Intramolecular Palladium(II)-Catalyzed 1,2-Addition to Allenes

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Abstract: Palladium(II)-catalyzed intramolecular 1,2-additions to allenes substituted with an internal nucleophile have been developed. Carboxylic acids, alcohols, *N*-substituted amides, and carbamates were used as internal nucleophiles in the palladium-catalyzed reaction, which afforded lactones, tetrahydropyrans, tetrahydrofurans, pyrrolidines, and oxazolidinones in good isolated yields. The reactions were performed in the presence of LiBr with $Pd(OAc)_2$ as the catalyst. Two different reoxidants, *p*-benzoquinone or $Cu(OAc)_2$, were used, the choice of oxidant being dependent on the substrate. The reaction proceeds through an external nucleophilic attack (Br^-) on a (π-allene)palladium complex to produce a (π-allyl)palladium intermediate. Subsequent intramolecular attack by the second internal nucleophile gives the product. The intermediate (π-allyl)palladium complexes were isolated and characterized. The scope and limitation of the reaction were studied together with its mechanism and selectivity, under different reaction conditions.

Introduction

Nucleophilic additions to unsaturated hydrocarbons coordinated to transition metals are important in organic synthesis.[1] In particular, palladium-catalyzed reactions involving nucleophilic attack on (π-olefin)- and (π-allyl)palladium complexes have been extensively studied, since they are often associated with high stereo- and regioselectivity.[2] Palladium-catalyzed processes employing allenes as substrates have been somewhat neglected compared with alkenes, alkynes, and 1,3-dienes. In recent years, however, palladium-catalyzed reactions of allenes have attracted considerable interest, and today many examples of palladium(0)-catalyzed carbopalladations,[3,4] hydropalladations,[5] and carbonylations[6] of allenes exist together with a variety of palladium(0)-catalyzed intramolecular variants.[7,8,9,10,11]

Our research group has been particularly engaged in the investigation of palladium-catalyzed oxidations, and in recent years we have developed several different palladium(II)-catalyzed 1,4-oxidations of conjugated dienes.,[12,13,14] In contrast to 1,3-dienes, the corresponding 1,2-dienes (allenes) have found

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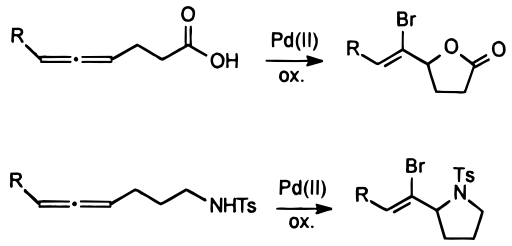
Scheme 1



limited use in palladium(II)-catalyzed oxidations.[15−18] Prior to our work,[17,18] palladium(II)-catalyzed 1,2-functionalization of allenes had been reported only for carbonylation reactions.[16]

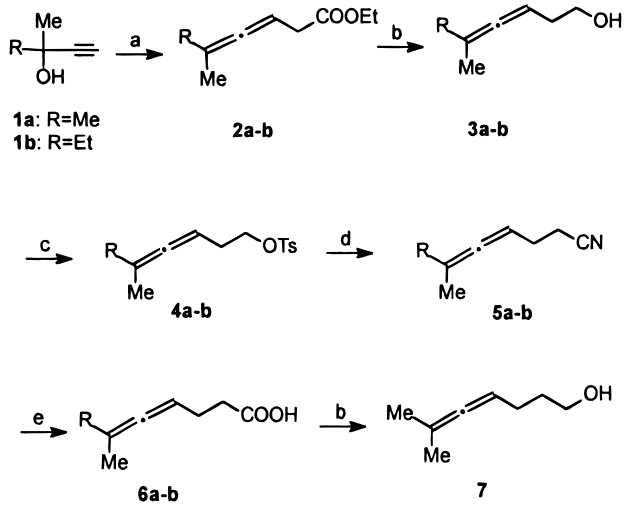
We recently reported on a mild palladium-catalyzed 1,2-oxidation of allenes in which two nucleophiles are added across the double bond.[17] These 1,2-additions were recently extended to intramolecular lactonization and amidation reactions (Scheme 1).[18]

We now give a full account of these palladium-catalyzed intramolecular 1,2-oxidations, report new results on the use of additional oxygen and nitrogen nucleophiles, and discuss the reaction mechanism and the scope and limitation of the reaction. This new methodology provides access to heterocyclic compounds that are useful synthetic intermediates.

