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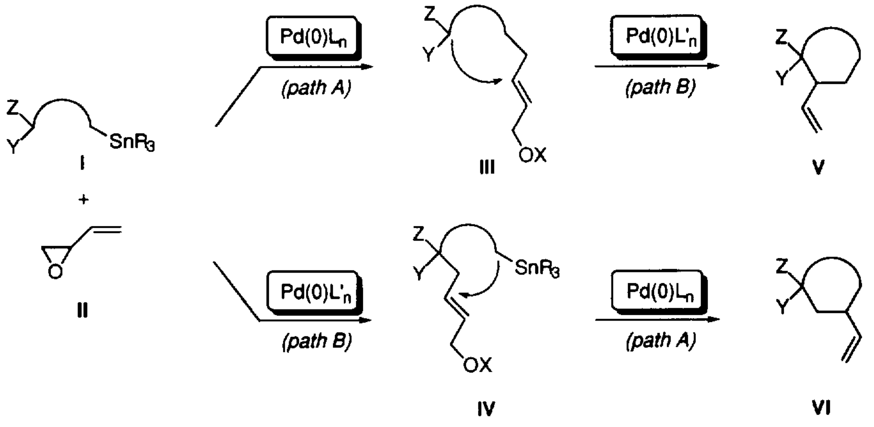
Palladium-Switchable Bisnucleophiles

Ana M. Castaño, María Ruano, and Antonio M. Echavarren*

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain[‡]

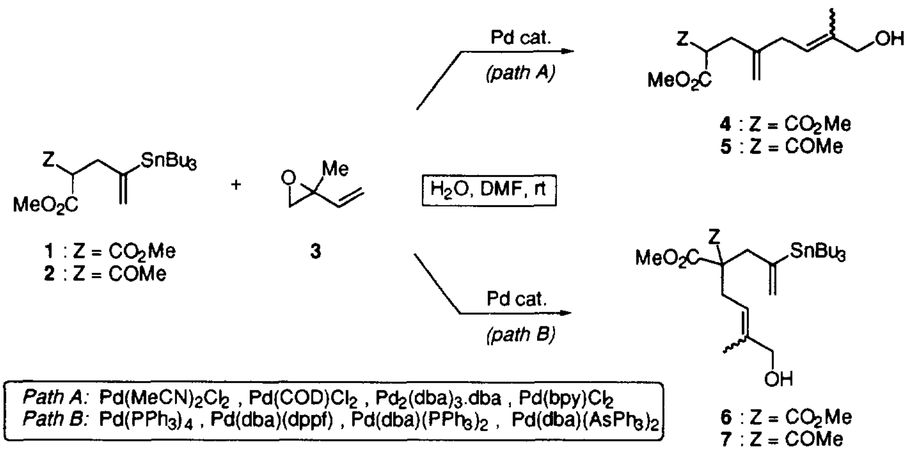
Abstract: The selective activation of substrates **I**, potential bisnucleophiles, was achieved by using different palladium catalysts. The synthetic potential of this strategy has been demonstrated in the regiodivergent synthesis of carbocycles using vinyl epoxides as the electrophiles in the palladium-catalyzed reaction with **I**. Copyright © 1996 Elsevier Science Ltd

The palladium-catalyzed alkylation of allylic substrates by stabilized enolates and mild organometallic reagents rank among the most efficient and selective methods for the formation of carbon-carbon bonds.[1,2,3] Stannanes have been extensively used as mild nucleophiles in palladium-catalyzed reactions because of their compatibility with most functional groups.[4] Although much effort has been made for the stereocontrolled attack of nucleophiles on (η^3-allyl)palladium complexes,[5] little attention has been paid to the issue of nucleophile chemoselectivity. We have now prepared bisnucleophiles of type **I** containing a malonate, or a similar group, and a stannane which can alkylate or couple with an allylic electrophile in the presence of the appropriate palladium catalyst. Thus, we hoped that vinyl epoxides (i.e. **II**) would react regio- and chemoselectively with the stannane (path A)[1,6] or the malonate enolate (path B)[1,7] of **I** to furnish allylic alcohols **III** or **IV** (X = H), respectively. It was expected that a second palladium-catalyzed reaction of activated derivatives of **III** and **IV** would provide carbocycles **V** and **VI**, respectively. Herein we report preliminary results on the successful application of this strategy that is based on the highly selective activation of substrates like **I** (switchable bisnucleophiles) with different palladium complexes.



