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Enantioselectivity in the catalytic hydroesterification of acenaphthylene: direct evidence of the racemization of Pd^{II}-alkyl species by a degenerate substitution equilibrium with Pd^0L_n†

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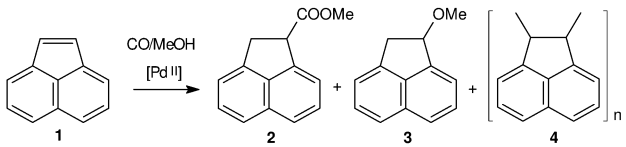
The palladium catalyzed hydroesterification of acenaphthylene takes place through a "hydride" mechanism, that is, through the selective *cis* insertion of the olefin into the palladium–hydride bond, an obvious prerequisite for the successful development of an enantioselective version of the reaction; however, a degenerate substitution equilibrium between Pd^0L_n and the Pd^{II}-alkyl species, involving the inversion of the alkyl carbon, is also operative producing a detrimental effect in the enantioselectivity of the reaction.

Palladium catalyzed carbonylation is considered an environmentally clean synthetic route for the preparation of 2-arylpropionic acids,[1] such as Ibuprofen[2] and Naproxen,[3] a class of non-steroidal anti-inflammatory agents (NSAIDs). This reaction is controllable when very simple vinyl aromatics (*e.g.* styrene) are used.[4] Unfortunately, when the reaction is carried out using lower reactivity arylethenes or functionalised substrates, activities and selectivities diminish to the point where the reaction is no longer useful for the commercial synthesis of carboxylic products. Lack of activity is an important problem, but also loss of selectivity because of side reactions, such as direct hydroalkoxylation and polymerization.[5,6] Very often, only one enantiomer is needed and in this line a number of attempts to achieve the enantioselective version of the reaction have been made, high asymmetric inductions (86–99% ee) have been reported in the hydroesterification of styrene, but the application of these asymmetric catalytic systems to lower reactivity arylethenes always produced lower optical yields.[5,7] By analogy with the behaviour of the chemoselectivity, the decrease in enantioselectivity using low reactivity olefins could be the result of a hitherto undetected side reaction, besides the particular asymmetric induction capability of the auxiliary ligand. In order to study this possibility, acenaphthylene **1** was chosen as model olefin because of the spectroscopic characteristics of the product,[8] which allows the precise determination of the nature of the deuterium incorporation profile in a straightforward manner, and also because it is a low reactivity arylethene allowing observation, in hydroesterification conditions, of the direct hydroalkoxylation and polymerization side products (Scheme 1).[6] Of direct interest are the processes that affect the enantioselective version of this catalytic carbonylation reaction in the highly polar, highly acidic conditions in which it takes place.‡

Deuterioesterification of acenaphthylene with monodentate ligands (Table 1) using $[PdCl_2(PhCN)_2]$/*p*-TsOH as catalyst precursor, resulted mainly in the monodeuterated ester (entry 1).§ The proton and deuterium NMR spectra of **2-d_1** revealed that the addition proceeds cleanly in a *cis* mode (Fig. 1). The monodeuterated ether **3** was the main byproduct of the reaction (6% **3-d_0**, 94% **3-d_1**), and residual acenaphthylene **1** showed less than 3% deuterium incorporation. High selectivity in the addition (measured here as high diastereoselectivity in the deuterioesterification) should be regarded as a prerequisite for the successful development of an enantioselective version. It also strongly supports the assumption that the "hydrido-route" is the operating mechanism of this system (Scheme 2, path a).[9]

In this mechanism the insertion of the olefin into the palladium–hydride bond is in agreement with the observed *cis* product and the subsequent steps should not affect the configuration of the formerly olefinic carbon atoms. It should be noted that, although the olefin insertion/β-hydrogen elimination



Scheme 1 The hydroesterification of acenaphthylene **1** with carbon monoxide and methanol catalyzed by palladium complexes yields a mixture of acenaphthene-1-carboxylic acid methyl ester **2**, 1-methoxyacenaphthene **3** and polyacenaphthylene **4**.

