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COMMUNICATIONS

Published on Web 03/01/2007

Insights into the Mechanism of the Negishi Reaction: ZnRX versus ZnR_2 Reagents

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Many palladium catalyzed cross-coupling reactions follow a quite general pathway: oxidative addition of R^1X to Pd(0) to give a $[PdR^1XL_2]$ intermediate, transmetalation from $[M]R^2$ to give $[PdR^1R^2L_2]$, and reductive elimination to afford the product R^1R^2 and regenerate the Pd(0) catalyst. The former and later steps are common to all the cycles and have been studied in some depth.[1,2] The various cross-coupling reactions differ in the nucleophile used for transmetalation and, consequently, in the transmetalation step. Powerful distinct synthetic protocols are available for different couplings partners using the Negishi process,[3] recently including alkyls.[4] The Negishi reaction is peculiar in that two types of organometallic reagent, ZnRX and ZnR_2, are available. Both are actually used depending on the protocol.[3] The choice of one or the other seems to be totally empirical or based on the ease of access to them.

Compared to other reactions (Stille, Suzuki-Miyaura), mechanistic proposals on the transmetalation step in Negishi couplings are purely speculative, and the essential stereochemical and kinetic aspects remain obscure. We report here what are the first experimental observations on the transmetalation in a Negishi coupling. An unexpected observation is made: in the transmetalation with $ZnMe_2$ or ZnMeCl, using $[PdRfCl(PPh_3)_2]$ (**1**, Rf = 3,5-dichloro-2,4,6-trifluorophenyl) as a model,[5] each methylating reagent affords stereoselectively a different isomer (cis or trans) of the $[PdRfMe(PPh_3)_2]$ coupling intermediate. Moreover, the isomerization of these isomers is a slow process. This is a key point to understand that the choice of the organozinc reagent could strongly affect the outcome of the Negishi cycle.

Observation and Isolation of Intermediates. In refluxing THF, the coupling reactions of $ZnMe_2$ or ZnClMe with RfI catalyzed by *trans*-$[PdRfCl(PPh_3)_2]$ afford in both cases RfMe. Hence the system is a real model of the Negishi coupling. At room temperature the reductive elimination of RfMe proceeds very slowly (this should be undesired for synthetic purposes, but it is convenient for the observation of intermediates and potential side reactions).[5] A mixture of *trans*-$[PdRfMe(PPh_3)_2]$ (**2**) and *cis*-$[PdRfMe(PPh_3)_2]$ (**3**) was produced in both cases, along with other products (see below). Both isomers were independently prepared and fully characterized.[6]

Studies on the Transmetalation Step. The transmetalation reactions of *trans*-$[PdRfCl(PPh_3)_2]$ (**1**) with $ZnMe_2$ and with ZnClMe were monitored by ^{19}F NMR, with concentrations of reagents as would be found in a catalysis with 5% Pd catalyst.

Transmetalation with $ZnMe_2$. Figure 1 shows the reaction course of **1** with $ZnMe_2$ (Zn/Pd = 20:1). The starting complex is consumed very fast giving rise to *trans*-$[PdRfMe(PPh_3)_2]$ (**2**) (eq 1). Then the methylated complex **2** progresses in two competitive ways: (i) to give *cis*-$[PdRfMe(PPh_3)_2]$ (**3**) in a very slow process (eq 2); and (ii) to give ZnRfMe (**4**) (eq 3).[7] Finally, the coupling product RfMe is produced slowly from **3** (eq 4).

In separate experiments the isolated complexes **2** and **3** were shown to react with $ZnMe_2$ (Zn/Pd = 20:1) to give ZnRfMe (**4**) and $[PdMe_2(PPh_3)_2]$ by aryl for methyl exchange between the metal centers. After 10 h standing at 298 K, about 60% of the Rf group was in the form of **4**, showing that in the working conditions the equilibrium was displaced toward ZnRfMe + $[PdMe_2(PPh_3)_2]$. This exchange reaction, which is slower than the methyl transfer from $ZnMe_2$ to **1**, explains most of the disappearance of **2** observed in Figure 1.