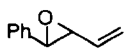
Stannanes **1** and **2** were readily prepared by palladium-catalyzed hydrostannylation[8] of dimethyl propargyl malonate and methyl propargyl acetoacetate with Bu$_3$SnH.[9] Reaction of **1** with 2-methyl-2-

vinyloxirane (**3**) in the presence of catalytic (5-10%) amounts of $Pd(MeCN)_2Cl_2$ and several equiv of H_2O in DMF at room temperature was highly regio- (1,4-addition) and chemoselective yielding **4** as a 3:1 mixture of *E* and *Z* isomers in 93% yield.[10a] Under these conditions exclusive reaction at the alkenyl tin function was observed. Similar results were observed using $Pd(COD)Cl_2$, $Pd_2(dba)_3$.dba, and $Pd(bpy)Cl_2$ as the catalysts. A similar reaction of **2** afforded **5** in 66% yield.[10a]



Attempts to make the malonate act as the nucleophile towards **3** preforming the malonate anion were unsuccessful under these reaction conditions. However, reaction of the sodium enolate of **1** with **3** in THF (23 °C, 17 h) proceeded in the presence of $Pd(PPh_3)_4$ to give **6** in low yield (31%, >9:1 *E/Z* mixture). Better results were obtained in DMF (51% yield) although the opposite diastereomer was favored in this case (1:1.8 *E/Z*). The use of $Pd(dba)(AsPh_3)_2$, prepared *in situ* from $Pd_2(dba)_3$.dba and $AsPh_3$,[11] in DMF containing 4.5 equiv of water led to **6** in 65% yield. The best results were obtained by using $Pd(dba)(PPh_3)_2$[12] as the catalyst in DMF containing *ca.* 5 equiv of water affording **6** (1:1.6 *E/Z* mixture) in 92% yield after 2 h at 23 °C. In the absence of water, the reaction was rather slow and unselective leading to mixtures of **4** and **6** in low yield. The reaction between acetoacetate **2** and vinyl epoxide **3** with $Pd(dba)(PPh_3)_2$ as the catalyst gave **7** in 77% yield.

The same reactivity was observed in the reaction between **1** and 2-phenyl-3-vinyloxirane (**8**) (6:1 *trans/cis*). Thus, reaction under conditions A ($Pd(MeCN)_2Cl_2$ as the catalyst, DMF) gave alcohols **9** in 75% yield as a *ca.* 5:1 mixture of stereoisomers. On the other hand, reaction with $Pd(dba)(PPh_3)_2$ led to **10** as a single isomer in 64% yield.



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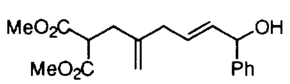

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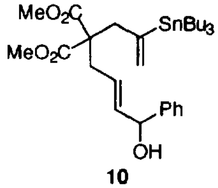

