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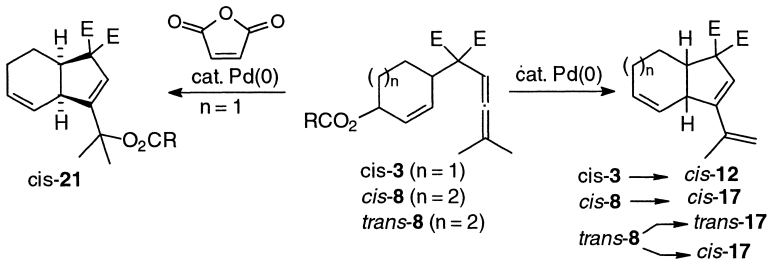

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Stereoselective Palladium-Catalyzed Carbocyclization of Allenic Allylic Carboxylates

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Abstract: Palladium(0)-catalyzed reaction of allene-substituted allylic carboxylates **3**−**8** employing 2−5 mol % of $Pd(dba)_2$ in refluxing toluene leads to the carbocyclization and elimination of carboxylic acid to give bicyclo[4.3.0]nonadiene and bicyclo[5.3.0]decadiene derivatives (**12**−**17**). The carbon−carbon bond formation is stereospecific, occurring syn with respect to the leaving group. Addition of maleic anhydride as a ligand to the above-mentioned procedures changed the outcome of the reaction, and under these conditions **3**−**5** afforded cycloisomerized products **21**−**23**. The experimental results are consistent with a mechanism involving oxidative addition of the allylic carboxylate to Pd(0) to give an electron-deficient (π-allyl)palladium intermediate, followed by nucleophilic attack by the allene on the face of the π-allyl opposite to that of the palladium atom. Furthermore, it was found that the $Pd(dba)_2$-catalyzed cyclization of the *trans*-cycloheptene derivative (*trans*-**8**) can be directed to give either the *trans*-fused (*trans*-**17**) or the *cis*-fused (*cis*-**17**) ring system by altering the solvent. The former reaction proceeds via a nucleophilic *trans*-allene attack on the (π-allyl)palladium intermediate, whereas the latter involves a *syn*-allene insertion into the allyl−Pd bond of the same intermediate. The products from the carbocylization undergo stereoselective Diels−Alder reactions to give stereodefined polycyclic systems in high yields.

Introduction

Intramolecular nucleophilic addition to (π-allyl)palladium intermediates offers a powerful methodology for the construction of a great variety of cyclic compounds under mild reaction conditions.[1,2] Some significant features that these types of reactions display are the high control of regio- and stereoselectivity. In catalytic reactions, the intermediate (π-allyl)-palladium complex can be generated from an allylic carboxylate,[3,4] a conjugated diene,[5,6] or an allene.[7,8] Intramolecular attack by heteroatom nucleophiles or a stabilized carbon anion on the π-allyl results in heterocyclic and carbocyclic products.[1,9] However, a major limitation of carbocyclization reactions is that the nucleophilic carbon partner in most cases is restricted to stabilized nucleophiles.

Unactivated carbon−carbon multiple bonds, that is, π-nucleophiles, are attractive carbon "nucleophiles" for (π-allyl)-palladium intermediates due to their broad functional group tolerance and easy accessibility.[10] After investigation of this concept, we were able to report on the first established example of *trans*-attack by an allenic double bond on a (π-allyl)palladium complex.[11] This concept was further developed to involve *trans*-allene attack on a (π-diene)palladium complex.[12] Such a *trans*-attack by a π-nucleophile on π-coordinated palladium ligand is rare,[13] and one of the few previously established examples is

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(10) Attack by an unactivated carbon−carbon double bond on a (π-allyl)-palladium complex has been inferred as a mechanistic possibility in catalytic carbon−carbon bond forming reactions, but so far no stereochemical evidence has been provided. (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (b) Oppolzer, W.; Gaudin, J. M.; Birkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239.
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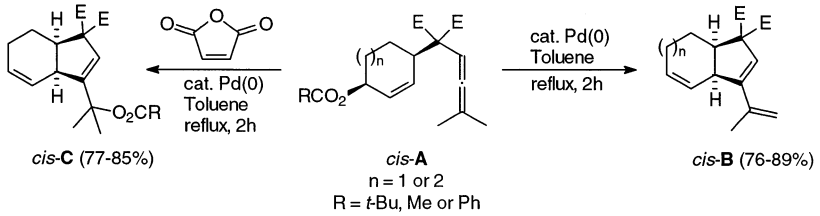
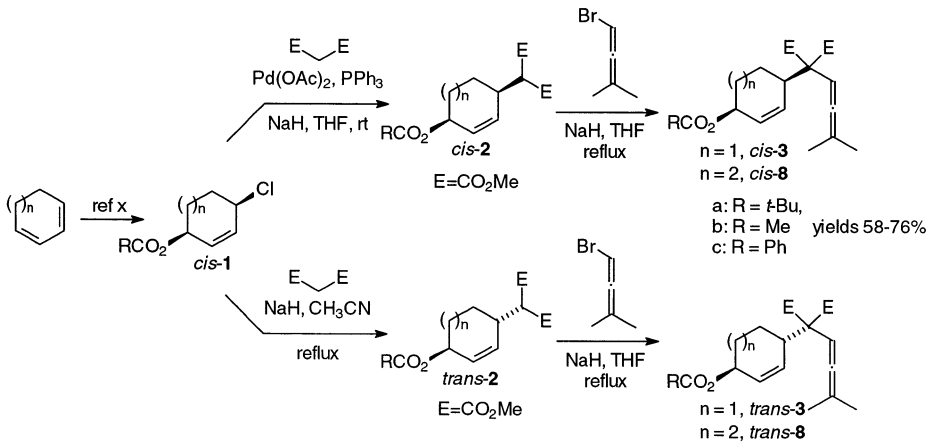
(12) Dorange, I.; Löfstedt, J.; Närhi, K.; Franzén, J.; Bäckvall, J. E. *Chem.-Eur. J.* **2003**, *9*, 3445.
(13) (a) In general, the use of unactivated double bonds as nucleophiles in organometallic chemistry is rare but has been proposed in palladium-catalyzed Cope rearrangment,[13b] in platinum-catalyzed intramolecular reactions of enynes,[13c−e] and in platinum-catalyzed dimerization of olefins[13f] as likely pathways. (b) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225. (c) Mendez, M.; Muños, Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (d) Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, *67*, 15. (e) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704. (f) Hahn, C.; Cucciolito, M. E.; Vitagliano, A. *J. Am. Chem. Soc.* **2002**, *124*, 9038.

