Studies on the desymmetrization of 4-cycloheptenol via the asymmetric Heck-Matsuda reaction

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Introduction

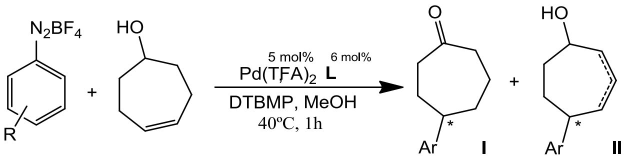
The Heck reaction is an important tool for asymmetric catalysis, namely for C-C bond formation.[1,2] Amongst other traditional Heck methodologies, the Heck-Matsuda reaction, which uses arene diazonium salts as the electrophile, presents many advantages.[3]

In 2012 the group of Correia has reported the first enantioselective Heck-Matsuda reaction, unveiling its potential for the synthesis of enantiomerically enriched compounds.[4] More recently this methodology has been successfully applied on the desymmetrization of 3-cyclopentenol.[5] Although some mechanistic considerations have been made on that work, further studies are necessary in order to attain a better understanding of the methodology and of its scope. Thus, herein we wish to present our preliminary results on the desymmetrization of 4-cycloheptenol via the asymmetric Heck-Matsuda reaction. Specifically, with such substrate we wish to evaluate how the size of the ring may affect the reaction outcome.

Results and Discussion

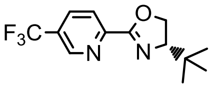
Based on previous results with 3-cyclopentenol we started our work with the reaction between 4-cycloheptenol and 4-(trifluoromethyl)benzenediazonium salt, according to the typical reaction presented below.

Figure 1. Desymmetrization of 4-cycloheptenol.



As shown on Figure 1, ketone products (**I**) and alcohol products (**II**) can be formed. In order to infer about its selectivity we first screened the reaction using several ligands. Our best result is presented on Table 1.

Table 1. Results with PyOx ligand (*S*)-4-(*tert*-butyl)-2-[4-(trifluoromethyl)pyridin-2-yl]-4,5-dihydrooxazole.

Ligand	y(GC)% (I)	e.e.% (I)	y(^{1}H NMR) % (II)
	50.2	70.0	29

Reaction solvent was screened next, and the best results were obtained with DMF (Table 2).

Table 2. Selected result regarding the solvent screening.

Solvent	η(GC) % (I)	e.e. % (I)	η(^{1}H NMR) % (II)
DMF	60.5	84.7	28

Although good e.e.'s were displayed the ratio between products **I** and **II** was only 2:1. Work is on going to increase both the product ratio and the enantiomeric excess.

Conclusions

So far, desymmetrization of 4-cycloheptenol has proven to be less selective than the one of 3-cyclopentenol thus showing that the size of the ring impacts the events taking place in the reaction.

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