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# An *in Situ* Generated Palladium on Aluminum Oxide: Applications in Gram-Scale Matsuda−Heck Reactions

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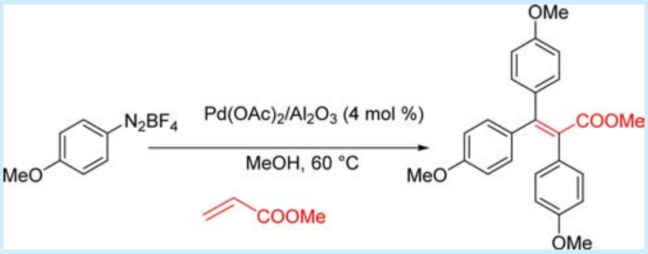
Supporting Information

**ABSTRACT:** *In situ* generated palladium on aluminum oxide provides an active catalytic system for Matsuda-Heck reactions in gram-scale. The novel catalyst proceeded through a significantly higher catalytic activity compared to the classical Pd/C system. Based on the high catalytic activity the first *α,β,β*-triarylation of methyl acrylate in good yields could be provided in one-step.



The Matsuda−Heck reaction[1,2] using aryldiazonium salts as electrophiles represents a powerful tool in the synthesis of suitable building blocks and natural products.[3−9]

The high reactivity of these starting materials enables benign reaction conditions combined with an ample tolerance against a plethora of functional groups including carbonyl groups as well as halides. The application of ligand-free conditions in alcoholic and/or aqueous media completes the positive features and nurtures a growing interest in the development of catalysts for applications toward more sustainable processes.

Hence, the design of more reactive and efficient catalytic systems has attracted a major interest.[10]

Specifically, the development of new supported palladium catalysts has attracted a significant interest because of an easier metal recovery and recycling in combination with a lower contamination of the product by toxic palladium residues. Therefore, a multitude of heterogeneous catalysts has been described in the literature.[11−13]

Beside the aforementioned aspects, the application of supported Pd-catalysts as a remarkable instrument for enhancing the reactivity and reduction of side products frequently presents an underappreciated tool in the scientific community for the Matsuda−Heck reaction. Thus, we could show that the utilization of an instantly generated palladium on charcoal had a tremendously positive aspect on the reaction rate and yield of functionalized benzalacetones obtained by the Matsuda-Heck reaction.[14]

Although a broad range of supporting materials like charcoal, carbon,[12,13] agarose[15] and calcium carbonate[16] was used the reports on aluminum oxide as supporting material are scarce. Thus, Beller et al.[17] reported the utilization of commercial available $Pd/Al_2O_3$.[18] Wei and co-workers recently described the coupling of diazonium salts with acrylates and styrene catalyzed by aluminum hydroxide supported palladium colloids.

However, it has to be pointed out that this catalytic system was prepared via a laborious sequence from $Pd(PPh_3)_4$ in the presence of tertraethylenglycole and aluminum-tri-*sec*-butoxide in butanol.[18]

Stimulated by the excellent results published by Felpin et al. concerning the high efficiency of homemade palladium/carbon catalysts[13] and the fact that alumina is a quite common supporting material in catalysis[19] we decided to embark on a simple catalytic system based on palladium immobilized on alumina.

Hence, this investigation represents our first preliminary results toward the utilization of *in situ* generated $Pd/Al_2O_3$ catalysts in the Matsuda−Heck reaction.

The starting point of our study was the examination and comparison of aluminum oxide versus charcoal as supporting materials for immobilized Pd-catalysts. Aluminum oxide 90, which is frequently used in chromatography, was chosen as palladium carrier. Before starting the Matsuda−Heck reaction, a reactive $Pd/Al_2O_3$ catalyst was prepared by 30 min prereduction of $Pd(OAc)_2$ by methanol in the presence of methyl acrylate and aluminum oxide 90 (1.9 wt % $Pd(OAc)_2$). Aside from the obtained yields and product ratios, both catalytic systems were compared by kinetic data like conversion rates and turnover frequencies (TOF)[14,4f] (Table 1):

Regarding the results presented in Table 1, it is obvious that the $Pd/Al_2O_3$ catalyst distinguishes itself on the one hand by a higher yield and on the other hand by a higher turnover frequency and conversion rates compared to the palladium on charcoal system.

