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Palladium-Catalyzed Carbocyclization of Allene−Diene Derivatives. Exploring Different Nucleophiles

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The palladium-catalyzed carbocyclization of allene−diene derivatives leading to the stereospecific formation of various 4-substituted [4.3.0] and [5.3.0] bicyclic systems is presented. Different functionalities were introduced at the C-4 position of the bicyclic systems by using a range of external nucleophiles such as carboxylic acids, alcohols, phenols, and thiophenols. In the previous protocol acetic acid was used as solvent and also served as nucleophile. In this new methodology, reactions were run in nonnucleophlic solvents such as CH_2Cl_2 or acetone in the presence of the appropriate nucleophile, making this new protocol a more versatile tool in organic synthesis. It is noteworthy that the Pd(II)-catalyzed cyclization of cycloheptadiene-derivative **1b** gave exclusively the trans-annulated bicycle **4**. Depending on the nature of the nucleophile, the regioselectivity of the reaction could be tuned to afford exclusively **4b** or **4c′** (Scheme 1). The mechanistic pathway is discussed.

Introduction

Bicyclo[4.3.0]non-2-ene and bicyclo[5.3.0]dec-2-ene are important frameworks in the synthesis of natural products.[1] Despite the large number of methods available for the synthesis of these compounds, these methods often suffer from lack of general applicability. The asymmetric construction of such units is even more restricted.[2] In this regard, the catalytic use of transition metals has been successfully applied, and it is known that various types of polyenes and enynes undergo intramolecular cyclization.[3−5] These reactions usually proceed under mild conditions with high control of stereoselectivity. Palladium(0)-catalyzed cyclization reactions of unsaturated substrates,[4,5b,6] as well as palladium(II)-catalyzed intramolecular heteroatom addition to allenes and 1,3-dienes,[7] have been thoroughly investigated. However, very few examples of palladium(II)-catalyzed carbocyclizations are known.[8,9]

We recently reported palladium-catalyzed intramolecular couplings between a diene derivative and a pendant allene that result in the stereospecific formation of bicyclic systems (**2** and **3**, Nu = AcO).[9] Unfortunately, these reactions required the use of acetic acid as solvent, which limits the nucleophile to AcO^- and makes this methodology less versatile in organic synthesis. In this paper, we report a new methodology for these carbocyclizations, with the use of various external nucleophiles (Scheme 1). Interestingly, we found that products **4** obtained from **1b** were trans fused.[10]

Result and Discussion

A. Palladium(0)-Catalyzed Carbocyclization. Our study commenced by testing the propensity of allene derivative **1**[9] to cyclize using a solvent other than acetic acid. We were pleased to observe that reaction of **1a** with 10 equiv of acetic acid in the presence of 5 mol % of $Pd(dba)_2$ and Li_2CO_3 in anhydrous CH_2Cl_2 led to the formation of **2a** in 73% yield (Table 1, entry 1).

Having confirmed that an organic solvent could be used in this reaction, we were now in position to investigate the extension to the use of other external nucleophiles. A variety of carboxylic acids,[11] with different electronic and steric properties, were reacted suc-

(1) (a) Wessels, M.; Koenig, G. M.; Wright, A. D. *J. Nat. Prod.* **2001**, *64*, 370. (b) McMorris, T. C.; Lira, R.; Gantzel, P. K.; Kelner, M. J.; Dawe, R. *J. Nat. Prod.* **2000**, *63*, 1557. (c) Paul, C.; Koenig, W. A.; Muhle, H. *Phytochemistry* **2001**, *57*, 307. (d) Jiang, R.-W.; Ma, S.-C.; But, P. P. H.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans. 1* **2001**, *22*, 2920.

(2) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566 and references herein.

(3) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(4) Aubert, C.; Buísìne, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

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(9) Löfstedt, J.; Franzen, J.; Bäckvall, J. E. *J. Org. Chem.* **2001**, *66*, 8015.

(10) In the previous paper[9] we had tentatively assigned product **4a** as the cis-fused [7,5] ring system. In this paper it is proven to be trans fused.

(11) Acidity seems to be an important factor and pK_a values close to acetic acid seem to be the best. However, benzyl alcohol contradicts this statement.

