Article

Eucalyptol as a Bio-Based Solvent for Buchwald-Hartwig Reaction on O,S,N-Heterocycles

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Abstract: We report here the use of eucalyptol as a bio-based solvent for the Buchwald–Hartwig reaction on O,S,N-heterocycles. These heterocycles containing oxygen, sulfur and nitrogen were chosen as targets or as starting materials. Once again, eucalyptol demonstrated to be a possible sustainable alternative to common solvents.

Keywords: eucalyptol; Buchwald–Hartwig reaction; O,S,N-heterocycles; greener methodology; bio-based solvent

1. Introduction

In organic synthesis reactions, a solvent is the component present in the greatest amount and constitutes the fundamental element of the environmental performance of processes [1]. Despite the efforts of organic chemists in recent years to limit the environmental impact of research in organic synthesis via, in particular, the reduction of catalyst quantities or the development of methods without metals, it is essential to investigate the nature of solvents. For the last few years, our team has been dedicated to and focused on the discovery of new solvents, as well as on the development of new methodologies and approaches for the synthesis of heterocycles using greener solvents. As demonstrated in our latest reported work, [2] eucalyptol can be an interesting, viable and sustainable alternative to common solvents. It is the main constituent of the essential oil of eucalyptus; a fast-growing tree that is experiencing a recrudescence at the plantation level due to its use in the paper industry.

Pursuing our objective of the development of new practices in the synthesis of heterocycles containing oxygen, sulfur and nitrogen, [3–8] we explored the potentialities of eucalyptol as a solvent in the Buchwald–Hartwig coupling reaction. This work began with a literature review to identify the best conditions for this kind of transformation. Once we had collected the main and most commonly used reaction conditions for the Buchwald–Hartwig coupling reaction, [9–27] we selected the conditions that mainly applied to the heterocycles frequently used by the team. The following conditions were identified as the starting point of this study (Table 1). The most commonly used conditions made use of Palladium sources as catalysts (Pd(OAc)₂ or (Pd₂dba₃), often associating certain types of ligands (TTBP-HBF₄, BINAP, Xantphos or PPh₃); for bases, the choice fell particularly at three: K₂CO₃, K₃PO₄ or Cs₂CO₃. The reaction time ranged from 3–48 h at a temperature of 70–115 °C. These conditions allowed us to begin our optimization work of the Buchwald–Hartwig reaction conditions when using eucalyptol as the solvent.

2. Results and Discussion

In Table 1 details a summary of the results obtained after combining all the possible conditions by varying palladium complex, ligand and base. As per the reaction temperature level, we observed
in the collection of published results that the reported ranges of temperature were between 70–115°C. Nevertheless, our previous work showed that a reaction temperature from 100 °C was required to reach a total dissolution and consequently, a good reaction progress [2]. In this work, we established that the best temperature was 110 °C. For the starting material, we used the 2-bromofluorene as the brominated derivative and chose aniline as the amine reagent (Scheme 1, Table 1). The stoichiometry has been chosen from the literature and experience from our previous work on the synthesis of O,S,N-heterocycles.

![Scheme 1. Substrates used to optimize reaction conditions.](image)

The expected compound was obtained by stirring at 110 °C for a duration between 17–48 hours, depending on the reagents (Table 1). This is in agreement with the average time interval found in various previously reported works regarding the application of the Buchwald reaction (3–48 h).

Regarding the different results listed in Table 1, in the first 12 entries devoted to the use of palladium acetate as catalyst, we varied the type of ligand and base.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd (5 mol%)</th>
<th>Ligand (10 mol%)</th>
<th>Base (2 eq.)</th>
<th>t (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)₂</td>
<td>TTBP-HBF₄</td>
<td>K₂CO₃</td>
<td>30</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)₂</td>
<td>TTBP-HBF₄</td>
<td>K₃PO₄</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂</td>
<td>TTBP-HBF₄</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂</td>
<td>BINAP</td>
<td>K₂CO₃</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>BINAP</td>
<td>K₃PO₄</td>
<td>17</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)₂</td>
<td>BINAP</td>
<td>Cs₂CO₃</td>
<td>17</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>K₂CO₃</td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)₂</td>
<td>Xantphos</td>
<td>K₃PO₄</td>
<td>17</td>
<td>72</td>
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<tr>
<td>9</td>
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<td>Xantphos</td>
<td>Cs₂CO₃</td>
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<td>68</td>
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<tr>
<td>10</td>
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<td>K₂CO₃</td>
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<tr>
<td>11</td>
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<td>PPh₃</td>
<td>K₃PO₄</td>
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<tr>
<td>12</td>
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<td>PPh₃</td>
<td>Cs₂CO₃</td>
<td>40</td>
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</tr>
<tr>
<td>13</td>
<td>Pd₂dba₃</td>
<td>TTBP-HBF₄</td>
<td>K₃PO₄</td>
<td>48</td>
<td>40</td>
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<tr>
<td>14</td>
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<td>Cs₂CO₃</td>
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<td>38</td>
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<tr>
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<td>BINAP</td>
<td>Cs₂CO₃</td>
<td>20</td>
<td>67</td>
</tr>
</tbody>
</table>
It can be noted that the choice of the base is dependent on the type of ligand used. When using cesium carbonate as the base, yields were generally high in the presence of BINAP or TTBP.HBF₄ as the ligand (Scheme 1, Table 1, entries 3 and 6). When we used PPh₃ as the ligand with K₃PO₄ as the base, the best result was found (Scheme 1, Table 1, Entry 11); the base which also allowed a good yield when used with TTBP.HBF₄ as the ligand (Scheme 1, Table 1, entry 2). The xantphos as the ligand with K₃PO₄ as the base proved to be a good option for a significant reduction in the reaction time (17 h) accompanied by a better yield compared with the use of K₂CO₃ or Cs₂CO₃ (Scheme 1, Table 1, entries 7–9). Following these results obtained with palladium acetate, we carried out three reactions with Pd₃dba₃ as the catalyst (Scheme 1, Table 1, entries 13–15) using ligands and bases which gave the best results with Pd(OAc)₂ (Scheme 1, Table 1, entries 2, 3 and 6). The best yield with this catalyst (67%) was obtained with BINAP and Cs₂CO₃ (Scheme 1, Table 1, entry 15) and this Pd source was no more advantageous compared to the time when the same ligand and base were used with palladium acetate (Scheme 1, Table 1, Entry 6).