Surprised and pleased by these interesting results we tried to rationalize the outcome by a more detailed investigation using scanning transmission electron microscopy (STEM) in SEM. In both cases the formation of Pd(0) clusters could be verified. However, it was revealed that the formation of smaller Pd-

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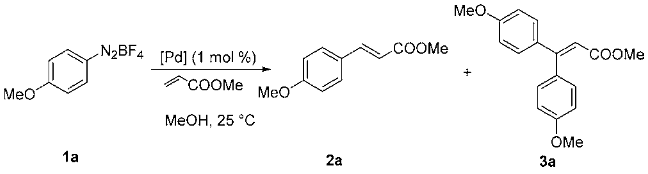
**Table 1. Comparison of the Catalytic Systems**



| entry | cat. | yield (%) | ratio **2a**:**3a** | conv rate (mmol*mL$^{-1}$*h$^{-1}$) | TOF (h$^{-1}$) |
|---|---|---|---|---|---|
| 1 | Pd/$Al_2O_3$ | 95 | 97.0:3.0 | 1.467 | 440 |
| 2 | Pd/C | 80 | 96.6:3.4 | 0.796 | 241 |

clusters is clearly favored on aluminum oxide in contrast to charcoal. This is distinctively reflected by the particle size distribution (Figure 1):

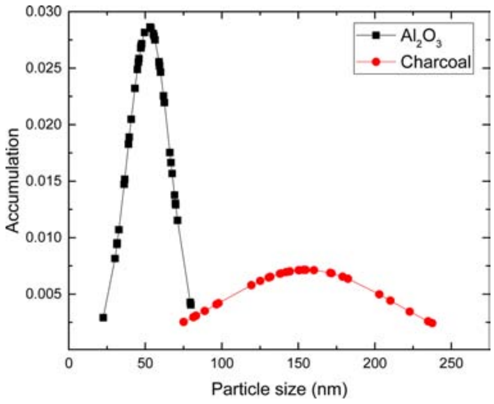


**Figure 1.** Particle size distribution of palladium on aluminum oxide and charcoal.

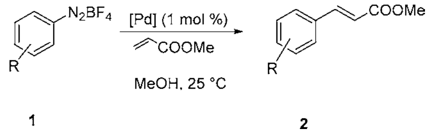
The two catalysts significantly distinguish themselves by their particle sizes of deposited Pd-clusters. In the case of charcoal the mean particle sizes of 149.3 nm is approximately three times larger than in the case of aluminum oxide (52.3 nm). Despite these large particle sizes, good results concerning yield and conversion rate were obtained in the case of charcoal. Charcoal also exhibits a very broad particle size distribution, whereas the range of particle sizes is comparatively narrow on aluminum oxide. These aspects might serve as an explanation for the differences in the catalytic activity of both systems. In spite of the higher reactivity and the superior yield realized with Pd/$Al_2O_3$ the same product ratio was obtained for each catalyst. In this regard, the high reactivity of the Pd/$Al_2O_3$-catalyst goes hand in hand with a good selectivity.

Based on this outcome, we explored the scope of our catalytic system with a variety of diazonium salts (Table 2):

It is noteworthy to mention that all reactions were conducted in gram-scale (10 mmol). As depicted in Table 2, all products were obtained in good to excellent yields. Surprisingly it had to be stated that in the case of 4-iodo-benzenediazonium tetrafluoroborate 10% of the diacrylate were formed (entry 6). Unfortunately, a reduction of the methyl acrylate quantity to 1 equiv did not diminish this side reaction (8% of the diacrylate were formed in the case of 1 equiv of methyl acrylate).

