

Allylic Substitution Mediated by Water and Palladium: Unusual Role of a Palladium(II) Catalyst and ESI-MS Analysis

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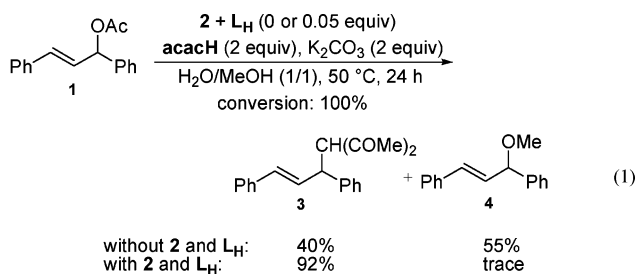
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Summary: Allylic substitution of $\text{PhCH}(\text{OAc})\text{CH}=\text{CHPh}$ by $\text{CH}_2(\text{COMe})_2$ in a basic $\text{MeOH}/\text{H}_2\text{O}$ mixture could be achieved in the absence of a palladium catalyst and lead to a mixture of $\text{PhCH}(\text{CH}(\text{COMe})_2)\text{CH}=\text{CHPh}$ and $\text{PhCH}(\text{OMe})\text{CH}=\text{CHPh}$ in 40% and 55% yields, respectively. The process is induced by water, and nucleophilic attack addition occurred on a stabilized carbocation as the intermediate. Addition of a catalytic amount of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ did not accelerate the reaction but improved the selectivity, and $\text{PhCH}(\text{CH}(\text{COMe})_2)\text{CH}=\text{CHPh}$ was then obtained in 92% yield while $\text{PhCH}(\text{OMe})\text{CH}=\text{CHPh}$ was observed in trace amounts. An ESI-MS analysis of the reaction mixture led us to assume that a palladium acetylacetonate complex is involved in the formation of $\text{PhCH}(\text{CH}(\text{COMe})_2)\text{CH}=\text{CHPh}$.

The use of water as solvent for organic synthesis is very attractive for environmental, economic, and safety reasons,¹ and we have recently shown that water may promote the allylic substitution of 1-acetoxy-1,3-diphenylpropene (**1**) with high yields in the absence of any palladium complex.² However, with acetylacetone (**acacH**) as nucleophilic species in a $\text{MeOH}/\text{H}_2\text{O}$ mixture, the selectivity toward the C–C bond formation was low; this was improved by addition of catalytic amounts of a Pd^{II} salt, namely $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (**2**) and the hydrophilic ligand $[(\text{HOCH}_2\text{CH}_2\text{NHCOCH}_2)_2\text{NCH}_2]_2$ (**L_H**).³ The reaction times needed to achieve the complete consumption of **1** were similar under both conditions (eq 1).²



Electrospray ionization mass spectrometry (ESI-MS)⁴ allows the observation of intermediates involved in

catalytic reactions, the data being directly acquired from the reaction mixture.⁵ ESI-MS has been recently used for the screening of palladium catalysts⁶ and for the determination of the mechanism of the Heck reaction with arene diazonium salts.⁷ Therefore, we have used this method to investigate the role of **2** and **L_H** in the reaction of **1** with **acacH** under aqueous conditions. The identification of the species detected by ESI-MS was aided by comparison between the observed and calculated isotope distribution patterns. Because ⁴⁶Pd and ¹⁷Cl display six and two isotopes, respectively, the ions containing these atoms should be mass-detected as clusters of isotopomeric ions whose center depends on the most abundant isotope (106 for Pd and 35 for Cl).⁸ All ESI-MS analyses were performed with samples dissolved in 1/1 $\text{MeOH}/\text{H}_2\text{O}$, since this mixture is the most appropriate in the allylic alkylation of **1** in the presence of **2** and **L_H**.² The mobile phase used in all ESI experiments was a 70:30 mixture of MeOH and H_2O .