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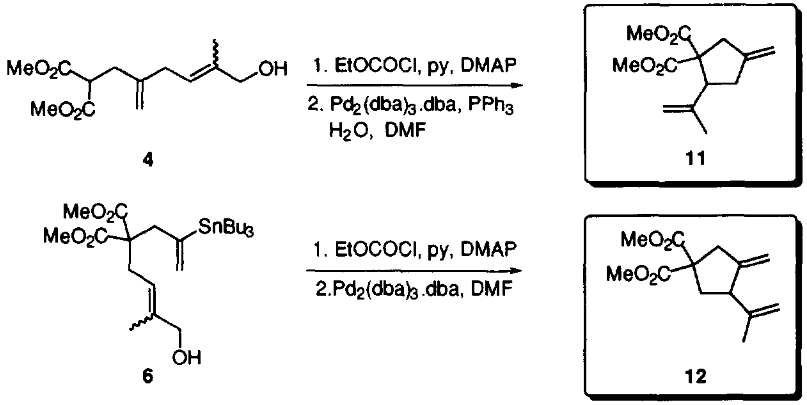
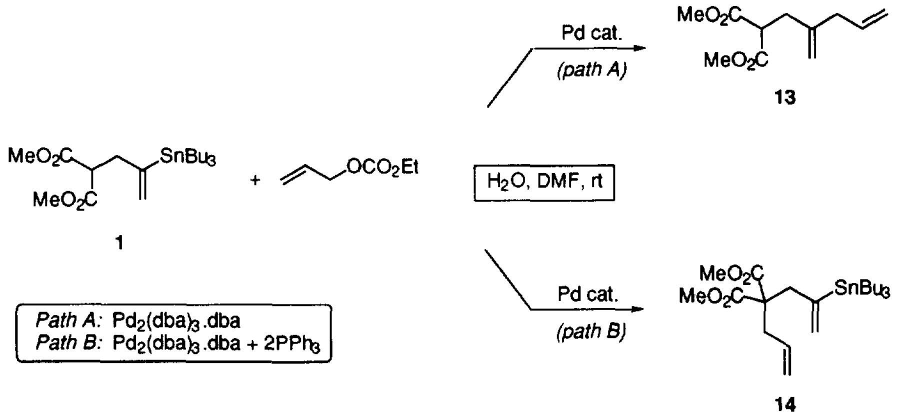
The ring closure of the allylic alcohols was demonstrated with substrates **4** and **6**. Thus reaction of **4** with ethyl chloroformate gave the corresponding ethyl carbonate (75% yield) which reacted at 23 °C with $Pd(dba)(PPh_3)_2$[12] as the catalyst in DMF containing 3 equiv of water to afford methylenecyclopentane **11** in 63% yield. It is interesting to note that the cyclization of the corresponding sodium malonate under the standard conditions ($Pd(PPh_3)_4$ catalyst, THF under reflux)[7] was less successful yielding carbocycle **11** in only 39% yield. The alternative ring closure of the ethyl carbonate derivative of **6**, prepared in 78% yield, was cleanly performed to give **12** in 81% yield (23 °C, 5 h) by using our recently developed palladium-catalyzed coupling of allyl carbonates with stannanes.[13] A similar result was obtained with $Pd(MeCN)_2Cl_2$ as the catalyst.



The chemoselective activation of **1** was further demonstrated in the reaction with allyl ethyl carbonate. Thus, reaction through the stannane afforded exclusively **13** (61% yield),[13] while the alternative allylation through the malonate was achieved by using a palladium complex with PPh_3 as the ligand giving cleanly **14** in 55% yield.[10b]



These results demonstrate that selective activation of bisnucleophiles of type **I** can be easily achieved by selecting the palladium catalysts with the appropriate ligands. Transmetallation of the organostannanes proceeds in the absence of phosphine or arsine ligands, while nucleophilic attack of the enolate occurs with these type of ligands on palladium under neutral conditions. The role of water in these processes is unclear, although formation of a hydroxo palladium(II) complexes is suggested by some recent work.[14] The described regiodivergent syntheses of **11** and **12** illustrate the application of this methodology for the stepwise [3+2] annulation of bisnucleophile **I** onto a 1,3-diene equivalent.[15] The selective activation of switchable bisnucleophiles of type **I** by the palladium complexes opens the way to the development of new tactics for the synthesis of carbocycles.[16] For example, stereocontrolled synthesis of bicyclic systems is expected by taking advantage of the stereochemical complementarity of the reactions of stabilized enolates and mild organometallic nucleophiles with (η^3-allyl)palladium(II) complexes.[1,5] Application to more complex systems is presently being undertaken.

