JOC Article

Mechanistic Insights into the Palladium-Induced Domino Reaction Leading to Ketones from Benzyl β-Ketoesters: First Characterization of the Enol as an Intermediate

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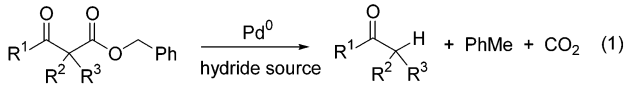
The monitoring by UV spectroscopy of the Pd-catalyzed hydrogenolysis in acetonitrile of 2-methyl-2-benzyloxycarbonyl-1-indanone and 2-methyl-2-benzyloxycarbonyl-1-tetralone showed the successive formation of corresponding β-ketoacids and enols to deliver finally the ketones. Some factors which influence the stability of the intermediates are determined. In contrast to the above benzyl β-ketoesters, the enol was not detected from benzyl (2-methylinden-3-yl) carbonate.

1. Introduction

The transformation of allyl β-ketoesters to the corresponding ketones is a one-pot reaction easily carried out in the presence of an hydride source and catalytic amounts of palladium. Since its discovery,[1] this domino reaction[2] has been widely expanded.[3] When ammonium formates are the hydride source, Tsuji and Mandai[3b] have proposed a palladium C-bound enolate as intermediate (Scheme 1, path a) while Shimizu and Ishii[4] postulated a ketoacid (Scheme 1, path b).

The hydrogenolysis of benzyl β-ketoesters over palladium is also a well-known reaction to provide the corresponding ketones (eq 1).[5] The literature did not contain any mechanistic scheme for this domino hydrogenolysis/decarboxylation reaction; enolic species related to those of Scheme 1 are nevertheless envisageable.[6]



The enolic intermediates suspected for these reactions led us to disclose enantioselective versions using a chiral amino alcohol to induce asymmetry in the last step.[7,8] Interestingly, only catalytic amounts of the amino alcohol[7,8] were required with benzyl β-ketoesters as substrates.

Previously, we have disclosed that laser irradiation of 2-methyl-2-isobutyl-1-indanone (**1**) in deuterated acetonitrile produced enol **E-5**, which was characterized by ^{1}H NMR and by its quantitative conversion into 2-methyl-1-indanone (Scheme 2).[9] A flash-photolysis study of **1** has allowed us to observe an UV absorption band (λ_{max} = 265−270 nm) attributable to the formation of **E-5**.[10] UV spectroscopy is indeed a very useful technique to characterize enols,[11] and subsequently, **E-5** was also detected with use of conventional photolysis and an UV spectrophotometer.[10]

The above observations induced us to study by UV spectroscopy the mechanism of the reactions of 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE-5**) and 2-methyl-2-benzyloxycarbonyl-1-tetralone (**KE-6**) under hydrogen atmosphere at room temperature in the presence of catalytic amounts of palladium on carbon. Here, we

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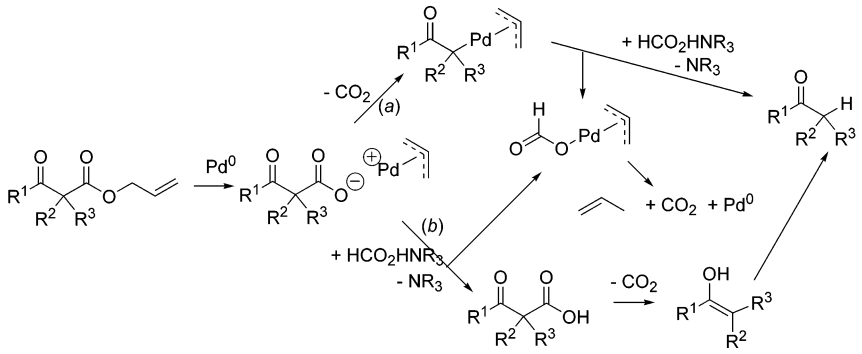
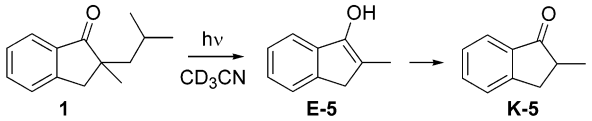
SCHEME 1



SCHEME 2



report that ketoacids **KA-5** and **KA-6** and enols **E-5** and **E-6** (Scheme 3) are readily produced under these conditions. These results led us to extend the analysis to the hydrogenolysis of benzyl enol carbonate **EC-5**

