Reaction of Vinyl Epoxides with Palladium-Switchable Bisnucleophiles: Synthesis of Carbocycles

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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 from substrates of type **I**, bearing malonate-type pronucleophiles and an alkenyl stannane, with vinyl epoxides. A selective palladium-catalyzed reaction of **I** with the vinyl epoxide gives rise to an allylic alcohol, which, after activation as a carbonate, led to the cyclization product by a second palladium-catalyzed reaction. The transmetalation process is favored with palladium catalysts without phosphines or arsines as the ligands. On the other hand, the use of palladium complexes with PPh_3 as the ligand inhibits the transmetalation pathway and promotes the nucleophilic attack of the malonate-type anions on the intermediate (η^3-allyl)-palladium complexes.

Introduction

The Pd(0)-catalyzed allylic alkylation is a very useful reaction that allows for the formation of C−C bonds in a general way under very mild conditions.[1] Although a number of allylic electrophiles have been used in this transformation, vinyl epoxides[2] are of main interest since the product of the palladium-catalyzed allylic alkylation is an allylic alcohol which can be used as the substrate for a second palladium-catalyzed C−C bond formation. Although several carbon nucleophiles have been utilized in reactions with diene epoxides, more general results have been obtained with stabilized enolates,[1,3,4] and organostannanes.[5,6,7,8] The reaction of stabilized enolates requires the presence of palladium complexes with phosphine ligands such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3{\cdot}CHCl_3$/dppe in THF as the solvent.[1,3] On the other hand, coupling of vinyl epoxides with organostannanes was carried out with $Pd(MeCN)_2Cl_2$ in DMF−H_2O.[5] Under the reaction conditions, the Pd(II) precatalyst is immediately reduced by the stannane to form the reactive "ligandless" Pd(0) species. Thus, in principle, bisnucleophiles of type **I** bearing a malonate (Z = CO_2R) or a related C−H activating group and an organostannane (M = SnR_3) could transmetalate with the intermediate (η^3-allyl)-palladium complex derived from vinyl epoxide **II** to give **III** (X = H) (Scheme 1). Alternatively, alkylation of the (η^3-allyl)palladium complex derived from the vinyl epoxide **II** would form the allylic alcohol **IV** (X = H). The desired chemoselective activation of the palladium-switchable bisnucleophiles **I** was expected to be achieved by using palladium catalysts with the appropriate ligands. In any case, capture of the intermediate (η^3-allyl)-palladium complexes by the nucleophile should be faster than potentially competitive rearrangement of these complexes to form the corresponding carbonyl compound.[9] Allylic alcohols **III** and **IV** could be activated by acylation (X = COR or CO_2R) and then subjected to a second palladium-catalyzed alkylation or transmetalation.[10] Herein, we describe the scope and limitation of the concept outlined in Scheme 1.[11,12]

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(1) (a) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, 1995. (b) Heumann, A.; Réglier, M. *Tetrahedron* **1995**, *51*, 975. (c) Godleski S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 3.3. (d) Harrington P. J. In *Comprehensive Organometallic Chemistry*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 797−904.

(2) For a recent lead reference on the synthesis of vinyl epoxides. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943.

(3) (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) Trost, B. M.; Granja, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 1044. (d) Trost, B. M.; Warner, R. W. *J. Am. Chem. Soc.* **1983**, *105*, 5940. (e) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025. (f) Blart, E.; Gênet, J. P.; Safi, M.; Savignac, M.; Sinou, D. I. *Tetrahedron* **1994**, *50*, 505.

(4) Synthetic applications: (a) Trost, B. M.; Hane, J. T.; Metz, P. *Tetrahedron Lett.* **1986**, *27*, 5695. (b) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988. (c) Larock, R. C.; Lee, N. H. *Tetrahedron Lett.* **1991**, *32*, 5911. (d) Trost, B. M.; Ceschi, M. A.; König, B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1486. (e) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L: *J. Am. Chem. Soc.* **2000**, *122*, 5968.

(5) (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.

(6) Application in natural product synthesis: (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970. (b) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 6224.

(7) (a) Palladium-catalyzed reaction of diene epoxides with organomercurials: Larock, R. C.; Ilkka, S. J. *Tetrahedron Lett.* **1986**, *27*, 2211. (b) Reaction with organoboranes: Miyaura, N.; Tanabe, Y.; Suginome, H. *J. Organomet. Chem.* **1982**, *233*, C13. (c) Reaction with organosilanes: Matsuhashi, H.; Asai, S.; Hirabayashi, K.; Hatanaka, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1943.

