Heck–Matsuda Catalysis for the Synthesis of Spiro-Heterocycles from Diazonium Salts and via Tandem Diazotization from Anilines

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Abstract

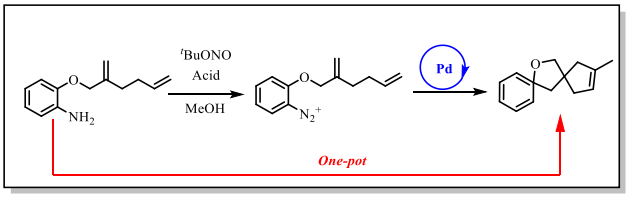
ABSTRACT - The arenediazonium salt 1-(2-((2-methylenehex-5-en-1-yl)oxy)phenyl)-2-(tetrafluoro-l5-boraneyl)diazene (**DZ1**) was synthesized from its corresponding aniline, 2-((2-methylenehex-5-en-1-yl)oxy)aniline (**AN1**), using HBF_4 and ^{t}BuONO (tert-butyl nitrite) in ethanol. **DZ1** was then subjected to a double Heck-Matsuda reaction using a palladium complex generated in-situ from $[Pd(OAc)_2]$ (10 mol%) and a chiral *N,N*-ligand (20 mol%), affording the spiro compounds 3'-methyl-2H-spiro[benzofuran-3,1'-cyclopentane]-3'-ene (major product **1**) and 3'-methyl-2H-spiro[benzofuran-3,1'-cyclopentane]-2'-ene (minor product **2**) in 36% overall yield. In addition, a tandem catalysis approach was employed to access the same products directly from the corresponding aniline in a one-pot process involving sequential diazotization and Heck-Matsuda reactions.

Keywords: Heck-Matsuda, organometallics, catalysis.

Introduction

C–C coupling reactions are typically catalyzed by palladium, demonstrating remarkable versatility and posing as a robust class of transformations in the pharmaceutical industry (1, 2). The Heck-Matsuda variant has gained much attention among C-C coupling reactions due to the ease with which the substrates used (diazonium salts) undergo oxidative addition with Pd(0) complexes, generating highly reactive cationic palladium species during the catalytic cycle. This approach enables the use of mild temperatures and tolerates a wide range of reagents, allowing for multiple reactions to be coupled via tandem catalysis, then broadening the scope of strategically functionalized compounds (3).

Arenediazonium salts bearing carbon chains with olefinic groups are attractive substrates for the synthesis of spiro compounds containing stereogenic centers, which can lead to enantioselective products. In this context, the present work aims to develop synthetic protocols for the enantioselective synthesis of spiro compounds via the Heck-Matsuda catalysis using palladium complexes (**Scheme 1**). Additionally, a tandem catalysis approach will also be considered, starting from the aniline to generate the arenediazonium salt in situ, followed by a one-pot Heck-Matsuda reaction.



Scheme 1. The synthetic strategy

Experimental

Synthesis of 1-((2-methylenehex-5-en-1-yl)oxy)-2-nitrobenzene (N1)

2-Methylenehex-5-en-1-ol (**A1**) was obtained following a previous procedure (4) and used without further purification. The reaction between **A1** (2.0 g, 17.8 mmol) and NaH (60% dispersed in mineral oil, 0.71 g, 17.8 mmol) in dried THF under N_2 at 0 ºC for 1 h afforded the deprotonated alcohol. 1-fluoro-2-nitrobenzene (1.25 mL, 11.9 mmol) was then added to the mixture to give **N1**, which was quenched by the addition of H_2O, and extracted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Yield: 87%.

Synthesis of 2-((2-methylenehex-5-en-1-yl)oxy)aniline (AN1)

Nitroarene **N1** (0.35 g, 1.5 mmol) was diluted in 10 mL of DMF, followed by the addition of $B_2(OH)_4$ (0.40 g, 4.5 mmol) and a solution of 0.5 M of 4,4'-bypiridine in DMF (30 µL, 15 µmol) and stirred at room temperature for 15 minutes. The mixture was then diluted in a H_2O:EtOAc mixture. The organic phase was collected, washed with brine, and dried over Na_2SO_4, filtered and concentrated under reduced pressure. Yield: 70%.

Synthesis of diazonium salt 1-(2-((2-methylenehex-5-en-1-yl)oxy)phenyl)-2-(tetrafluoro-l5-boraneyl)diazene (DZ1)

An aqueous solution of 48 w.t% (0.27 mL, 2.1 mmol) was added to a solution containing **AN1** (0.21 g, 1.0 mmol) in 1 mL of ethanol at room temperature. The system was allowed to cool to 0 ºC, and ^{t}BUONO (240 µL, 4.2 mmol) was added. The reaction was stirred for 15 minutes at 0 ºC and then for 2 h at room temperature. Cold ethyl ether (15 mL) was

added to the mixture and the reaction kept in the freezer for 1 week, giving the arenediazonium **DZ1**, which was filtered under vacuum. Yield: 20%.

