Pergamon

Tetrahedron Letters, Vol. 36, No. 35, pp. 6305-6308, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01278-8

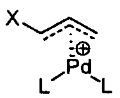
Regioselectivity in the Addition of Carbon Nucleophiles to 1-Fluoro and 1,1-Difluoro π–Allylpalladium Complexes

Guo-qiang Shi*, Xian-hai Huang and Fang-Jiang Zhang

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Academia Sinica
354 Fenglin Lu, 200032 Shanghai, China

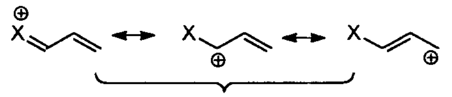
Abstract: Attack on 1-fluoro and 1,1-difluoro π-allylpalladium complexes by stabilized carbon nucleophiles occurs preferentially at the nonfluorinated terminus, wheras the attack of a nonstabilized carbon nucleophile takes place at the fluorinated end.

Palladium-catalyzed nucleophilic substitution of allylic compounds has become an important method for modern organic synthesis.[1, 2] Among several factors that can influence the regioselectivity of this reaction, steric factors are known to be paramount when the substituents on the allyl termini are alkyl or aryl groups.[2] Electronic factors become significant when the allyl termini are substituted with various functional groups,[2] including carbonyls, nitriles, as well as heteroatoms such as SR, OR, OAc. However, the influence of heteroatoms on the regiochemical outcome is not always obvious. For example, by simple extrapolation of the electrophilicity imparted to the allyl ligand by the Pd(II) in **1** to the extreme of an allyl cation **2**, one would predict a greater charge localization on the allyl terminus bearing the heteroatom group and preferential nucleophilic attack there. In reality, sulfur groups have been demonstrated to induce addition of carbon nucleophiles to the remote terminus.[3] With an acetoxy group,[4] variable selectivities were observed depending on the nucleophiles. With carbohydrates[5] or an alkoxy group,[6] the substitution was found to occur preferentially at the π-allyl terminus alpha to oxygen. The ability of these groups to induce widely differing regioselectivities has thus appeared to be governed not only by simple electronic factors but also by their steric influences and/or their possible internal coordination with the metal.[4] In order to investigate the electronic influences exerted by the heteroatoms on the regioselectivity, it is desirable to carry out experiments with a simple model by which steric effects and potential internal coordination influences were minimized.



1

X = SR, OAc, OR, halogens etc.

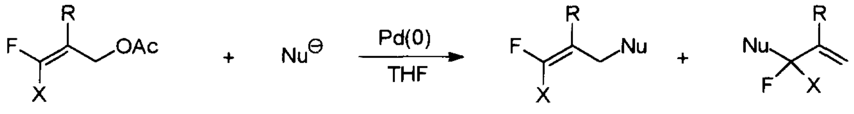


2

Due to our pertaining interest in developing new methodologies for the synthesis of selectively fluorinated organic compounds, we have conceived the possibility of Pd(0)-catalyzed nucleophilic substitution of allylic acetates bearing fluorine atoms at the terminal positions. It was envisaged that such a reaction would not only be of potential utility for the synthesis of selectively fluorinated compounds but also offer the opportunity to examine the neat electronic influence on the regioselectivity by taking advantage of the fact that fluorine is almost isosteric with hydrogen and possesses little complexing capacity for organometallic reagents.[7] To this end, we have examined the behavior of 3-fluoro- and 3,3-difluoroallyl acetates as the substrates in Pd(0)-catalyzed substitution reactions with carbon nucleophiles.

Fluorinated allylic acetates **3a-d** were prepared by appropriate methods.[8, 9] Compared with their nonfluorinated counterparts, these fluorinated substrates generally showed diminished reactivity towards nucleophilic substitution. For example, competition between **3a** or **3b** (1 equiv. each) and methallyl acetate (1 equiv.) for diethyl sodiomethylmalonate (1 equiv.) under Pd(0) catalysis at 25 °C showed rather high chemoselectivity (>3:97) in favor of the fluorine-free substrate. Nevertheless, the fluorinated substrates still possess sufficient reactivity towards nucleophilic substitution and their reactions with two carbon nucleophiles, the malonate anion **6**, and the tin enolate **7**, lead to the normal alkylation products (Scheme 1).