10.1021/ja037398u CCC: $25.00

Scheme 1



Scheme 2



the use of an allylsilane as a nucleophile on (π-allyl)palladium and (π-diene)palladium complexes.[14]

During the past decade, palladium-catalyzed reactions of allenes have attracted considerable interest.[7,8,15,16] We have recently reported on the intramolecular palladium(II)-catalyzed carbocyclizations of allene substituted 1,3-dienes.[16] In the present paper, we have studied the synthetic applications, scope, and limitations of the palladium(0)-catalyzed reaction of allenes with allylic carboxylates. We have found that oxidative addition of a palladium(0) catalyst to allylic carboxylates **A** leads to a (π-allyl)palladium intermediate, which is attacked by the allene on the coordinated allyl group in an intramolecular reaction with carbon−carbon bond formation. The cyclized products **B** were obtained in good yields (Scheme 1). Under these reaction conditions, the new carbon−carbon bond is stereospecifically formed with syn stereochemistry with respect to the allylic carboxylate. Thus, for the catalytic cyclization of the seven-membered rings of type **A**, the *cis*-substrate gave the *cis*-fused product, whereas the *trans*-substrate afforded the *trans*-fused product. It was also demonstrated that the reaction path can be altered from *trans*-allene attack to the more commonly observed *syn*-allene insertion[17] by changing the ligand/solvent system. In this way, catalytic cyclization of the *trans* seven-membered ring substrate could be directed to give either the *trans*- or the *cis*-fused product by simply altering the solvent. It was also possible to change the course of the reaction to favor the cycloisomerized product **C**, by adding maleic anhydride to the $Pd(dba)_2$ reaction mixture (Scheme 1).

Results and Discussion

The substrates chosen for this study were readily available via the palladium(II)-catalyzed *cis*-1,4-chloroacyloxylation of the corresponding 1,3-diene to give *cis*-**1** (Scheme 2).[18] Subsequent substitution of the chloride with either retention (Pd^0) or inversion (heat) afforded *cis*- and *trans*-allylic malonates **2**, respectively.[19] A coupling of the latter products with 1-bromo-3,3-dimethylallene[20] yielded, in each case, the required substrates *cis*- and *trans*-**3** in good to moderate yields (for further details, see Supporting Information).[21]

Intramolecular Palladium(0)-Catalyzed Allylations of Allenes. The palladium(0)-catalyzed reaction of *cis*-**3a** resulted in a carbocyclization to produce *cis*-**12**. The reaction conditions were varied (Table 1), and it was found that the use of 2 mol % of $Pd(dba)_2$ in refluxing toluene gave the best result. Under these conditions, *cis*-**12** was obtained in 76% isolated yield after 2 h of reaction time (Table 1, entry 7). If the temperature or catalyst load was lowered, the reaction time increased. Refluxing

(14) Allylsilanes have been proven to act as nucleophiles on (π-diene)- and (π-allyl)palladium complex: (a) see ref 13d. (b) Castaño, A. M.; Persson, B. A.; Bäckvall, J. E. *Chem.-Eur. J.* **1997**, *3*, 482. (c) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.

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(16) Löfstedt, J.; Franzén, J.; Bäckvall, J. E. *J. Org. Chem.* **2001**, *66*, 8015.

(17) It has been shown in previous studies that the carbon−carbon multiple bond, for example, olefins,[17a−c] dienes,[17d] and allenes,[17e,f] can inset into (π-allyl)palladium bonds. (a) See ref 10a,b. (b) Cárdenas, D. J.; Alcamí, M.; Cossío, F.; Méndez, M.; Echavarren, A. M. *Chem.-Eur. J.* **2003**, *9*, 96. (c) Gómez-Bengoa, E.; Cuerva, J. M.; Echavarren, A. M.; Martorell, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 767. (d) Trost, B. M.; Luengo, J. I. *J. Am. Chem. Soc.* **1988**, *110*, 8239. (e) Stoichiometric reactions, see: Hughes, R. P.; Powell, J. *J. Organomet. Chem.* **1969**, *20*, P17; **1973**, *60*, 409. (f) Catalytic reactions, see: Doi, T.; Yanagisawa, A.; Nakanishi, S.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 2602.

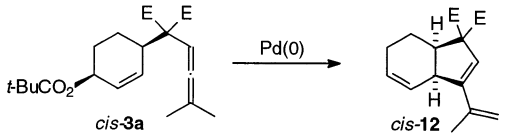
(18) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

(19) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

(20) Sigman, S. S.; Eaton, B. E. *J. Am. Chem. Soc.* **1996**, *118*, 11783.

(21) To succeed in the coupling reaction of bromoallene with the acetate and benzoate analogues **2**, it was essential that the sodium hydride (60% dispersion in mineral oil) was of good quality. Sodium hydride that has been exposed to air moisture can contain substantial amounts of sodium hydroxide, which leads to degradation of the acetate and benzoate analogues **2** most likely via hydrolysis of the ester functions under the reaction condition used (see Scheme 2). However, the pivalic analogues of **2** were not sensitive to the quality of the sodium hydride due to steric hindrance toward hydrolysis from the *tert*-butyl-group.

Table 1. Cyclization of *cis*-**3a** under Different Reaction Conditions[a]



entry	solvent	catalyst	amount (mol %)	conv. (%)	reaction time (h)	isolated yield of *cis*-**12** (%)	reaction temp. (°C)
1	THF	$Pd(PPh_3)_4$	10	30	16	not det.	66
2	THF	$Pd(dba)_2$	13	100	30	54	66
3	THF	$Pd(dba)_2$	2	15	15	not det.	66
4	CH_3CN	$Pd(dba)_2$	10	100	<1	not det.	82
5	CH_3CN	$Pd(dba)_2$	2	100	<2	68	82
6	toluene	$Pd(dba)_2$	10	100	<1	76	111
7	**toluene**	**$Pd(dba)_2$**	**2**	**100**	**<2**	**76**	**111**
8	AcOH	$Pd(dba)_2$	10	100	18	not det.	90

[a] Allenic carboxylate *cis*-**3a** and the catalyst were dissolved in the specific solvent (10 mL/mmol) and heated to the indicated temperature.

