Studies on the enantioselective Heck arylation of *N*-carboethoxy 3-pyrroline with aryldiazonium salts

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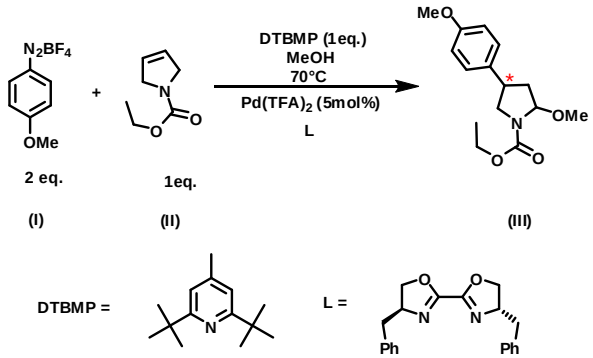
INTRODUCTION

The Heck-Matsuda reaction is an useful methodology to create new C-C bonds from olefins and aryldiazonium salts as substrates.[1] There are very few reports describing this enantioselective reaction.[2,3] Because of the great interest in the synthesis of chiral compounds, new enantioselective methods are welcome. Since the first example of the enantioselective Heck-Matsuda reaction was reported,[2] the Correia's group has been intensely studying this reaction. In this context, arylation of substrates such as *N*-carboethoxy 3-pyrroline (**II**) was elected as a key challenge. Once synthesized, these Heck adducts could be used as a building block to access enantioenriched biologically active compounds.[4]

RESULTS AND DISCUSSION

Previously established conditions[2] were used to prepare the Heck adduct (**III**) (Scheme 1). With this protocol the Heck product was obtained in only 6% yield with an *ee* of 51%. In view of the low yield, new reaction conditions were evaluated.



Scheme 1. Initial Heck-Matsuda reaction conditions

This reaction was also performed with different heating sources (microwave and sealed reactor), olefin concentration (2-4 equivalents with respect to the aryldiazonium salt) and reaction times (10-60 min). Improvements in yields were observed by increasing reaction time, but *ee's* were not affected significantly. Changes in olefin concentration do not affect the yield neither the *ee's* in a range of 2 – 3.5 equivalents. Application of microwave heating or performing the reaction in a sealed reactor for 1h, allowed formation of the desired product in 35% yield and 40% *ee.*

Different solvents were evaluated and the best condition was obtained using MeOH (entry 1). Another promising condition is the system H_2O:MeOH (entry 8). This system gave an excellent yield, although the *ee* was very poor.

Table 1. reaction scope in different solvents

Entry	Solvent	Yield (%)	*e.e* (%)
1	MeOH	35	40
2	Diox:MeOH (10%)	4	———
3	THF:MeOH (10%)	———	———
4	PhMe:MeOH (10%)	———	———
5	DMSO:MeOH (10%)	67	7
6	DMF:MeOH (10%)	54	12
7	H_2O:MeOH (10%)	99	9

CONCLUSION

In this work, the product of interest (**III**) was obtained in an excellent yield, but with rather low *ee* (Table, entry 8), or in moderated yield and *ee* (entry 1). Others reaction parameters are under evaluation, such as the palladium source and the base aiming at improving the enantioselectivity of the Heck-Matsuda reaction.

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