(8) Nickel-catalyzed reaction of diene epoxides with arylborates: Kobayashi, Y.; Takahisa, E.; Usmani, S. B. *Tetrahedron Lett.* **1998**, *39*, 597.

(9) (a) Suzuki, M.; Oda, Y.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 1623. (b) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2, 2095. See also: (c) Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1997**, *62*, 6547. (d) Kulasegaram, S.; Kulawiec, R. J. *Tetrahedron* **1998**, *54*, 1361 and references therein.

(10) Castaño, A. M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6587.

(11) Preliminary results by using malonate-stannane **1**: Castaño, A. M.; Ruano, M.; Echavarren, A. M. *Tetrahedron Lett.* **1996**, *37*, 6591.

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Scheme 1

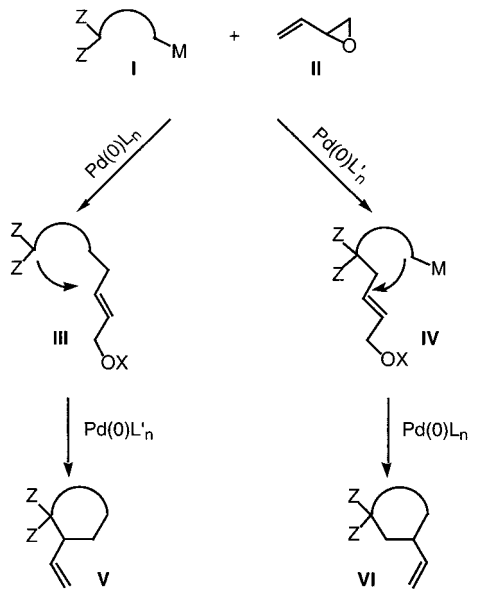
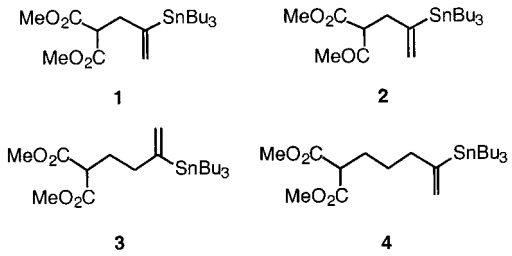


Chart 1

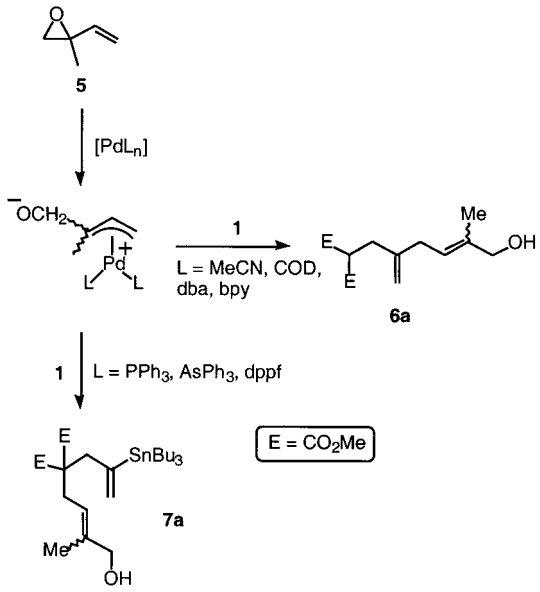


Results and Discussion

Synthesis of Stannanes 1−4. The required bisnucleophiles **1**−**4** (Chart 1) were prepared by the hydrostannylation of the corresponding terminal alkynes with Bu_3SnH in the presence of $Pd(PPh_3)_2Cl_2$ as the catalyst.[13] Besides the desired 2-tributylstannylalkenes which were obtained after column chromatography on silica gel in 50−55% yield, the hydrostannylation also furnished significant amounts of the 1-tributylstannyl derivatives as mixtures of *E* and *Z* isomers, as well as some 1,2-(bis)tributylstannyl alkenes. Nevertheless, purification of these stannanes was simplified by brief treatment of the crude mixtures with *p*-TsOH, which led to the selective cleavage of the 1-stannyl derivatives. The selectivity of these hydrostannylation reactions were highly dependent on the source and quality of the tin hydride used, best results being obtained with freshly prepared Bu_3SnH.[14] The use of $Pd(PPh_3)_4$ as the catalyst instead of $Pd(PPh_3)_2Cl_2$ gave similar results.[15]