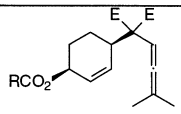
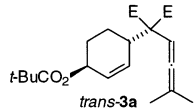
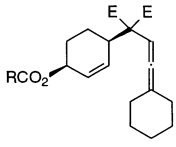
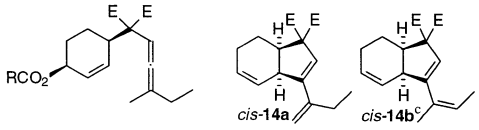
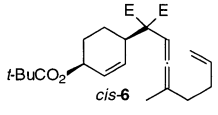
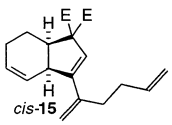
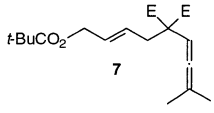
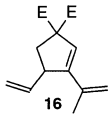
acetonitrile could also be used, but the yield was slightly lower (Table 1, entry 5). In THF, the catalyst load had to be increased in combination with prolonged reaction time to obtain full conversion (Table 1, entries 2 and 3).

Using the conditions of entry 7 in Table 1 (2 mol % of Pd(dba)$_2$, refluxing toluene), we smoothly converted compounds *cis*-**3**−**6** into the bicyclic systems *cis*-**12**−**15** in good to high yields (Table 2). All reactions gave full conversion within 2 h with no detectable amount of side products according to ^{1}H NMR. Three different leaving-groups were investigated in the cyclization. The reactions with acetates *cis*-**3b**−**5b** and benzoates *cis*-**3c**−**5c** all gave higher yields than the corresponding reactions with pivalates *cis*-**3a**−**5a**, which was expected due to the better leaving-group ability of these allylic carboxylates in palladium(0)-catalyzed oxidative addition reactions (Table 2, entries 1−3 and 5−10).

It is noteworthy that the regioselectivity in the cyclization of *cis*-**6** was higher than that of *cis*-**5** (Table 2, entries 8−11). The alkene in the side chain of *cis*-**6** most likely acts as an intramolecular ligand for palladium, giving a complex where β-hydride elimination of one of the methyl hydrogen is favored (see also Scheme 8). Treatment of the acyclic substrate **7** in refluxing toluene with Pd(dba)$_2$ gave **16** in low yield, together with an unidentified byproduct. However, exchanging the solvent for acetonitrile suppressed the formation of byproducts, and **16** could be isolated in 59% yield.

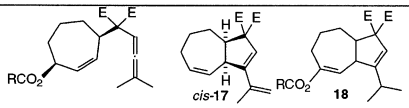
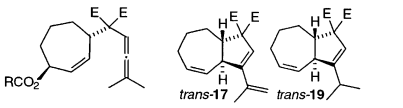
The influence of the relative stereochemistry between the leaving-group and the pendant allene on the outcome of the cyclization was investigated. Attempts to cyclize the six-membered ring *trans*-**3a** under the reaction conditions used for the *cis*-substrates (Pd(dba)$_2$, toluene) were unsuccessful, and no reaction occurred (Table 2, entry 4). The analogous comparison of the reactivity of the seven-membered ring compounds, *cis*-**8** and *trans*-**8**, was also investigated. The seven-membered ring analogues *cis*-**8a**−**c** gave the *cis*-fused ring system *cis*-**17** (Table 3, entries 1−5); for example, *cis*-**8b** in refluxing decane gave

Table 2. Palladium(0)-Catalyzed Cyclization of Cyclohexene Derivatives[a]

Entry	R	Substrate	Product(s)	Yield (%)[b]
1	*t*-Bu	*cis*-**3a**		76
2	Me	*cis*-**3b**		88
3	Ph	*cis*-**3c**		89
4			--	Only S.M. back
5	*t*-Bu	*cis*-**4a**		68
6	Me	*cis*-**4b**		76
7	Ph	*cis*-**4c**		92
8	*t*-Bu	*cis*-**5a**		66
9	Me	*cis*-**5b**		92
10	Ph	*cis*-**5c**		95
11				68
12[d,e]				59

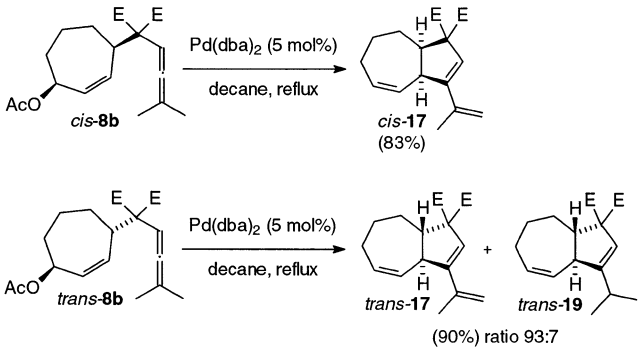
[a] Unless otherwise noted, the allenic carboxylate and Pd(dba)$_2$ (2 mol %) were dissolved in toluene (10 mL/mmol) and refluxed for 2 h. [b] Isolated yield. [c] *E*:*Z* = 76:24. [d] 5 mol % of Pd(dba)$_2$ was employed. [e] Acetonitrile was used as solvent (10 mL/mmol), and the reaction mixture was refluxed for 5 h.

Table 3. Palladium(0)-Catalyzed Cyclization of Cycloheptene Derivatives **8**[a]

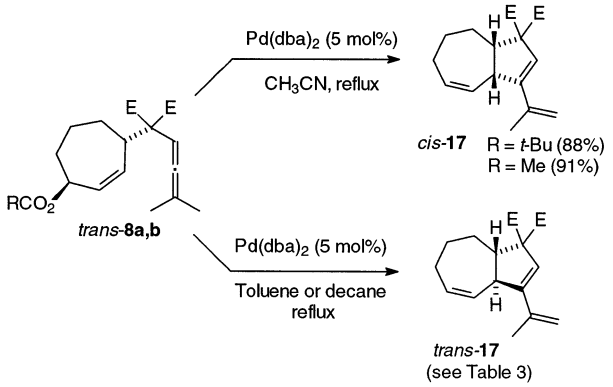
Entry	R	Substrate	Product(s)	Ratio	Yield[b]
1	*t*-Bu	*cis*-**8a**		66:34	76
2[c]	*t*-Bu	*cis*-**8a**		76:24	67
3	Me	*cis*-**8b**		74:26	86
4[c]	**Me**	***cis*-8b**		**100:0**	**83**
5	Ph	*cis*-**8c**		68:32	89
6	*t*-Bu	*trans*-**8a**		47:53	83
7[c]	*t*-Bu	*trans*-**8a**		77:23	73
8[d]	*t*-Bu	*trans*-**8a**		100:0	not det.
9	Me	*trans*-**8b**		60:40	not det.
10[c]	**Me**	***trans*-8b**		**93:7**	**90**

[a] Unless otherwise noted, allenic carboxylate and $Pd(dba)_2$ (5 mol %) were dissolved in toluene (10 mL/mmol) and refluxed for 20 h. [b] Isolated yield. [c] Decane was used as solvent (5 mL/mmol), and the reaction mixture was refluxed for 2 h. [d] 1 equiv of $Pd(dba)_2$ was used.

