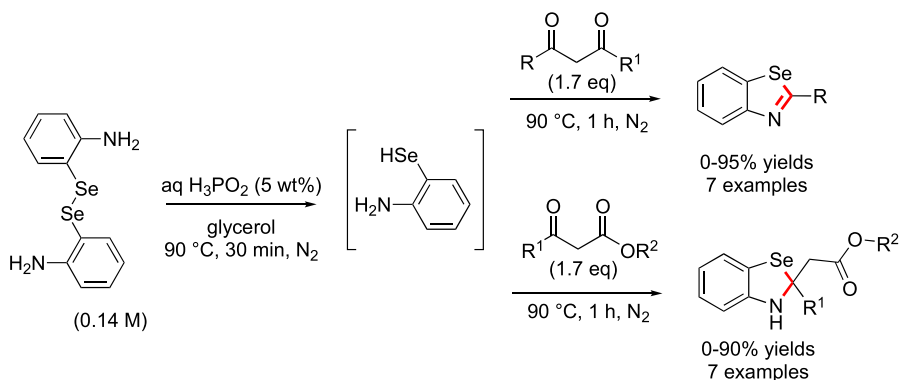
Scheme 62. Catalytic transfer hydrogenation between carbonyl compounds and glycerol in the presence of $\text{Fe}_3\text{O}_4\text{-Ni}$ (Gawande et al., 2012).



Scheme 63. Enantioselective catalytic transfer hydrogenation of carbonyl compounds in glycerol using $[\text{RuCl}(\text{p-cymene})\{(\text{R,R})\text{-TsDPEN}\}]$ (Guyon et al., 2013).



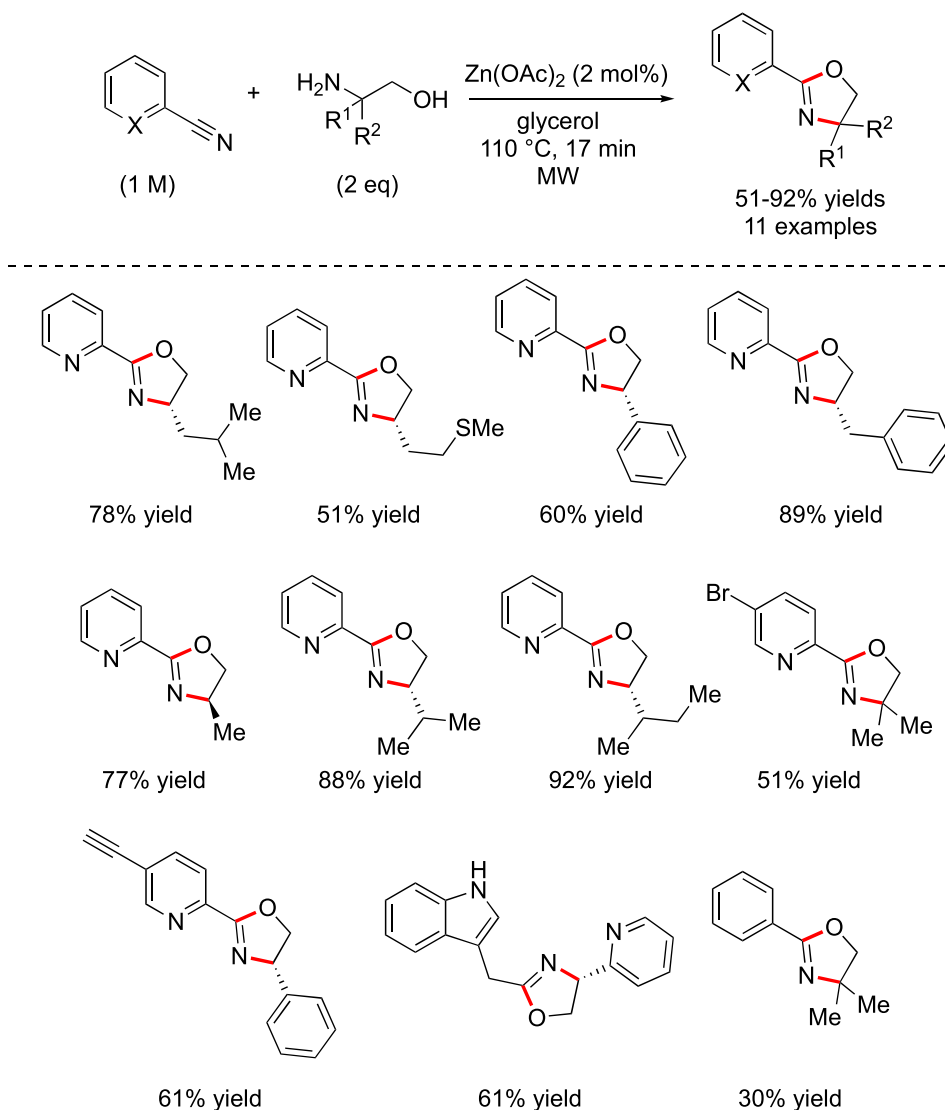
Scheme 64. Catalyst-free synthesis of 2-arylbenzoxazoles in glycerol (Bachhav et al., 2011).



Scheme 65. One-pot synthesis of benzoselenazoles and benzoselenazolines in glycerol (Balaguez et al., 2015).

secondary alcohol, respectively (Scheme 58).

The catalytic transfer hydrogenation of carbonyl compounds to produce their corresponding alcohols was investigated, utilizing either glycerol as a reducing solvent or glycerol as a solvent coupled with a reducing agent. A reaction mixture containing benzaldehyde and the iridium(I) complex $\text{HIr}(\text{cod})(\text{PNP})$ (I) (1 mol%) in glycerol, heated to 100 °C for 3 h, yielded the respective benzyl alcohol with a 46% yield (Scheme 59) (Crotti et al., 2010). The authors noted that the yield of dihydroxyacetone (DHA) is generally lower compared to that of the corresponding hydrogenated compounds. This discrepancy is likely attributed to iridium-catalyzed benzaldehyde dimerization, a process that doesn't involve glycerol dehydrogenation. However, the Ir(I) complex exhibited minimal activity (yields <8%) in the reduction of acetophenone to 1-phenylethanol, as per the findings.

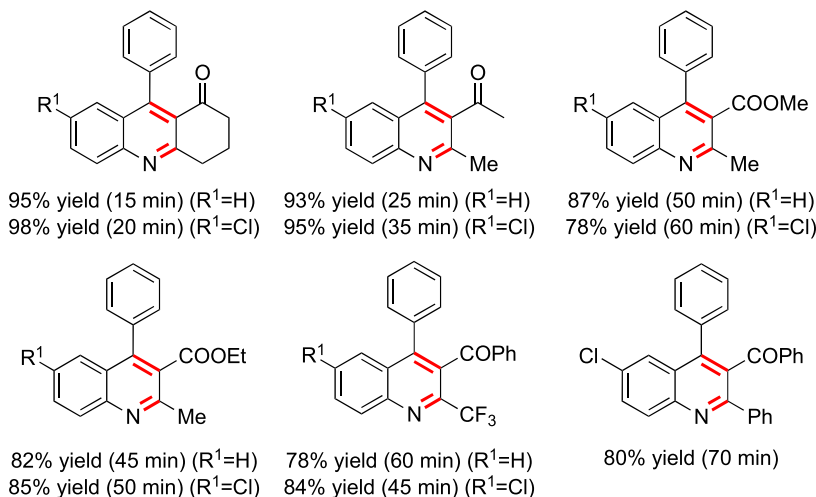
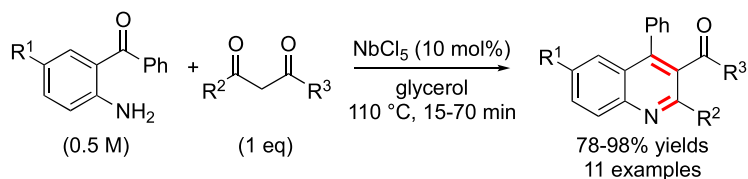


Scheme 66. Synthesis of 2-oxazolines in glycerol under microwave irradiation (Carmona et al., 2013).

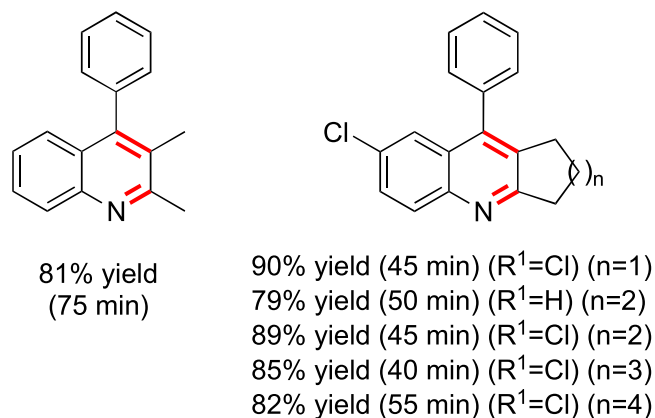
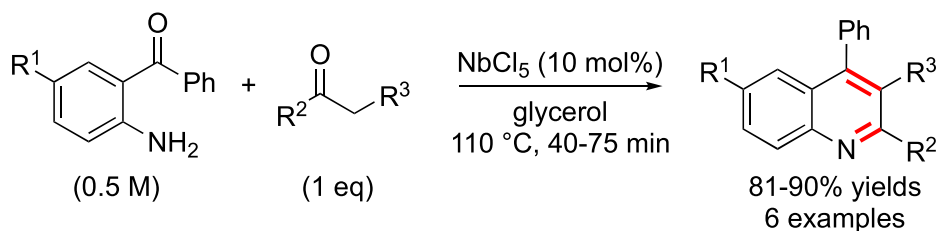
The catalysts $[\text{IrI}_2(\text{AcO})(\text{bis-NHC})]$ used for the reduction of C–C double bond was tested for the formation of reduction of carbonyl compounds (Azua et al., 2011). The proposed catalyst exhibited good activity in the reduction of aromatic ketones and aldehydes, and low activity in the reduction of dialkyl ketones (Schemes 60 and 61). Obviously, the reduction of benzaldehyde yielded higher yields (66–99%) compared to the reduction of benzophenone (39–91%). The authors noted that the catalytic activity of the Ir(III) catalysts in the reduction of carbonyl compounds in glycerol was significantly improved compared to the current state of the art. The reason should be the introduction of sulfonate groups attached to the ligand that promotes a higher solubility of the catalysts in glycerol.

The same research group presented analogous methodologies utilizing alternative technologies, including microwave irradiation and ultrasonic activation (Azua et al., 2012). Under microwave (MW) activation, the reduction of carbonyl groups to yield corresponding alcohols was accomplished in brief reaction durations (1–2 h), at relatively mild temperatures (80–120 °C), yielding satisfactory results (60–95%). In contrast, ultrasonic (US) irradiation significantly expedited reaction times (20 min at 20% amplitude) and delivered favorable outcomes (64% yield) for aldehyde reduction. This advancement can be attributed to the improved dispersion of reactants within the reaction medium. Additionally, the destiny of the catalyst was probed through transmission electron microscopy (TEM) analysis of the reaction mixture, revealing catalyst deactivation under both MW and US conditions. Specifically, the Ir(III) complex underwent transformation into spherical nanoparticles of Ir(0).

For a facile, uncomplicated, and environmentally conscious catalytic transfer hydrogenation approach, the reduction of carbonyl compounds using Fe_3O_4 –Ni magnetic nanoparticles was explored (Gawande et al., 2012). This strategy facilitated the synthesis of alcohols with impressive yields at 80 °C for 2–2.5 h (Scheme 62). The outcomes achieved in this research aligned with existing protocols. Importantly, no alterations in the morphology of the magnetic nanoparticles (MNPs) were noted. Furthermore, the absence



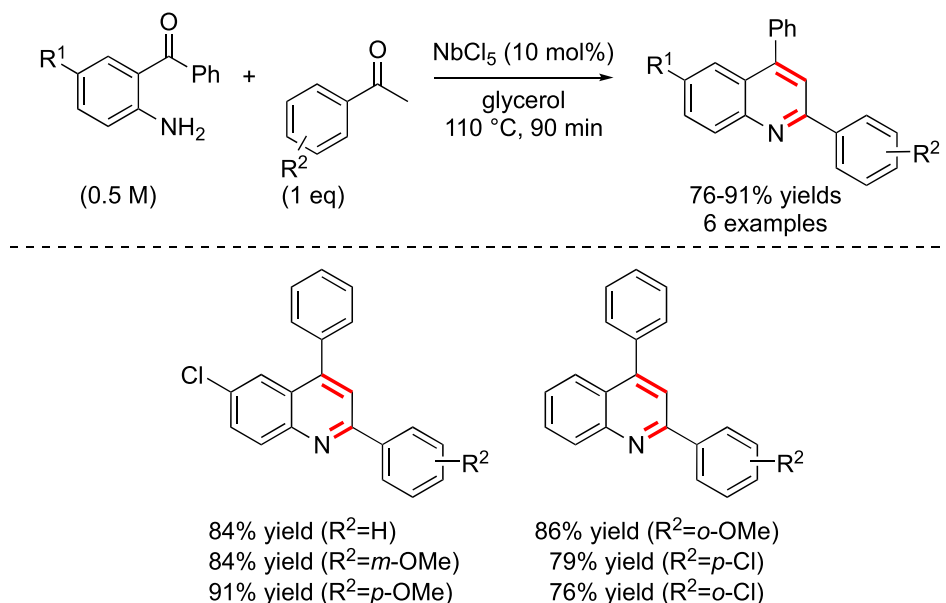
Scheme 67. Synthesis of 2,3-substituted 4-phenylquinoline catalyzed by NbCl₅ catalyst in glycerol (Nasseri et al., 2015).



Scheme 68. Synthesis of 2,3-dialkyl-4-phenylquinoline catalyzed by NbCl₅ catalyst in glycerol (Nasseri et al., 2015).

of Fe and Ni species in the filtrate (confirmed via TEM and ICP-AES analyses, respectively) provided evidence that the reaction occurred within a heterogeneous phase, showcasing excellent stability.

Another metal, ruthenium (Ru(II)), was investigated for the reduction of ketones to yield the corresponding alcohols. A catalytic enantioselective transfer hydrogenation process involving both aliphatic and aromatic ketones was reported using [RuCl(*p*-cymene)]{(*R,R*)-TsDPEN} catalyst (Guyon et al., 2013). This reaction took place in a biphasic mixture of glycerol and 2-MeTHF at 40 °C over a



Scheme 69. Synthesis of 2,4-diphenylquinolines catalyzed by NbCl₅ in glycerol (Nasseri et al., 2015).

24-h period. The resultant alcohols were obtained with exceptional enantioselectivities, reaching up to 97% (Scheme 63). It is notable that glycerol did not act as reducing agent, NaH₂PO₂ acted as hydrogen donor.

2.7. Formation of more than one bond with atoms of different nature

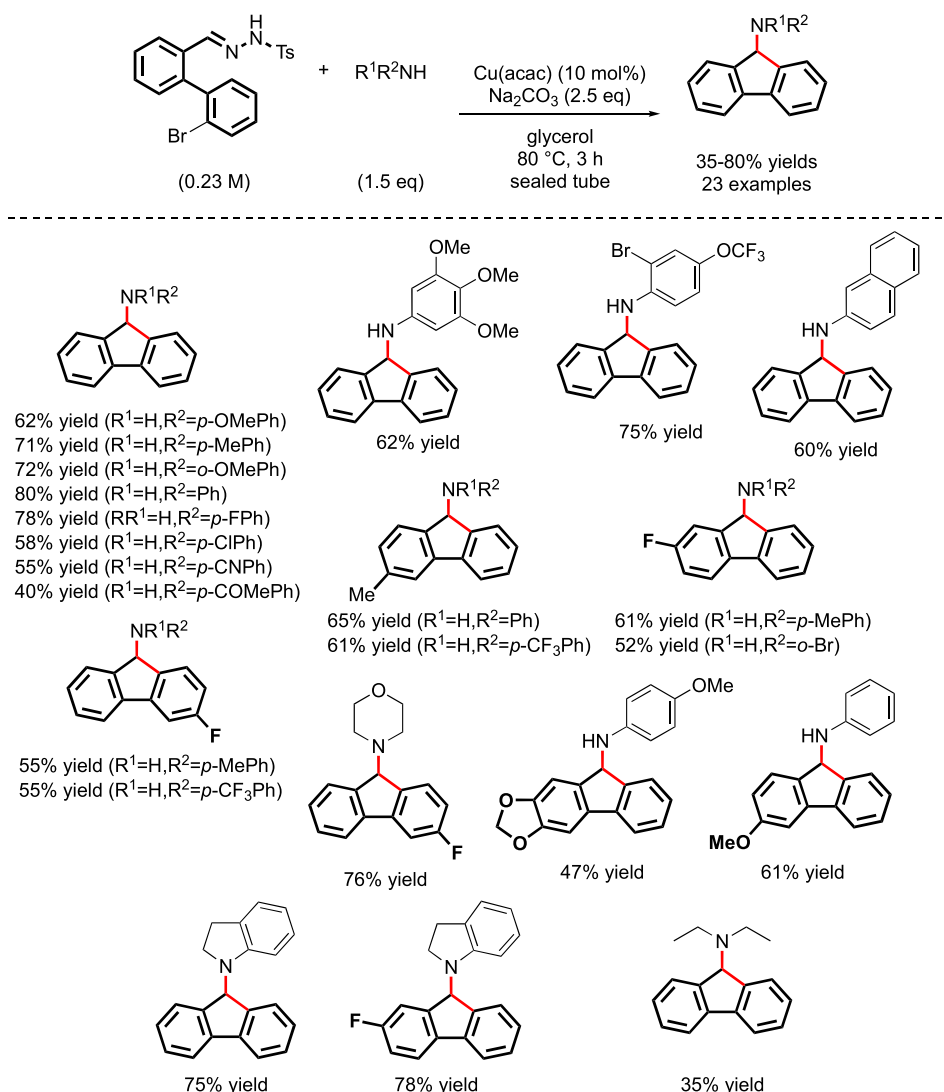
The formation of C–C, C–N, C–O, C–H, N–H and O–H bonds in glycerol as solvent has been detailed in previous chapters. The synthesis of molecules by the creation of bonds involving atoms of different kinds has also been examined. By way of example, synthesis involving the formation of C–N/C–O, C–C/C–N type bonds with two, three and more components in glycerol will be discussed.

Two components reactions involving CN + CO, CN + CS, CN + CSe or CC=CN bond formation was reported in glycerol. The use of the same strategy developed for the synthesis of benzimidazoles (Bachhav et al., 2011) was examined starting from *o*-aminophenol for the formation of 2-arylbenzoxazoles (Scheme 64).

The synthesis of selenium-containing heterocycles, especially 1,3-benzoselenazoles, presents a notable challenge within the realm of heterocyclic chemistry (Mayo et al., 2014). In response to this challenge, a one-pot approach for synthesizing benzoselenazoles and benzoselenazolines using bis(2-aminophenyl) diselenide and β -dicarbonyl compounds has been reported (Scheme 65) (Balaguez et al., 2015). The reduction of the Se–Se bond within bis(2-aminophenyl) diselenide was accomplished by treating it with hypophosphorous acid (H₃PO₂) in glycerol at 90 °C for 30 min under a nitrogen atmosphere. This process led to the *in situ* generation of 2-amino-benzoselenenol. It's noteworthy that this approach had been previously developed for C–Se bond formation (Thurow et al., 2013). Following this, when the *in situ* formed 2-amino-benzoselenenol reacted with 1,3-diketones, benzoselenazoles were obtained with commendable yields within a short reaction timeframe. Likewise, the reaction of 2-amino-benzoselenenol with β -keto esters yielded benzoselenazolines with similarly good yields.

The 2-oxazoline moiety is present in a range of biologically active compounds and has garnered significant attention due to its usefulness in organic synthesis, particularly as a protective group. A catalytic system that combines glycerol and zinc(II) acetate was employed to facilitate the reaction between aromatic nitriles and 2-aminoethanol derivatives under microwave irradiation at 110 °C for 17 min (Scheme 66) (Carmona et al., 2013). Notably, conventional heating did not notably enhance the reaction, as even at 110 °C, the desired oxazoline was achieved with an 88% yield after a 2-h reaction period. Starting with benzonitrile, the target oxazoline was obtained in a 30% yield, indicating that benzonitrile is less reactive compared to the other nitriles used. The application of this method to 2-arylacetonitriles enabled the synthesis of the corresponding oxazolines with yields ranging from 61% to 63%. Moreover, the glycerol-zinc(II) catalytic system could be recovered and reused for the same transformation up to four times, albeit with a slight decrease in activity (yield range: 85-55%). The authors emphasized the absence of exogenous by-products under the optimized reaction conditions.

Quinolines hold a pivotal position in the pharmaceutical sector, notably contributing to the treatment of diseases such as malaria and cancer. Commencing with 2-aminobenzophenone and a variety of carbonyl compounds (1,3-diketones, β -keto esters, ketones, acetophenone), the synthesis of quinolines encompassing C–C and C–N bond formations was achieved (Nasseri et al., 2015). This reaction yielded four classes of quinolines, facilitated by NbCl₅ (10 mol%) serving as the acid catalyst at 110 °C in glycerol (Schemes 67–69). As a result, this methodology demonstrated robustness and the capability to accommodate various functional groups present within the carbonyl substrates. However, it's worth noting that this study did not delve into the potential mechanism of the reaction or

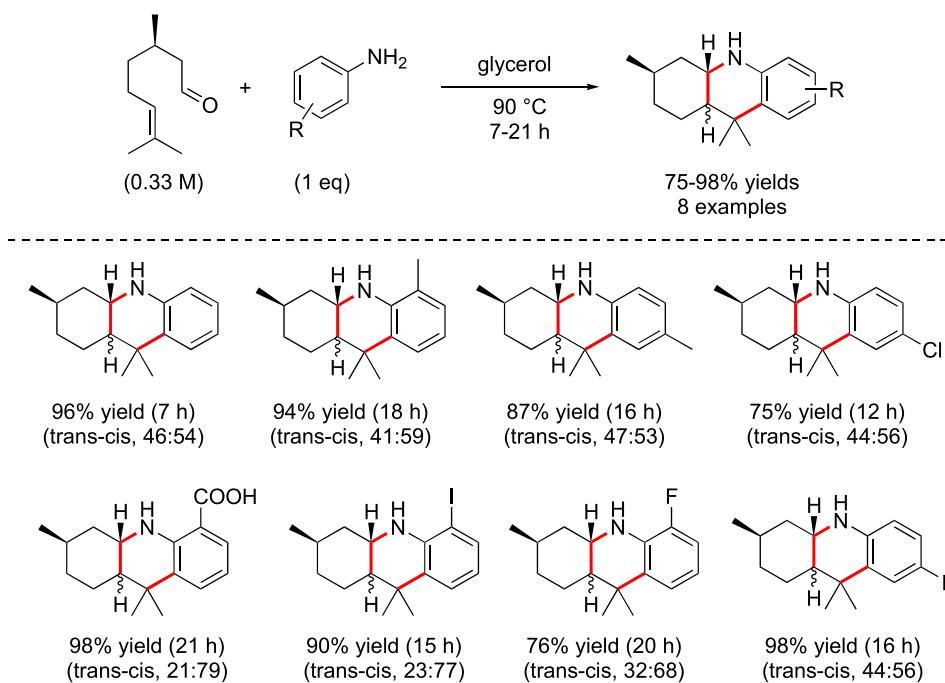


Scheme 70. Cross-coupling reaction for the synthesis of 9H-fluoren-9-amine **53** using copper catalyst (Aziz et al., 2014).