Results and Discussion

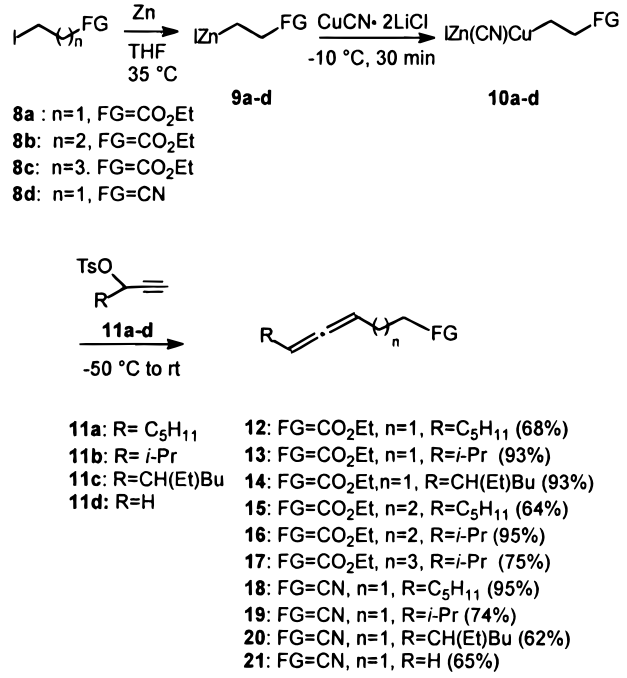
A. Preparation of Starting Materials. A number of methods are reported for the preparation of allenes,[19] and all of the starting allenes were prepared through the application of known or slightly modified procedures. The synthesis of the γ-allenic acids **6a** and **6b** and γ-allenic alcohol **7** are outlined in Scheme 2.[20] The synthesis starts with an *ortho*-Claisen rearrangement, which was carried out by heating the propargylic alcohols **1a** and **1b** with excess triethyl orthoacetate in the presence of a small amount of propionic acid. The resulting β-allenic esters

Scheme 2[a]



[a] Reagents and conditions: (a) $(EtO)_3CCH_3$, EtCOOH (cat.), 78−79%; (b) $LiAlH_4$, Et_2O, 87−95%; (c) TsCl, pyridine, 78−89%; (d) NaCN, DMSO, 95%; (e) NaOH, EtOH/H_2O, 81−95%.

Scheme 3



2a and **2b** were then reduced with $LiAlH_4$,[20b] tosylated, and reacted with NaCN in DMSO to form the allenic nitriles **5a** and **5b**. Subsequent alkaline hydrolysis with NaOH in EtOH/H_2O afforded the allenic acids **6a** and **6b**. The allenic alcohol **7** was in turn obtained after reduction with $LiAlH_4$.

The monosubstituted allenic acids were prepared via a copper(I)-mediated S_N2' displacement of the propargylic tosylates **11a**−**d**[21] (Scheme 3). Treatment of the appropriate iodide **8a**−**d**[22] with activated zinc (1,2-dibromoethane and TMSCl) in