Scheme 3



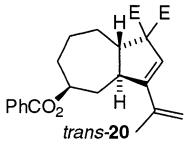
Scheme 4. Solvent Effect in the Cyclization of *trans*-**8**



cis-**17** as the single product in 83% yield. The isomeric seven-membered ring compounds *trans*-**8a**,**b** gave *trans*-**17** as the major product with no observable formation of *cis*-**17** (Table 3, entries 6−10). Thus, the cyclization of the seven-membered ring substrates *cis*-**8a**−**c** and *trans*-**8a**−**b** is stereospecific, proceeding with overall syn stereochemistry. As demonstrated in Scheme 3, the two isomers of **8b** cyclized under the same reaction conditions ($Pd(dba)_2$, decane) to give a specific isomer in each case, that is, *cis*-**8b** → *cis*-**17** and *trans*-**8b** → *trans*-**17**.

Cyclization of the seven-membered ring compounds required a higher catalytic loading and prolonged reaction time to reach full conversion as compared to the six-membered ring analogues. Reaction of compounds *cis*-**8a**−**c** with 5 mol % of $Pd(dba)_2$ in refluxing toluene for 20 h gave *cis*-**17** together with the corresponding product **18**[22] in a ratio of approximately 2:1 to 3:1 (Table 3, entries 1, 3, and 5). We argued that this was an effect of slower oxidative addition to the seven-membered rings as compared to the corresponding six-membered rings. By increasing the temperature in the reaction of *cis*-**8b** ($Pd(dba)_2$, refluxing decane), we could suppress the formation of *cis*-**18**, and *cis*-**17** was formed as a single product in 83% yield (Table 3, entry 4).

Cyclization of *trans*-**8** was sluggish and irreproducible under the standard conditions ($Pd(dba)_2$, refluxing toluene). However, *trans*-**17** could be isolated together with the reduced product *trans*-**19**. The ratio between *trans*-**17** and *trans*-**19** varied between the experiments, but *trans*-**19** was the dominating product for the cyclization of *trans*-**8a** in toluene (Table 3, entry 6). For the cyclization of *trans*-**8b** in toluene, *trans*-**17** and *trans*-**19** were formed in a ratio of 60:40 (Table 3, entry 8). The catalytic cycle for the formation of *trans*-**19** is not clear, but it is believed to involve a palladium-hydride species,[23] whereas formation of *trans*-**17** involves oxidative addition and formation of a (π-allyl)palladium intermediate. When the reaction temperature was increased, oxidative addition was favored over the Pd-hydride route,[24] and with 5 mol % of $Pd(dba)_2$ in refluxing decane, *trans*-**8b** cyclized to give *trans*-**17** and *trans*-**19** with a ratio of 93:7 and 90% total yield (Table 3, entry 10).[25] Attempts to cyclize allylic benzoate *trans*-**8c** with $Pd(dba)_2$ in refluxing toluene resulted in a slow conversion of the substrate and the formation of a crude mixture of products where only traces of *trans*-**17** and *trans*-**19** could be detected. Interestingly, cyclization of *trans*-**8c** with $Pd(dba)_2$ in refluxing decane gave compound *trans*-**20** in 58% isolated yield.



When the ring size of the starting material was reduced to a five-membered ring (**9**) or an additional carbon was placed between the allylic moiety and the allene (**10**, **11**),[26] the reaction failed (Figure 1). When lithium chloride was added to the reaction of **3**−**8**, the catalytic reaction was completely inhibited in all cases, and the starting material was recovered.

(22) The stereochemistry of the bridgehead protons has not been assigned.
(23) Addition of H−Pd−O_2CR to one of the allenic double bonds in *trans*-**8** could give a vinylpalladium species followed by insertion of the olefin into the vinylpalladium bond and subsequent elimination of RCO_2 to yield *trans*-**19**.
(24) This is in accordance with a more positive $\Delta S^{\ddagger}$ for the oxidative addition pathway.
(25) Reaction of *cis*- and *trans*-**8b** in refluxing decane in the absence of Pd(dba)$_2$ for 2 h resulted in complete degradation of the substrate without any detectible formation of **17**.
(26) No cyclization occurred, see also ref 17f.

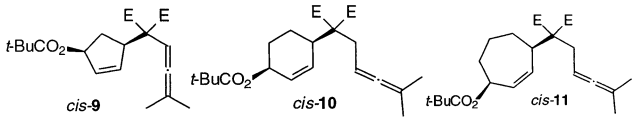
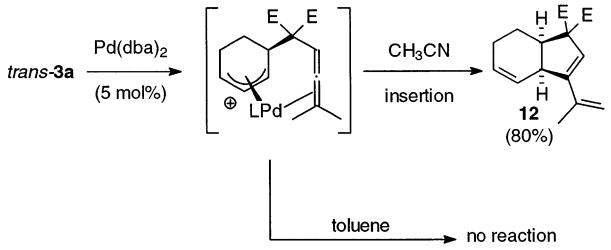


Figure 1. Unsuccessful cyclization substrates.

Scheme 5. Cyclization of *trans*-**3a** via Insertion



Control of Stereochemistry in the Carbocyclization Reaction. When *trans*-**8a** was treated with a stoichoimetric amount of palladium and LiCl in refluxing acetonitrile, *cis*-**17** was obtained. The catalytic reaction, as previously mentioned, gave the opposite stereochemistry and afforded *trans*-**17** (Table 3, entries 6−11). Initial attempts to transform *trans*-**8a** to *cis*-**17** in a catalytic reaction failed, but further studies revealed that LiCl had to be removed to obtain a catalytic process. Reaction of *trans*-**8a**,**b** in refluxing acetonitrile in the presence of 5 mol % of $Pd(dba)_2$ afforded *cis*-**17a** and *cis*-**17b** in 88% and 91% yield, respectively. As previously discussed (Table 3), cyclization of *trans*-**8a**,**b** in a noncoordinating solvent such as toluene or decane gave *trans*-**17**. Thus, the stereochemistry of the product can be controlled, by simply altering the solvent (Scheme 4).

The solvent effect was further demonstrated in the cyclization of *trans*-**3a**, which gave no cyclized product under catalytic conditions with $Pd(dba)_2$ in toluene (Table 2, entry 4). However, with 10 mol % of $Pd(dba)_2$ in refluxing acetonitrile, *trans*-**3a** yielded *cis*-1**2** in 80% yield (determined by ^1H NMR) (Scheme 5). The reaction involves formation of the indicated *cis*-palladium intermediate followed by coordination to the allene and insertion into the (π-allyl)palladium bond.[17f]

Unfortunately, there was no solvent effect observed in the reaction with the *cis*-substrates. Both *cis*-**3** and *cis*-**8** gave the corresponding products *cis*-**12** and *cis*-**17** in acetonitrile as well as in toluene.