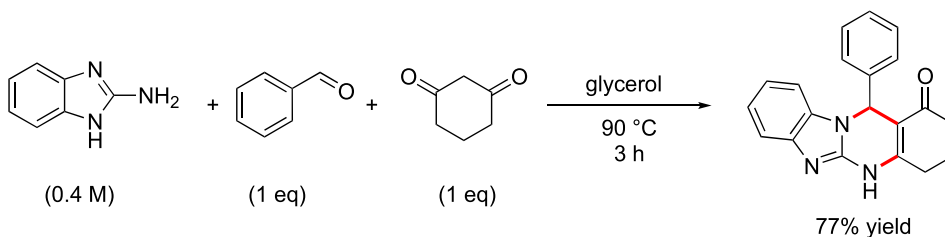
the recyclability of the NbCl₅/glycerol catalytic system.

In 2014, a novel ligand-free copper-mediated addition sequence was reported, enabling the simultaneous formation of both a C(sp³)-N and a C(sp³)-C(sp²) bond at the same carbene center of *N*-tosylhydrazones. This study investigated the use of glycerol as an environmentally friendly solvent in coupling reactions aimed at synthesizing C–C and C–N bonds. By subjecting 2-bromo-biaryl-*N*-tosylhydrazones to primary and secondary amines in the presence of Cu(acac)₂ (10 mol%) and Na₂CO₃ in glycerol at 80 °C, and maintaining the reaction in a sealed tube for 3 h, the target 9H-fluoren-9-amines were produced in yields ranging from 35% to 80% (Scheme 70) (Aziz et al., 2014). However, the potential recyclability of the catalytic system was not investigated. In conclusion, this work highlights the potential for carbene moieties to undergo unprecedented transformations within complex structures.

In the quest to explore the applications and chemical modifications of essential oil components, a methodology centered around the hetero-Diels-Alder (HDA) reaction involving (*R*)-citronellal and aryl amines bearing electron-donating or electron-withdrawing groups attached to the aromatic ring was investigated. This study utilized glycerol as an environmentally friendly, sustainable, and reusable solvent for the catalyst-free reaction. The result was the generation of octahydroacridines with yields ranging from good to excellent (75–98%) through a simple mixture of the two reactants at 90 °C (Scheme 71) (Nascimento et al., 2011). According to the authors, glycerol consistently demonstrated superior efficiency in the synthesis of octahydroacridines compared to other solvents like DMSO, MeCN, and EtOH, which only yielded minimal amounts of the desired product. The desired yield decreased when the reaction was conducted in water (62%). Since octahydroacridines are insoluble in glycerol, the less dense product could be easily separated from the glycerol through a straightforward decantation process. Following the complete removal of the product, glycerol was directly reused in subsequent HDA reactions, illustrating sustained efficiency with high yields (>72%) over five consecutive reactions. This was achieved by introducing fresh starting reagents into the reaction vessel to synthesize octahydroacridines.



Scheme 71. Hetero-Diels-Alder (HDA) reaction for the synthesis of octahydroacridines from (*R*)-citronellal and arylamines in glycerol (Nascimento et al., 2011).



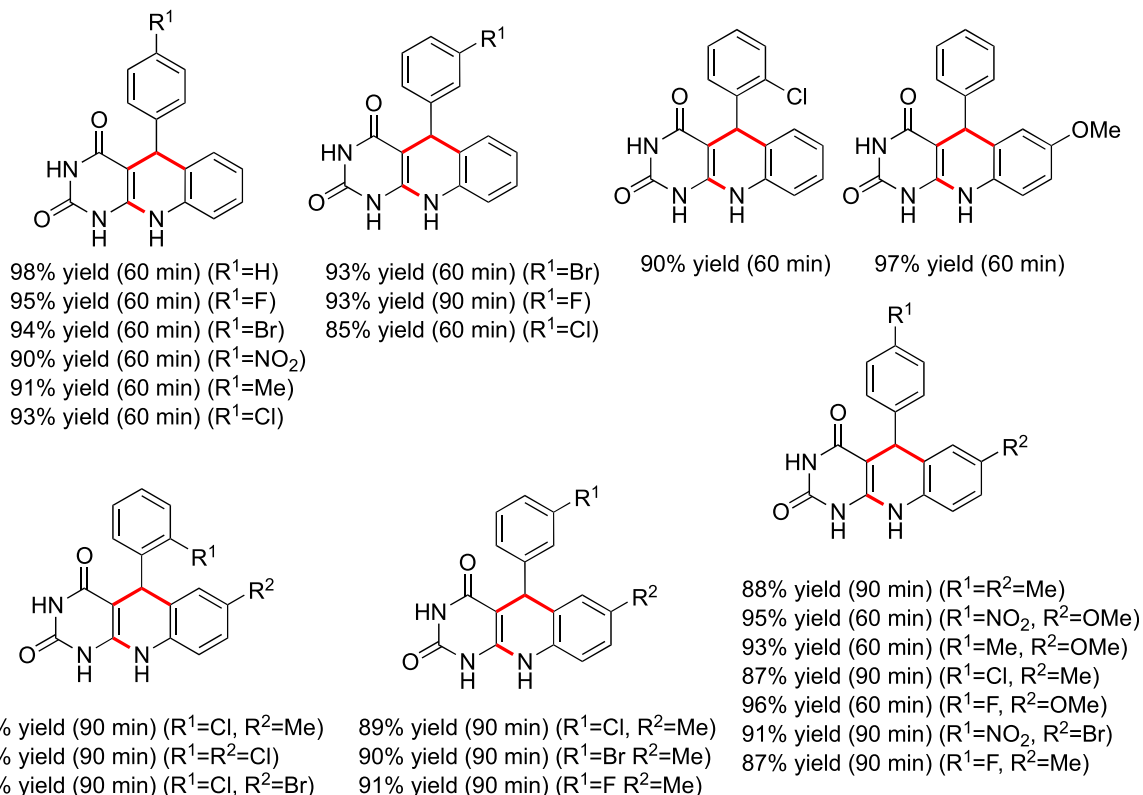
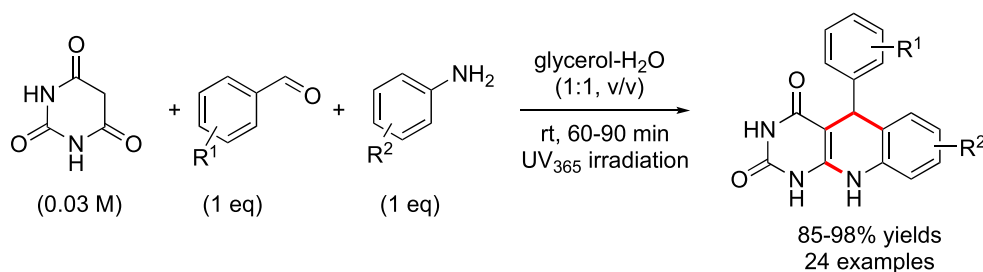
Scheme 72. MCR for the synthesis of benzimidazoquinazolinone in glycerol (Mahire et al., 2017).

A Multicomponent reaction (MCR) is a synthetic approach where three or more reactants converge within a single reaction vessel to yield a novel product. The defining feature of MCRs lies in the fact that the resultant products encompass nearly all constituent parts of the starting substrates, yielding minimal by-products. This characteristic renders MCRs an exceptionally advantageous and environmentally conscious reaction methodology. Desired compounds can be synthesized within a single reaction setup, minimizing the need for numerous intervening steps. Consequently, MCRs have garnered significant attention across diverse research domains, ranging from the identification of lead compounds in medicinal chemistry to applications in combinatorial chemistry.

Different MCRs were reported using two common types of chemicals: 1,3-diketones and aldehydes. A multicomponent synthesis of benzimidazole-quinazolinone involving the reaction of 2-aminobenzimidazole, 3-nitrobenzaldehyde, and 1,3-cyclohexadione in glycerol was realized at 90 °C for 3 h, resulting in the target compound with a yield of 77% (Scheme 72) (Mahire et al., 2017).

Starting from barbituric acid, anilines, and benzaldehydes in an aqueous glycerol medium, the pyrimido[4,5-*b*]quinolinone-2,4-diones were obtained via photochemical activation, eliminating the need for a photocatalyst (Scheme 73) (Nongthombam et al., 2018). The mechanism of this reaction involves the generation of free radicals from the carbonyl group of barbituric acid upon photoirradiation. These free radicals subsequently interact with the -NH group of the arylamine component. Simultaneously, the aryl aldehyde also generates a free radical upon photoirradiation and participates in the free radical interactions. This series of reactions ultimately culminates in the final step, accompanied by tautomerization to restore the aromaticity of the third ring, thereby resulting in the formation of the target molecule.

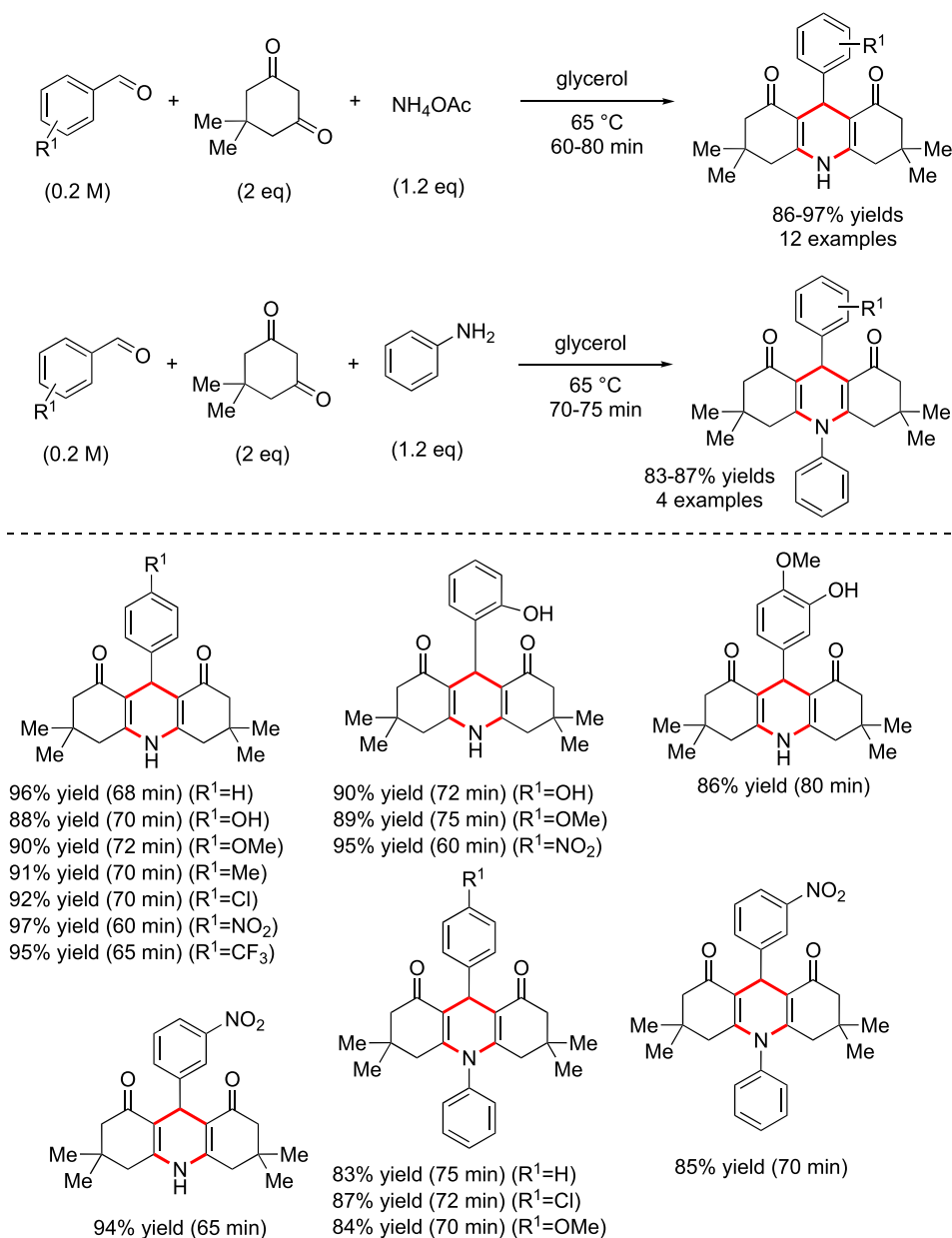
The synthesis of derivatives of 1,4-dihydropyridine (1,4-DHP) in glycerol via a one-pot multicomponent Hantzsch reaction has been reported (Tiwari et al., 2020). Glycerol serves as a promoter medium under gentle, metal-free reaction conditions (Scheme 74). This approach offers a sustainable, cost-effective, and efficient route to synthesizing biologically important 1,4-DHPs, yielding good to excellent results. The study highlights the versatility of this method by successfully reacting various aldehydes, dimedone, and



Scheme 73. MCR for the synthesis of pyrimido[4,5-*b*]quinolinone-2,4-diones in glycerol (Nongthombam et al., 2018).

ammonium acetate. Aromatic aldehydes, featuring both electron-donating and electron-withdrawing groups at different positions, were effectively transformed into the desired products with significant yields, achieved within reaction times spanning 60–80 min. When aniline was employed instead of ammonium acetate, the corresponding 1,4-dihydropyridines were attained with similar yields. Importantly, glycerol demonstrated a recycling efficiency of 83% in the 5th consecutive run.

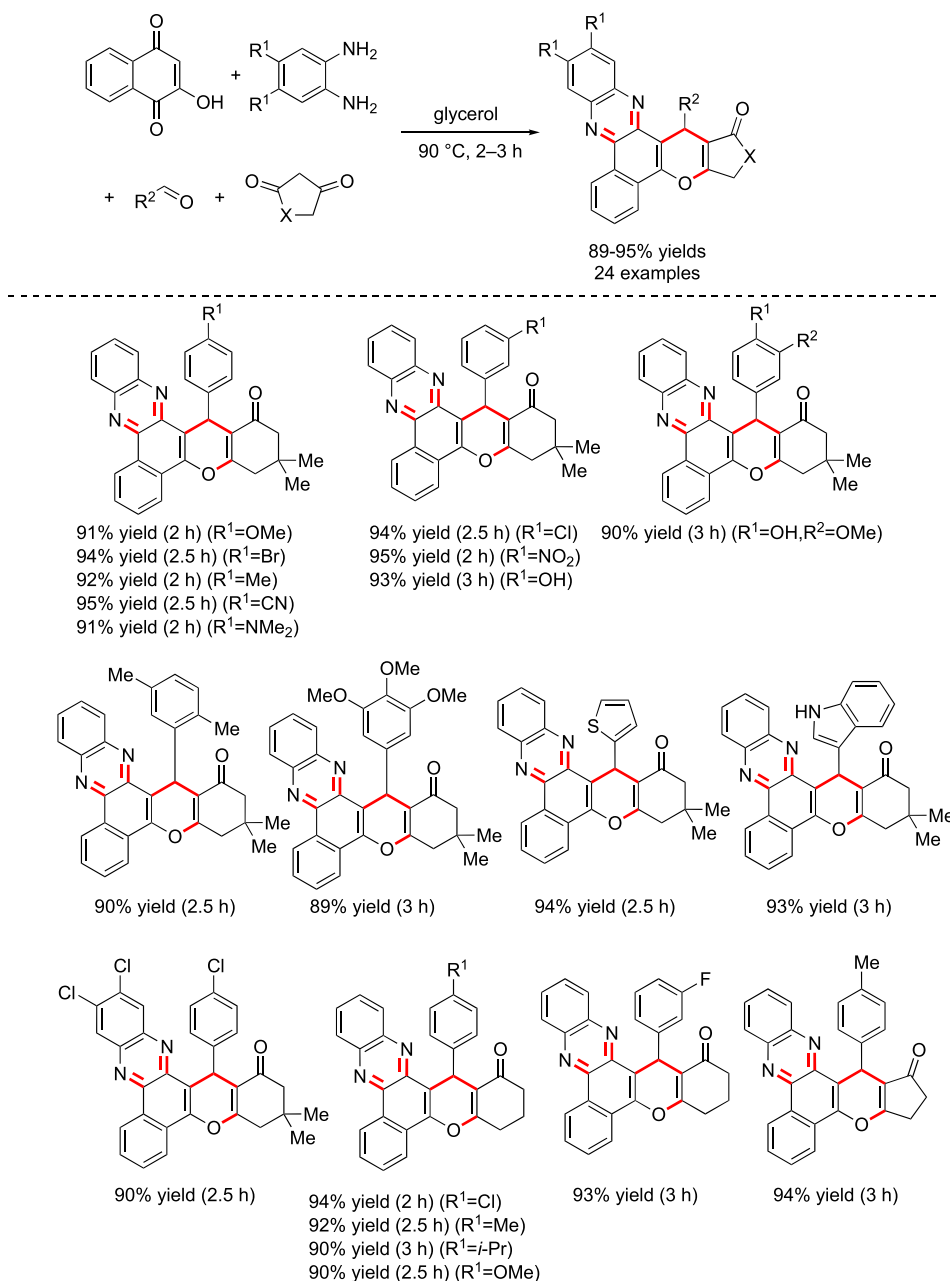
While numerous methods for synthesizing benzo[*a*]chromeno[2,3-*c*]phenazines have been documented in literature, these approaches typically rely on toxic or expensive catalysts, solvents based on volatile organic compounds (VOCs), or necessitate specialized and harsh reaction conditions. Consequently, a green and operationally straightforward protocol, devoid of catalysts, was investigated to efficiently synthesize diverse highly functionalized benzo[*a*]chromeno[2,3-*c*]phenazines using glycerol as a promoter through a four-component domino reaction (Scheme 75) (Nazeef et al., 2020). Starting from 2-hydroxynaphthalene-1,4-dione, *o*-phenylenediamine, 4-chlorobenzaldehyde, and dimedone at 90 °C for 2 h, the target compounds were achieved with yields exceeding 95%. Lower temperatures (80 °C) still yielded satisfactory results, producing the product with an 89% efficiency within 3 h. The study explored various reactant molecules featuring diverse functional groups, encompassing both electron-releasing and electron-withdrawing substituents, by incorporating *o*-phenylenediamines and aromatic aldehydes. A detailed reaction mechanism was proposed, involving the Knoevenagel condensation of 2-hydroxynaphthalene-1,4-dione and *o*-phenylenediamines, leading to the formation of the initial benzo[*a*]phenazin-5-ol-derived intermediate. This intermediate then underwent further Knoevenagel condensation with aromatic aldehydes, yielding benzo[*a*]phenazin-5(6H)-ones. Subsequent cyclization ensued through the Michael attack of benzo[*a*]phenazin-5(6H)-ones on cyclic 1,3-dicarbonyls, followed by dehydration, ultimately resulting in the synthesis of benzo[*a*]chromeno[2,



Scheme 74. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Tiwari et al., 2020).

3-*c*]phenazine derivatives. The study also underscored that the recycled glycerol maintained its efficacy, yielding between 95% and 80% even after five cycles.

Starting from benzaldehyde and a 1,3-diketone like dimedone, the addition of malononitrile for the synthesis of 4H-pyran derivatives in glycerol has been reported (Scheme 76) (Safaei et al., 2012). Other starting materials were used with success instead of dimedone for the synthesis of the corresponding 4H-pyran. This tandem reaction involves Knoevenagel condensation followed by Michael addition, resulting in the desired 4H-pyran product with a high yield of 93% at 80 °C in just 1 h. Other solvents, such as poly (ethylene glycol) 400 (PEG400), ethylene glycol, and water, also produced high product yields (83%, 80%, and 71%, respectively) under identical conditions. Furthermore, glycerol has proven to be easily recyclable, as the authors were able to recover the solvent phase twenty times for the condensation of benzaldehyde and dimedone with malononitrile without any loss of activity. The results of this study demonstrate the successful application of this methodology with compounds sensitive to acids and bases, including heteroaromatic aldehydes. This approach allows for the synthesis of corresponding 4H-pyrans in a short time with excellent yields and

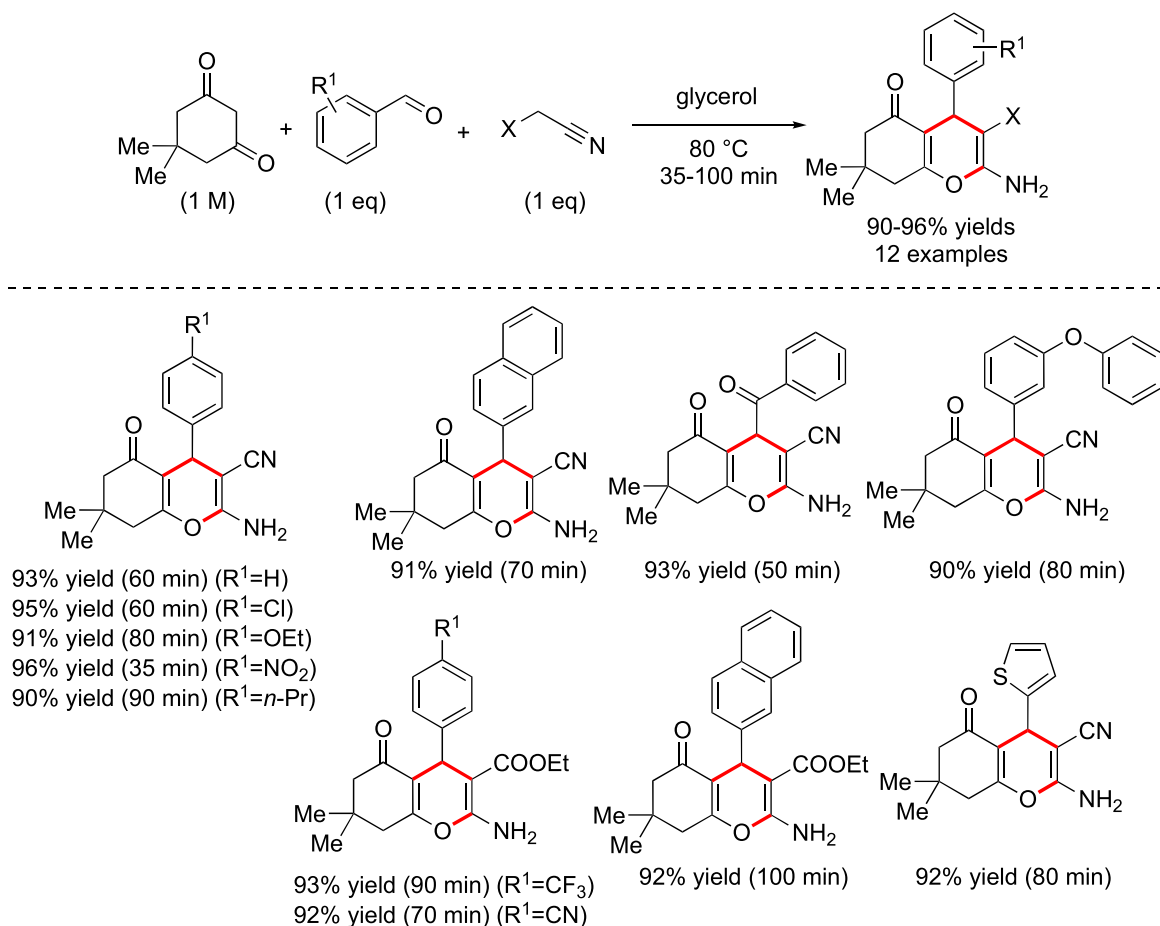


Scheme 75. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Nazeef et al., 2020).

without the formation of any byproducts.