2. Results and Discussion.

2.1. Hydrogenolysis of 2-Methyl-2-benzyloxycarbonyl-1-indanone. As shown in Figure 1, the UV

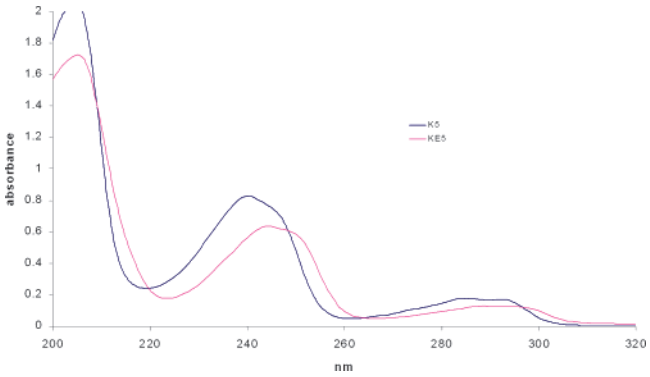


FIGURE 1. UV absorption spectra of 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE-5**) and 2-methyl-1-indanone (**K-5**).

spectra, in particular the λ_{max} values of **KE-5** ($c = 7.8 \times 10^{-5}$ M, $\lambda_{max} = 244$ ($\epsilon = 8110$), 288 ($\epsilon = 1610$), 295 ($\epsilon = 1600$) nm) and **K-5** ($c = 7.8 \times 10^{-5}$ M, $\lambda_{max} = 240$ ($\epsilon = 10590$), 285 ($\epsilon = 2260$), 292 ($\epsilon = 2150$) nm) are very similar. The very low stability of ketoacid **KA-5** in solution precludes its purification and the recording of a reliable UV spectrum. Nevertheless, the UV spectrum of a crude sample recorded quickly after its preparation showed a $\lambda_{max} \cong 248$ nm. Since the absorbances at 265−270 nm of these three compounds were very low, we could expect to detect **E-5** by UV analysis if this enol was formed in the course of the Pd-induced domino reaction.

The development of **KE-5** ($c_0 = 2.5 \times 10^{-2}$ M) in the presence of Pd/C and hydrogen was monitored by UV spectroscopy. The absorption peak at $\lambda_{max} = 245$ nm of the successive aliquots ($c_{0,d} = 6.2 \times 10^{-5}$ M after filtration and dilution) decreased with time and this phenomena was accompanied by the appearance of an absorption peak centered at $\lambda = 268$ nm (Figure 2). The latter

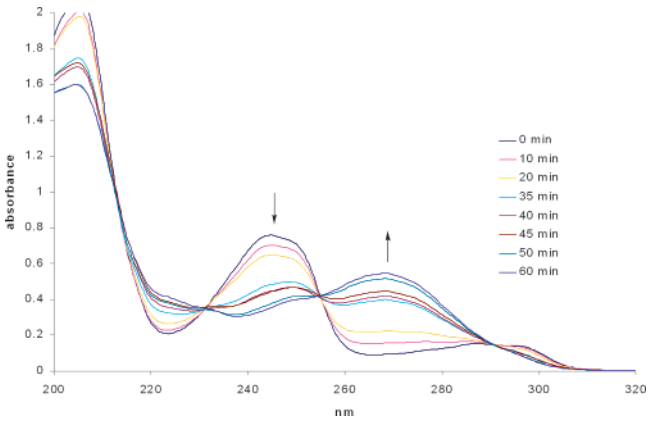
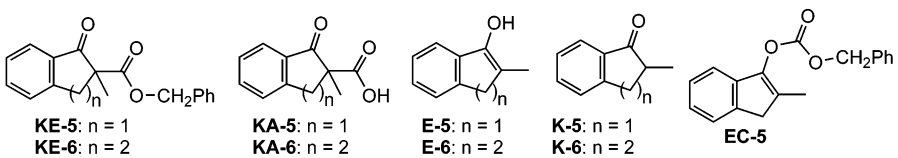


FIGURE 2. UV absorption spectra of the hydrogenolysis reaction progress of 2-methyl-2-benzyloxycarbonyl-1-indanone (**KE-5**): formation of 2-methyl-2-inden-3-ol (**E-5**).

reached a maximum intensity at $t = 60$ min; this corresponded also to the extinction of the maxima at 288 and 295 nm.