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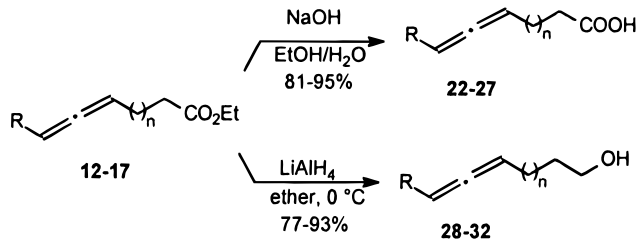
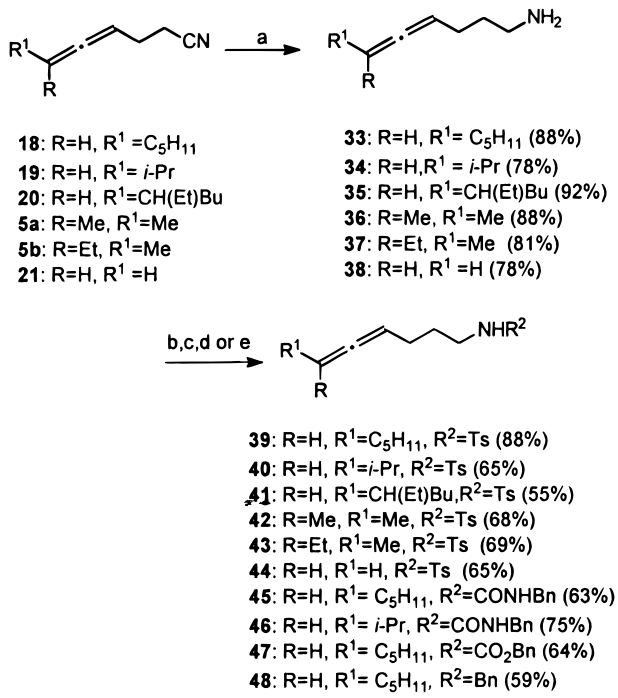
(22) **8a**−**d** were prepared from the corresponding bromide (Aldrich, Lancaster) by treatment with sodium iodide in refluxing acetone. Finkelstein, H. *Chem. Ber.* **1910**, *43*, 1528.

Scheme 4



Scheme 5[a]



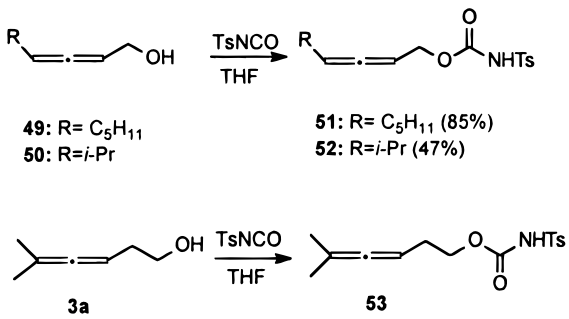
[a] Reagents and conditions: (a) $LiAlH_4$, ether, −20 °C, 78−92%; (b) TsCl, pyridine, 0 °C 55−88%; (c) BnNCO, ether, 63−75%; (d) BnOCOCl, THF, 64%; (e) (i) benzaldehyde, ethanol; (ii) $NaBH_4$, 59%.

THF at 35 °C followed by transmetalation with CuCN·2LiCl generated the organocopper species **10a**−**d**,[23] which in turn were reacted with the propargylic tosylates **11a**−**d**[24] to afford the γ-allenic esters **12**−**14**, δ-allenic esters **15** and **16**, ϵ-allenic ester **17**, and γ-allenic nitriles **18**−**21** in good isolated yields.

The resulting allenic esters **12**−**17** were either hydrolyzed by NaOH in EtOH/H_2O to allenic acids **22**−**27** or reduced with $LiAlH_4$ in diethyl ether to allenic alcohols **28**−**32** (Scheme 4). These compounds constitute starting materials for intramolecular palladium-catalyzed 1,2-oxidation reactions.

The starting materials for the intramolecular amidation reaction were prepared by first converting the allenic nitriles **5a**,**b** and **18**−**21** to the corresponding primary amines **33**−**38** (Scheme 5). The required *N*-tosyl amides **39**−**44** were then obtained by reaction with tosyl chloride in pyridine.[25] The allenic ureas **45** and **46** were synthesized from the primary amines **33** and **34**, respectively, via addition of benzyl isocyanate in

Scheme 6



ether,[34a] and the allenic carbamate **47** was obtained from **33** after treatment with benzyl chloroformate in THF.[26] *N*-Benzylamine **48** was prepared by treatment of **33** with benzaldehyde in ethanol followed by reduction of the resulting imine with $NaBH_4$.[16c]

The carbamates **51** and **52** and its one-carbon-higher homologue **53** were prepared from the α-allenic alcohols **49** and **50** and β-allenic alcohol **3a**, respectively, by treatment with a small excess of TsNCO[27] (Scheme 6). The α-allenic alcohols **49** and **50** were obtained according to known literature procedures.[28]