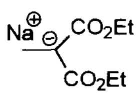
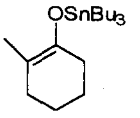
Scheme 1



3 **4** **5**

3a: X = H, R = CH_3 **3c**: X = H, R = OEt
3b: X = F, R = CH_3 **3d**: X = F, R = OEt

Table 1. Palladium catalyzed alkylation of fluorinated allyl acetates

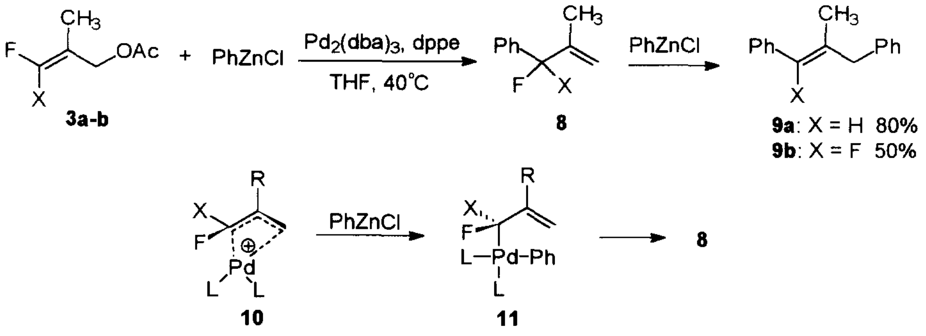
entry	nucleophile	substrate	conditions[a]	regioselectivity[b] 4 : 5	yield[c], %
1	 **6**	**3a**	$Pd(PPh_3)_4$, 60℃, 10h	80 : 20	80
2		**3b**	$Pd(PPh_3)_4$, 60℃, 12h	100 : 0	76
3		**3b**	$Pd_2(dba)_3$,dppe, 40℃, 8h	100 : 0	90
4		**3c**	$Pd(PPh_3)_4$, 60°C, 8h	68 : 32	80
5		**3d**	$Pd(PPh_3)_4$, 60℃, 10h	100 : 0	61
6	 **7**	**3a**	$Pd(PPh_3)_4$, 25℃, 10h	95 : 5	80
7		**3b**	$Pd(PPh_3)_4$, 25℃, 12h	100 : 0	50
8		**3c**	$Pd(PPh_3)_4$, 25°C, 8h	65 : 35	76
9		**3d**	$Pd(PPh_3)_4$, 25℃, 10h	100 : 0	85

[a] All reactions were run in THF using 2.0 equiv. of the nucleophile and 5mol% of the Pd catalyst for 1.0 equiv. of the allylic substrate. [b] Determined on the crude product by ^{19}F and/or ^1H NMR (300 MHz) and checked with GLC. [c] Yield of the isolated products (**4** + **5**).

The results were summarized in Table 1. The methyl-substituted malonate anion[10] **6** was first employed as the nucleophile. The reaction of monofluorinated substrates with this nucleophile was found to occur preferentially at the fluorine-free terminus. In the case of the geminally difluorinated substrates, the asymmetry on the allyl ligand was further increased so that exclusive attack at the unsubstituted terminus was observed. With the tin enolate **7** as the nucleophile, which is known to react with π-allylpalladium complexes via a pathway analogous to that defined for stabilized nucleophiles such as malonates,[11] nucleophilic attack at the unsubstituted terminus was again found to be preferred in the case of monofluorinated substrates and to be exclusive in the case of difluorinated substrates. The ratio of the two regioisomers was conveniently determined by ^{19}F and ^{1}H NMR spectroscopy based on their distinct chemical shifts.

The observed selectivity for preferential attack by stabilized nucleophiles at the terminus remote from the fluorine substituent is somewhat unexpected. It has already been well demonstrated that fluorine, like oxygen and a few other heteroatoms, can greatly stabilize an α-carbocation by sharing its lone-pair electrons with the adjacent vacant p-orbital.[12] Thus, based on the model of a simple allyl cation, one would expect that nucleophilic substitution should occur at the fluorinated terminus, where the positive charge is more pronounced.[13] In the present case, the electronic properties enjoyed by fluorine appears mainly to be its ability to withdraw electrons in the σ-sense so that the positive charge on the π-allyl ligand prefers to be more localized at the unsubstituted end and nucleophilic attack occurs preferentially at that end.

Quite different results were obtained when phenylzinc chloride was employed as the nucleophile. The latter reacted with **3a** and **3b** under Pd(0) catalysis at 40 °C in THF to give compound **9a** and **9b** as the only product in 80% and 50% yield, respectively[14]. The fact that compound **9a** or **9b** could only be formed via a further S_N2' reaction of the initially formed **8** with another equivalent of phenylzinc chloride implied that the initial attack at the π-allyl ligands had occurred regiospecifically at the fluorinated terminus. It is known that nonstabilized nucleophilic organometallics such as phenylzinc chloride react primarily with π-allyl palladium complex by initial attack at the metal center followed by rearrangement to a σ-complex, e.g. **11**, and transfer of the new organic ligand to the allyl system by rapid reductive elimination[2a]. According to this mechanism, the phenyl substituted σ-complex **11** must be formed under kinetic control from the intermediate allyl palladium complex **10**, which should be asymmetric in that palladium is positioned closer to the fluorinated carbon. Such asymmetric bonding can also explain the regioselectivity presented above since the attack on **10** by stabilized nucleophiles must occur preferentially at the carbon center sustaining less bonding to the metal.

