Designing *N,N*-based Ligands for the Enantioselective Pd-Catalyzed Synthesis of Quaternary Stereogenic Centers through Heck Reactions.

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Introduction

Enantioselective Pd-catalyzed Heck reaction is a powerful tool to synthesize complex molecules. Very recently, our and Sigman groups have independently reported the efforts to achieve high stereoselectivities for the Heck arylation of acyclic olefins, so far, a challenging on literature.[1,2] A common feature of these reports is the use of *N,N*-based ligands such as bisoxazolines and pyridine-oxazolines.

In this scenario, we present herein our results concerning the development of new *N,N*-based ligands for the arylation of trisubstituted olefins through the Heck-Matsuda reaction. As the construction of quaternary stereogenic centers via Heck reactions remains a challenging, new methods addressing these objectives are highly desirable.[3]

Results and Discussion

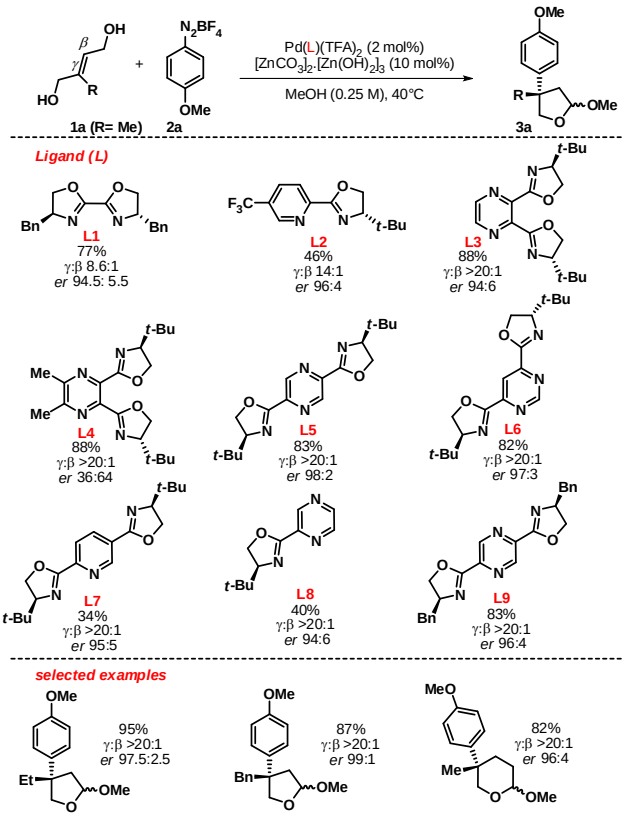
We began our studies with trisubstituted allylic alcohol **1a** as a model for the enantioselective Heck-Matsuda reaction (Scheme 1).

The previously reported ligands **L1** and **L2** failed to provide the Heck product *O*-methyl-lactol **3a** with the desired combination of high yields, regio and enantioselectivities. Next, we decided to synthesize the new ligands **L3** and **L4** combining both C_2-symmetry of **L1** and the electron deficient pyridine moiety of **L2**. The pyrazine based **L3** provided **3a** in 88% yield with a regioselectivity higher than 20:1 in favor of the desired product, and an excellent *er* of 94:6.

Besides the improvement generated by **L3**, formation of isomeric Pd(II) complexes were observed due the proximity between the oxazolines, also present in **L4**. Pleasingly, this drawback was circumvented after the synthesis of the isomeric ligands **L5** and **L6**. They were capable of improving the *er's* of **3a** to 98:2 and 97:3, respectively.

Presence of both oxazoline and endocyclic nitrogens proved essential to attain high *er's* and chemical yields as observed when **L7** and **L8** were used. Finally, replacement of the bulky *t*-Bu substituent by a benzyl group in **L9** did not affect the efficiency of the catalyst.

Scheme 1. Enantioselective Pd-catalyzed arylation of trisubstituted olefins.



Conclusion

We described herein a highly regio and enantioselective Heck arylations of acyclic olefins to provide quaternary stereogenic centers. New pyrimidine and pyrazines decorated with chiral oxazolines proved efficient ligands for those transformations, providing the desired products with enantiomeric ratios up to 99:1.

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