Review
Eucalyptol, an All-Purpose Product
Joana F. Campos and Sabine Berteina-Raboin *

Institute of Organic and Analytical Chemistry (ICOA), University of Orleans, UMR-CNRS 7311, BP 6759, Rue de Chartres, CEDEX 02, 45067 Orleans, France; joana-filomena.mimoso-silva-de-campos@univ-orleans.fr
* Correspondence: sabine.berteina-raboin@univ-orleans.fr

Abstract: Eucalyptus plants have attracted the attention of researchers and environmentalists worldwide because they are a rapidly growing source of wood and a source of oil used for multiple purposes. The main and the most important oil component is 1,8-cineole (eucalyptol: 60–85%). This review summarizes the literature reported to date involving the use of 1,8-cineole for the treatment of disorders. Additionally, we describe our efforts in the use of eucalyptol as a solvent for the synthesis of O,S,N-heterocycles. Solvents used in chemistry are a fundamental element of the environmental performance of processes in corporate and academic laboratories. Their influence on costs, safety and health cannot be neglected. Green solvents such as bio-based systems hold considerable additional promise to reduce the environmental impact of organic chemistry. The first section outlines the process leading to our discovery of an unprecedented solvent and its validation in the first coupling reactions. This section continues with the description of its properties and characteristics and its reuse as reported in the various studies conducted. The second section highlights the use of eucalyptol in a series of coupling reactions (i.e., Suzuki–Miyaura, Sonogashira–Hagihara, Buchwald–Hartwig, Migita–Kosugi–Stille, Hiyama and cyanation) that form O,S,N-heterocycles. We describe the optimization process applied to reach the ideal conditions. We also show that eucalyptol can be a good alternative to build heterocycles that contain oxygen, sulfur and nitrogen. These studies allowed us to demonstrate the viability and potential that bio solvents can have in synthesis laboratories.

Keywords: eucalyptol; 1,8-cineole; heterocyclic chemistry; green synthesis; biology

1. Introduction
As solvents are the most important constituents of chemical transformations in terms of quantity, acting on solvents and replacing standard solvents with safe products can have a great ecological impact. While the chemistry community has made significant efforts towards identifying greener processes, minimizing the quantity of catalysts, or using multicomponent reactions and one-pot processes, solvents are a major portion of the environmental performance of a process and influence safety and health issues. The green synthesis of O,S,N-heterocycles has been a core focus of our research group for some time, as progress in this area can have a direct impact on the identification of innovative tactics for the production of interesting scaffolds. Putting all these considerations together, we studied solvent replacement as a strategy to discover and develop an innovative and environmentally benign chemistry. Based on the work of our group on synthetic methods using mild, efficient and environmentally benign protocols, we designed and implemented a series of couplings in order to demonstrate a more eco-sustainable perspective.

2. Eucalyptus
These trees of the genus Eucalyptus belong to the Myrtaceae family and were named by the French botanist Charles Louis L’Héritier de Brutelle in 1788 [1]. This plant is native to Australia and Tasmania and was reclassified by Hill and Johnson in 1995 based on morphology and molecular characteristics [2–7]. The natural distribution of Eucalyptus is mainly limited to the southern hemisphere [8]. These plant species have a variety of
physical structures, appearing as trees, mallees (i.e., multi-stemmed dwarf forms), or shrubs. Units of some species can reach 400–500 years of age [8]. This tall evergreen tree (Figure 1) has been successfully introduced into many countries around the world, where it is currently one of the most widely planted trees [3,9–13].

Eucalyptus species are grown in the tropics and subtropics, including Asia, America, Europe and Africa. Globally, more than 17.9 million hectares of eucalypt plantations have been planted, mainly in Brazil, India, China, South Africa, Spain and Portugal [9]. Among all the species, *Eucalyptus globulus* (one of the earliest eucalyptus species to be officially described) has been widely introduced abroad [14]. This tree is a major supplier of essential oils in the International Pharmacopoeia [15,16].

The main and the most important oil component is 1,8-cineole (eucalyptol: 60–85%) [17,18]. Due to its natural origin, 1,8-cineole is also termed eucalyptol (Figure 2), but it should not be confused with eucalyptus oil, which is a mixture of many other components [19]. Cineole is obtained from eucalyptus tree leaves by distillation. One thousand tons of cineole type oil (yield 1.5%) is produced in Portugal, South Africa and Spain. The content of cineole in eucalyptus oil varies depending on the species and is determined by aspects such as geographical location and the season [18,20–22]. Two major important tree species for the commercial production of cineole are *Eucalyptus globulus* (cineole content of oil 70–75%) and *Eucalyptus poly bractea* (cineole content of oil 80–85%) [23].