With these best conditions in hand, we proceeded to the analysis of scope and limitations using Pd(OAc)₂ (5 mol%) as the Pd source, BINAP (10 mol%) as the ligand and Cs₂CO₃ (2 equiv.) as the base at 110°C.

We selected five brominated products as the substrate containing oxygen, sulfur and nitrogen (Figure 1) and several amine derivatives (Figure 2).

It should be noted that the reaction time varied depending on the classes of compounds; this is the reason why we decided to display the results by class of heterocycle.
2.1. From 2-Bromofluorene

In the literature, only the use of toluene was mentioned for the Buchwald reaction on 2-bromofluorene and we found three teams who reported synthetic work using this substrate. In Graph 1, we present the average yield values on three reactions from the Nakano team, and one reaction in both Wang’s team and Jeon’s team [28–30].

Graph 1. Average yield (%) reported for the Buchwald–Hartwig reaction of 2-Bromofluorene using toluene as the solvent.

The commercially available 2-Bromofluorene was then reacted with various amines in eucalyptol as the solvent at 110°C for 17 h (Figure 3, Supplementary Materials). Compounds 1a to 1f were obtained with good yields (49%–88%). The average yield for the Buchwald–Hartwig reaction of 2-Bromofluorene using eucalyptol as the solvent was 71%. In comparison with yields described for this reaction with the same substrate in toluene, those obtained using eucalyptol were generally similar, except in two cases (1c,1f) where they were slightly lower (Graph 1). However, since toluene is classified as problematic [31], eucalyptol is a very good alternative for this transformation.

Figure 3. Buchwald–Hartwig reaction in eucalyptol starting from 2-Bromofluorene.
2.2. From 4-Bromo-1,2-methylenedioxybenzene

Using 4-Bromo-1,2-methylenedioxybenzene as the starting material, we found five studies reported in the literature that applied the Buchwald reaction to it. The solvents used by these research groups were 2-methyl-2-propanol, DMF and toluene. With this substrate, the average yields were provided on six reactions in 2-methyl-2-propanol, six reactions in toluene and only one reaction in DMF [32–36].

The commercially available 4-Bromo-1,2-methylenedioxy benzene underwent the same coupling reaction conditions as 2-Bromofluorene in Eucalyptol as the solvent at 110 °C for 24 h. Also in this case, we were able to synthesize the desired compounds 2a to 2e with good yield (Figure 4, Supplementary Materials). Eucalyptol gave better results compared to DMF and 2-methyl-2-propanol (Graph 2). The average yield for the Buchwald–Hartwig reaction of 4-Bromo-1,2-methylenedioxybenzene using Eucalyptol as the solvent was 72%. Similarly, the toluene showed slightly higher yield; however, this slight increase in yield does not justify its use since toluene is classified as problematic [31]. Likewise, our new solvent is an excellent opportunity to reduce the environmental impact of this chemical transformation.

**Graph 2.** Average yield (%) reported for the Buchwald–Hartwig reaction of 4-Bromo-1,2-methylenedioxybenzene in the most commonly used solvents.

**Figure 4.** Buchwald–Hartwig reaction in eucalyptol starting from 4-Bromo-1,2-methylenedioxybenzene.
2.3. From 6-Bromo-2-methylquinoline

We found five references regarding the Buchwald–Hartwig reaction using 6-Bromo-2-methylquinoline as the starting material. The solvents used by the researchers were xylene, THF and toluene. We also calculated the average yield here (Graph 3); we found 70% yield on five reactions in toluene, 75% which is the yield of only one example in xylene and 60% average yield on two reactions in THF [37–41].

Graph 3. Average yield (%) reported for the Buchwald–Hartwig reaction of 6-Bromo-2-methylquinoline in the most commonly used solvents.