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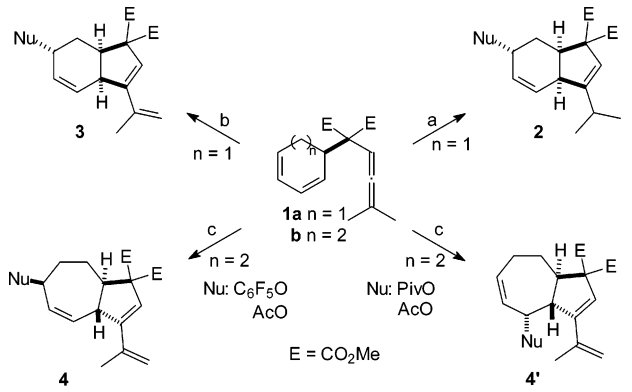
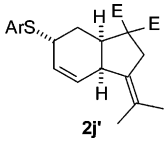
SCHEME 1[a]



[a] Reagents and conditions: (a) 0.05 equiv of $Pd(dba)_2$, 5 equiv of Li_2CO_3, 10 equiv of NuH, CH_2Cl_2, rt, 24 h. (b) 0.10 equiv of $Pd(OAc)_2$, 2 equiv of BQ, 5 equiv of Li_2CO_3, 20 equiv of NuH, acetone, rt. (c) 0.10 equiv of $Pd(OAc)_2$, 2 equiv of BQ, 10 equiv of NuH, acetone, rt.

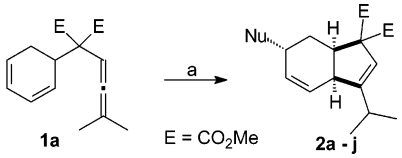
cessfully (Table 1, entries 1−7). The yield varied from 80% for pivalic acid to a moderate 43% for 3-butenoic acid. With the general concept of this protocol established, we turned our attention to non-carboxylate nucleophiles. Different alcohols were tested. Whereas neat benzyl alcohol reacted to give **2d** in moderate yield, aliphatic and chlorinated alcohols such as ethanol and trichloroethanol were unsuccessful as nucleophiles under the reaction conditions employed. Pentafluorophenol reacted to afford **2h** in moderate yield, whereas phenol and CF_3COOH did not react.[11] In contrast, thiophenol afforded **2j** along with **2j′** as a minor product in good



yield.[12] Despite the fact that they are commonly used in similar reactions,[13] amines such as piperidine or ammonium salts, as well as nitromethane and dimethylmalonate, were unreactive or gave a complex mixture of unidentified products.

B. Palladium(II)-Catalyzed Carbocyclization. The reaction conditions used for the Pd(0)-catalyzed reactions were first tested for the Pd(II)-catalyzed reactions of **1a** and **1b**. Unfortunately, the use of anhydrous CH_2Cl_2 did not yield satisfying results and further tuning of the solvent was required. The use of dry acetone[14] proved to be successful, and when a mixture of **1a**, 10 mol % of $Pd(OAc)_2$, and 20 equiv of acetic acid along with lithium carbonate and benzoquinone was allowed to react in dry acetone at room temperature, **3a** was obtained in a higher yield compared to the reaction performed in neat acetic acid (Table 2, entry 1).[9,15] This methodology was extended to other nucleophiles and the results are given in Table 2. As in Table 1, there was a large variation in yields

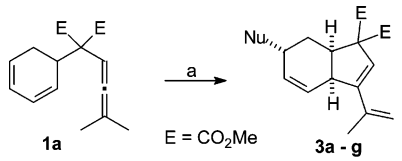
TABLE 1. Pd(0)-Catalyzed Carbocyclization of 1 with Various External Nucleophiles[a]



entry	2	nucleophile	yield,[b] %
1	**2a**	CH_3COOH	73[c]
2	**2b**	*t*-BuCOOH	80
3	**2c**	PhCOOH	65
4	**2d**	$Ph_2CHCOOH$	46
5	**2e**	$ClCH_2COOH$	49
6	**2f**	CH_2═$CHCH_2COOH$	43
7	**2g**	sorbic acid[d]	71
8	**2h**	C_6F_5OH	44
9	**2i**	BnOH[e]	53
10	**2j**	PhSH[f]	78

[a] A solution of 5 mol % of palladium dibenzylidene acetone, 10 equiv of nucleophile, and 5 equiv of lithium carbonate in dichloromethane was stirred for 24 h. [b] Isolated yield after flash chromatography. [c] Neat AcOH gave the same product in 50% yield.[9] TMSOAc (85% yield), AcOAc, and NH_4OAc gave the same product as with AcOH. [d] 2,4-Hexadienoic acid. [e] 5 mol % of palladium dibenzylidene acetone and 3.5 equiv of lithium carbonate in neat benzyl alcohol were stirred for 24 h. [f] Gave a 3:2 ratio of **2j**/**2j′**.

