

Quantification Analysis by Raman and ATR-IR of the Palladium Catalyzed Conjugate Addition of 4-iodoanisole to Benzylideneacetone

Wendy van Bruggen 1682830

Received July 23rd 2010

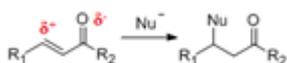
Abstract

Palladium catalyzed conjugate additions can be completed relatively quickly under microwave irradiation. The goal of this project was therefore to find a spectroscopic quantification analysis technique that was also quick, easy and reproducible. Two techniques that were tried for this purpose were Raman and ATR-IR spectroscopy. The results are discussed in this paper.

1. Introduction

1.1 Conjugate Addition Reaction

A well known reaction in organic chemistry is the conjugate addition, or 1,4-addition is shown in Scheme 1. C=C double bonds

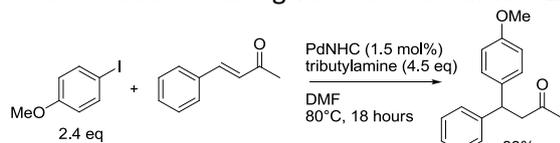


Scheme 1: Conjugate addition of a nucleophile to an α,β -unsaturated ketone.

conjugated with carbonyl groups are electrophilic (indicated with δ^+) due to the electron withdrawing character of the oxygen atom. This facilitates a nucleophile to attack at this position.^[1]

In the past much research has proved that certain metal species^{[2],[3]}, including palladium species, catalyze conjugate addition to very high yields and enantioselectivities.^{[4],[5],[6]}

Lately the conjugate addition of aryl halides to α,β -unsaturated ketones has become an interesting topic in research. This reaction was performed for this research with 1,3-Bis(2,4,6-trimethylphenyl) imidazol-2-ylidene (1,4-naphthoquinone) palladium(0) dimer (PdNHC, Figure 1) as the catalyst. The total reaction is given in Scheme 2.



Scheme 2: Palladium catalyzed conjugate addition of 4-iodoanisole to benzylideneacetone.

This is a biphasic reaction as tributylamine and DMF are immiscible. The proposed mechanism for this reaction is presented in

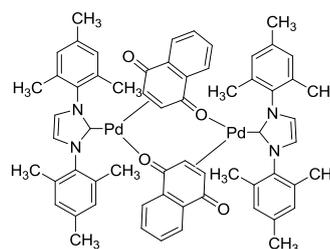
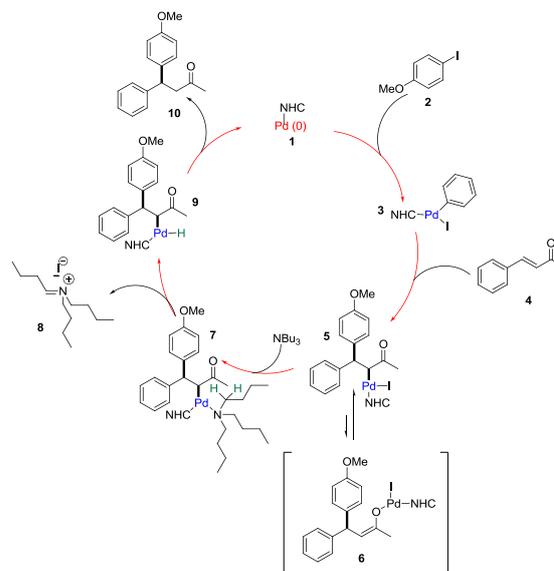


Figure 1: Structure of 1,3-Bis(2,4,6-trimethylphenyl) imidazol-2-ylidene (1,4-naphthoquinone) palladium(0) dimer (PdNHC).



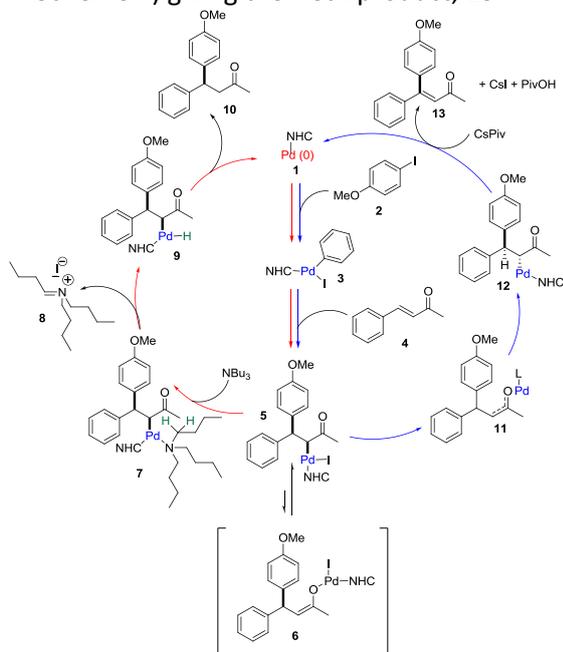
Scheme 3: Proposed catalytic cycle of the palladium catalyzed conjugate addition of 4-iodoanisole to benzylideneacetone.