Chemoselectivity Studies. Crucial for the success of the strategy outlined in Scheme 1 was the question of the chemoselective reaction of the intermediate (η^3-allyl)-palladium complex with bisnucleophiles **1**−**4**. To determine the optimum conditions we examined the reactions between **1** and isoprene oxide (**5**) in the presence of different palladium complexes (Scheme 2 and Table 1).

Scheme 2



In analogy with that found for the palladium-catalyzed coupling of allyl carbonates with stannanes,[10] we expected that palladium complexes without strongly coordinating ligands would favor Pd/Sn transmetalation. Thus, employment of palladium complexes bearing MeCN, COD, or dba as the ligands led selectively to transmetalation-based cross coupled product **6a** in moderate to good yields with *E*/*Z* selectivities ranging between 1.1:1 to 3:1 favoring the *E* isomer (Table 1, entries 1−3). Best results were obtained by using DMF as the solvent containing 2−5 equiv of water.[5] Strong σ-donating ligands such as bipyridine (bpy) also favored formation of alcohols **6a** (Table 1, entry 4). The optimum conditions were obtained by using $Pd(MeCN)_2Cl_2$ as the catalyst which furnished **6** as a 3:1 mixture of *E* and *Z* isomers (Table 1, entry 1). In this case, the active Pd(0) species probably is a $Pd(DMF)_n$ ($n \leq 4$) or a palladium cluster.[16]

On the other hand, while the reaction of malonate anion with epoxide **5** was unsuccessful, direct reaction of **1** with **5** using $Pd(PPh_3)_4$ in THF in the presence or absence of water gave **7a** as the only characterizable product, contaminated with impurities that could not be easily removed by flash chromatography. Better results were obtained in DMF, although allylic alcohol **7a** was obtained as a 1.4:1 mixture of *E* and *Z* stereoisomers in moderate yield (Table 1, entry 5). It is important to note that none of the alternative product **6a** was detected in these experiments. A similar yield was obtained by using $Pd(OAc)_2$ and PPh_3, although the reaction was faster (Table 1, entry 6). The best result was obtained by using $Pd_2(dba)_3$·dba and 2 equiv of PPh_3 as the catalyst (Table 1, entry 7). Under these conditions, **7a** was obtained as a 1.6:1 *Z*/*E* mixture), which suggest that full syn-anti equilibration of the intermediate (η^3-allyl)palladium complex does not takes place in this case. The active catalyst formed under these conditions has been demonstrated to be $Pd(dba)(PPh_3)_2$.[17] A catalyst prepared with PBu_3

(12) For lead references on the synthesis of five-membered ring heterocycles by palladium-catalyzed 3 + 2 processes: Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067.

(13) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(14) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.

(15) Bussaca, C. A.; Swestock, J.; Johnson, R. E.; Bailey, T. R.; Musza, L.; Rodger, C. A. *J. Org. Chem.* **1994**, *59*, 7553.

(16) For lead references on Pd clusters: (a) Reetz, M. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. (b) Reetz, M. T.; Maase, M. *Adv. Mater.* **1999**, *11*, 773.

Table 1. Influence of the Catalyst System on the Chemoselectivity of the Reaction between 1 and Epoxide 5[a]

entry	catalyst system (mol %)	H_2O (mol equiv)	reaction time (h)	product	yield (%)
1	$Pd(MeCN)_2Cl_2$ (5)		1	**6a**	93
2	$Pd(COD)_2Cl_2$ (10)	7	19	**6a**	75
3	$Pd_2(dba)_3$·dba (5)	5	3	**6a**	69
4	$Pd(bpy)_2Cl_2$ (10)	6	23	**6a**	63
5	$Pd(PPh_3)_4$ (5)	8	17	**7a**	51
6	$Pd(OAc)_2$ (10)/PPh_3 (20)	2	3	**7a**	53
7	$Pd_2(dba)_3$·dba (5)/PPh_3 (20)	8	2	**7a**	92
8	$Pd_2(dba)_3$·dba (2.5)/$AsPh_3$ (10)	4	1	**7a**	65
9	$Pd_2(dba)_3$·dba (5)/dppf (10)	4	6.5	**7a**	57