† Electronic supplementary information (ESI) available: experimental details; mass spectra for **2-d_0**, **2-d_1**, and polydeuterated **2**; ^{1}H NMR spectra of **2**, ee measurements; IR spectra of freshly prepared hydroesterification mixtures. See http://www.rsc.org/suppdata/cc/b3/b304553f/

Table 1 Deuterium distribution in deuterioesterification product **2** determined by MS analysis using monophosphines[a]

Entry	Catalyst precursor	PR_3	[MeOD]/M	*p*-TsOH/Pd ratio	Conversion[b] (%)	**2-d_0** (%)	**2-d_1** (%)	**2-d_2** (%)	**2-d_3** (%)
1	$[PdCl_2(PhCN)_2]$	PPh_3	0.82	2.5	70	10	85	5	0
2	$[PdCl_2(PhCN)_2]$	PPh_3	0.82	0	18	5	89	6	0
3	$[PdCl_2(PhCN)_2]$	PPh_3	4.10	2.5	60	0	42	31	27
4	$Pd(AcO)_2$	PPh_3	0.82	2.5	40	3	24	46	27
5	$Pd(AcO)_2$ + 2HCl	PPh_3	0.82	2.5	64	0	97	3	0
6	$Pd(AcO)_2$	$P(p\text{-}FC_6H_4)_3$	0.82	2.5	20	10	59	28	3
7	$Pd(AcO)_2$	$P(p\text{-}MeC_6H_4)_3$	0.82	2.5	38	2	19	46	33
8	$Pd(AcO)_2$	PPh_3	0.82	0	1	9	84	6	1

[a] Reaction conditions: acenaphthylene 4.0 mmol, catalyst precursor 0.04 mmol, PR_3 0.16 mmol, 1,2-dichloroethane/methanol-d_1 30 mL, CO pressure 30 bar, temperature 80 °C, reaction time 24 h. [b] As % of acenaphthylene converted to acenaphthene-1-carboxylic acid methyl ester **2**.

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step is reversible, no appreciable deuterated residual olefin was observed because the stereochemistry of the elimination is typically *syn*. Alternatively, the hydroesterification reaction could be thought to proceed *via* the "carboalkoxy-route"[10] (Scheme 2, path b) in which the insertion of olefin into the Pd–acyl bond is expected to be *cis* and the stereochemistry of the product depends on the selectivity of the subsequent protonolysis elimination step. It is intriguing that very little or no *trans* ester is formed, since it would only require the apparently unhindered *exo* protonolysis. Moreover, in the absence of *p*-TsOH (entries 2 and 8), Pd^{II} carbomethoxy complexes have been described as the resident metallic species, pointing to a "carboalkoxy route".[11] Deuterium NMR spectra of **2-d$_1$** showed a clean *cis* addition at the β-carbonyl possition, but the conversions in these reactions were lower. In these cases, *cis*-addition alone does not completely preclude an alkoxycarbonyl mediated process because protonolysis in the absence of acid is most probably caused by *cis*-coordinated methanol, as recently shown.[12] The typical side products of alkoxycarbonyl mediated reactions have not been detected.