Scheme 3. In the presence of an aryl halide a palladium(0) catalyst **1** can undergo an oxidative addition of this halide **2** to form species **3**.^[7] In the next step the benzylideneacetone **4** enters which gives insertion of the alkene. The α -palladated species, **5**, that is formed is in equilibrium with the Pd-O enolate, **6**. The equilibrium is largely

in favour of species **5**, to which the tributylamine coordinates to form species **7**. Then β -hydride elimination gives the iminium, **8**, and species **9**. Finally the conjugate addition product, **10**, is generated from reductive elimination of the palladium species.

1.2 Conjugate Addition vs. Heck Reaction

Another reaction that is closely related to the conjugate addition reaction and can take place in the presence of a palladium catalyst is the Heck reaction. Compared to the catalytic cycle of the palladium catalyzed conjugate addition (Scheme 3) it is found that the α -palladated species is in equilibrium with the Pd-O enolate giving species **11** followed by β -hydride elimination from the substrate (shown in Scheme 4) giving the Heck product, **13**.^[6]



Scheme 4: Proposed catalytic cycle of the palladium catalyzed conjugate addition (left) versus the Heck reaction (right) with 4-iodoanisole and benzylideneacetone.

1.3 Microwave

Recently an increasing number of reactions are being performed under microwave irradiation. The advantage of microwave chemistry is that a reaction time can be reduced significantly, from hours or days to minutes. Secondly, direct microwave heating is known to alter product distribution and increase yields.^{[8],[9]}

This is the result of the dipoles or ions aligning in the applied electric field when irradiating a sample at microwave frequencies. As this applied field oscillates the dipole or ion field tries to realign itself with the alternating electric field which gives molecular friction and dielectric loss. This causes energy to be lost in the form of heat. Furthermore, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules that are present in the reaction mixtures, unlike when heating the mixture with an oil-bath for example, as shown in figure 2.

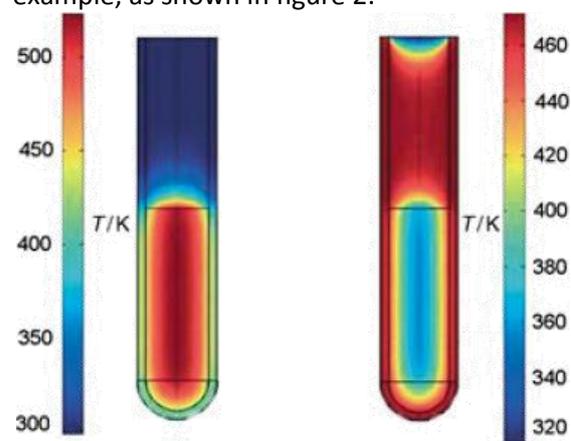
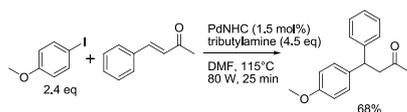


Figure 2: Difference in temperature profiles after 1 minute of heating in the microwave (left) and in an oil bath (right).^[8]

Logically, the efficiency of this microwave heating is dependent on the dielectric properties of the solvent and reagents. Polar additives can even be added to reaction mixtures to increase the absorbance level of the medium.^[8]

As mentioned in section 1.1 our group previously performed the conjugate addition of benzylideneacetone to 4-iodoanisole in an oil bath. It was found that this reaction can also be efficiently performed in the microwave, decreasing the reaction time to approximately 10 minutes.

For this project we performed both the conjugate addition reaction and the Heck reaction of benzylideneacetone with 4-iodoanisole. For the conjugate addition reaction (given in Scheme 5) a mixture of 4-iodoanisole (2.4 mmol, 561 mg),



Scheme 5: Palladium catalyzed conjugate addition of 4-iodoanisole to benzylideneacetone.

benzylideneacetone (1.0 mmol, 146 mg), PdNHC (1.5 mol%, 17 mg), tributylamine (4.5 mmol, 1.1 mL) and 1 mL of DMF were irradiated for 25 minutes at 80 W, yielding the conjugate addition product in 68% yield (0.68 mmol, 173 mg).

For the Heck reaction a mixture of 4-iodoanisole (2.0 mmol, 468 mg), benzylideneacetone (3.0 mmol, 438 mg), PdNHC (1.5 mol%, 34 mg), cesium pivalate (4.0 mmol, 936 mg) and 2 mL of DMF were irradiated for 25 minutes at 80 W, yielding the Heck product in 90% (1.8 mmol, 454 mg).

Quantification analysis was previously done by GC, GC-MS and isolation, which was very time consuming. Having reduced the reaction time significantly our goal was to find a spectroscopic technique to perform quantification with in a shorter time as well. The two techniques that were used were Raman and IR spectroscopy.