[a] The reactions were run in DMF at 23 °C in a 0.01−2 mmol scale.

was less efficient. Interestingly, $P(OPh)_3$ led to a palladium catalyst that gave coupled product **6a** as the major product. On the other hand, the reaction in the presence of $Pd(dba)(AsPh_3)_2$ as the catalyst in dry DMF was rather sluggish leading to a mixture of **6a** and **7a** in low yield.[18] However, when the reaction was performed in the presence of 4−5 equiv of H_2O, **7a** was cleanly obtained as a 1.3:1 mixture of *E* and *Z* isomers (Table 1, entry 8). Similar results were obtained with Pd(dba)-(dppf) as the catalyst (Table 1, entry 9).[17b,19]

From these results it is clear that phosphine or arsine ligands do not promote the Pd(II)/Sn transmetalation, presumably as a consequence of the by reduced electrophilicity of the (η^3-allyl)palladium complex, thus leading to the nucleophilic attack of the malonate-type anion.[1,3] On the other hand, intermediate (η^3-allyl)palladium complexes with MeCN, DMF, COD, dba, or bpy as ligands are more electrophilic and therefore undergo clean transmetalation with the organostannane to yield coupled product **6a**.[20] The role of water in the mechanism of the nucleophilic attack of the malonate and the transmetalation of the organostannane is not clear yet since it improves the performance of both reaction pathways of Scheme 2.

The chemoselectivity observed in the reaction of **1** and epoxide **5** is general (Chart 2 and Table 2). Thus, 1,3-butadiene epoxide (**8**) reacts with $Pd(MeCN)_2Cl_2$ (method A) as the catalyst to give **10a** (69%) (Table 2, entry 1), while $Pd_2(dba)_3$·dba/ PPh_3 (method B) gave **11a** in 69% yield (Table 2, entry 2). Similarly, 2-phenyl-3-vinyloxirane (**9**) (3:1 trans/cis) afforded **12a** (Table 2, entry 3) or **13a** (Table 2, entry 4) chemoselectively. Alcohols **12** were obtained as a ca. 4:1 mixture of *E* and *Z* stereoisomers. However, when the reaction was realized with diastereoisomerically pure trans-**9**, alcohol *E*-**12a** was obtained stereoselectively. *β*-Ketoester **2**, as well as malonates **3**-**4** also react selectively under conditions A or B to afford, respectively, cross coupled products (Table 2, entries 5, 7, and 9) or nucleophilic opening derivatives (Table 2, entries 6, 8, and 10).

Synthesis of Carbocycles V by Cyclization of Substrates of Type III. Allyl carbonates have been commonly used as reactive substrates in palladium-catalyzed allylic alkylations by malonate-type nucleophiles.[1,3,21] These reactions can be carried out under neutral conditions, since the leaving group decarboxylates to generate in situ the alkoxide which acts as the base

Chart 2

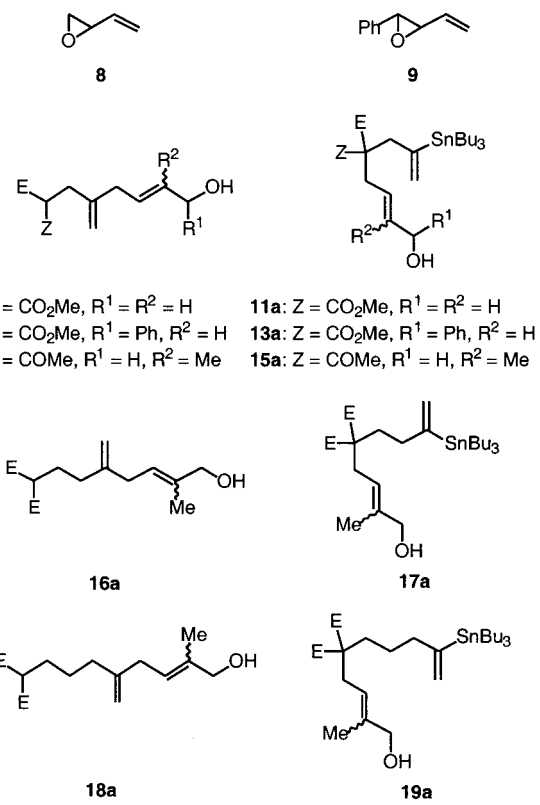


Table 2. Reaction of Stannanes 1−4 with Epoxides 5, 8, and 9[a]

