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Recent Achievements in Organic Reactions in Alcohols

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1.1 Introduction

Almost all manufacturing and processing industries now rely on the extensive use of solvents, and conventional synthesis depends heavily on environmentally incompatible organic solvents [1]. Most often, the solvents used in organic synthesis are volatile, so they can be removed from the reaction mixture by simple evaporation. The widespread use of these volatile organic solvents raises environmental concerns due to their intrinsic properties. With the growing awareness of the impact of solvents on environmental pollution, energy use, on-air quality, and climate change, sustainable solvents are a topic of increasing interest to the science community and the chemical industry [2].

Alcohols are a more desirable class of green solvents used in a wide range of organic reactions. In the last 15 years, alcohols have started to attract attention as alternatives to traditional organic solvents. These alcohols are able to work as solvents in general and include monohydric alcohols (methanol, ethanol, isopropanol, etc.), dihydric alcohols (ethylene glycol), tertiary alcohols (glycerol), fluorinated alcohols (2,2,2-trifluoroethanol [TFE], hexafluoroisopropanol [HFIP]), perfluoro *tert*-butyl alcohol [PFTB]), and polymers (polyethylene glycol [PEG], polypropylene glycol [PPG]), as shown in Scheme 1.1. Alcohols are typical proton-polar solvents and are widely used as inexpensive general solvents. The physical and chemical properties of some alcohols are depicted in Table 1.1 [3].

Nowadays, numerous solvent selection guides have emerged from the pharmaceutical industry, such as those from Pfizer [4], GlaxoSmithKline (GSK) [5], and Sanofi [6]. In this regard, Table 1.2 lists several commonly used alcohols evaluated by selected guidelines in Table 1.2 [2]. As a consequence, most of the several short-chain aliphatic alcohols appear to be the preferred solvents from a green chemistry perspective. High-boiling alcohols, glycerol, PEG, and PPG are also considered green solvents for various reactions. Furthermore, fluorinated alcohols are frequently used as solvents in chemical reactions due to their unique properties.

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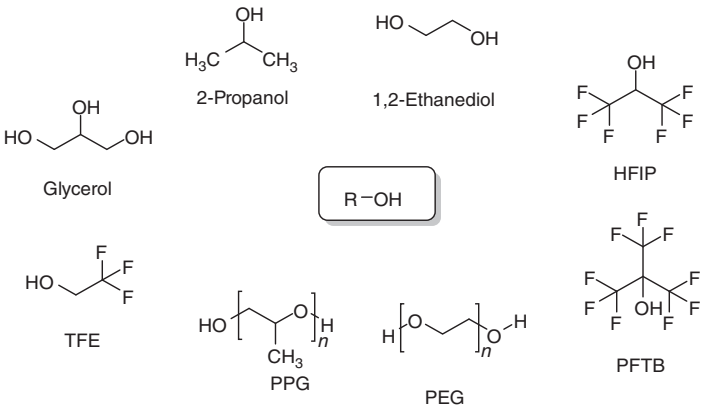


Scheme 1.1 Structure of alcohols.

Table 1.1 Physical and chemical properties of alcohols [3].

Alcohol properties	Methanol	Ethanol	2-propanol	Ethylene glycol	PEG-400	Glycerol	TFE	HFIP
Melting point (°C)	−98	−114	−89.5	−13	64–66	18	−44	−4
boiling point (°C)	65.4	78	82.5	197.6	>250	290	73	58
Relative density (g/mL)	0.791	0.789	0.786	1.113	1.27	1.25	1.391	1.596
Dielectric constant	32.7	24.6	19.9	37.7	—	42.5	24.5	16.7
Dipole moment (D)	1.69	1.7	1.65	2.31	—	2.56	0.61	0.61
Viscosity (mpa·s)	0.59 (20 °C)	1.07 (20 °C)	2.43 (20 °C)	25.66 (16 °C)	—	$1.41*10^3$ (20 °C)	—	—
Flash point (°C)	11.1	12.0	11.7	111.1	270.0	177.0	29.0	4.4
Surface tension (mN/m)	22.7	22.3	22.6	46.5	—	63.4	16.1	14.1
pKa (25 °C)	15.2	15.9	17.1	14.2	—	14.2	12.4	9.3
Polarizability (π^*)	0.63	0.54	0.48	0.92	0.91	1.04	0.73	0.65
Hydrogen-bond donor (α)	0.93	0.83	0.76	0.90	0.31	0.93	1.51	1.96
Hydrogen-bond acceptor (β)	0.62	0.77	0.95	0.52	0.75	0.67	0.18	0.03
Polarity	12.3	8.8	6.1	11.0	—	12.1	10.2	11.8
Hydrogen bonding forces	22.3	19.4	16.4	26.0	—	29.3	—	—

Table 1.2 Guidelines for solvents for common alcohols.

Solvent	Pfizer[a)]	GSK[b)]	Sanofi[c)]
Methanol	Preferred	Some issues	Recommended
Ethanol	Preferred	Some issues	Recommended
1-Propanol	Preferred	Some issues	Recommended
2-propanol	Preferred	Some issues	Recommended
1-Butanol	Preferred	Few issues	Recommended
2-Butanol	–	Few issues	Recommended
tert-Butanol	Preferred	Some issues	Substitution advisable
Ethylene glycol	Usable	–	Substitution advisable
2-Methoxyethanol	–	Major issues	Substitution requested
Benzyl alcohol	–	–	Substitution requested

a) Selection guide by Pfizer.
b) GSK's solvent selection guide.
c) Sanofi's solvent selection guide.

Monohydric alcohols are organic compounds containing one hydroxyl group, including methanol, ethanol, and isopropanol. They are the most commonly used solvents in the thermochemical processing of lignocellulose due to their easy recovery and low cost. These alcohols have similar solvent properties, such as solvent strength, dielectric constant, critical point, and hydrogen supply capacity. They are usually soluble in polar solvents such as water, ether, and acetone but not in non-polar solvents such as petroleum ether. The hydroxyl groups in monohydric alcohol molecules give them polarity and can form hydrogen bonds with other polar molecules, resulting in high boiling points, melting points, and surface tension. These alcohols can be obtained from various sources such as fossil fuels, biomass, and waste. Methanol can be used in the production of other chemicals such as formaldehyde, methyl methacrylate, and dicarboxylic acid. Ethanol has wide applications in pharmaceuticals, beverages, coatings, cosmetics, and spices. Ethanol can be used to produce chemicals such as ethyl acetate, vinyl acetate, and acetaldehyde. Isopropanol can be used to produce plastics, paints, coatings, and solvents. It can also be used to prepare other chemicals, such as acetone and methyl isopropanol. They have low toxicity and are important clean fuels that can replace traditional fuels [1].

Ethylene glycol, a colorless, odorless, relatively non-volatile, low hygroscopic, and low-viscosity liquid, is the simplest representative of 1,2-diols. Owing to its unique structure, that is, two hydroxyl groups (OH) at adjacent positions along the hydrocarbon chain, allows it to engage in reactions such as esterification, dehydration, oxidation, and halogenation. In terms of solubility, ethylene glycol is completely miscible with numerous polar solvents (such as water, alcohols, glycol ethers, and acetone), but only slightly soluble in nonpolar solvents such as benzene, toluene,

dichloroethane, and chloroform. Other than that, it is difficult to crystallize, but becomes highly viscous supercooled mass that solidifies to deliver a glassy substance upon gradual cooling. With regard to toxicity, ethylene glycol is inherently low in toxicity, but can yield toxic metabolites (Oral-rat LD_{50}: 4700 mg/kg; Oral-mouse LD_{50}: 5500 mg/kg) [7].

Glycerol is a ternary alcohol derived from biomass, which can be obtained from biodiesel production as a coproduct at a low price [8]. It has the same solubility as polar solvents such as water, DMSO, and DMF. In addition, it is immiscible with some common organic solvents such as hydrocarbons, ethers, and esters, which allows the reaction products to be separated by simple liquid–liquid phase extraction when using glycerol as a solvent. Glycerol is nonvolatile at atmospheric pressure and has a high boiling point (290 °C), so the reaction products can be separated using distillation techniques. Compared to most organic solvents, glycerol is a nontoxic (LD_{50} [rat oral] = 12 600 mg/kg), biodegradable, and nonflammable solvent that does not require special handling precautions or storage [9]. Glycerol has a greater polarity value ($\pi^* = 1.04$) than other alcohols, as listed in Table 1. Glycerol molecules contain three hydroxyl groups capable of forming hydrogen bonds with reactants or intermediates. The hydrogen bonding force (29.3) is relatively high compared to other alcohols, as shown in Table 1.1. This strong hydrogen bonding network presumably plays a significant role in facilitating organic synthesis. These characteristics of glycerol render it widely used as an environmentally benign solvent in organic chemistry. In this context, glycerol mainly has four applications in organic reactions: (i) working as a promoting medium for organic synthesis, (ii) serving as a solvent to improve the product selectivity, (iii) enhancing the separation of products, and (iv) facilitating catalyst design and the recovery of catalytic systems. However, there also are some limitations of using glycerol as a solvent. First, its high viscosity can cause poor mass diffusion of the reactants in the medium, eventually leading to reduced reactivity. Second, the three hydroxyl groups of glycerol may provide coordination sites that may cause deactivation of specific organometallic complexes [10].

PEGs are also considered suitable alternatives to conventional organic solvents due to their attractive physicochemical properties (e.g. chemically inert, thermally stable, and nontoxic). In particular, PEGs are stable even at high temperatures up to 150–200 °C. [11]. Low-molecular-weight PEGs, such as PEG-300, have a greater polarity value ($\pi^* = 0.91$) than methanol (0.63) as listed in Table 1.1. The hydrogen bond accepting ability ($\beta = 0.75$) is similar to that of methanol (0.62), while the hydrogen bond donating ability ($\alpha = 0.31$) is less than that of methanol (0.93) [11]. As a hydrophilic oligomer, PEG is readily soluble in water and most organic solvents, such as toluene, methylene chloride, alcohols, and acetone; however, it is insoluble in aliphatic hydrocarbons such as hexane, cyclohexane, or ether. Liquid PEG is proportionally miscible with water, and solid PEG with a higher molecular weight is also extremely soluble in water [12]. For example, PEG-2000 has a solubility of about 20% in water at 60 °C. Water-soluble PEG is considered a cosolvent for organics in water, because it can contribute to a significant reduction in the polarity of aqueous solutions, which can be used as an alternative to other solvents such as ionic liquids,

supercritical carbon dioxide, and micellar systems for reactions such as substitution, reduction, oxidation, and conventional or free-phase transfer catalysts (PTCs). PEGs as linear counterparts of crown ethers, are considered "host" solvents with regard to their ability to coordinate with metal cations to form complexes that transfer such cations from the aqueous phase to the organic phase. In order to remain electrically neutral, the PEG–metal complex has to carry the equivalent anion into the organic phase, enabling the anion to react with the organic reactants, so that PEGs can act as PTCs. Several factors influence the catalytic activity such as PEG molecular weight, chain end effects, and the nature of the relevant cations and anions [13].

In coordination with metals, PEGs have a more flexible structure compared to crown ether. Crown ether metal complexation depends on the size of the crown center cavity (fixed size). Whereas PEGs show a more flexible selectivity in the binding of metal cations of different sizes, as a result of the variation in the PEG helical conformation. Hence, PEG can coordinate metal cations with different sizes. Overall, PEG offers a more flexible structure for metal cation complexation. Besides, PEG complexation can also bring significant cost savings in extraction compared to crown ether complexation [14].

PPG is a viscous liquid with negligible vapor pressure, which is stable under normal reaction conditions and is easily recoverable. The majority of commercially available PPG, in contrast to PEG, has a molecular weight ranging from 250 to 4000 Da and is a viscous liquid. While PPG has an inverse relationship with temperature and solubility, low-molecular-weight PPG-250 Da to PPG-425 Da are soluble in water, and such solubility rapidly decreases as the molecular weight increases. These physical characteristics will restrict the use of PPG as a reaction medium because it is considerably more hydrophobic than PEG [15].

The use of fluorinated solvents as chemical reaction media in place of traditional volatile organic solvents has increased significantly. Fluorinated alcohols have unique physicochemical properties, including lower boiling point, higher melting point, high polarity, high hydrogen bond donor capacity, high ionizing power, and solvation capacity [16]. Among several fluorinated alcohols, the most commonly used and cheapest ones are TFE and HFIP, which have reached commercial scale and are often used as cosolvents, catalysts, or additives in addition reactions, condensation reactions, and ring-opening reactions [17]. Reactions in fluorinated solvents are usually highly selective, with no other effluents, so the product is easily separated and the solvent can be recovered by distillation for reuse. Moreover, due to the weak acidity ($pK_a = 12.4$ for TFE, $pK_a = 9.3$ for HFIP) and strong ionization capacity of fluorinated alcohols, the use of Brønsted or Lewis acids is avoided in the reactions. Due to the low boiling point and low viscosity, reactions complete faster. In addition, fluorinated alcohols have a significant stabilizing effect on cationic substances because of their high polarizability and low nucleophilicity. This highly ionized solvent can stabilize the polarity transition state of the reaction well. Despite these advantages, fluorinated solvents are currently not widely used commercially, probably due to disadvantages such as high cost, environmental persistence, and biological half-life time [3c, 18].

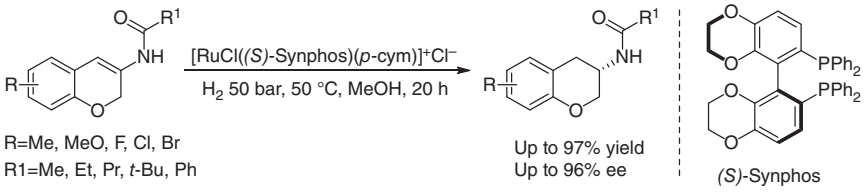
In this chapter, alcohols applied to various organic reactions are introduced in detail according to their roles in organic reactions, mainly including methanol, ethanol, ethylene glycol, glycerol, TFE, HFIP, PFTB, PEG, and PPG. Some alcohols are used not only as solvents but also as catalysts or hydrogen donors, mostly for reduction reactions, coupling reactions, condensation reactions, and some other reactions. In particular, PEG plays an essential role in CO_2 capture and conversion due to its unique properties. In addition, fluorinated alcohols (TFE and PFTB) also have significant applications in ring-opening reactions.

1.2 Alcohols as Green Solvents

Based on Green Chemistry principles, alcohols are less hazardous, and more environmentally benign green solvents, mainly due to their low toxicity, non-flammability, non-mutagenicity, and wider availability. In addition, they are cost-effective, easy to handle, and recyclable [19]. As versatile green solvents, alcohols have applications in many types of reactions, including hydrogenation/reduction reactions, oxidation reactions, substitution reactions, addition reactions, cyclization reactions, coupling reactions, and condensation/ring condensation reactions. The properties of alcohols enable the catalytic system or solvent to be recovered after reaction and reused several times.

1.2.1 Hydrogenation/Reduction Reaction

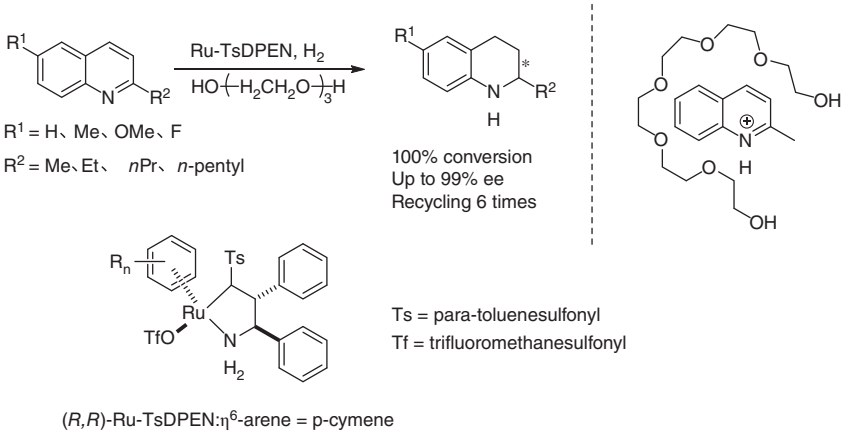
Methanol plays an important role in improving enantioselectivity. The structure derivatives are synthesized through asymmetric hydrogenation in an atomically economical and clean way. Wu et al. successfully achieved the first general and efficient enantioselective Ru-Synphos-catalyzed asymmetric hydrogenation of readily available trisubstituted enamides derived from 3-chromanones (Scheme 1.2) [20]. Polar solvents are found to give higher enantioselectivity than nonpolar solvents, and methanol is the most effective one. This solution is atomically economical and clean, with high chemical yield and enantiomeric excesses up to 96%.



Scheme 1.2 Ruthenium-catalyzed asymmetric hydrogenation of chromanone.