B. Palladium(II)-Catalyzed Intramolecular Bromolactonization. Reaction of γ-allenic acid **22** in the presence of 5 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.5 equiv of *p*-benzoquinone (BQ), and 2.5 equiv of LiOAc in acetic acid at 40 °C afforded the γ-lactone product **54** in 84% yield, of mainly (*Z*)-configuration (*Z*/*E* = 92/8) (Table 1). The substrate had to be added slowly (16−18 h) with a syringe pump in order to prevent side reactions. The LiOAc was added in an attempt to speed up the reaction, which proved successful, and the reaction times could be reduced to 24 h in most cases. The stereochemical assignment was made by means of NOE measurements. For example, irradiation of the olefinic proton in **54** resulted in NOE to the allylic CH−O proton in the (*Z*)-isomer. The corresponding irradiation for the (*E*)-isomer of **54** gave no detectable NOE to the allylic CH−O protons. A few other γ-allenic acids **23**, **24**, **6a**, and **6b** were also shown to undergo the palladium-catalyzed bromolactonization reaction (Table 1). The size of the allenic substituent seems to have an effect on the stereochemical outcome. Thus, increasing the size of the allenic substituent from a pentyl group (Table 1, entry 1) to an isopropyl group (Table 1, entry 4) reduced the selectivity from *Z*/*E* = 92:8 to *Z*/*E* = 76:24.

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(24) **11a**−**d** were prepared from the corresponding alcohol by treatment with tosyl chloride and powdered KOH in ether at −50 °C. Westmuze, H.; Vermeer, P. *Synthesis* **1979**, 390.

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(32) Kind gift from Prof. Norbert Krause, University of Bonn, Germany.

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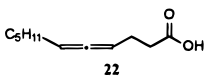
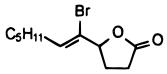
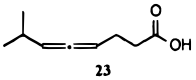
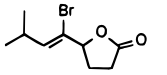
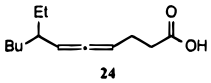
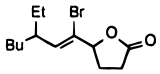
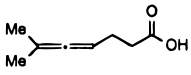
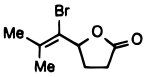
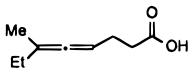
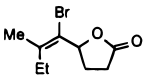
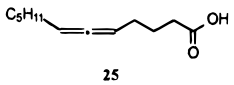
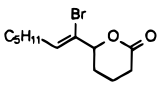
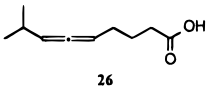
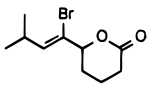
Table 1. Palladium-Catalyzed Intramolecular Bromolactonization of Allenic Acids

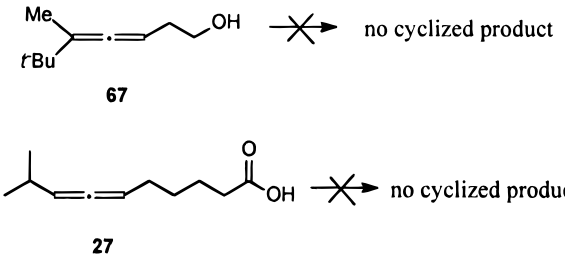
entry	allenic acid	method	product	yield[b]	*Z*/*E*[c]
1	 **22**	A	 **54**	84%	92/8
2		B		89%	54/46
3		C		89%	88/12
4	 **23**	A	 **55**	70%	76/24
5		B		90%	37/63
6		C		78%	80/20
7	 **24**	A	 **56**	52%	82/18
8	 **6a**	A	 **57**	68%	-
9		B		74%	-
10	 **6b**	A	 **58**	67%	59/41
11	 **25**	B	 **59**	83%	90/10
12		C		35%	85/15
13	 **26**	B	 **60**	82%	88/12

[a] Method A: In a typical procedure the substrate was added slowly over 16−18 h to a solution of 5 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.5 equiv of LiOAc, and 2.5 equiv of BQ in acetic acid (0.27 M) at 40 °C. The reaction times varied from 24 to 48 h. Method B: The reactions were carried out at room temperature in acetonitrile (0.15 M) employing 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.2 equiv of K_2CO_3 under an atmospheric pressure of O_2. The reaction times varied from 0.5 to 1 h. Method C: The reactions were carried out in CH_2Cl_2/THF 4:1 in the presence of 1.2 equiv of NBS. The reaction times varied from 2 to 24 h. [b] Isolated yield after flash chromatography. [c] Determined by means of NOE measurements and the *Z*/*E* ratio was determined by ^1H NMR.