1.4 Raman spectroscopy

Raman spectroscopy is a suitable technique for quantification analysis in catalytic studies.^{[10],[11]} Raman spectroscopy is based on a light scattering technique. The scattered light from the molecule can give information about the structure of the molecule. Raman scattered light is frequency-shifted with respect to the excitation frequency and is therefore a characteristic property of the sample.^[12]

Fluorescence inhibits Raman measurements because the fluorescence signal is also shifted from the laser frequency, and so can be very difficult to avoid.^[12]

1.5 IR spectroscopy

IR spectroscopy is complementary to Raman spectroscopy. This technique can be used to analyze solids, liquids and gases by means of transmitting the infrared radiation directly through the sample, where the intensity is determined by the thickness of the sample in the case of liquids and solids.^[13] This

technique does not come without issues; first of all the complexity of the sample preparation makes it harder to reproduce. Moreover, preparing the sample can be messy and time consuming.

1.6 ATR-IR

Improvement led to a special form of IR spectroscopy which is independent of the thickness of the sample, namely attenuated total reflection (ATR). With this technique more sensitive measurements can be done and sample preparation is much faster and easier.^[14] For this technique the changes that occur in a totally internally reflected infrared beam is measured.^[13] The working of this technique is schematically shown in Figure 3.

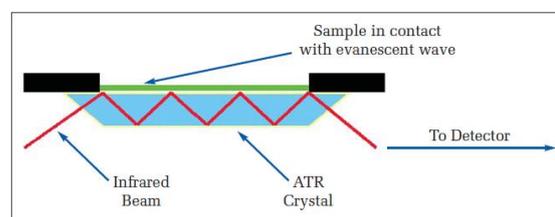


Figure 3: A multiple reflection ATR system.^[13]

An infrared beam is directed onto an optically dense zinc selenide or germanium crystal with a high refractive index at a certain angle. This internal reflectance creates an evanescent wave that extends beyond the surface of the crystal into the sample held in contact with the crystal. One can imagine this evanescent wave as a bubble of infrared that sits on the surface of the crystal.

In regions of the infrared spectrum where the sample absorbs energy the evanescent wave will be attenuated or altered. The attenuated energy from each evanescent wave is passed back to the IR beam, which then exits the opposite end of the crystal and is passed to the detector in the IR spectrometer where an infrared spectrum is generated.

To perform analyses on liquids with this technique the crystal is completely covered with a small drop of the sample and multiple scans are made of it. This takes only a few seconds for each sample.

2. Results and discussion

2.1 Analysis by Raman

We first tried in situ Raman spectroscopy on the reaction mixture with PdNHC as the catalyst (shown in Figure 1). These measurements were performed by placing the reaction vessel in a probe through which the laser was pointed onto the sample. A schematic representation of this probe is given in Figure 4. The major advantages of this

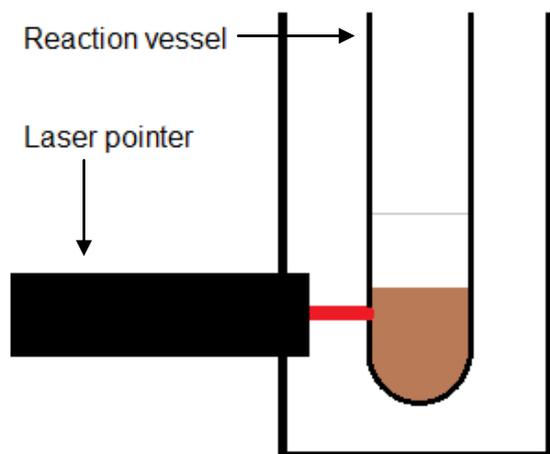


Figure 4: Probe in which Raman measurements were performed.

technique are that the laser can be pointed at any desirable position on the reaction vessel, so both layers can be measured independently. This technique requires only a few seconds to measure a sample.

The results of these measurements are shown in Figure 5. As it can be seen from the spectra, after the reaction an increase of fluorescence had taken place, making it impossible to analyze the spectrum.

Our initial hypothesis was that this was probably a result of the formation of naphtaquinones from the ligands, so we tried quenching these by adding sodium persulfate. We also tried spiking the peaks of the starting material but this gave no success in both cases.

We then tried the reaction with different catalysts, namely palladium acetate, tris (dibenzylideneacetone) dipalladium(0) ($\text{Pd}_2(\text{dba})_3$) and palladium chloride so there would be no formation of naphtaquinones. As can be seen in Figure 6, in all these cases a relatively good spectrum was obtained before

the reaction, but after completion of the reaction we once again observed fluorescence. These results indicate that fluorescence is due to another factor besides the formation of naphtaquinones. Our hypothesis was that this could be due to the formation of nanoparticles.

Due to the constraints on time, further investigations into this technique were not feasible, so we decided to move on to a different spectroscopic technique.

2.2 Analysis by ATR-IR

We then tried quantification by ATR-IR. For this we first made calibration curves of the molarity against the peak height of specific peaks of both the starting materials, the conjugate addition product and the Heck product. We chose these specific peak heights on no mutual overlap, which can be seen in Figure 7. This figure shows absorption spectra of benzylideneacetone, 4-iodoanisole, the conjugate addition product and the Heck product **A**: placed above one another to clearly see the differences and **B**: placed on top of one another to clearly see which peaks do not overlap. The specific peaks we finally used are given in Table 1. The obtained calibration curves are depicted in Figure 8.