In another study, the synthesis of 1,4-dihydropyridine through a multicomponent condensation reaction involving dimedone, benzaldehyde, malononitrile, and ammonium acetate in glycerol was reported (Scheme 77) (Sohal et al., 2014b). Compared to other organic solvents (which yielded 67–90%), glycerol exhibited favorable results, yielding 87–92% in just 1 h of reaction at 110 °C. This underscores its suitability as a solvent in a four-component MCR. The synthesized compounds were easily purified through recrystallization.

The first catalyst-free synthesis of triazolo[1,2-*a*]indazole-triones in glycerol was investigated, utilizing cyclic 1,3-diketones, *N*-phenyl urazoles, and aromatic aldehydes with both electron-withdrawing and -donating groups (Scheme 78) (Shekouhy et al., 2015). Regardless of the substituents, no significant effects were observed on the yields or reaction times, underscoring the broad applicability of this approach. Furthermore, the authors explored the synthesis of indazolo[2,1-*b*]phthalazine-triones by reacting benzaldehydes,



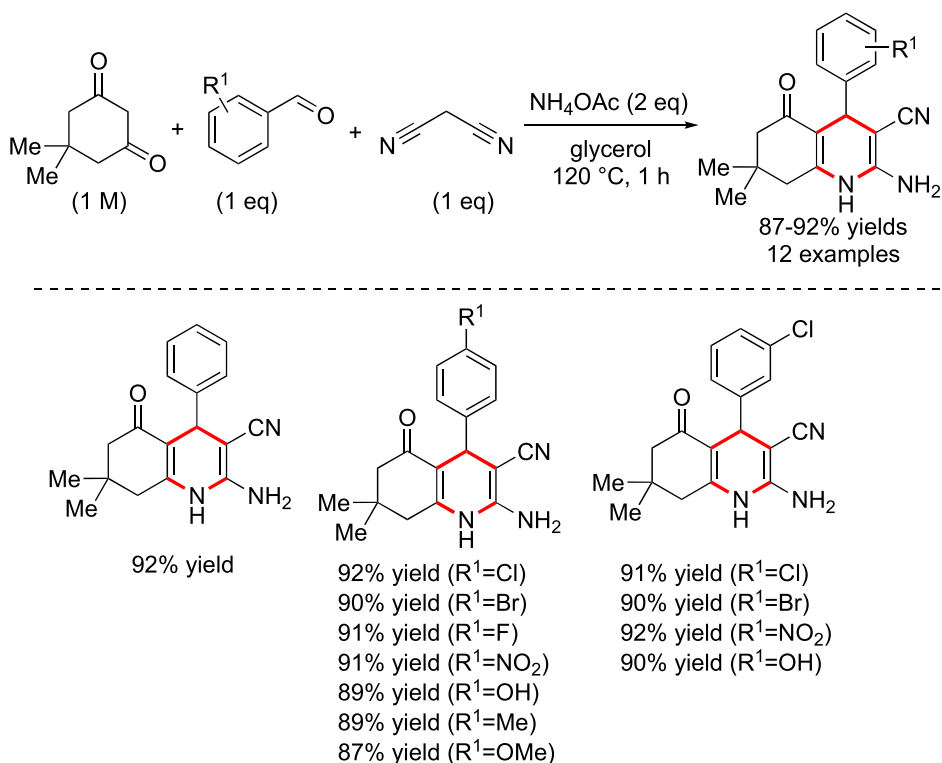
Scheme 76. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Safaei et al., 2012).

cyclic 1,3-diketones, and phthalhydrazide in glycerol as both solvent and activator. The desired product was obtained with a 94% yield after 4 h at 100 °C. The reaction was scaled up to 25 mmol, resulting in the desired product with an 85% yield after 8 h.

On the other hand, the application of ultrasound in organic transformations has emerged as a green synthetic approach and a promising tool for the synthesis of derivatives of 5-[(indol-3-yl)-aryl methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (Lu et al., 2017). In this context, a catalyst-free Yonemitsu condensation of indoles with Meldrum's acid and aldehydes in glycerol under ultrasonic irradiation at room temperature was realized. The authors explored the substrate scope by using various aromatic aldehydes with different electronic and steric groups, achieving moderate to excellent yields (Scheme 79). The absence of a catalyst, clean reaction conditions, tolerance to substrates with diverse functional groups, and the use of an environmentally acceptable medium are the most notable characteristics of this process.

Glycerol has demonstrated its effectiveness as a medium for facilitating multicomponent reactions involving three or more reagents in a single-step reaction, enabling the formation of complex molecules. In the absence of any catalyst, various styrenes readily reacted with 1,3-cyclohexanediones and paraformaldehyde to yield the corresponding three-component adducts in reasonable to excellent yields (Schemes 80) (Li et al., 2010). The study highlighted that glycerol not only facilitated efficient reactions but also allowed for easy product separation through extraction due to its strong hydrophilic nature. According to the report, glycerol used in the reaction between styrene, formaldehyde, and dimedone exhibited excellent recoverability and maintained its activity (65%) even after three consecutive runs. These findings underscore glycerol as an innovative and effective solvent for the development of previously unexplored organic reactions. The Hantzsch reaction starting from primary amines gave the corresponding 2-arylamino derivatives in good yield.

In contrast with the MCRs described above, other MCRs were reported using two other common types of chemicals: β -keto esters and aldehydes. In this context, a sequential two-step reaction involving phenylhydrazine, β -keto esters, formaldehyde was investigated in glycerol to produce a highly functionalized [2,3-*c*]pyrazole in moderate yields (Scheme 81) (Tan et al., 2010). This study demonstrated that these pyrazole derivatives can be synthesized via a Knoevenagel/Michael tandem reaction pathway in glycerol



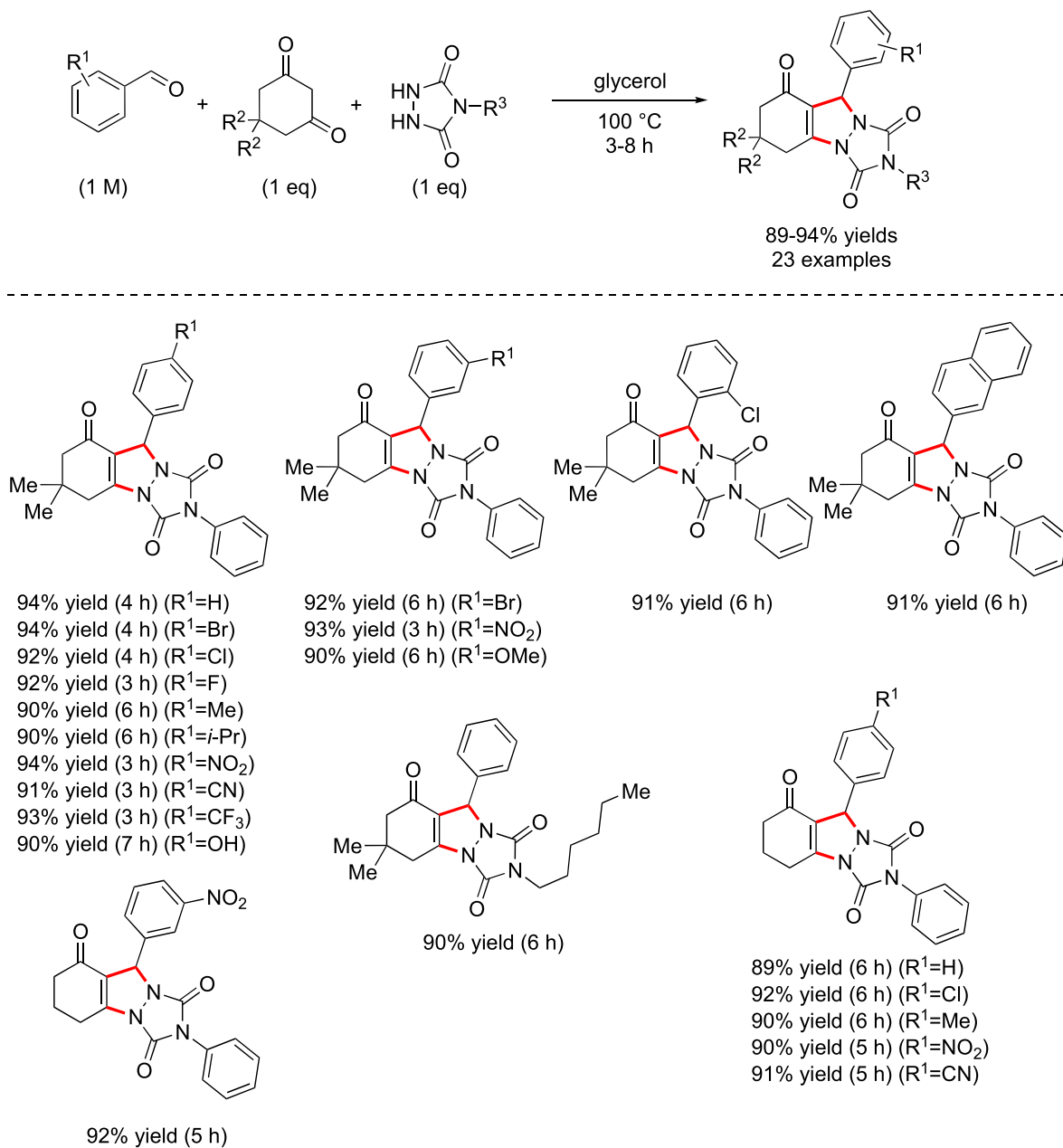
Scheme 77. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Sohal et al., 2014b).

without the need for a catalyst. The authors demonstrated that when all four compounds were initially introduced into the reaction, it resulted in the formation of a chaotic mixture. To achieve the desired outcome, styrene and formaldehyde needed to be added in a subsequent step, following the formation of 2,4-dihydro-3H-pyrazol-3-one, without isolating it in between. While the study addressed various aspects of green chemistry, such as a simple processing procedure, recyclable solvent, and waste minimization, the authors also emphasized that these sequential multicomponent reactions not only offer a direct route to the target compounds but also significantly enhance synthetic efficiency. Considering the broad application of pyrazole derivatives in the pharmaceutical industry, this method shows promise for the synthesis of biologically active compounds. The same group extended this work for the synthesis of 1,3-diaryl-2-[(1-alkyl-2-phenylindol-3-yl)methyl]-5-pyrazolones starting from 1-alkyl-2-phenylindoles and formaldehyde in glycerol.

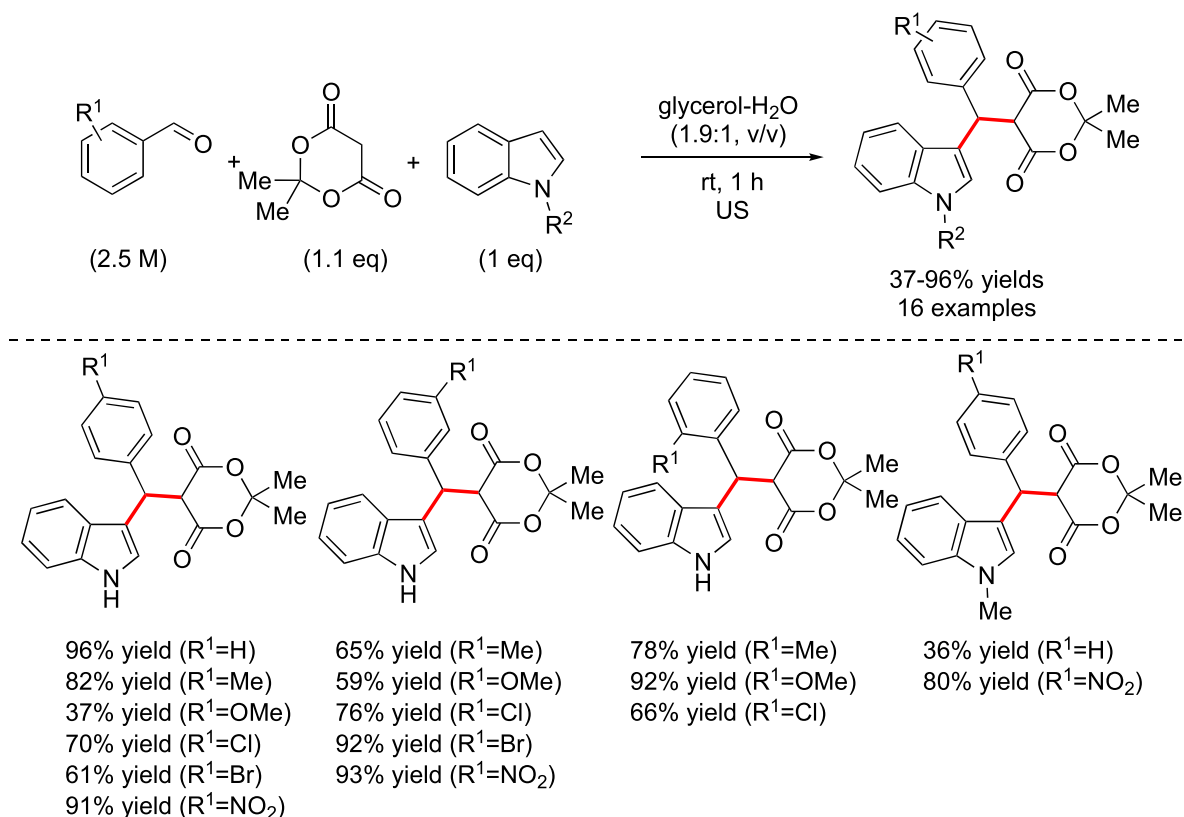
A similar strategy was reported for the synthesis of dihydropyran[2,3-c]pyrazoles through the condensation of ethyl acetoacetate, hydrazine, an aromatic aldehyde, and malononitrile using glycerol as the solvent (Scheme 82) (Sohal et al., 2013). The article emphasizes that glycerol, as a solvent, yielded superior results compared to other organic solvents, highlighting the efficacy of this protocol.

Another multicomponent reaction was published involving ethyl acetoacetate, aromatic aldehydes, malononitrile, and hydrazine derivatives in glycerol for the synthesis of 6-amino-5-cyano-4-aryl-1,4-dihydropyran[2,3-c]pyrazoles (Scheme 82) (Hamid et al., 2017). Compared with the previous work, the yields of pyrazoles were similar but an excess of hydrazine (1.5 eq vs 1 eq), a lower concentration (0.1 M vs 1 M) and a lower temperature (20 °C vs 80 °C) were used. Remarkably, glycerol served as both the solvent and catalyst, and the reactions were conducted at room temperature. After establishing optimal conditions and exploring various substrates, the reaction exhibited broad applicability with different aryl-substituted aromatic aldehydes and hydrazines. The reaction proceeded efficiently and smoothly, yielding slightly improved results with electron-withdrawing substituents (Scheme 83). The protocol achieved high EcoScale scores of 94 and 94.5 for the synthesis of pyranopyrazoles, surpassing previous reports in the literature. Concerning the mechanism, the authors proposed two possibilities. This method offers several advantages, including its environmentally friendly nature, high EcoScale rating, and atom economy. Furthermore, it proves valuable for synthesizing a wide range of polyfunctionally substituted heterocycles.

Another groundbreaking study on the synthesis of bis(3-methyl-1H-pyrazol-5-ols) and 2,3-dihydroquinazolin-4(1H)-ones (Ramesh et al., 2017). Glycerol was used as a solvent in the absence of metal catalysts. Initially, the reaction involving ethyl acetoacetate, hydrazine hydrate, and benzaldehyde at room temperature for 3 min in glycerol for the synthesis of 4,4'-(phenylmethylene)bis(3-methyl-1H-pyrazol-5-ol). Other polar solvents were used resulting in low yields and longer reaction times. The study indicated that a temperature of 80 °C was optimal, leading to 91% yield of 4,4'-(phenylmethylene)bis(3-methyl-1H-pyrazol-5-ol) within 3 min



Scheme 78. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Shekouhy et al., 2015).



Scheme 79. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Lu et al., 2017).

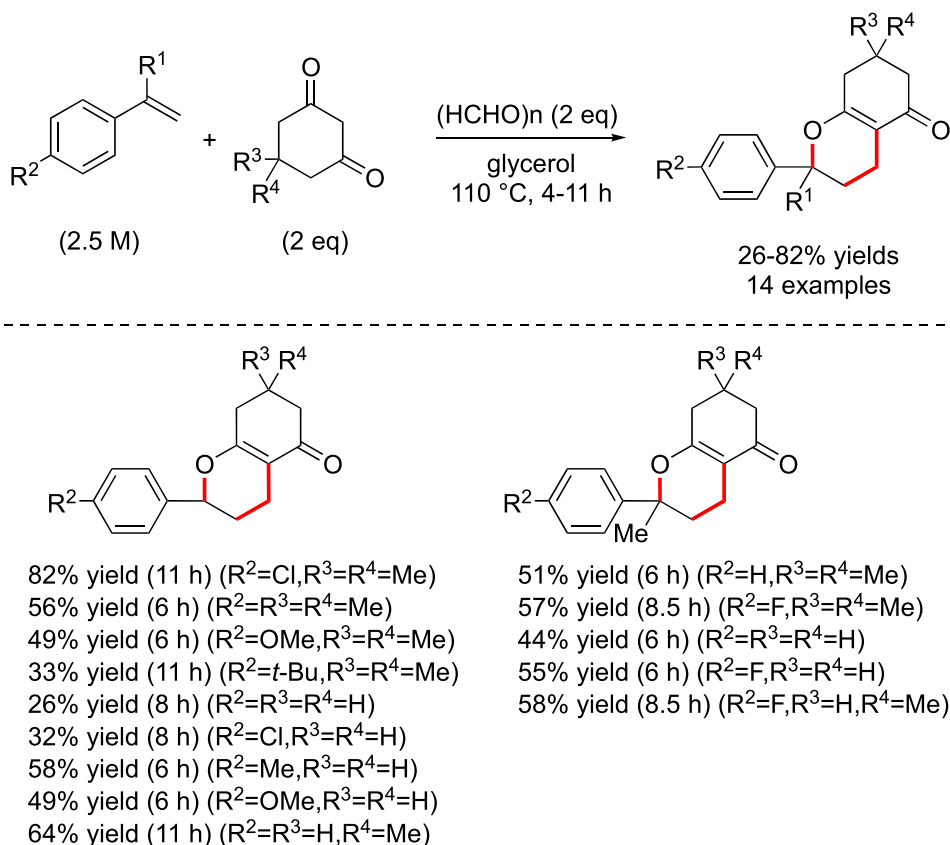
(Scheme 84). Building upon these optimized conditions, the authors examined the generality and effectiveness of the methodology, successfully obtaining good yields (85–94%) for a wide range of aromatic aldehydes with electron-donating and electron-withdrawing substituents. The study revealed that electronic effects did not directly influence the reaction yields, but steric effects were more prominent in substituted aldehydes positioned at the meta and ortho positions, requiring up to 13 min for optimal yields.

Continuing the exploration of four-component synthesis, same authors published a method for synthesizing 1,4-dihydropyridines by condensing ethyl acetoacetate, aldehydes, and ammonium acetate, with glycerol as the solvent (Scheme 85) (Sohal et al., 2014a). It is worth noting that similar yields were obtained when using methyl acetoacetate. In their study to assess the generality of the reaction, the impact of electron-donating and electron-withdrawing groups was evaluated, and no significant changes were observed due to electronic effects, as the yields remained within the range of 84–95%. This confirmed the robustness of the methodology when conducted at 90 °C for 75 min. In both studies, the authors hypothesized that after an initial condensation reaction between dimedone and ammonium acetate to form an intermediate, a subsequent Michael reaction occurs with the Knoevenagel condensation intermediate, followed by intramolecular cyclization to produce the desired compounds.

Biginelli reaction was examined for the synthesis of 3,4-dihydropyrimidinones catalyzed by PS-PEGOSO₃H in glycerol (Quan et al., 2011). Starting from ethyl acetoacetate, arylaldehyde and urea at 100 °C for 8 h, the target compounds were obtained in yield higher than 75% (Scheme 86). Moreover, the recovered glycerol and the acid catalyst system maintained 60% yields of 3,4-dihydropyrimidinones even after five cycles, demonstrating its high recyclability.

Many other MCRs exist without a combination of aldehydes and 1,3-diketones or β -ketoesters and selected examples are described below. The acid catalyst PS-PEGOSO₃H used for the synthesis of 3,4-dihydropyrimidinones was studied for the preparation of amidoalkyl naphthols in glycerol (Scheme 87) (Quan et al., 2011). In this work, the reaction between amide, 2-naphthol, and aldehydes gave the desired naphthols in yield higher than 80%.

Pirazolopyrimidines are a class of drugs that exhibit sedative and anxiolytic effects similar to benzodiazepines. A MCR between pyrazolone and its derivatives, aldehydes, and urea/thiourea, catalyzed by *p*-toluenesulfonic acid (PTSA) in glycerol was reported (Scheme 88) (Goyal et al., 2014). This reaction yielded the respective derivatives of pyrazolo[3,4-*d*]pyrimidin-6-one/thione in good to excellent yields (ranging from 75 to 91%) within a reaction time of 2–4 h. These results demonstrated that electron-donating and electron-withdrawing groups on the aromatic ring had minimal impact on the observed effects. The use of poly(*N*-vinylpyridinium)



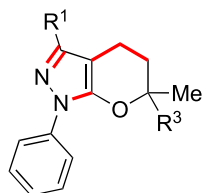
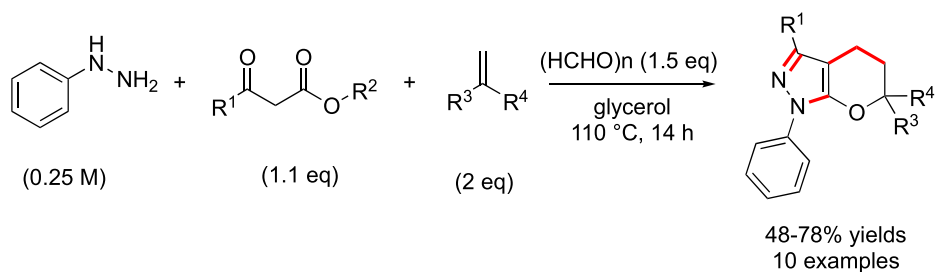
Scheme 80. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Li et al., 2010).

hydrogen sulfate as heterogeneous catalyst was developed by another group and different pyrazolo[3,4-*d*]pyrimidine-6-ones were obtained in 90–95% yield (Hamid et al., 2016).