Palladium(0)-Catalyzed Cycloisomerization. In an attempt to use a more electron-withdrawing ligand on the palladium catalyst, maleic anhydride was added to the reaction mixture. Interestingly, the palladium-catalyzed reaction of *cis*-**3a** in the presence of maleic anhydride gave the cycloisomerized product **21a** in 77% isolated yield, and no traces of **12** could be detected (Table 4, entry 1). The corresponding carbocylizations of cyclohexyl- and methyl-ethyl-substituted allenes *cis*-**4a** and *cis*-**5a** afforded products **22a** and **23a**, respectively (Table 4, entries 4 and 7).

The acetate (*cis*-**3b**−**5b**) and benzoate derivatives (*cis*-**3c**−**5c**) also underwent cycloisomerization with the $Pd(dba)_2$/maleic anhydride catalyst system to give **21b**−**23b** and **21c**−**23c**, respectively. However, under these reaction conditions, the corresponding products **12**−**14** were formed as side products (Table 4).

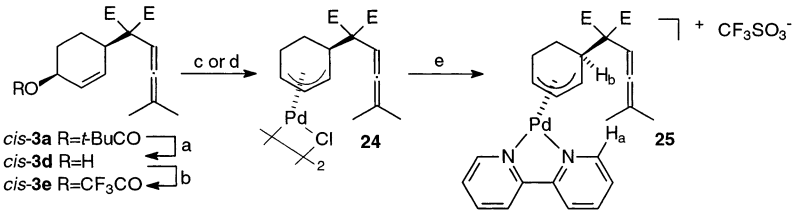
Unfortunately, this reaction was not as general as the cyclization previously discussed (*cis*-**3a** → *cis*-**12**), and substrates *trans*-**3**, *cis*-**6**, **7**, *cis*-**8**, and *trans*-**8** failed to undergo cycloisomerization. Neither *trans*-**3a**, *cis*-**8**, nor *trans*-**8** reacted, and only the starting material was recovered. Allene *cis*-**6** was not affected by the addition of maleic anhydride and cyclized to give *cis*-**15**.[27] The acyclic substrate **7** gave a complex mixture of products that were not characterized.

Isolation of Reaction Intermediates. We have previously found that (π-allyl)palladium complex **24** can be isolated via the allylic trifluoroacetate *cis*-**3e** (Scheme 5).[11] Trifluoroacetate *cis*-**3e** was obtained by transformation of the pivalic ester *cis*-**3a** to alcohol *cis*-**3d**, followed by esterification with trifluoroacetic anhydride. Subsequent treatment of *cis*-**3e** with $Pd(dba)_2$ and LiCl in acetonitrile gave chloro-complex **24** as a single product. Complex **24** was also obtained by treatment of *cis*-**3e** with $Pd(dba)_2$ and Bu_4NCl in toluene. This shows that the solvent has no effect on the stereochemistry of the oxidative addition.[28] Ligand exchange using 2,2′-bipyridine gave the cationic complex, **25**, which proved to be very stable and could be stored at room temperature for several weeks. An NOE was observed between H_a and H_b, which confirms that the stereochemistry between palladium and the allenic moiety is *trans* (**25**, Scheme 6).[29]

When chloro-complex **24** was treated with $AgBF_4$ in toluene and heated to reflux for 2 h, *cis*-**12** was obtained as a single product (Scheme 7).

When pivalate **3a** was treated with stoichiometric amounts of $Pd(dba)_2$ and lithium chloride in acetonitrile, none of complex **24** could be detected. A reasonable explanation is that oxidative addition of the allylic pivalate to Pd(0) is slower than the carbon−carbon bond formation and on prolonged reaction time at increased temperature the cyclized complex *cis*-**26** was obtained as a single product. Compounds *cis*-**3a** and *trans*-**3a** gave the same palladium complex *cis*-**26**. On the other hand, *cis*-**8a** did not react at all with stoichiometric amounts of Pd-$(dba)_2$ and lithium chloride, whereas *trans*-**8a** gave palladium

Scheme 6 [a]



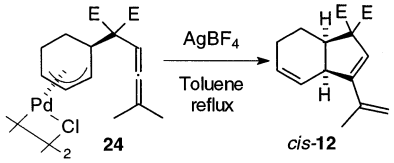
[a] (a) NaOMe, MeOH, reflux; (b) $(CF_3CO)_2O$, Et_2O, 0 °C; (c) $Pd(dba)_2$ (1 equiv), LiCl, CD_3CN (14 mL/mmol), room temperature; (d) $Pd(dba)_2$ (1 equiv), Bu_4NCl, toluene; (e) AgOTf, bipyridine, room temperature.

Table 4. Palladium(0)-Catalyzed Cycloisomerizations[a]

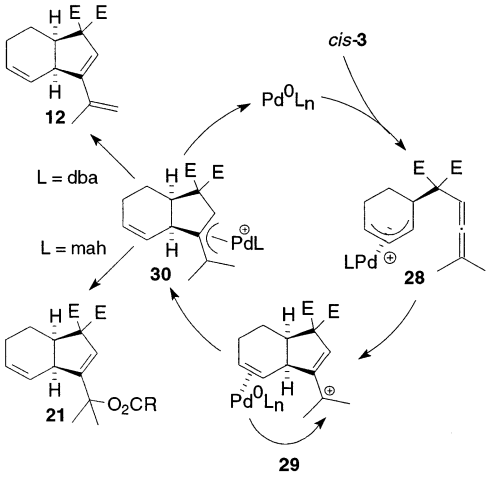
Entry	R	Substrate	Product(s)	Ratio	Total Yield (%)[b]
1[c]	*t*-Bu	*cis*-**3a**	**21a**	-	77
2	Me	*cis*-**3b**	**21b+12**	86:14	83
3	Ph	*cis*-**3c**	**21c+12**	79:21	81
4[c]	*t*-Bu	*cis*-**4a**	**22a**	-	76
5	Me	*cis*-**4b**	**22b+13**	79:21	85
6	Ph	*cis*-**4c**	**22c+13**	82:18	66
7[c]	*t*-Bu	*cis*-**5a**	**23a**[d]	-	45
8	Me	*cis*-**5b**	**23b**[d]**+(14a:14b)**[e]	70:30	86
9	Ph	*cis*-**5c**	**23c**[d]**+(14a:14b)**[e]	67:33	87

[a] Unless otherwise noted, the allenic carboxylate, maleic anhydride (1 equiv), and $Pd(dba)_2$ (2 mol %) were dissolved in toluene (10 mL/mmol) and refluxed for 15 min. [b] Isolated yield. [c] 1 h reaction time. [d] 1:1 mixture of diastereoisomers. [e] **14a**:*E*-**14b**:*Z*-**14b**, ratio 50:38:12.