**Figure 1.** Tree known as Eucalyptus (Latin), Eucalypt (English), Neelgiri (Hindi) and Sugandh Patra (Sanskrit).

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**Figure 2.** 1,8-cineole structure and properties.

Due to their wide range of uses, the production and use of essential oils continues to grow. Therefore, based on modern scientific knowledge, it is necessary to systematically cultivate oleaginous plants in order to maintain a regular supply of high-quality plant materials for essential oil production. The growth and development of aromatic/essential
oil-bearing plants and, frequently, the nature and quantity of essential oils are affected by temperature, rainfall, day length, radiation characteristics and altitude [24].

Eucalyptus plants have attracted the attention of researchers and environmentalists worldwide because they are a rapidly growing source of wood and a source of oil used for multiple purposes. In 2016, Tuskan’s team discussed and demonstrated the feasibility of Eucalyptus plantations as a source for terpene production [25].

Because of their inherent ability to synthesize, transport, accumulate and store these compounds, plants are an attractive system for producing specific terpenes on a commercial scale. Many plant leaf tissues (such as eucalyptus species) exhibit a wide range of terpene content and composition [26]. The production of terpenes on an industrial scale is potentially neutral in terms of carbon dioxide emissions, because plants collect large amounts of carbon. Planting eucalyptus trees and harvesting the biomass can produce biofuels with little ecological impact [27].

The purpose of this brief review is, firstly, to summarize our current scientific knowledge about 1,8-cineole in order to demonstrate its beneficial health properties and potential uses. Then, we describe our studies based on the information provided in this previous work.

We focus on studies in which the biological activity tested was achieved only by the presence of the terpene 1,8-cineole. This distinction appeared relevant because there is a vast literature available for consultation reporting various biological activities, but using eucalyptus oil, which is a mixture of various constituents. Examples of these well-documented studies have shown a wide range of biological activities—anticancer [28,29], repellent [30–35], antimicrobial [18,36–54], antitussive [55], antioxidant [56–58] and immune response activities [18,59]. Several reviews have compiled a large number of other activities, such as antihyperglycemic, anthelmintic, anti-inflammatory, antimalarial, anti-HIV, anti-dental plaque formation, insecticide, herbicidal, acaricidal and nematicidal activities, and use for treatment of skin disorders [10,60–68].

While 1,8-cineole was the major component, it remains to be seen whether the positive results of a given study were due to its presence or to the synergistic effect between all the constituents present in the extract mixture.

3. Use of 1,8-Cineole for the Treatment of Disorders

3.1. Cardiovascular Treatments

In 2002, the team of Leal-Cardoso demonstrated that intravenous administration of 1,8-cineole significantly reduced the blood pressure of both conscious and anesthetized rats. Measurements with isolated rat aorta showed that 1,8-cineole had a vasodilating effect, suggesting that the hypotensive effect probably resulted from a decrease in peripheral vascular resistance due to the direct relaxation of vascular smooth muscle [69]. They subsequently showed that this vasodilatation appears to depend on the integrity of the vascular endothelium and the release of nitric oxide [70]. The Vassallo group studied the effects of 1,8-cineole on papillary muscle preparations from rat ventricle. In these trials, 1,8-cineole induced relaxation, probably due to the inhibition of Ca\(^2+\) influx through the membrane [71]. In 2014, Moon et al. presented the antihypertensive effects of 1,8-cineole on hypertension induced by chronic exposure to nicotine. The results indicated that 1,8-cineole may lower blood pressure and that this effect may be associated with the regulation of nitric oxide and oxidative stress [72].