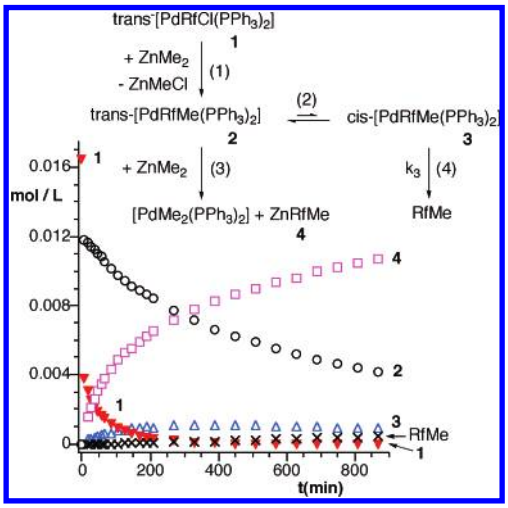

Figure 1. Concentration/time data for the reaction **1** + $ZnMe_2$ obtained by ^{19}F NMR, in THF at 298 K. Starting conditions: [**1**] = 1.65×10^{-2} M; [$ZnMe_2$] = 0.33 M.

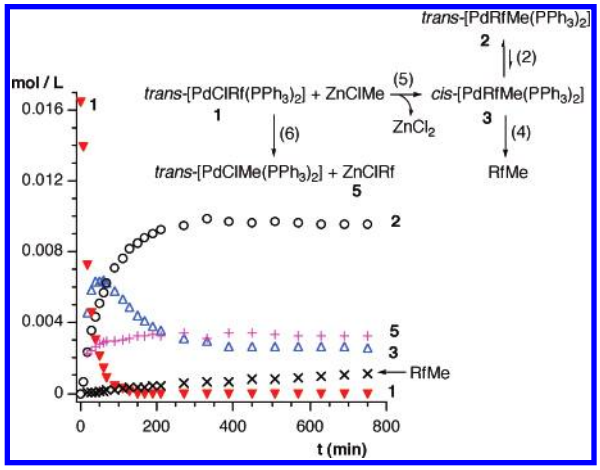

Figure 2. Concentration/time data obtained from ^{19}F NMR in THF, at 298 K for the reaction **1** + ZnMeCl. Starting conditions: [**1**] = 1.65×10^{-2} M; [ZnMeCl] = 0.33 M.

Transmetalation with ZnMeCl. Figure 2 shows the reaction course of **1** with ZnMeCl (Zn/Pd = 20:1). The Me transfer from zinc to palladium (measured as the consumption of **1**) is slower with ZnMeCl than with $ZnMe_2$, as expected from the lower nucleophilicity of ZnMeCl. Initially *cis*-$[PdRfMe(PPh_3)_2]$ (**3**) is

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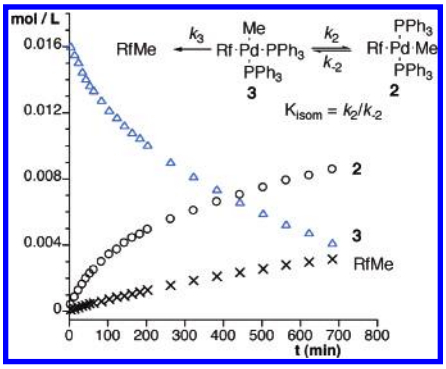


Figure 3. Concentration/time data obtained from ^{19}F NMR in THF at 298 K for the isomerization and reductive elimination process.

produced, while *trans*-[PdRfMe(PPh_3)$_2$] (**2**) is formed only at a slower rate, possibly by isomerization of **3** (see later). Thus the behavior of ZnMeCl is different from that observed for the reaction with $ZnMe_2$, for which the kinetic product is the trans isomer **2**.

The concentration of **3** reaches a maximum and then decreases owing to its isomerization to **2**. On the other hand, some ZnRfCl (**5**) (amounting toabout 20% of total Rf) is formed fast at the early stages of the reaction, but then its concentration changes only modestly during the reaction. In separate experiments the reactions **2** or **3** with ZnMeCl (Pd/Zn = 20:1) afforded, after 12 h, only small amounts of ZnRfCl (**5**) (10% of the total of fluorinated products) showing that this exchange is shifted toward the fluoroaryl group on the palladium complex.