PEG has shown the ability to microregulate fine-tuned reactions via supramolecules, which has been reported in asymmetric hydrogenation reactions and the recycling of chiral metal catalysts, especially as a host molecule participating in

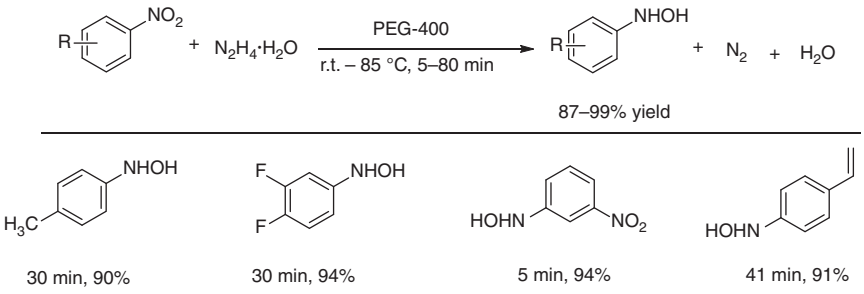
the modification of the reaction outcome. For example, the reaction of quinoline with chiral cationic ruthenium diamine complexes in PEG has been employed in asymmetric hydrogenation reactions (Scheme 1.3) [21]. In oligoethylene glycols (OEGs) and PEGs with different molecular weights, the Ru catalyst loses reactivity giving a wide variation in the reactivity of the hydrogenation reaction, which is mainly attributed to the encapsulation of quinoline salts by PEG or long-chain OEG molecules. The hydrogenation of quinoline is "turned on" by the addition of a small quantity of MeOH.



Scheme 1.3 Asymmetric hydrogenation of quinoline derivatives catalyzed by a chiral cationic Ru catalyst in 3-OEG.

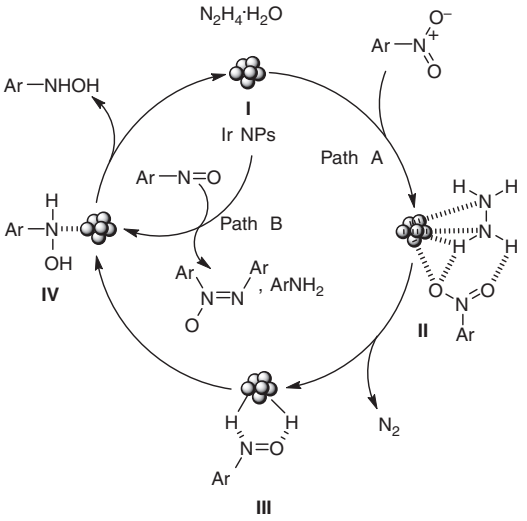
Evidence from mass spectrometry and control experiments indicates that long-chain OEG molecules encapsulating quinoline salts through supramolecular interactions are the main reason for this switchable hydrogenation reaction. In addition, an asymmetric hydrogenation of 2-substituted quinoline derivatives performs in triethylene glycol (3-OEG), resulting in excellent reactivity and enantioselectivity (up to 99% ee) for 1,2,3,4-tetrahydroquinoline. In addition, the Ru catalyst is easily recovered and reused in pure 3-OEG and biphasic 3-OEG/hexane systems without any significant loss of reactivity and enantioselectivity.

Similarly, polystyrene-stabilized iridium (Ir@PS) nanoparticles (NPs) have been developed as a heterogeneous catalyst and characterized by infrared spectroscopy (IR), UV–Vis ultraviolet–visible (UV–Vis), energy dispersive X-ray (EDX), X-ray diffraction (XRD), scanning electron microscope (SEM), and transmission electron microscope (TEM) studies. The developed Ir@PS catalyst exhibits outstanding reactivity for the chemoselective and regioselective controlled hydrogenation of functionalized nitroarenes to the corresponding *N*-arylhydroxylamine, utilizing hydrazine hydrate as the reducing source and PEG-400 as the green solvent (Scheme 1.4) [22]. In this method, a wide range of substrates can be adapted to a wide range of reduction-compatible functional groups. The reactions are conducted at 85 °C or ambient temperature and completed in 5–80 minutes with yields as high as 87–99%. The catalyst can be easily filtered out of the reaction mixture and reused.



Scheme 1.4 *N*-arylhydroxylamine synthesis via transfer hydrogenation reaction in PEG-400.

Based on these results, a rational mechanistic pathway for the semi-hydrogenation of nitroaromatics to *N*-arylhydroxylamines is mapped. Initially, hydrazine hydrate is chemisorbed on the catalyst surface I, which in turn participates in the H-bonding with the nitro group of the substrate via intermediate II. The N—H bond of the hydrazine hydrate might also be weakened and its disintegration into H_2 and N_2 facilitated by the non-covalent interaction between the hydrazine hydrate and the nitroarenes across the catalytic surface. Together with the temporary nitrosoarene intermediate III, the free hydrogen is chemisorbed onto the heterogeneous surface, enabling the transfer hydrogenation process via intermediate IV to produce *N*-arylhydroxylamine as the final product (Scheme 1.5).

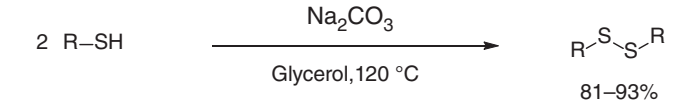


Scheme 1.5 Proposed mechanism for semi-hydrogenation of nitroarenes-catalyzed by Ir@PS in PEG.

1.2.2 Oxidation Reaction

Alcohols have certain applications as green solvents in oxidation reactions. In this context, Jacob et al. developed a method for the dehydrogenation and oxidation

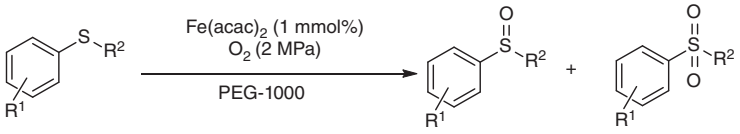
of thiols in glycerol by microwave radiation to obtain the corresponding disulfides (Scheme 1.6) [23]. The reaction is fast with simple work-up procedure. Once the reaction is complete, the product can be obtained by simple extraction; thus, the glycerol can be easily recovered and used for next-run reactions. This method is able to extend to the application of green solvents in oxidation reactions.



R=C_6H_5, CH_2CH_3, $(CH_2)_7CH_3$, $C(CH_3)_3$, 4-$NH_2C_6H_4$, 4-ClC_6H_4, 2-furyl, etc.

Scheme 1.6 Glycerol as a green solvent in the oxidation of thiols to disulfides.

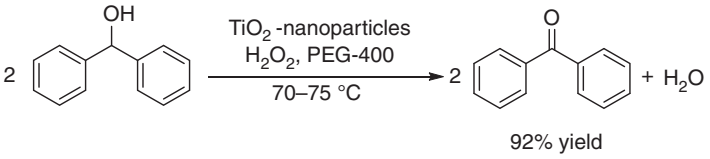
PEG possesses an acyclic polyether with flexible polyethylene oxide chains, which allows it to have an ionic dipole interaction with metal salts that can effectively immobilize and stabilize metal catalysts that can provide a more active oxidant by binding oxygen to the peroxide species. In the highly selective conversion of various aromatic and aliphatic sulfides to the corresponding sulfoxides, an oxidation reaction regime consisting of an inexpensive and easily available $Fe(acac)_2$ as the catalyst and molecular oxygen as an oxidant in PEG is regarded as an effective method for the highly selective oxidation of sulfides to sulfoxides (Scheme 1.7) [24]. High conversions (>99%) and excellent chemoselectivity of up to 94% at 100 °C can be achieved. This protocol represents an environmentally friendly access to sulfonation oxidation with potential economic performance. It is worth noting that PEG-1000 may provide an electron-rich environment, thereby playing a crucial role in stabilizing the *in situ* formation of the Fe (IV)-oxo species, which are believed to be responsible for sulfide oxidation. Therefore, PEG facilitates the sulfide oxidation to sulfoxide.



Scheme 1.7 Selective oxidation of sulfides to sulfoxides in PEG-1000.

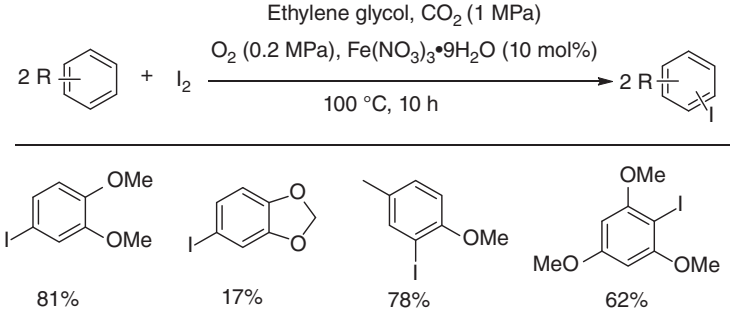
Furthermore, the oxidation of alcohols to carbonyl compounds also is of great importance in synthetic organic chemistry owing to their practical utility in various products such as pharmaceuticals, agrochemicals, and fragrances. The green catalytic regime using heterogeneous nanocrystalline TiO_2(TiO_2-np) as a multiphase catalyst, H_2O_2 as a reagent, and PEG as a green solvent to perform the oxidation of *para*-alcohols to ketones would be a very economical and simple approach to convert *para*-alcohols into the corresponding ketones (Scheme 1.8) [25]. As a result, this protocol is eco-friendly with simple posttreatment and mild reaction

conditions. Over and above this, the reactions are completely clean, consisting of green solvents, green reagents, and catalysts, as well as only water as a by-product.



Scheme 1.8 Model reaction for aromatic alcohol oxidation to ketone using TiO_2 nanoparticles in PEG-400.

Besides, iodoaromatics are recognized as essential synthetic intermediates and precursors in organic transformations that can undergo oxidative addition and are also a widespread component of biologically active molecules, including pesticides and drugs. Given the outstanding and versatile properties of iodoaromatics, efforts have been made to optimize their preparation in the field of scientific research and industrial manufacturing. The high-efficiency iron-catalyzed oxidative iodination of electron-rich aromatics in the presence of oxygen with the aid of an environmentally benign and reversible acidic system of *in situ* acidic carbon dioxide/glycol is a very typical instance (Scheme 1.9) [26]. Notably, in the absence of any conventional acid additives or organic solvents, moderate-to-high isolation yields of aryl iodides (up to 97%) with considerable regioselectivity are obtained when $Fe(NO_3)_3{\cdot}9H_2O$ is used as a catalyst with molecular iodine under 1 MPa CO_2 conditions.

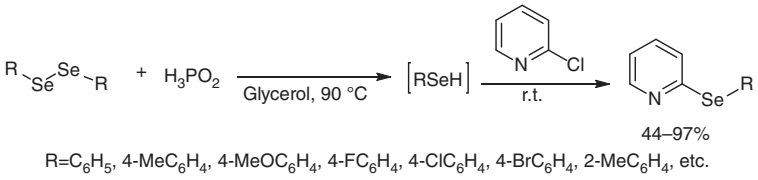


Scheme 1.9 Aerobic oxidative iodination of electron-rich aromatics in ethylene glycol.

1.2.3 Substitution Reaction

Alcohols are also commonly used as green solvents in substitution reactions. For example, the use of glycerol as a solvent and H_3PO_2 as a reducing agent can effectively promote the reaction of 2-chloropyridine with organylselenols generated *in situ* by diorganyl diselenides to afford the corresponding 2-organoselenopyridine, as depicted in Scheme 1.10 [27]. Significantly, the product is easily extracted with hexane/ethyl acetate = 95/5. The glycerol/H_3PO_2 system can be directly recycled

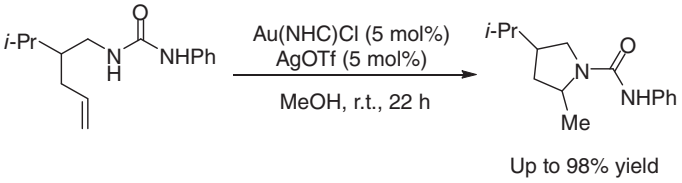
more than four times after drying under vacuum, and no additional reducing agent is needed for the reaction.



Scheme 1.10 An efficient system for the synthesis of 2-organylselanyl pyridines using glycerol/hypophosphoric acid as solvent-reducing agent.

1.2.4 Addition Reaction

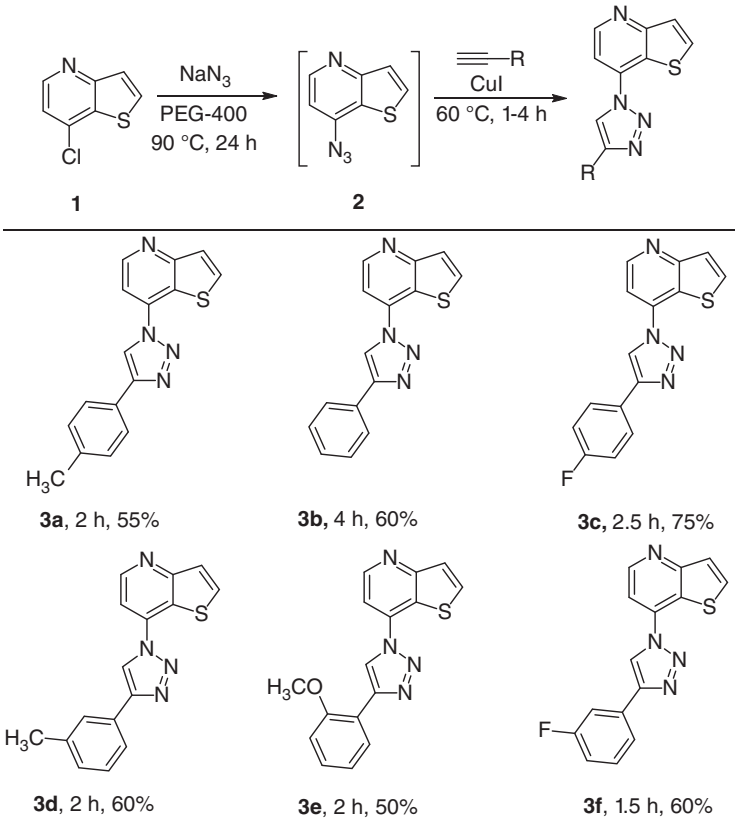
Methanol can significantly increase the reaction rate in the hydrogenation of olefins. A gold(I) carbene complex as a catalyst was first used in the intramolecular *exo*-hydroamination of unactivated alkenes (Scheme 1.11) [28]. The catalyst system has high activity in the external hydroamination of *N*-4-pentenyl or *N*-5-hexenyl urea, forming the corresponding nitrogen-containing heterocyclic ring with excellent yield, good regioselectivity, and 5.5 : 1 non-steroidal selectivity. As for the selection of solvents, experiments show that the hydroamination rate can be increased by two times when dioxane is substituted by methanol.



Scheme 1.11 Room-temperature intramolecular *exo*-hydroamination of *N*-alkenyl urea catalyzed by a gold(I) *N*-heterocyclic carbene complex.

Organic solvents are widely used in various chemical processes and gave rise to several serious environmental challenges. Hence, social and economic needs for sustainable development have prompted the scientific community to explore alternative reaction media for replacing solvents that are volatile, spontaneously combustible, toxic, and difficult to recover. For solving the problems caused by volatile organic solvents, PEG has been subjected to an increasing number of scientific studies in view of the nontoxic and nonhazardous properties, in addition to the fact that the chemical reactions in PEG have different thermodynamic and kinetic behavior than those in conventional solvents. More frequently, PEG is typically employed as a green reaction medium due to its low cost, thermal stability, and biodegradability. For example, in the research and development of antitumor-active drugs, 7-[4-alkyl- and (hetero)aryl-1*H*-1,2,3-triazol-1-yl]thio[3,2-*b*]pyridines **3a-f** are afforded in high yield through the formation of the azide **2** via S_NAr of chlorinated heteroaromatic

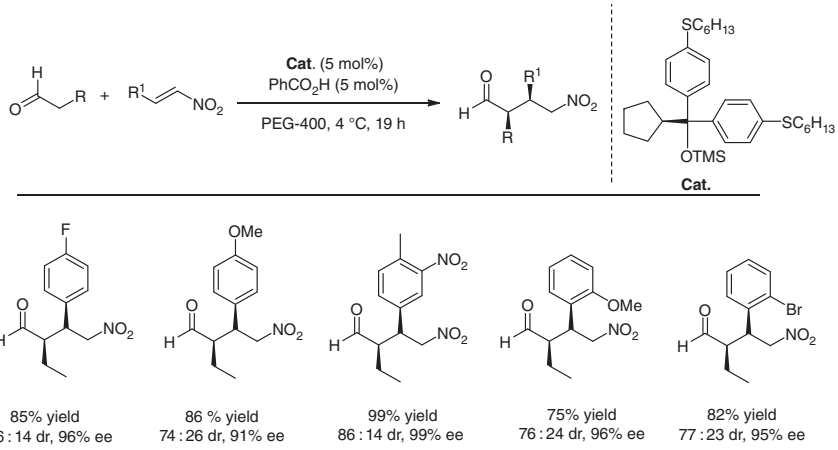
compound **1** with NaN_3, followed by CuAAC reaction with different alkynes in the eco-friendly solvent PEG-400 (Scheme 1.12) [29].



Scheme 1.12 Synthesis of azides from chlorinated heteroaromatic compounds in PEG-400 under the optimal conditions.