entry	substrate	epoxide	catalyst[b]	product	yield (%)
1	**1**	**8**	A	**10a**	69
2	**1**	**8**	B	**11a**	60
3	**1**	**9**	A	**12a**	75
4	**1**	**9**	B	**13a**	64
5	**2**	**5**	A	**14a**	66
6	**2**	**5**	B	**15a**	94
7	**3**	**5**	A	**16a**	71
8	**3**	**5**	B	**17a**	66
9	**4**	**5**	A	**18a**	72
10	**4**	**5**	B	**19a**	81

[a] The reactions were run in DMF at 23 °C in the presence of 10−20 molar equiv of H_2O at ca. 0.1 M in substrate for 12−24 h. [b] Method A: $Pd(MeCN)_2Cl_2$ (5 mol %). Method B: $Pd_2(dba)_3$·dba (2.5mol %)/PPh_3 (10 mol %).

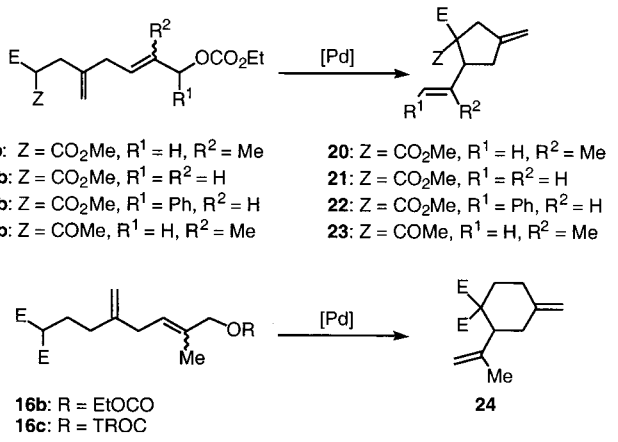
(17) (a) Review of palladium-dba complexes: Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511. See also: (b) Amatore, C.; Broeker, G.; Jutand, A.; Fhalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. (c) Amatore, C.; Fuxa, A.; Jutand, A. *Chem. Eur. J.* **2000**, *6*, 1474. (d) Amatore, C.; Gamez, S.; Jutand, A.; Meyer, G.; Moreno-Mañas, M.; Morral, L.; Pleixats, R. *Chem. Eur. J.* **2000**, *6*, 3372.

(18) For the use of this catalyst in cross coupling reactions: (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.

(19) Alcazar-Roman, L. M.; Hartwig, J. F.; Rheingold, A. L.; Liable-Snads, L. M.; Guzei, I. A. *J. Am. Chem. Soc.* **2000**, *122*, 4618.

(20) For a new mechanistic interpretation of the transmetalation step in the Stille cross-coupling reaction see: Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1989**, *111*, 8979.

Scheme 3



6b: Z = CO_2Me, R^1 = H, R^2 = Me
10b: Z = CO_2Me, R^1 = R^2 = H
12b: Z = CO_2Me, R^1 = Ph, R^2 = H
14b: Z = COMe, R^1 = H, R^2 = Me

20: Z = CO_2Me, R^1 = H, R^2 = Me
21: Z = CO_2Me, R^1 = R^2 = H
22: Z = CO_2Me, R^1 = Ph, R^2 = H
23: Z = COMe, R^1 = H, R^2 = Me

16b: R = EtOCO
16c: R = TROC

24

Table 3. Palladium-Catalyzed Cyclization of Allyl Carbonates of Scheme 3[a]

entry	substrate	reaction time (h)	product	yield (%)
1	**6b**	24	**20**	63
2	**10b**[b]	20	**21**	62
3	**12b**	24	**22**	65
4	**14b**[b]	24	**23**	59
5	**16c**	14	**24**	31
6	**16c**	14[c]	**24**	54

[a] The reactions were run in DMF at 23 °C in the presence of 2 molar equiv of H_2O at ca. 0.1 M in substrate with $Pd_2(dba)_3$·dba (2.5 mol %)/PPh_3 (10 mol %). [b] 0.01 M in substrate. [c] The enolate was preformed by reaction with NaH.