Table 1: Specific peaks used for ATR-IR measurements.

Compound	Wavelength
Benzylideneacetone	1205 cm^{-1}
4-iodoanisole	1286 cm^{-1}
Conjugate addition product	730 cm^{-1}
Heck product	925 cm^{-1}

We then made model mixtures containing the starting materials and the conjugate addition product in DMF to see if these corresponded to these calibration curves (see Figures 7 and 9).

Up to this point this technique seemed to go well and this looked like a suitable way to quantify the palladium catalyzed conjugate addition. We therefore tried measurements on an actual reaction. Unfortunately, we observed that the concentrations in the DMF layer calculated from the calibration curves did not correspond to the actual used concentrations; measuring the peak heights of

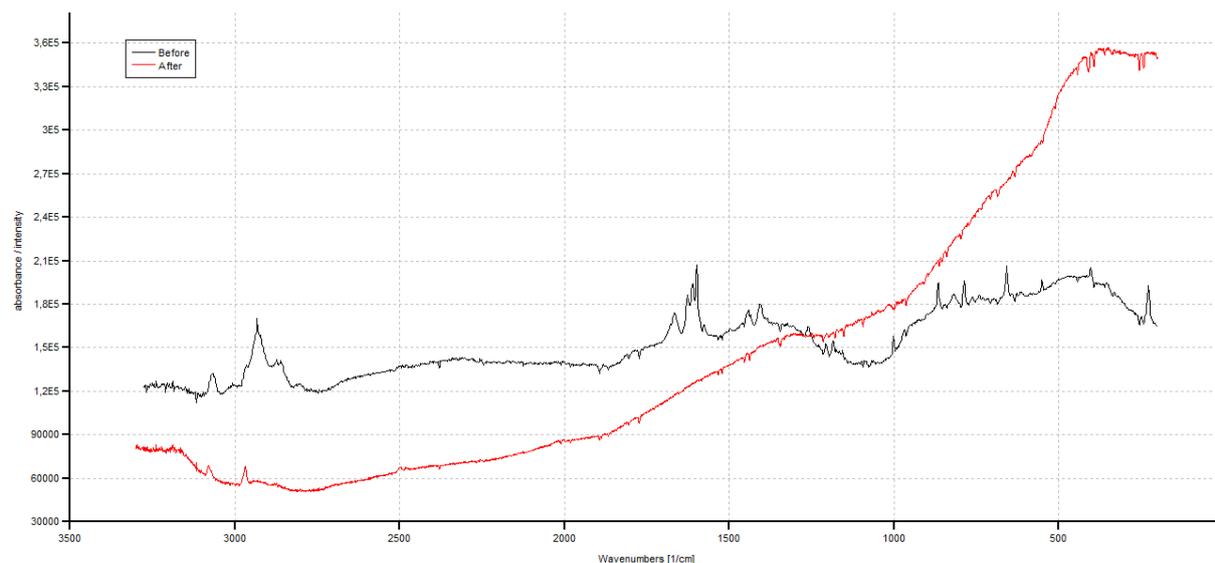


Figure 5: Raman spectra of reaction mixture with PdNHC before (black) and after completion of the reaction (red). After completion of the reaction there had been an increase in fluorescence, mainly in the region between 0 and 1500 cm^{-1} .

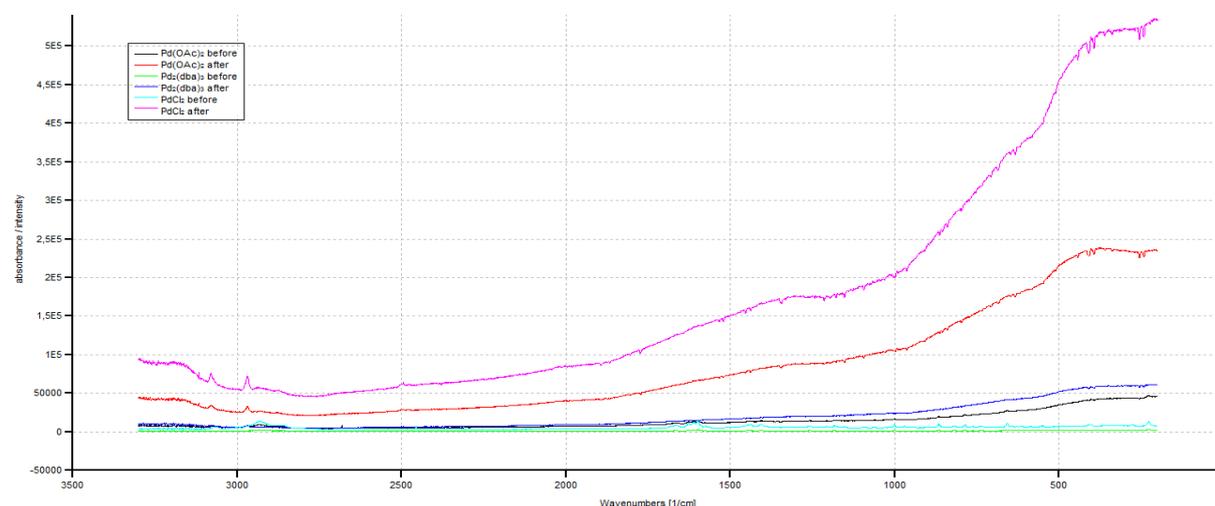


Figure 6: Raman spectra of reaction mixture with $\text{Pd}(\text{OAc})_2$ before and after, $\text{Pd}_2(\text{dba})_3$ before and after and PdCl_2 before and after completion of the reaction respectively.

the characteristic peaks on the IR spectrum before the reaction and converted into mass from the calibration curves the quantity of the starting materials seemed to be lower.

