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### Eucalyptol as bio-based solvent for Migita–Kosugi–Stille coupling reaction on O, S, N-Heterocycles

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**Abstract:** We report herein an investigation on the use of eucalyptol as new solvent for organic transformations applied to the Migita-Kosugi-Stille palladium-catalyzed cross-coupling reaction. Heterocycles containing oxygen, sulfur and nitrogen were chosen as starting materials. Eucalyptol turned out to be a viable sustainable alternative to common solvents for this reaction.

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*keywords:* Migita-Kosugi-Stille, heterocycles, bio-based solvent; Pd-Cross Coupling

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## 1. Introduction

The *O,S,N*-heterocyclic compounds and their synthetic pathways are widely studied because of their numerous potential biological activities whether for therapeutic or agrochemical purposes. In recent years, many teams of researchers have been studying solvent replacement solutions. Since the solvent is the component in the greatest quantities during chemical transformations, it seems necessary to replace it with greener alternatives in order to reduce the environmental impact of the organic chemist. Several papers report bio-sourced solvents as effective substitutes to conventional petroleum-derived solvents for the synthesis of *O, S, N*-heterocyclic compounds [1-16].

Access to these compounds of interest often involves the development of a palladium-catalyzed methodology that has become an approach of choice in modern organic synthesis processes [17-20].

Continuing our efforts in the development of greener synthesis processes applied to the preparation of various heterocycles that may contain oxygen, sulfur and / or nitrogen [21-27], we have explored in this work the potentialities of Eucalyptol as bio-sourced solvent for the Migita-Kosugi-Stille coupling reaction on chlorinated *O,N*-heterocycles *S,N,N*-heterocycles or polynitrogen-heterocycles.

The study about the application of eucalyptol in the development or pharmacomodulation of several heterocyclic core structures has shown its potential and its effectiveness as a greener alternative [28,29].


This bio-solvent belongs to the class of terpene compounds. Terpenes are natural hydrocarbons produced by a wide variety of plants. Essential oils and resins often come from plant wastes. In our case Eucalyptol is extracted from Eucalyptus leaves of which it is the main constituent [30]. However, in recent years the Eucalyptus plantations have increased in quantity due to the use of wood for the paper industry. Eucalyptus being a fast-growing tree allows rapid regeneration of forests and therefore sustainable management or ecosystem management of forests.

Eucalyptol is a colorless liquid, which solvatochromic parameters have been determined together with a large number of other natural liquid polymers or solvents issued from petrochemistry [31]. No other information than these parameters could be identified in the literature. To our knowledge, there is, to date, no occurrence of a publication on the use of this solvent in organic synthesis with the exception of our recent work [28,29].

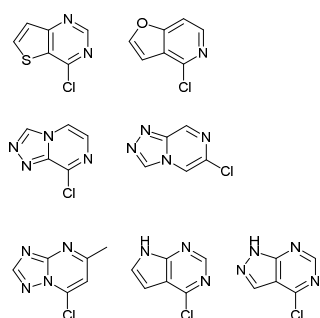
Besides, the molecule has been referenced for its effectiveness in the medical field, with effects of the corresponding essential oil on chronic diseases [32] and for its anti-inflammatory properties [33,34].

Excited by the results obtained in our first studies [28,29], we decided to explore other well-known reactions from some commercially available starting materials (Fig. 1), some of which we have already used in publications [21,27-29,31], and to assess the relevance of this solvent.

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**Fig. 1:** heterocyclic core structures used

## 2. Experimental, Results and Discussion

A literature review about functionalization of the *O*, *S*, *N*-containing fused heterocycles of interest to us and involving Stille coupling, allowed identifying two research teams; Sigita Tumkevicius and Mikhail S. Nechaev [35-37], who have mentioned a similar synthesis. On the basis of these publications, we have optimized the reaction conditions on one of the envisioned starting materials; 4-chlorothieno[3,2-*d*]pyrimidine **1** (*S,N,N*-heterocycle). The different tests and results are summarized in Table 1.

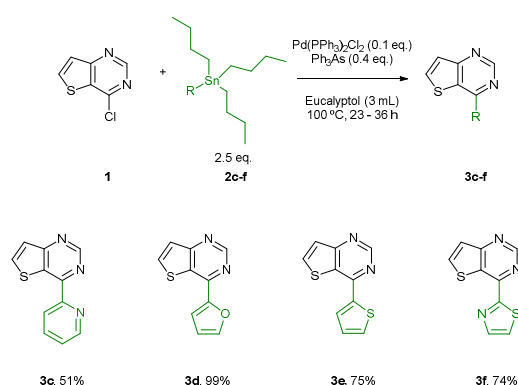
The best conditions for reacting this starting material, among those previously selected, were obtained using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (10 mol%) and Ph<sub>3</sub>As (40 mol%) in Eucalyptol at 100 °C for 23h.