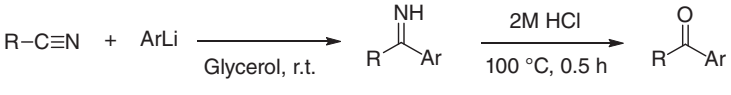
Among all the developed methods, the application of PEG-400 as a recoverable reaction medium in asymmetric organocatalytic Michael addition to trans-β-nitrosostyrene is a good model (Scheme 1.13) [30]. A highly stereoselective organocatalytic Michael addition of aldehydes to trans-β-nitrosostyrene using PEG as a recoverable solvent medium has been proposed, as depicted in Scheme 13. The scope of this organocatalytic system is demonstrated by the formation of several Michael adducts with good yields and stereoselectivity. Furthermore, application of this new scheme to acetaldehyde, simple form syntheses of (*R*)-primethalin, (*R*)-phenibut, and (*R*)-baclofluorene have been disclosed with good yields and excellent enantioselectivity. Faster and higher stereoselective reactions could be achieved compared to other environmentally friendly solvents. This innovative and promising result might be attributed to the host–guest complex, PEG–nitrosostyrene, facilitating the nucleophilic addition of enamines formed from the aldehyde and the organocatalyst. Moreover, it is noteworthy that the PEG is efficiently and

completely recovered and reused after the extraction of the Michael addition product with ether.



Scheme 1.13 Application of PEG-400 in asymmetric organocatalytic Michael addition to trans-β-nitrosostyrene.

In addition to mono- and diols, glycerol can also be utilized as an environmentally friendly reaction medium in addition reaction for the fast and chemically selective addition of aryllithium reagents to nitriles, to access a range of bis(aryl) ketones at room temperature without an inert atmosphere (Scheme 1.14) [31]. The addition reaction occurs under nonhomogeneous conditions due to the insufficient solubility of the nitrile in glycerol. The nonhomogeneous conditions and the intermolecular hydrogen bonding formed by glycerol may be responsible for favoring the successful nucleophilic addition of organolithium reagents to the nitrile rather than competitive hydrolysis. The application of glycerol in organic lithium chemistry has opened a prospect for the development of more sustainable, air- and moisture-resistant, metal-mediated organic synthesis.



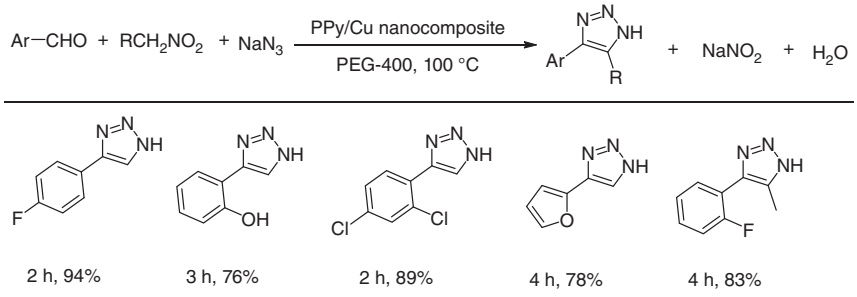
R=Ph, (*m*-Me)C_6H_4, (*o*-Me)C_6H_4, (*o*-F)C_6H_4, (*p*-OMe)C_6H_4, (*p*-Br)C_6H_4, *n*-hexyl, etc.
Ar=(*m*-Me)C_6H_4, (*m*-F)C_6H_4, (*o*-OMe)C_6H_4, [3,5-$(CF_3)_2$]C_6H_3

Scheme 1.14 Synthesis of aromatic ketones by chemically selective addition of aryl lithium reagents to nitriles.

1.2.5 Cyclization Reaction

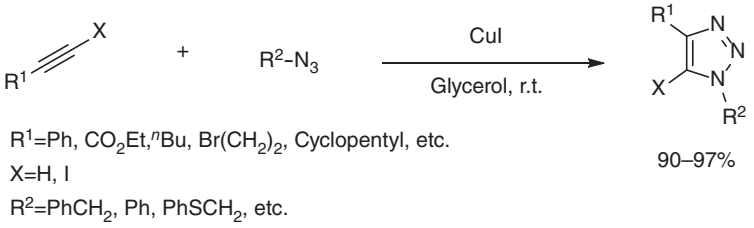
Alcohols are widely used as green solvents in cyclization reactions, including ethylene glycol, PEG, glycerol, and TFE.

These reactions are grouped into numerous biologically essential compounds such as anticancer, anti-HIV, antibacterial, antimicrobial, and antiallergic drug molecules. For instance, 4-aryl-NH-1,2,3-triazoles, which belong to the group of 1,2,3-triazoles, have gained considerable attention in the field of pharmaceutical industry. Taking the synthesis of polypyrrole (PPy)/Cu(II) nanocomposite as an efficient multiphase catalyst for the synthesis of 4-aryl-NH-1,2,3-triazole as an example, the catalyst together with the solvent PEG-400 can be easily recovered and reused for four consecutive cycles, thus maintaining the consistency of catalytic activity (Scheme 1.15) [32].



Scheme 1.15 Application of polypyrrole/Cu(II) in the synthesis of 4-aryl-NH-2,3,4-triazoles in PEG-400.

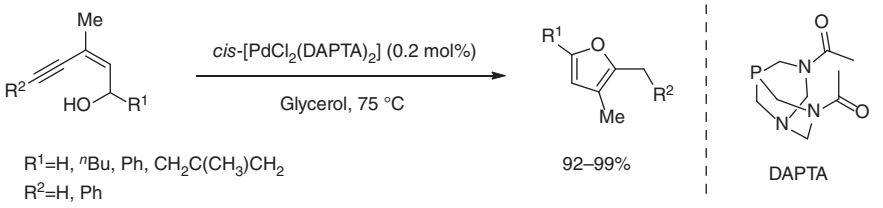
Similarly, the combination of CuI and glycerol for the 1,3-dipole cycloaddition reaction of azides with terminal and 1-iodoalkynes also exhibits versatile and high catalytic activity (Scheme 1.16) [33]. This catalytic system is the first example of the copper-catalyzed 1,3-dipolar cycloaddition reaction carried out in pure glycerol as a solvent. The catalytic system CuI–glycerol can be recycled up to six consecutive runs, and the product can be directly separated through simple filtration.



Scheme 1.16 Base-free Cu(I)-catalyzed 1, 3-dipolar cycloaddition of azides with terminal alkyne or 1-iodoalkynes.

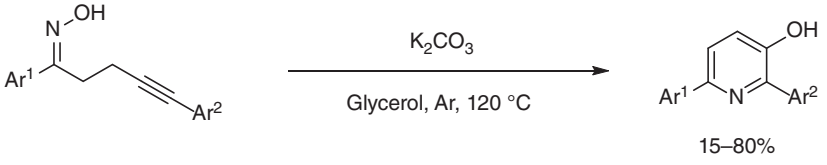
The construction of furan rings has gained much attention as it is widely found in natural products. Among them, the ring isomerization of (*Z*)-alkynol has been considered an effective method to synthesize furan rings. In glycerol, hydrophilic palladium(II) *cis*-$[PdCl_2(DAPTA)_2]$ can effectively promote the metal-catalyzed cycloisomerization of (*Z*) -2-en-4-yn-1-ol derivatives to form corresponding furan compounds (Scheme 1.17) [34]. Although the yield in water is higher, glycerol as

solvent is more conducive to the recovery and reuse of the catalyst. With water as the solvent, the activity of the catalyst decreases rapidly with successive reactions and can be recycled up to five times. With glycerol as the solvent, the system can be recycled up to 17 times, and its cumulative conversion number (TON) reached up to 8190. Notably, the high boiling point of glycerol makes product separation easier by Kügelrohr distillation of the crude reaction mixtures, thus avoiding the use of organic solvents.



Scheme 1.17 Palladium-catalyzed cycloisomerization of (*Z*)-enynols into furans in glycerol.

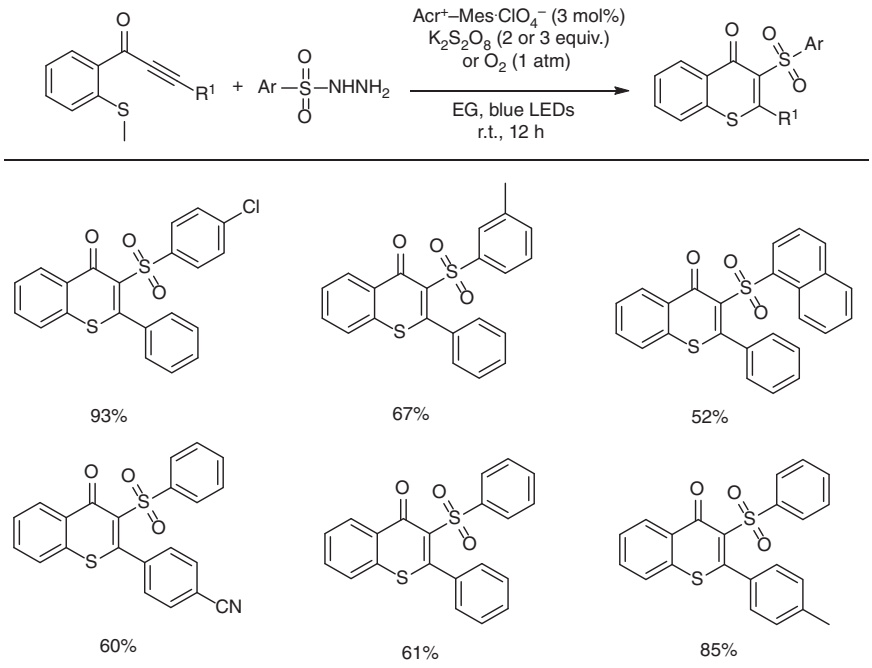
In addition to this, K_2CO_3-mediated cyclization and [1,3] rearrangement reaction of γ,δ-alkynyl oximes for the synthesis of 3-hydroxylpyridines was described by Guan and coworkers (Scheme 1.18) [35]. The reaction proceeds through nucleophilic addition of oximes onto alkynes, followed by [1,3] rearrangements of *o*-vinyl oxime intermediates to form pyridols under mild conditions. The reaction works best when the high boiling point proton solvent such as glycerol is used. This process does not require the use of either a transition metal or a stoichiometric amount of oxidant, which makes it an environmentally friendly complement to the existing strategies.



Scheme 1.18 K_2CO_3-mediated cyclization and rearrangement to form pyridols.

Sulfonyl-containing compounds play an overwhelming role in pharmaceuticals, agrochemicals, and materials science. In this context, cascade sulfonation/cyclization reactions triggered by sulfonyl radicals are one of the most promising strategies for constructing valuable heterocyclic scaffolds and introducing sulfonyl groups simultaneously. For this purpose, a versatile and practical photocatalytic system has been developed to conduct various cascade sulfonation/cyclization reactions using ethylene glycol as a unique green medium (Scheme 1.19) [36]. Through this versatile transition metal-free process, sulfone-containing heterocycles, including thioflavones, oxindoles, and quinoline-2,4(1*H*, 3*H*)-diones, are successfully constructed by irradiation with blue light in room temperature. It is

intriguing to note that ethylene glycol might be critical for the stability of the ionic intermediates in the reaction.

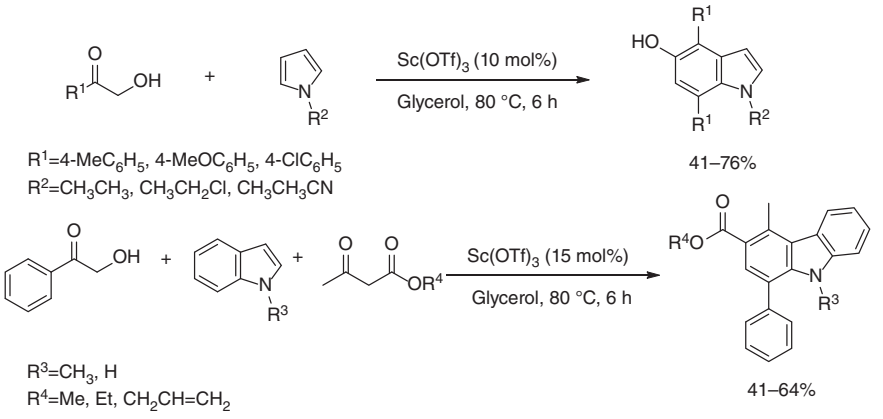


Scheme 1.19 Application of ethylene glycol in visible-light-promoted aerobic transition metal-free cascade sulfonation/cyclization reaction.

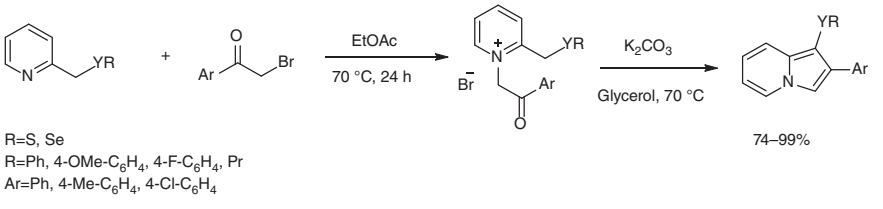
Recently, Gu and coworkers developed the $Sc(OTf)_3$-catalyzed [4 + 2] annulation reaction of α-hydroxyacetophenone, the oxidative depolymerization products of lignin, with pyrrole or indole for the synthesis of indole and carbazole derivatives (Scheme 1.20) [37]. The reaction was carried out in the green solvent glycerol with moderate-to-excellent yields, and the use of glycerol is conducive to the separation of the products and the recycling of the $Sc(OTf)_3$ catalyst. Intriguingly, both the solvent and catalyst can be recovered and reused, and high catalytic activity is maintained at least eight times.

Taking advantage of the solubility of glycerol, Lenardao et al. prepared a variety of 1-sulfanylindolizines and 1-selanylindolizines by means of readily prepared chalcogen-containing pyridinium salts (Scheme 1.21) [38]. The intramolecular cyclization of pyridinium salt uses glycerol as a cost-effective and green solvent, which can effectively promote the reaction medium by dissolving the whole substrate.

TFE is commonly utilized as solvent in cycloaddition reactions. TFE shows a booster effect as reaction media and promotes various reactions through the pure solvent effect. An expedient and clean protocol for the synthesis of the easily separable *trans*/*cis*-octahydroacridines, using substituted aniline and citronellal

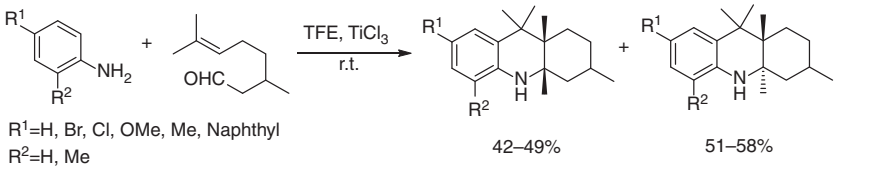


Scheme 1.20 $Sc(OTf)_3$-catalyzed [4 + 2] annulation reaction of α-hydroxyacetophenones with pyrroles or indoles.



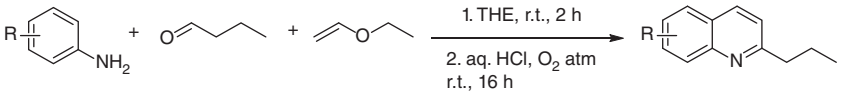
Scheme 1.21 Synthesis of 1-sulfanyl- and 1-selanylindolizines.

catalyzed by $TiCl_3$ in TFE at room temperature, has been reported by Mayekar et al. (Scheme 1.22) [39]. The reaction proceeds via intramolecular Aza–Diels–Alder reaction.



Scheme 1.22 Synthesis of octahydroacridine catalyzed by $TiCl_3$ from substituted aniline and citronellal in TFE.

TFE and HFIP have booster functions as reaction media, and their hydrogen bonding ability has been widely used in the activation of carbonyl functional groups. TFE and HFIP promote various reactions through the pure solvent effect. Propyl quinoline drugs against leishmaniasis have been successfully synthesized. In this study, the Povarov reaction of butyl aldehyde, aromatic amine, and ethyl vinyl ether in TFE, followed by oxidation, provides a convenient pathway for 2-propylquinoline with various substituents (Scheme 1.23) [40].



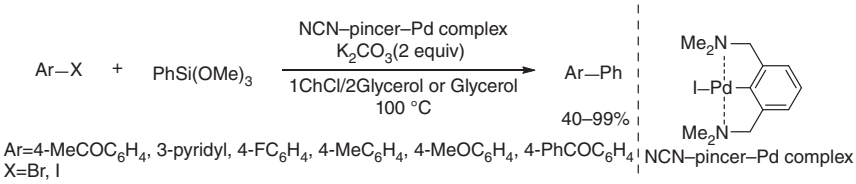
R=H, 6,7-diOMe, 5,8-diOMe, 8-CH$(CH_3)_2$, 5,8-diMe, 5-Me-8-OH, 8-SMe, 5-Cl-8-OH, 5-Cl-8-OMe, 5-Cl, 5-CF_3, 8-CF_3, 1,3-dioxol

Scheme 1.23 One-pot synthesis of 2-propylquinolines from anilines through the Povarov reaction.

1.2.6 Coupling Reaction

In 2006, Wolfson and Dlugy successfully performed palladium-catalyzed Heck and Suzuki C–C coupling reactions in glycerol as the reaction solvent. The target product can be isolated by simple extraction with glycerol-immiscible solvents in high yields, and the catalyst can be recovered [41]. This work clearly demonstrates the feasibility of using glycerol as a solvent, thus paving a new avenue to find greener organic solvents.