After further investigation we found that when adding tributylamine, which is immiscible with DMF, some of the starting materials went into the tributylamine layer. To see how much this was, it was first checked with IR; a spectrum was taken before adding the tributylamine, then the tributylamine was added and mixed well and another spectrum was taken of the DMF layer. The difference between the heights of the characteristic peaks in these spectra were measured and converted into concentrations based on the calibration curves. These concentrations were

then converted into mass to determine in percentages how much of each compound went into the tributylamine layer. Using this method it was found that in the DMF layer there was a loss of 19% for benzylideneacetone, 22% for 4-iodoanisole and 3% for the conjugate addition product.

To check the reliability of these measurements, the layers were separated and the compounds were isolated from them by adding DCM and washing the tributylamine out with 50% HCl and the DMF with 10% HCl. A lot of the compound was lost in this way so extraction was tried with pentane. This also did not recover all of the compound, probably because it was done on such a small scale (1.5 mmol in 1 mL), but if scaling it up it might not

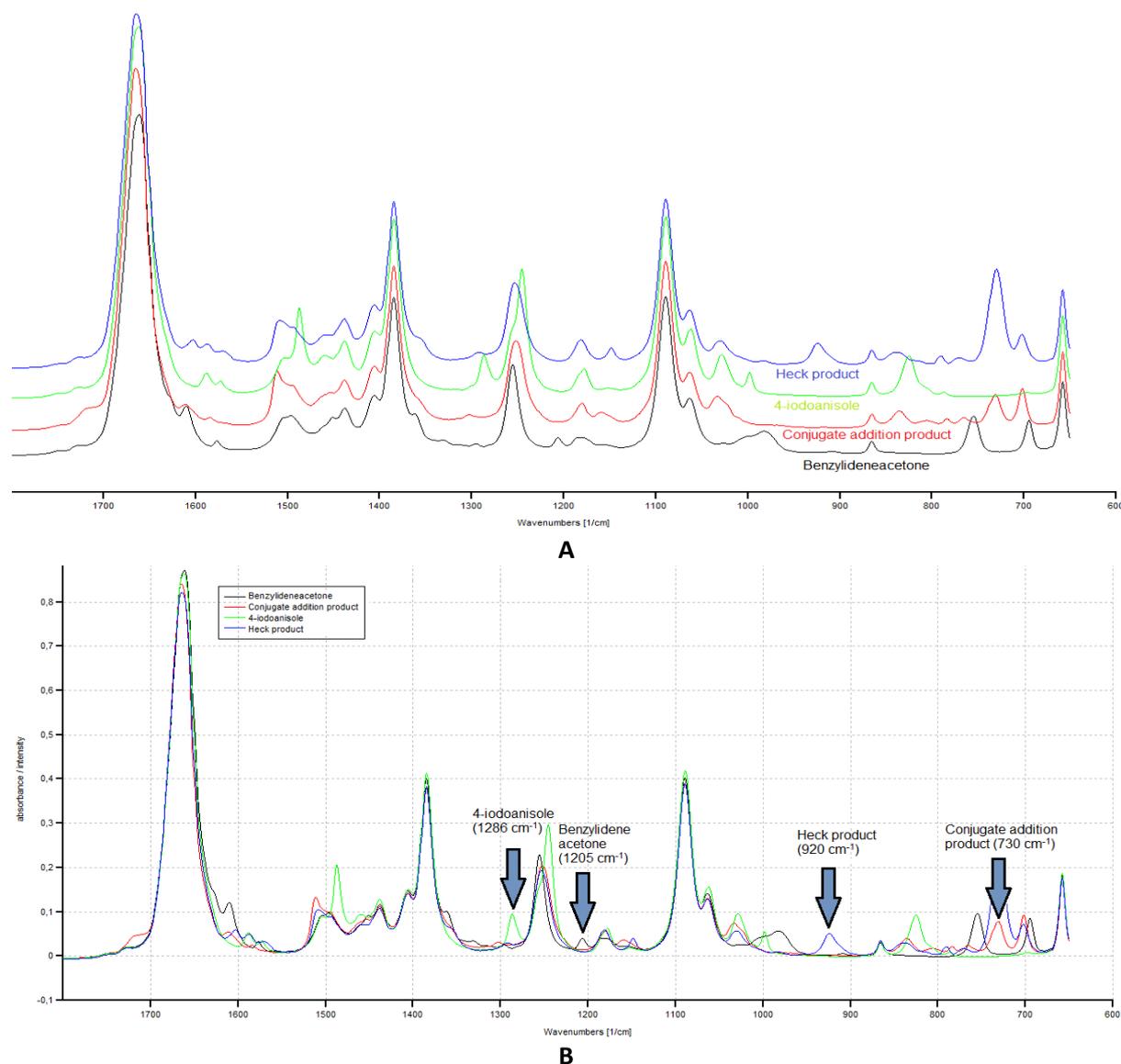