The reaction was also carried out under the conditions (method B) developed for the intramolecular amidation reaction.[18b] Treatment of γ-allenic acid **22** and **23** with 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.1 equiv of K_2CO_3 in acetonitrile under an atmosphere of oxygen afforded lactone **54** and **55** in high yield (90%) after only 30 min. These variations of the reaction conditions had a dramatic effect on the stereochemical outcome of the reaction, and lactone **54** (Table 1, entry 2) was isolated as a nearly equal mixture of (*Z*)- and (*E*)-isomers (54:46) whereas **55** had the reversed stereochemistry (*Z*/*E* = 37:63) compared to that obtained with Pd/BQ.

To study if the bromolactonization reactions could be applied to allenic acids having one more carbon in the tether between the allene and the nucleophile, the one-carbon-higher homologues **25** and **26** were prepared (Schemes 3 and 4). However, subjecting δ-allenic acid **25** to the cyclization conditions, using benzoquinone as the oxidant, resulted in only trace amounts of the pyranone **59** after 48 h. The reaction was apparently too slow to be synthetically useful. On the other hand with palladium-catalysis conditions, utilizing Cu(II) as the reoxidant, allenic acid **25** was smoothly converted to the six-membered lactone **59** in 83% yield (*Z*/*E* = 90:10) after 1 h. Similarly, subjecting δ-allenic acid **26** to the latter reaction conditions afforded lactone **60** in good yield (82%) with a *Z*/*E* ratio of 88:12.

Scheme 7



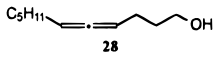
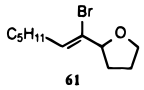
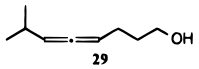
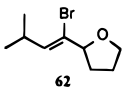
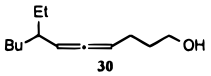
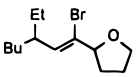
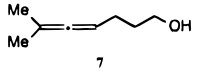
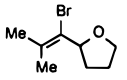
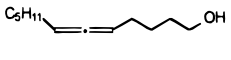
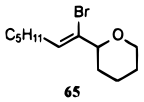
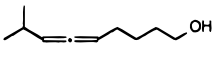
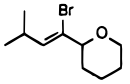
Walkup et al.[29] developed, a few years ago, cyclizations of γ-silyloxy allenes to form (iodovinyl)tetrahydrofurans in the presence of *N*-iodosuccinimide and Gallagher et al.[30] and Friesen et al.[31] have developed I_2-mediated cyclization of *N*-substituted allenic amines and carbamates, respectively, to form medium ring nitrogen heterocycles. Inspired by these reports, we decided to study the equivalent cyclization of allenic acids **22**, **23**, and **25**, in the presence of *N*-bromosuccinimide and compare the results to our newly developed palladium-catalyzed reaction. Treatment of γ-allenic acids **22** and **23** with 1.2 equiv of NBS in THF/CH_2Cl_2 (1:4) furnished the bromolactones **54** and **55** after 2 h (Table 1, entries 3 and 6). Yields and selectivity were in the same range as for the palladium-catalyzed reaction, which utilizes BQ as the reoxidant. The reaction of the δ-allenic acid **25** was, on the contrary, very slow with NBS and after reaction for 24 h lactone **59** was isolated in only 35% yield together with unreacted starting material and a mixture of side products (Table 1, entry 12). This should be compared with the palladium-catalyzed reaction (entry 11), which afforded **59** in 83% yield after 1 h.

Thus, the palladium-catalyzed intramolecular reactions with carboxylic acids as the internal nucleophile work well to give five- and six-membered lactones.