TABLE 2. Pd(II)-Catalyzed Carbocyclization of 1a with Different External Nucleophiles[a]



Entry	3	nucleophile	yield,[b] %
1	**3a**	CH_3COOH	79
2	**3b**	C_6F_5OH	85
3	**3c**	PhCOOH	50
4	**3d**	C_2H_5COOH	42
5	**3e**	H_2C═$CHCH_2COOH$	19
6	**3f**	$(CH_3)_2CHCOOH$	15
7	**3g**	*t*-BuCOOH	traces

[a] To an acetone solution of 10 mol % of palladium acetate, 5 equiv of Li_2CO_3, 2 equiv of BQ, and 20 equiv of NuH was added the starting material during 20 h at room temperature. [b] Isolated yield after flash chromatography.

with respect to the nucleophile. Interestingly, pentafluorophenol[16] afforded **3b** in high yield, whereas when phenol, benzyl alcohol, *o*-nitrophenol, or thiophenol were used as the nucleophile, only the starting material was recovered.

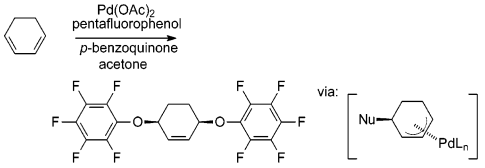
(12) Following the reaction by ^1H NMR revealed that **2j′** was formed simultaneously with **2j**.

(13) Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857.

(14) Acetone was dried over molecular sieves.

(15) For a similar approach see: Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

(16) To investigate the nucleophilic properties of pentafluorophenol it was allowed to react with 1,3-cyclohexadiene and catalytic amounts of $Pd(OAc)_2$ in the presence of *p*-benzoquinone at ambient temperature. It was shown that the stereochemistry of the product was cis, indicating that the nucleophile had added externally on the (π-allyl)palladium intermediate (see also ref 7b).



SCHEME 2

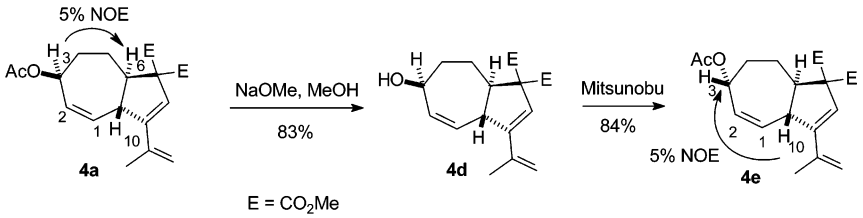
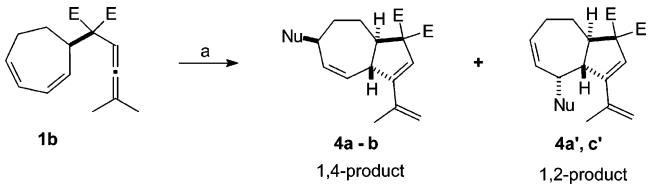


TABLE 3. Pd(II)-Catalyzed Carbocyclization of 1b with Different External Nucleophiles[a]



entry	4	nucleophile	yield,[b] %	1,4-product, %	1,2-product, %
1	**4a**−**a′**	CH_3COOH	90	50	50
2	**4b**	C_6F_5OH	87	100	
3	**4c′**	*t*-BuCOOH	65		100

[a] The starting material was added to an acetone solution of 10 mol % of palladium acetate, 2 equiv of BQ, and 10 equiv of NuH at room temperature over a 20-h period. [b] Isolated yield after flash chromatography.