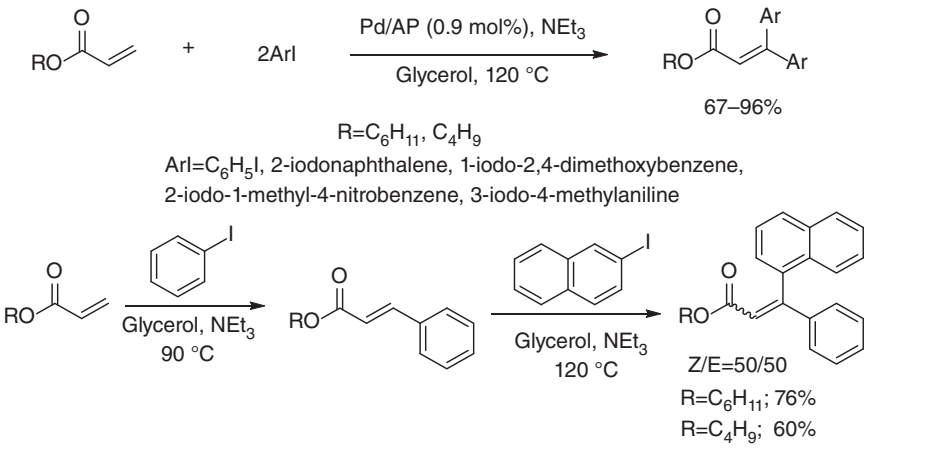
An NCN–pincer–Pd complex has been applied to the Hiyama-type cross-coupling reaction between aryl halides and several organosilanes in a biomass-derived eutectic mixture such as 1 choline chloride (ChCl)/2 glycerol or glycerol (Scheme 1.24). This work is the first report on the use of glycerol as a reaction medium to recover the catalyst in the Hiyama reaction. In addition, the catalytic system can be efficiently used at least three times without the addition of additional catalysts. The corresponding biaryl products can be obtained by simple liquid–liquid extraction with no need for aqueous treatment or chromatographic steps [42].



Ar=4-$MeCOC_6H_4$, 3-pyridyl, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$PhCOC_6H_4$
X=Br, I
NCN–pincer–Pd complex

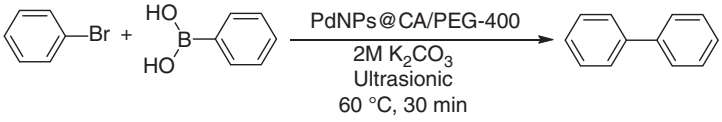
Scheme 1.24 Hiyama-type reaction in neoteric biomass-derived solvents involving glycerol.

Jérôme and coworkers investigated the palladium NP-catalyzed regioselective β, β-diarylation of acrylate derivatives in glycerol (Scheme 1.25) [43]. The palladium NPs are readily prepared by using biomass-derived sugar-based surfactants. Diarylated olefins can be selectively extracted from the glycerol–palladium-catalyzed phase using supercritical carbon dioxide, thus making post-processing more convenient. Interestingly, by adjusting the reaction temperature, the monoarylation and diarylation steps of alkenes can be controlled, providing a convenient route for the synthesis of asymmetric diarylation alkenes. Furthermore, PEG as a solvent in the Mizoroki–Heck coupling reaction has been reported. The use of PEG enhances the activity of the NPs and enables the catalytic system and solvent to be recycled [44].



Scheme 1.25 Symmetrical and unsymmetrical β, β-diarylation of acrylates derivatives.

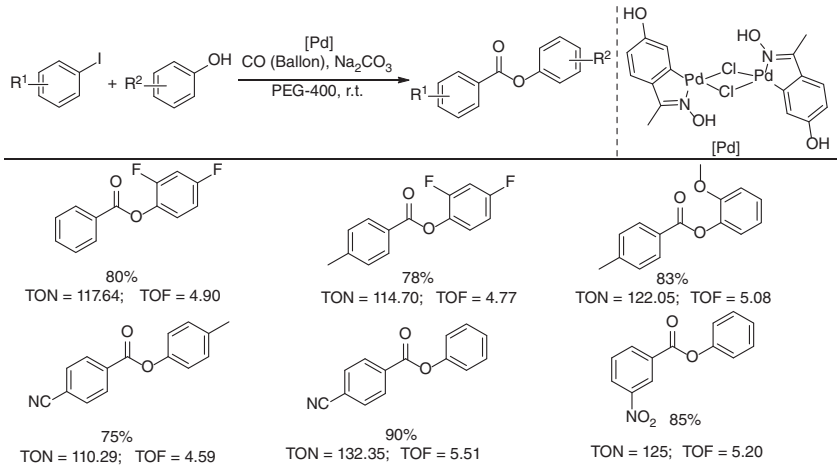
Furthermore, the use of PEG as a green solvent for coupling reactions has also been demonstrated in the synthesis of co-arylated compounds. In this aspect, a solid palladium NP (PdNPs@CA) is prepared from palladium chloride by a novel ultrasonically driven bioreduction method using wasabi extract as a bioreducing agent. In about 30 minutes, aryl halides and aryl boronic acids combine to produce bioaryl compounds with excellent reaction yields (Scheme 1.26) [45]. The results show that the PdNPs@CA could be effectively recovered and reused for seven cycles without loss of catalytic performance using PEG as a green solvent.



Scheme 1.26 Schematic presentation of Suzuki cross-coupling reaction between bromobenzene and phenyl boronic acid catalyzed by PdNPs@CA in PEG-400.

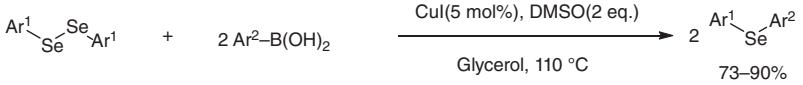
In addition, the synthesis of aromatic esters has been realized by carbonylation using di-μ-chlorobis[5-hydroxy-2-[1-(hydroxyimino-κN)ethyl]phenyl-κC] palladium(II) dimer, a palladacycle as depicted in Scheme 1.27, as a catalyst in PEG-400 with carbon monoxide as the carbonylation reagent [46]. Comparative study of palladacycle with conventional Pd precursors such as $PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$ shows that palladacycle is superior in activity and selectivity, and brings about higher conversion at very low catalyst loading (0.6 mol%) with high TON and TOF. It is feasible to reuse the Pd/PEG-400 system up to a fifth time without loss of activity and selectivity.

Alcohol is not only used in the palladium-catalyzed coupling reactions, but also in copper-catalyzed coupling reactions. In this regard, glycerol has been proved to be a good medium for the CuI-catalyzed reaction of diaryl diselenides with arylboronic acids (Scheme 1.28) [47]. The catalytic system consisting of CuI/glycerol could



Scheme 1.27 Phenoxycarbonylation of aryl iodides with phenols in PEG.

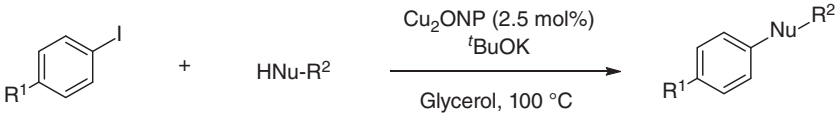
be easily recovered and used for further cross-coupling reactions, maintaining good efficiency levels of 88–86% after three repeated runs. After four runs, the glycerol efficiency is reduced to 71%.



Ar^1=C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-MeC_6H_4, 4-ClC_6H_4, 3-$CF_3C_6H_4$, 2, 4, 6-MeC_6H_2
Ar^2=C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-BrC_6H_4, 2-BrC_6H_4, 3-$CF_3C_6H_4$

Scheme 1.28 Copper-catalyzed cross-coupling reactions of diaryl diselenides with aryl boronic acids.

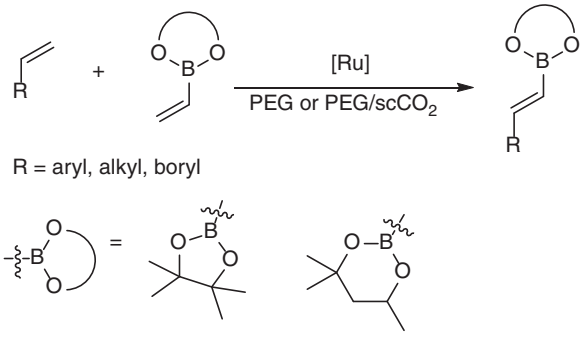
Glycerol is a green solvent to the synthesis of metal NPs and their application in catalysis. For instance, Cu_2O NPs (Cu_2ONP) well coated by poly(vinylpyrrolidone) were prepared in glycerol and applied to C-heteroatom cross-coupling reactions by Gómez et al. (Scheme 1.29). The catalyst system can be reused for 10 cycles without loss of activity and selectivity [48].



R^1=NO_2, OMe
R^2=Cy, *n*-hexyl, *n*-dodecyl,4-MeC_6H_4, H
Nu=NH, S

Scheme 1.29 C−N and C−S bond formation reactions catalyzed by Cu_2ONP in glycerol.

In the same way, alcohols can also be used in ruthenium-catalyzed coupling reactions. Organoboronic compounds, especially unsaturated molecules, such as streptavidinyl borates, are one of the most frequently applied intermediates in modern organic synthesis. Alkenyl boronic esters have been introduced using PEG as a green medium and synthesized via a coupling reaction between vinyl boronate and olefin in the presence of a Ru-based catalyst (Scheme 1.30) [49]. Intriguingly, the hydrogenated ruthenium catalyst [Ru (CO)Cl(H)(PCy_3)$_2$] (2 mol%) is immobilized in a series of PEGs with different molecular weights and end groups, allowing the catalyst and PEG to be recycled 8–10 times with high product yields, catalyst activity, and stability. When the catalyst dosage is doubled, it was possible to successfully acquire 16 cycles. Furthermore, this protocol is suitable for the synthesis of various functionalized alkenyl borates, including bis(boryl)ethylene, with favorable selectivity for electronic isomers. The application of the biphasic catalytic system PEG/$scCO_2$ is found to eliminate aliphatic solvents, especially hexane, which is neurotoxic, from the extraction process and significantly reduce the Ru content in the final product (<0.5 ppm). The high TON values in the PEG-mediated catalytic process hint at the high activity and stability of the catalytic system based on hydrogenated ruthenium complexes. In the single-phase system, the catalyst stability of dimethyl-terminated-PEG-2000 is the best, while in the biphasic boryl coupling reaction, the biphasic PEG-600/$scCO_2$ system and the biphasic PEG-2000/$scCO_2$ system exhibit the best catalyst stability. Thus, the advantages of alkenyl borate synthesis in green solvent PEG are (i) effective catalyst immobilization, (ii) recyclability in subsequent use, (iii) reduced amount of transition metals in the final product mixture, (iv) simplified product isolation procedures, and (v) minimized application of environmentally harmful volatile organic solvents.

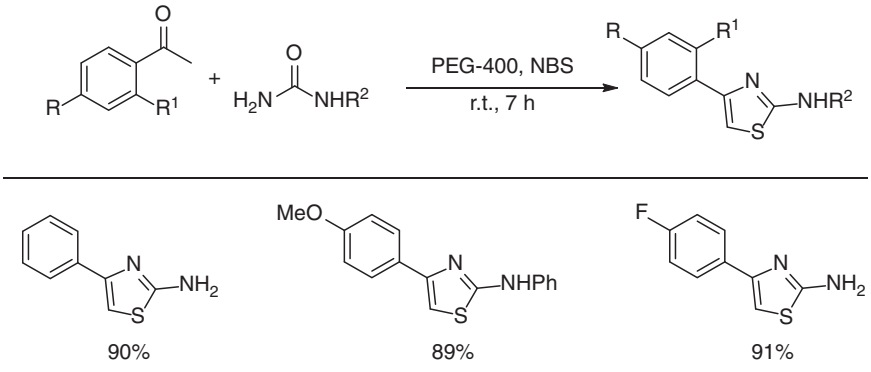


Scheme 1.30 PEG-mediated recyclable borylative coupling of vinyl boronates with olefins.

1.2.7 Condensation/Ring Condensation Reaction

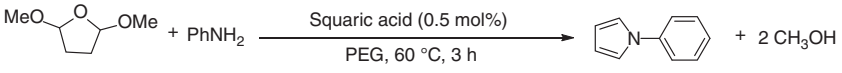
PEG-400 as a solvent for organic transformation has been applied to the reaction of acetophenone, *n*-bromosuccinimide with thiourea or arylthiourea in room temperature to obtain the corresponding 2-aminothiazole derivatives with high yields (Scheme 1.31). The formation of 2-aminothiazole by using PEG-400 might be owing

to the hydrogen bonding between the PEG ether-based oxygen and the sulfur of thiourea (enol form) weakening the S–H bond and enhancing the nucleophilicity of sulfur to the electron-deficient α-carbon in acetophenone. The electropositivity of the acetophenone carbonyl carbon can be strengthened by the formation of hydrogen bonds with the –OH group at the end of PEG-400 [50].



Scheme 1.31 Synthesis of 2-aminothiazoles in PEG-400.

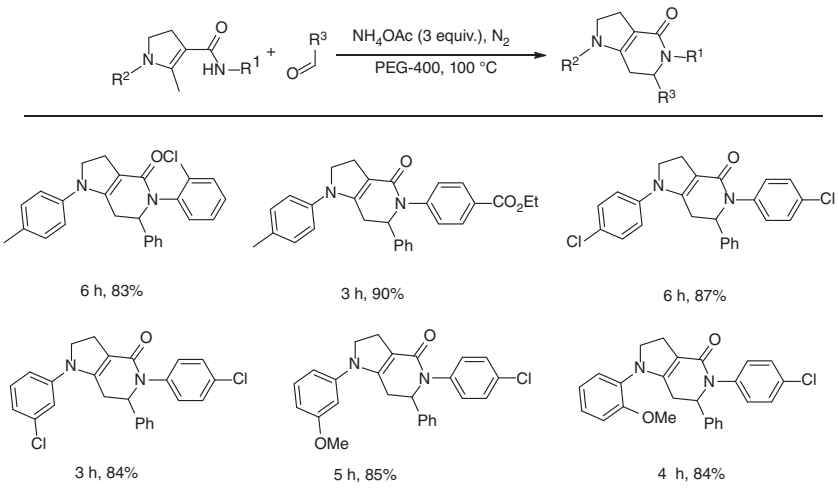
It is no coincidence that heterocyclic pyrrole-containing compounds with pharmacological properties, such as *N*-aryl pyrrole derivatives, are an important class of compounds that have been well prepared using alcohols as reaction media. The synthesis of *N*-substituted pyrroles has been achieved in good-to-excellent yields by the reaction of 2,5-dimethoxytetrahydrofuran and 2,5-hexanedione with arylamines under ultrasonic irradiation or thermal conditions using a PEG green reaction medium (Scheme 1.32) [51].



Scheme 1.32 Synthesis of *N*-arylpyrroles from 2,5-dimethoxytetrahydrofuran in PEG.

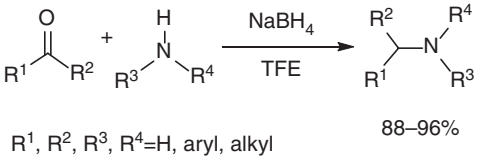
Pyrrolo[3,2-*c*]pyridines, which are important azo-containing heterocyclic compounds with diverse bioactivities, have been constructed through a one-pot process in the green solvent PEG-400 in an eco-friendly and economically feasible manner with a wide range of substrates (Scheme 1.33) [52]. For instance, 2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*] pyridin-4(5*H*)-ones have been synthesized by a one-pot domino condensation reaction in the green solvent PEG-400, with 2-methyl-3-carbamoylpyrroles and aldehydes in the presence of ammonium acetate (3.0 equiv.) as a promoter. This high atomic economy reaction, using readily available starting materials, gives good-to-excellent yields with a wide range of substrates.

TFE is also widely used as a solvent in condensation reactions. A simple and convenient procedure is reported for the high-yielding direct reductive amination of



Scheme 1.33 Ammonium acetate-promoted one-pot tandem aldol condensation/aza-addition reactions in PEG-400.

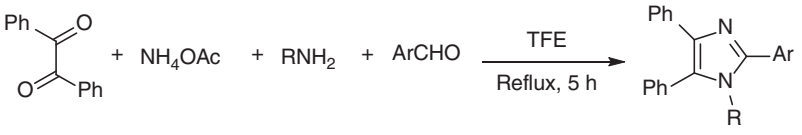
aldehydes and ketones with $NaBH_4$ in TFE (Scheme 1.34). Interestingly, TFE accelerates the amination, which occurs very slowly in ethanol and methanol. Reactions in other solvents such as water, acetonitrile, and tetrahydrofuran (THF) do not yield acceptable product yields even over longer periods of time. Furthermore, TFE can be easily recovered and reused through the distillation process [53].



Scheme 1.34 Reductive amination of aldehydes and ketones.

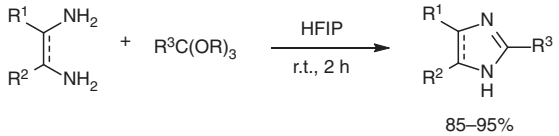
2,3,4-Trisubstituted imidazole derivatives are simply and efficiently synthesized by condensation reaction of aldehyde, benzene, and ammonium acetate with TFE as the solvent (Scheme 1.35). The solution has several attractive features, such as short reaction time, avoidance of catalysts, high chemical selectivity, no side reactions, ease of product separation/purification, and simplicity of process and handling [54].

Similarly, HFIP can also be used as a solvent to synthesize imidazole derivatives by *o*-phenylenediamine and conformal ester (Scheme 1.36). This scheme has the advantages of short reaction time, 85–95% yield, simple operation, direct use of amine, and cost-effectiveness. As strong hydrogen bond donors, HFIP can activate *o*-esters for nucleophilic attacks by the amine group and greatly simplify the separation process. The reusable and nontoxic HFIP media make this method an important alternative to previously reported methods [55].



