Regioselective palladium-catalysed coupling reactions of vinyl chlorides with carbon nucleophiles

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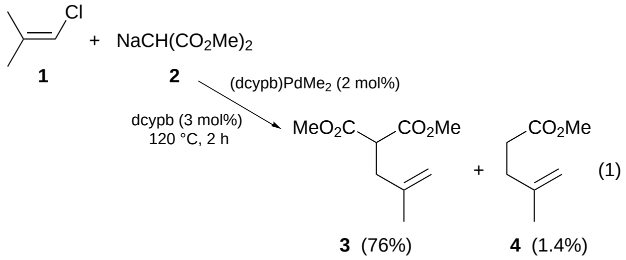
Vinyl chlorides bearing methyl groups in the 2-position can be activated catalytically by palladium(0)-complexes of 1,4-bis(dicyclohexylphosphino)butane, the process involving vinyl–allyl isomerization *via* CH-activation followed by nucleophilic attack of C-nucleophiles on the intermediate palladium–π-allyl species.

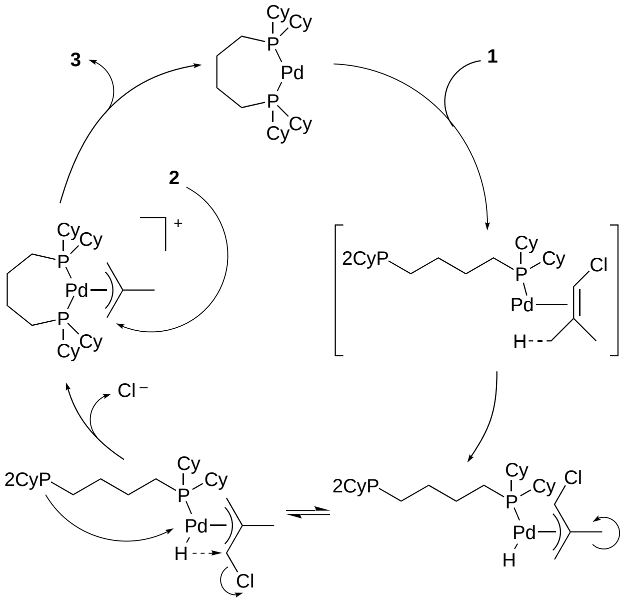
The palladium-catalysed activation of carbon–chlorine bonds in Heck reactions of chloro-aromatics is of great industrial interest because these substrates are much cheaper than the considerably more reactive bromo or iodo analogues.[1] One interesting approach recently published by Milstein makes use of the 1,4-bis(diisopropylphosphino)butane bidentate ligand (dippb), which is believed to open and reclose reversibly with respect to palladium complexation during the catalytic cycle.[2] While the quest for higher efficiency and broader synthetic scope continues in this area, very little is known concerning the catalytic activation of vinyl chlorides.[3] Here we report a serendipitous finding according to which this class of compounds can be induced to undergo unusual C–C bond forming reactions with carbon nucleophiles such as sodium malonates.[4]

In initial attempts to perform a Heck reaction of 1-chloro-2-methylprop-1-ene **1** with styrene, we essentially used the Milstein protocol described for chlorobenzene, except that dippb was replaced by a geometrically and electronically similar ligand which is more readily available, namely 1,4-bis(dicyclohexylphosphino)butane (dcypb). However, only 5–20% of the Heck coupling product 1,1-dimethyl-4-phenylbutadiene was formed. Speculating that the problem could be due to the formation of a catalytically non-active palladium–π-allyl species following Heck-type C–C bond formation, we repeated the reaction in the presence of sodium dimethylmalonate **2** as a carbon nucleophile in hope of inducing a tandem Heck[5]–allyl substitution process [2 mol% $Pd(OAc)_2$, 5 mol% dcypb, DMF, 150 °C, 18 h]. To our surprise none of the expected tandem reaction product was observed, the major products being 2-methylallylmalonic acid dimethyl ester **3** (55%) and its decarboxylated form **4** (20%). Since styrene is not involved, the reaction was repeated in the absence of this olefin at a lower temperature [2 mol% $Pd(OAc)_2$, 5 mol% dcypb, DMF; 120 °C, 18 h]. Again the methallylated products **3** (70%) and **4** (12%) were formed. Other ligands are less effective, the yields of **3**/**4** being lower, as in the case of PPh_3 (8%/3%), 1,2-bis(diphenylphosphino)ethane (4%/5%) and 1,4-bis(diphenylphosphino)butane (32%/26%). In further optimization it was discovered that the best catalyst system is the dimethylpalladium complex of the ligand (dcypb) $PdMe_2$ (2 mol%) in the presence of additional dcypb (3 mol%) at 120 °C, 2 h, leading to products **3** (76%) and **4** (1.4%) eqn. (1).†