3.2. Antimicrobial Effects

In 2009, Lambert’s team evaluated the antimicrobial activity of 1,8-cineole against *Staphylococcus aureus*, Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans* grown in planktonic and biofilm cultures [73]. Li et al. measured the efficiency of 1,8-cineole against *Staphylococcus aureus*, *Escherichia coli* and *Salmonella enteritidis* using the broth dilution method. The antibacterial action was also investigated by transmission electron microscopy. The results showed that the oil caused
ultrastructural changes in bacterial cells [74]. In two subsequent studies, Vlachojannis reported antibacterial activity against Enterococcus faecalis, Eikenella corrodens, Streptococcus mutans and the yeast Candida albicans. These studies were based on the fact that 1,8-cineole is a component of many brands of mouthwash, showing anti-plaque activity in humans and anti-bacterial activity in vitro against pathogens [75,76].

3.3. Anti-Inflammatory Effects

Santos and Rao examined the potential of 1,8-cineole as an anti-inflammatory and antinociceptive agent. They demonstrated that 1,8-cineole was effective following oral administration and was substantially more potent at a dose of 400 mg/kg. It not only inhibited carrageenan oedema and increased capillary permeability, but also inhibited granuloma formation [77]. In the last few years, the positive anti-inflammatory activity of 1,8-cineole has gained prominence in the particularly sensitive area of respiratory pathologies.

3.4. Respiratory Disorders

As mentioned above, 1,8-cineole evidenced a great potential for use in various respiratory disorders. Proof of this, perhaps also motivated by the current health crisis that we are all facing, are the most recent reviews by the team of Malcolm and Juergens, who have been studying the mechanisms of 1,8-cineole for some years [78–80]. In 2009, Juergens et al. investigated the 1,8-cineole as an inhibitor of the production and synthesis of tumor necrosis factor-α, interleukin-1β, leukotriene B4 and thromboxane B2 in human blood monocytes. The team suggested that 1,8-cineole was a potent cytokine inhibitor that could be suitable for the long-term treatment of airway inflammation in bronchial asthma and other steroid-sensitive disorders [81]. Then, in 2003, in a double-blind, placebo-controlled study, the anti-inflammatory effect of 1,8-cineole was estimated in patients with severe asthma. The effectiveness of this molecule provided a new rationale for its use as a mucolytic agent in upper and lower respiratory tract disorders. The study demonstrated a significant reduction in oral steroid dose and improvements of symptoms or symptom scores against placebo [82]. Worth et al. reported that concomitant treatment with 1,8-cineole reduced exacerbations as well as dyspnea and improved lung function and health status. Additionally, 1,8-cineole was proposed as an active controller of airway inflammation in chronic obstructive pulmonary disease by intervening in the pathophysiology of airway inflammation of the mucus membrane [83]. In 2011, Bastos et al. reported that inhalation of 1,8-cineole inhibited ovalbumin-induced respiratory inflammation in guinea pigs [84].

3.5. Toxicity Side Effects

The use of plants for medical purposes to treat, cure and prevent diseases is one of the oldest medical practices in humans. For many years, the use of ancient medicinal plants has shown that certain plants contain potentially dangerous substances. Many of them contain potentially aggressive substances; therefore, they should be used with caution in view of their toxicological risk. 1,8-cineole, as all components from a natural source, is no exception and can also present toxicity/adverse effects if not carefully used. However, the available literature on reported cases is scarce. Additionally, in some cases, the episodes occurred with the use of eucalyptus oil (a mixture of various constituents) or oils containing high levels of 1,8-cineole. In 1995, Theis and Koren reported an incident that happened to a 3-year-old girl weighing 15 kg. She used a chest rub with camphor oil for nasal congestion and her father mistakenly gave her a teaspoon of the oil. Twenty minutes later she had a generalized tonic–clonic seizure. In another episode with the same result, a 15-month-old boy weighing 10 kg took a bottle of camphor oil and drank 20 mL. After 10 min, he likewise developed a generalized tonic–clonic seizure [85]. In 1999, the team of Haenggeli described a case of a 1-year-old girl (without a previous history of epilepsy) who was given baths in an immersion containing an undetermined quantity of eucalyptus, pine and thyme oils. Shortly after the last bath, she had several episodes of tonic convulsions.
and over the next few days her seizures became more frequent and could not be controlled by anticonvulsants. Ultimately, the girl underwent developmental delay and suffered from repeated seizures [86]. In 2009, Culic et al. reported that 1,8-cineole and camphor were both able to induce seizures in rat, at a dosage of 0.5 mL/kg [87]. In 2011, Reid’s group reported the first use of naloxone for the reversal of eucalyptus oil induced central nervous system depression. This episode took place with a 74-year-old woman after unintentional ingestion of around 20–30 mL of eucalyptus oil. Her only co-morbidities were hypertension and hypercholesterolemia and she had no allergies. No adverse event occurred and she recovered completely [88].