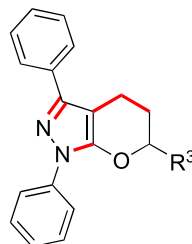
The synthesis of highly pure α -aminophosphonates through a multicomponent reaction involving aromatic and aliphatic aldehydes, amines, and dialkyl phosphite derivatives was examined. Interestingly, no catalyst was required for this reaction, which was carried out in glycerol (Scheme 89). The authors compared various solvents and found that glycerol provided superior results, yielding 70% compared to less than 40% in conventional organic solvents such as toluene, tetrahydrofuran, dichloromethane, chloroform, acetonitrile, methanol, ethanol, and water at room temperature for 10 h. Optimizing the temperature revealed that the range of 60–80 °C yielded consistent results (92–94%) for α -aminophosphonates (Azizi et al., 2014). By using the optimized reaction conditions, the study successfully obtained the corresponding compounds in good to excellent yields (70–95%) in short reaction times. Furthermore, the recyclability of glycerol was evaluated in the reaction between aniline, benzaldehyde, and dimethyl phosphite, showing excellent results for up to four successive reactions, with product yields ranging from 90% in the first use to 80% in the fourth. The authors proposed that the reaction proceeds through the activation of glycerol's hydrogen bond, facilitating the *in situ* formation of the imine intermediate through hydrogen bonding between the hydroxyl groups and the carbonyl oxygen atom. Subsequently, the imine carbon is attacked by dimethyl phosphite, leading to the desired product.

The catalyst-free MCR of spiroindolyl-pyrazolines in aqueous glycerol involving isatin as the carbonyl compound, hydrazines, and cyclic dimedone was described. At 75 °C for 2.5–4 h, the compounds were obtained (Scheme 90) (Singh et al., 2015). Furthermore, the study explored the behavior of ketones in the reaction, resulting in the synthesis of eleven spirooxindole-pyrazoline products with good to excellent yields. Although the study did not investigate the recyclability of glycerol, it emphasized the superior results achieved compared to other solvents.

The synthesis of 2,3-dihydroquinazolin-4-ones and 1-amidoalkyl-2-naphthols involved the use of substituted aldehydes, isatoic anhydride, and ammonium acetate in glycerol at 80 °C (Scheme 91) (Hajjami et al., 2015). On the other hand when an acid catalyst such as glycerol sulfonic acid physisorbed on silica was used in the presence of arylaldehyde, 2-naphthol, and acetamide at 80 °C the corresponding 2,3-dihydroquinazolin-4(1H)-ones were obtained in 97% yield after 6 h (Scheme 92) (Hajjami et al., 2015). This study reported for the first time the use of glycerosulfonic acid physisorbed on silica gel as an efficient and heterogeneous catalyst for the

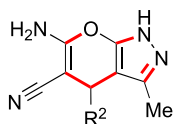
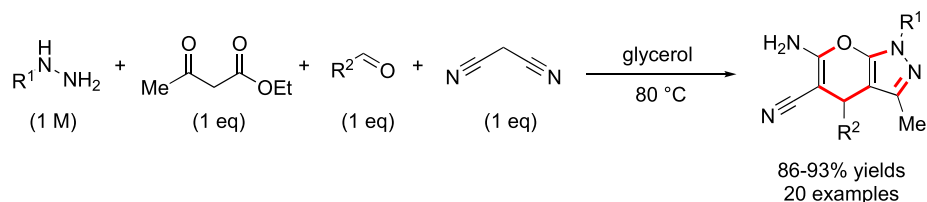


78% yield ($R^1=R^3=Ph$)
67% yield ($R^1=Me, R^3=Ph$)
69% yield ($R^1=n\text{-Pr}, R^3=Ph$)
69% yield ($R^1=i\text{-Pr}, R^3=Ph$)
73% yield ($R^1=t\text{-Bu}, R^3=Ph$)
75% yield ($R^1=p\text{-OMePh}, R^3=Ph$)
47% yield ($R=p\text{-ClPh}$)
75% yield ($R=p\text{-FPh}$)

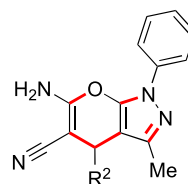


48% yield ($R=Ph$)
59% yield ($R=p\text{-MePh}$)

Scheme 81. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Tan et al., 2010).

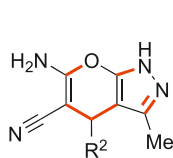
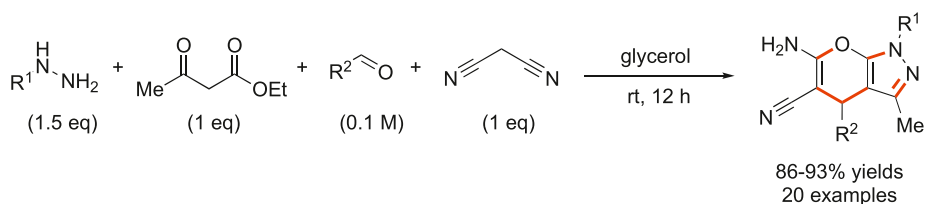


93% yield ($R^2=Ph$)
91% yield ($R^2=p\text{-ClPh}$)
90% yield ($R^2=o\text{-ClPh}$)
92% yield ($R^2=p\text{-NO}_2Ph$)
86% yield ($R^2=o\text{-NO}_2Ph$)
90% yield ($R^2=m\text{-NO}_2Ph$)
90% yield ($R^2=p\text{-OHPh}$)
92% yield ($R^2=p\text{-OMePh}$)
88% yield ($R^2=PhCH=CH$)
89% yield ($R^2=p\text{-MePh}$)

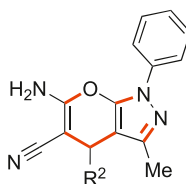


92% yield ($R^2=Ph$)
91% yield ($R^2=p\text{-ClPh}$)
88% yield ($R^2=o\text{-ClPh}$)
87% yield ($R^2=p\text{-NO}_2Ph$)
89% yield ($R^2=o\text{-NO}_2Ph$)
91% yield ($R^2=m\text{-NO}_2Ph$)
90% yield ($R^2=p\text{-OHPh}$)
92% yield ($R^2=p\text{-OMePh}$)
87% yield ($R^2=PhCH=CH$)
89% yield ($R^2=p\text{-MePh}$)

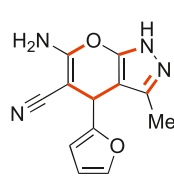
Scheme 82. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Sohal et al., 2013).



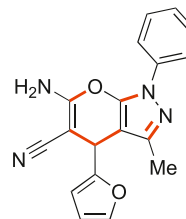
90% yield ($R^2=\text{Ph}$)
93% yield ($R^2=p\text{-ClPh}$)
93% yield ($R^2=o\text{-ClPh}$)
91% yield ($R^2=o\text{-OMePh}$)
94% yield ($R^2=p\text{-NO}_2\text{Ph}$)
91% yield ($R^2=p\text{-OMePh}$)



69% yield ($R^2=\text{Ph}$)
73% yield ($R^2=p\text{-NO}_2\text{Ph}$)
70% yield ($R^2=o\text{-OMePh}$)

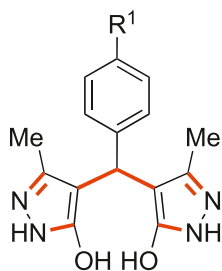
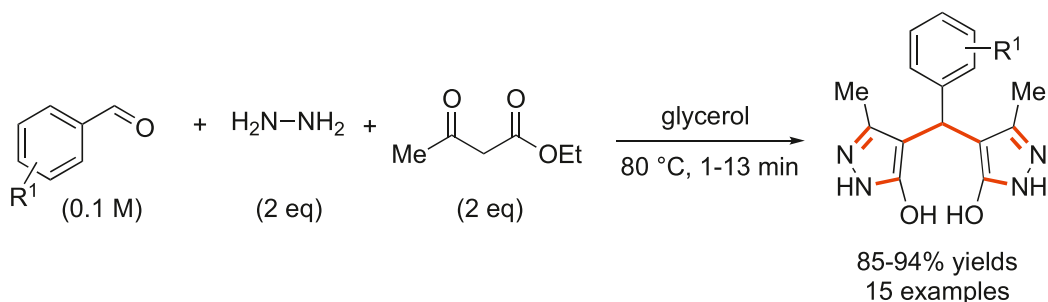


91% yield

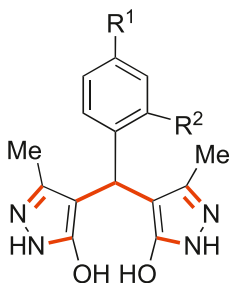


70% yield

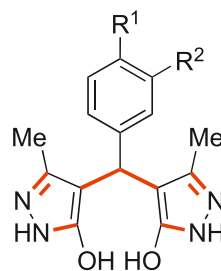
Scheme 83. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Hamid et al., 2017).



91% yield (3 min) ($R^1=\text{H}$)
94% yield (3 min) ($R^1=\text{Cl}$)
91% yield (2 min) ($R^1=\text{Br}$)
94% yield (1 min) ($R^1=\text{NO}_2$)
88% yield (4 min) ($R^1=\text{OH}$)
90% yield (2 min) ($R^1=\text{Me}$)
89% yield (1 min) ($R^1=\text{OMe}$)

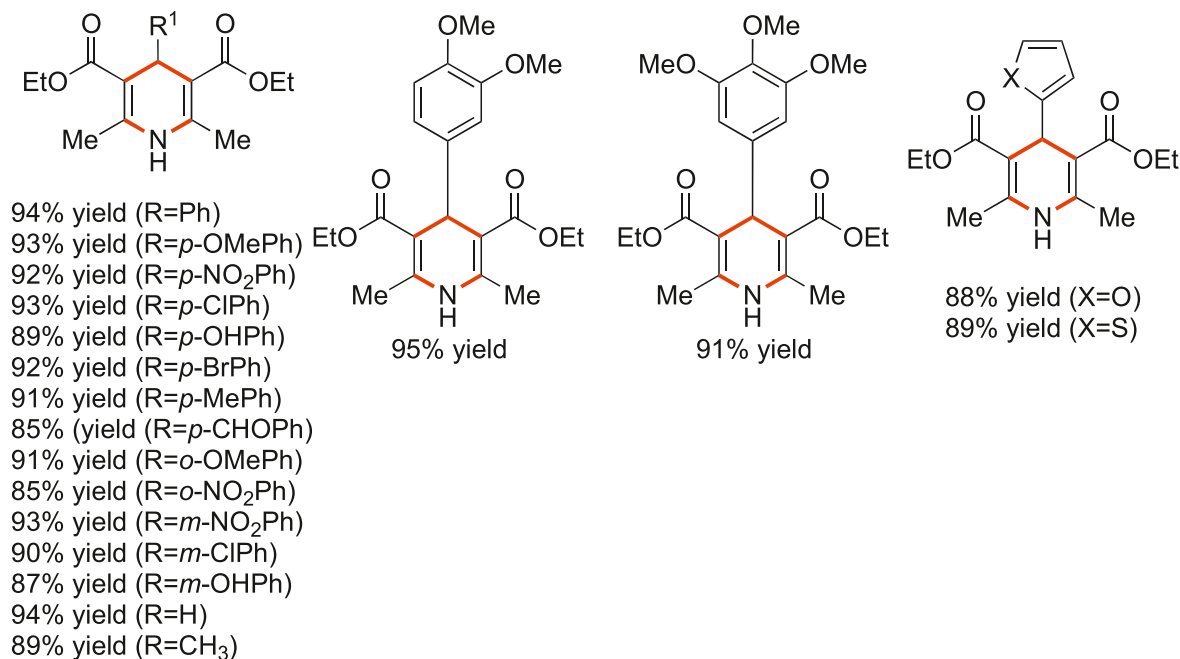
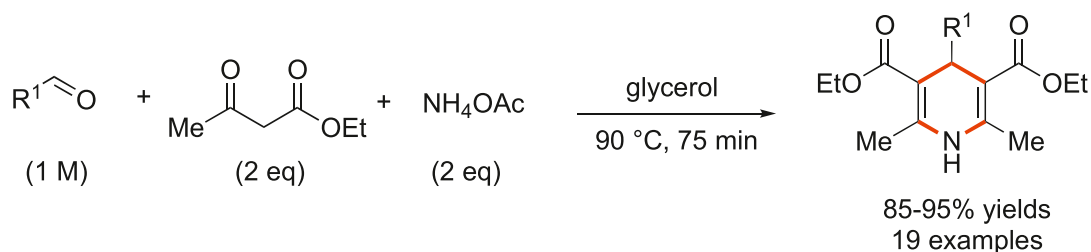


90% yield (13 min) ($R^1=R^2=\text{Cl}$)
92% yield (1 min) ($R^1=\text{H}, R^2=\text{Cl}$)
91% yield (1 min) ($R^1=\text{H}, R^2=\text{NO}_2$)
89% yield (2 min) ($R^1=\text{H}, R^2=\text{OH}$)



86% yield (10 min) ($R^1=R^2=\text{OMe}$)
85% yield (3 min) ($R^1=\text{OH}, R^2=\text{OMe}$)
90% yield (6 min) ($R^1=\text{H}, R^2=\text{NO}_2$)
86% yield (9 min) ($R^1=\text{H}, R^2=\text{OH}$)

Scheme 84. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Ramesh et al., 2017).



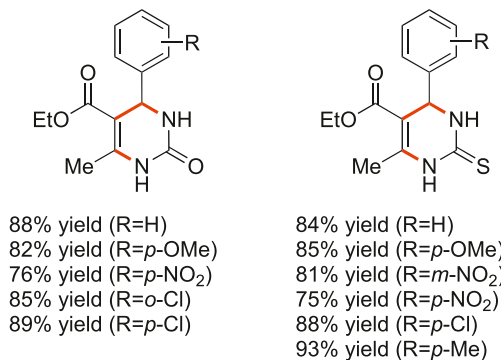
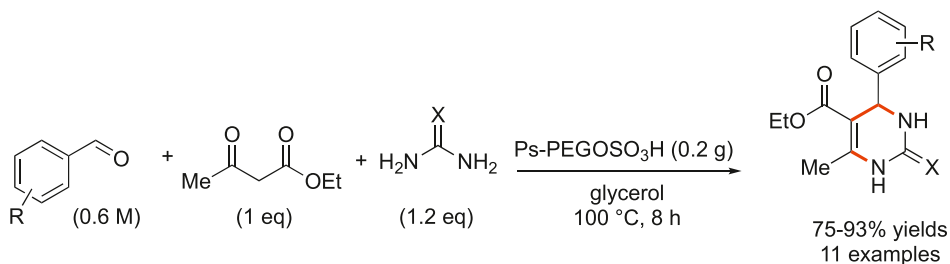
Scheme 85. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Sohal et al., 2014a).

one-pot synthesis of various 1-amidoalkyl-2-naphthols in the presence of glycerol as a green solvent. Among different catalyst contents tested, the best yield (92%) of the desired product was achieved with 30 wt% of catalyst after 4.5 h of reaction at 80 °C, using 4-chlorobenzaldehyde, 2-naphthol, and acetamide in the presence of glycerol. The study also conducted a comparative analysis with aldehydes containing various substituents on the aromatic ring, which yielded satisfactory results, with the 1-amidoalkyl-2-naphthols obtained in yields ranging from 88% to 98%.

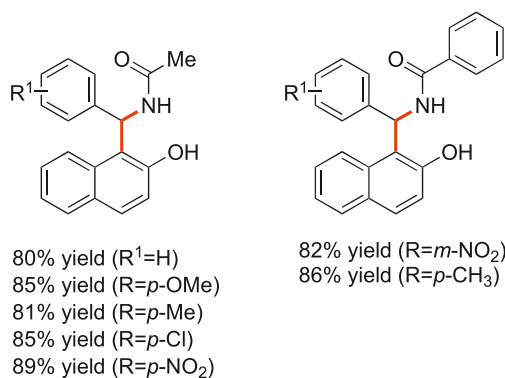
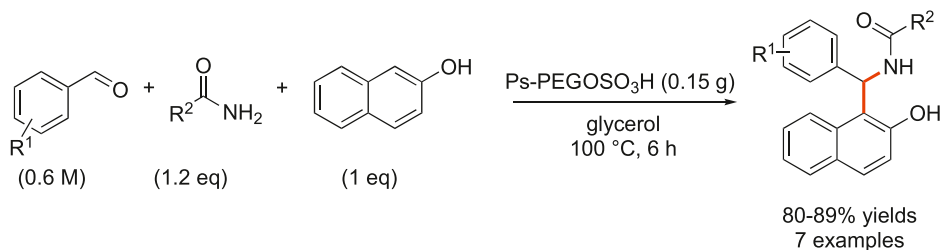
In the absence of a catalyst, the reaction between 2-naphthol, amines, and aldehydes in glycerol yielded the desired Betti bases with yields of up to 91% (Scheme 93) (Ganesan et al., 2013). The authors themselves attributed the rapid reaction rate to the high polarity and strong hydrogen bonding network of glycerol as a solvent. Based on these findings, this method offers numerous advantages, including the use of an environmentally friendly solvent, shorter reaction times, and easy product isolation. It is worth noting that the synthesis of benzoxanthene derivatives required methanesulfonic acid as a catalyst.

A valuable multicomponent Patis boron-Mannich (PBM) reaction that enables the efficient synthesis of complex tertiary amines in a single step has been developed, utilizing secondary amines, boronic acids, aldehydes, or pyridines in glycerol (Scheme 94) (Rosholm et al., 2015). The mechanism is similar to the mechanism described previously for the synthesis of the 2-styrylbenzimidazoles (Taduri et al., 2014). Interestingly, the researchers successfully employed crude glycerol as a solvent and compared it to the use of pure glycerol, observing only a slight decrease in the yield of the desired tertiary amines (Scheme 94). These findings contribute as new additions to the repertoire of reactions that make use of waste generated by the biodiesel industry, showcasing its potential for valorization.

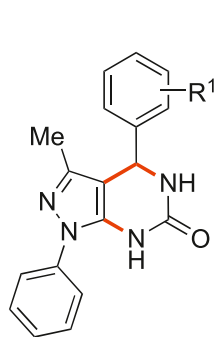
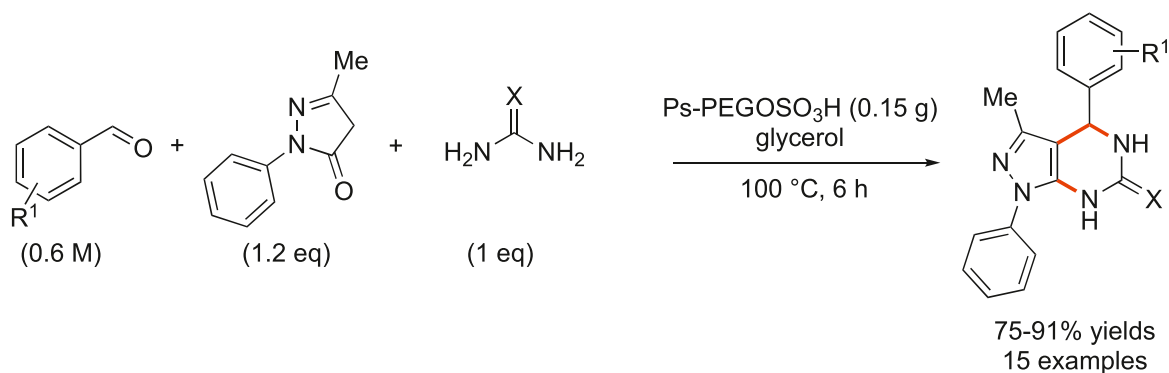
The synthesis of oxazidiones (3-aryl-3,4-dihydro-2H-naphtho[2,3-*e*][1,3]oxazin-5,10-diones) and their derivatives through a multicomponent reaction involving naphthoquinones (2-hydroxy-1,4-naphthoquinone), aromatic amines, and formaldehyde in glycerol was described (Scheme 95) (Gupta et al., 2016). Other solvents were tested, but only glycerol yielded satisfactory results in the



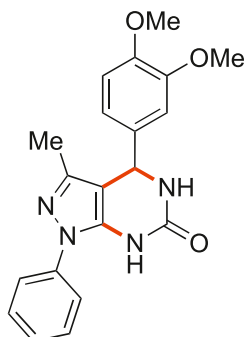
Scheme 86. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Quan et al., 2011).



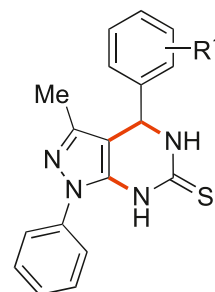
Scheme 87. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Quan et al., 2011).