Figure 7: Absorption spectra of benzylideneacetone, 4-iodoanisole, the conjugate addition product and the Heck product **A:** placed above one another to clearly see the differences and **B:** placed on top of one another to clearly see which peaks do not overlap. Note that at 730 cm⁻¹ the peak of the conjugate addition product overlaps with a peak of the Heck product, so quantification based on this peak can only be done when there is no Heck product present, so no peak at 920 cm⁻¹.

be representative compared to actual reaction conditions. For 4-iodoanisole 25% (0.38 mmol, 89 mg) was lost with this method and for benzylideneacetone 21% (0.31 mmol, 45 mg).

Given the time we had and the complications that kept arising we had to stop this research at this point. A closer look should be taken at the partition issues. If the amount of compound that goes into the tributylamine layer is always more or less the same this can be taken into account for quantification. If this is random, however, it must be precisely measured each time.

3. Conclusion

The goal of this project was to develop a spectroscopic technique for fast and accurate analysis of conversions, selectivity and yields for palladium catalyzed conjugate addition type reactions.

As we saw, Raman spectroscopy is not possible for these reaction due to fluorescence. Given the fact that we observed fluorescence for all the palladium catalysts used, it could be concluded that this was not only due to the formation of naphthaquinones, which was thought at first. Another reason

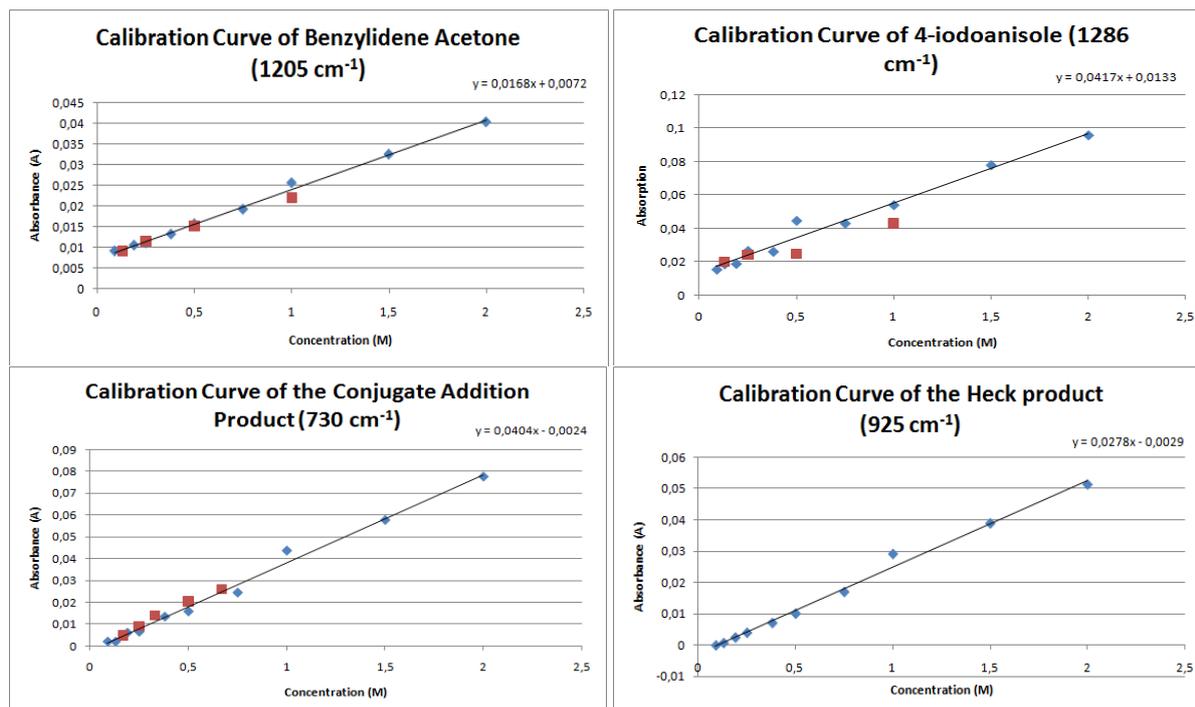


Figure 8: Calibration curves in 2.0, 1.5, 1.0, 0.75, 0.50, 0.38, 0.25, 0.19, 0.13 and 0.09 M respectively as a function of absorption (peak height) (♦) and model mixtures (■).