From our previous observations,[10] we assigned the band at $\lambda_{max} = 268$ nm to enol **E-5**. When such a sample of **E-5** is left in the UV cuvette, the UV absorptions evolved slowly to afford the UV spectrum of ketone **K-5**, 15 h being required when $c_{0,d} = 1.1 \times 10^{-4}$ M. In contrast, the addition of (−)-ephedrine to **E-5** ($c_{0,d} = 1.1 \times 10^{-4}$ M) led the complete transformation of **E-5** to **K-5** in less than 6 min (Figure S1, Supporting Information). Without ephedrine, the transformation to **K-5** took 10 min for an unfiltered sample of **E-5** ($c_0 = 2.23 \times 10^{-2}$ M). Therefore, it appears that (−)-ephedrine like the Pd catalyst ac-

SCHEME 3



celerated the **E-5** → **K-5** reaction. **KE-5**, **KA-5**, **K-5**, and PhMe having a low absorbance at 268 nm, the extinction coefficient of **E-5** is estimated to be ≅ 8800 $dm^3\ mol^{-1}\ cm^{-1}$.

The curves of Figure 2 suggested the presence of three isobestic points (λ = 230, 255, and 291 nm) and consequently a **KE-5** → **E-5** reaction without any intermediate! A close inspection showed, however, that for each of them, the crossing of the curves was not exactly at the same point. Having noted above that ketoacid **KA-5** has a very low stability particularly in diluted solution, we suspected its formation as a transient species. This led us to repeat the hydrogenolysis of **KE-5**; after reaction for 15 min, the heterogeneous mixture was filtered, cooled to 0 °C, and laced with a solution of diazomethane. After the addition of a small amount of silicagel, filtration, and evaporation of the solvent, the ^{1}H NMR spectrum of the crude mixture showed the presence of **KE-5**, **K-5**, and 2-methyl-2-methoxycarbonyl-1-indanone. Consequently, **KA-5** is effectively a reaction intermediate. In agreement with this assertion, the monitoring of the evolution of an acetonitrile solution of a partially degraded sample of **KA-5** has allowed the detection of **E-5** by UV spectroscopy.

2.2. Hydrogenolysis of 2-Methyl-2-benzyloxycarbonyltetral-1-one. The UV characteristics of **KE-6** are λ_{max} = 248 (ϵ = 9430), 291 (ϵ = 1260) nm and those of **K-6** are λ_{max} = 245 (ϵ = 8330), 288 (ϵ = 1610) nm. **KA-6** being much more stable than **KA-5**, its UV characteristics have been determined: λ_{max} = 248 (ϵ = 8830), 291 (ϵ = 1260) nm. Since the UV spectra of **KE-6** and **KA-6** are very similar, it was not possible to monitor the transformation **KE-6** → **KA-6** by UV spectroscopy. Nevertheless, we observed by TLC that the Pd-catalyzed hydrogenolysis of a solution of **KE-6** in MeCN ($c_0 = 2.18 \times 10^{-2}$ M) was complete at room temperature in 70 min; an aliquot was thus withdrawn, filtered, and diluted: its UV spectrum was almost identical with that of **KA-6** (Figure S2, Supporting Information). The above mother liquor and a more concentrated solution of **KA-6** ($c = 3.04 \times 10^{-2}$ M) alike were almost not transformed in 70 min. In contrast, a more diluted solution of **KA-6** ($c = 6.5 \times 10^{-5}$ M) led to the fast formation of **K-6**, which was deferred by the addition of small amounts of AcOH. This stability of **KA-6** in relatively concentrated solutions or in the presence of AcOH could be due to the formation of stabilizing intermolecular hydrogen bonds.

Hence, further experiments have been performed in the absence of the palladium catalyst with use of an UV cuvette containing a diluted solution of **KA-6** in MeCN ($c = 6.5 \times 10^{-5}$ M). Under these conditions, we observed the decrease with time of the band centered at 248 nm and the appearance of two absorptions which, after 120 min, were centered at 224 and 280 nm (Figure 3). Then, an apparent reverse development was observed during 180 min, the bands at λ_{max} = 224 and 280 nm decreased while an absorption band, finally centered at 245 nm, appeared (Figure 4). This UV spectrum, obtained about 300 min after the dissolution of **KA-6**, was indeed the UV spectrum of **K-6**. From the previous results, the λ_{max} = 280 nm was assigned to **E-6**.