Ar=C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 4-CNC_6H_4
R=C_6H_5, $CH_2C_6H_5$

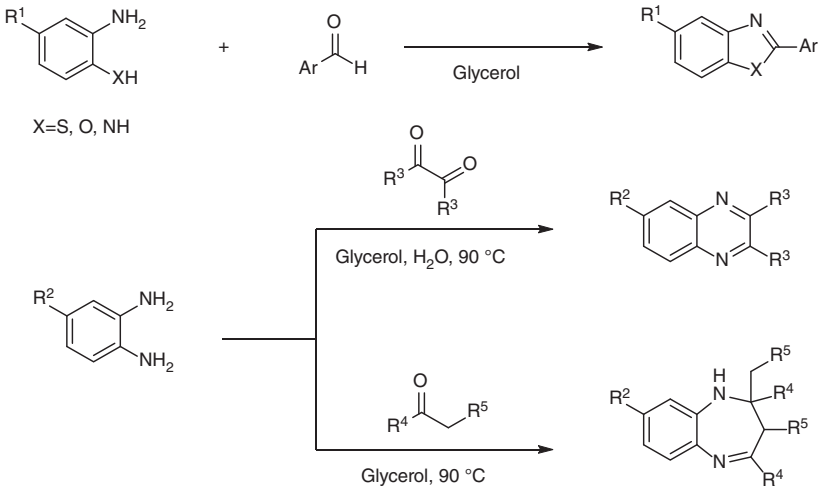
Scheme 1.35 Condensation reaction of benzil, benzaldehyde, and ammonium acetate.



Diamine=*o*-Phenylenediamine, 4-Methyl-*o*-phenylenediamine, 3-Methyl-*o*-phenylenediamine, 4,5-Dimethyl-*o*-phenylenediamine, 4-Chloro-*o*-phenylenediamine
R^3=H, Me, Et

Scheme 1.36 Benzimidazole derivatives were synthesized by reaction of *o*-phenylenediamine with conformal ester in HFIP.

Considering the inherent properties of glycerol, such as high boiling point, unique solubility for polar organic compounds, and the ability to form hydrogen bonds, the direct use of glycerol as a solvent for condensation reactions is consistent with the demand for green chemistry. An efficient and more sustainable catalyst-free method has been developed for the synthesis of benzimidazole, benzothiazole, benzoxazole, quinoxaline, and benzodiazepine heterocyclic compounds in glycerol or glycerol–water system, as depicted in Scheme 1.37 [56]. Aminothiophenol, *o*-aminophenol, or *o*-phenylenediamine can react with aldehydes to produce the corresponding 2-substituted benzothiazole, benzoxazole, and benzimidazole derivatives in good yields, and the reactions are suitable for aromatic, heterocyclic, and unsaturated aldehydes. Under the same reaction conditions, *o*-phenylenediamine can also be condensed with 1,2-dione, or ketones to afford the corresponding quinoxalines and benzodiazepine derivatives in high yields. In particular, glycerol can be reused as a solvent for further condensation reactions, enabling recovery and recycling. The possible reasons for glycerol as a green solvent for this type of condensation reaction are that the high solubility of glycerol for the reactants makes them susceptible to interact with each other, and the carbonyl carbon of the aldehyde is activated due to intermolecular hydrogen bonds formed with the hydroxyl group of glycerol, making them readily reactive. What is more, the intermediate in the reaction can form hydrogen bonds with glycerol to stabilize itself. 2-Arylbenzothiazole can also be synthesized efficiently in PEG-400 as the reaction medium due to the hydrogen bonding between the terminal hydroxyl group of PEG-400 and the substrates [57].



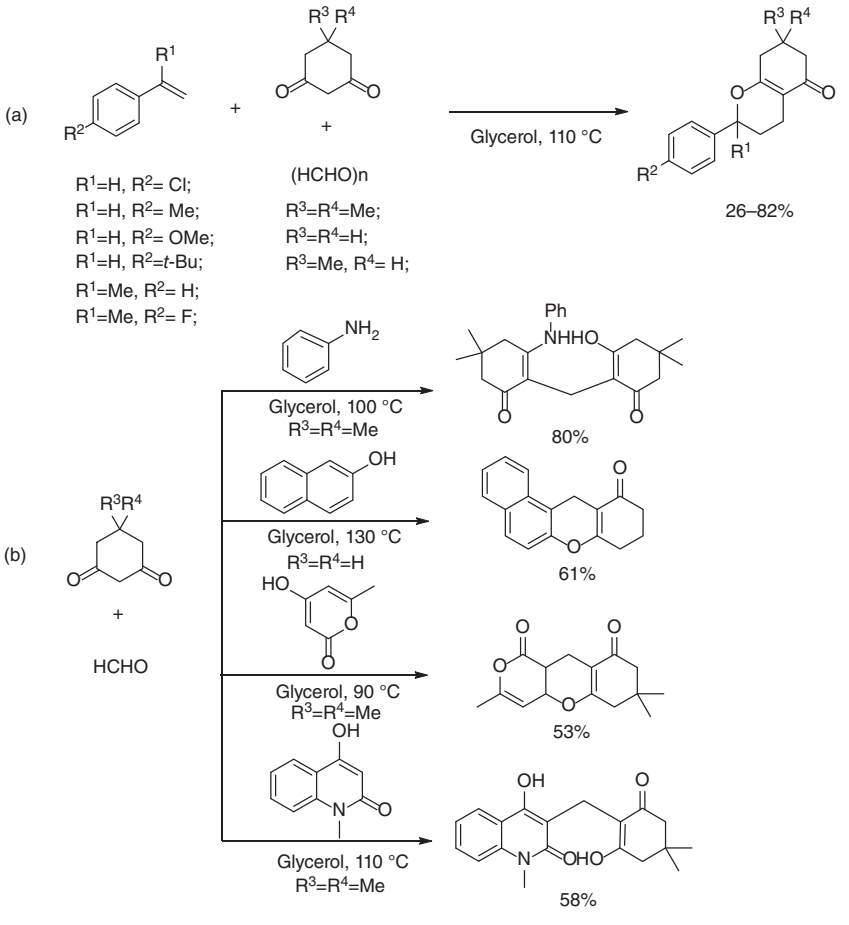
Scheme 1.37 The synthesis of benzimidazole, benzothiazole, benzoxazole, quinoxaline, and benzodiazepine heterocyclic compounds

As shown in Scheme 1.38, Gu and coworkers reported the multicomponent reaction of styrenes with 1,3-cyclohexanediones and paraformaldehyde in glycerol under catalyst-free conditions. This reaction proceeds through a tandem Knoevenagel/hetero-Diels–Alder sequence, where glycerol as a polar proton solvent not only affects the Knoevenagel reaction but also enhances the rate of the Diels–Alder reaction. The recovered glycerol can be reused without significant loss of activity. Furthermore, the method can be extended to other substrates, such as amines, 2-naphthol, 4-hydroxy-6-methyl-2-pyrone, and 4-hydroxy-1-methyl-2-quinolone, which can react with 1,3-cyclohexanediones and paraformaldehyde to yield the corresponding three-component adducts [58].

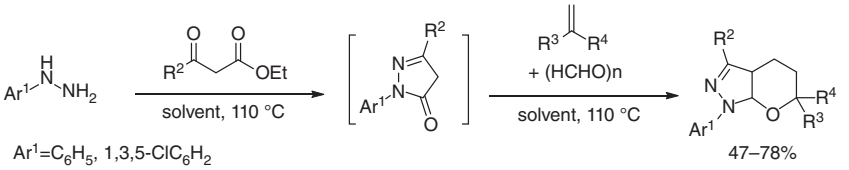
Subsequently, a stepwise one-pot reaction of phenylhydrazines, β-ketone esters, formaldehyde, and styrenes was further developed, as depicted in Scheme 1.39. This multicomponent reaction is carried out in a glycerol or carboxylic acid-functionalized ionic liquid [MIm-CO_2H]BF_4 through a tandem Knoevenagel/hetero-Diels–Alder sequence. Remarkably, glycerol and [MIM-CO_2H]BF_4 could improve the selectivity of the reaction, and pyrano[2,3-*c*]pyrazole derivatives are obtained with good yields [59].

Methanol is also used as a solvent in condensation reactions for the synthesis of 2,5-dihydropyridine skeleton by β-ketone ester and propylamine catalyzed by gold(III) (Scheme 1.40). Methanol has the best effect according to the screening of solvents, which makes the reaction yield up to 91%. The method is simple, universal, and easy to obtain starting materials [60].

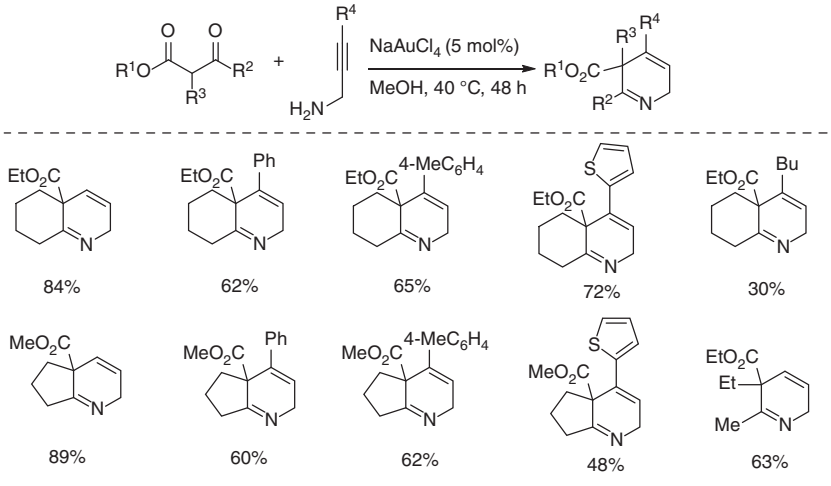
In addition, ethylene glycol has also been reported as a solvent in the synthesis of thiazolopyrimidine derivatives of heterocyclic compounds containing nitrogen and sulfur atoms. The preparation of thiazolopyrimidine–quinoline derivatives by domino reaction in the green solvent ethylene glycol with 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*] pyrimidin-7-one, aromatic aldehydes, and dimeric cyanones as



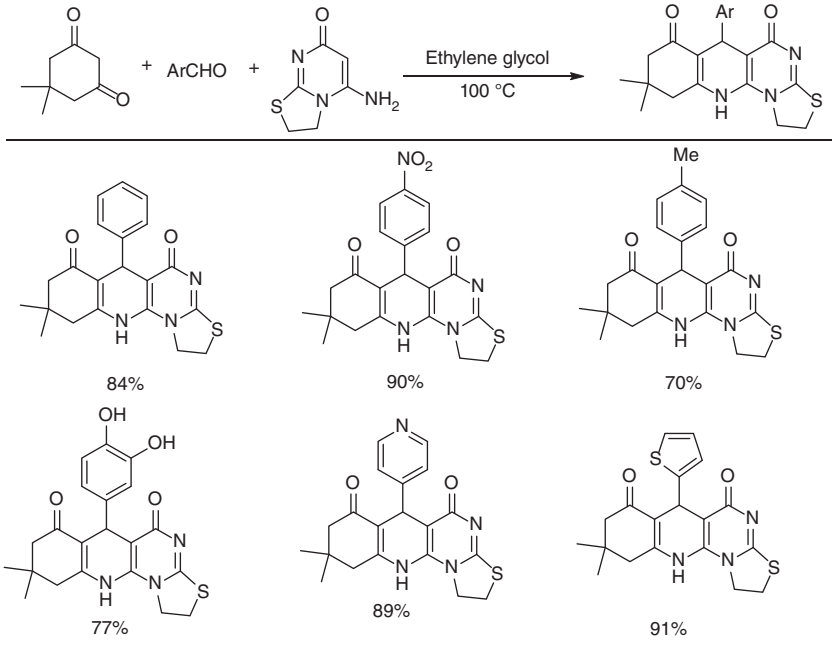
Scheme 1.38 Three-component reactions of 1,3-cyclohexanediones and formaldehyde in glycerol.



Scheme 1.39 Two-step sequential reactions of arylhydrazines, HCHO, β-ketone esters, and styrenes in glycerol.



Scheme 1.40 Synthesis of 2,5-dihydropyridine derivatives by gold-catalyzed reactions of β-ketone ester and propylamine.



Scheme 1.41 One-pot three-component reaction of 5-amino-2,3-dihydro-7*H*-thiazolo [3,2-*a*] pyrimidin-7-one, aromatic aldehyde, and dimedone in ethylene glycol.

reactants is a good example, which has received considerable attention due to its relatively wide application in bioactive molecules. Thiadiazolo[3,2-*a*]pyrimidine is the main heterocyclic core. This scheme with catalyst-free, green solvent, mild reaction conditions, easy handling procedures, and good-to-excellent yields are the significant merits of this scheme (Scheme 1.41) [61].

1.3 Alcohols as Green Solvents and Catalysts

Alcohols can be used not only as solvents but also as catalysts to accelerate the reaction. Alcohol molecules contain hydroxyl groups, which can form hydrogen bonds with reactants or intermediates and participate in reactions, mainly in addition reactions, cyclization reactions, and condensation reactions. In addition, glycerol as the main green solvent and catalyst in alcohols, can also participate in the catalytic cycle of the system as a ligand in the coupling reaction.

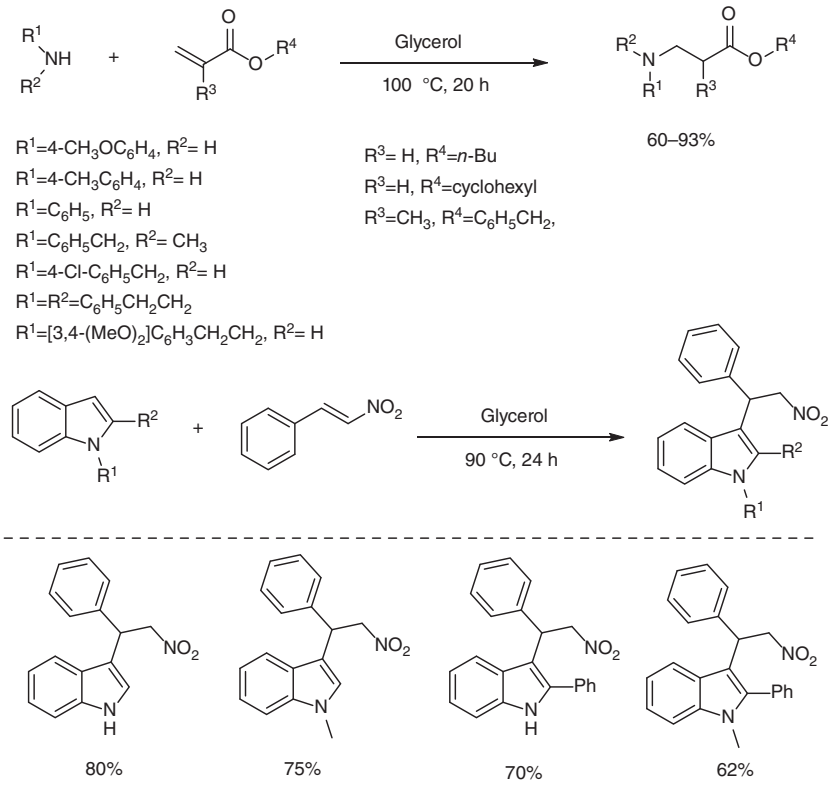
1.3.1 Addition Reaction

Glycerol is able to promote aza-Michael reactions of amines or anilines without the addition of any catalyst, as depicted in Scheme 1.42. Only trace products can be obtained in water or solvent-free conditions, and lots of organic solvents such as toluene, DMF, DMSO, and 1,2-dichloroethane are ineffective for this reaction. This method shows glycerol as a potential catalyst to drive organic conversion, avoiding the use of catalysts, thus simplifying the reaction procedure and improving the greenness of the synthesis method. Similarly, the Michael addition of indoles with nitrite styrene can also be developed in glycerol with a high yield and without a catalyst in Scheme 1.42. In addition, the product separation and recycling of glycerol can be easily realized by simple liquid–liquid phase extraction [62].

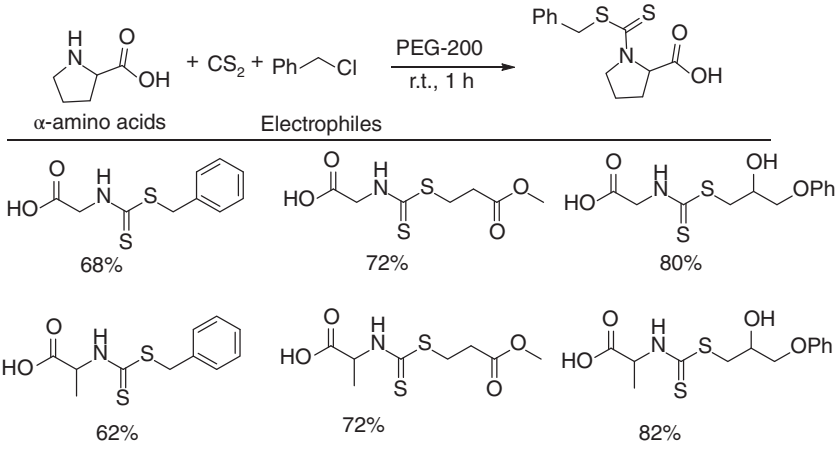
Dithiocarbamates and its derivatives are of great importance in medicinal chemistry with respect to their biological activity. In this way, the green solvent, that is, PEG is considered an emerging alternative to traditional hazardous organic solvents. For example, a one-pot three-component reaction of α-amino acid, carbon disulfide, and an electrophilic reagent, such as alkyl halide performs well in a deep eutectic solvent with PEG as both the catalyst and reaction medium to afford the amino acid-based dithiocarbamates, which are regarded as multifunctional synthetic intermediates (Scheme 1.43) [63]. The dithiocarbamate then reacts with epoxides, alkyl halides, and α,β-unsaturated alkenones by addition at room temperature to obtain products in 62–92% yields with short reaction times and without tedious steps. The deep eutectic solvent and PEG can be recovered and reused with no activity and reduced yield.