The commercially available 6-Bromo-2-methylquinoline was reacted with the same amine reagents as previously, in the same conditions, to lead to expected Buchwald–Hartwig coupling products in good yield (61%–99%) (Figure 5, Supplementary Materials). The average yield for the Buchwald–Hartwig reaction of 6-Bromo-2-methylquinoline using eucalyptol as the solvent was 89%. The yields obtained in eucalyptol were better when compared to results already reported with common solvents.

Figure 5. Buchwald–Hartwig reaction in eucalyptol starting from 6-Bromo-2-methylquinoline.
2.4. From 7-Bromo-6-phenylthieno[2,3-b]pyrazine and 3-Bromo-2-phenylthieno[3,2-b]pyridine

To the best of our knowledge, there is no report in the literature to date on the use of 7-Bromo-6-phenylthieno[2,3-b]pyrazine and 3-Bromo-2-phenylthieno[3,2-b]pyridine as the starting material involved in pallado-catalyzed coupling reactions of the Buchwald–Hartwig type. In order to have a comparison point and to be able to view the comportment of thieno-fused derivatives, we looked for similar compounds and found Buchwald–Hartwig studies using dioxane and 2,4,6-collidine as solvents in reaction on benzo[b]thiophene [42–45]. In this case, the average yields were given on two reactions for each solvent and, as can be seen from Graph 4, they were very low: 15% in dioxane and 5% in 2,4,6-collidine.

Graph 4. Average yield (%) reported for the Buchwald–Hartwig reaction of benzo[b]thiophene in the most commonly used solvents.

It was decided to test our solvent starting from 7-Bromo-6-phenylthieno[2,3-b]pyrazine and 3-Bromo-2-phenylthieno[3,2-b]pyridine using the previous conditions, even though the reactivity of these heterocycles was often reported as reduced (Figure 6). We were pleasantly surprised to find that the results obtained with our conditions were particularly good or excellent since they ranged from 62% to 99% for the synthesis of desired compounds 4a–c and 5a–c (Supplementary Materials).

The average yield for the Buchwald–Hartwig reaction of thienopyridine thienopyrazine using eucalyptol as the solvent was 84%. Analysing the mean values obtained by the various teams in the development of the approach for the Buchwald–Hartwig studies using thieno-fused derivatives, we can conclude that the use of eucalyptol is a particularly interesting option also for this type of pallado-catalyzed coupling reaction, which is not usually easy to handle.

Figure 6. Buchwald–Hartwig reaction in eucalyptol starting from 7-Bromo-6-phenylthieno[2,3-b]pyrazine and 3-Bromo-2-phenylthieno[3,2-b]pyridine.
2.5. Recyclability of the solvent.

As reusability of the solvent is essential from an economic and environmental perspective, we have shown its feasibility throughout the present study. This is in line with results from our previous work [2], wherein an average 70% solvent recovery (from using rotary evaporator system) was observed for each reaction series without noticeable loss of properties.

3. Materials and Methods

General Methods

All reagents were purchased from commercial suppliers Sigma Aldrich, St Quentin Fallavier Cedex, France; Fluorochem, Derbyshire, SK131QH, UK and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation (Merck, St Quentin Fallavier Cedex, France). Flash column chromatography was performed on silica gel 60 (230 – 400 mesh, 0.040 – 0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes and are uncorrected. 1H and 13C NMR spectra were recorded on a Bruker avance II spectrometer (Bruker, Wissembourg, France) at 250 MHz (1H, 62.9 MHz) and on a Bruker avance III HD nanobay (Bruker, Wissembourg, France) 400 MHz (1H 100.62 MHz). Chemical shifts are given in parts per million from tetramethylsilane (TMS) or deterred solvent (MeOH-d4, Chloroform-d) as internal standard. The following abbreviations are used for the proton spectra multiplicities: b: broad, s: singlet, d: doublet, t: triplet, q: quartet, p: pentuplet, m: multiplet. Coupling constants (J) are reported in Hertz (Hz). Multiplicities were determined by the DEPT 135 sequence. High-resolution mass spectra (HRMS) were performed on a Maxis UHR-q-TOF mass spectrometer (Bruker, Wissembourg, France) Bruker 4G with an electrospray ionisation (ESI) mode (Bruker, Wissembourg, France).

4. Conclusions

We have shown that eucalyptol could be an interesting alternative to conventional solvents for the Buchwald–Hartwig reaction on O,S,N-heterocycles. This solvent, derived from biomass, was effective for all substrates of heteroatom-containing heterocycles, such as oxygen, sulfur and nitrogen that are used in this study. As mentioned in our previous work, the use of eucalyptol as a green solvent is also related to its safety and pharmacological profiles: Eucalyptol is considered to be a safe chemical when taken in normal doses. It becomes hazardous via ingestion, skin contact or inhalation at higher doses and does not show genotoxicity or carcinogenicity [46].

For all these reasons and the positive experimental results that we achieved in the laboratory, we will continue to study other reactions using eucalyptol as the solvent.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1

Author Contributions: J.F.C. and S.B.R. conceived, designed the experiments, analyzed the data and wrote the paper. J.F.C. performed the experiments.

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References


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