*Procedure for Heck-Matsuda reaction of **DZ1** to produce 3'-methyl-2H-spiro[benzofuran-3,1'-cyclopentan]-3'-ene (product **1**) and 3'-methyl-2H-spiro[benzofuran-3,1'-cyclopentan]-2'-ene (product **2**)*

2 mL of HPLC grade methanol was added to a vial containing [$Pd(OAc)_2$] (2.2 mg, 10 µmol) and 4-(tert-butyl)-2-(4-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole (***N,N*** ligand) (4.8 mg, 20 µmol) and stirred for 15 minutes at 40 ºC. **DZ1** (30 mg, 0.1 mmol) was then added to the solution containing the pre-catalyst, followed by the addition of $ZnCO_3$ (6.2 mg, 0.05 mmol). Next, the reaction was maintained under stirring at 40 ºC for 24 h. The crude mixture was rotaevaporated and filtered through a flash column of silica in EtOAc to give the crude product, which was rotaevaporated and analyzed by NMR using 0.1 mmol of 1-methyl-3,5-bis(trifluoromethyl)benzene as internal standard.

*Procedure for tandem diazotation/Heck-Matsuda reaction from **AN1***

1.0 mL of HPLC grade methanol was added to a vial containing **AN1** (0.1 mmol, 20.0 mg), followed by the addition of 2,6-di-tert-butyl-4-methylpyridine ($DTBMPHBF_4$) (0.6 g, 0.2 mmol) and ^{t}BUONO (0.4 mL, 0.3 mmol). The mixture was added to a vial containing [$Pd(OAc)_2$] (2.2 mg, 10 µmol) and the ***N,N***-ligand (5.3 mg, 20 µmol), which were previously mixed for 15 minutes in 1.0 mL of methanol at 40 ºC. The mixture was rotaevaporated and filtered in a flash column of silica using EtOAc to give the crude product, which was rotaevaporated and analyzed by NMR using 0.1 mmol of 1-methyl-3,5-bis(trifluoromethyl)benzene as internal standard.

Results and Discussion

*Heck-Matsuda reaction from **DZ1** and **AN1***

The crude product of Heck-Matsuda reaction from **DZ1** with [$Pd(OAc)_2$] and the chiral *N,N*-ligand was initially characterized by ^{1}H NMR (**Figure 1**), and the hydrogens were attributed using HMBC and HSQC techniques. The spectrum displayed multiplets between 7.00 and 6.50 ppm related to the aromatic hydrogens. The olefinic hydrogen of the cyclopentene moiety was observed at approximately 5.20 ppm as two distinct signals: a singlet and a multiplet, corresponding to the mixture of regioisomeric products. This is in accordance with the signal for the hydrogens from the methyl group around 1.70 ppm, with 2 singlets. In both cases, the ratio between the major and minor signals of the products was 0.88, supporting this observation, indicating 88% of product 1. The hydrogens from CH_2 from the tetrahydrofuran moiety were identified as a dd at 4.25 ppm ($^2J_{H,H}$ = 8.61 Hz), followed by two multiplets related to the CH_2 from the cyclopentene moiety.

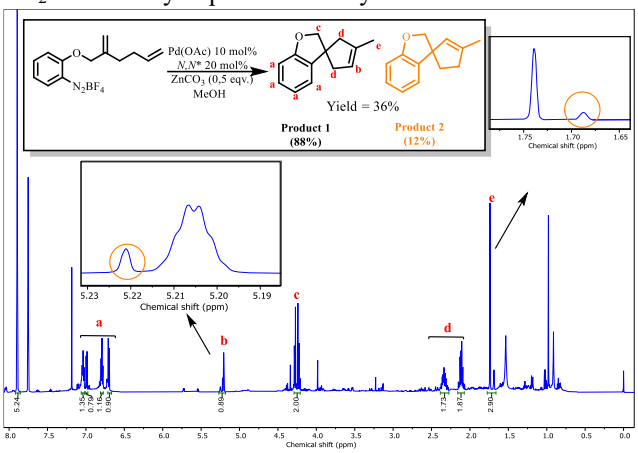
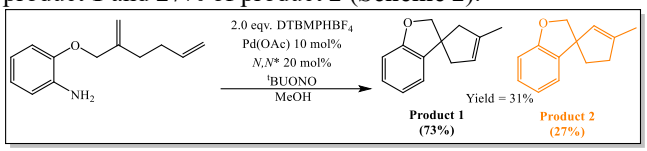


Figure 1. ^{1}H NMR of the product obtained from Heck-Matsuda reaction from **DZ1**.

Similarly, the tandem reaction of diazotation/Heck-Matsuda from **AN1** afforded the same products in 31% yield, however with a lower regioselectivity of 73% of product **1** and 27% of product **2** (**Scheme 2**).



Scheme 2. Products obtained from tandem diazotation/Heck-Matsuda reaction from **AN1**.

Conclusions

A double Heck-Matsuda reaction was successfully performed from **DZ1**, affording products **1** and **2** in 36% yield, with high regioselectivity toward product **1** (88%). The reaction also proved suitable for obtaining the same products from the corresponding aniline **AN1** through a tandem diazotization/Heck-Matsuda sequence, yielding 31% of products, with 73% selectivity for product **1**.

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References

1. M. J. Buskes, M. Blanco, Molecules. **2020**, 25, 3493.
2. H. Neumann, A. G. Sergeev, A. Spannenberg, M. Beller, Molecules. **2020**, 25, 3421.
3. P. L. M. O. Leão, O. D. KÖSTER, L. J. Duarte, A. A. C. Braga, C. R. D. Correia, J. Org. Chem. **2025**.
4. A. Tsimelzon, R. Braslau, J. Org. Chem. **2005**, 70, 10854.