4. Study and Application of Eucalyptol for Greener Coupling Reactions

In the perspective of sustainable development, it is imperative to find compound alternatives from non-renewable resources. Although organic chemists have limited the impact of organic synthesis research on the environment in recent years by reducing the number of catalysts or developing metal-free methods, it is still crucial to study the nature of solvents, since solvents are the largest component of the chemical conversion process. Therefore, it is necessary to replace solvents with greener alternatives to reduce the environmental impact of organic chemistry [89]. Due to the high environmental impact of solvents, much research has been dedicated to searching for more ecological and sustainable alternatives and solvent selection guides have been published that included bio-based solvents [90–96]. Among biomass solvents, those made from food waste exemplify an attractive approach because their use could contribute to a more circular economy. Several articles state that solvents of biological origin can effectively replace traditional petroleum-derived solvents for the synthesis of O,S,N-heterocyclic compounds [97–112]. The bio solvent chosen for study by our team was 1,8-cineole. Eucalyptol is a saturated oxygenated terpene that is abundant in numerous plants and their essential oil fractions. Its use as green solvent is also associated to its safety and pharmacological profiles; it is considered to be a safe chemical when taken in normal doses. Eucalyptol [113] is often described as being present in up to 90% in eucalyptus essential oil, depending on the species. For example, the chemical composition of eucalyptus oil isolated from fresh leaves by GCMS analysis showed that the three main components are Eucalyptol (84.39%), Limonene (5.92%) and α-Terpineol (5.55%), with 17 other compounds occurring in less than 0.5% each (Figure 3).

![Chemical composition of eucalyptus oil isolated from fresh leaves by GCMS analysis](image)

**Figure 3.** Chemical composition of eucalyptus oil.

This is a very interesting ratio, because, in the past few decades, eucalyptus forests have made great progress for use in the paper industry due to their rapid growth (from
7 to 10 years). The main producers of eucalyptus essential oil are Australia, China, Portugal, Spain and South Africa. Because eucalyptus is a very large tree, it grows rapidly and the leaves can produce eucalyptus essence, so there is no problem of supply. France Agrimer estimated, in 2015, the world’s eucalyptus essential oil production from *Eucalyptus globulus* and *Eucalyptus radiata* at 4000 tons per year. The number of eucalyptus plantations has increased due to the use of wood in the paper industry; fast-growing trees can quickly regenerate the forest, making sustainable management or eco-system management of forests possible. Eucalyptol is a colorless liquid whose solvatochromic parameters have been determined together with a large number of other natural liquid polymers or solvents derived from petrochemistry [114]. Eucalyptol is miscible with ether, ethanol or chloroform but is insoluble in water. It could be compared to 2-MethylTHF, which is mainly used to replace THF. The main reason for using 2-MeTHF instead of THF is its higher boiling point, 78–80 °C. However, similar to THF, it can generate peroxides. This is not the case with eucalyptol, which has also the advantage of being less expensive.

To date, apart from these parameters, no other information could be found in the literature.

4.1. Suzuki–Miyaura Coupling Reaction

The Suzuki–Miyaura reaction is one of the strongest and most suitable reactions for constructing C-C bonds. Its use is effective on a variety of substrates, making this cross-coupling reaction a versatile tool [115–119]. It was probably for this reason that the authors decided to study it first, thus contributing to more sustainable conditions for this coupling [120]. The optimization steps were accomplished starting from two chloro derivatives (i.e., 4-chlorothieno[3,2-d]pyrimidine and 7-chloro-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine) and using 4-methylphenyl boronic acid. The use of different palladium sources, such as catalyst and sodium bicarbonate, potassium carbonate or cesium carbonate, as base was examined. In the presence of Pd(PPh₃)₄, the yields were higher than with Pd(OAc)₂ or Pd(PPh₃)₂Cl₂ and the best conditions were found using Pd(PPh₃)₄ and K₂CO₃ or Na₂CO₃, depending on the starting material. Based on these results, the authors tested various boronic acids with several chloro derivatives (4-chlorothieno[3,2-d]pyrimidine, 7-chloro-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine, 8-chloro[1,2,4]triazolo[4,3-a]pyrazine, 6-chloro[1,2,4] triazolo[4,3-a]pyrazine and 4-chlorofuro[3,2-c]pyridine) to evaluate the reaction scope. The final products 1–17 were accessed, using optimized conditions in 1,8-cineole, in moderate to excellent yields (Figure 4).

