Snapshots of a Stille reaction

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The main sequential intermediates involved in a real catalytic cycle of the Stille reaction (the coupling of ROTf with CH_2 =CHSnBu₃ catalyzed by [PdR(OTf)(dppe)]; R = aryl) are observed and characterized unequivocally before the coupling product is released.

Only in rare occasions can real intermediates in a catalytic cycle be observed and unambiguously identified. The Stille reaction (palladium-catalyzed coupling of organotin reagents with carbon electrophiles) is nowadays one of the most powerful synthetic methods for the formation of carbon-carbon bonds.1 Its catalytic cycle involves a number of intermediates, but evidence for these only comes from model reactions outside a real cycle. Echavarren and coworkers have synthesized oxaand aza-palladacycles using the oxidative addition of haloarylstannanes to Pd(0) complexes, followed by an intramolecular transmetalation, thus the products can be considered intermediates of a frustrated Stille cycle, which do not undergo coupling because of the high energy of the coupling product.² We have shown that the coupling of halides R¹I with SnR²Bu₃ $(R^2 = vinyl \text{ or phenyl})$ follows a S_E2 mechanism involving an associative L-for-R² substitution on trans-[PdR¹IL₂]. This Pd(II) complex, which can be prepared separately, was actually observed as involved in the catalytic cycle.³ More recently we have observed the formation and fading out of trans-[PdR¹R²L₂] in the coupling of triflates R¹OTf with Sn(vinyl)Bu₃.⁴ Here we present a catalytic Stille coupling in which all the main intermediates involved are observed, as they are formed and disappear, using ¹H, ¹⁹F and ³¹P NMR spectroscopy.

 $[Pd(C_6F_5)(OTf)(dppe)]$ **1a** [dppe = 1,2-bis(diphenylphosphino)ethane] is a poor catalyst for the coupling, in THF at 50 °C (Pd:Sn = 1:20), of C₆F₅OTf and CH₂=CHSnBu₃ 2 to give CH₂=CHC₆F₅. When the reaction was carried out in THF d^8 at low temperature, starting with $[Pd(C_6F_5)(OTf)(dppe)]$ and CH₂=CHSnBu₃ in 1:1 molar ratio, several intermediate species could be detected and identified until the coupling product was formed. For an easier monitoring of the cycle the studies were repeated on $[Pd(C_6Cl_2F_3)(OTf)(dppe)]$ **1b** $(C_6Cl_2F_3 = 3,5-di$ chlorotrifluorophenyl), which behaves identically to 1a and shows the same intermediates, but has more simple ¹⁹F NMR spectra, facilitating a more accurate integration of the signals.⁵ Scheme 1 shows, step by step, the mechanism of the catalytic cycle and the ¹H NMR spectra of the intermediates identified in the stoichiometric cycle for 1b while Fig. 1 shows the evolution of the reaction, as monitored by ¹⁹F NMR.

The first intermediate in the cycle is **1a** (or **1b**). Under catalytic conditions **1a** is formed very slowly by oxidative addition of C_6F_5 OTf to [Pd(0)], but stoichiometrically these compounds are better prepared from [PdRCl(dppe)] ($R = C_6F_5$, $C_6Cl_2F_3$) and AgOTf. Complexes **1a** and **1b** are stable in the solid state and have been isolated and fully characterized.⁶ In solution in dry THF they give the ionic species [PdR(dppe)-(THF)](OTf) (specific molar conductivity, $\Lambda_m = 4.66$ S cm⁻¹ mol⁻¹ for **1a**),⁷ on which the transmetallation occurs.⁴

The next step is the transmetalation on **1b** leading to a σ -vinyl complex [Pd(C₆Cl₂F₃)(CH=CH₂)(dppe)] **3**, characterized by NMR. Its ¹⁹F NMR spectrum shows the characteristic resonances expected for a C₆Cl₂F₃ group linked to Pd(II), with the



Scheme 1 Catalytic cycle showing the ¹H NMR spectra of the products detected in the range of vinylic protons.

 F_{ortho} coupled to the *trans* phosphorus atom (coupling to the *cis* phosphorus is not observed). In the ³¹P{¹H} NMR spectrum two signals are observed: one for the P *trans* to C₆Cl₂F₃, which appears as an overlapped doublet of triplets, and one for the *cis* phosphorus which appears as a doublet. The ¹H NMR spectrum (Scheme 1) shows three resonances for the three vinylic protons, coupled to phosphorus (see changes upon ³¹P irradiation in the corresponding ¹H{³¹P} NMR spectrum).

Complex 3 is unstable and can be observed only at low temperature.⁸ In spite of the *cis* configuration of this complex, the reductive elimination step takes place less easily than with PPh₃ because of the small bite angle chelating ligand,⁹ and this stabilizes the compound sufficiently for it to be observed.¹⁰ The



Fig. 1 Profiles of the reaction between $[Pd(C_6Cl_2F_3)(OTf)(dppe)]$ **1b** and CH₂=CHSnBu₃ **2** in THF at 243 K. Concentrations were obtained by integration in the ¹⁹F NMR spectra. Starting concentration: 0.02 mol L⁻¹ in **1b**.

coupling product remains coordinated stabilizing a Pd⁰ complex $[Pd(dppe)(\eta^2-CH_2=CHC_6Cl_2F_3)]$ 4. Its ¹H NMR spectrum (Scheme 1) shows three broadened signals, at higher field than in the σ -vinyl complex 3 due to the bigger shielding produced by the metallic center. They are coupled to each other (as seen by ¹H COSY) and also coupled with the phosphorus nuclei of the dppe ligand. In the ${}^{1}H{}^{31}P{}$ NMR spectrum (Scheme 1) only the coupling between protons is observed. The ³¹P NMR spectrum of 4 shows an AB system. This chemical inequivalence of the two P atoms is consistent with a trigonalplanar coordination of the palladium, with the double bond of the asymmetric olefin lying in the plane containing the palladium atom and two phosphorus atoms. Similar complexes have been reported in the literature.¹¹ This compound is again rather stable and can be observed even at room temperature in the stoichiometric reaction. Upon decomposition (or when it undergoes oxidative addition) the olefin CH_2 =CHC₆Cl₂F₃ **5** is released.

In catalytic conditions the cycle should close upon oxidative addition to **4** or to a low coordinated [Pd(0)] complex formed by decoordination of **5**. This oxidative addition is extremely slow and decomposition pathways compete, causing the low efficiency of the catalyst.^{11a} However, four to five turnovers are observed showing that the cycle is actually catalytic. Alternatively, the oxidative addition step can be accelerated very efficiently by adding LiCl once **4** has been formed [the accelerating effect of LiCl on some Stille catalytic cycles is well documented in ref. 1(*a*), and is discussed in ref. 11(*a*)]. This leads to the easy formation of [PdRCl(dppe)] on which, however, transmetalation is extremely slow. A thorough discussion of these observations will be made in a forthcoming full paper.

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