In contrast to the above experiments, the UV study of the **KA-6** → **K-6** reaction in hexane ($c = 5.3 \times 10^{-6}$ M) did not allow us to detect the intermediate formation of **E-6**. It has been reported that (i) enols of ketones may

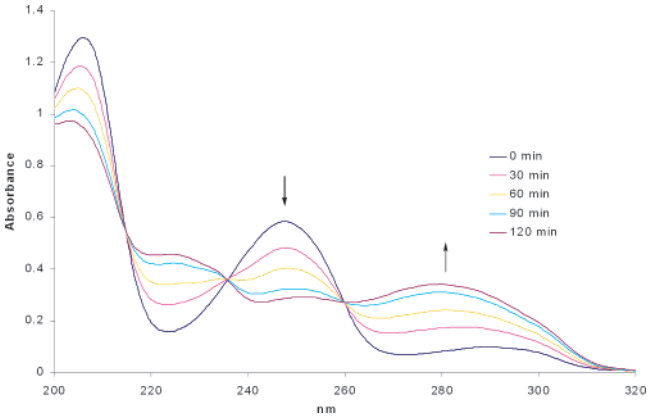


FIGURE 3. Change of the UV absorption spectra of 2-carboxy-2-methyl-1-tetralone (**KA-6**): formation of 2-methyl-1-tetralen-1-ol (**E-6**).

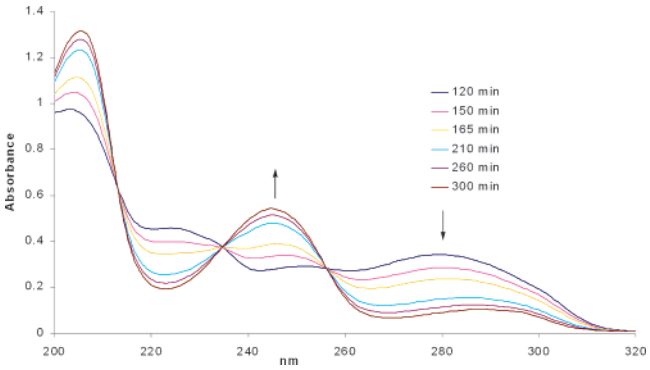


FIGURE 4. Change of the UV absorption spectra of 2-methyl-3,4-dihydro-1-naphthol (**E-6**): formation of 2-methyl-1-tetralone (**K-6**).

be relatively stable in polar solvents[9,12] and (ii) the Kamlet−Taft hydrogen bond accepting parameter, β,[13] is convenient to correlate the effect of solvent with the stability of enols.[14] The strong difference of the β values between acetonitrile (β = 0.31) and hexane (β = 0.00) may explain why the enol was not observed in hexane. Acetonitrile may stabilize the enol in serving as hydrogen bond acceptor for intermolecular hydrogen bonding with the OH of the enol.[12c,14b,15]

It is interesting to underline the presence of three clear isobestic points in both Figures 3 (λ = 214, 235, 259 nm) and 4 (λ = 213, 234, 256 nm). Those of Figure 3 indicate that **KA-6** would be completely transformed into **E-6** before the **E-6** → **K-6** reaction takes place; this denotes some stabilization of the enol by the ketoacid and could be related to the observation of Miller who has disclosed

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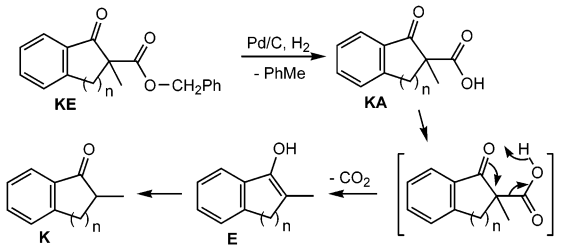
SCHEME 4



that enols are formed more effectively in acetic acid than in hexane.[16] Whatever the explanation, it appears that **KA-6** may have a complementary role to MeCN in the stabilization of **E-6**.