**Table 1.** Optimization of Pd-coupling condition of 4-chlorothieno[3,2-*d*]pyrimidine **1**.

Entry	Catalyst (eq.)	Ligand (eq.)	Base	T (°C)	t (h)	Yield <sup>a</sup> (%)
1	Pd(OAc) <sub>2</sub> (0.1)	P(Cy <sub>3</sub> ) (0.2)	CsF (1.5)	100	21	<b>3a</b> , 79
2	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (0.1)	Ph <sub>3</sub> As (0.4)		100	21	<b>3b</b> , 98
3	Pd(OAc) <sub>2</sub> (0.1)	P(Cy <sub>3</sub> ) (0.2)	CsF (1.5)	100	25	<b>3b</b> , 62
4	Pd(PPh <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> (0.1)	Ph <sub>3</sub> As (0.4)		100	23	<b>3a</b> , 99

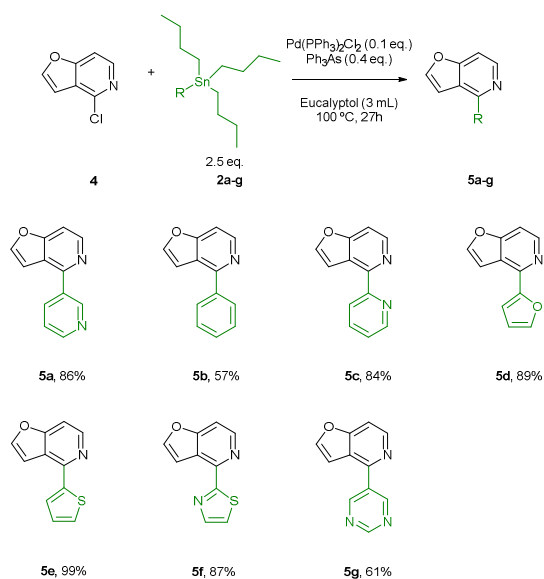
<sup>a</sup>isolated yields after purification via flash chromatography.

Based on these results (Table 1) the scope and limitations of the Stille coupling reaction on 4-chlorothieno[3,2-*d*]pyrimidine **1**, were assessed using several hetero-tributylstannyl derivatives (Fig. 2).



**Fig. 2** Migita–Kosugi–Stille coupling on 4-chlorothieno[3,2-*d*]pyrimidine **1**

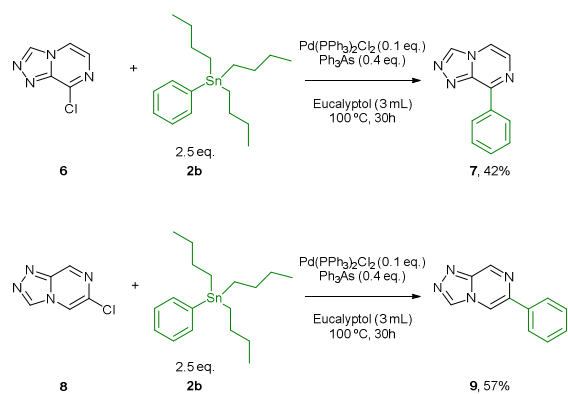
Starting from 4-chlorothieno[3,2-*d*]pyrimidine **1** the desired compounds **3c-f** were obtained in moderate to excellent yield (Fig. 2). It should be noted that the poorest result of 51% was achieved with the tributylstannylated pyridine derivative, which is generally not very reactive. The same conditions were applied to other heterocycles. These Pd-conditions were used on 4-chlorofuro[3,2-*c*]pyridine **4** (*O,N*-heterocycle) and for all the tributylstannyl derivatives which were used, the heterocyclic starting material was consumed in 27 hours. Obtained results are summarized in Fig. 3.



**Fig. 3** Migita-Kosugi-Stille coupling on 4-chlorofuro[3,2-*c*]pyridine **4**.

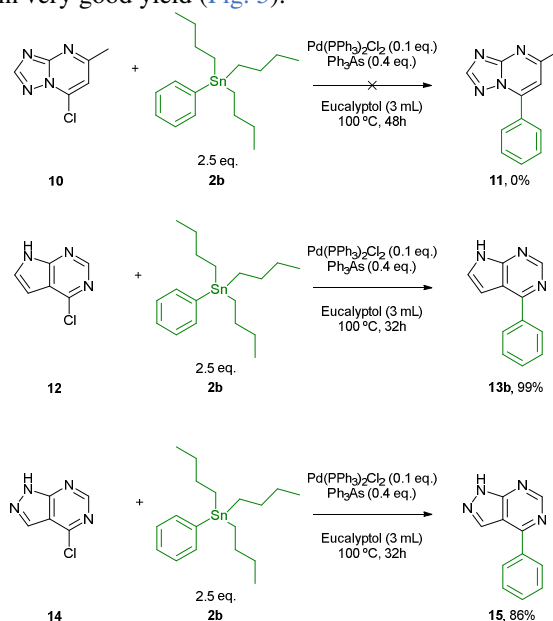
All the desired compounds **5a-g** were obtained in moderate to excellent yield (Fig. 3).