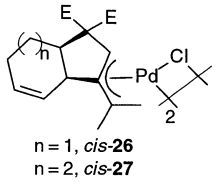
Scheme 7



Scheme 8. Cyclization of **3** via *anti*-Allene Attack



complex *cis*-**27** under these conditions.



Mechanism. The NMR characterization of complex **24** via the corresponding bipyridine complex **25** establishes that palladium and H_b are on the same face of the ring and that the side chain with the allene is *trans* to palladium (Scheme 6). Stripping off the chloride ligands from complex **25** with $AgBF_4$ triggered an external attack from the allene on the π-allyl group from the face opposite to that of palladium, giving rise to **12** (Scheme 7). A proposed mechanism is presented in Scheme 8. Oxidative addition of the allylic carboxylate to Pd(0) with inversion of configuration gives intermediate **28**, and the electron-withdrawing ligand (i.e., dba or maleic anhydride) generates an electron-deficient (π-allyl)palladium intermediate. Subsequent *trans*-attack by the allene generates the carbon−carbon bond and produces **29**. The allylic cation is trapped by palladium(0)[30] which gives rise to (π-allyl)palladium complex **30**. When the ligand is dba, β-hydride elimination yields **12**, whereas when the ligand is maleic anhydride (mah), the π-allyl complex **30** is activated toward nucleophilic attack by the carboxylate and yields **21** (Scheme 8).[31]

The normal reactivity of carbon−carbon multiple bonds with (π-allyl)palladium complex usually involves initial coordination of the multiple bond to the metal followed by insertion.[17] In our case, coordination of the allene to the metal in the cyclization of *cis*-**3** would require an isomerization of palladium complex *trans*-**28** to the corresponding *cis*-palladium complex.[32]

The corresponding reaction of *trans*-**3a** with $Pd(dba)_2$ would give palladium complex *cis*-**28** via oxidative addition. Carbon−carbon bond formation via 1,2-insertion leads to **30**. When the reactivities of *cis*-**3a** and *trans*-**3a** in the catalytic reaction were compared, an isomerization of *trans*-palladium complex **28** to *cis*-palladium complex **28** followed by insertion to give product

(27) The alkene moiety in the side chain prevents the coordination of maleic anhydride.

(28) (a) It has been shown that oxidative addition of allylic chlorides[28b] and allylic trifluoroacetates[28c] to Pd(0) can, under certain circumstances, be controlled to proceed either via inversion or retention of configuration by altering the solvent. For other examples of syn oxidative addition, see: ref 28d−f. (b) Kurosawa, H.; Kajimaru, H.; Ogoshi, S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417. (c) Vitagliano, A.; Åkermark, B.; Hansson, S. *Organometallics* **1991**, *10*, 2592. (d) Starý, I.; Kocovský, P. *J. Am. Chem. Soc*. **1989**, *111*, 4981. (e) Starý, I.; Zajícek, J.; Kocovský, P. *Tetrahedron* **1992**, *48*, 7229. (f) Farthing, C. N.; Kocovský, P. *J. Am. Chem. Soc*. **1998**, *120*, 6661.

(29) Bipyridyl ligands have been previously employed as reporter ligands to assign the stereochemistry of various (π-allyl)palladium complexes. (a) Albinati, A.; Amman, C.; Pregosin, P. S.; Rüegger, H. *Organometallics* **1990**, *9*, 1826. (b) Albinati, A.; Amman, C.; Kunz, R. W.; Pregosin, P. S. *Organometallics* **1991**, *10*, 1800. (c) Bäckvall, J. E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem.* **1993**, *58*, 5445. (d) Gogoll, A.; Gomes, J.; Bergkvist, M.; Grennberg, H. *Organometallics* **1995**, *14*, 1354. (e) Gogoll, A.; Johansson, C.; Axén, A.; Grennberg, H. *Chem.-Eur. J.* **2001**, *7*, 396.

(30) This involves dissociation of palladium(0) from (π-olefin)palladium intermediate and trapping of the carbonium ion. Transient free Pd(0) complex may help in this trapping.

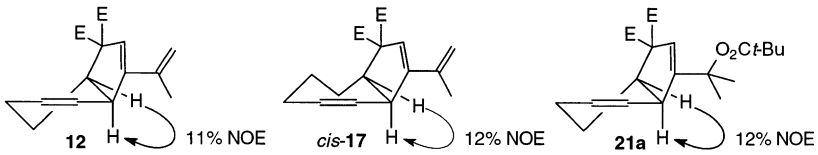
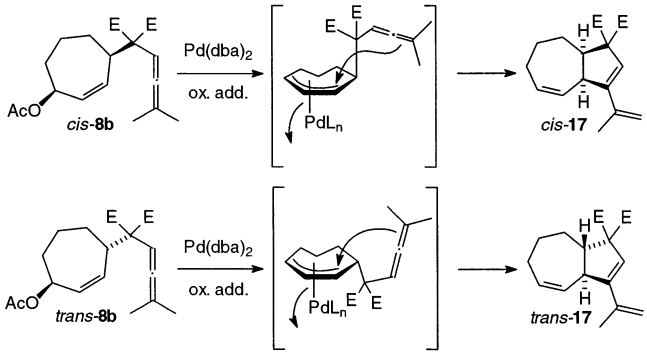


Figure 2. NOE measurements of key compounds.

12 seems highly unlikely. If an isomerization would be involved, both *cis*-**3a** and *trans*-**3a** would yield *cis*-**12** under the same reaction conditions.

In the catalytic reaction of *cis*-**3** using $Pd(dba)_2$, the operating mechanism involves *trans*-attack by the allene according to Scheme 8. This is most apparent in the catalytic cyclization of *cis*-**8b** and *trans*-**8b**. External allene attack affords *cis*-**17** and *trans*-**17**, respectively, via the (π-allyl)-intermediate indicated in Scheme 9.