- (1) (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (b) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic: London, 1998. (c) Cornils, B.; Herrmann, W. A. *Aqueous-Phase Organometallic Catalysis*; Wiley: New York, 1998.
- (2) Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **2003**, *44*, 8099.
- (3) Le Bras, J.; Muzart, J. *Tetrahedron Lett.* **2002**, *43*, 431.
- (4) (a) For a monograph on ESI-MS: Cole, R. B. *Electrospray Ionization Mass Spectrometry, Fundamentals, Instrumentation and Applications*; Wiley: New York, 1997. For the application of ESI-MS to inorganic and organometallic chemistry, see the following reviews and references therein: (b) Colton, R.; D'Agostino, A.; Traeger, J. C. *Mass Spectrom. Rev.* **1995**, *14*, 79. (c) Henderson, W.; Nicholson, B. K.; McCaffrey, L. J. *Polyhedron* **1998**, *17*, 4291. (d) Traeger, J. C. *Int. J. Mass Spectrom.* **2000**, *200*, 387. (e) Plattner, D. A. *Int. J. Mass Spectrom.* **2001**, *207*, 125.
- (5) (a) Wilson, S. R.; Pérez, J.; Pasternak, A. *J. Am. Chem. Soc.* **1993**, *115*, 1994. (b) Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985. (c) Ripa, L.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 7147. (d) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657. (e) Hii, K. K.; Claridge, T. D. W.; Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 984. (f) Aramendia, M. A.; Lafont, F.; Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *J. Org. Chem.* **1999**, *64*, 3592. (g) Griep-Raming, J.; Meyer, S.; Bruhn, T.; Metzger, J. O. *Angew. Chem., Int. Ed.* **2002**, *41*, 2738. (h) Moreno-Mañas, M.; Pleixats, R.; Spengler, J.; Chevrin, C.; Estrine, B.; Bouquillon, S.; Hénin, F.; Muzart, J.; Pla-Quintana, A.; Roglans, A. *Eur. J. Org. Chem.* **2003**, *274*. (i) Chen, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 2832.
- (6) (a) Markert, C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2498. (b) Tomazela, D. M.; Gozzo, F. C.; Ebeling, G.; Livotto, P. R.; Eberlin, M. N.; Dupont, J. *Inorg. Chim. Acta* **2004**, *357*, 2349.
- (7) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514.

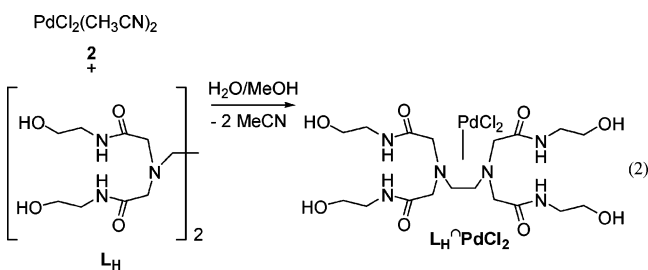
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Table 1. Electrospray Mass Spectral Data for Various Mixtures

entry	mixture	identified species ^a
1	1 , room temp	ESI(+): 193, [1 - OCOCH ₃] ⁺
2	L_H , room temp	ESI(+): 465, [L_H + H] ⁺ ; 487, [L_H + Na] ⁺
3	L_H + PdCl ₂ (CH ₃ CN) ₂ , room temp	ESI(+): 465, [L_H + H] ⁺ ; 567–574 (569), [L_H PdCl ₂ - 2Cl - H] ⁺ ; 603–611 (607), [L_H PdCl ₂ - Cl] ⁺ ESI(-): 601–609 (605), [L_H PdCl ₂ - Cl - 2H] ⁻ ; 637–645 (641), [L_H PdCl ₂ - H] ⁻
4	1 + L_H + PdCl ₂ (CH ₃ CN) ₂ , room temp	ESI(+): 193, [1 - OCOCH ₃] ⁺ ; 465, [L_H + H] ⁺ ; 567–574 (569), [L_H PdCl ₂ - 2Cl - H] ⁺ ; 603–611 (607), [L_H PdCl ₂ - Cl] ⁺
5	1 + L_H + PdCl ₂ (CH ₃ CN) ₂ + 2 acacH + 2 K ₂ CO ₃ , 50 °C for 1 or 24 h	ESI(+): 331, [3 + K] ⁺ ; 503, [L_H + K] ⁺ ; 605–612 (607), [L_H PdCl ₂ - 2Cl - 2H + K] ⁺ ; 641–649 (645), [L_H PdCl ₂ - Cl - H + K] ⁺ ; 705–712 (707), [L_H PdX acac - H - X + K] ⁺ (X = Cl, OAc)
6	1 + L_H + PdCl ₂ (CH ₃ CN) ₂ + 2 acacH + 2 K ₂ CO ₃ , 50 °C for 24 h	ESI(-): 565–572 (567), [L_H PdCl ₂ - 2Cl - 3H] ⁻ ; 601–609 (605), [L_H PdCl ₂ - Cl - 2H] ⁻ ; 701–709 (705), [L_H PdCl acac - H] ⁻
7 ^b	L_H + PdCl ₂ (CH ₃ CN) ₂ + acacH + 2 K ₂ CO ₃ , room temp	ESI(+): 567–574 (569), [L_H PdCl ₂ - 2Cl - H] ⁺ ; 605–612 (607), [L_H PdCl ₂ - 2Cl - 2H + K] ⁺ ; 641–649 (645), [L_H PdCl ₂ - Cl - H + K] ⁺ ; 667–674 (669), [L_H PdCl acac - Cl] ⁺ ; 705–712 (707), [L_H PdCl acac - H - Cl + K] ⁺
8	L_H + PdCl ₂ (CH ₃ CN) ₂ + acacH , room temp	ESI(+): 567–574 (569), [L_H PdCl ₂ - 2Cl - H] ⁺ ; 603–611 (607), [L_H PdCl ₂ - Cl] ⁺ ; 667–674 (669), [L_H PdCl acac - Cl] ⁺
9 ^b	1 (excess) + L_H + PdCl ₂ (CH ₃ CN) ₂ + acacH + 2 K ₂ CO ₃ , 50 °C for 1.5 h	ESI(+): 293, [3 + H] ⁺ ; 331, [3 + K] ⁺ ; 567–574 (569), [L_H PdCl ₂ - 2Cl - H] ⁺ ; 605–612 (607), [L_H PdCl ₂ - 2Cl - 2H + K] ⁺ ; 641–649 (645), [L_H PdCl ₂ - Cl - H + K] ⁺ ; 667–674 (669), [L_H PdX acac - X] ⁺ (X = Cl, OAc); 705–712 (707), [L_H PdX acac - H - X + K] ⁺ (X = Cl, OAc)
10	1 + 0.2 L_H + 0.2 PdCl ₂ (CH ₃ CN) ₂ + 2 acacH + 2 Na ₂ CO ₃ , 50 °C for 1.5 h	ESI(+): 315, [3 + Na] ⁺ ; 487, [L_H + Na] ⁺ ; 589–596 (591), [L_H PdCl ₂ - 2Cl - 2H + Na] ⁺ ; 689–696 (691), [L_H PdX acac - H - X + Na] ⁺ (X = Cl, OAc)
11	1 + Pd(PPh ₃) ₄	ESI(+): 559–566 (561), [Pd(Ph(CH ₃) ₃ Ph)(PPh ₃)] ⁺ ; 821–828 (823), [Pd(Ph(CH ₃) ₃ Ph)(PPh ₃) ₂] ⁺