89% yield (2.5 h) ($R^1=H$)
91% yield (2.2 h) ($R^1=p\text{-Cl}$)
90% yield (2 h) ($R^1=p\text{-NO}_2$)
88% yield (2.8 h) ($R^1=p\text{-OH}$)
85% yield (3 h) ($R^1=p\text{-OMe}$)
82% yield (2.5 h) ($R^1=m\text{-NO}_2$)
79% yield (3.5 h) ($R^1=o\text{-NO}_2$)
76% yield (3.2 h) ($R^1=o\text{-Cl}$)



80% yield (3.2 h)



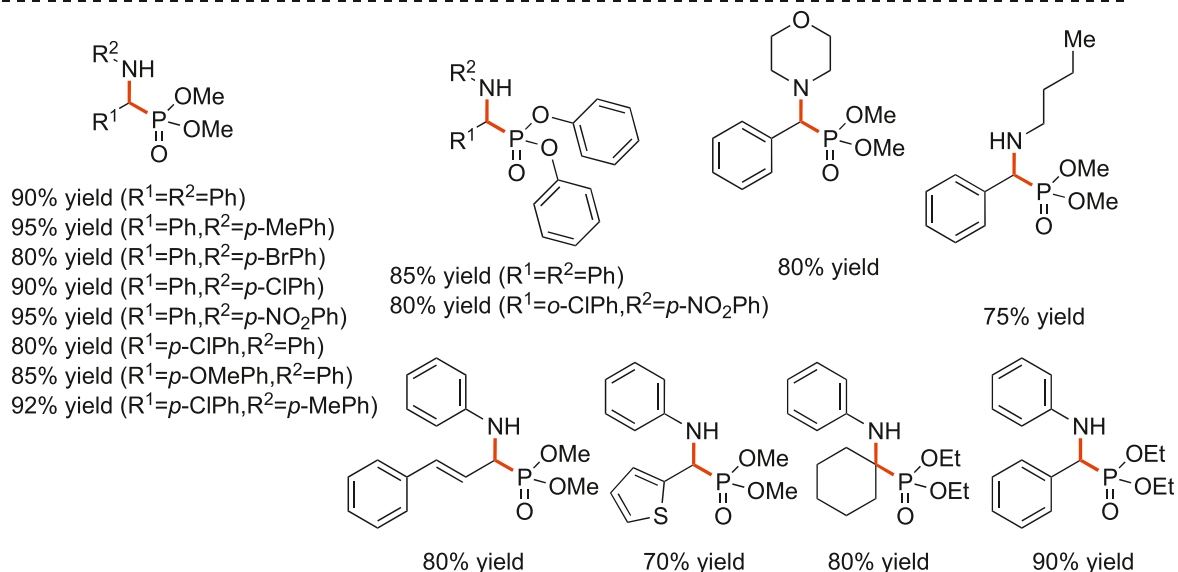
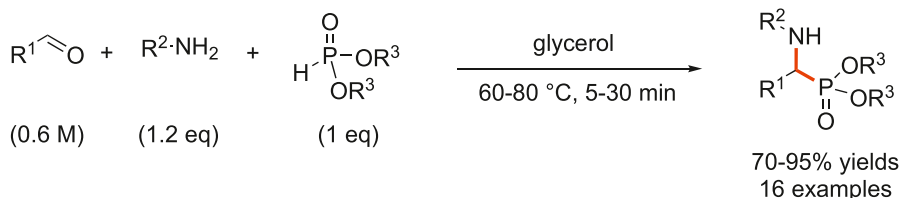
84% yield (4 h) ($R^1=H$)
82% yield (3.2 h) ($R^1=p\text{-Cl}$)
80% yield (3.5 h) ($R^1=p\text{-NO}_2$)
76% yield (3 h) ($R^1=p\text{-OH}$)
77% yield (4 h) ($R^1=p\text{-OMe}$)
75% yield (4 h) ($R^1=m\text{-NO}_2$)

Scheme 88. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Goyal et al., 2014).

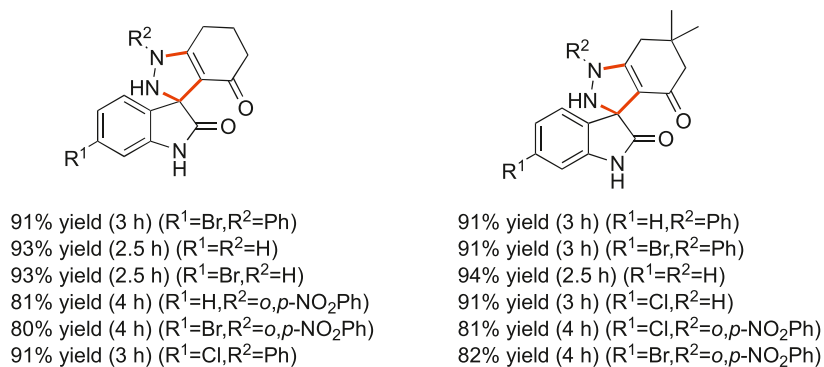
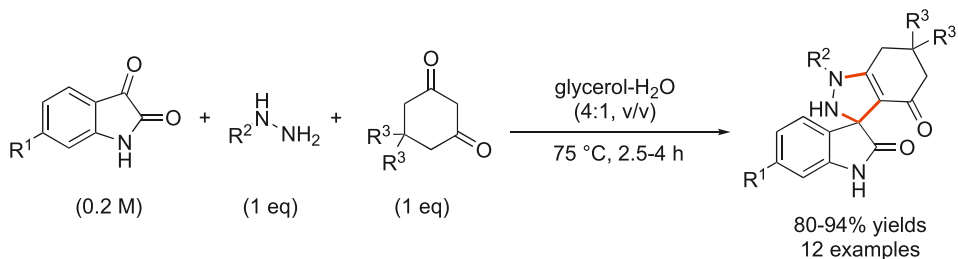
formation of the target compounds. The electronic effects of substituents, both electron-withdrawing and electron-releasing groups, on the aromatic ring of anilines did not have a direct influence on reaction times and yields. The study also investigated the recovery and reuse capacity of glycerol, which exhibited a marginal loss in yield in the second and third cycles (90% and 88%), gradually decreasing to 85% and 82% in the fourth and fifth cycles.

An alternative approach to synthesizing thiazolyl hydrazono-indolin-2-one derivatives under mild reaction conditions was investigated. The study demonstrated that the reaction between carbonyl compounds, such as aldehydes, ketones, thiosemicarbazide, and phenacyl bromide, could be facilitated in a glycerol micellar medium with catalytic amounts of cetyltrimethylammonium bromide (CTAB) serving as a phase transfer catalyst (Scheme 96) (Tiwari et al., 2018). The use of micellar catalysis in glycerol was a crucial aspect of this methodology, showcasing its superiority over using glycerol alone. Furthermore, the products were obtained with excellent to good yields (94%–86%) even after glycerol was reused four times, highlighting the sustainability of this environmentally friendly approach. When isatins were used instead of aldehydes and ketone, the isatin annulated 2,4-disubstituted thiazole molecules were obtained successfully with good to excellent yield (86–95% yield) and short reaction time (1.5–2.5 h).

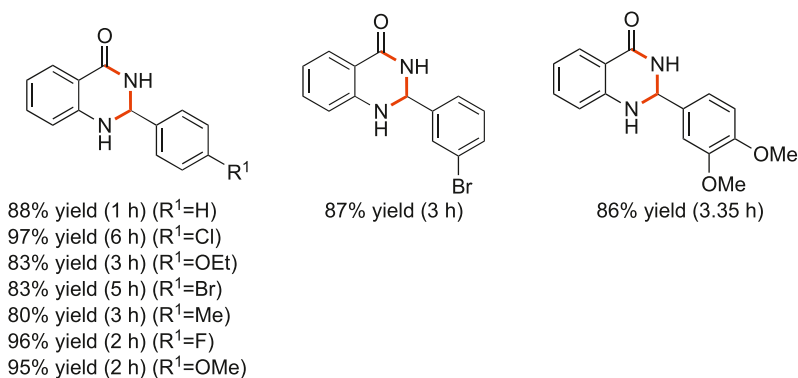
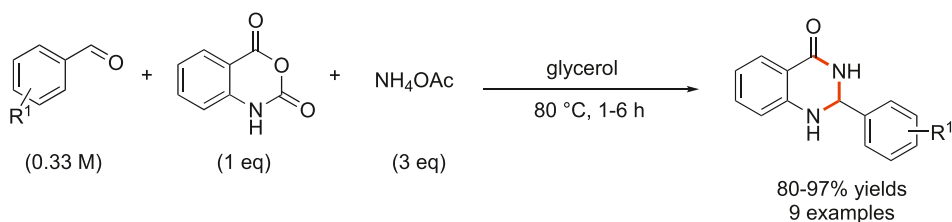
A simple, efficient, and catalyst-free synthesis of 2,4,5-triaryl derivatives involving the condensation of benzil with a wide range of benzaldehydes, and ammonium acetate in glycerol at 90 °C was reported (Scheme 97) (Nemati et al., 2016). The study demonstrated that the presence of electron-withdrawing or electron-donating groups, heteroaromatic moieties, or high steric hindrance in the aromatic aldehydes had no significant impact on the product yield within short reaction times. Furthermore, when four components, namely benzil, aryl aldehydes, aromatic amines, and ammonium acetate, were condensed in glycerol for the synthesis of 1,2,4,5-tetrasubstituted imidazoles, the yields ranged from good to excellent (91%–96%) (Nemati et al., 2016). The article emphasized that this



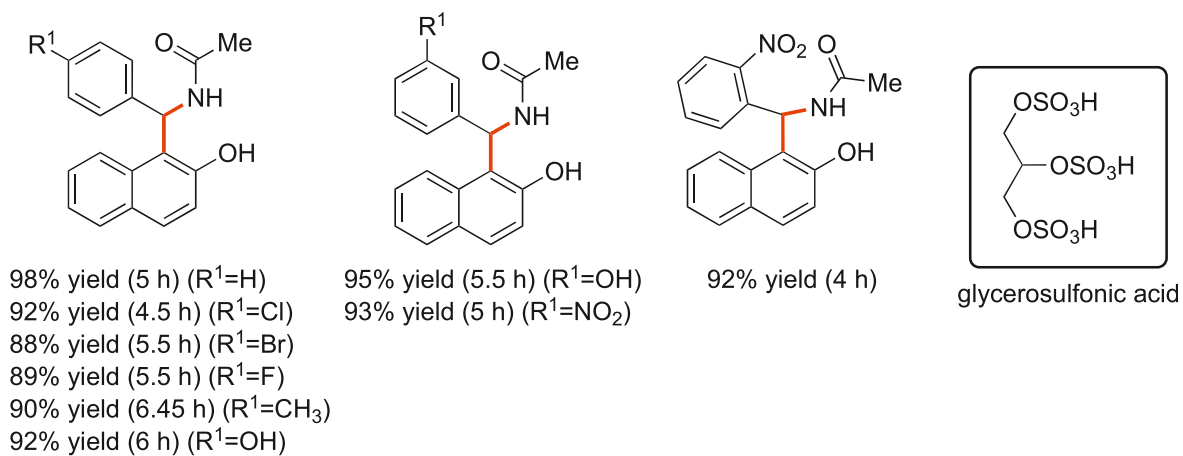
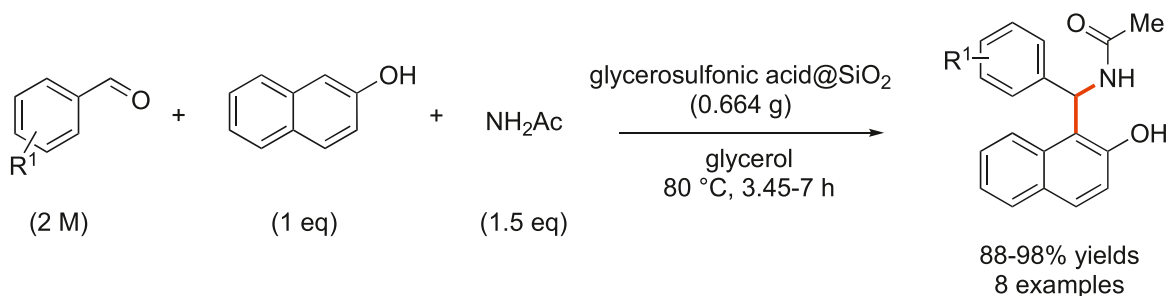
Scheme 89. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Azizi et al., 2014).



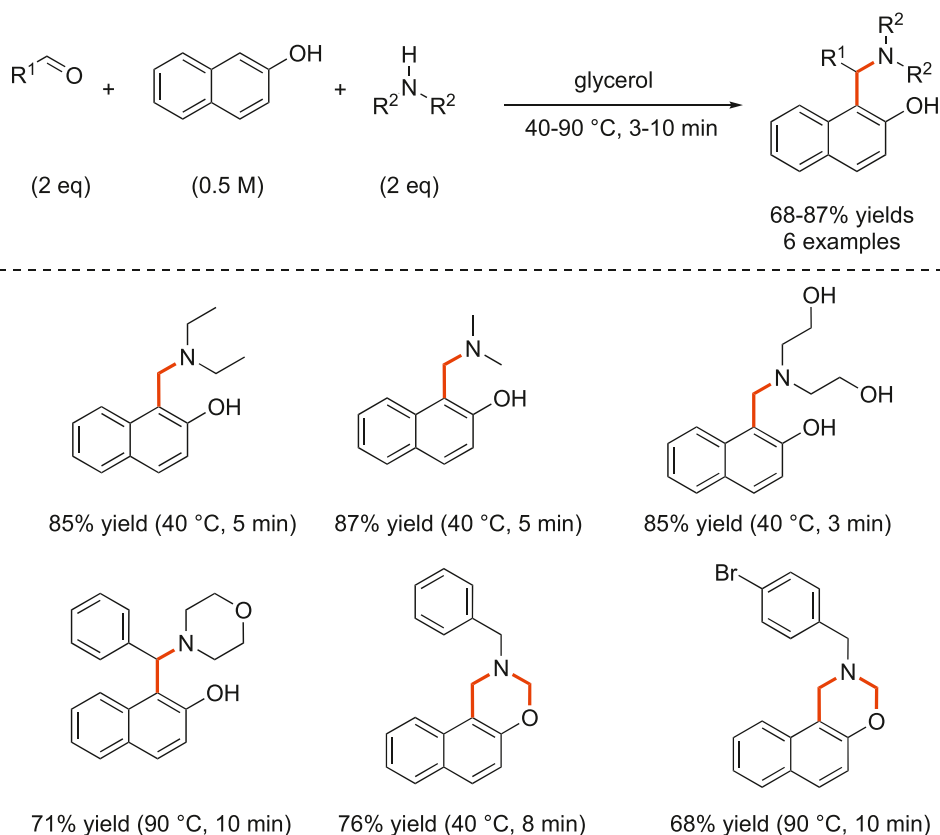
Scheme 90. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Singh et al., 2015).



Scheme 91. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Hajjami et al., 2015).



Scheme 92. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Hajjami et al., 2015).



Scheme 93. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Ganesan et al., 2013).

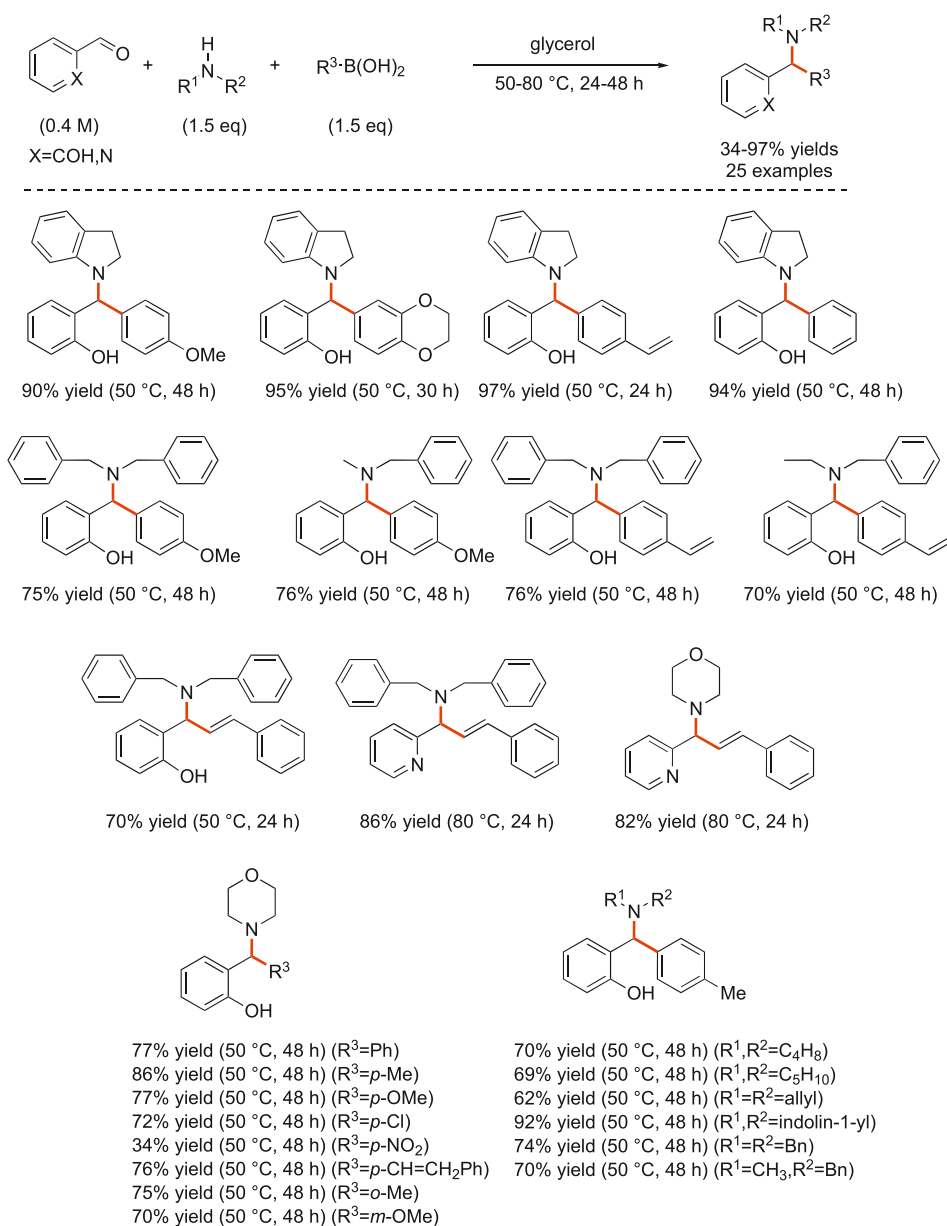
protocol yielded product yields (specifically 2,4,5-triphenyl-1H-imidazole) that were competitive with or even superior to those obtained using other conventional media reported in specialized literature.

An environmentally friendly synthetic route for the synthesis of catalyst-free pyrido[2,3-*d*]pyrimidines in glycerol as a promoting medium was investigated using 6-amino-1-methyluracils, benzaldehyde, and malononitrile (Scheme 98) (Singh et al., 2016). Whatever the substituents on the aromatic aldehydes, the desired products were obtained with high yields ranging from 84% to 94% but electron-withdrawing groups were found to accelerate the reaction and enhance the product yield, while electron-donating groups slowed down the reaction and decreased the product yield. Furthermore, the study demonstrated the recyclability of glycerol, with a higher recycling efficiency of 90% maintained after four cycles. However, the efficiency dropped to 81% in the fifth cycle, indicating the feasibility of glycerol's recyclability.

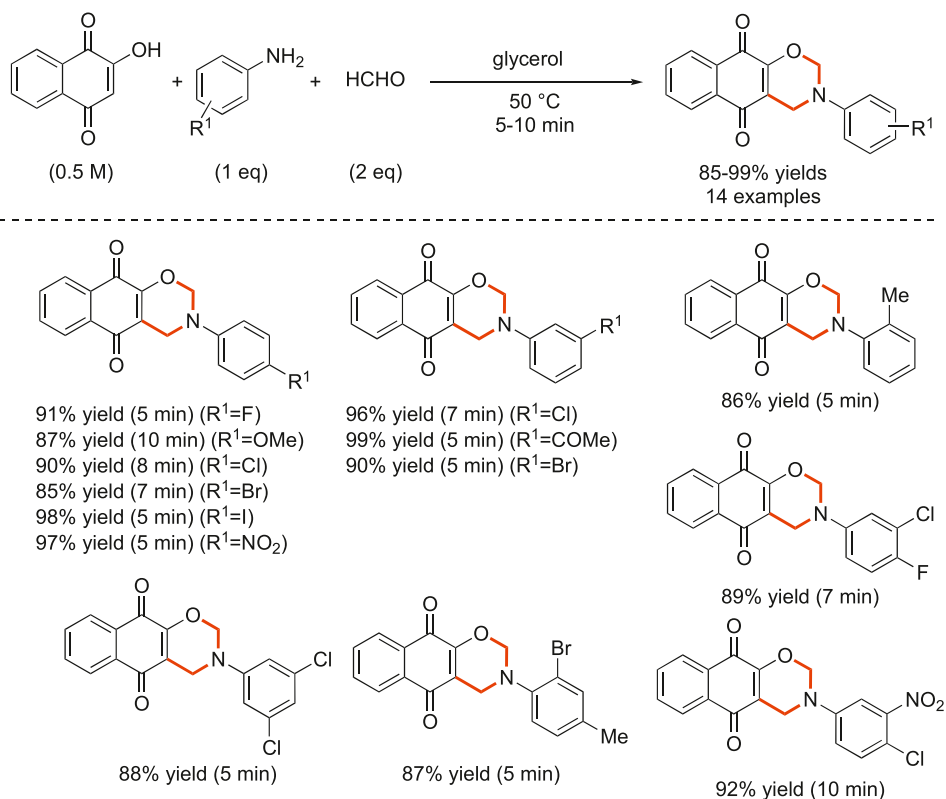
Using the same catalyst used for the C–N bond formation in glycerol, a study was conducted on the one-pot catalytic synthesis of heterocycles. The synthesis of 2-benzylisoindoline-1,3-dione was achieved with a yield of 90–99% through Pd-catalyzed carbonylative cyclization. This involved using 2-iodobenzoic acid and various amines in the presence of CO, 1,4-diazabicyclo[2.2.2]octane (DABCO), and Pd NPs at 120 °C for 30 min in glycerol (Scheme 99) (Chahdoura et al., 2015). Similar outcomes were obtained with other starting materials such as 2-iodobenzamide, methyl 2-iodobenzoate, and 1,2-diiodobenzene. The article highlighted the remarkable recyclability of the glycerol and Pd NPs catalytic phase, maintaining both activity and selectivity even after 10 cycles, yielding results between 94% and 98%. Comprehensive analyses including TEM, ICP-AES, and SEM confirmed the stability of the catalytic solution, with no detectable palladium leaching after each successive run.

2.8. Miscellaneous

Several reactions beyond C–C, C–N, C–P, C–O, C–S, and C–Se bond formations, as well as MCRs in glycerol, have been documented in the literature. Below, we provide selected examples, including S–S bond formation and the formation of amides from aldoximes. Oxidation and reduction reactions play a vital role in organic synthesis as they enable the interconversion of different functional groups, making them invaluable tools for synthesis in both linear and convergent routes. Given the significance of these reactions, new methodologies for such transformations are regularly reported in the literature, particularly for olefins and carbonyl compounds



Scheme 94. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Rosholm et al., 2015).