The final stage of this study consisted of the extension of this methodology to cycloheptadiene derivative **1b** (Table 3). As in the case of **1a**, the use of acetone as solvent gave the best result in the carbocyclization of **1b**. Palladium(II)-catalyzed reaction of **1b** in the presence of 10 equiv of acetic acid in acetone gave **4a**/**4a′** in high yield. It is noteworthy that under these reaction conditions a higher yield was obtained compared to the analogous reaction run in acetic acid.[9] As in the case with the reaction run in acetic acid, a 1:1 mixture of 1,4-product (**4a**)/1,2-product (**4a′**) was obtained for the reaction in acetone. These products, which are identical with those obtained in neat acetic acid, were erroneously assigned in the previous study,[9] and we have now established that products **4** have a trans ring junction (see below). By changing the external nucleophile, the outcome of the reaction was dramatically changed. Thus, when pentafluorophenol was employed as the nucleophile, a highly selective 1,4-addition across the diene occurred, and **4b** was obtained as the single product in high yield (87%). Finally, with pivalic acid as the nucleophile, a clean 1,2-addition across the 1,3-diene took place to give **4c′** as the sole product in 65% yield. It is interesting to note that for both products **4b** and **4c′**, the trans-fused rings were obtained.[17] Furthermore, product **4b** is formed via a trans 1,4-addition of the allenic carbon and pentafluorophenol, whereas **4c′** is formed via a cis 1,2-addition of the allenic carbon and the oxygen nucleophile.

C. Stereochemical Assignment. The stereochemistry of compounds **2** and **3** was assigned in the same way as previously reported.[9,18] The stereochemistry of **4a** was assigned as follows: the trans ring junction was established by NOE experiments. In the case of compound **4a**

(17) No cis junction was detected by ^{1}H NMR spectroscopy.

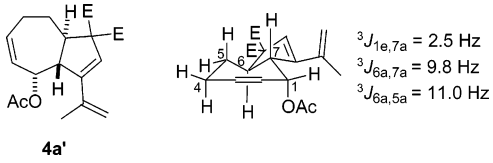


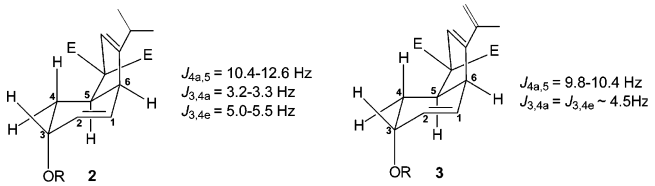
FIGURE 1. Stereochemical assignment of **4a′**.

a small NOE enhancement (2%) was observed between the two bridgehead protons when irradiating the allylic one (H-10, Scheme 2). This NOE originally led us to erroneously assign a cis ring junction.[9,10] Irradiation of H-3 resulted in a 5% NOE enhancement for H-6, but none for H-10, indicating that H-3 and H-6 are located on the same side of the ring. To further obtain evidence for the stereochemistry of **4a,** the epimer **4e** was synthesized from **4a** via hydrolysis to the alcohol and subsequent Mitsunobu reaction.[19] Irradiation of H-10 in the epimeric compound **4e** gave a 5% NOE on H-3, which shows that these hydrogens are on the same side of the ring. Since the acetate is below the ring in **4e**, hydrogen H-10 has to be above the ring and hence the ring junction is trans.

The trans ring junction of compound **4a′** was established by ^{1}H NMR. The stereochemistry at the C-1 position was assigned based upon the analysis of the coupling constants (^{1}H NMR, $CDCl_3$, 300 MHz, Figure 1). The large value of $^3J_{6,7}$ (9.8 Hz) indicates a diaxial coupling, and hence a trans relationship of the bridgehead protons. The small value of $^3J_{1,7}$ (2.5 Hz) implies that H-1 is equatorial and therefore that the acetate is located on the same side as the bridgehead proton H-6.