Scheme 9. Cyclization of *cis*- and *trans*-**8b** via *trans*-Allene Attack



The corresponding intermediates are also involved in the reaction of *cis*-**3a** and *trans*-**3a**, where *cis*-**3a** follows the *anti*-allene attack type of mechanism, outlined in Scheme 8. On the other hand, *trans*-**3a** gives the *cis*-(π-allyl)palladium intermediate (see Scheme 5), which cannot undergo *trans*-allene attack due to its strained transition state. It is also interesting to point out that under these reaction conditions ($Pd(dba)_2$, toluene, reflux), no insertion of the (π-allyl)palladium bond into the allene occurs and only starting material is recovered. In a control experiment, *cis*- and *trans*-**3a** were mixed and reacted together; only *cis*-**3a** was found to react after 24 h, whereas *trans*-**3a** remained unreacted. These observations support that there is no isomerization process involved in the catalytic reaction.

***anti*-Allene Attack versus *syn*-Allene Insertion.** As mentioned above, a dramatic solvent effect was observed in the carbocyclization of *trans*-**8** (Scheme 4). In toluene and decane,

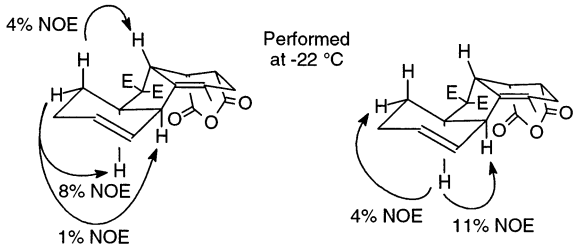


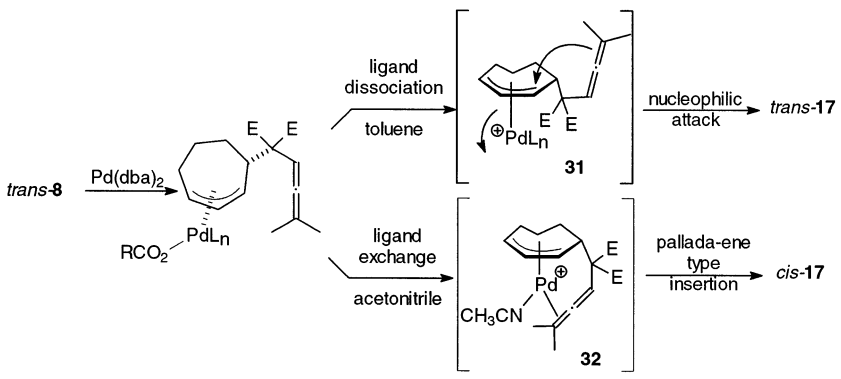
Figure 3. NOE measurements on compound **33**.

only the *anti*-allene attack product *trans*-**17** was observed, whereas in acetonitrile, *cis*-**17** was obtained as a single product. The latter result is best explained by a mechanism that proceeds via coordination of the allene to palladium followed by insertion. These results can be interpreted as an increase of the electron density on the π-allyl part of the (π-allyl)palladium complex when going from toluene to acetonitrile as solvent.[33] Apparently, electron-withdrawing ligands (e.g., dba) on palladium are necessary for the *trans*-allene attack on the π-allyl group to occur. This type of ligand increases the electrophilicity of the allyl group, and the nucleophilic attack is most likely induced by the dissociation of carboxylate from the palladium species that gives a carbocationic palladium intermediate **31** (Scheme 10).

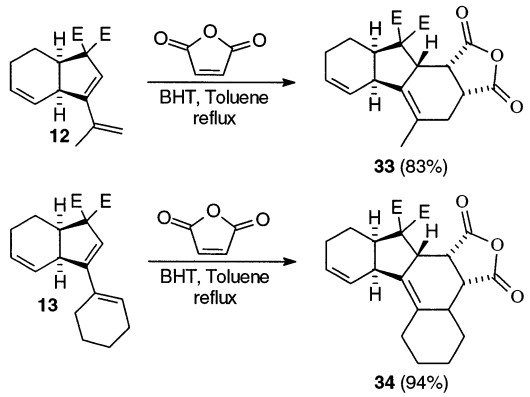
The pathway via *anti*-allene attack is less favored in the presence of acetonitrile. Thus, with acetonitrile ligands on palladium in the (π-allyl)palladium complex, double bond insertion of the allene into the allyl−palladium bond occurs to give *cis*-**17** via π-allyl complex **32** (Scheme 10).[34] In this way, a dual stereocontrol was obtained in the reaction of *trans*-**8** via its corresponding π-allyl complexes.

Synthetic Application. The products **12**−**17** contain a conjugated diene moiety, which can undergo stereoselective [4+2] cycloadditions[35] to give polycyclic systems in high yields (Scheme 11). This provides a simple, direct route to more complex polycyclic systems having a controlled stereochemistry. The synthetic utility of compounds **12**−**17** was demonstrated by the reaction of **12** and **13** with maleic anhydride to give cycloadducts **33** and **34**, respectively, as a single diastereoisomer in each case (Scheme 11). NOE experiments are consistent with

Scheme 10. Stereocontrol by Ligand Tuning in the Cyclization of *trans*-**8**



Scheme 11



the stereochemistry assigned for **33** (see Figure 3), which is in accordance with the stereochemistry of compounds **12** and addition of maleic anhydride to the less hindered face of bicyclic compounds **12**.

Stereochemical Assignment. The stereochemistry of the bicyclic products **12** and **21** was assigned from NOE measurements (Figure 2). A large NOE between the bridge-junction protons in *cis*-**17** and lack of the same in *trans*-**17** made it possible to differentiate between the two stereoisomers.

The Diels−Alder adduct **32** was carefully investigated, and at −22 °C in $CDCl_3$ all proton signals separated. The addition from the less sterically hindered face of **12** was proven due to a 4% NOE signal from the axial CH_2 proton to the CH proton, as indicated in Figure 3.

Conclusion

Palladium(0)-catalyzed reaction of **3**−**8** led to bicyclic products **12**−**17** via carbon−carbon bond formation. The reaction is stereospecific and high yielding (Table 2). The mechanism of the catalytic reaction (2 mol % of $Pd(dba)_2$, toluene) involves a nucleophilic attack by the allene on an electron-deficient (π-allyl)palladium intermediate. The operating mechanism was found to be determined by the electron density on the palladium species, and the reaction could be controlled to proceed either via *anti*-allene attack or via insertion by tuning the ligands on the (π-allyl)palladium intermediate (Schemes 8 and 10). Ligand exchange from dba to acetonitrile gave a relatively electron-rich (π-allyl)palladium intermediate that cyclized via insertion. This dual stereocontrol was demonstrated by the catalytic cyclization of *trans*-**8** to give either *trans*-**17** (5 mol % of $Pd(dba)_2$/decane) or *cis*-**17** (5 mol % of $Pd(dba)_2$/acetonitrile) with complete stereoselectivity. The products from the carbocylization are useful substrates for further functionalizations, for example, a highly stereoselective Diels−Alder reaction, which leads to stereodefined polycyclic systems.