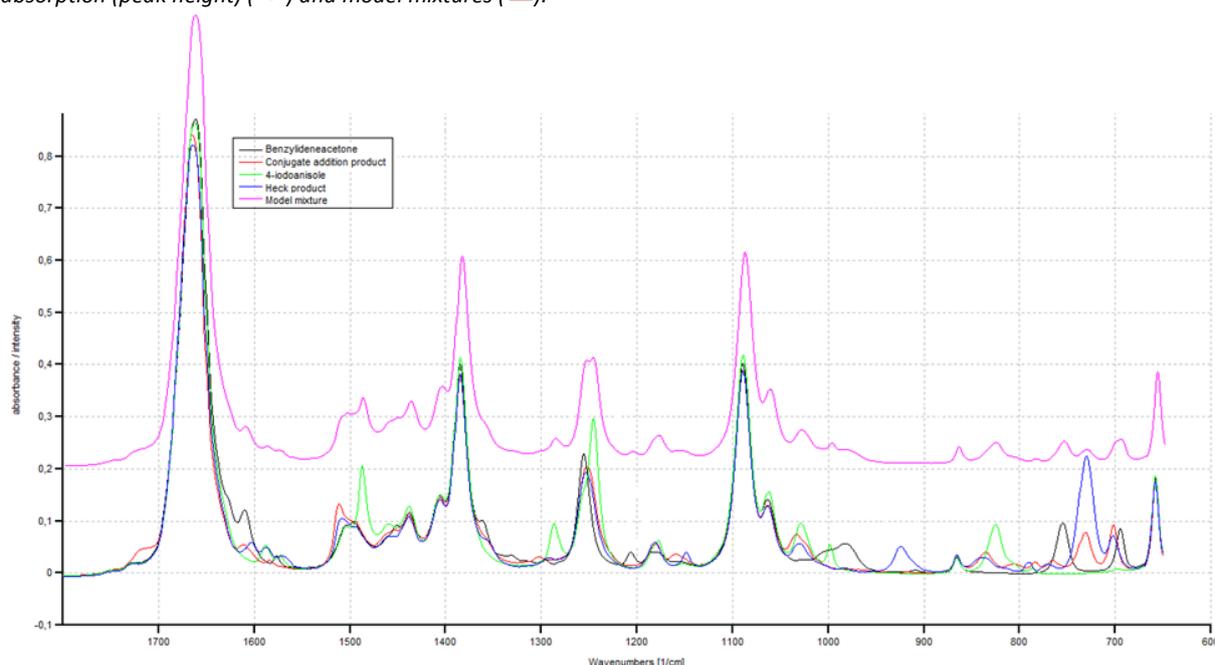


Figure 9: Absorption spectra of benzylideneacetone, 4-iodoanisole, the conjugate addition product, the Heck product and the model mixture with benzylideneacetone, 4-iodoanisole and the conjugate addition product in DMF. (The baseline of the spectrum of the model mixture is shifted to make it clearer where the characteristic peaks are positioned).

for the fluorescence could be the formation of nanoparticles, but this requires more research.

ATR-IR does seem to work; Looking at the model mixtures they seem to correspond quite well to the calibration curves. However,

when adding the tributylamine a part of the compounds goes into this layer. This must be investigated more closely to be able to draw conclusions.

4. References

- [1] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry 1st edition* **2001**, Oxford University Press, New York, 227-231
- [2] Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L., *Chem. Rev.* **2008**, *108*, 2824-2852
- [3] Caporusso, A. M.; Giacomelli, G.; Lardicci, L., *J. Org. Chem.* **1982**, *47*, 4640-4644
- [4] (a) Cacchi, S.; La Torre, F.; Misiti, D., *Tetrahedron Lett.* **1979**, *20*, 4591-4594. (b) Cacchi, S.; Misiti, D.; Palmieri, G., *Tetrahedron* **1981**, *37*, 2941-2946. (c) Cacchi, S.; Misiti, D.; Palmieri, G., *J. Org. Chem.* **1982**, *47*, 2995-2999.
- [5] Cacchi, S.; Arcadi, A., *J. Org. Chem.* **1983**, *48*, 4236-4240
- [6] Gini, F., PhD Thesis, *New Enantioselective Reactions in Palladium Catalysis* **2007**
- [7] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P., *Organic Chemistry 1st edition* **2001**, Oxford University Press, New York, 1324-1325
- [8] Kappe, C. O., *Angew. Chem. Int. Ed.* **2004**, *43*, 6250-6284
- [9] Collins, M. J., *Introduction to Microwave Chemistry*
- [10] Wang, C.-B.; Deo, G.; Wachs, I. E., *J. Phys. Chem. B* **1999**, *103*, 5645-5656
- [11] Quincy, R. B.; Houalla, M.; Hercules, D. M., *J. Cat.* **1987**, *106*, 85-92
- [12] National Institute of Standards and Technology, Physics Laboratory Optical Technology Division, *Raman spectroscopy*; <http://physics.nist.gov/Divisions/Div844/facilities/raman/Ramanhome.html>
- [13] Perkin Elmer, *FT-IR Spectroscopy, Attenuated Total Reflectance (ATR)* **2005**
- [14] Fahrenfort, J.; Visser, W. M., *Spectrochimica Acta* **1962**, *18*, 1103-1116
- [15] Larhed, M.; Hallberg, A., *J. Org. Chem.* **1996**, *61*, 9582-9584

5. Supporting information

5.1 General experimental

¹H-NMR and ¹³C-NMR spectra were recorded on Varian AMX400 (400, 100.59 MHz respectively) and/or Varian NMR 200 (200 MHz) spectrometers using CDCl₃ as the solvent. Spectra are referenced to residual chloroform ($\delta = 7.26$ ppm, ¹H; 77.23 ppm, ¹³C). Chemical shifts are reported in parts per million, multiplicities are indicated by s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants, *J*, are reported in Hertz, and integration is provided and assignments are indicated.

