

Highly Regio- and Stereoselective Arylation of Trisubstituted Olefins via Heck-Matsuda Reactions.

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Abstract

A new Heck reaction is presented herein for the synthesis of diverse substituted ketones bearing two consecutive stereocenters.

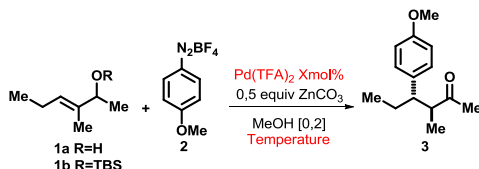
Introduction

The Heck-Matsuda reaction is a very useful tool for the formation of C-C bonds. However, its use in the arylation of challenging trisubstituted olefins is rare. The very few studies available indicate the formation of quaternary stereocenters in those reactions. Herein, we report an unusual arylation of trisubstituted olefins allowing the regio- and stereoselective construction of two consecutive stereocenters, including the unconventional construction of α -substituted ketones from silyl allylic alcohols.

Results and Discussion

Table 1 briefly shows the optimization of the reaction with the protected and unprotected alkenols (**1a** and **1b**), varying the temperature and the amount of palladium.

Table 1. Optimization of Heck-Matsuda reaction.

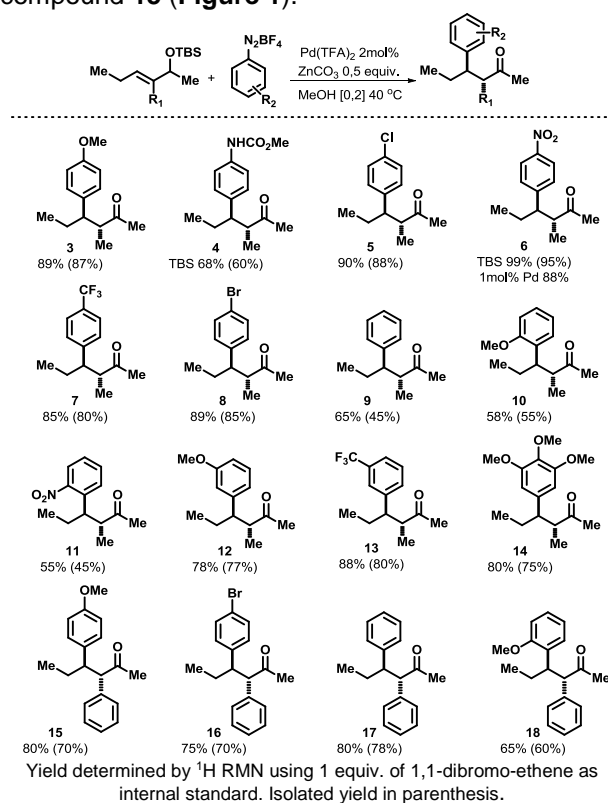


#	R	Temp. (°C)	Pd (mol%)	Yield (%) ^b
1	H	60	10	60
2	H	40	10	70
3	H	40	5	62
4	H	40	2,5	60
5	TBS	60	10	98
6	TBS	40	10	99
7	TBS	40	5	98
8	TBS	40	2	89

a. olefin: arenediazonium salt 1:2; 0.5 equiv. ZnCO₃, [0.2 M]. b. Yield determined by ¹H RMN using 1 equiv. of 1,1-dibromo-ethene as internal standard.

The use of TBS protected alcohol proved to be more efficient than the free alcohol. It was effective even with 2 mol% of palladium. The reaction condition in entry **8** was selected as best due its optimal balance of catalyst loading and yield of the desired product. This reaction condition was further evaluated with structurally diverse arenediazonium salts and olefins

(Scheme 1). It is important to point out that in all cases the desired ketones were obtained as a single stereoisomer in good to excellent yields. The relative stereochemistry was confirmed by X-ray analysis of compound **15** (Figure 1).



Scheme 1. Scope of the reaction.

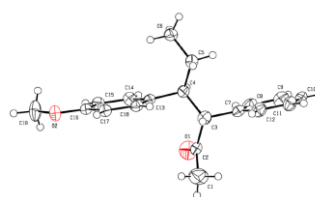


Figure 1. X-ray structure of compound **15**.

Conclusions

A new methodology for the arylation of trisubstituted olefins is described herein. Due to its remarkable increase in the structural complexity, we are now applying this method for the synthesis of pharmacologically relevant molecules.

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