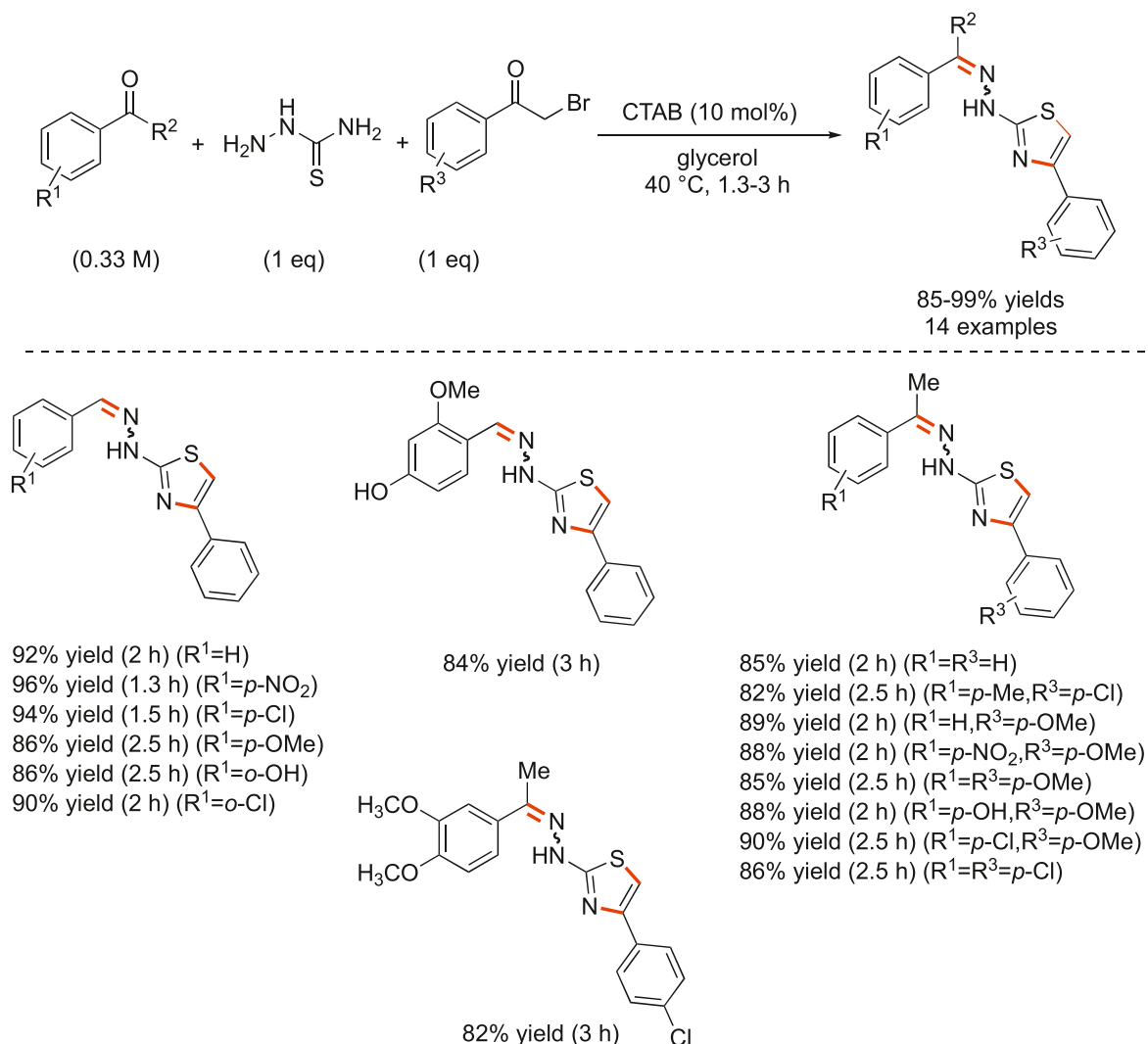
Scheme 95. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Gupta et al., 2016).

(Lenardão et al., 2017; de S. Oliveira et al., 2014). In organic synthesis, the choice of solvent is crucial, and therefore, the development of green solvents derived from renewable resources has garnered significant interest, considering the extensive use of solvents in various chemical industries.

The S–S bond formation for the synthesis of disulfides is an important oxidation reaction. Indeed, the disulfides are essential moieties of biologically active compounds for peptide and protein stabilization. The synthesis of disulfides from a range of thiols using Na₂CO₃ at 120 °C for 15 min in glycerol under microwave irradiation was reported (Scheme 100) (Cabrera et al., 2012). The study elucidated the behavior of diverse substrates, demonstrating the generality of the methodology unaffected by electronic effects. Furthermore, the authors investigated the reusability of glycerol for other oxidation reactions, demonstrating that diphenyl disulfide could be obtained with consistently high yields in five successive cycles (92%, 92%, 90%, 89%, and 88%) despite longer reaction times required after the third cycle. This approach enables the recycling of glycerol, thereby reducing the overall costs associated with the proposed method.

The synthesis of primary amides from aldoximes by rearrangement was investigated with bis(allyl)ruthenium(IV) complex [$\{\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})_2\}$] (C₁₀H₁₆ = 2,7-dimethylocta-2,6-diene-1,8-diyl) as a catalyst under both conventional heating and microwave irradiation (MW) (Gonzales-Liste et al., 2015). The results demonstrated that the reactions proceeded cleanly in a water/glycerol (1:1, v/v) mixture at temperatures ranging from 120 to 150 °C using conventional thermal heating and microwave irradiation (Scheme 101). Importantly, the synthetic route and rearrangement mechanism were thoroughly described, and the study reported a recycling efficiency of 94% in the sixth cycle with conventional heating and microwave heating. As a general trend, the use of MW irradiation appeared as the most convenient methodology for the rearrangement of aromatic, heteroaromatic, and aliphatic aldoximes, while thermal heating seems to be more convenient for the α,β -unsaturated ones.

The plasma technique has been employed to decompose glycerol and enhance the production potential of value-added products. Specifically, non-thermal (low temperature or cold) plasma, such as parallel plate dielectric barrier discharge (DBD) plasma, can be utilized in a catalyst-free process known as "plasma reforming." The use of DBD plasma reactor to hydrogenate palm oil using glycerol as a hydrogen donor instead of hydrogen gas was reported (Kongprawes et al., 2023). Unfortunately, the technology is not mature, and no selectivity was obtained.

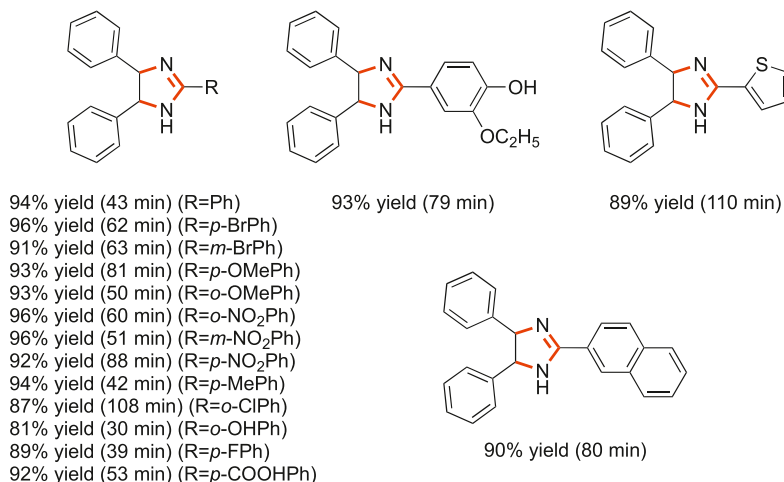
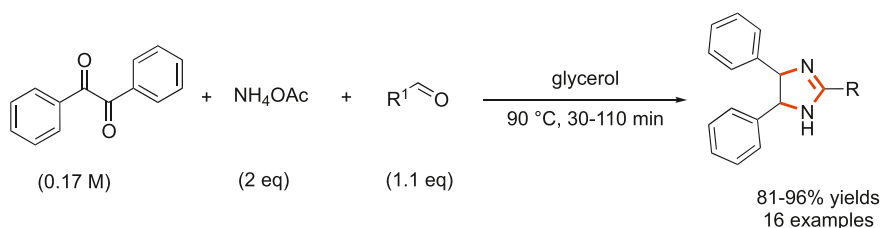


Scheme 96. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Tiwari et al., 2018).

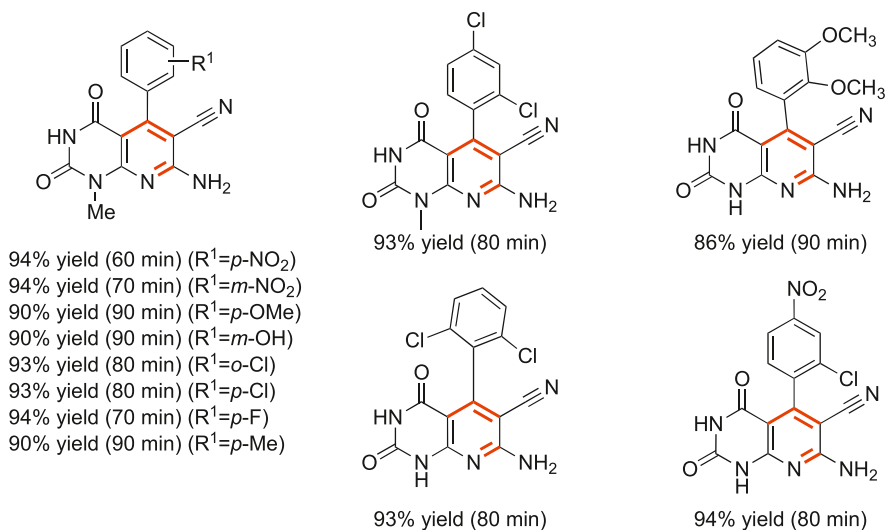
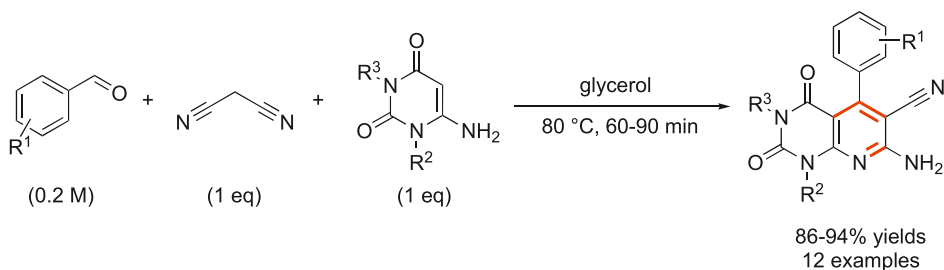
2.9. Conclusions and perspectives

This contribution was aimed to provide an overview of advances in the field of organic chemistry and catalysis utilizing glycerol as a solvent since 2010. Glycerol emerged as a standout option due to its exceptional solvent properties, marked by its ability to dissolve a wide range of organic compounds as well as relevant eco-friendly credentials. As industries worldwide continue to prioritize sustainability, glycerol stands out as a solvent that aligns perfectly with these goals. Glycerol's versatility as a solvent, coupled with its environmentally responsible profile, positions it as one of solvents of choice for the future. Its pivotal role in diverse industries, from pharmaceuticals to cosmetics, underscores its significance in driving both innovation and sustainable practices, ultimately benefiting both industry and the environment.

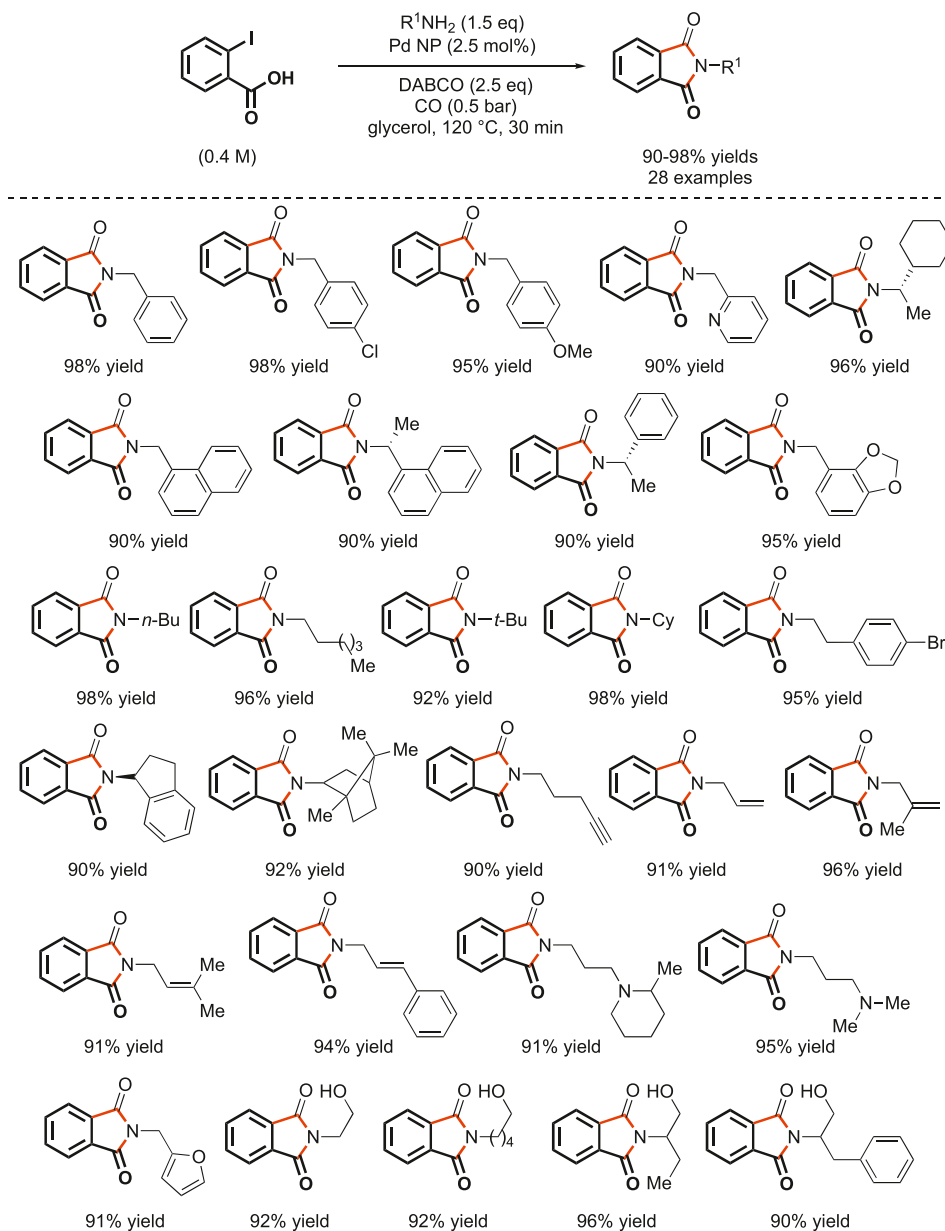
The use of glycerol is showcased in this contribution through its involvement in numerous bond-forming processes including C–C bond formation via Suzuki-Miyaura, Heck-Mizoroki, Sonogashira, Barbier, aldol condensation, metathesis cyclization, and Pauson-Khand carbocyclization reactions. Additionally, glycerol has been employed in C–N and C–P bond formation via Buchwald-Hartwig reaction, while also participating in C–H bond activation, condensation reactions between aryl amines and carbonyl compounds and the condensation of nitroarenes and benzyl alcohol. Other chemistries in which glycerol has been extensively involved include the Huisgen azide-alkyne cycloaddition as well as in the formation of C–O, C–S, C–Se, and C–Te bonds through O-alkylation, thiol addition to alkynes, coupling reactions, cycloisomerization, C–H bond activation and condensation reactions involving aryl thiol and carbonyl compounds. An intriguing aspect of glycerol's utility is the description of catalytic enantioselective transfer hydrogenation in the presence of Ru(II), which facilitates the synthesis of chiral alcohols in high enantiomeric excess. Beyond individual bond-forming



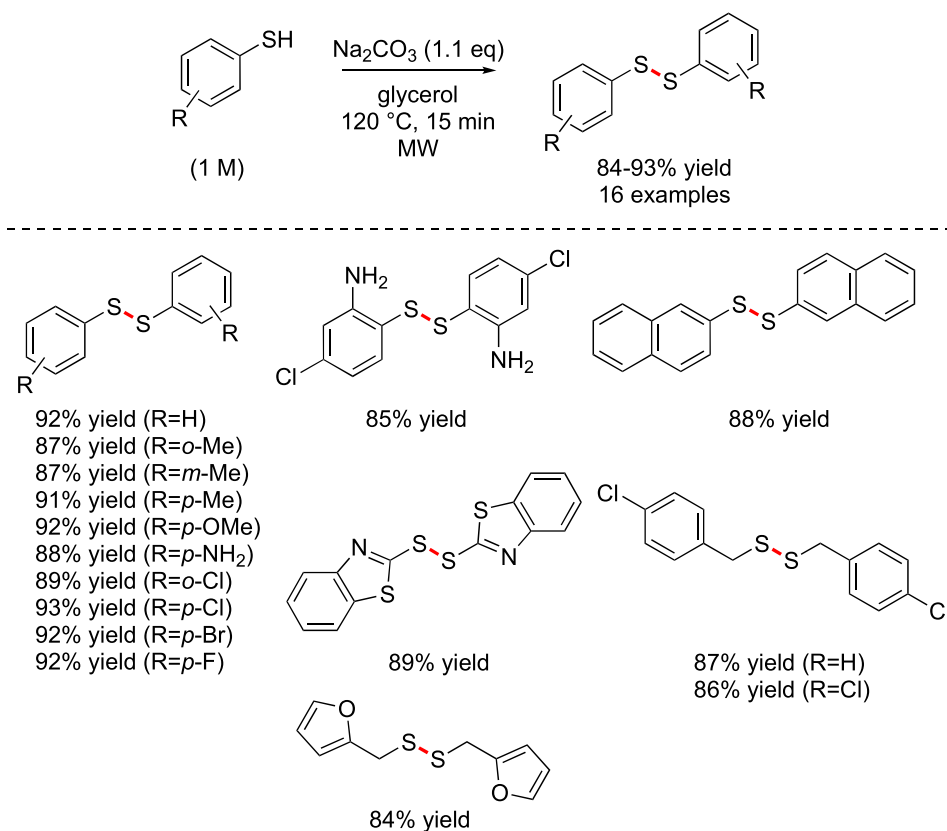
Scheme 97. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Nemati et al., 2016).



Scheme 98. MCR for the synthesis of 1,4-dihydropyridines in glycerol (Singh et al., 2016).



Scheme 99. Pd-catalyzed three-component carbonylative cyclization for the synthesis of 2-benzylisoindoline-1,3-dione from 2-iodobenzoic acid in glycerol (Chahdoura et al., 2015)



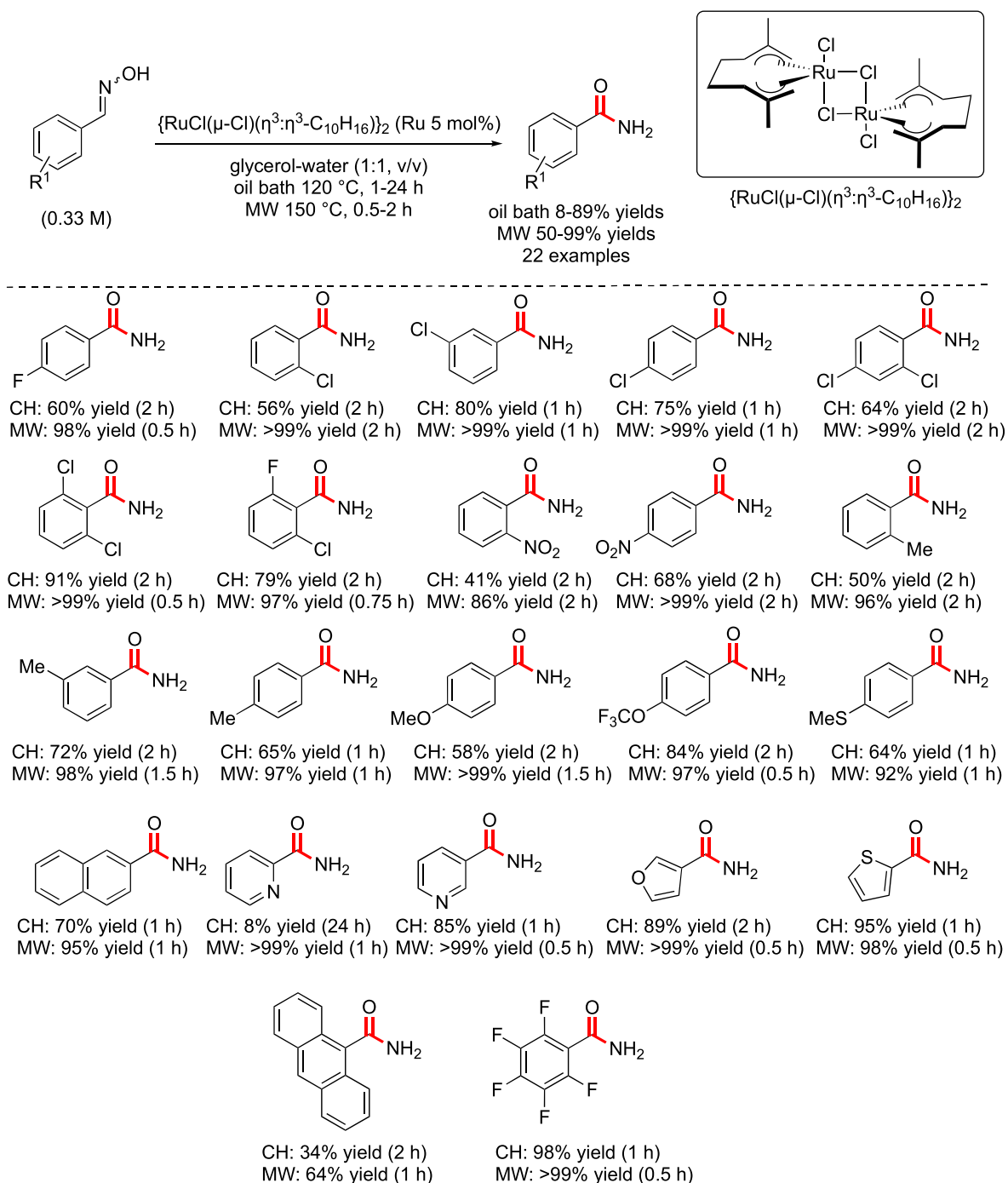
Scheme 100. Selected oxidation reactions of thiol to disulfide (Cabrera et al., 2012).

reactions, glycerol is also explored as a solvent in the synthesis of molecules that involve the creation of at least two bonds of different natures, such as C–C + CO, C–C + C–N as well as multicomponent reactions featuring three or four reactants. These studies have demonstrated that many of these reactions can yield desired compounds in good to excellent yields using various catalyst systems, including homogeneous, heterogeneous and even catalyst-free approaches. Notably, some reactions have shown promise in terms of catalyst recyclability, owing to the advantageous properties of glycerol as both a solvent and a catalyst medium.

In conclusion, glycerol usefulness extends across various catalyst systems and reactions, offering potential benefits in terms of recyclability and sustainability in chemical processes.