Microwave chemistry was performed in a CEM Discover Microwave. Heating was performed as Power Time with a maximum temperature of 150°C. Cooling was turned on at 115°C so a constant temperature was maintained.

Analytical thin-layer chromatography was performed on Merck silica gel 60, kieselguhr F₂₅₄ plates. Visualization was accomplished with UV light and Seebach's stain: a mixture of phosphomolybdic acid (25 g), cerium(IV)sulphate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL). *R_f* values reported were measured using a 7x2 cm TLC plate in a developing chamber containing the solvent system described.

Flash chromatography was performed using Merck silica gel 60, 40-63 μ m (230-400 mesh).

Analytical GC-MS measurements were done on Hewlett Packard 5973 Mass Selective Detector, HP 6890 Series GC system.

Analytical Raman spectra were recorded on Perkin Elmer Raman Flex 400 Raman Spectrometer. The reaction vessel was placed in a probe where the laser pointer entered from the side. The reaction vessel was repositionable with respect to the laser pointer so both layers could be measured separately. The laser was then turned on and the scattered light was measured to generate a spectrum in a few seconds time.

Analytical ATR-IR measurements were recorded on a Perkin Elmer FT-IR system and peaks are reported in cm⁻¹. A drop of the sample was dropped on the crystal so it was completely covered. Then 16 scans were performed and after several seconds an IR spectrum was generated.

Literature Preparations

The following compounds were prepared by literature methods: 4-(4-methoxyphenyl)-4-phenylbutan-2-one and 4-(4-methoxyphenyl)-4-phenylbut-3-en-2-one.

5.2 Experimental procedure of the palladium catalyzed conjugate addition of 4-iodoanisole to benzylideneacetone to 4-(4-methoxyphenyl)-4-phenylbutan-2-one

4-iodoanisole (2.4 mmol, 561 mg), benzylideneacetone (1.0 mmol, 146 mg), 1.5 mol% of palladium catalyst (0.015 mmol, 17 mg) and tributylamine (4.5 mmol, 834 mg) were mixed in 1 mL of DMF and placed under nitrogen atmosphere. The mixture was irradiated in the microwave at 80 W for 25 minutes at approximately 110°C. A black precipitate was present in the reaction mixture.

After cooling to room temperature completion was checked with TLC (20% ether in pentane, $R_f=0.4$) and the mixture was poured into water and extracted 3 times with DCM. The combined extracts were washed 3 times with water, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

Column chromatography (10% ether in pentane) yielded a yellow oil in 68%. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 7.10-7.28 (m, 7H), 6.82 (m, 2H), 4.54 (t, $J = 7.6$ Hz, 1H), 3.76 (s, 3H), 3.15 (d, $J = 7.6$ Hz, 2H), 2.07 (s, 3H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ ppm 207.03, 158.09, 144.21, 135.95, 128.64, 128.55, 127.58, 126.35, 113.95, 55.20, 45.29, 30.65.

5.3 Experimental procedure of the palladium catalyzed Heck reaction of 4-iodoanisole with benzylideneacetone to 4-(4-methoxyphenyl)-4-phenylbut-3-en-2-one^[15]

4-iodoanisole (2.0 mmol, 468 mg), benzylideneacetone (3.0 mmol, 438 mg), 1.5 mol% of PdNHC (0.03 mmol, 34 mg) and cesium pivalate (4.0 mmol, 936 mg) were mixed in 2 mL of DMF and placed under nitrogen atmosphere. The mixture was irradiated in the microwave at 80W for 25 minutes at 113°C. A black precipitate was present in the reaction mixture.

After cooling to room temperature completion was checked with TLC (20% ether in pentane, $R_f=0.3$) and the mixture was poured into water and extracted 3 times with DCM. The combined extracts were washed 3 times with water, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure.

Column chromatography (10% ether in pentane) yielded a brown oil in 90%. This was a mixture of the *E* and *Z* isomers in a 1:1 ratio, determined by GC-MS. 1H -NMR (400 MHz, $CDCl_3$) δ ppm 7.13-7.25 (m, 7H), 6.93 (m, 2H), 6.8 (dd, 2H), 6.50 (d, 1H), 3.83 (d, 3H), 1.90 (d, 3H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ ppm 131.31, 129.88, 129.56, 129.39, 128.67, 128.62, 128.37, 127.38, 125.94, 113.81, 55.28, 30.25.