

Evaluating the influence of the protecting group on the enantioselective Heck-Matsuda reaction of 3-cyclo-penten-1-ol.

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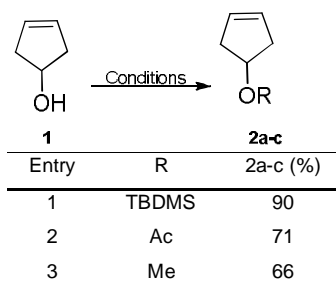
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Introduction

The first examples of the enantioselective Heck-Matsuda reaction were reported by Correia *et al* in 2012 and since then many improvements have been made.^{1,2} In a recent paper we described a new enantioselective Heck-Matsuda desymmetrization reaction using 3-cyclopentenol to produce chiral five-membered 4-aryl cyclopentenol scaffolds as main products.² Mechanistically, it was postulated that the hydroxyl group of 3-cyclopentenol acts as a directing group and is responsible for the unexpected *cis* stereochemistry observed in the 4-aryl-cyclopentenols. To evaluate the influence of the hydroxyl group in the arylating process we disclose here our results of the Heck-Matsuda reaction of protected derivatives of 3-cyclo-penten-1-ol **1**.

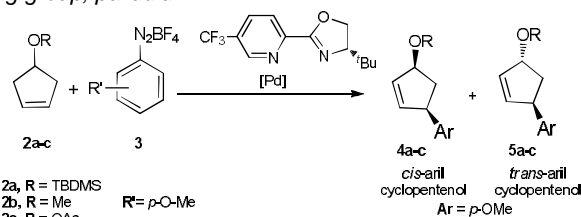
Results and discussion

We prepared three new cyclopentenol derivatives **2a-c** containing different protecting groups such as TBDMS, Ac and Me. The derivatives **2a-c** were prepared in good yields using well established procedures (**Scheme 1**).



Scheme 1: Preparation of derivatives **2a-c**.

Next, the compounds were submitted to the enantioselective Heck-Matsuda reaction using previous reported conditions. In all cases the reaction led to a mixture of the *cis* and *trans* 4-aryl-cyclopentenols (**Scheme 2**).



Scheme 2: HM reaction of compounds **2a-c**.^a

Interestingly, the *cis/trans* ratio of the products depended strongly on the protecting group on the oxygen atom. The best selectivity was obtained with derivative **4c** (OAc) (**Entry 3, Table 1**).

Table 1: Selectivity of HM reaction of compounds **2a-c**.

Entry	R group	<i>cis:trans</i> ratio ^b	yield %
1	TBDMS	0.7:1	56
2	Me	0.9:1	71
3	Ac	0.2:1	77

^b Determined by ¹H RMN. *ee*'s were not evaluated.

These results supports our hypothesis that a weak Lewis acid-base interaction of the *endo* oriented hydroxyl protected group towards the cationic Pd (II) is the major driving force favoring the formation of the *cis*-4-aryl-cyclopent-2-enol Heck product. This influence is minimized when the hydroxyl group is protected leading to the formation of *trans*-4-aryl-cyclopent-2-enol as the major Heck product.

Conclusion

In conclusion, we have shown that the interaction between the hydroxyl group and the palladium metallic center plays an important role to the formation of aril-cyclopentenols in the *cis* configuration. The presence of a protecting group on the hydroxyl resulted in the formation of the *trans* aril-cyclopentenols as the major Heck products.

Acknowledgments

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¹ Correia, C. R. D.; Oliveira, C. C.; Salles Jr., A. G.; Santos, E. A. F. *Tetrahedron Lett.* **2012**, 53, 3325.

² Angnes, R. A.; Oliveira, J. M.; Oliveira, C. C.; Martins, N. C.; Correia, C. R. D. *Chem. Eur. J.* **2014**, 20, 13117.

^a Pd(TFA)₂ (2.5 mol%), **L** (3.0 mol%), 1 equiv of DTBMP, 40 °C, 0.1 mmol scale.