While considerable efforts have been made to harness glycerol's potential in various chemically relevant reactions, there remains a significant amount of groundwork to be laid in order to fully realize the objectives of green and sustainable chemistry, which the scientific community, spanning academia and industry, is striving to achieve. It is noteworthy that glycerol predominantly finds application as a solvent, replacing polar solvents typically sourced from the petroleum industry. However, these transitions often occur without the systematic undertaking of specific physicochemical studies or modeling, highlighting the need for a more rigorous scientific approach. Nonetheless, there are instances where glycerol's unique properties shine, particularly as a synthetic intermediate in specific reactions. Prominent examples include its role in facilitating the Suzuki reaction and hydrogen transfer catalysis, where glycerol proves instrumental in achieving desired outcomes.

Another aspect that merits attention is the considerable cost disparity between pharmaceutical-grade glycerol and crude glycerol. This cost differential underscores the importance of delving deeper into the utilization of crude glycerol, exploring its potential in chemically relevant reactions that hold value for both academic research and industrial applications. Such an exploration could open doors to more cost-effective and sustainable practices. Additionally, there's an interest in transitioning from traditional batch reactors to continuous flow systems for chemical reactions involving glycerol. This shift presents an intriguing perspective, with the potential to enhance productivity, streamline processes and further bolster the case for glycerol as a solvent of choice. The more widespread utilization of glycerol as solvent and reagent needs a more systematic and comprehensive approach, spanning rigorous scientific inquiry, cost-efficiency considerations, and innovative reactor technologies. By addressing these challenges, we can pave the way for a greener, more sustainable future of glycerol utilization.



Scheme 101. Catalytic rearrangement of aldoximes by the $\{RuCl(\mu-Cl)(\eta^3-\eta^3-C_{10}H_{16})\}_2$ complex in a mixture of glycerol-water (Gonzales-Liste et al., 2015).

CRedit authorship contribution statement

Alex de Nazaré de Oliveira: Methodology. Massimo Melchiorre: Methodology. Ana Alice Farias da Costa: Methodology. Linéia Soares da Silva: Methodology. Rutiléia de Jesus Paiva: Methodology. Amelie Auvigne: Methodology. Weiyi Ouyang: Methodology. Rafael Luque: Writing – original draft, Conceptualization. Geraldo Narciso da Rocha Filho: Methodology. Renata Coelho Rodrigues Noronha: Methodology. Roberto Esposito: Writing – original draft, Conceptualization. Luís Adriano Santos do Nascimento: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. Christophe Len: Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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References

- Abdullah, A., Zuhairi, A., Ahmed, M., Khan, J., Shahadat, M., Umar, K., Alim, A., 2022. A review on recent developments and progress in sustainable acrolein production through catalytic dehydration of bio-renewable glycerol. *J. Clean. Prod.* 341, 130876 <https://doi.org/10.1016/j.jclepro.2022.130876>.
- Alves, D., Sachini, M., Jacob, R.G., Lenardao, E.J., Contreira, M.E., Savegnago, L., Perin, G., 2011. Synthesis of (Z)-organylthioenynes using KF/Al_2O_3 /solvent as recyclable system. *Tetrahedron Lett.* 52, 133–135. <https://doi.org/10.1016/j.tetlet.2010.11.009>.
- Appa, R.M., Lakshmidivi, J., Naidu, B.R., Venkateswarlu, K., 2021. Pd-Catalyzed oxidative homocoupling of arylboronic acids in WEPA: a sustainable access to symmetrical biaryls under added base and ligand-free ambient conditions. *Mol. Catal.* 501, 111366 <https://doi.org/10.1016/j.mcat.2020.111366>.
- Aziz, J., Frison, G., Gómez, M., Brion, J.D., Hamze, A., Alami, M., 2014. Copper-catalyzed coupling of *N*-tosylhydrazones with amines: synthesis of fluorene derivatives. *ACS Catal.* 4, 4498–4503. <https://doi.org/10.1021/cs5014877>.
- Azizi, K., Karimi, M., Heydari, A., 2014. A catalyst-free synthesis of α -aminophosphonates in glycerol. *Tetrahedron Lett.* 55, 7236–7239. <https://doi.org/10.1016/j.tetlet.2014.11.057>.
- Azua, A., Mata, J.A., Peris, E., 2011. Iridium NHC based catalysts for transfer Hydrogenation processes using glycerol as solvent and hydrogen donor. *Organometallics* 30, 5532–5536. <https://doi.org/10.1021/om200796c>.
- Azua, A., Mata, J.A., Peris, E., Lamaty, F., Martinez, J., Colacino, E., 2012. Alternative energy input for transfer hydrogenation using iridium NHC based catalysts in glycerol as hydrogen donor and solvent. *Organometallics* 31, 3911–3919. <https://doi.org/10.1021/om300109e>.
- Azua, A., Mata, J.A., Heymes, P., Peris, E., Lamaty, F., Martinez, J., Colacino, E., 2013. Palladium *N*-heterocyclic carbene catalysts for the ultrasound-promoted Suzuki-Miyaura reaction in glycerol. *Adv. Synth. Catal.* 355, 1107–1116. <https://doi.org/10.1002/adsc.201201047>.
- Bachhav, H.M., Bhagat, S.B., 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. <https://doi.org/10.1016/j.tetlet.2011.08.105>.
- Bakhrou, N., Lamaty, F., Martinez, J., Colacino, E., 2010. Ring-closing metathesis in glycerol under microwave activation. *Tetrahedron Lett.* 51, 3935–3937. <https://doi.org/10.1016/j.tetlet.2010.05.101>.
- Balaguez, R.A., Kruger, R., Radatz, C.S., Rampon, D.S., Lenardao, E.J., Schneider, P.H., Alves, D., 2015. Synthesis of benzoselenazoles and benzoselenazolines by cyclization of 2-amino-benzeneselenol with beta-dicarbonyl compounds. *Tetrahedron Lett.* 56, 2735–2740. <https://doi.org/10.1016/j.tetlet.2015.04.020>.
- Beatriz, A., Araújo, Y.J.K., de Lima, D.P., 2011. Glycerol: a brief history and their application in stereoselective syntheses. *Quim. Nova* 34, 306–319.
- Beletskaya, I.P., Cheprakov, A.V., 2000. The Heck reaction as a sharpening stone of palladium. *Chem. Rev.* 100, 3009–3066. <https://doi.org/10.1021/cr9903048>.
- Bharathi, M., Indira, S., Vinoth, G., Bharathi, K.S., 2019. Immobilized Ni-Schiff-base metal complex on MCM-41 as a heterogeneous catalyst for the green synthesis of benzimidazole derivatives using glycerol as a solvent. *J. Porous Mater.* 26, 1377–1390. <https://doi.org/10.1007/s10934-019-00736-8>.
- Bhojane, J.M., Sarode, S.A., Nagarkar, J.M., 2016. Nickel-glycerol: an efficient, recyclable catalysis system for Suzuki cross-coupling reaction using aryl diazonium salt. *New J. Chem.* 40, 1564–1570. <https://doi.org/10.1039/c5nj01833a>.
- Cabrera, D.M.L., Líbero, F.M., Alves, D., Perin, G., Lenardão, E.J., Jacob, R.G., 2012. Glycerol as a recyclable solvent in a microwave-assisted synthesis of disulfides. *Green Chem. Lett. Rev.* 5, 329–336. <https://doi.org/10.1080/17518253.2011.631942>.
- Cargnelutti, R., da Silva, F.D., Abram, U., Lang, E.S., 2015a. Metal complexes with bis(2-pyridyl)diselenoethers: structural chemistry and catalysis. *New J. Chem.* 59, 7948–7953. <https://doi.org/10.1039/C5NJ01400J>.
- Cargnelutti, R., Lang, E.S., Schumacher, R.F., 2015b. Bis(2-pyridyl) diselenoethers as versatile ligands for copper-catalyzed C–S bond formation in glycerol. *Tetrahedron Lett.* 56, 5218–5222. <https://doi.org/10.1016/j.tetlet.2015.07.060>.
- Carmona, R.C., Schevchiv, E.P., de Albuquerque, J.L.P., Wendler, E.P., Dos Santos, A.A., 2013. Joint use of microwave and glycerol-zinc (II) acetate catalytic system in the synthesis. *Green Process. Synth.* 2, 35–42. <https://doi.org/10.1515/gps-2012-0085>.
- Chahdoura, F., Dubrulle, L., Fourmy, K., Durand, J., Madec, D., Gómez, M., 2013a. Glycerol-a non-innocent solvent for Rh-catalysed Pauson-Khand carbocyclisations. *Eur. J. Inorg. Chem.* 2013, 5138–5144. <https://doi.org/10.1002/ejic.201300651>.
- Chahdoura, F., Pradel, C., Gómez, M., 2013b. Palladium nanoparticles in glycerol: a versatile catalytic system for C–X bond formation and hydrogenation processes. *Adv. Synth. Catal.* 355, 3648–3660. <https://doi.org/10.1002/adsc.201300753>.
- Chahdoura, F., Favier, I., Gómez, M., 2014a. Glycerol as suitable solvent for the synthesis of metallic species and catalysis. *Chem. Eur. J.* 20, 10884–10893. <https://doi.org/10.1002/chem.201403534>.
- Chahdoura, F., Pradel, C., Gómez, M., 2014b. Copper(I) oxide nanoparticles in glycerol: a convenient catalyst for cross-coupling and azide-alkyne cycloaddition processes. *ChemCatChem* 6, 2929–2936. <https://doi.org/10.1002/cctc.201402214>.
- Chahdoura, F., Mallet-ladeira, S., 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. <https://doi.org/10.1039/c4qo00338a>.
- Chari, M.A., Shobha, D., Kenawy, E., Al-deyab, S.S., Reddy, B.V.S., Vintu, A., 2010. Nanoporous aluminosilicate catalyst with 3D cage-type porous structure as an efficient catalyst for the synthesis of benzimidazole derivatives. *Tetrahedron Lett.* 51, 5195–5199. <https://doi.org/10.1016/j.tetlet.2010.07.132>.
- Chari, M.A., Shobha, D., Sasaki, T., 2011. Room temperature synthesis of benzimidazole derivatives using reusable cobalt hydroxide (II) and cobalt oxide (II) as efficient solid catalysts. *Tetrahedron Lett.* 52, 5575–5580. <https://doi.org/10.1016/j.tetlet.2011.08.047>.
- Chilakamary, C.R., Sakinah, A.M.M., Zulairisam, A.W., Sirohi, R., Khilji, I.A., Reddy, V.J., Pandey, A., 2022. Bioconversion of glycerol into biofuels - Opportunities and challenges. *Bioenergy Res* 15, 46–61. <https://doi.org/10.1007/s12155-021-10353-6>.
- Chinchilla, R., Najera, C., 2007. The Sonogashira reaction: a booming methodology in synthetic organic chemistry. *Chem. Rev.* 107, 874–922. <https://doi.org/10.1021/cr050992x>.
- Cordovilla, C., Bartolome, C., Martinez-Illarduya, J.M., Espinet, P., 2015. The Stille reaction, 38 years later. *ACS Catal.* 5, 3040–3053. <https://doi.org/10.1021/acscatal.5b00448>.
- Cravotto, G., Orio, L., Gaudino, C., Martina, K., 2011. Efficient synthetic protocols in glycerol under heterogeneous catalysis. *ChemSusChem* 4, 1130–1134. <https://doi.org/10.1002/cssc.201100106>.
- Cristino, A.F., Matias, A.S., Bastos, D.E.N., Galhano, R., Ribeiro, A.P.C., Martins, L.M.D.R.S., 2020. Glycerol role in nano oxides synthesis and catalysis. *Catalysts* 10, 1406. <https://doi.org/10.3390/catal10121406>.
- Crotti, C., Kaspar, J., Farnetti, E., 2010. Dehydrogenation of glycerol to dihydroxyacetone catalyzed by iridium complexes with P–N ligands. *Green Chem.* 12, 1295–1300. <https://doi.org/10.1039/c003542d>.

- Cui, X., Zhang, C., Shi, F., Deng, Y., 2012. Au/Ag–Mo nano-rods catalyzed reductive coupling of nitrobenzenes and alcohols using glycerol as the hydrogen source. *Chem. Commun.* 48, 9391–9393. <https://doi.org/10.1039/c2cc34178f>.
- Cui, X., Deng, Y., Shi, F., 2013. Reductive N-alkylation of nitro compounds to N-alkyl and N,N-dialkyl amines with glycerol as the hydrogen source. *ACS Catal.* 3, 808–811. <https://doi.org/10.1021/cs400049b>.
- da Costa, A.A.F., De Oliveira, A.D.N., Esposito, R., Len, C., Luque, R., Noronha, R.C.R., Rocha Filho, G.N., Nascimento, L.A.S., 2022. Glycerol and catalysis by waste/low-cost materials – a review. *Catalysts* 12, 570. <https://doi.org/10.3390/catal12050570>.
- da Costa, A.A.F., De Oliveira, A.D.N., Esposito, R., Auvigne, A., Len, C., Luque, R., Noronha, R.C.R., do Nascimento, L.A.S., 2023. Glycerol and microwave-assisted catalysis: recent progress in batch and flow devices. *Sustain. Energy Fuels* 7, 1768–1792. <https://doi.org/10.1039/d2se01647h>.
- del Pozo, J., Salas, G., Alvarez, R., Casares, J.A., Espinet, P., 2016. The Negishi catalysis: full study of the complications in the transmetalation step and consequences for the coupling products. *Organometallics* 35, 3604–3611. <https://doi.org/10.1021/acs.organomet.6b00660>.
- Delamplé, M., Villandier, N., Douliet, J.P., Camy, S., Condoret, J.S., Pouilloux, Y., Barrault, J., Jerome, F., 2010. Glycerol as a cheap, safe and sustainable solvent for the catalytic and regioselective β , β -diarylation of acrylates over palladium nanoparticles. *Green Chem.* 12, 804–808. <https://doi.org/10.1039/b925021b>.
- Díaz-Álvarez, A.E., Crochet, P., Cadierno, V., 2011. Ruthenium-catalyzed reduction of allylic alcohols using glycerol as solvent and hydrogen donor. *Catal. Commun.* 13, 91–96. <https://doi.org/10.1016/j.cattcom.2011.07.006>.
- Díaz-Álvarez, A.E., Francos, J., Crochet, P., Cadierno, V., 2014. Recent advances in the use of glycerol as green solvent for synthetic organic chemistry. *Curr. Green Chem.* 1, 51–65. <https://doi.org/10.2174/2213346101131218094907>.
- Dubey, A.V., Gharat, S.B., Kumar, A.V., 2017. Glycerol as a recyclable solvent for copper-mediated ligand-free C-S cross-coupling reaction: application to synthesis of Gemmacin precursor. *ChemistrySelect* 2, 4852–4856. <https://doi.org/10.1002/slct.201700684>.
- Farhang, M., Akbarzadeh, A.R., Rabbani, M., Ghadiri, A.M., 2022. A retrospective-prospective review of Suzuki-Miyaura reaction: from cross-coupling reaction to pharmaceutical industry applications. *Polyhedron* 227, 116124. <https://doi.org/10.1016/j.poly.2022.116124>.
- Fattah, I.M.R., Ong, H.C., Mahlia, T.M.I., Mofijur, M., Silitonga, A.S., Rahman, S.M.A., Ahmad, A., 2020. State of the art of catalysts for biodiesel production. *Front. Energy Res.* 8, 1–17. <https://doi.org/10.3389/fenrg.2020.00101>.
- Favier, I., Pla, D., 2018. Metal-based nanoparticles dispersed in glycerol: an efficient approach for catalysis. *Catal. Today* 310, 98–106. <https://doi.org/10.1016/j.cattod.2017.06.026>.
- Francos, J., Cadierno, V., 2010. Palladium-catalyzed cycloisomerization of (Z)-enynols into furans using green solvents: glycerol vs. water. *Green Chem.* 12, 1552–1555. <https://doi.org/10.1039/c0gc00169d>.
- Gadekar, L.S., Arbad, B.R., Lande, M.K., 2010. Eco-friendly synthesis of benzimidazole derivatives using solid acid scolecite catalyst. *Chin. Chem. Lett.* 21, 1053–1056. <https://doi.org/10.1016/j.ccllet.2010.03.038>.
- Galadima, A., Muraza, O., 2020. Waste materials for production of biodiesel catalysts: technological status and prospects. *J. Clean. Prod.* 263, 121358. <https://doi.org/10.1016/j.jclepro.2020.121358>.
- Galy, N., Nguyen, R., Blach, P., Sambou, S., Luat, D., Len, C., 2017. Glycerol oligomerization in continuous flow reactor. *J. Ind. Eng. Chem.* 51, 312–318. <https://doi.org/10.1016/j.jiec.2017.03.020>.
- Gandeepan, P., Kaplaneris, G., Santoro, S., Vaccaro, L., Ackermann, L., 2019. Biomass-derived solvents for sustainable transition metal-catalyzed C-H activation. *ACS Sustainable Chem. Eng.* 9, 8023–8040. <https://doi.org/10.1021/acssuschemeng.9b00226>.
- Ganesan, S.S., Rajendran, N., Sundarakumar, I., Ganesan, A., 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. <https://doi.org/10.1055/s-0033-1338430>.
- Garg, G., Foltran, S., Favier, I., Pla, D., Medina-González, Y., Gómez, M., 2020. Palladium nanoparticles stabilized by novel choline-based ionic liquids in glycerol applied in hydrogenation reactions. *Catal. Today* 346, 69–75. <https://doi.org/10.1016/j.cattod.2019.01.052>.
- Gawande, M.B., Rath, A.K., Branco, P.S., Nogueira, I.D., Velhinho, A., Shrikhande, J.J., Indulkar, U.U., Jayaram, C.A.A., Bundaleski, N., Teodoro, O.M.N.D., 2012. Regio- and chemoselective reduction of nitroarenes and carbonyl compounds over recyclable magnetic ferrite-nickel nanoparticles (Fe_3O_4 -Ni) by using glycerol as a hydrogen source. *Chem. Eur. J.* 18, 12628–12632. <https://doi.org/10.1002/chem.201202380>.
- Gokhale, T.A., Phatake, V.V., Bhanage, B.M., 2022. MnO_2 nanostructures as sustainable catalysts for selectivity tuning and syntheses of amine coupling products with bio-derived glycerol. *Mol. Catal.* 533, 112771. <https://doi.org/10.1016/j.mcat.2022.112771>.
- Goncalves, L.C., Fiss, G.F., Perin, G., Alves, D., Jacob, R.G., Lenardao, E.J., 2010. Glycerol as a promoting medium for cross-coupling reactions of diaryl diselenides with vinyl bromides. *Tetrahedron Lett.* 51, 6772–6775. <https://doi.org/10.1016/j.tetlet.2010.10.107>.
- Goncalves, L.C.C., Lima, D.B., Borba, P.M.Y., Perin, G., Alves, D., Jacob, R.G., Lenardao, E.J., 2013. Glycerol/CuI/Zn as a recyclable catalytic system for synthesis of vinyl sulfides and tellurides. *Tetrahedron Lett.* 54, 3475–3480. <https://doi.org/10.1016/j.tetlet.2013.04.119>.
- Goncalves, L.C.C., Victória, F.N., Lima, D.B., Borba, P.M.Y., Perin, G., Savegnago, L., Lenardao, E.J., 2014. CuI/glycerol mediated stereoselective synthesis of 1, 2-bis-chalcogen alkenes from terminal alkynes: synthesis of new antioxidants. *Tetrahedron Lett.* 55, 5275–5279. <https://doi.org/10.1016/j.tetlet.2014.07.109>.
- Gonzales-Liste, P.J., Cadierno, V., Garcia-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 $[(\text{RuCl}(\mu\text{-Cl})(\eta^3\text{-}\eta^3\text{-C}_{10}\text{H}_{16})_2)]_2$. *ACS Sustainable Chem. Eng.* 3, 3004–3011. <https://doi.org/10.1021/acssuschemeng.5b01107>.
- Goyal, A., Sohal, H.S., Kumar, S., Khare, R., 2014. Multicomponent, efficient approach for the synthesis of pyrazolo[3,4-d]pyrimidine derivatives using glycerol as green solvent. *J. Applied Chem.* 7, 63–66. <https://doi.org/10.9790/5736-07216366>.
- Goyal, S., Hernández, N.B., Cochran, E.W., 2021. Mini-review an update on the future prospects of glycerol polymers. *Polym. Int.* 70, 911–917. <https://doi.org/10.1002/pi.6209>.
- Gu, Y., Jérôme, F., 2010. Glycerol as a sustainable solvent for green chemistry. *Green Chem.* 12, 1127–1138. <https://doi.org/10.1039/c001628d>.
- Gupta, S., Khanna, G., Khurana, J.M., 2016. A facile eco-friendly approach for the one-pot synthesis of 3,4-dihydro-2H-naphtho[2,3-e][1,3]oxazine-5,10-diones using glycerol as a green media. *Environ. Chem. Lett.* 14, 559–564. <https://doi.org/10.1007/s10311-016-0570-6>.
- Guyon, C., Métay, E., Duguet, N., Lemaire, M., 2013. Biphasic glycerol/2-MeTHF, ruthenium-catalysed enantioselective transfer hydrogenation of ketones using sodium hypophosphite as hydrogen donor. *Eur. J. Org. Chem.* 2013, 5439–5444. <https://doi.org/10.1002/ejoc.201300506>.
- Hajjami, M., Bakhti, F., Ghiasbeygi, E., 2015. Incredible role of glycerol in multicomponent synthesis of 2,3-dihydroquinazoline-4(1H)-ones and 1-amidoalkyl-2-naphthols. *Croat. Chem. Acta* 88, 197. <https://doi.org/10.5562/cca2637>.
- Hamel, A., Sacco, M., Mnasri, N., Lamaty, F., Martinez, J., De Angelis, F., Colacino, E., Charnay, C., 2014. Micelles into glycerol solvent: overcoming side reactions of glycerol. *ACS Sustainable Chem. Eng.* 2, 1353–1358. <https://doi.org/10.1021/sc500207r>.
- Hamid, S.B.A., Titinchi, S.J.J., Abbo, H., Khaligh, N.G., 2016. One-pot multicomponent synthesis of pyrazolo[3,4-d]pyrimidine-6-one derivatives. *Polycycl. Aromat. Comp.* 38, 1–10. <https://doi.org/10.1080/10406638.2016.1194298>.
- Hamid, A.A., Abd-Elmonem, M., Hayallah, A.M., Elsoud, F.A.A., Sadek, K.U., 2017. Glycerol: a promising benign solvent for catalyst free one-pot multi-component synthesis of pyrano[2,3-c]pyrazoles and tetrahydro-benzo[b]pyrans at ambient temperature. *ChemistrySelect* 2, 10689–10693. <https://doi.org/10.1002/slct.201702011>.
- Hikmawanti, P.N.E., Ramadan, D., Jantan, I., Mun'im, A., 2021. Natural deep eutectic solvents (NADES): phytochemical extraction performance enhancer for pharmaceutical and nutraceutical product development. *Plants* 10, 2091. <https://doi.org/10.3390/plants10102091>.
- Hilali, S., Wils, L., Chevalley, A., Clément-Larosière, B., Boudesocque-Delaye, L., 2022. Glycerol-based NADES as green solvents for ultrasound-assisted extraction of phycoerythrin from *Arthrospira platensis* — RSM optimization and ANN modelling. *Biomass Convers. Biorefin.* 12, S157–S170. <https://doi.org/10.1007/s13399-021-02263-6>.
- Jovanović, M.B., Konstantinović, S.S., Ilić, S.B., Veljković, V.B., 2013. The synthesis of vanillin-semicarbazone in a crude glycerol as a green solvent. *Adv. Met. Technol.* 2, 38–44.
- Kaur, J., Sarma, A.K., Hha, M.K., Gera, P., 2020. Valorisation of crude glycerol to value-added products: perspectives of process technology, economics and environmental issues. *Biotechnol. Rep.* 27, e00487. <https://doi.org/10.1016/j.btre.2020.e00487>.