Removal of Pd-traces from crude product has attracted considerable attention in the pharmaceutical industry. To our pleasure only traces of palladium (<10 ppm), determined via ICP-MS could be detected after filtration of the catalyst in the crude product **2a**.

**Table 2. Scope of the Catalytic System**

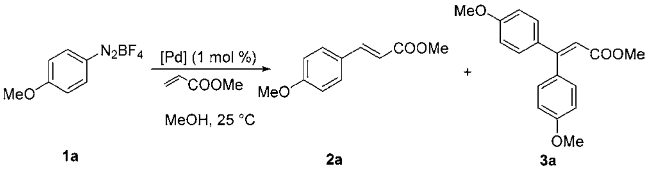


| entry | R | product | yield (%) |
|---|---|---|---|
| 1 | 4-OMe | **2a** | 95[a] |
| 2 | 3-OMe | **2b** | 75 |
| 3 | 2-OMe | **2c** | 93 |
| 4 | 4-Cl | **2d** | 98 |
| 5 | 4-Br | **2e** | 94 |
| 6 | 4-I | **2f** | 86[b] |
| 7 | 4-$NO_2$ | **2g** | 82 |
| 8 | 2-$NO_2$ | **2h** | 91 |
| 9 | 4-COOMe | **2i** | 78 |
| 10 | 4-CN | **2j** | 97[c] |
| 11 | 4-$SO_3H$ | **2k** | 75 |
| 12 | H | **2l** | 96 |
| 13 | 3,4,5-OMe | **2m** | 63[c] |

[a] 3.0% diarylated product determined by HPLC. [b] 10% of dimethyl-3,3′-(1,4-phenylene)(2*E*,2′*E*)-diacrylate was formed. [c] Reaction was conducted at 40 °C.

For all experiments discussed in this study a prereduction of 30 min was performed. We noticed over the time that the color of supporting material turned from yellow to gray within approximately 15 min. Our curiosity and former findings of Felpin et al.[13] animated us to run additional investigations concerning the impact of the preconditioning time on the one hand and the supporting material on the other hand (Table 3).

**Table 3. Impact of Pre-reduction Time**

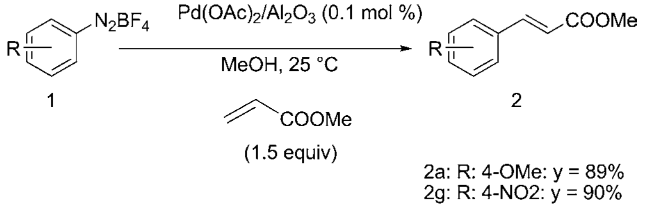


| entry | prereduction | yield (%) | ratio **2a**:**3a** | $Al_2O_3$ | TOF (h$^{-1}$) |
|---|---|---|---|---|---|
| 1 | 30 min | 95 | 97.0:3.0 | yes | 440 |
| 2 | 15 min | 98 | 95.9:4.1 | yes | 478 |
| 3 | – | 98 | 94.9:5.1 | yes | 595 |
| 4 | 30 min | 97 | 95.2:4.8 | no | 341 |

For the comparison of the four experiments, it revealed that longer prereduction times correspond to reduced conversion rates, which might be related to a pronounced Pd-agglomeration (entries 1–3). Nevertheless, a prereduction time up to 30 min did not have a significant impact on the yield, but seemed to be beneficial for the selectivity. However, the renouncement of a prereduction goes along with an increase of the catalyst activity (entry 3). This result is in accordance with the findings of Felpin et al. for the palladium on carbon catalysts.[13] Especially, the abandonment of any supporting material (entry 4) reveals the benefit of the utilization of aluminum oxide as supporting material in our catalytic system. Without using the supporting material, a significant decrease of catalytic activity had to be stated (entry 4).