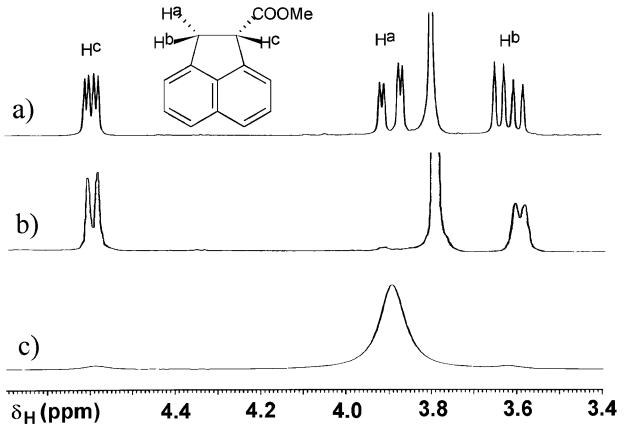
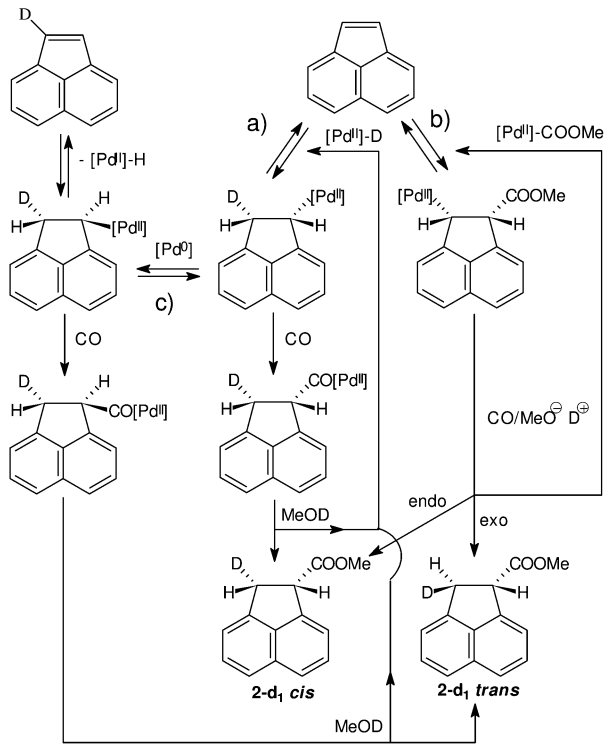


Fig. 1 a) ^{1}H NMR of isolated **2** obtained by hydroesterification. b) ^{1}H NMR and c) ^{2}H NMR of isolated **2-d$_1$** obtained by deuterioesterification using $[PdCl_2(PhCN)_2]$ as catalyst precursor. Deuterium is selectively incorporated in the *a* position during the deuterioesterification process (Spectra are not in the same vertical scale).



Scheme 2 Schematic pathways for the hydroesterification of acenaphthylene: a) "hydrido route", b) "carboalkoxy route" and c) degenerate substitution equilibrium between Pd^{II}-alkyl and Pd^0 species.

Surprisingly, the use of $Pd(OAc)_2$ as catalyst precursor, in exactly the same conditions, gave a mixture of mono-, di- and tri-deuterated esters **2** (entry 4), with incorporation of deuterium in both α and β carbons (Fig. 2). The ether **3** (1% **3-d$_0$**, 45% **3-d$_1$**, 39% **3-d$_2$**, 15% **3-d$_3$**) and the residual acenaphthylene (7% **1-d$_0$**, 40% **1-d$_1$**, 53% **1-d$_2$**) also showed an appreciable degree of polydeuteration. This result can also be explained by the hydride mechanism, but only if it is accepted that a degenerate substitution equilibrium between a Pd^0L_n and a Pd^{II}-alkyl species is also operative in this system (Scheme 2, path c).[13] Nucleophilic substitution involves the inversion of the alkyl carbon and allows the formation of the **2-d$_1$** *trans* isomer, with the potentially highly detrimental effect that this represents for the development of the enantioselective version of the reaction. In addition, only after inversion the β-hydrogen elimination processes from these intermediates generated deuterated olefins, which were converted into di- and tri-deuterated products.