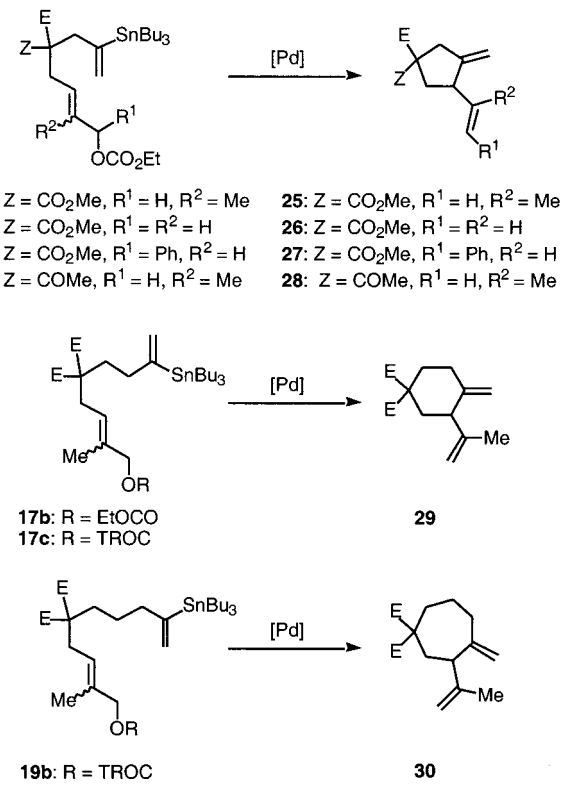
to form the desired enolate from the malonate-type substrate.[1] Therefore, for the synthesis of carbocycles **V** (Scheme 1), substrates **III** (i.e., allylic alcohols **6a**, **10a**, **12a**, **14a**, **16a**, and **18a**) were first activated by formation of the corresponding ethyl carbonates or trichloroethyl (TROC) carbonates under standard conditions.

Cyclization of ethyl carbonates **6b**, **10b**, **12b**, and **14b** was best carried out by using in situ prepared Pd(dba)-$(PPh_3)_2$[17] as the catalyst at room temperature in DMF containing 2 equiv of water (Scheme 3 and Table 3). Carbocycles **20** and **22** were obtained in satisfactory yield by the cyclization of ethyl carbonates **6b** and **12b** (Table 3, entries 1 and 3). However, cyclization of **10b** and **14b** under these conditions (ca. 0.1 M) gave cyclopentene derivatives **21** and **23** in 19% and 22% yield, respectively. Satisfactory results were obtained by performing the reaction at lower concentration (10^{-2} M) (Table 3, entries 2 and 4). Carbocycle **23** was obtained as an inseparable mixture of isomers.

Cyclization of **16b** failed to proceed under the standard conditions. Using TROC derivative **16c** allowed for the preparation of the six-membered ring carbocycle **24** in low yield (Table 3, entry 5). A better yield was obtained in this case by preforming the malonate enolate with NaH (Table 3, entry 6). However, neither ethyl- nor TROC carbonates of alcohol **18** afforded the expected seven-membered ring carbocycle and gave instead elimination products.[22]

Synthesis of Carbocycles VI by Cyclization of Substrates of Type IV. The alternative cyclization

Scheme 4



7b: Z = CO_2Me, R^1 = H, R^2 = Me
11b: Z = CO_2Me, R^1 = R^2 = H
13b: Z = CO_2Me, R^1 = Ph, R^2 = H
15b: Z = COMe, R^1 = H, R^2 = Me

25: Z = CO_2Me, R^1 = H, R^2 = Me
26: Z = CO_2Me, R^1 = R^2 = H
27: Z = CO_2Me, R^1 = Ph, R^2 = H
28: Z = COMe, R^1 = H, R^2 = Me

17b: R = EtOCO
17c: R = TROC

29

19b: R = TROC

30

outlined in Scheme 1 could in principle be achieved by the Stille coupling of the acetates of allylic alcohols **7a**, **11a**−**15a**, **17a**, and **19a** under the described conditions.[23] However, when the acetate of **7a** was treated with Pd_2-$(dba)_3$·(dba) as the catalyst in the presence of LiCl (3 equiv) in THF as the solvent, carbocycle **25** was obtained in only 40% yield. Best results were obtained by using the intramolecular version of the Stille coupling of allyl carbonates with stannanes.[10] Thus, ethyl carbonates **7b**, **11b**, **13b**, and **15b** gave five-membered ring carbocycles **25**−**28** in good yields by using $Pd(MeCN)_2Cl_2$ as the catalyst in DMF at 23 °C (Scheme 4 and Table 4, entries 1−4).