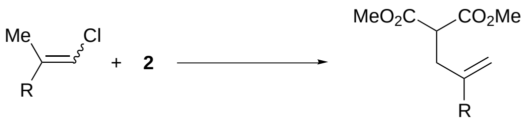
A plausible mechanism involves palladium-catalysed isomerization of the otherwise non-reactive vinyl chloride **1** to methallyl chloride followed by classical palladium-catalysed allylic substitution in which the malonate participates as the carbon nucleophile. Separate NMR experiments revealed that the reaction is initiated by thermolytic decomposition of (dcypb)$PdMe_2$ with formation of (dcypb) Pd° (or its dimer).[4] It is likely that the reactive palladium(0)-catalyst then coordinates to the double bond of **1** and induces CH-activation in one of the methyl groups, the first step in the isomerization. Methallyl chloride may not actually be set free, since palladium can remain coordinated to the π-allyl system, chloride being expelled with intermediate formation of $[Pd\{\eta^3\text{-}(CH_2CMe=CH_2)\}(dcypb)]^+$. Indeed, upon heating (dcypb)$PdMe_2$ in the presence of **1** as the sole reaction partner, this cationic palladium–π-allyl species was identified as the major product by NMR spectroscopy; its BF_4^- salt was synthesized by an independent route and its structure proven by X-ray structural analysis.[4] Scheme 1 shows a possible catalytic cycle which is in accord with all of the present data, including the observation that other ligands are less effective.

Regioselectivity and therefore the possibility of two different products becomes relevant in the case of unsymmetrically substituted vinyl chlorides. In order to test whether the reaction is regioselective, substrates **5** [eqn. (2)] were subjected to the isomerization–substitution reaction. In all cases complete regioselectivity was observed in that CH-activation occurs solely at the methyl groups.





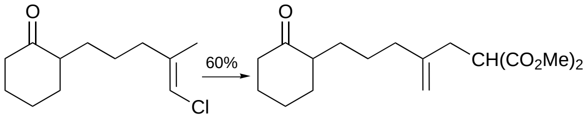
Scheme 1



(2)

	5	**6**
a	*E*, R = cyclo-C_6H_{11}	75%
b	*Z*, R = cyclo-C_6H_{11}	65%

Finally, more highly functionalized substrates such as **7** [eqn. (3)] are also amenable to the reaction. In this case a small amount of a double bond isomer was also observed (14%). Substrates bearing groups larger than methyl do not react analogously, probably due to steric reasons. The bulky ligands due not tolerate additional alkyl groups in the substrate, *e.g.* in the palladium–π-allyl species (Scheme 1).



(3)

7 **8**

In summary, vinyl chlorides having at least one methyl group in the 2-position can be activited catalytically using palladium(0)-complexes of 1,4-bis(dicyclohexylphosphino)butane. The gross features of the mechanism involve vinyl–allyl isomerization *via* CH-activation at the methyl groups followed by classical nucleophilic attack by sodium malonate on the intermediate cationic palladium–π-allyl species. The results suggest that the catalytic activation of otherwise inert vinyl chlorides should be possible in other types of processes using palladium or other transition metal catalysts.

Footnote

† *Typical procedure*: A dry 25 ml Schlenk tube under an argon atmosphere is charged with **1** (0.5 ml, 5 mmol), (dcypb)PdMe$_2$ (58 mg, 0.1 mmol), dcypb (68 mg, 0.15 mmol), **2** (5 mmol) in DMF (5 ml) and heated to 120 °C for 2 h. The mixture is diluted with ethyl acetate (15 ml), treated successively with 10% HCl solution, water and NaHCO$_3$ and NaCl solutions and dried over MgSO$_4$. Most of the solvent is removed and the residue analysed by gas chromatography. **3** is purified by chromatography (silica, pentane–Et$_2$O 4 : 1).

References

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