^a Reported *m/z* values are from the lowest to the highest mass in the isotope envelope of the clusters; the value in parentheses is the most abundant peak. ^b An analogous experiment was performed using Na₂CO₃ instead of K₂CO₃, observing the same species as sodium adducts. The observation of the same species as sodium and potassium adducts confirms the identity of the species detected.

The ESI(+)-MS of **1** showed one peak at *m/z* 193 corresponding to the cationic allylic structure [**1** - OCOCH₃]⁺ (Table 1, entry 1) while the spectrum of **L_H** afforded two peaks at *m/z* 465 and 487, consistent with the protonated ligand [**L_H** + H]⁺ and the sodium adduct [**L_H** + Na]⁺ (entry 2).⁹ The analysis of the ESI(+) mass spectrum of a 1/1 mixture of **2** and **L_H** led us to assume the formation of the complex **L_H** PdCl₂ (eq 2),



since two clusters attributable to the cationic species [**L_H** PdCl₂ - 2Cl - H]⁺ and [**L_H** PdCl₂ - Cl]⁺ were observed at *m/z* 569 and 607, respectively (entry 3). Injecting the same mixture in negative-ion mode ESI(-) showed a cluster centered at *m/z* 605, corresponding to the same species as above, but as the anionic form [**L_H** PdCl₂ - Cl - 2H]⁻. In addition, a new cluster was observed centered at *m/z* 641 and was consistent with the species [**L_H** PdCl₂ - H]⁻ (entry 3).

The ESI(+)-MS spectrum of a stoichiometric mixture of **1**, **2**, and **L_H** (entry 4) afforded the signals of the clusters already observed in entries 1–3, and furthermore, a similar spectrum was obtained after heating the

mixture at 50 °C for 1.5 h. No new species were observed on working in negative-ion mode ESI(-).