We started from tributylstannylbenzene, that gave the worst result with previous heterocycle, to evaluate the feasibility of the coupling with triazolopyrazines. The same catalytic conditions were applied to the 8-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **6** and 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **8** to lead to expected compounds **7** and **9** respectively after 30 h of reaction at 100 °C in moderate yield (Fig. 4).



**Fig. 4** Migita-Kosugi-Stille coupling on 8-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **6** and 6-chloro-[1,2,4]triazolo[4,3-*a*]pyrazine **8**

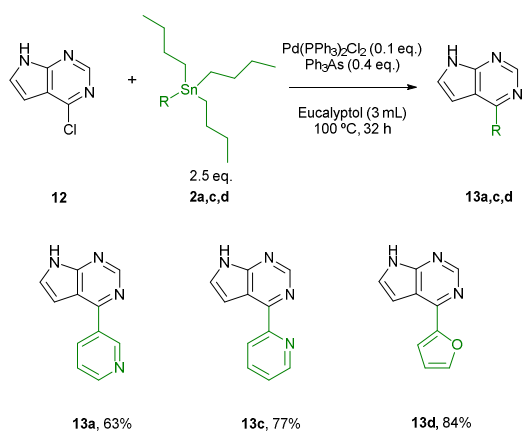
Unfortunately when we used 7-chloro-5-methyl[1,2,4]triazolo[1,5-*a*]pyrimidine **10** in our optimized conditions with less efficient tributylstannylbenzene, we were not able to synthesize the expected coupled compound **11** even after 48h of reaction (the starting material was recovered). No traces of compound were detected while 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **12** or 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine **14** lead to desired compounds **13b** et **15** in very good yield (Fig. 5).



**Fig. 5** Migita-Kosugi-Stille coupling on 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **12** or 4-chloro-1*H*-pyrazolo[3,4-*d*]pyrimidine **14**

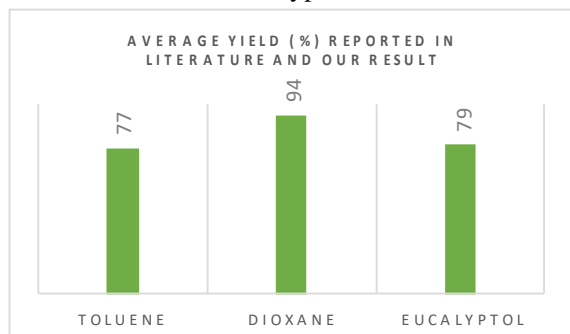
The 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **12**, that gave the best result with tributylstannylbenzene (99% yield) was used with other hetero-tributylstannylated reagents and especially with two barely reactive pyridine derivatives, giving the expected products **13a** and **13c** with very acceptable yield of respectively 63 and 77%.

The results of the palladium catalyzed coupling reaction on 4-Chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine **12** are summarized in Fig. 6.



**Fig. 6** Migita–Kosugi–Stille coupling on 4-chloro-7H-pyrrolo[2,3-d]pyrimidine **12**

Analysing the various yields obtained by different teams in the development of the Migita–Kosugi–Stille palladium cross-coupling for the synthesis of *O,S,N*-heterocycles, we can conclude that Eucalyptol is a valid option (Graph 1). The average yields were calculated, depending on published examples, on 11 reactions in Toluene, 2 reactions in Dioxane, and on the 21 reactions described herein in Eucalyptol.



**Graph 1.** Average yield (%) reported for Migita–Kosugi–Stille coupling reaction on several O, S, N-containing fused heterocycles.

Although we obtained an average yield comparable to those obtained in toluene and slightly lower than those obtained in dioxane (Graph 1) [35–37], the results observed in eucalyptol are very encouraging. The comparison with Dioxane remains hypothetical given the small number of experiments (2) with which the average was calculated, moreover the reaction time is improved compared to reaction time

observed in these two conventional solvents (toluene: 48–72h and dioxane: 70h). Eucalyptol substitution is a valid option because of the known properties of toluene and dioxane. The Well's group compared the scores and rankings of commonly used solvents and these two classical solvents were classified as hazardous (dioxane) and problematic (toluene) [38].

### 3. Conclusion

We have developed an efficient, environmentally sound method for the Migita–Kosugi–Stille coupling reaction on various *O,S,N*-containing fused heterocycles in Eucalyptol. We herein demonstrated the feasibility of another catalytic process for this natural compound, its use as solvent. In addition, after reaction, eucalyptol can be recovered by distillation under reduced pressure, and reused immediately for the next step. Considering its recyclability, its very low toxicity and the very interesting results we have already obtained in metallo-catalyzed reactions, eucalyptol is an outstanding alternative to traditional solvents.

### Appendix A. Supplementary Information

Supplementary information associated with this article can be found, in the online version, at <http://dx.doi.org/>

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