Attempts to prepare four- or seven-membered rings containing oxygen proved difficult. β-Alcohol **67**[32] has previously been subjected to the palladium-catalyzed conditions employing *p*-benzoquinone as the oxidant which resulted in no 1,2-oxidation products (Scheme 7).[18a] Subjecting ϵ-allenic acid **27** to either the Pd−BQ or the Pd−Cu(II) conditions gave only recovered starting material together with a complex mixture of byproducts. Apparently, the rate of cyclization to give four- and seven-membered rings was not high enough to promote the reaction.[33]

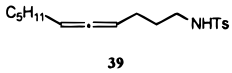
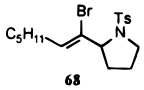
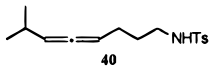
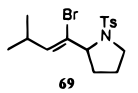
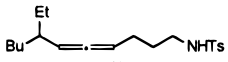
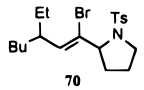
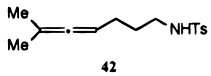
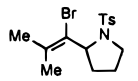
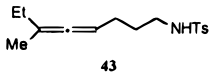
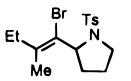
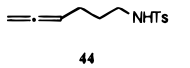
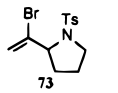
C. Palladium-Catalyzed Intramolecular Oxybromination of Allenic Alcohols. During the course of this study, we considered the possibility of extending the intramolecular reactions to include alcohols as internal nucleophiles. Thus the γ-allenic alcohol **28** was slowly added (14 h) to a solution of 5 mol % $Pd(OAc)_2$, 5 equiv of LiBr, and 2.5 equiv of BQ in acetic acid at 40 °C. After 8 h tetrahydrofuran **61** was isolated in 75% yield with mainly (*Z*)-stereochemistry (*Z*/*E* = 94:6) (Table 2). The cyclization of the alcohols was found to proceed faster than that of the corresponding acid derivatives, and no addition of LiOAc was necessary. For example, the reaction of γ-allenic alcohol **28** was complete after 8 h, whereas the cyclization of the corresponding γ-allenic acid **22**, to form lactone **54**, took 24 h. (Table 1, entry 1). To demonstrate the generality of the

Table 2. Palladium-Catalyzed Intramolecular Oxybromination of Allenic Alcohols

entry	allenic alcohol	method	product	yield[b]	*Z*/*E*[c]
1	 **28**	A	 **61**	75%	94/6
2		B		46%	84/16
3		C		64%	94/6
4	 **29**	A	 **62**	70%	88/12
5	 **30**	A	 **63**	62%	90/10
6	 **7**	A	 **64**	70%	-
7		B		71%	-
8	 **31**	B	 **65**	78%	96/4
9		C		31%	87/13
10	 **32**	B	 **66**	70%	94/6

[a] Method A: In a typical procedure the substrate was added slowly over 14 h to a solution of 5 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, and 2.5 equiv of BQ in acetic acid (0.27 M) at 40 °C. The reaction times were 8 h. Method B: The reactions were carried out at room temperature in acetonitrile (0.15 M) employing 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.2 equiv of K_2CO_3 under an atmospheric pressure of O_2. The substrate was added over 2 h. Reaction times varied from 0.5 to 2 h. Method C: The reactions were carried out in CH_2Cl_2/THF 4:1 in the presence of 1.2 equiv of NBS. The reaction time was 2 h. [b] Isolated yield after flash chromatography. [c] Determined by means of NOE measurements and the *Z*/*E* ratio was determined by ^{1}H NMR.