1.3.2 Cyclization Reaction

In the cyclization reactions, the hydroxyl group in the alcohol molecule can be used to stabilize the reaction substrate and intermediate, thus accelerating the



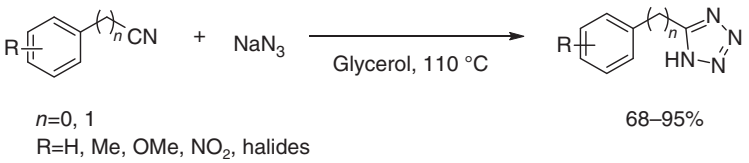
Scheme 1.42 Michael reactions of amines, anilines, and indoles with α,β-unsaturated compounds in glycerol under catalyst-free conditions.



Scheme 1.43 Synthesis of amino acid-based dithiocarbamate by a three-component reaction with PEG as catalyst and reaction medium.

reaction process. Among these alcohols, glycerol is widely used in cyclization reactions because of its high boiling point and nonvolatile properties that allow easy separation of reaction products.

Bhosale et al. has developed for the first time the use of glycerol [2,3] in cycloaddition reaction from organic nitriles and sodium azide under catalyst-free conditions to efficiently furnish 5-substituted 1*H*-tetrazoles (Scheme 1.44) [64]. Interestingly, glycerol enhances the reaction rate by forming intramolecular hydrogen bonds with the nitrile and intermediates, and facilitates subsequent product separation.



Scheme 1.44 Glycerol-mediated synthesis of 5-substituted 1*H*-tetrazole.

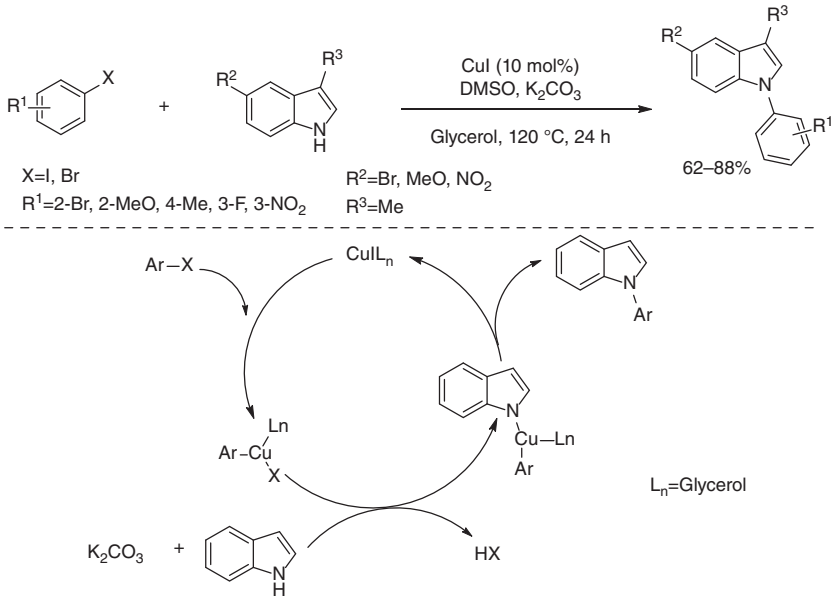
1.3.3 Coupling Reaction

The main application of glycerol as a catalyst and green solvent in coupling reactions is as a ligand or activating metal catalyst. For example, the copper-catalyzed cross-coupling reaction of indole and aryl halides with glycerol as a green recyclable solvent and dimethyl sulfoxide as an additive was reported by Bhanage et al. as depicted in Scheme 1.45 [65]. In this aspect, glycerol acts as a ligand in this coupling reaction and participates in the catalytic cycle. Moreover, glycerol in this reaction might act as a ligand to coordinate with Cu(I) and undergo oxidative addition to aryl halides, and then dehalogenation and reductive elimination of the oxidative addition product to obtain *n*-arylated indoles.

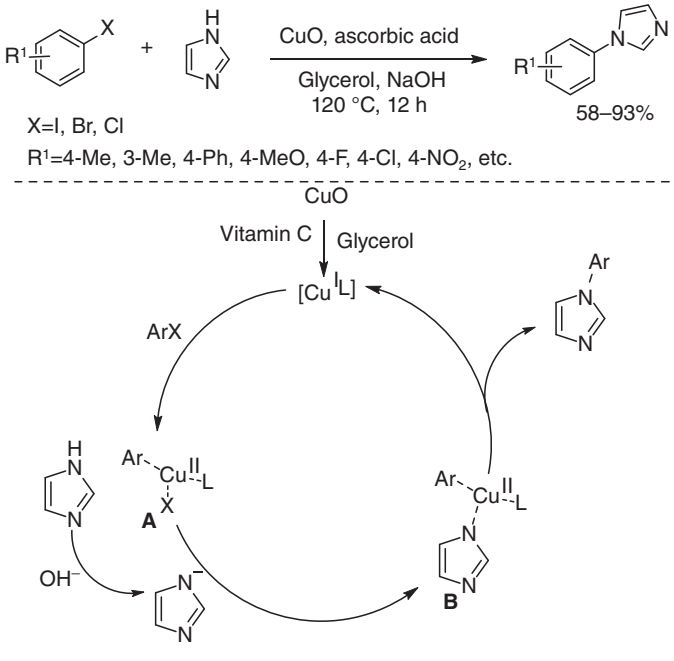
Recently, the "CuO/vitamin C and glycerol"-promoted reaction of aryl halides and imidazoles for the synthesis of *N*-arylation imidazole derivatives has been reported (Scheme 1.46) [66]. Simple and mild conditions render this reaction to be scaled up to the gram scale for the preparation of structurally diverse *N*-arylation products. In this reaction, glycerol serves not only as the solvent but also activates CuO. A possible mechanism is proposed based on controlled experiments, after the coordination of vitamin C with CuO to $[Cu^{I}L]$ in the presence of glycerol, $[Cu^{I}L]$ reacts with ArX to form intermediate A by oxidative addition. Subsequently, intermediate A reacts with imidazole anion to obtain intermediate B and then reduces elimination to generate the target product.

1.3.4 Condensation Reaction

The polar hydroxyl groups in the alcohol molecule able to form hydrogen bonds thus promote the condensation reaction. The hydroxyl groups can form hydrogen bonds with the reactants or intermediates involved in the reaction, thus polarizing them to facilitate nucleophilic reagent attack or to stabilize the intermediates in the



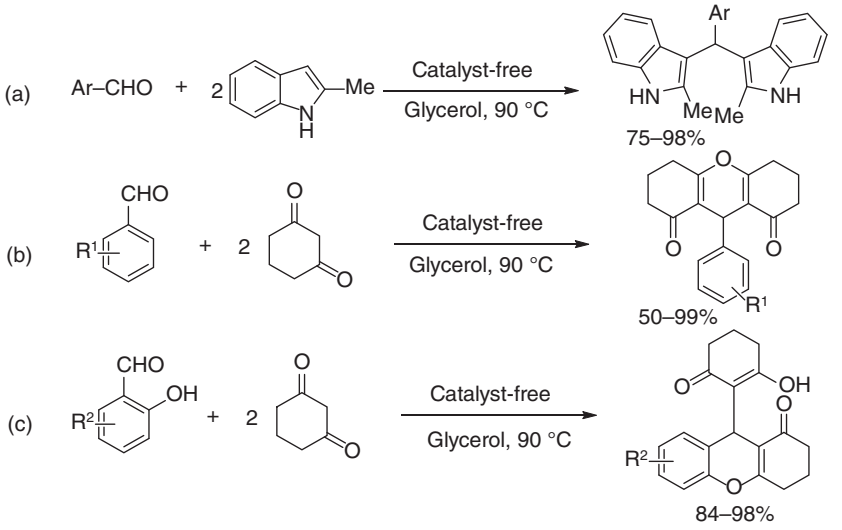
Scheme 1.45 *N*-arylation of indoles with aryl halides using copper/glycerol.



Scheme 1.46 "Vitamin C/glycerol"-promoted copper (II)-catalyzed *N*-arylation of aryl halides and imidazoles.

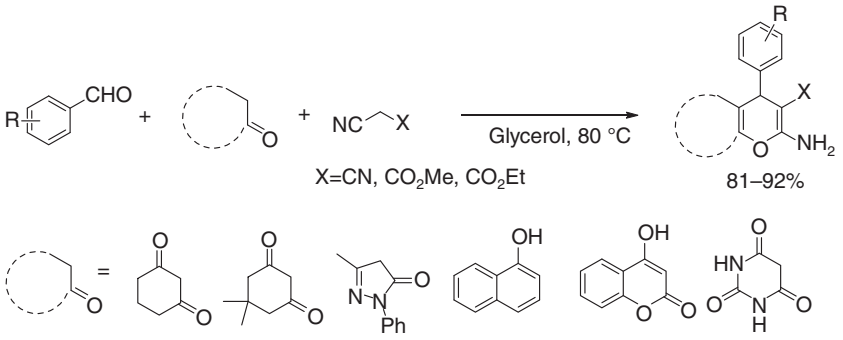
transition state so that the reaction can proceed under mild conditions. In this kind of condensation reaction, aldehydes are the main substrates.

Glycerol, as a green solvent and catalyst, has important applications in the synthesis of a wide range of heterocyclic compounds. In 2009, glycerol was used as a green and effective medium to promote the electrophilic activity of aldehydes. Some condensation reactions of aromatic aldehydes that are usually carried out using acid catalysts could be performed in the presence of glycerol as the reaction medium without the assistance of any catalyst. Many aromatic aldehydes react with indoles or 1,3-cyclohexanediones in glycerol in excellent yields to afford di(indolyl)methane derivatives (Scheme 1.47a), 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(*2H*)-diones (Scheme 1.47b) and 1-oxo-hexahydroxanthenes (Scheme 1.47c), respectively [67].



Scheme 1.47 Catalyst-free synthesis of di(indolyl)methanes, xanthene-1,8(*2H*)-diones, and 1-oxo-hexahydroxanthenes with aldehydes and indole derivatives/1,3-cyclohexanedione.

Pyranoid heterocyclic derivatives are an important class of heterocyclic compounds containing oxygen. Moreover, 4*H*-pyrans are useful intermediates for the synthesis of various compounds. The most direct method of synthesizing these heterocyclic rings is multicomponent coupling currently. However, in most of the reported methods, catalysts are not recyclable. In 2012, a highly efficient catalyst-free one-pot, three-component synthesis of carbonyl compounds, specifically those possessing a reactive α-methylene group, and alkylmalonates, using glycerol as a solvent, was developed to synthesize 4*H*-pyrans in high yields and short reaction times, as shown in Scheme 1.48 [68]. The presence of the reactive –OH groups in the structure of glycerol plays a major role in this reaction. It is speculated that it is the polar amphiphilic hydroxyl group of glycerol that facilitates the interaction of the weakly acidic and basic components, due to the stabilization of the corresponding transition states and intermediates through hydrogen bonding.

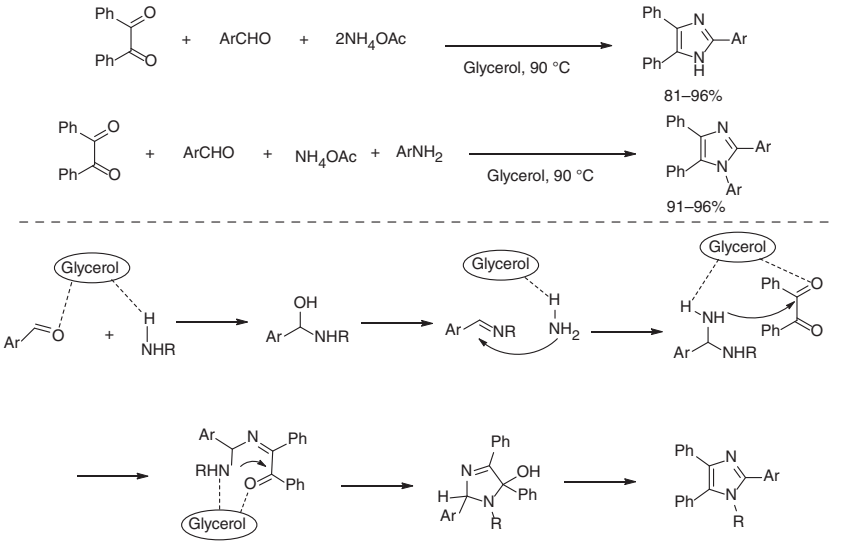


Scheme 1.48 One-pot three-component synthesis of 4*H*-pyrans of carbonyl compounds, carbonyl compounds, and alkylmalonates in glycerol.

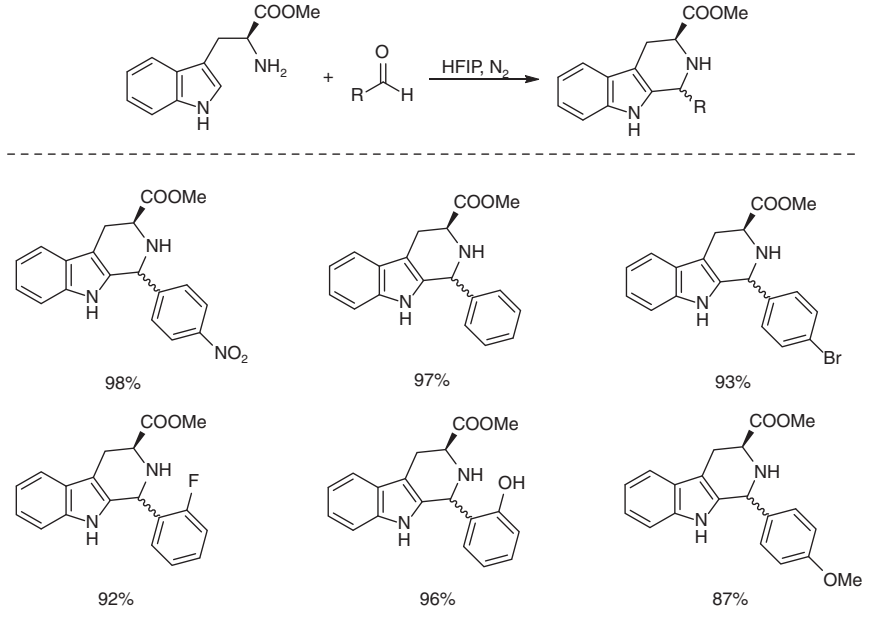
In the same way, a one-pot three-component reaction of aldehydes, malononitrile, and resorcinol or dimedone in TFE without the use of catalysts or any other additives is developed as a novel and efficient regioselective synthesis of 4*H*-pyrans derivatives. The weak Brønsted acidity and strong ionizing power may be relevant to its unique role in this transformation. The polarity effect and hydrogen bond donor ability might not be important in this case. Actually, the hydrogen bond donating ability of these solvents drops as temperature rises owing to the fact that hydrogen-bond formation is exothermic. Although fluorinated alcohols are known to have a remarkable stabilizing effect for cationic species due to their high polarizability and low nucleophilicity, the synthesis of pyrans does not go through a discrete carbocation intermediate. The polar transition state of the reaction could be stabilized well by the high ionizing solvent, TFE. After the reaction, TFE is easily separated by distillation and reused without reducing its activity [69].

Glycerol not only enables high product conversion and selectivity, but also is safe to use. It has a low environmental impact and cost, is easy to separate products, and is reusable. 2,4,5-Triaryl and 1,2,4,5-tetraaryl imidazole derivatives in glycerol via one-pot condensation reaction of benzimidazole with various aldehydes, aromatic primary amines, and ammonium acetate are developed, as shown in Scheme 1.49 [70]. In the absence of glycerol, the reaction proceeds slowly, which indicates that glycerol is an important component of the reaction. This may be due to the intermolecular hydrogen bond formed by glycerol with carbonyl compounds and amines, which activates carbonyl compounds and weakens the N–H bond, enhancing the nucleophilicity of nitrogen.

Interestingly, HFIP can be used as both solvent and catalyst to promote Pictet–Spengler reaction between tryptamine derivatives and aldehydes or active ketones to obtain tetrahydro-β-carbolines in high yields (Scheme 1.50) [71]. It is worth mentioning that HFIP-enhanced Pictet–Spengler reaction avoids the use of Brønsted or Lewis acids. In this reaction, the HFIP can be recovered directly by distillation, leaving the product pure enough for most further transformations. HFIP can be recycled several times. This method is simple to operate and harmless to the environment, which has broad application prospects.

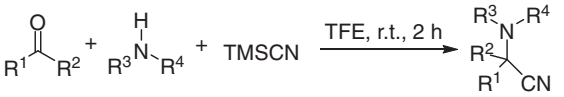


Scheme 1.49 Catalyst-free synthesis of 2,4,5-triaryl and 1,2,4,5-tetraaryl imidazole derivatives in glycerol.