- Khan, A.T., Parvin, T., Choudhury, L.H., 2009. A simple and convenient one-pot synthesis of benzimidazole derivatives using cobalt (II) chloride hexahydrate as catalyst a simple and convenient one-pot synthesis. *Synth. Commun.* 39, 2339–2346. <https://doi.org/10.1080/00397910802654815>.
- Kong, P.S., Kheireddine, M., Mohd, W., Wan, A., 2016. Conversion of crude and pure glycerol into derivatives: a feasibility evaluation. *Renew. Sust. Energ. Rev.* 63, 533–555. <https://doi.org/10.1016/j.rser.2016.05.054>.
- Kongprawes, G., Wongsawaeng, D., Hosemann, P., Ngaosuwan, K., Kiatkittipong, W., Assabumrungrat, S., 2023. Dielectric barrier discharge plasma for catalytic-free palm oil hydrogenation using glycerol as hydrogen donor for further production of hydrogenated fatty acid methyl ester (H-FAME). *J. Clean. Prod.* 401, 136724 <https://doi.org/10.1016/j.jcleprod.2023.136724>.
- Lakshmidivi, J., Vakati, V., Naidu, B.R., Raghavender, M., Rao, K.S.V.K., Venkateswarlu, K., 2021. Pd(5%)-KIT-6, Pd(5%)-SBA-15 and Pd(5%)-SBA-16 catalysts in water extract of pomegranate ash: a case study in heterogenization of Suzuki-Miyaura reaction under external base and ligand free conditions. *Sustain. Chem. Pharm.* 19, 100371 <https://doi.org/10.1016/j.scp.2020.100371>.
- Len, C., Bruniaux, S., Delbecq, F., Parmar, V.S., 2017. Palladium-catalyzed Suzuki-Miyaura cross-coupling in continuous flow. *Catalysts* 7, 146–168. <https://doi.org/10.3390/catal7050146>.
- Lenardão, E.J., Silva, M.S., Lara, R.G., Marczewski, J.M., Sachini, M., Jacob, R.G., Alves, D., Perin, G., 2011. Synthesis of vinyl sulfides using glycerol as a recyclable solvent. *ARKIVOC* (Gainesville, FL, U. S.) 272–282. <https://doi.org/10.3998/ark.5550190.0012.222>.
- Lenardão, E.J., Barcellos, A.M., Penteado, F., Alves, D., Perin, G., 2017. Glycerol as a solvent in organic synthesis. *Rev. Virtual Quim.* 9, 192–237. <https://doi.org/10.21577/1984-6835.20170015>.
- Li, M., Chen, C., He, F., 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. <https://doi.org/10.1002/adsc.200900770>.
- Lima, P.J.M., da Silva, R.M., Neto, C.A.C.G., Silva, N.C.G.E., da Silva Souza, J.E., Nunes, Y.L., Dos Santos, J.C.S., 2021. An overview on the conversion of glycerol to value-added industrial products via chemical and biochemical routes. *Biotechnol. Appl. Biochem.* 69, 2794–2818. <https://doi.org/10.1002/bab.2098>.
- Lobo, H.R., Singh, B.S., 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. <https://doi.org/10.1080/17518253.2012.669500>.
- Lu, C.W., Wang, J.J., Liu, Y.H., Shan, W.J., Sun, Q., Shi, L., 2017. A combination of green solvent and ultrasonic irradiation promotes the catalyst-free reaction of aldehydes, indoles and Meldrum's acid. *Res. Chem. Intermed.* 43, 943–949. <https://doi.org/10.1007/s11164-016-2675-8>.
- Luo, X., Ge, X., Cui, S., Li, Y., 2016. Value-added processing of crude glycerol into chemicals and polymers. *Bioresour. Technol.* 215, 144–154. <https://doi.org/10.1016/j.biortech.2016.03.042>.
- Mahdavinia, G.H., Rostamizadeh, S., Amani, A.M., Sephrian, H., 2012. Fast and efficient method for the synthesis of 2-arylbenzimidazoles using MCM-41-SO₃H. *Heterocycl. Commun. Now.* 18, 33–37. <https://doi.org/10.1515/hc-2011-0056>.
- Mahire, V.N., Patel, V.E., Mahulikar, P.P., 2017. Facile DES-mediated synthesis and antioxidant potency of benzimidazoquinazolinone motifs. *Res. Chem. Intermed.* 43, 1847–1861. <https://doi.org/10.1007/s11164-016-2734-1>.
- Mandi, U., Roy, A.S., Kundu, S.K., Roy, S., Bhaumik, A., Islam, M.S., 2016. Mesoporous polyacrylic acid supported silver nanoparticles as an efficient catalyst for reductive coupling of nitrobenzenes and alcohols using glycerol as hydrogen source. *J. Colloid Interface Sci.* 472, 202–209. <https://doi.org/10.1016/j.jcis.2016.03.037>.
- Mayo, M.S., Yu, X., Zhou, X., Feng, X., Yamamoto, Y., Bao, M., 2014. Convenient Synthesis of benzothiazoles and benzimidazoles through Brønsted acid catalyzed cyclization of 2-amino thiophenols/anilines with β -diketones. *Org. Lett.* 3, 764–767. <https://doi.org/10.1021/ol403475v>.
- Melchiorre, M., Amoresano, A., Budzelaar, P.H.M., Cucciolito, M.E., Mocerino, F., Pinto, G., Ruffo, F., Tuzi, A., Esposito, R., 2022. Parts-per-million (Salen)Fe(III) homogeneous catalysts for the production of biodiesel from waste cooking oils. *Catal. Lett.* 152, 3785–3794. <https://doi.org/10.1007/s10562-022-03948-x>.
- Mesquita, K.D., Waskow, B., Schumacher, R.F., Perin, G., Jacob, R.G., Alves, D., 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. <https://doi.org/10.5935/0103-5053.20140104>.
- Min, Z.L., Zhang, Q., Hong, X., Cao, X.L., Hu, X.M., 2015. A green protocol for catalyst-free syntheses of pyrazole in glycerol-water solution. *Asian J. Chem.* 27, 3205–3207. <https://doi.org/10.14233/ajchem.2015.18394>.
- Mišan, A., Nadpal, J., Stupar, A., Pojić, M., Verpoorte, R., Choi, Y.H., 2019. The perspectives of natural deep eutectic solvents in agri-food sector. *Crit. Rev. Food Sci. Nutr.* 60, 2564–2592. <https://doi.org/10.1080/10408398.2019.1650717>.
- Mohd Amin, U.S.B., Osman, N.B., Uemura, Y., Majid, N.M.N.A., 2020. Catalytic transfer hydrogenation of Castor oil using glycerol - based reaction. *Waste Biomass Valor* 11, 5591–5597. <https://doi.org/10.1007/s12649-020-01010-8>.
- Morelli Venturi, D., Campana, F., Marmottini, F., Costantino, F., Vaccaro, L., 2020. Extensive screening of green solvents for safe and sustainable UiO-66 synthesis. *ACS Sustainable Chem. Eng.* 8, 17154–17164. <https://doi.org/10.1021/acssuschemeng.0c05587>.
- Nascimento, J.E.R., Barcellos, A.M., Sachini, M., Perin, G., Lenardão, E.J., Alves, D., Jacob, R.G., Missau, F., 2011. Catalyst-free synthesis of octahydroacridines using glycerol as recyclable solvent. *Tetrahedron Lett.* 52, 2571–2574. <https://doi.org/10.1016/j.tetlet.2011.03.045>.
- Nascimento, J.E.R., de Oliveira, D.H., Abib, P.B., Alves, D., Perin, G., Jacob, R.G., 2015. Synthesis of 4-arylselanylpyrazoles through cyclocondensation reaction using glycerol as solvent. *J. Braz. Chem. Soc.* 26, 1533–1541. <https://doi.org/10.5935/0103-5053.20150127>.
- Nasseri, M.A., Zakerinasab, B., Kamayestani, S., 2015. Proficient Procedure for preparation of quinoline derivatives catalyzed by NbCl₅ in glycerol as green solvent. *J. Applied Chem.* 2, 1–7. <https://doi.org/10.1155/2015/743094>.
- Nazeef, M., Saquib, M., Tiwari, K., Yadav, V., Ansari, S., 2020. Catalyst free, multicomponent green approach to benzo[a]chromeno[2,3-c]phenazines using glycerol as a recyclable and biodegradable promoting medium. *ChemistrySelect* 5, 14447–14454. <https://doi.org/10.1002/slct.202003732>.
- Nda-Umar, U.I., Ramli, L., Taufiq-Yap, Y.H., Muhammad, E.N., 2019. An overview of recent research in the conversion of glycerol into biofuels, fuel additives and other. *Catalysts* 9, 1–47. <https://doi.org/10.3390/catal9010015>.
- Nemati, F., Hosseini, M.M., Kiani, H., 2016. Glycerol as a green solvent for efficient, one-pot and catalyst free synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives. *J. Saudi Chem. Soc.* 20, S503–S508. <https://doi.org/10.1016/j.jscs.2013.02.004>.
- Nguyen, R., Galy, N., Singh, A., Paulus, F., Stoeber, C., Schlessner, C., Sharma, S.K., Haag, R., Len, C., 2017. A simple and efficient process for large scale glycerol oligomerization by microwave irradiation. *Catalysts* 7, 123–134. <https://doi.org/10.3390/catal7040123>.
- Nguyen, R., Galy, N., Alasmay, F.A., Len, C., 2021. Microwave-assisted continuous flow for the selective oligomerization of glycerol. *Catalysts* 11, 166. <https://doi.org/10.3390/catal11020166>.
- Nongthombam, S.G., Kharmawlong, G.K., Kumar, J.E., Nongkhaw, R., 2018. UV365 light promoted catalyst-free synthesis of pyrimido[4,5-b]quinoline-2,4-diones in aqueous-glycerol medium. *New J. Chem.* 42, 9436–9442. <https://doi.org/10.1039/C8NJ01459K>.
- OECD/FAO OECD-FAO Agricultural Outlook 2022-2031, 2022. OECD Publishing, Paris. ISBN 9789264588707.
- Oliveira, S.S. de S., Fiaux, S.B., Barreto, I.R.L., Muri, E.M.F., Ramos, M. da C.K.V., Aquino Neto, F.R., Dias, L.R.S., 2014. Glycerol as green solvent for efficient obtention of beta-hydroxyesters. *Quim. Nova* 37, 545–548. <https://doi.org/10.5935/0100-4042.20140088>.
- Perin, G., Mello, L.G., Radatz, C.S., Savegnago, L., Alves, D., Jacob, R.G., Lenardão, E.J., 2010. Catalyst-free thioacetalization of carbonyl compounds using glycerol as recyclable solvent. *Tetrahedron Lett.* 51, 4354–4356. <https://doi.org/10.1016/j.tetlet.2010.06.049>.
- Perin, G., Mesquita, K., Calheiro, T.P., Silva, M.S., Lenardão, E.J., Alves, D., Jacob, R.G., 2014. Synthesis of β -aryl- β -sulfanyl ketones by a sequential one-pot reaction using KF/Al₂O₃ in glycerol. *Synth. Commun.* 44, 49–58. <https://doi.org/10.1080/00397911.2013.788720>.
- Pinto, J.R.M., Ribeiro, M.G.T.C., Machado, A.A.S.C., 2019. The solvent challenge in synthesis –The workup as example. *Quim. Nova* 42, 971–982. <https://doi.org/10.21577/0100-4042.20170400>.
- Quaglia, G., Campana, F., Latterini, L., Vaccaro, L., 2022. Green solvent selection for green-to-blue upconversion based on TTA. *ACS Sustainable Chem. Eng.* 10, 9123–9130. <https://doi.org/10.1021/acssuschemeng.2c01948>.
- Quan, Z.J., Ren, R.G., Da, Y.X., Zhang, Z., Wang, X.C., 2011. Glycerol as an alternative green reaction medium for multicomponent reactions using PS-PEG-OSO₃H as catalyst. *Synth. Commun.* 41, 3106–3116. <https://doi.org/10.1080/00397911.2010.517373>.

- Radatz, C.S., Silva, R.B., Perin, G., Lenardao, E.J., Jacob, R.G., Alves, D., 2011. Catalyst-free synthesis of benzodiazepines and benzimidazoles using glycerol as recyclable solvent. *Tetrahedron Lett.* 52, 4132–4136. <https://doi.org/10.1016/j.tetlet.2011.05.142>.
- Rajabi, F., De, S., Luque, R., 2015. An efficient and green synthesis of benzimidazole derivatives using SBA-15 supported cobalt nanocatalysts. *Catal. Lett.* 145, 1566–1570. <https://doi.org/10.1007/s10562-015-1546-z>.
- Ramesh, R., Nagasundaram, N., Meignanasundar, D., Vadivel, P., Lalitha, A., 2017. Glycerol assisted eco-friendly strategy for the facile synthesis of 4,4'-(arylmethylene)bis(3-methyl-1H-pyrazol-5-ols) and 2-aryl-2,3-dihydroquinazolin-4(1H)-ones under catalyst-free conditions. *Res. Chem. Intermed.* 43, 1767–1782. <https://doi.org/10.1007/s11164-016-2728-z>.
- Ravichandiran, P., Gu, Y., 2017. Glycerol as eco-efficient solvent for organic transformations. In: Jérôme, F., Luque, R. (Eds.), *Bio-based Solvents*, pp. 1–28.
- Reina, A., Pradel, C., Martin, E., Teuma, E., Gómez, M., 2016. Palladium nanoparticles stabilised by cinchona-based alkaloids in glycerol: efficient catalysts for surface assisted processes. *RSC Adv.* 6, 93205–93216. <https://doi.org/10.1039/C6RA19230K>.
- Ricordi, V.G., Freitas, C.S., Perin, G., Lenardao, E.J., Jacob, R.G., Savegnago, L., Alves, D., 2012. Glycerol as a recyclable solvent for copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids. *Green Chem.* 14, 1030–1034. <https://doi.org/10.1039/c2gc16427b>.
- Rodríguez-Rodríguez, M., Gras, E., Pericas, M.A., Gómez, M., 2015. Metal-free intermolecular azide–alkyne cycloaddition promoted by glycerol. *Chem. Eur. J.* 21, 18706–18710. <https://doi.org/10.1002/chem.201503858>.
- Rosholm, T., Gois, P.M.P., Franzen, R., Candeias, N.R., 2015. Glycerol as an efficient medium for the petasis borono–Mannich reaction. *ChemistryOpen* 4, 39–46. <https://doi.org/10.1002/open.201402066>.
- Ruiz-Castillo, P., Buchwald, S.L., 2016. Applications of palladium-catalyzed C–N cross-coupling reactions. *Chem. Rev.* 19, 12564–12649. <https://doi.org/10.1021/acs.chemrev.6b00512>.
- Safaei, H.R., Shekouhy, M., Rahmanpur, S., Shirinfeshan, A., 2012. Glycerol as a biodegradable and reusable promoting medium for the catalyst-free one-pot three component synthesis of 4H-pyrans. *Green Chem.* 14, 1696–1704. <https://doi.org/10.1039/c2gc35135h>.
- Santoro, S., Marrochi, A., Lanari, D., Ackermann, L., Vaccaro, L., 2018. Towards sustainable C–H functionalization reactions: the emerging role of bio-based reaction media. *Chem. Eur. J.* 24, 13383–13390. <https://doi.org/10.1002/chem.201801114>.
- Sharma, N., Sharma, A., Shard, A., Kumar, R., Saima, Sinha, A.K., 2011. Pd-catalyzed orthogonal Knoevenagel/Perkin condensation–decarboxylation–Heck/Suzuki sequences: tandem transformations of benzaldehydes into hydroxy-functionalized antidiabetic stilbene–cinnamoyl hybrids and asymmetric distyrylbenzenes. *Chem. Eur. J.* 17, 10350–10356. <https://doi.org/10.1002/chem.201101174>.
- Shekouhy, M., Sarvestani, A.M., Khajeh, S., Khalafi-Nezhad, A., 2015. Glycerol: a more benign and biodegradable promoting medium for catalyst-free one-pot multicomponent synthesis of triazolo[1,2-a]indazole-triones. *RSC Adv.* 5, 63705–63710. <https://doi.org/10.1039/c5ra13805a>.
- Singh, S., Saquib, M., Singh, S.B., Singha, M., Singh, J., 2015. Catalyst free, multicomponent-tandem synthesis of spiroindole-indazolones and spirooxindole-pyrazolines: a glycerol mediated green approach. *RSC Adv.* 5, 45152–45157. <https://doi.org/10.1039/c5ra02794b>.
- Singh, S., Saquib, M., Singh, M., Tiwari, J., Tufail, F., Singh, J., Singh, J., 2016. Catalyst free, multicomponent-tandem facile synthesis of pyrido [2, 3-d]pyrimidines using glycerol as a recyclable promoting media. *New J. Chem.* 40, 63–67. <https://doi.org/10.1039/c5nj01938a>.
- Sohal, H.S., Goyal, A., Sharma, R., Khare, R., Kumar, S., 2013. Glycerol mediated, one pot, multicomponent synthesis of dihydropyrano[2,3-c]pyrazoles. *Eur. J. Chem.* 4, 450–453. <https://doi.org/10.5155/eurjchem.4.4.450>.
- Sohal, H.S., Goyal, A., Sharma, R., Khare, R., 2014a. One-pot, multicomponent synthesis of symmetrical Hantzsch 1,4-dihydropyridine derivatives using glycerol as clean and green solvent. *Eur. J. Chem.* 5, 171–175. <https://doi.org/10.5155/eurjchem.5.1.171>.
- Sohal, H.S., Khare, R., Goyal, A., Woolley, A., Singh, K., Sharma, R., 2014b. Multi-component approach for the synthesis of fused dihydropyridines via unsymmetrical Hantzsch condensation using glycerol as green solvent. *Am. J. Chem.* 4, 29–34. <https://doi.org/10.5923/j.chemistry.20140401.04>.
- Taduri, A.K., Babu, P.N.K., Devi, B.R., 2014. Glycerol containing triacetylborate mediated syntheses of novel 2-heterostyryl benzimidazole derivatives: a green approach. *Org. Chem. Int* 2014, 260726. <https://doi.org/10.1155/2014/260726>.
- Tagliapietra, S., Orio, L., Palmisano, G., Penoni, A., Cravotto, G., 2015. Catalysis in glycerol: a survey of recent advances. *Chem. Pap.* 69, 1519–1531. <https://doi.org/10.1515/chempap-2015-0166>.
- Tan, J., Li, M., 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. <https://doi.org/10.1039/b924699a>.
- Tavor, D., Gefen, I., Dlugy, C., Wolfson, A., 2011. Transfer hydrogenations of nitrobenzene using glycerol as solvent and hydrogen donor. *Synthetic Commun* 41, 3409–3416. <https://doi.org/10.1080/00397911.2010.518276>.
- Thurow, S., Webber, R., Perin, G., Lenardao, E.J., Alves, D., 2013. Glycerol/hypophosphorous acid: an efficient system solvent-reducing agent for the synthesis of 2-organylselanyl pyridines. *Tetrahedron Lett.* 54, 3215–3218. <https://doi.org/10.1016/j.tetlet.2013.04.057>.
- Thurow, S., Penteado, F., Perin, G., Jacob, R.G., Alves, D., Lenardao, E.J., 2014. Metal and base-free synthesis of arylselanyl anilines using glycerol as a solvent. *Green Chem.* 16, 3854–3859. <https://doi.org/10.1039/c4gc00874j>.
- Tiwari, J., Singh, S., Tufail, F., Jaiswal, D., Singh, J., Singh, J., 2018. Glycerol micellar catalysis: an efficient multicomponent-tandem green synthetic approach to biologically important 2,4-disubstituted thiazole derivatives. *ChemistrySelect* 3, 11634–11642. <https://doi.org/10.1002/slct.201802511>.
- Tiwari, S.K., Shivhare, K.N., Patel, M.K., Yadav, V., Siddiqui, I.R., 2020. A metal free, Hantzsch synthesis for privileged scaffold 1, 4-dihydropyridines: a glycerol promoted sustainable protocol. *Polycycl. Aromat. Comp.* 1–13. <https://doi.org/10.1080/10406638.2020.1764988>.
- Valladares-Diestra, K., Vandenberghhe, L.P.D.S., Soccol, C.R., 2020. Oilseed enzymatic pretreatment for efficient oil recovery in biodiesel production industry: a review. *Bioenergy Res* 13, 1016–1030. <https://doi.org/10.1007/s12155-020-10132-9>.
- Venkateswarlu, K., 2021. Ashes from organic waste as reagents in synthetic chemistry: a review. *Environ. Chem. Lett.* 19, 3887–3950. <https://doi.org/10.1007/s10311-021-01253-4>.
- Vidal, C., García-Álvarez, J., 2014. Glycerol: a biorenewable solvent for base-free Cu(I)-catalyzed 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes. Highly efficient transformations and catalyst recycling. *Green Chem.* 16, 3515–3521. <https://doi.org/10.1039/c4gc00451e>.
- Wolfson, A., Snezhko, A., Meyouhas, T., Tavor, D., 2012. Glycerol derivatives as green reaction mediums. *Green Chem. Lett. Rev.* 5, 7–12. <https://doi.org/10.1080/17518253.2011.572298>.
- Yusoff, M.N.A.M., Zulkifli, N.W.M., Sukiman, N.L., Chyuan, O.H., Hassan, M.H., Hasnul, M.H., Zulkifli, M.S.A., Abbas, M.M., Zakaria, M.Z., 2021. Sustainability of palm biodiesel in transportation: a review on biofuel standard, policy and international collaboration between Malaysia and Colombia. *Bioenergy Res* 14, 43–60. <https://doi.org/10.1007/s12155-020-10165-0>.
- Zhou, W.J., Zhang, X.Z., Sun, X.B., Wang, B., Wang, J.X., Bai, L., 2013. Microwave assisted synthesis of quinoxaline derivatives using glycerol as a green solvent. *Russ. Chem. Bull.* 62, 1244–1247. <https://doi.org/10.1007/s11172-013-0171-5>.