An explanation for the different behaviour of these otherwise very similar catalyst precursors, could be the existence of different palladium resident species during the catalytic process. It has been documented that the HX acid (X^- = Cl^- or AcO^-) formed by addition of *p*-TsOH to the catalyst precursor can regenerate, *via* oxidative addition,[14] the active Pd^{II} species from the Pd^0 that may be formed by final acyl alcoholysis or by independent alcohol promoted reduction of palladium.[15] The oxidative addition to a neutral palladium(0) complex involves initial protonation of the metal to produce a cationic palladium(II) species, and the higher dissociation degree of HCl in polar solvents, compared to AcOH, allows to suppose that the oxidative process is more efficient. Therefore, a smaller amount of Pd^0 resident species should be expected for the $[PdCl_2(PhCN)_2]$ systems. In fact, IR spectra of fresh hydroesterification mixtures showed in both cases carbonyl absorptions at 1820 and 1880 cm^{-1}, that could correspond to $[Pd^0(CO)(PPh_3)_x]_y$ complexes,[16] but only when $[PdCl_2(PhCN)_2]$ was used, absorptions assignable to cationic Pd^{II}-CO species were observed (ν_{CO} 1985 cm^{-1}). Moreover, addition of the stoichiometric amount of HCl to the $Pd(OAc)_2$ precursor gave a catalytic system with high diastereoselectivity in the **2-d$_1$** *cis* isomer (entry 5), and the same results were obtained when HOAc was added to $[PdCl_2(PhCN)_2]$.

Other reaction parameters can also affect the relative abundance of Pd^0/Pd^{II} complexes in the reaction mixtures. In this line, when a large concentration of methanol-d_1 was used (entry 3), the consequences of a very active degenerate substitution equilibrium was observed, even using

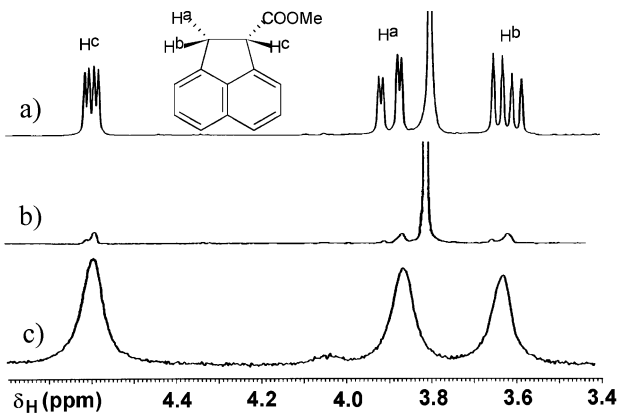


Fig. 2 a) ^{1}H NMR of isolated **2** obtained by hydroesterification. b) ^{1}H NMR and c) ^{2}H NMR of isolated **2** obtained by deuterioesterification using $Pd(OAc)_2$ as catalyst precursor. Deuterium is incorporated in the C_α-*c*, C_β-*a* and C_β-*b* positions during the deuterioesterification process (Spectra are not in the same vertical scale).

Table 2 Deuterium distribution in deuterioesterification product **2** determined by MS analysis using diphosphines[a]

Entry	Catalyst precursor	Diphosphine	Conversion[b] (%)	**2-d$_0$** (%)	**2-d$_1$** (%)	**2-d$_2$** (%)	**2-d$_3$** (%)
1	$[PdCl_2(PhCN)_2]$	dppf	20	9	78	13	0
2	$[PdCl_2(PhCN)_2]$	*rac*-BINAP	12	2	98	0	0
3	$Pd(AcO)_2$	dppf	50	7	48	35	10
4	$Pd(AcO)_2$	*rac*-BINAP	60	1	70	26	3

[a] Reaction conditions: acenaphthylene 4.0 mmol, catalyst precursor 0.04 mmol, diphosphine 0.04 mmol, *p*-TsOH 0.1 mmol, toluene/methanol-d_1 30 mL [MeOD] 0.82 M, temperature 80 °C, CO pressure 30 bar, reaction time 24 h. [b] As % of acenaphthylene converted to acenaphthene-1-carboxylic acid methyl ester **2**.

$[PdCl_2(PhCN)_2]$ as catalyst precursor. This can be explained by the lack of stability of the Pd^{II} complexes to the alcohol promoted reduction at high alcohol concentrations. A decrease in the nucleophilicity of the Pd^0 species, by using the less-basic phosphine P(*p*-$FC_6H_4)_3$, resulted in a lower polydeuteration degree (entry 6). Conversely, Pd^0-P(*p*-$MeC_6H_4)_3$ complexes, with higher nucleophilic character, caused the opposite effect (entry 7).