It should be noted that the boiling point of Eucalyptol is quite high; however, it is easy to evaporate it quickly with a normal pump using a coolant such as monoethylene glycol in a conventional rotary evaporator system. Furthermore, the authors have shown that it was possible to recover this solvent from the reaction media by simple distillation, which was very important from an environmental and economic point of view, since the recovered Eucalyptol could be reused for some runs [120].

Regarding the effectiveness of eucalyptol as solvent, it also should be noted that the authors compared the yields obtained with eucalyptol with those obtained in various other solvents, when it was possible, for the various couplings mentioned in this review. For example, the average yields (%) reported in the literature for the Suzuki–Miyaura coupling reaction of chlorothieno[3,2-d]pyrimidine were compared with those obtained using eucalyptol (79%), showing the interest in this solvent since the yields were as follows, in various solvents: THF (72%), Toluene (62%), DMF (61%), Dioxane (38%) and DME (62%) [120].
Figure 4. Suzuki–Miyaura coupling products in eucalyptol [120].

4.2. Sonogashira–Hagihara Coupling Reaction

Palladium and other transition metal-catalyzed couplings of aryl or vinyl halides with a terminal acetylene, universally known as the Sonogashira cross-coupling reaction, are another example of the widely used sp²–sp carbon–carbon bond formation reactions in organic synthesis [121,122]. Starting with 4-chlorothieno[3,2-d]pyrimidine, using 4-methoxyphenyl acetylene and changing the catalytic system and base, the same authors achieved the optimization of the Sonogashira reaction in eucalyptol [120]. In this case, the catalyst conditions reported earlier [123] (i.e., Pd(PPh₃)₂Cl₂ (5 mol.%), CuI (10 mol.%) in a mixture of 1,8-cineole and Et₃N) were not the best option. When the reaction was carried out in the presence of Pd(PhCN)₂Cl₂ and P(Cy₃), in 1,8-cineole, in presence of Cs₂CO₃ as base instead of Et₃N, the yield increased [120]. In addition, the optimized conditions are in line with other conditions described in which the use of CuI with aryl chlorides was not necessary [124-127]. Based on these results, the scope and limitations of the Sonogashira coupling reaction in eucalyptol using several acetylens were evaluated; starting from 7-chloro-5-methyl[1,2,4]triazolo[1,5-a]pyrimidine, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine
and 4-chlorofuro[3,2-c]pyridine gave the expected products 18–28 with moderate to good yields (Figure 5) [120]. A limitation of the use of 1,8-cineole was found for the Sonogashira–Hagihara coupling reaction with starting material containing nitrogen on the 5-membered ring. However, the use of eucalyptol as solvent in Sonogashira coupling using thieno[3,2-d]pyrimidine as starting material allowed them to improve the yield and work under Cu-free conditions.

Figure 5. Sonogashira–Hagihara coupling products in eucalyptol [120].

4.3. Migita–Kosugi–Stille Coupling Reaction

In this work, the research group examined the potential properties of eucalyptol as a solvent derived from biological sources in the Migita–Kosugi–Stille coupling reaction on chlorinated O,S,N-heterocycles or polynitrogen-heterocycles [128]. Based on
published literature reviews [129–131], they optimized the reaction conditions on one of the envisioned starting materials, 4-chlorothieno[3,2-d]pyrimidine. Among those previously selected, the best conditions for the reaction of this starting material were obtained using Pd(PPh₃)₂Cl₂ (10 mol.%) and PPh₃As (40 mol.%) in Eucalyptol at 100 °C for 23 h. Based on these results, the scope and limitations of the Stille coupling reaction were investigated using several hetero-tributylstannyl derivatives and chloro derivatives (4-chlorothieno[3,2-d]pyrimidine, 4-chlorofuro[3,2-c]pyridine, 8-chloro[1,2,4]triazolo[4,3-a]pyrazine, 6-chloro[1,2,4]triazolo[4,3-a]pyrazine, 4-chloro-7H-pyrrolo[2,3-d]pyrimidine, or 4-chloro-1H-pyrazolo[3,4-d]pyrimidine). The desired final compounds 29–48 were achieved in moderate to excellent yields (Figure 6). The average yields (%) reported for the Migita–Kosugi–Stille coupling reaction on several O,S,N-containing fused heterocycles are the following: Toluene (77%), Dioxane (94%) and Eucalyptol (79%) [128]. The average yield obtained with eucalyptol was comparable to those obtained in Toluene and lower than those obtained with dioxane (but, with dioxane, the average yield was made in only two experiments). The results obtained in eucalyptol remain very interesting.