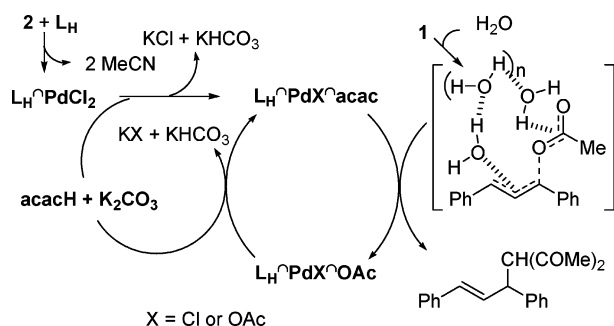
The reaction of an equimolecular mixture of **1**, **2**, and **L_H** with 2 equiv of both **acacH** and K₂CO₃ in MeOH/H₂O at 50 °C was then monitored (entry 5). After 1 h, the ESI(+) mass spectrum showed a variety of signals: (i) two peaks at *m/z* 331 and 503, corresponding to the potassium adducts of the substitution product [**3** + K]⁺ and the ligand [**L_H** + K]⁺ respectively;¹⁰ (ii) two clusters at *m/z* 607 and 645, attributed to the cationic species [**L_H** PdCl₂ - 2Cl - 2H + K]⁺ and [**L_H** PdCl₂ - Cl - H + K]⁺; one cluster at *m/z* 707, attributed to [**L_H** PdX acac - H - X + K]⁺ (X = Cl, OAc), consistent with the formation of the palladium enolate complex **L_H** PdX acac.

(8) Electrospray mass spectrometry analyses were recorded on a Navigator quadrupole mass spectrometer (Finnigan AQA ThermoQuest) equipped with an electrospray ion source. The instrument was operated either in the positive ESI(+) or in the negative ESI(-) ion mode at a probe tip voltage of 3 kV. The samples were taken directly from the reaction mixture and dissolved in MeOH to get an approximate concentration of 4 mM. The samples were introduced into the mass spectrometer ion source directly through a Rheodyne injector with a 20 μ L sample loop. The mobile phase flow (100 μ L/min of 70/30 v/v MeOH/H₂O) was delivered by a P2000 HPLC pump (ThermoQuest) to the vaporization nozzle of the electrospray ion source (165 °C for ESI(+) and 140 °C for ESI(-)), and nitrogen was employed as both a drying and a nebulizing gas. Skimmer cone voltages were varied between 10 and 100 eV. Spectra were typically an average of 15–20 scans. Theoretical isotope patterns were calculated by use of the Isoform program and used to aid assignment.

(9) Association of the substrate with ions is common. [M + H]⁺ and [M + Na]⁺ are often observed; the latter appears from the reaction with traces of cations present even in HPLC-grade solvent.^{4c}

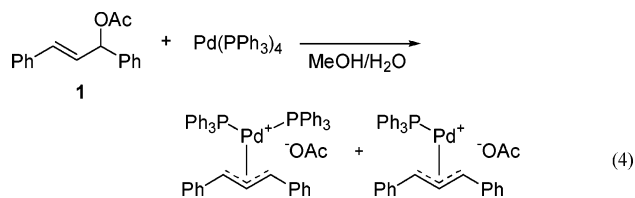
(10) No adduct was observed between product **3** and Pd(II) in the reaction medium or in a mixture of **3**, **L_H**, and **2**.

Scheme 1



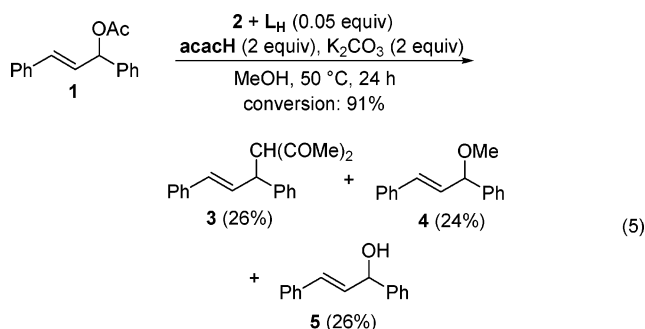
$[\text{L}_\text{H}^-\text{PdCl}_2 - 2\text{Cl} - 2\text{H} + \text{Na}]^+$ and $[\text{L}_\text{H}^-\text{PdX}^-\text{acac} - \text{H} - \text{X} + \text{Na}]^+$ (X = Cl, OAc) (entry 10).

Under all above experimental conditions, we have not been able to detect a cluster containing a $\text{Ph}(\text{CH}_3)_3\text{Ph}$ fragment, although (η^3 -allyl)palladium intermediates are observable by ESI(+)-MS under Pd^0 conditions. Indeed, two clusters centered at m/z 561 and 823 corresponding to $[\text{Pd}(\text{Ph}(\text{CH}_3)_3\text{Ph})(\text{PPh}_3)]^+$ and $[\text{Pd}(\text{Ph}(\text{CH}_3)_3\text{Ph})(\text{PPh}_3)_2]^+$, respectively, were revealed from the ESI(+)-MS analysis of a stoichiometric mixture of **1** and $\text{Pd}(\text{PPh}_3)_4$ in $\text{MeOH}/\text{H}_2\text{O}$ (entry 11), these clusters probing the in situ formation of η^3 -allyl complexes (eq 4).