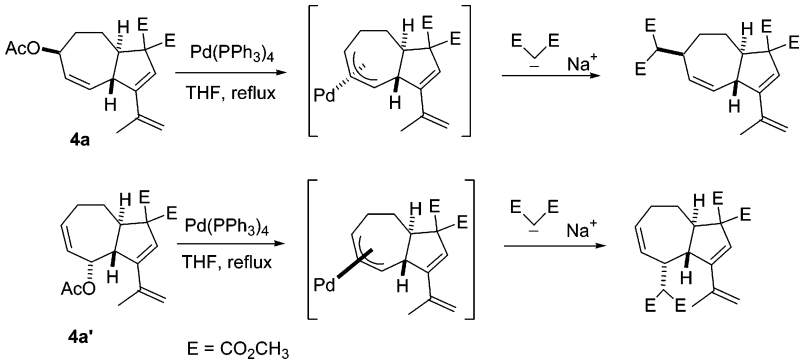
Also for **4a′** there was only a small NOE between the bridgehead protons (2%), which is consistent with the trans compound. To confirm that the acetate stereochemistry in relation to the bridge is different in compounds **4a** and **4a′**, both compounds were allowed to react with sodium malonate in a Pd(0)-catalyzed reaction. It was found that the reaction gave rise to two different compounds as shown in Scheme 3, which proves that the acetate stereochemistry is different in compounds **4a** and

(18) The stereochemistry was confirmed for compounds **2b**−**j′** and **3b**−**g** by comparing the coupling constants with previous NMR assignments for **2a** and **3a**.[9] H-3 shows only small couplings to protons H-4 and, as a consequence, H-3 must be equatorial. Furthermore the large value of $^3J_{4a,5}$ indicates that H-5 and H-4a are axial and trans to one another.

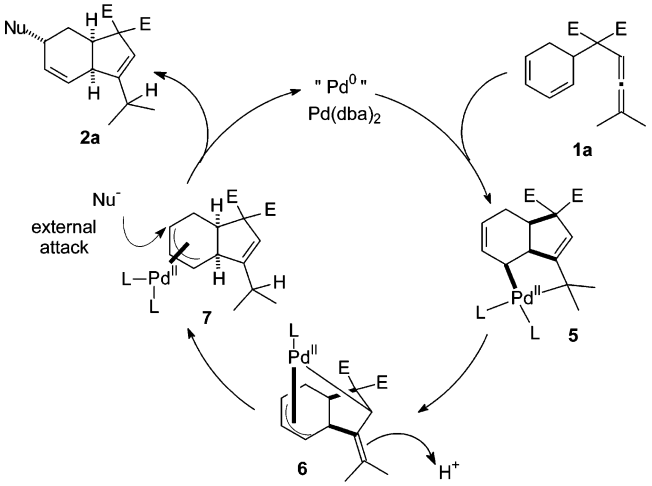


(19) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624.

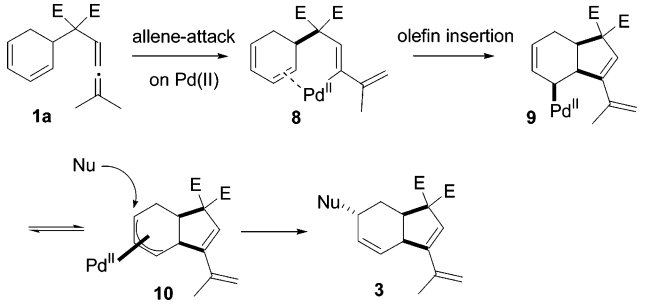
SCHEME 3



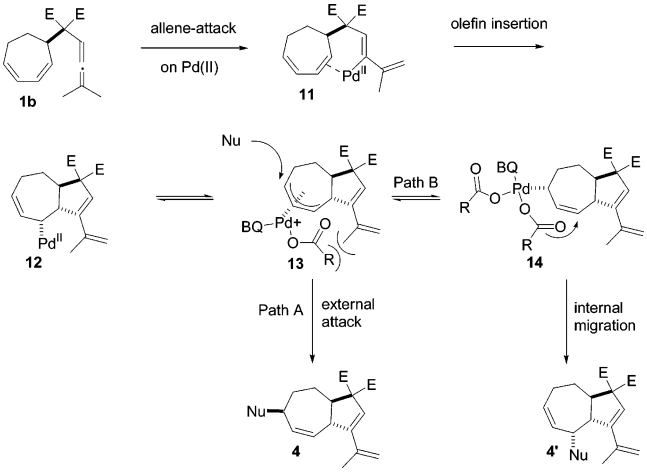
SCHEME 4



SCHEME 5



SCHEME 6



4a′. If the acetate stereochemistry had been the same in relation to the bridge, **4a** and **4a′** would lead to the same (π-allyl) intermediate and consequently the same product.