2.3. NMR Analysis. As pointed out in the Introduction, **E-5** has been previously characterized by ^{1}H NMR spectroscopy from the photolysis of **1**.[9] Using the same procedure for the characterization of **E-6** led to complex spectra. In contrast, we have been able to detect **E-6** by NMR from the decarboxylation of **KA-6** (Figure S3, Supporting Information). The ^{1}H NMR monitoring of a CD_3CN solution of **KA-6** (c = 0.01 M) showed the appearance of signals at 1.21 (d, J = 6.5 Hz) and 1.39 (s) ppm. When the signal of the methyl group of **KA-6** (s at 1.44 ppm) completely disappeared, (−)-ephedrine was added and we observed the disappearance of the singlet at 1.39 ppm while the doublet at 1.21 ppm, which corresponds to the methyl group of **K-6**, was maintained. Consequently, the singlet at 1.39 ppm was due to the methyl group of **E-6**.

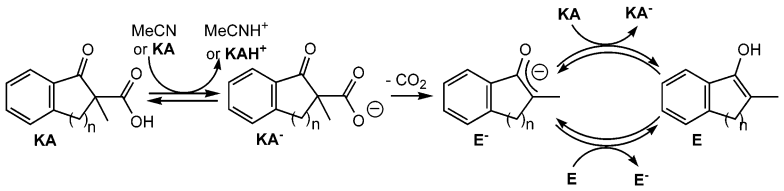
2.4. Mechanism. Under the above conditions, we have demonstrated the production of **KA** and **E** from **KE** in relatively large amounts when acetonitrile was the solvent. For the preparative experiments which lead to **K** from **KE**, palladium is present in the mixture the entire reaction time, and the formation of the palladium carboxylate ***KA*-Pd** and/or the palladium enolate ***E*-Pd** cannot be excluded. Since only 0.025 equiv of palladium is used in the preparative experiments, ***KA*-Pd** and ***E*-Pd** would be at best produced in minute amounts. Hence, even if we consider the formation of ***KA*-Pd** and ***E*-Pd** and then their hydrolysis in the course of the preparation of the UV samples, the concentrations of **KA** and **E** detected by UV analysis of samples withdrawn from the palladium-induced domino reaction (Figures S2 and 2, respectively) imply that notable amounts of **KA** and **E** are already present in the mother solutions. These remarks led us to assume that Scheme 4 depicts the main mechanism pathway of the **KE** → **K** domino reaction; this scheme does not exclude some assistance of the **KA** → **E** and **E** → **K** steps by the Pd-catalyst when the whole transformation **KE** → **K** is carried out in the presence of palladium. One referee has suggested that the **KA** → **E** transformation involves the ionization of **KA** and decarboxylation of $\mathbf{KA}^-$ to afford $\mathbf{E}^-$ which would be protonated in the medium on the more electronegative oxygen; this possibility, which is compatible with our results, is depicted in Scheme 5.

From the literature, the ketonization of an enol occurs through O-protonation, C-protonation, or a cyclic mechanism.[17] The above **E** → **K** reaction being observed in anhydrous acetonitrile in the absence of any additive implies a self-ketonization under these experimental conditions and Scheme 6 outlines the different possibilities. To make a choice between these plausible mechanistic pathways was out of the scope of the present work.

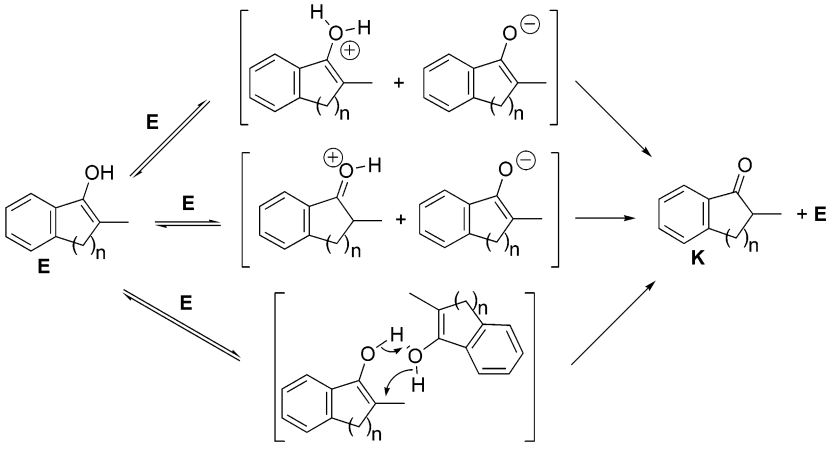
3. Extended Analysis

These results urged us to monitor also the hydrogenolysis of a 2.22 × 10^{-2} M acetonitrile solution of the benzyl enol carbonate **EC-5** by UV spectroscopy since we have previously carried out this reaction in a chiral