The use of diphosphines as auxiliary ligands (Table 2) produced a lower degree of polydeuteration, compared to monophosphines, most probably because palladium chelating diphosphine complexes undergo reductive elimination more slowly.[17] Therefore, a greater stability of Pd^{II} resident species in front of the alcohol promoted reduction can be expected. However, as in the case of monophosphines, when $Pd(OAc)_2$ was used as catalyst precursor the degenerate substitution equilibrium between Pd^0L_n and Pd^{II}-alkyl species was more important, compared to $[PdCl_2(PhCN)_2]$. Very interestingly, this is also reflected in the enantioselective version of the reaction. By using (*R*)-(+)-BINAP as auxiliary ligand and in the reaction conditions presented in Table 2, the $[PdCl_2(PhCN)_2]$ catalytic system gave an enantiomeric excesses of 39–45% in the levorotatory enantiomer of **2** while the $Pd(OAc)_2$ system produced only 33–34%. The use of (*S*)-(−)-BINAP produces similar enantiomeric excesses in the dextrorotatory enantiomer.¶

All these results focus attention on the palladium hydride and alkyl species, as well as on the Pd^{II}/Pd^0 couple, as directly responsible for the hydroesterification product, including its stereochemistry. A degenerate substitution equilibrium between the Pd^0L_n and the Pd^{II}-alkyl has been detected, it affects the palladium alkyl carbon, producing a decrease in the enantioselectivity of the reaction. This undesired process could be minimized in at least three ways. First, stabilizing the active Pd^{II} species in front of the alcohol promoted reduction, by using chelating diphosphines instead of monophosphines. Second, assuring the effective regeneration of the active Pd^{II} species from any Pd^0 that would be formed, by using catalyst precursors with counteranions derived from strong acids, and thirdly decreasing the nucleophilicity of the Pd^0 resident species by using phosphines of low basicity or by using diphosphines.

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Notes and references

‡ Typical procedure for hydroesterification and deuterioesterification. A solution of acenaphthylene (4 mmol), the catalyst precursor (0.04 mmol), and when necessary the corresponding amount of phosphorous ligand, HCl or *p*-TsOH, in a mixture of methanol (or methanol-d_1)/solvent (total solvent 30 ml) prepared under a nitrogen atmosphere was introduced into an evacuated reactor *Chemipress* (Trallero & Schlee S. L.). The reactor was pressurized with CO and heated to the reaction temperature. Once the system reached thermal equilibrium, the reaction pressure was adjusted and the stirring started. After each run, the reactor was cooled, its contents were removed and the volatile products analyzed by gas chromatography. Samples of purified ester **2** can be obtained by Flash chromatography in a mixture of hexane/ethyl acetate (9.5/0.5).

§ Isotopic distribution measurements. The crude reaction mixture was analyzed by mass spectrometry in order to determine the deuterium content, which was calculated from the molecular ion region. In the electron impact ionization mass spectra of the products present in the reaction mixture, the abundance of the molecular ions enables us to determine the deuterium content with satisfactory accuracy.

¶ Enantiomeric excess measurements. A sample of purified acenaphthene-1-carboxylic acid methyl ester **2** was diluted with deuteriochloroform and placed in a NMR tube. $[Eu(hfc)_3]$ was added in small portions until a neat splitting of the peak of the methyl protons was observed in the ^1H NMR spectrum.

1 R. A. Sheldon, *J. Chem. Technol. Biotechnol.*, 1997, **68**, 381; C. B. Dartt and M. E. Davis, *Ind. Eng. Chem. Res.*, 1994, **33**, 2887; R. A. Sheldon, *Chem. Ind.*, 1992, 903.

2 V. Elango, M. A. Murphy, G. N. Mott, E. G. Zet, B. L. Smith and G. L. Moss (Hoechst Celanese Corp.), *EP0400892*, 1990*Chem. Abstr.*, 1990, **113**, 80954d.

3 H. Y. Zhou, J. Cheng, S. J. Lu, H. X. Fu and H. Q. Wang, *J. Organomet. Chem.*, 1998, **556**, 239; A. Seayad, S. Jayasrre and R. V. Chaudhari, *Catal. Lett.*, 1999, **61**, 99.