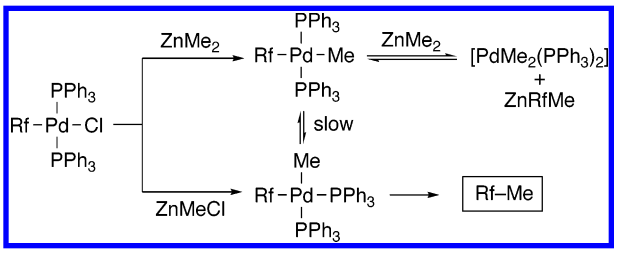
Study of the Cis−Trans Isomerization. The cis−trans isomerization in THF, observed during the transmetalation reactions was monitored as an isolated step by ^{19}F NMR. An evolution to a cis−trans equilibrium was observed, whether starting from **2** or from **3** (Figure 3). In a competitive coupling process, RfMe is formed from **3**.

The reaction kinetics was fitted to a model that takes into account these competitive reactions.[8] At equilibrium the isomerization is shifted toward the trans isomer **2**, affording $K_{isom} = 1.9$ by ^{19}F NMR integration when the equilibrium has been reached. The same K_{isom} value is obtained from the rate constants obtained in the experimental kinetic studies on the **3** to **2** ($k_2 = 3.7 \times 10^{-5}$ s^{-1}; $k_{-2} = 1.9 \times 10^{-5}$ s^{-1}; $k_3 = 8.9 \times 10^{-6}$ s^{-1}) and **2** to **3** (same values within experimental error) isomerization.

The observation that, under the conditions used, the trans−cis isomerization is very slow in both senses compared to the methylation of **1**, supports that the methylation step, whether with $ZnMe_2$ (keeping the trans stereochemistry of the palladium complex) or with ZnMeCl (changing the trans stereochemistry of **1** to cis in the transmetalated product), is stereoselective to the isomer observed in each case.

Some preliminary conclusions can be drawn from Scheme 1, which summarizes our main observations. The transmetalation has unexpected complications. The coupling reaction using ZnMeCl is very direct, as the transmetalation gives directly a cis complex from which the coupling product is obtained. On the contrary the reaction with $ZnMe_2$, although producing a faster transmetalation, gives a trans complex which cannot couple unless it previously isomerizes to the cis isomer. This isomerization is slow (it can be very slow, depending on the ligands), allowing for other side processes to occur. One observed here is the transmetalation Rf/Me, which is

Scheme 1



induced by the presence of the reagent $ZnMe_2$, while it is a very minor problem with ZnMeCl. This side reaction can eventually lead to homocoupling products.

Note that these conclusions should not be extrapolated to less conventional ligands, solvents, or reagents. Further studies of other systems are under way.

Acknowledgment. We thank the Ministerio de Ciencia y Tecnología (Grant CTQ2004-07667), Consolider Ingenio 2010 (Grant CSD2006-0003), and the Junta de Castilla y León (Grant VA-060-04) for support.

Supporting Information Available: Details of syntheses, characterization of the complexes, and kinetics experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The use of this fluorinated aryl slows down the reactions and facilitates NMR studies by ^{19}F, as applied in studies on the Stille reaction. See for instance: (a) Casares, J. A.; Espinet, P.; Salas, G. *Chem.—Eur. J*. **2002**, *8*, 4843−4853. (b) Casado, A. L.; Espinet, P.; Gallego, A. M.; Martínez-Ilarduya, J. M. *Chem. Commun*. **2001**, 339−340. (c) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc*. **2000**, *122*, 11771−11782. (d) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc*. **1998**, *120*, 8978−8985.

(6) Compound **2** was isolated in good yield from the reaction of *trans*-[PdRfCl(PPh_3)$_2$] with $ZnMe_2$ at 0 °C, using an excess of PPh_3 to quench its further evolution. Complex **3** was independently prepared from [PdMeCl(COD)] (COD = 1,5-cyclooctadiene) by arylation with LiRf and then COD displacement with PPh_3. For details see Supporting Information.

(7) ZnRfMe was identified by its ^{19}F NMR signals compared with those from a pure sample of ZnRfMe prepared independently mixing $ZnMe_2$ with $ZnRf_2$ in THF.

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JA070235B