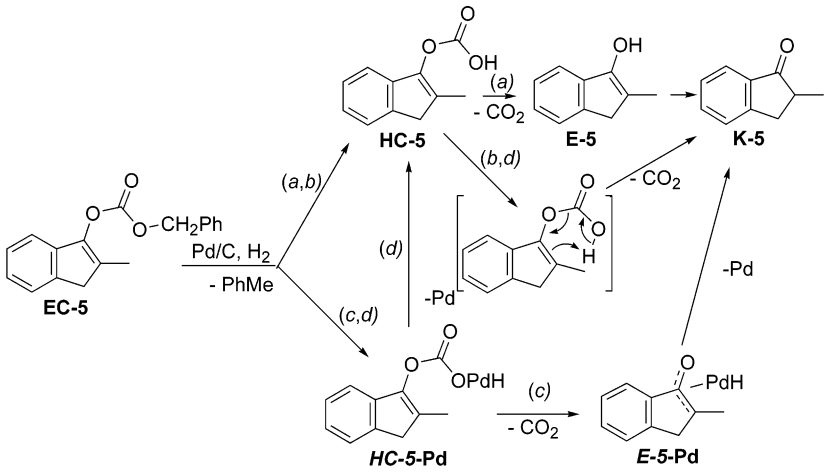
SCHEME 5



SCHEME 6



SCHEME 7



medium.[8a,b,18] The experiments from **KE-5** and **KE-6** led us to suspect the formation of hydrogen enol carbonate **HC-5** and **E-5** as intermediates (Scheme 7, path a). However, we have not been able to detect an intermediate and we only observed the complete **EC-5** → **K-5** reaction in less than 5 min (Figure S4, Supporting Information). This leads to various hypotheses: (i) **E-5** would be consumed as soon as it is produced because it will not be stabilized by intermolecular interactions with a ketoacid, or (ii) **E-5** is not produced, **HC-5** leading directly to **K-5** (Scheme 7, path b), or (iii) palladium is involved in all steps and **K-5** would be produced through hydridopalladium enol carbonate ***HC-5*-Pd** and hydridopalladium enolate ***E-5*-Pd** intermediates (Scheme 7, path c), or (iv) ***HC-5*-Pd** evolves to **HC-5** (Scheme 7, path d). At the present time, we have no argument to favor one of these proposals.

4. Conclusion

We now have clear evidence that the palladium-catalyzed hydrogenolysis of a benzyl β-ketoester such as **KE-5** or **KE-6** involves, at least in MeCN as solvent, the intermediate formation of the corresponding ketoacid and the enol of the terminal ketone. Under similar experimental conditions, the benzyl enol carbonate **EC-5** led also to the corresponding ketone but with a different reactivity. Whatever the mechanism from the benzyl enol carbonate, this difference of reactivity may explain the differences of enantioselectivities obtained for the reactions **KE-5** → **K-5** and **EC-5** → **K-5**, when they are carried out under identical palladium-catalyzed hydrogenolysis conditions in the presence of the same enantiopure amino alcohol.[7,8a,b] It now would be of interest to similarly monitor the domino reaction of allyl β-ketoesters in the aim to settle between the proposals depicted in Scheme 1.

5. Experimental Section

Typical UV Analysis Procedure: Hydrogenolysis of KE-5. In a 25-mL round-bottomed flask containing a stir bar, **KE-5** (50 mg, 0.178 mmol), and acetonitrile (8 mL) was added Pd/C (20 mg, 0.025 equiv). The flask was purged for 0.5−1 min by a slight flow of hydrogen, then connected to a rubber balloon filled with hydrogen and the stirring was started. At the times indicated in Figure 2, an aliquot (0.5 mL) was drawn with a syringe and immediately injected into a flask through an HPLC filter; 25 μL of the filtrate was placed in a 5-mL volumetric flask that was filled with MeCN. After a brief shaking to ensure mixing, a quartz cuvette (path length: 10 mm) was charged with this solution and immediately placed in the cell holder of the UV spectrophotometer to perform the analysis over the range 200−400 nm.

Supporting Information Available: Figures S1, S2, S3, and S4, standard experimental procedures, and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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