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References and Notes

‡ FAX: 341 3973966; e-mail: aechav@ccuam3.sdi.uam.es

1. (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (b) Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975. (c) Harrington, P.J. In *Comprehensive Organometallic Chemistry II*; Abel, E.W.; Stone, F.G.A.; Wilkinson, G. Eds., Pergamon: Oxford, 1995; Vol. 12, Chapter 8.2.
2. For a discussion of the factors that determine the nucleophilic attack on (η^3-allyl)palladium complexes, see: Szabó, K. J. *Organometallics* **1996**, *15*, 1128, and references therein.
3. (a) Reaction of alkenyl boranes with allyl halides: Miyaura, N.; Suginome, H.; Suzuki, A. *Tetrahedron Lett.* **1984**, *25*, 761. (b) Reaction of alkenyl boranes with vinyl epoxides: Miyaura, N.; Tanabe, Y.; Suginome, H.; Suzuki, A. *J. Organomet. Chem.* **1982**, *233*, C13. (c) Harder organometallics with allylic derivatives in the presence of palladium catalysts: Tamao, K. In *Comprehensive Organic Synthesis*; Trost, B.M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 2.2.
4. For reviews of the Stille coupling reaction of tetraorganostannanes, see: (a) Farina, V. In *Comprehensive Organometallic Chemistry II;* Abel, E.W.; Stone, F.G.A.; Wilkinson, G. Eds.; Pergamon: Oxford, 1995; Vol. 12, Chapter 3.4. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Mitchell, T. N. *Synthesis* **1992**, 803. (d) Ritter, K. *Synthesis* **1993**, 735.
5. For a recent review; see: Trost, B. M.; Van Vranken, D.L. *Chem. Rev.* **1996**, *96*, 395.
6. (a) Echavarren, A.M.; Tueting, D.R.; Stille, J.K. *J. Am. Chem Soc.* **1988**, *110*, 4039. (b) Tueting, D.R.; Echavarren, A.M.; Stille, J.K. *Tetrahedron* **1989**, *45*, 979.
7. (a) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575. (b) Trost, B.M.; Molander, G.A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (c) Larock, R.C.; Lee, N.H. *Tetrahedron Lett.* **1991**, *32*, 5911. (d) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025.
8. Zhang, H.X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
9. (a) Best yields and reproducible results were obtained with freshly prepared Bu_3SnH. Mixtures of the terminal stannane (*E* and *Z*) as well as some 1,2-distannane were obtained in this reaction with $Pd(PPh_3)_2Cl_2$ as the catalyst. Crude stannanes were purified by treatment with *p*-TsOH.H_2O in CH_2Cl_2 to destannylate the terminal stannanes followed by flash chromatography to give pure stannanes **1** (36-40% yield) and **2** (55-60% yield). (b) The use of $Pd(PPh_3)_4$ as the catalyst did not eliminated the formation of the unwanted regioisomers: Bussacca, C.A.; Swestock, J.; Johnson, R.E.; Bailey, T.R.; Musza, L.; Rodger, C.A. *J. Org. Chem.* **1994**, *59*, 7553. (c) For a lead reference on hydrostannylation reactions, see: Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442.
10. (a) Yields are based on the stannanes **1** or **2**. In the reactions with $Pd(MeCN)_2Cl_2$ as the catalyst, yields have been corrected to account for the reduction of Pd(II) to Pd(0) by the stannane. (b) Yield corrected for conversion.
11. For the improvement observed in several coupling reactions with $AsPh_3$, see: (a) Farina, V.; Roth, G.; Krishnan, B.; Marshall, D.R. *J. Org. Chem.* **1993**, *58*, 5434. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
12. This complex was prepared *in situ*. See: Amatore, C.; Jutand, A.; Khalil, F.; M'Barki, M.; Mottier, L. *Organometallics* **1993**, *12*, 3168.
13. Castaño, A.M.; Echavarren; A.M. *Tetrahedron Lett.* previous communication.
14. For leading references on hydroxo palladium(II) complexes, see: (a) Grushin, V.V.; Alper, H. *Organometallics* **1993**, *12*, 1890. (b) Ruiz, J.; Rodríguez, V.; López, G.; Chaloner, P.A.; Hitchcock, P.B. *Organometallics* **1996**, *15*, 1662.
15. For the palladium-catalyzed trimethylenemethane [3+2] cycloaddition, see: Trost, B.M.; Grese, T.A. *J. Am. Chem. Soc.* **1991**, *113*, 7363, and references therein.
16. Reaction of 2-butene-1,4-diol monocarbonates is expected to lead to similar results. See: Genet, J.P.; Balabane, M.; Legras, Y. *Tetrahedron Lett.* **1982**, *23*, 331.

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