4 R. Naigre, T. Chenal, I. Cipres, P. Kalck, J. C. Daran and J. Vaissermann, *J. Organomet. Chem.*, 1994, **480**, 91; C. W. Lee and H. Alper, *J. Org. Chem.*, 1995, **60**, 250; K. Nozaki, M. L. Kantam, T. Horiuchi and H. Takaya, *J. Mol. Catal. A: Chem.*, 1997, **118**, 247; J. Y. Yoon, E. J. Jang, K. H. Lee and J. S. Lee, *J. Mol. Catal. A: Chem.*, 1997, **118**, 181; M. C. Bonnet, A. L. Monteiro and I. Tkatchenko, *J. Mol. Catal. A: Chem.*, 1999, **143**, 131.

5 S. Oi, M. Nomura, T. Aiko and Y. Inoue, *J. Mol. Catal. A: Chem.*, 1997, **115**, 289.

6 J. Gironès, J. Duran, A. Polo and J. Real, *J. Mol. Catal. A: Chem.*, 2003, **198**, 77.

7 H. Y. Zhou, J. G. Hou, S. J. Lu, H. X. Fu and H. Q. Wang, *J. Organomet. Chem.*, 1997, **543**, 227; H. Y. Zhou, S. J. Lu and J. G. Hou, *Chem. Lett.*, 1996, **5**, 339.

8 C. K. Fay, J. B. Grutzner, L. F. Johnson, S. Sternhell and P. W. Westerman, *J. Org. Chem.*, 1973, **38**, 3122.

9 G. R. Eastham, B. T. Heaton, J. A. Iggo, R. P. Tooze, R. Whyman and S. Zacchini, *Chem. Commun.*, 2000, 609; C. Benedek, A. Gömöry, B. Heil and S. Töros, *J. Organomet. Chem.*, 2001, **622**, 112; C. Benedek, G. Szalontai, A. Gömöry, S. Törös and B. Heil, *J. Organomet. Chem.*, 1999, **579**, 147; G. R. Eastham, R. P. Tooze, M. Kilner, D. F. Foster and D. J. Cole-Hamilton, *J. Chem. Soc., Dalton Trans.*, 2002, 1613.

10 D. M. Fenton, *J. Org. Chem.*, 1973, **38**, 3192; K. H. Shaughnessy and R. M. Waymouth, *Organometallics*, 1997, **16**, 1001.

11 F. Rivetti and U. Romano, *J. Organomet. Chem.*, 1978, **154**, 323; R. Bertani, G. Cavinato, L. Toniolo and G. Vasapolo, *J. Mol. Catal.*, 1993, **84**, 165.

12 P. W. N. M. van Leeuwen, M. A. Zuideveld, B. H. G. Swennenhuis, Z. Freixa, P. C. J. Kamer, K. Goubitz, J. Fraanje, M. Lutz and A. L. Spek, *J. Am. Chem. Soc.*, 2003, **125**, 5523.

13 K. S. Y. Lau, R. W. Fries and J. K. Stille, *J. Am. Chem. Soc.*, 1974, **96**, 4983; J. Real, E. Prat, S. González-Cabello, M. Pagès and A. Polo, *Organometallics*, 2000, **19**, 4715.

14 R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley, New York, 1988, pp. 121–141.

15 A. Vavasori and L. Toniolo, *J. Mol. Catal. A: Chem.*, 1996, **110**, 13; A. Seayad, A. A. Kelkar, R. V. Chaudhari and L. Toniolo, *J. Mol. Catal. A: Chem.*, 2000, **151**, 47; A. Vavasori, G. Cavinato and L. Toniolo, *J. Mol. Catal. A: Chem.*, 2001, **176**, 11.

16 A. Seayad, S. Jayasree, K. Damodaran, L. Toniolo and R. V. Chaudhari, *J. Organomet. Chem.*, 2000, **601**, 100.

17 A. Gillie and J. K. Stille, *J. Am. Chem. Soc.*, 1980, **102**, 4933.

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