Scheme 1.50 The Pictet–Spengler reactions of L-tryptophan methyl ester and aldehydes.

In addition, the effectiveness of TFE as a reusable catalyst or solvent for the generation of α-amino nitriles has also been explored. Such a scheme uses the one-pot three-component coupling of aldehydes or ketones, amines (primary and secondary), and trimethylsilyl cyanide (TMSCN) using TFE as a reusable solvent (Scheme 1.51) [72]. The main advantage of fluorinated alcohols, such as TFE, is that it can undergo reactions that typically require Lewis acid or catalyst assistance without accelerators. Using TFE as solvent and catalyst can activate $(Boc)_2O$ for tertiary butyl carbonylation of amines and amine derivatives.



R^1=C_6H_5, 4-ClC_6H_4, C_6H_5CH=CH, cyclohexanyl
R^2=H
R^3=C_6H_5, $C_6H_5CH_2$, 4-CNC_6H_4
R^4=H, $C_6H_5CH_2$

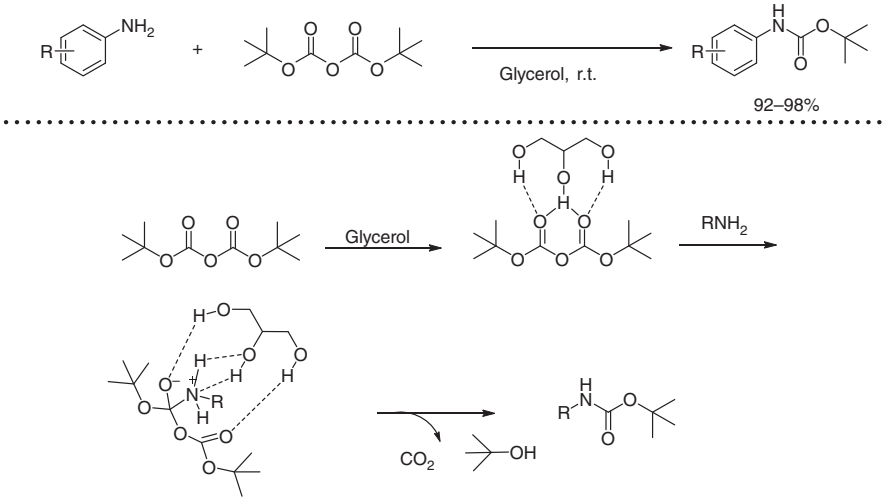
Scheme 1.51 Condensation of trimethyl phosphite with acetaldehyde and aniline.

1.3.5 Metathesis Reaction

The protection and deprotection of amino groups play an important role in organic conversion. *N-tert*-butyloxycarbonyl (*N*-Boc) derivatives are widely used in the synthesis of small organic molecules and natural products as a class of important reagents for protecting amino functional groups. Therefore, the development of a safe, environmentally benign, efficient, and catalyst-free protocol using a cost-effective and recyclable solvent for *N*-Boc protection of amines is attractive. In this context, a catalyst-free, efficient, and green methodology was developed by Ingale and coworkers for the chemically selective *N*-Boc protection of amines by using glycerol as solvent at room temperature (Scheme 1.52) [73]. Glycerol maintains good efficiency after three reuses. A possible mechanism is proposed (Scheme 1.52). The hydrogen bond formation between glycerol and the carbonyl oxygen atoms of Boc_2O makes the carbonyl group more vulnerable to nucleophilic attack. The hydrogen bonding enhances the electrophilicity of carbonyl and the nucleophilicity of nitrogen in the intermediate, making it easier for the nitrogen atom to perform an intramolecular nucleophilic attack on the carbonyl carbon, which subsequently eliminates CO_2 and ^{t}BuOH to form the product *N*-Boc protected amine.

1.4 Alcohols as Green Solvents and Hydrogen Donors

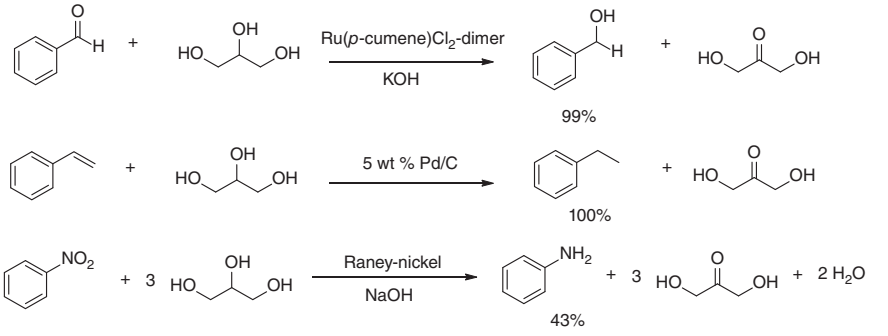
Alcohols have been shown to be reducing agents and are commonly used in transfer hydrogenation reactions under mild conditions in the presence of loaded Pd or other noble metal catalysts.



Scheme 1.52 Catalyst-free methodology for chemoselective *N-tert*-butyloxycarbonylation of amines in glycerol.

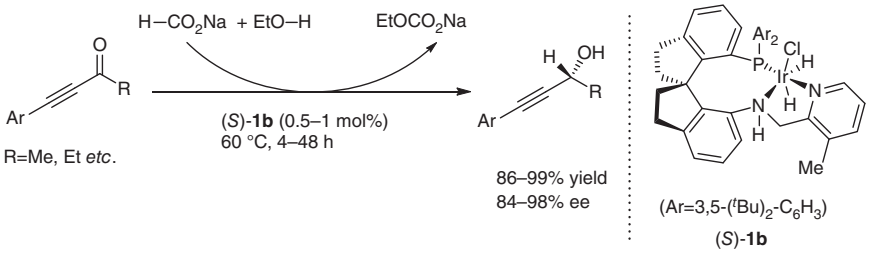
Glycerol, a biodegradable and virtually nontoxic chemical, can be used as a green solvent and hydrogen donor. Glycerol has been successfully used as an environmentally friendly "donor solvent" in transfer hydrogenation–dehydrogenation reactions for the reduction of alkenes, aldehydes, ketones, and aromatic nitro compounds [74].

In 2009, Wolfson et al. reported the use of glycerol as a green solvent and hydrogen donor in catalytic transfer hydrogenation–dehydrogenation reactions (Scheme 1.53) [75]. In this reaction, glycerol not only donates hydrogen to various unsaturated organic compounds (carbonyl compounds, alkenes, and nitrobenzene), but also acts as a solvent for easy product separation and catalyst recovery. Subsequent studies also demonstrated the design of novel, efficient, recyclable, and inexpensive ferrite-nickel magnetic nanoparticles (Fe_3O_4-Ni-MNPs) and copper nanoparticles (CuNPs) that can also be used for the reduction of aromatic nitro compounds in the presence of glycerol, a sacrificial hydrogen source [76].



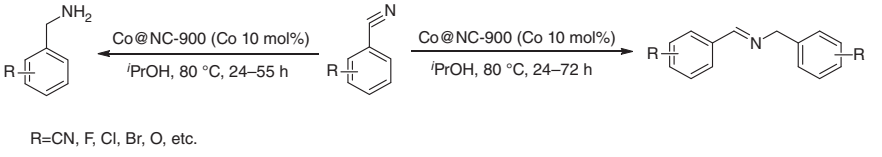
Scheme 1.53 Transfer hydrogenations of representative unsaturated organic compounds in glycerol.

Ethanol is also a renewable resource, a feedstock for the chemical industry, and an environmentally friendly and human-friendly solvent. Similarly, ethanol can be used as a hydrogen donor to reduce ketones to alcohols. Zhang et al. studied a green and efficient iridium-catalyzed asymmetric transfer hydrogenation of acetone to chiral propargyl alcohol (Scheme 1.54) [77]. Using sodium formate and ethanol as hydrogen sources, a series of acetophenones were hydrogenated with the chiral iridium catalyst (*S*)-**1b**, and optically active chiral propargyl alcohol with up to 98% ee was obtained under alkali-free conditions, with high yield and good enantioselectivity. This scheme provides a practical and sustainable method for the preparation of optically active propargyl alcohol.



Scheme 1.54 Iridium-catalyzed asymmetric transfer hydrogenation of alkynyl ketones by ethanol as hydrogen donor.

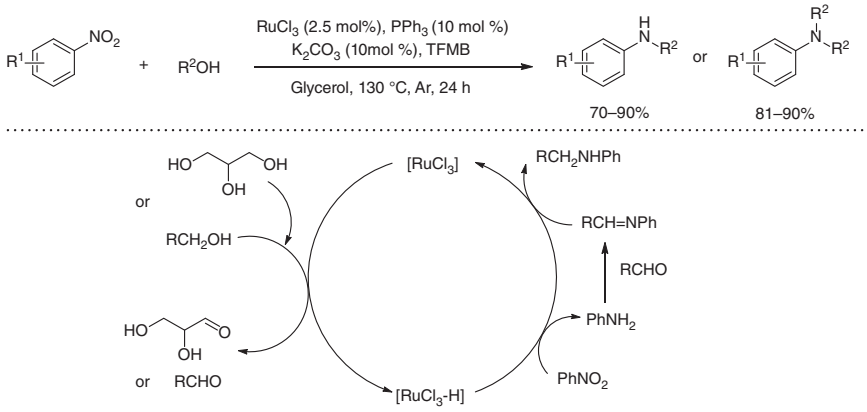
The transfer hydrogenation of nitriles is an important alternative method for producing primary amines or imines. Under alkali-free conditions, using isopropanol as the proton donor and solvent, the optimized Co@NC-900 catalysts can convert nitriles into primary amines or imines with a selectivity of up to 90% (Scheme 1.55) [78]. Compared to traditional hydrogenation processes, transfer hydrogenation utilizes various substitutes, including phosphates, formic acid salts, and inorganic hydrides as proton donors to replace the molecular hydrogen used in traditional schemes. Among them, alcohols (especially isopropanol) are very promising candidates due to their nontoxic and mild reaction conditions. The use of isopropanol as a proton donor for nitrile transfer hydrogenation can avoid handling high-pressure sterilizers and hydrogen gas, making it a green, safe, and economical solution.



Scheme 1.55 Bifunctional *N*-doped Co@C catalysts for base-free transfer hydrogenations of nitriles.

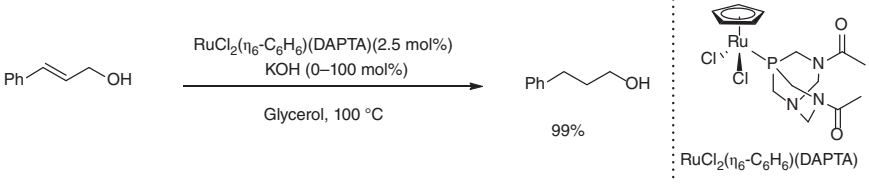
Glycerol can be directly used as a hydrogen source for reducing amination. The Ru-catalyzed one-pot synthesis of monosubstituted and disubstituted amines is successfully achieved using nitrobenzene and ethanol as raw materials and glycerol as

a reducing agent, as shown in Scheme 1.56 [79]. In these catalytic systems, the oxidation products of glycerol occur on the terminal hydroxyl group, and a portion of the alcohol is oxidized to the corresponding aldehyde. Next, nitrobenzene is reduced with the admixture [Ru-H] to produce aniline, which reacts with aldehydes to produce *N*-benzyl-4-methylaniline, and then *N*-benzyl-4-methylaniline is reduced by glycerol to produce *N*-alkylamine.



Scheme 1.56 Reductive *N*-alkylation of nitro compounds with an equivalent number of alcohols to *N*-alkyl or *N*,*N*-dialkyl amines using glycerol as the reducing agent.

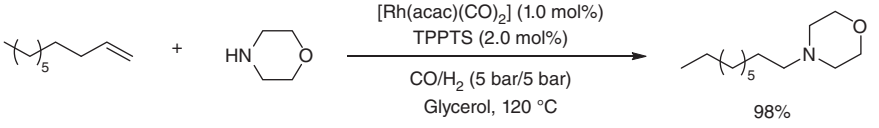
Similarly, the catalytic reduction of allyl alcohols is also possible with ruthenium as the catalyst. The hydrophilic arene-Ru(II) $[RuCl_2(\eta_6\text{-}C_6H_6)(DAPTA)]$ complex can be associated with KOH to reduce allyl alcohols to the corresponding saturated alcohols in yields up to 90% (Scheme 1.57) [80]. The reaction is a tandem process involving the oxidation of the allyl alcohol and subsequently the transfer hydrogenation of the resulting carbonyl compound in glycerol as the green solvent and hydrogen donor.



Scheme 1.57 Ruthenium-catalyzed reduction of allylic alcohols.

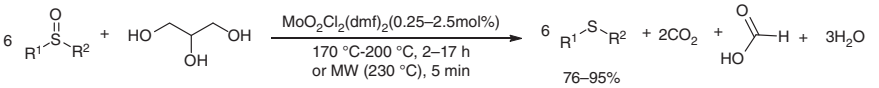
Recently, it has been reported that the hydrogenation ammomethylation of terminal alkenes in glycerol catalyzed by $[Rh(acac)(CO)_2]$/TPPTS catalyst. The reaction is a multicomponent tandem transformation (Scheme 1.58) [81]. Rh-catalyzed hydroformylation of olefins occurs first, followed by condensation of the resulting aldehyde with an amine to produce an enamine (or imine/imine) intermediate, which

then undergoes metal-catalyzed hydrogenation with water as the only by-product. Glycerol acts as a hydrogen transfer agent and facilitates the Rh-catalyzed reduction of the enamine intermediate by ensuring that the reaction proceeds at relatively low pressure.



Scheme 1.58 Rh-catalyzed hydroaminomethylation reaction in glycerol.

Furthermore, glycerol has been demonstrated to be used as a solvent and reducing agent for the Mo-catalyzed chemically selective deoxidation of sulfoxides, where it acts only as a reducing agent and not as a hydrogen donor, as depicted in Scheme 1.59 [82].



R^1=4-$CH_3C_6H_4$, C_6H_5, 4-BrC_6H_4, 4-ClC_6H_4, 4-CNC_6H_4, 2-$CO_2MeC_6H_4$, 4-$NO_2C_6H_4$
R^2= CH_3, 4-$CH_3C_6H_4$, C_6H_5, $CH_2C_6H_5$, 4-ClC_6H_4, cyclopropyl, etc.

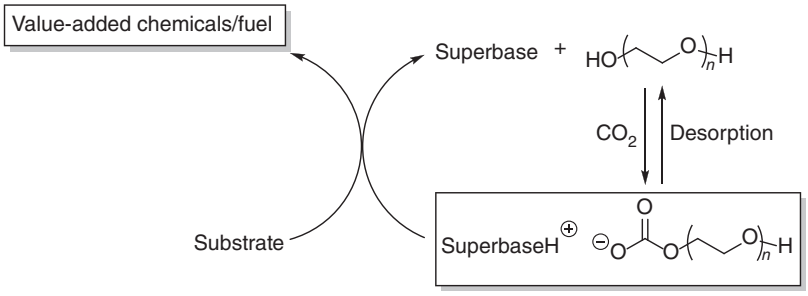
Scheme 1.59 Glycerol as a chemical selective reductant of sulfoxide.

1.5 Miscellaneous

1.5.1 Polyethylene Glycol as a Solvent for CO_2 Capture and Conversion

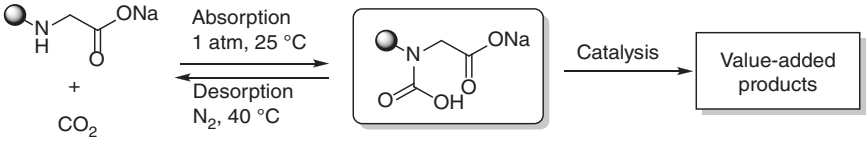
PEG not only serves as an essential green solvent but also plays an important role in CO_2 capture and conversion. Recently, much attention has been focused on developing cost-effective and powerful absorption agents and CO_2 capture and storage (CCS) technologies. Nevertheless, the large energy input during desorption becomes a key obstacle to achieving practical CCS. Alternatively, reactions involving CO_2 are typically conducted at high pressures, which may be economically undesirable and a concern for safety. The challenge is to develop catalysts that can activate CO_2 at low pressure (preferably 1 atm) and thus catalyze the binding of CO_2 into the structures of organic molecules. In order to settle the problem of energy loss in the CCS procedure, PEG has gained attention as a CO_2-friendly material. A highly efficient binary system consisting of PEG/superbase has been developed to capture and simultaneously activate CO_2, thus successfully converting the captured CO_2 directly into value-added chemicals or fuels and avoiding desorption (Scheme 1.60) [83]. Experimental results have indicated that the superbase/PEG system has proven to be an excellent system for fast and reversible iso-molar CO_2 sorption, and that the amidazolium alkyl carbonate obtained by capturing CO_2 with superbase and PEG may be more reactive than free CO_2. As a consequence, CO_2 uptake may lead to its activation

and the desorption process using this strategy requires few external energy inputs. In overview, the CO_2 fixation can be catalyzed into value-added chemicals/fuels under extremely mild reaction conditions (1 atm, 40 °C, metal-free process).



Scheme 1.60 CO_2 capture and activation by superbase/PEG and its subsequent conversion.