Figure 6. Migita–Kosugi–Stille coupling products in eucalyptol [128].

4.4. Buchwald–Hartwig Coupling Reaction

The investigation of the potential of eucalyptol as a solvent in Buchwald–Hartwig coupling began with a literature review to determine the best conditions for this type of transformation [132–144]. After compiling the main and most widely used reaction conditions for this coupling, the authors chose the conditions that were mainly applicable to the heterocycles frequently used by their team. The results obtained after combining all the possible conditions (by varying palladium complex, ligand and base) were very
significant and constructive. Stoichiometry was selected from the literature and experience from their previous work on the synthesis of various O,S,N-heterocycles. The expected compound was obtained by stirring at 110 °C for a duration between 17 and 48 h, depending on the reagents. With the best conditions in hand, they analyzed the scope and limitations using Pd(OAc)$_2$ (5 mol%) as the Pd source, BINAP (10 mol%) as the ligand and Cs$_2$CO$_3$ (2 equiv.) as the base at 110 °C in 1,8-cineole. For the starting materials as the substrate containing oxygen, sulfur and nitrogen, they selected five brominated products (i.e., 2-bromofluorene, 4-bromo-1,2-methylenedioxybenzene, 6-bromo-2-methylquinoline, 7-bromo-6-phenylthieno[2,3-b]pyrazine and 3-bromo-2-phenylthieno[3,2-b]pyridine) and several amine derivatives [145]. They were able to synthesize the desired compounds 49–71 in moderate to excellent yields (Figure 7). A comparison was made with the solvents commonly used for this type of transformation and the possible recycling of eucalyptol was also demonstrated. For each reaction series, an average 70% solvent recovery was observed without noticeable loss of properties.

### Figure 7. Buchwald–Hartwig coupling products in eucalyptol [145].

#### 4.5. Palladium Catalyzed Cyanation Reaction

Cyanation is a suitable alternative to the Rosemund–Von Braun reaction [146–150], which often uses severe reaction conditions and sometimes requires intensive work up, and efforts have been made to find more ecological conditions [151]. After reviewing previously reported information, they applied this study to three compounds commonly used in their team [120,152,153]. The authors carried out an optimization study in order to find the...
ideal conditions for each scaffold (i.e., 4-chlorothieno[3,2-d]pyridine, 7-chlorothieno[3,2-b]pyridine and 7-bromo-6-phenyl-thieno[2,3-b]pyrazine).

The best results from chloro derivatives were obtained when the reaction was performed using eucalyptol as solvent with Pd$_2$(dba)$_3$ (5 mol%), dpff (10 mol%), Zn(CN)$_2$ (60 mol%) and Zn (20 mol%) at 170 °C for 26 h. Starting from a bromo derivative, the cyanation product 73 was attained in good yields at only 140 °C for 27 h with Pd$_2$(dba)$_3$/dpff as the catalyst system and Zn(CN)$_2$ as the cyanide source (Figure 8) [151].