D. Mechanism of the Palladium(0)-Catalyzed Reaction. A plausible mechanism for these reactions is outlined in Scheme 4. The first step is thought to be an oxidative cycloaddition that leads to bis(allyl)palladium complex **5**, which after rearrangement gave rise to bis-(σ−π-allyl)palladium complex **6**. Proton transfer from the external pronucleophile would afford (π-allyl)palladium complex **7**, which after external attack of the nucleophile yields product **2**.[20,21]

E. Mechanism of the Palladium(II)-Catalyzed Reaction. Among several plausible mechanisms[9] the one outlined in Scheme 5 best rationalizes the regio- and stereochemical outcome of these reactions. Recent work from our laboratories shows that the pending allene has nucleophilic properties,[22,23] thus the first step of the mechanism consists of an attack of the center carbon of the allene on the electrophilic palladium center, giving rise to vinyl palladate **8.** Stabilization by coordination of the metal to the olefin would facilitate cis olefin insertion,[24] leading to (π-allyl) complex **10**. Attack by the external nucleophile from the face opposite to that of the palladium atom yields product **3**. One cannot completely rule out trans attack by the allene on a (π-diene)-palladium complex[22] to give a (π-allyl)palladium intermediate followed by migration of the nucleophile from palladium to the allyl carbon. This pathway seems less likely at least for the pentafluorophenol since this nucleophile is less prone to undergo a cis migration.[16]

The seven-membered-ring **1b** follows a similar path (Scheme 6). Thus, allene attack on the metal leads to complex **11**. Olefin insertion into the vinylic carbon−palladium bond yields (π-allyl) complex **13**.

Depending on the nature of the external nucleophile, complex **13** can be engaged in two competing routes: the

(20) Grennberg, H.; Langer, V.; Bäckvall, J. E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190.

(21) Pentafluorophenol[16] and benzyl alcohol are two nucleophiles that do not have the ability to migrate and therefore support this mechanism pathway. Competition between migration versus external attack has been proven to be dependent on the conformation, as previously investigated.[20]

(22) Dorange, I.; Löfstedt, J.; Närhi, K.; Franzén, J.; Bäckvall, J. E. *Chem. Eur. J.* **2003**, *9*, 3445.

(23) Franzén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 11246.

(24) For review see: (a) Oppolzer, W. *Pure Appl. Chem.* **1988**, *60*, 39. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38.

analogous route (path A) as for the six-membered ring (external attack), giving rise to **4**, or the migration route (path B). Due to steric interactions between the metal ligands and the isoprenyl moiety in complex **13**,[25] the equilibrium between the (σ-allyl)- and the (π-allyl)-palladium complexes is shifted to the right, namely to the thermodynamically most stable complex (**14**). Migration of the ligand from the metal center to the olefinic carbon rationalizes the formation of the 1,2-product **4′**. Therefore, for a nonmigrating nucleophile such as pentafluorophenol,[16] the only path available is path A, leading exclusively to product **4b**. In the case of a migrating ligand such as acetate, both pathways are accessible, and a mixture of **4a** and **4a′** is observed. If the migrating ligand is more cumbersome (pivalate), π-allyl complex **13** is less favored compared to σ-allyl complex **14** and the only product observed is **4c′**.

Conclusion

Palladium-catalyzed carbocyclization of allene−diene derivatives **1** in the presence of various nucleophiles leads to 1,4-addition (or 1,2-addition) of an allenic carbon and the nucleophile across the 1,3-diene. These reactions were shown to proceed smoothly in nonnucleophilic solvents allowing the use of nucleophiles that are solids. The amount of nucleophile could be lowered to 10 equiv and yields improved compared to the previously reported reactions run in neat acetic acid. The cyclization of the seven-membered-ring **1b** turned out to be an efficient way of generating the *trans*-bicyclo[5.3.0]dec-2-ene system and the regioselectivity of the reaction could be fully controlled to give either the 1,2-product **4c′** or the 1,4-product **4b**. The results obtained in this study have led to a better understanding of the mechanism of the reaction.

Experimental Section

^{1}H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded with chloroform-d_1 (7.26 ppm ^{1}H, 77 ppm ^{13}C) as internal standard, unless otherwise stated. All reactions were performed under argon atmosphere, unless otherwise stated.