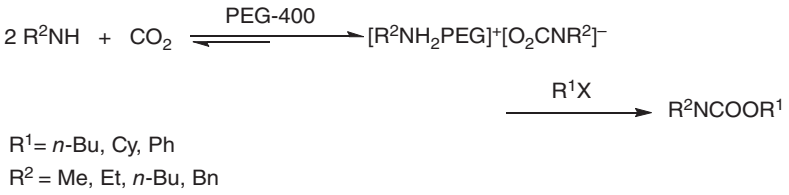
Similarly, the flexible PEG chains can coordinate with alkali metal cations, which can increase the capacity of the counterions. Readily available amino acid salts of *N*-substituted groups have a very high CO_2 capacity in PEG solutions, which are nearly equivalent to capture, and have been exploited to some extent in the field of CO_2 capture (Scheme 1.61) [84].



Scheme 1.61 Equimolar CO_2 capture by *N*-substituted amino acid salts and subsequent conversion.

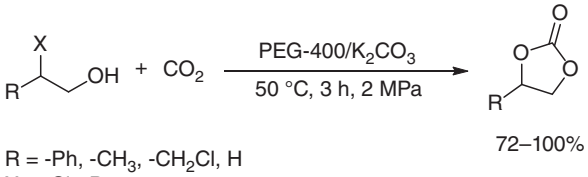
Besides, organo-carbamates have a great variety of applications in the medicinal industry and agriculture and are widely used as protecting groups or key intermediates in synthetic chemistry. Conventional organo-carbamate synthesis involves the use of highly toxic phosgene as a carbonylating agent, which requires organic solvents and can easily cause environmental problems. However, organo-carbamates which are chemically selectively synthesized from the PEG-enhanced amines, carbon dioxide, and alkyl halides have excellent features such as environmental friendliness and high efficiency. In this work, amines, CO_2, and alkyl halides are subjected to a three-component reaction with the help of K_2CO_3 and PEG (MW ¼ 400) to produce organo-carbamates under ambient conditions (Scheme 1.62) [85]. PEG in this reaction is used as a solvent and a PTC. Notably, the presence of PEG can also suppress the alkylation of amines and carbamates, thereby enhancing the selectivity for the targeted carbamates.

From the perspective of environmental protection and resource utilization, the chemical conversion of CO_2 into useful chemicals is of increasing interest. One of the most promising approaches for the chemical fixation of CO_2 is the synthesis of



Scheme 1.62 PEG-enhanced chemoselective synthesis of organic carbamates from amines, CO_2, and alkyl halides.

five-membered cyclic carbonates, which have been used in a range of applications, for instance, as polar nonprotonic solvents, intermediates for organic and polymer synthesis, chemical components for pharmaceutical/fine chemicals for biomedical applications, and as lithium secondary battery electrolytic components for lithium secondary batteries (Scheme 1.63) [86]. In this context, PEG has already been used as an efficient reaction medium to synthesize cyclic carbonates by reacting ortho–halo alcohols with carbon dioxide in the presence of a base. Notably, PEG-400 exhibits a unique impact on reactivity as an environmentally friendly solvent compared to conventional organic solvents. First, PEG-400 can come up with complexes via coordinating the potassium cation in the same way that crown ether does, which influences the basicity of K_2CO_3. Second, the "CO_2-expansion of PEG" impact alters the physical characteristics of the reaction mixture, such as viscosity and solubility of the reactants, which enhances the synthesis process. High yields and excellent selectivity of cyclic carbonates are achieved under mild reaction conditions. Furthermore, the product can be isolated easily by extraction, which is considered a cost-effective way to produce cyclic carbonate in an environmentally friendly manner.

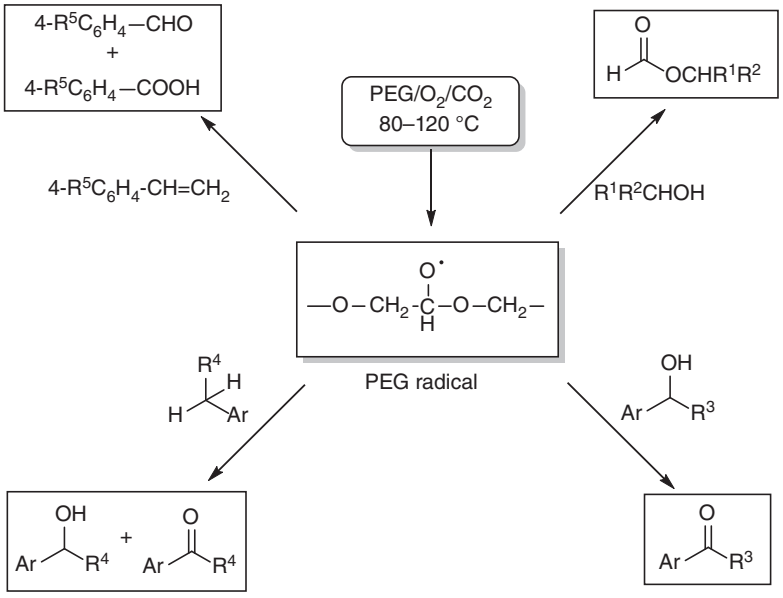


Scheme 1.63 Synthesis of cyclic carbonate from vicinal halohydrins and CO_2 in PEG-400.

1.5.2 Polyethylene Glycol Radical-Initiated Oxidation Reactions in Compressed Carbon Dioxide

PEG and its derivatives are usually recognized as a thermally stable, cheap, toxicologically harmless, and relatively environmentally friendly medium for chemical reactions and as PTCs. On the other hand, PEG, being susceptible to oxidative attack by free radicals in the presence of oxygen at high temperatures (above 70 °C), can afford the formation of numerous complicated low-molecular-weight PEG peroxides through a random chain-breaking process. In this case, when combined with compressed CO_2, the PEG radicals induced by thermal oxidative degradation can

initiate a series of radical reactions such as selective formylation of primary and secondary fatty alcohols, oxidation of benzyl alcohols, benzyl C—C bond cleavage and benzyl sp^3 C–H oxidation, as shown in Scheme 1.64 [87], representing great synthetic potential utility in a cost-effective, practical, and environmentally friendly manner. The whole procedure does not require any catalyst or additional free radical initiator. In this work, hexadecanol is chosen as the model compound for the preliminary study. As a consequence, hexadecanol is mixed with PEG-1000, oxygen (2.5 MPa), and carbon dioxide (13.5 MPa) at 100 °C for 12 h, hexadecyl formate in 68% isolated yield, and 15% palmitic acid is obtained along with 15% recovery of the hexadecanol. This method allows for a metal-free, cost-effective synthetic transformation with environmentally friendly characteristics compared to conventional processes.

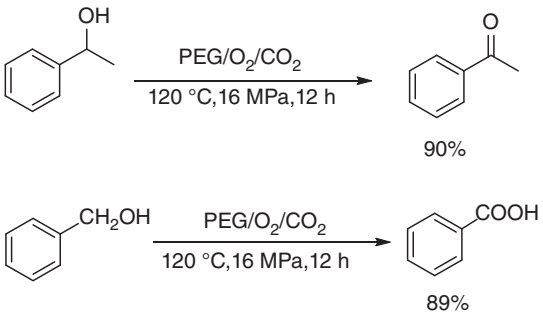


Scheme 1.64 Organic reactions involving PEG radicals in compressed carbon dioxide.

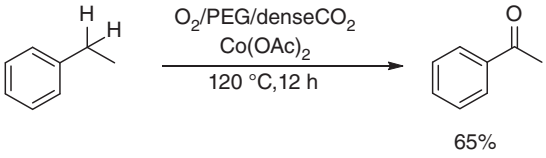
In this similar way, $PEG/O_2/CO_2$ is also used as an initiator, oxidizer, and solvent to oxidize primary and secondary alcohols to aldehydes or acids and ketones, respectively (Scheme 1.65) [88]. Compressed CO_2 here could offer a relatively safe environment for the oxidation of molecular oxygen as an oxidant in the reaction and could also be used to adjust the selectivity of the target product by altering its pressure to improve reactivity and to render product separation easier.

Based on the abovementioned experimental achievements, the application of PEG radicals in the oxidation of benzyl hydrocarbons is further explored (Scheme 1.66) [89]. In this regard, PEG oxidation/thermal degradation plays a critical role in the oxidation of ethylbenzene to acetophenone.

To investigate the oxidation reaction process during thermal degradation of PEG by *in situ* generation of radicals, the radical species, the trace formylation



Scheme 1.65 PEG radical-initiated oxidation of benzylic alcohols in compressed carbon dioxide.

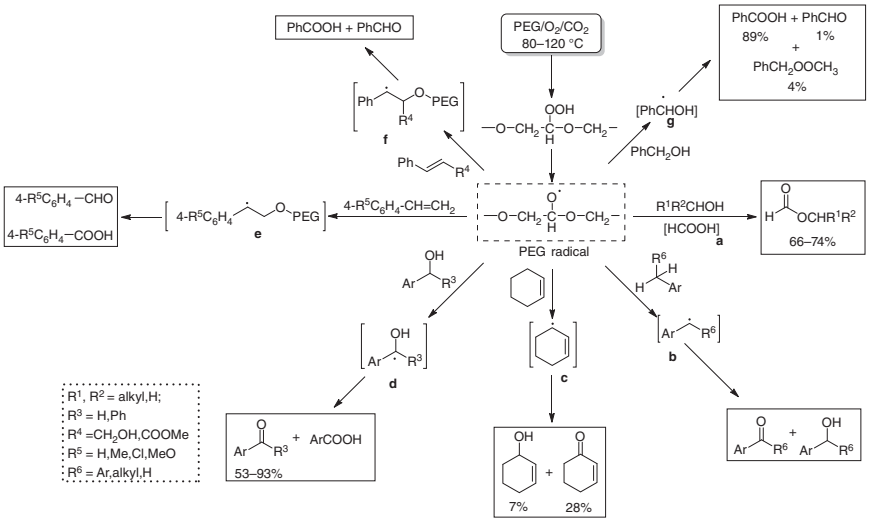


Scheme 1.66 PEG radical-initiated benzylic C—H bond oxygenation in compressed carbon dioxide.

products under the action of PEG radicals, the extended distribution of relative molecular masses of PEG, the generation of peroxide intermediates determined by KI/starch method, and the inhibition of the reaction by TEMPO (2,2,6,6-tetramethylpiperidine-1-yloxy) have been investigated, respectively. Then a rationalized radical mechanism is proposed, as shown in Scheme 1.67 [87]. The PEG radical generated by the reaction of PEG with oxygen initiates the substrate to produce a relatively stable radical, e.g. b–g, depending on the substrate structure. As expected, benzyl or allyl may favor the formation of benzyl radicals or allyl radicals, and thus primarily undergo oxidation, such as benzyl alcohol oxidation, benzyl C–C cleavage reactions, and benzyl/allyl sp_3 C–H oxidation, while aliphatic alcohols may preferentially pass through the formylation pathway.

1.5.3 Ring-Opening Reaction

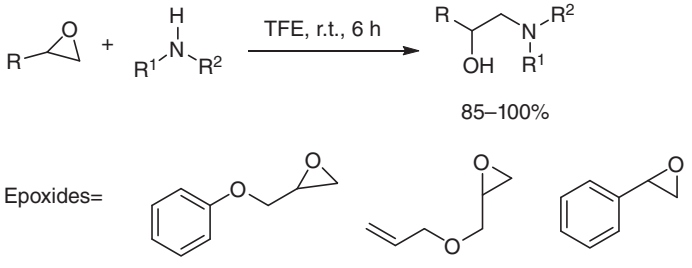
Fluorinated alcohols are good hydrogen bond donors and have high polarity, high ionizing power, and low nucleophilicity. Therefore, TFE and PFTB can promote the opening of epoxides by heteroatom or carbon nucleophiles. TFE and PFTB both contain highly nucleophilic fluorine atoms, which can act as nucleophilic reagents to react with epoxides, attacking the carbon–oxygen bond in epoxide molecules and opening up the ring structure. The fluorine atoms in fluorinated alcohols can polarize the O—H bond in the alcohol, making it more polar and thus more easily attracting nucleophilic reagents. In addition, fluorine atoms can also increase the electrophilicity of alcohols, thereby reducing the bond energy of the C—O bond and making epoxides easier to open. Therefore, fluorinated alcohols can promote the



Scheme 1.67 The structural formulae and proposed pathways of organic reactions initiated by PEG radicals generated by thermal oxidative degradation.

ring-opening reaction of epoxides by increasing the electrophilicity of oxygen atoms in epoxides and reducing the bond energy of the C—O bond.

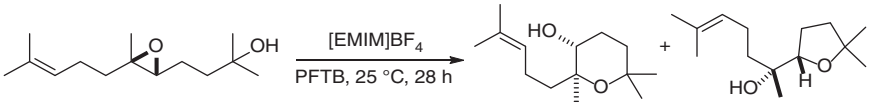
Epoxides are important and useful intermediates in organic synthesis because of their easy formation and high reactivity. In this method, TFE serves as both a reusable catalyst and medium, while aliphatic and aromatic amines act as nucleophiles to efficiently open the epoxide ring, resulting in the formation of β-amino alcohols with high yield and good regioselectivity (Scheme 1.68). It is worth noting that the high polarity and hydrogen bonding interactions between TFE and epoxides may be the reasons for promoting the reaction [90].



R^1=C_6H_5, 4-ClC_6H_4, 4-BrC_6H_4, $C_6H_5CH_2$,
R^2=H,
R^1, R^2=morpholine, piperidine, tertiary amine

Scheme 1.68 Ring opening of epoxides with amines.

In addition, the ring opening of epoxy alcohols usually occurs through the 5-*exo* selective pathway of producing THF rings, rather than through the desired 6-*endo* selective pathway of producing tetrahydropyran rings. The synergistic effect of PFTB and 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIM]BF_4) can promote the internal selective ring-opening reaction of trisubstituted epoxides (Scheme 1.69). Starting from readily accessible homochiral polyepoxy alcohols with a methyl group at all the *endo*-cyclization sites, polyethers up to five consecutive fused 6-, 7-, and/or 8-membered rings can be constructed in one step. The partial positive charge on the stable transition state of BF_4 salt is used to further improve the internal selectivity. In the presence of [EMIM]BF_4, the reaction rate increases due to the small amount of HF produced by the dissolution of the BF_4 anion in the PFTB. When using [EMIM]BF_4, which is more easily soluble in PFTB than Ph_4PBF_4, the internal selectivity slightly increases [91]. Therefore, through the combined use of PFTB and [EMIM]BF_4, a selective inversion from *exo*-selectivity to *endo*-selectivity can be achieved, thereby quickly and effectively synthesizing the multi-ring porous core structure of marine stepped polyether molecules.



Scheme 1.69 The synergistic action of PFTB and [EMIM]BF_4 promotes the internal selective ring-opening reaction of triple-substituted epoxides.

1.6 Summary and Concluding Remarks

In this chapter, the different reactions involving various alcohol as solvents are summarized, among which the different roles of glycerol, PEG, and fluorinated alcohols in organic reactions are mainly introduced according to the functional characteristics of alcohols.

Alcohols are ideal media for many reaction processes as a cheap, abundantly available, and low-toxic solvent, mainly in reduction reactions, coupling reactions, and condensation reactions, but also in other reactions. Some bio-based alcohols that can be prepared by petrochemical industry procedures or from renewable sources are widely used in laboratories and industries, such as bioethanol, 2-propanol, and glycerol. In particular, glycerol, as an important green solvent combining the advantages of water and ionic liquids, has great advantages in improving the catalytic rate and selectivity in organic synthesis, product separation, and catalyst and solvent recovery, which provides an innovative solution to replace traditional volatile solvents. Interestingly, PEG is used as a green and cheap solvent for various types of organic transformations due to its good compatibility. Secondly, it has remarkable cationic complexing ability as an acyclic analog of crown ethers. In metal-catalyzed reactions, the catalytic system "PEG-metal" can be easily recovered and reused without significant loss of activity. Furthermore,

fluorinated alcohols have unique properties and are a very attractive solvent for organic reactions, allowing for many challenging reactions, although it is not very green.

Although great strides have been made by utilizing alcohol as a solvent and a variety of valuable chemicals have been obtained, there is still major room for improvement in the future:

(1) The reason for glycerol as a solvent to facilitate the reaction needs to be further investigated in depth. Second, technical-grade glycerol (80%) is more desirable as a green solvent for direct industrial and laboratory applications, but there are few successful examples. Finally, glycerol as a high-boiling-point polar solvent faces the same problem as many ionic liquids, How to remove the polar compounds from glycerol? This is an important question that needs to be addressed.
(2) The interactions and mechanical details of the multiphase catalytic interface in the presence of PEG as a solvent are yet to be explored in depth. Second, the solvation of solutes in PEG is largely unknown, and the interaction of PEG with metal cations and how it affects the solvation of resistant anions also remains to be addressed. In addition, studies on how the phase behavior of PEG enhances product recovery are yet to be thoroughly investigated.
(3) Fluorinated alcohols are less used in green chemistry due to their corrosiveness, toxicity, and cost, and it is critical to develop methods that reduce the use of fluorinated solvents while continuing to utilize their inherent properties. Moreover, the interaction mechanism between fluorinated alcohols and substrates in the reaction process needs to be further studied.

In short, we hope that the content presented in this chapter will inspire organic chemists to give more consideration to alcohol solvents in their future research to achieve the goal of green chemistry.

Acknowledgments

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