4.6. Hiyama Coupling Reaction

Hiyama coupling is the palladium-catalyzed C-C bond formation (between aryl, alkenyl, or alkyl halides or pseudohalides and organosilanes). A particular feature of this coupling is that it requires an activator (fluoride ion or a base) [154,155]. The same authors [151] decided to investigate this coupling because they thought it may be interesting to compare their results with the Sonogashira coupling results previously reported by them [120]. Similar to the previous studies described, this work started with a literature review [156–159] to test the conditions in their scaffold and find the best coupling conditions. Optimization, in 1,8-cineole, was attained starting from 7-chlorothieno[3,2-b]pyridine using 1-phenyl-2-trimethylsilylacetylene and by changing the quantity and type of Pd source with or without ligand and/or the type and quantity of activating agent (fluoride ion or a base). The best conditions were found at 100 °C for 48 h with Pd(CH$_3$CN)$_2$Cl$_2$/PPPh$_3$ as the catalyst system and Cs$_2$CO$_3$ as the base. Based on these results, the scope and limitations of the Hiyama coupling on 7-chlorothieno[3,2-b]pyridine and 4-chlorofuro[3,2-c]pyridine were assessed using several silylacetylenes. The compounds 74–80 were synthesized in moderate to good yields, indicating the generalizability of this method. As shown earlier, when they synthesized the same product 25 by Sonogashira coupling, the 4-chlorofuro[3,2-c]pyridine presented lower reactivity (Figure 9) [120,151].
shown earlier, when they synthesized the same product by Sonogashira coupling, the 4-chlorofuro[3,2-c]pyridine presented lower reactivity (Figure 9) [120,151].

Figure 9. Hiyama coupling products in eucalyptol [151].

5. Reaction Leading to the Formation of O,S,N-Heterocycles

5.1. Synthesis of Imidazo[1,2-a]pyridines

Imidazo[1,2-a]pyridine is one of the most promising bicyclic 5–6 heterocyclic rings. Due to its wide range of applications in medicinal chemistry, it is considered as a “drug prejudice” scaffold. This scaffold is also present in various commercially available formulations, such as zolimidine, zolpidem and alpidem. Consequently, considerable work has been carried out to propose the synthesis and structural modification of the scaffold with the aim of discovering and developing new therapeutic agents [160,161]. This work [120] was based on methodologies previously published by our team [162]. It started by optimizing the condensation using 2-aminopyridine and 2-bromoacetophenone in presence of several bases in limonene or eucalyptol as the solvents. 2-phenylimidazo[1,2-a]pyridine 81 was obtained in good yield after 22 h at 105 °C in the presence of NaHCO₃ both in limonene and eucalyptol [120]. This research group then studied the C-H activation at position C-3 of 2-phenylimidazo[1,2-a]pyridine using bromobenzene and by varying the amount of
Pd(OAc)$_2$ in limonene or eucalyptol. When the reaction was executed in limonene, the results were poor. As the C-H activation at position C-3 of 2-phenylimidazo[1,2-a]pyridine was more effective in eucalyptol and in order to carry out a one-pot procedure, they chose this solvent to study the scope of the reaction with various 2-bromo acetophenones. The various groups in position 4 on the aromatic ring had no influence and the expected products were obtained in moderate to excellent yields. The one-pot method was then performed with 2-bromo-4-fluoroacetophenone, aryl bromides and 2-aminopyridine in 1,8-cineole. 2,3-diarylimidazo[1,2-a]pyridines 85–90 were obtained in moderate to excellent yield, validating the generality of this method. The average yields in DMF (74%), PEG (64%), DMA (73%) and Eucalyptol (75%) were made, depending on published examples, on 18 reactions in DMF, 20 reactions in PEG, 16 reactions in DMA and on the 7 reactions in Eucalyptol described [120]. The yields shown in Figure 10 correspond to tests carried out on a scale of 1 mmol of 2 aminopyridine. The authors also checked that the results were equivalent on a larger scale. Indeed, from 10.6 mmol of 2-aminopyridine (1.0 g), 2-(4-fluorophenyl)-3-(4-nitrophenyl)imidazol[1,2-a]pyridine 87 was isolated in 98% yield (3.47 g).

Figure 10. Synthesis of various Imidazo[1,2-a]pyridines in eucalyptol [120].

5.2. Synthesis of Highly Functionalized Pyridines

The class of molecules chosen for synthesis with a more eco-compatible solvent were highly functionalized pyridines [163]. After reviewing the most widely used reaction conditions [164–166] and stoichiometry applied, the reactions were performed using Eucalyptol...
as solvent [151]. The expected compound 91 was obtained in 28–54% yield. In general, when adding a catalyst in the reaction, the yield obtained was lower than that of a reaction performed with the same stoichiometry and temperature. In 1,8-cineole, the best result was obtained without catalyst using benzaldehyde (1 equiv.), pyrrolidine (2 equiv.) and malonitrile (2 equiv.) [151]. With these conditions in hand, the authors analyzed the scope and limitations. They were able to synthesize the several derivatives (91–96) in 45–68% yield. The nature of the aldehyde did not cause major discrepancies in yields of the different final compounds. Using the aldehyde that presented the highest yield, the potential of Eucalyptol was then analyzed using other sources of amines, such as phenylpiperazine, piperidine, thiomorpholine and 2,6-dimethylmorpholine, leading to compounds (97–100) in moderate (from 57% to 75%) but interesting yields (Figure 11).