General Procedure for the Preparation of 2: Compound 2a. To **1** (0.085 g, 0.31 mmol) dissolved in 3 mL of CH_2Cl_2 were added lithium carbonate (0.11 g, 1.5 mmol), $Pd(dba)_2$ (0.009 g, 0.015 mmol), and acetic acid (176 μL, 3.0 mmol). The reaction was stirred at room temperature for 24 h. Water (30 mL) was added, the organic phase was collected, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (pentane:Et_2O, 75:25) to give 0.078 g (73%) of **2a**. Spectral data were identical with those reported in ref 9.

Compound 2b. 1 (0.080 g, 0.29 mmol) was treated as in the general procedure for **2,** but with pivalylic acid. Flash chromatography (pentane:Et_2O, 75:25) gave 0.088 g (80%**)** of **2b**. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 6.07 (dd, J = 9.9, 4.4 Hz, 1 H), 5.94 (ddd, J = 10.2, 5.5, 2.2 Hz, 1 H), 5.44 (dd, J = 3.0, 1.6 Hz, 1 H), 5.11 (td, J = 5.5, 3.3 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.59 (m, 1 H), 3.39 (dt, J = 10.4, 6.3, Hz, 1H), 2.32 (br pent, J = 7.1, 1H), 1.52 (m, 2H), 1.19 (s, 9H), 1.10 (d, J = 6.9 Hz 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 178.3, 170.8 (2C), 155.9, 131.5, 125.6, 118.9, 68.1, 65.1, 52.9, 52.5, 45.4, 39.0, 38.9, 28.1, 27.4 (2C), 27.2, 26.9, 21.6, 20.9; MS (EI) m/z 212 (100), 157 (75).

Compound 2c. 1 (0.076 g, 0.28 mmol) was treated as above but with benzoic acid. Flash chromatography (pentane:Et_2O, 75:25) gave 0.071 g (65%**)** of **2c**. ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.04 (d, J = 7.1 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 6.05 (m, 2H), 5.43 (br s, 1H), 5.38 (td, J = 5.1, 3.2 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.65 (m, 1 H), 3.55 (m, 1H), 2.34 (br pent, J = 6.8 Hz, 1H), 1.65 (m, 2H), 1.13 (d, J = 6.7 Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 170.8, 170.7, 166.3, 155.8, 133.1, 131.9, 130.7, 130.0, 128.5, 125.5, 119.0, 68.1, 65.9, 52.9, 52.6, 45.4, 38.9, 28.2, 27.1, 21.6, 20.9. MS (EI) m/z 212 (100), 157 (64).

Compounds **2d**−**h**, **2j**, and **2j′** were prepared according to the general procedure described above. Compound **2i** was prepared as above with the exception that benzyl alcohol served as nucleophile and as solvent. NMR data are reported in the Supporting Information.

General Procedure for the Preparation of 3: Compound 3a. Compound **1** (0.123 g, 0.45 mmol), dissolved in acetone (0.6 mL), was added over 15 h to a solution of $Pd(OAc)_2$ (0.01 g, 0.045 mmol), Li_2CO_3 (0.165 g, 2.2 mmol), acetic acid (0.54 g, 8.9 mmol), and benzoquinone (0.096 g, 0.90 mmol) dissolved in acetone (0.9 mL) at 20 °C; when the addition was complete, stirring was continued for another 4 h and then water (3 mL) and ether (3 mL) were added. The phases were separated, and the aqueous phase was extracted with ether (2 × 3 mL). The combined organic phases were washed with 2 M NaOH (5 × 2 mL). The alkaline aqueous phases were back-extracted with ether (1 × 10 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation followed by flash chromatography (pentane:Et_2O, 2:1) gave 0.117 g (79% yield) of **3a**. Spectral data were identical with those reported in ref 9.

Compound 3b. The reaction was carried out as in the general procedure for **3**, replacing acetic acid with pentafluorophenol to give **3b** in 85% yield. ^{1}H NMR (benzene-d_6, 400 MHz) δ 6.09 (ddd, J = 10.3, 3.9, 0.9 Hz, 1H), 6.04 (d, J = 2.3 Hz, 1H), 4.87 (br s, 2H), 4.33 (q, J = 4.5 Hz, 1H), 4.04 (ddd, J = 9.8, 6.8, 5.1 Hz, 1H), 3.83 (br s, 1H), 3.35 (s, 1H), 3.27 (s, 1H), 2.06 (ddd, J = 13.9, 9.8, 4.5 Hz, 1H), 1.96 (dt, J = 13.9, 5.1 Hz, 1H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 170.7, 170.1 (aromatic carbons are not clearly detectable due to C−F coupling), 148.7, 138.4, 133.0, 124.7, 124.4, 115.5, 76.1 (broaden due to C−F coupling), 68.0, 53.1, 52.6, 44.3, 38.7, 27.8, 21.6.