From the above ESI-MS analysis, it appears that the classical (η^3 -allyl)palladium intermediate is absent from both **1**/**2**/**L_H** and **1**/**acacH**/ M_2CO_3 /**2**/**L_H** (M = K, Na) aqueous mixtures. In addition, a mixture of **2**, **L_H**, and K_2CO_3 in $\text{MeOH}/\text{H}_2\text{O}$ heated to 50 °C led to black particles, due to the reduction of Pd^{II} species,¹³ while such particles were not observed in the course of the palladium-mediated reaction depicted in eq 1. Since the reaction time to obtain the full consumption of **1** under the reaction conditions depicted in eq 1 was independent of the presence of palladium, this latter species is not a catalyst of the acetate anion displacement. In contrast, the **3** selectivity was increased from 40 to 92% under the Pd^{II} conditions. Ether **4** is not an intermediate in the formation of **3**, since its conversion was lower than 5% when subjected to the Pd -catalyzed conditions for 24 h. Without palladium, the selectivity depends on the relative nucleophilicity and stability of the potassium enolate, **acacK**, and potassium methanolate, **MeOK**, in the aqueous medium. The high selectivity of the reaction carried out in $\text{MeOH}/\text{H}_2\text{O}$ in the presence of **2** and **L_H** is probably connected to the formation of the palladium enolate complex $[\text{L}_\text{H}^-\text{PdX}^-\text{acac}]$, which could be a more

effective nucleophile than **acacK** and **MeOK**. We have also observed that the selectivity decreased strongly when the Pd -catalyzed reaction was carried out in MeOH instead of $\text{MeOH}/\text{H}_2\text{O}$ (eq 5):



the ether **4** and alcohol **5** were isolated in addition to **3**. As observed in the metal-free process,² water favors the formation of **3** and the corresponding process may be described as shown in Scheme 1, which involves the nucleophilic attack of $[\text{L}_\text{H}^-\text{PdX}^-\text{acac}]$ on the water-activated substrate. We should point out that, in this scheme, **L_H** may be exchanged for the corresponding mono (or multi)-deprotonated ligand.

To test the potential of **L_H** as a hydrophilic ligand for the immobilization of palladium, catalytic amounts of **L_H** and **2** (0.05 equiv of each) were first reacted with **1** and 2 equiv of both **acacH** and K_2CO_3 in $\text{MeOH}/\text{H}_2\text{O}$ at 50 °C for 24 h. Extraction of the mixture by CH_2Cl_2 and separation of the organic phase yielded 90% of **3**. Successive recycling experiments performed using the recovered aqueous phases afforded **3** in 85, 84, 85, and 85% yield. All of these runs provided slight traces of the ether **4**. These results led us to assume that a Pd^{II} complex is truly immobilized in water by means of **L_H**.

In conclusion, the present study has revealed the surprising role of a Pd^{II} salt in the allylic substitution reaction of 1-acetoxy-1,3-diphenylpropene with acetylacetone carried out in an aqueous medium. ESI-MS studies have not allowed the observation of an (η^3 -allyl)-palladium intermediate but have demonstrated the formation of a palladium acetylacetonate complex. This enolate would react with the substrate to afford 3-(1,3-diphenyl-2-propenyl)-2,4-pentanedione through a highly selective reaction which involves a dramatic role of water. Ligand **L_H** is also adapted for the immobilization of Pd^{II} in water, since recycling experiments have been carried out without noticeable loss of activity.

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(12) For the preparation of palladium enolate complexes of 1,3-diketones, see: (a) Shaw, B. L.; Perera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361. (b) Nowotny, M.; Henefeld, U.; Van Koningsveld, H.; Maschmeyer, T. *Chem. Commun.* **2000**, 1877. (c) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, 124, 11240 and references cited therein. (d) Gavrielatos, E.; Athanasellis, G.; Heaton, B. T.; Steiner, A.; Bickley, J. F.; Igglessi-Markopoulou, O.; Markopoulos, J. *Inorg. Chim. Acta* **2003**, 351, 21.

(13) Muzart, J. *Tetrahedron* **2003**, 31, 5789.

Supporting Information Available: Figures giving observed electrospray mass spectra and calculated isotopic distribution of all detected species tabulated in Table 1. This material is available free of charge via the Internet at <http://pubs.acs.org>.