Figure 11. Multicomponent reaction products in eucalyptol [151].
5.3. Synthesis of Pyridoquinazolinone Derivatives

Fused quinazolinones have significant medicinal value and many 11H-pyrido[2,1-b]quinazolin-11-one derivatives have been extensively described, mainly replaced by electron-donating or electron-withdrawing groups [167,168].

The same team as above sought to expand the chemical space and investigate the possibility of condensing polycyclic anthranilic acid derivatives with 2-bromopyridines to synthesize a series of new tetracyclic pyridoquinazolinone derivatives [169]. They proposed the synthesis of novel heteroaromatic systems in which the 11H-pyrido[2,1-b]quinazolin-11-one ring was fused on its aromatic part by heterocycles containing oxygen, sulfur or nitrogen atoms using eucalyptol as solvent. In the first experiments, methyl 6-aminobenzo[d]thiazole-7-carboxylate was reacted with 2-bromopyridine using the metal-free conditions already described [170]. Unfortunately, the desired product was not obtained after several tests. Therefore, they applied the metal-catalyzed conditions earlier described for the condensation of thiophenic amino acid analogs [169]. The addition of a catalytic amount of Pd(OAc)₂ (3 mol%) and Xantphos (4 mol%) in eucalyptol allowed successful synthesis of the expected tetracyclic pyridoquinazolinone derivative 105 to be obtained in excellent yield. Then, the scope of this methodology was extended to various starting methylantranilic esters (methyl 6-aminobenzo[d]thiazole-7-carboxylate, methyl 6-aminobenzo[d]thiazole-5-carboxylate, 7-amino-2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid methyl ester and methyl 6-amino-1H-indazole-7-carboxylate) and various 2-bromopyridines. In general, the desired final compounds 101, 103, 105–116 were obtained in good to excellent yield. However, they were not successful in the synthesis of 102 and 104 when methyl 6-amino-1H-indazole-7-carboxylate was stirred in the same conditions as those described for its analogues (Figure 12).

Figure 12. Pyridoquinazolinone derivatives in eucalyptol [169].
6. Conclusions

Compiled research shows that eucalyptol (1,8-cineole) is considered a safe chemical at normal doses. The toxicological data available for eucalyptus oil and the various compounds it contains are quite limited and of poor quality. Pharmacological studies conducted on eucalyptol (1,8-cineole) have confirmed the huge potential of this component in the treatment of various diseases.

In recent years, teams have highlighted the importance of finding methodologies with a lower ecological impact. Substituting the solvent with derivatives of biological origin has been highlighted as a valid option. Several laboratories have risen to the challenge and responded positively, reporting effective solutions for the synthesis of skeletons with interesting potentials in terms of their use for a wide variety of diseases. One of the central issues in demonstrating real alternatives for solvent replacement is related to the need, during the development of methodologies, to maintain the level of yields of the final products at levels close to and if possible higher than those previously reported. In addition, the development of coupling reactions that do not require the use of dry solvents or inert atmosphere increases the potential for the widespread application of these methods. In this account, one team provided insight into its design and thought process toward planning the synthesis of O,S,N-heterocycle scaffolds through greener approaches than the most commonly used coupling reactions (i.e., Suzuki–Miyaura, Sonogashira–Hagihara, Buchwald–Hartwig, Migita–Kosugi–Stille, Hiyama and cyanation coupling reactions). Accordingly, this team demonstrated the use of eucalyptol as a solvent that presents an effective strategy for coupling reactions and the construction of heterocycles containing oxygen, sulfur and nitrogen. The experimental results already obtained with eucalyptol and its physical properties suggest that it can advantageously replace a large number of solvents, including in alphabetical order, Diethyl ether, DMF, DMA, DME, 1,4-Dioxane, Ethyl acetate, THF, Toluene and others less used ones, thus responding to a number of the 12 principles of green chemistry [171]. Other new bio-solvents should also be extensively studied, in order to increase applications and continue efforts in the implementation of eco-friendly methodologies.

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