Compounds **3c**−**g** were prepared according to the general procedure described above. NMR data are reported in the Supporting Information.

Compound 4a. To a solution of $Pd(OAc)_2$ (10 mol %, 0.005 g), benzoquinone (2 equiv, 0.044 g), and acetic acid (10 equiv, 1.0 mL) in acetone (0.7 mL) was added **1a** (0.058 g, 0.19 mmol) over a 17- h period with a syringe pump. The mixture was then stirred at room temperature for an additional 1.5 h. Workup as for compound **3a** followed by flash chromatography (pentane:EtOAc, 7:3) afforded 0.058 g of a 1:1 mixture of **4a**:**4a′** (90%). Characteristic data were identical with those reported in ref 9. Additional characteristic data follow. Anal. Calcd for (**4a′**) $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.71; H, 7.08.

Compound 4b. The same procedure as above was followed with **1b** (0.100 g, 0.34 mmol), $Pd(OAc)_2$ (10 mol %, 0.0076 g), benzoquinone (2 equiv, 0.081 g), pentafluourophenol (10 equiv, 0.63 g), and acetone (1.3 mL). Workup as for compound **3a** followed by flash chromatography (pentane:EtOAc, 7:3) afforded 0.140 g (87%) of **4b** as a yellowish oil (that solidifies in the freezer). ^{1}H NMR ($CDCl_3$ 600 MHz) δ 6.24 (dd, J = 11.0, 3.3 Hz, 1H), 5.78 (d, J = 2.3 Hz, 1H), 5.75 (ddd, J = 11.0, 5.4, 2.3, 1H), 5.09 (br s, 1H), 4.89 (m, overlap with 4.88 ppm peak, 1H), 4.88 (br s, 1H), 4.11 (dd, J = 9.9, 3.3 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 2.64 (ddd, J = 12.0, 10.0, 3.6 Hz, 1H), 2.3 (m, 1H), 2.17 (m, 1H), 2.06 (ddd, J = 20.8, 13.2, 4.2 Hz, 1H),

(25) The same outcome was previously observed: Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, *4*, 577.

1.96 (m, overlap with 1.93 ppm peak, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 171.3, 170.3, 150.7 (aromatic carbons are not clearly detectable due to C−F coupling), 140.1, 137.9, 127.8, 125.0, 116.0, 81.5, 68.5, 52.8, 52.6, 51.2, 48.0, 31.1, 25.5, 21.2.

Compound 4c′. The same procedure as above was followed with $Pd(OAc_2)$ (10 mol %, 0.0076 g), benzoquinone (2 equiv, 0.081 g), pivalic acid (10 equiv, 0.28 g) in acetone (1.3 mL), and **1b** (0.100 g, 0.34 mmol). Workup as for **3a** followed by flash chromatography (pentane:EtOAc, 75:25) afforded 0.087 g (65%) of **4c′** as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.89 (ddd, J = 12.0, 6.8, 4.6 Hz, 1H), 5.82 (ddd, J = 12.0, 5.6, 1.8 Hz, 1H), 5.77 (d, J = 2 Hz, 1H), 5.69 (dd, J = 5.6, 1.9 Hz, 1H), 5.05 (apparent t, J = 1.2 Hz, 1H), 4.95 (br s, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.30 (ddd, J = 12.0, 9.2, 3.2 Hz, 1H), 3.26 (apparent dt, J = 9.2, 1.9 Hz, 1H), 2.35 (m, 1H), 2.24 (m, 1H), 2.16 (m, 1H), 1.87 (s, 3H), 1.40 (m, 1H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 177.5, 171.6, 170.7, 149.7, 138.3, 134.1, 128.1, 126.0, 114.4, 69.0, 68.3, 52.8, 52.6, 52.4, 46.3, 39.2, 28.2, 27.3, 27.2, 21.9.

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Supporting Information Available: Text describing experimental procedures and characterization data and NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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