Experimental Section

^1H NMR (400 or 300 MHz) and ^{13}C NMR (100 or 75 MHz) spectra were recorded using chloroform-d_1 (7.26 ppm ^1H, 77 ppm ^{13}C) as the internal standard. Elemental analyses were performed by Analytische laboratorien, Lindlar, Germany. Toluene was dried over sodium and degassed with argon immediately prior to use.

General Procedure for the Preparation of Allenes 3−8. Allene *cis*-3a. To a solution of *cis*-**2a** (1.20 g, 3.85 mmol) in THF (40 mL) was added NaH (60% in mineral oil, 0.17 g, 4.23 mmol), and the mixture was stirred for 10 min at room temperature. 1-Bromo-3,3-dimethylallene (3.06 g, 7.70 mmol) was added, and the resulting mixture was refluxed for 4 h. Water (40 mL) was added, and the aqueous phase was extracted with Et_2O (4 × 20 mL). The combined organic phases were washed with water (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, followed by flash chromatography of the residue (pentane:Et_2O, 85:15), which afforded 1.22 g (84% yield) of *cis*-**3a**. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.01 (dddd, J = 10.3, 2.0, 1.3, 0.7 Hz, 1H), 5.82 (dddd, J = 10.3, 4.8, 2.6, 1.3 Hz, 1H), 5.49 (septet, J = 2.9 Hz, 1H), 5.09 (m, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.96 (m, 1H), 1.87 (m, 1H), 1.77−1.56 (m, 9H), 1.16 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 202.3, 178.2, 170.4, 170.3, 134.5, 125.8, 99.6, 87.2, 65.6, 61.8, 52.8, 52.6, 41.5, 38.9, 28.1, 27.3 (3C), 20.3, 20.0, 19.9.

General Procedure for the Preparation of Compounds 12−17. Cyclization of *cis*-3a To Give *cis*-12. A solution of *cis*-**3a** (0.20 g, 0.53 mmol) and $Pd(dba)_2$ (0.006 g, 0.01 mmol) in toluene (5 mL) was refluxed for 2 h. The resulting mixture was partitioned between Et_2O (10 mL) and aqueous NaOH (0.5 M, 10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic phases were washed with water (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, followed by flash chromatography (pentane:Et_2O, 90:10) to give 0.11 g (76% yield) of *cis*-**12**. Spectral data were in accordance with those previously reported.[36]

General Procedure for the Preparation of Compounds 21−23. Cyclization of *cis*-3a To Give *cis*-21a. A solution of *cis*-**3a** (100 mg, 0.26 mmol), maleic anhydride (26 mg, 0.26 mmol), and $Pd(dba)_2$ (3.0 mg, 0.005 mmol) in toluene (2.5 mL) was refluxed for 1 h. The resulting mixture was partitioned between Et_2O (10 mL) and 0.5 M NaOH (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), and the combined organic phases were washed with water (20 mL) and dried (Na_2SO_4). The solvent was removed in vacuo, followed by flash chromatography (pentane:Et_2O, 85:15) which gave 77.1 mg (77% yield) of *cis*-**21a**. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.86 (ddt, J = 10.1, 4.2, 2.1 Hz, 1H), 5.76 (J = Hz, 1H), 5.58 (dd, J = 2.9, 0.7 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.46 (m, 1H), 3.08 (td, J = 8.3, 6.0 Hz, 1H), 1.98 (m, 2H), 1.57 (m, 3H), 1.53 (m, 3H), 1.33 (m, 2H), 1.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.1, 170.8, 170.1, 154.3, 128.2, 126.7, 120.5, 79.6, 68.1, 52.9, 52.4, 45.2, 43.6, 39.3, 27.4 (4C), 26.9, 24.3, 21.6. Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.80; H, 8.13.

General Procedure for the Preparation of Compounds 33 and 34. Compound 33. Diene *cis*-**12a** (100 mg, 0.26 mmol), maleic anhydride (26 mg, 0.26 mmol), and one crystal of 2,6-di-*tert*-butyl-4-methylphenol (BHT) were dissolved in toluene (2.5 mL) and refluxed for 2 h. The solvent was removed by evaporation, followed by flash chromatography (pentane:Et_2O, 67:33) which gave 77.1 mg (77% yield)

(31) The pivalate released in the oxidative addition re-adds to the formed π-allyl in **30**.

(32) Isomerization could occur either via a palladium(0)-catalyzed route (Granberg, K. L.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858) or via a syn re-addition of the leaving-group (Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730).

(33) It is known from previous studies that [(π-allyl)Pd(CH_3CN)$_2$]BF_4 has electronic properties similar to those of bis-[(π-allyl)PdCl]. Åkermark, B.; Krakenberger, B.; Hansson, S. *Organometallics* **1987**, *6*, 620. It has also been shown that bis-[(π-allyl)PdCl] inserts into allenes. See ref 17f.

(34) It was suggested by one of the referees that ionization of the Pd−X bond to form a separated ion pair will be highly disfavored in nonpolar solvent (i.e., toluene or decane) and thus might prevent coordination of the allene. It was argued that such ionization should be more facile in acetonitrile, thereby permitting allene coordination and insertion. It was therefore proposed that excess anion ligand would inhibit the reaction. However, adding LiOAc (20 equiv) to the cyclization reaction of *trans*-**8a** ($Pd(dba)_2$ (5 mol %) CH_3CN, reflux) had no effect on the outcome of the reaction, and *cis*-**17** was observed as the only product.

(35) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255.

(36) Franzén, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2003**, *125*, 6056.

of **33**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.80 (ddt, J = 10.1, 4.2, 2.2 Hz, 1H), 5.68 (dddd, J = 10.1, 4.0, 3.1, 2.0 Hz, 1H), 3.93 (dd, J = 9.3, 4.6 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.41 (m, 3H), 3.07 (dd, J = 13.6, 7.3 Hz, 1H), 2.47 (m, 2H), 2.01 (dddd, J = 18.5, 9.9, 4.4, 2.7 Hz, 1H), 1.92 (ddtd, J = 18.5, 5.8, 3.9, 2.0 Hz, 1H), 1.79 (m, 3H), 1.56 (td, J = 7.3, 5.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1,172.8, 171.8, 170.7, 140.7, 126.9, 126.0, 125.4, 64.0, 53.2, 53.1, 45.5, 44.3, 43.9, 42.1, 41.9, 32.8, 23.1, 21.5, 20.1.

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Supporting Information Available: Experimental details and spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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