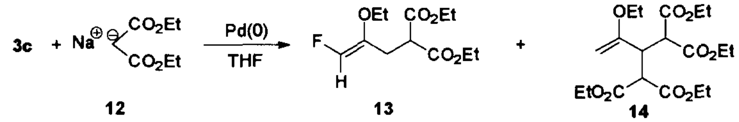


In conclusion, the addition of stabilized carbon nucleophiles to 1-fluoro and 1,1-difluoro π-allylpalladium complexes occurred preferentialy at the fluorine-free terminus, and that of a nonstabilized nucleophile in the opposite sense. These results are not only useful in the design of palladium-catalyzed allylic substitution reactions for organofluorine synthesis but also help to understand the electronic influences exerted by heteroatoms on the regioselectivity of palladium-catalyzed alkylation of allylic substrates.

Acknowledgment. This work was supported by grants from the National Natural Science Foundation of China and Shanghai Municipal Scientific Committee.

References and Notes

1. (a) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, **1980**. (b) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869. (c) Trost, B. M. *Chemtracts* **1989**, *1*, 415. (d) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (e) Tsuji, J. *Synthesis* **1990**, 739.
2. (a) Godleski, S. A. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, **1991**, Vol. 4, p 585. (b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.
3. Godleski, S. A.; Villhauer, E. B. *J. Org. Chem.* **1986**, *51*, 486.
4. (a) Lu, X.; Huang, Y.; *J. Organomet. Chem.* **1984**, *268*, 185. (b) Trost, B. M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131. (c) Lu, X.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 1615.
5. (a) Dunkerton, L. V.; Enske, J. M.; Serino, A. *J. Carbohydr. Res.* **1987**, *171*, 89. (b) Brakta, M.; Lhoste, P.; Senou, D. *J. Org. Chem.* **1989**, 54, 1890.
6. Vicart, N.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1995**, *36*, 535.
7. (a) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. (b) Kiplinger, J. L.; Richmond, T. G.; Osterberg, C. E. *Chem. Rev.* **1994**, *94*, 373.
8. **3a** and **3b**: (a) McDonald, I. A.; Bey, P. *Tetrahedron Lett.* **1985**, *26*, 3807. (b) Taguchi, T.; Morikawa, T.; Kitagawa, O.; Mishima, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5137. **3c**: The corresponding allylic alcohol was prepared by reduction of ethyl 2-ethoxy-3,3-difluoropropenoate with $LiAlH_4$. For a related example of this kind of reduction, see Watanabe, S.; Sugahara, K.; Fujita, T.; Sakamoto, M. *J. Fluorine Chem.* **1993**, *62*, 201. **3d**: The corresponding allylic alcohol was prepared by reduction of ethyl 2-ethoxy-3,3,3-trifluoropropanoate with $LiAlH_4$ and treatment of the resulting 2-ethoxy-3,3,3-trifluoropropanol with 2 equivalents of LDA in THF. More details relevant to the preparation of **3c,d** can be found in our recent paper: Shi, G.-Q; Cao, Z.-Y.; Cai, W.-L. *Tetrahedron* **1995**, *17*, 5011.
9. For the Pd-catalyzed substitution of the nonfluorinated 2-ethoxy-2-propenyl acetate, see Trost, B. M.; Gowland, F. W. *J. Org. Chem.* **1979**, *44*, 3448.
10. When unsubstituted malonate anion **12** was used as the nucleophile, the reactions were complicated by the *in situ* dehydrofluorination from the regioisomer formed from attack at the fluorinated terminus and further reactions. Thus, when **12** was reacted with **3c** under Pd(0) catalysis, a 70:30 mixture of compound **13** and **14** was obtained.



11. Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.
12. Smart, B. E. in *Chemistry of Halides, Pseudo-halides and Azides*; Patai, S.; Rapoport, Z. Eds.; John Wiley & Son: New York, 1983, p604.
13. For reactions involving a fluorine-substituted allyl cation, see (a) Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 957. (b) Fujita, M.; Hiyama, T.; *Tetrahedron Lett.* **1986**, *27*, 3659. (c) Tellier F.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1987**, *28*, 3335. (d), Tellier, F.; Sauvetre, R. *Tetrahedron Lett.* **1991**, *32*, 5963. (e) Tellier, F.; Sauvetre, R. *Tetrahedron Lett.* **1993**, *34*, 5433.
14. Under the same reaction conditions, the fluorinated substrates **3c** and **3d** did not react with phenylzinc chloride. This can be attributed to the substitution of an ethoxy group in these two substrates which hampers the formation of the initial olefin-palladium(0) complex (see reference 9). Reactions performed at an elevated temperature of refluxing THF led to complex mixture presumably due to the incompatibility of the ester group in **3c,d** with phenylzinc chloride.

(*Received in China* 3 *May* 1995; *accepted* 28 *June* 1995)