Again, formation of six- and seven-membered ring carbocycles proved to be a more difficult task. Thus, cyclization of ethyl carbonate **17b** failed to give **29**. The use of TROC derivative **17c** allowed for the cyclization to proceed, giving rise to **29** in 42% yield (Table 4, entry 5). Since destannylation of the starting material was observed under these conditions, the reaction was carried out in the presence of *i*-Pr_2NEt as the base, which lead to a modest increase in the yield (Table 4, entries 6 and 7). Formation of a seven-member ring compound was possible by palladium-catalyzed cyclization of the TROC derivative **19b**. Thus, cyclization of **19c** furnished carbocycle **30** (Table 4, entries 8−10). The best results were again obtained by performing the cyclization at 45 °C in the presence of *i*-Pr_2NEt (Table 4, entry 10).

(21) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *42*, 1523. (c) Minami, I.; Ohashi, Y.; Shimizu, I.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 2449. (d) Genêt, J. P.; Ferroud, D. *Tetrahedron Lett.* **1984**, *25*, 3579. (e) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, *32*, 2025.

(22) (a) Takahasi, T.; Nakagawa, N.; Minoshima, T.; Yamada, H.; Tsuji, J. *Tetrahedron Lett.* **1980**, *31*, 4333. (b) Mandai, T.; Matsumoto, T.; Tsuji, J.; Saito, S. *Tetrahedron Lett.* **1993**, *34*, 2513. (c) Keinan, S.; Kumar, S.; Dangur, V.; Vaya, J. *J. Am. Chem. Soc.* **1994**, *116*, 11151. (d) Anderson, P. G.; Schab, S. *Organometallics* **1995**, *14*, 1. (e) Takacs, J. M.; Lawson, E. C.; Clement, F. *J. Am. Chem. Soc.* **1997**, *119*, 5956. (f) Braun, M.; Mross, S. *Synthesis* **1998**, 83. (h) Schwarz, I.; Braun, M. *Chem. Eur. J.* **1999**, *5*, 2300.

(23) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 5, 3019.

Table 4. Palladium-Catalyzed Cyclization of Allyl Carbonates of Scheme 4[a]

entry	substrate	reaction time (h)	product	yield(%)
1	**7b**	1.5	**25**	81
2	**11b**	24	**26**	62
3	**13b**	8	**27**	69
4	**15b**	24	**28**	95
5	**17c**	17[b]	**29**	42
6	**17c**	18[b,c]	**29**	52
7	**17c**	19[b−d]	**29**	58
8	**19b**	17[b]	**30**	27
9	**19b**	17[b,d]	**30**	37
10	**19b**	17[b−d]	**30**	55

[a] The reactions were run in DMF at 23 °C in the presence of 2 molar equiv of H_2O at ca. 0.1 M in substrate with $Pd(MeCN)_2Cl_2$ (5 mol %) or $Pd_2(dba)_3$·dba (2.5 mol %). [b] [c] $Pd_2(dba)_3$·dba (10 mol %) in anhydrous DMF. [d] 1 equiv of *i*-Pr_2NEt was added. [e] Reaction carried out at 45 °C.

Conclusions

Transmetalation of organostannanes with allyl carbonates and vinylepoxides is favored with palladium catalysts without phosphines or arsines as the ligands. Best results were obtained by using $Pd(MeCN)_2Cl_2$ as the catalyst in wet DMF as the solvent. On the other hand, the use of palladium complexes such as $Pd(dba)(PPh_3)_2$ inhibits the transmetalation pathway and promotes the nucleophilic attack of the malonate-type anions on the intermediate (η^3-allyl)palladium complexes. Again, the use of wet DMF as the solvent gave the best results in most cases.

By using malonates or acetoacetates bearing alkenylstannanes functions as binucleophiles and diene monoepoxides as the electrophiles a regiodivergent synthesis of carbocycles has been achieved. In these carbocyclizations, two carbon−carbon bonds are formed chemospecifically between the bisnucleophile and the alkenyl function of the diene monoepoxide. These carbocyclizations proceed under mild conditions and are general for the formation of five-membered ring compounds. Lower yields were obtained for the preparation of six- and seven-membered ring carbocycles. In all cases, the carbon−carbon formations take place with complete regioselectivity.