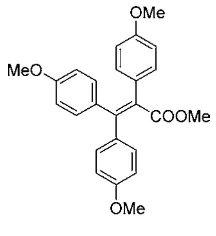
Having these results in our hand the palladium loading could be lowered up to 10 times by abandonment of the prereduction. Hence, electron-rich as well as electron-poor diazonium salts could easily be converted in excellent yields using classical glassware (Scheme 1):

**Scheme 1. Matsuda−Heck Reaction Using 0.1 mol % $Pd(OAc)_2$ on $Al_2O_3$**



Stimulated by our findings and the high activity of our catalytic systems we prospected to rewarding synthetic targets. Correia et al. have described in a series of excellent publications the diarylation of acrylates[20] and maleic acid anhydride.[21,3f] These publications represent a landmark concerning the utilization of the Matsuda-Heck reaction for multiple arylations of olefins. However, a *α,β,β*-triarylation was not yet described to our best knowledge.

Triarylated *α,β,β*-unsaturated carbonylic compounds are frequently described as nonsteroidal estrogen antagonists.[22] A well-known representative of these compounds is the methyl-tri-(4-methoxyphenyl)acrylate **4** (Figure 2).



**4**

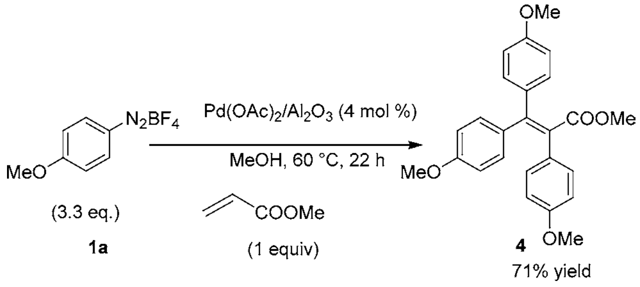
**Figure 2.** Example for a nonsteroidal estrogen antagonist.

The preparation of these derivatives is normally accomplished by a multistep synthesis. Thus, Cattaneo and Gelmi[23] could synthesize methyl-tri-(4-methoxyphenyl) acrylate **4** starting from anisophenone in a synthetic four-step sequence in a total yield of 51%. Despite the good results, this presented synthetic procedure is laborious on the one hand and on the other hand, the utilization of moisture sensitive and/or hazardous reagents like butyllithium and diazomethane hampers the usefulness of this synthetic approach. Therefore, an improved synthetic access to this valuable class of substances is still tempting.

The synthetic usefulness of our new catalytic procedure could be extended to the facile preparation of the nonsteroidal estrogen antagonist **4**. Therefore, 3.3 equiv of 4-methoxybenzenediazonium tetrafluoroborate were converted at 60 °C using 4 mol % of $Pd(OAc)_2$ in the presence of aluminum oxide in methanol with methyl acrylate to the nonsteroidal estrogen antagonist in a one-pot procedure in an overall yield of 71%. (Scheme 2).

To our best knowledge, this is the first *α,β,β*-triarylation of an olefin via Matsuda-Heck conditions. The surprisingly good yield of this synthetic protocol compared to the multistep synthesis of Cattaneo and Gelmi indicates a new synthetic access to this biological important class of substances.

**Scheme 2. One-Pot Synthesis of a Nonsteroidal Estrogen Antagonist 4 via Matsuda−Heck Reaction Using $Pd(OAc)_2$ on $Al_2O_3$**



In summary, we report a novel catalytic system that can be easily prepared by mixing palladium acetate and commercially available and low-cost aluminum oxide. This protocol features benign reaction conditions combined with high catalytic activity and excellent yields. The high catalytic activity could be validated by kinetic investigations in combination with scanning transmission electron microscopy (STEM). As such, the new catalyst helps to increase the realm of catalysts for the Matsuda-Heck reaction. Due to the high catalytic activity, the first *α,β,β*-triarylation of methyl acrylate could be realized in good yields. Further developments will be reported in due course.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03268.

Experimental procedures and analytical data for all isolated products (PDF)

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### Notes

The authors declare no competing financial interest.

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