Beyond the synthetic interest of this carbocyclization methodology, these results demonstrate that stannanes and soft nucleophiles such as malonate enolates can be orthogonally activated toward allylic electrophiles by using the appropriate palladium complexes as catalysts.

Experimental Section

Synthesis of Alkenylstannanes 1−4 by Hydrostannylation of Alkynes. Typical Procedure. Dimethyl propargylmalonate (7.90 mmol) was added to a solution of palladium catalyst [1−2 mol % of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$] in THF (50 mL), followed by addition of Bu_3SnH (7.90 mmol). The reaction mixture was stirred at 23 °C for 2−3 h and then the solvent was evaporated. Chromatography (12:1 hexanes−EtOAc) gave stannane **1** contaminated with the terminal isomers. Treatment of the crude mixture with 0.3−0.4 equiv of *p*-TsOH in CH_2Cl_2 followed by chromatography gave **1**[13] as an oil in 65% yield.

General Procedure for Coupling between Vinyl Epoxides and Stannanes (I + II → III, Scheme 1). To a solution of $Pd(MeCN)_2Cl_2$ (0.05 mol %) in DMF (1 mL) and H_2O (2−5 equiv) were added the vinyl epoxide (0.22 mmol) and the stannane (0.22 mmol). The reaction mixture was stirred at 23 °C until TLC showed full conversion of stannane. Then H_2O and Et_2O were added. After extractive workup and chromatography (hexanes−EtOAc 2:1) the desired alcohols were obtained as oils.

General Procedure for Nucleophilic Opening of Vinyl Epoxides by the Enolates of 1−4 (I + II → IV, Scheme 1). A solution of stannane (0.21 mmol), $Pd_2(dba)_3$·dba (0.025 mol %), and PPh_3 (0.1 equiv) in DMF (1 mL) was stirred for a few minutes (change from red to yellow), and then H_2O (2−5 equiv) was added, followed by the epoxide (0.21 mmol) (change to pale yellow). The reaction mixture was stirred at 23 °C until TLC showed full conversion. Then Et_2O and H_2O were added. After extractive workup and chromatography (4:1 hexanes−EtOAc), the allylic alcohols were obtained as oils.

General Procedure for the Formation of Carbonates. To a solution of allyl alcohol (0.25 mmol) and DMAP (0.02 mmol) in CH_2Cl_2 (4 mL) at 0 °C were added successively pyridine (1.1 equiv) and EtOCOCl (1.1 equiv). The reaction was stirred at 0 °C for 15 min and then 2 h at 23 °C. The solvent was evaporated and the residue taken up in Et_2O, filtered through silica gel (hexanes−EtOAc 4:1 as eluent) and evaporation yields the corresponding carbonate. Alternatively, the reaction mixture was diluted with CH_2Cl_2 and treated with 1.2 M HCl. Extractive workup and evaporation gave the crude carbonates. Usually carbonates were used in the cyclization reaction without further purification.

Cyclization Reactions of Scheme 3 (Table 3). A solution of $Pd_2(dba)_3$·dba (2.5 mol %) and PPh_3 (10 mol %) in DMF (1 mL) was stirred for a few minutes (the color changes from red to yellow), and then H_2O (2 equiv) was added, followed by the allyl carbonate. The reaction mixture was stirred at 23 °C until TLC showed full conversion and then Et_2O and H_2O were added. Extractive workup and chromatography (15:1 hexanes−EtOAc) gave cyclized compounds.

Cyclization Reactions of Scheme 4 (Table 4). To a solution of the allyl carbonate in DMF (1 mL) was added $Pd_2(dba)_3$·dba or $Pd(MeCN)_2Cl_2$ as the catalyst. For the reactions of **17c** and **19b** *i*-Pr_2NEt (1 equiv) was added to minimize destannylation of the starting material. The reaction mixture was stirred at 23or 45 °C until TLC showed full conversion and then the mixture was washed with saturated aqueous solution of KF. Extractive workup and chromatography (15:1 hexanes−EtOAc) gave cyclized compounds.

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Supporting Information Available: Characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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