Table 3. Palladium-Catalyzed Intramolecular Bromoamidation of *N*-Tosyl Allenic Amides

entry	allenic amide	method	product	yield[b]	*Z*/*E*[c]
1	 **39**	B	 **68**	72%	93:7
2		C		80%	92:8
3	 **40**	B	 **69**	76%	89:11
4		C		78%	92:8
5	 **41**	B	 **70**	80%	89:11
6	 **42**	B[d]	 **71**	68%	-
7	 **43**	B[d]	 **72**	71%	65:35
8		C		63%	60:40
9	 **44**	B[e]	 **73**	69%	-

[a] Method B: Unless otherwise noted, the reactions were carried out at room temperature in acetonitrile (0.15 M) employing 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.2 equiv of K_2CO_3 under an atmospheric pressure of O_2. The reaction times varied from 2 to 5 h. Method C: The reactions were carried out in CH_2Cl_2/THF 4:1 in the presence of 1.2 equiv of NBS. The reaction times varied from 2 to 12 h. [b] Isolated yield after flash chromatography. [c] Determined by means of NOE measurements and the *Z*/*E* ratio was determined by ^{1}H NMR. [d] $CuCl_2$ was used instead of $Cu(OAc)_2$. [e] $Cu(OTf)_2$ was used instead of $Cu(OAc)_2$ and no K_2CO_3 was added.

overall process and to study the effect of the R substituent on the stereoselectivity, the palladium-catalyzed reaction was also applied to three other γ-allenic alcohols **29**, **30**, and **7** (Table 2). The stereoselectivity was in accordance with that of the bromolactonization reaction, and a similar trend for decreased stereoselectivity with higher steric hindrance on the allenic substituent was observed.

γ-Allenic alcohol **28** was also applied to the two other cyclization conditions (Table 2, entries 2 and 3). Treatment of **28** with NBS in CH_2Cl_2/THF gave tetrahydrofuran **61** in 64% yield, with a *Z*/*E* ratio of 94/6. The selectivity was in the same range as for the Pd/BQ cyclization, but the yield was slightly reduced. Cyclization of the γ-allenic alcohol **28** (Table 2, entry 2) under the Pd/Cu(II) conditions proved more difficult, giving tetrahydrofuran **61** in only 46% yield, together with a complicated mixture of side-products. The stereoselectivity was lower (*Z*/*E* = 84/16) than that of the corresponding Pd/BQ reaction (*Z*/*E* = 94/6) but much improved in comparison with the selectivity of the corresponding lactonization reaction with γ-allenic acid **22** (cf. Table 1, entry 2, *Z*/*E* = 54/46).

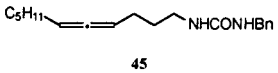
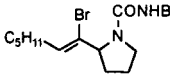
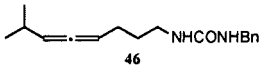
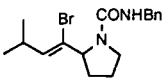
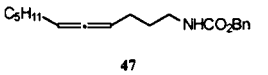
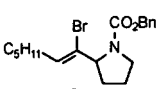
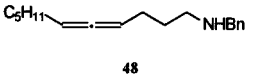
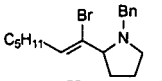
The reaction for the one-carbon-higher homologue δ-allenic alcohol **31** (Table 2, entry 8) worked best with the Pd/Cu(II) system, in analogy with the δ-allenic acids **25** and **26**, and the corresponding tetrahydropyran **65** was isolated in 65% yield. The yield was further improved by adding the substrate slowly over a period of 2 h. The tetrahydrofuran **65** was then isolated in 78% yield with good selectivity (Table 2, entry 8). A similar result was obtained when δ-allenic alcohol **32** was subjected to the Pd/Cu(II) conditions affording tetrahydropyran **66** in good yield (70%) and high selectivity (*Z*/*E* = 94:6). When NBS was used as the electrophilic mediator in the cyclization of δ-allenic alcohol **31**, the reaction was finished after 2 h. The tetrahydropyran **65** could, however, only be isolated in 31% yield together with a complicated mixture of byproducts (Table 2, entry 9).

Thus, the palladium-catalyzed intramolecular reactions with alcohols as the internal nucleophile work well to give tetrahydrofurans and tetrahydropyrans in good isolated yields.

D. Palladium-Catalyzed Oxidations Involving Nitrogen Nucleophiles. *N*-tosylated γ-allenic amines **39**−**44** were smoothly cyclized to pyrrolidines **68**−**73** in the presence of catalytic amounts of $Pd(OAc)_2$, LiBr (5 equiv), Cu(II) salt (2.1 equiv), and K_2CO_3 (1.2 equiv) in acetonitrile under an atmosphere of oxygen (Table 3).[34] The reaction times for these cyclizations were short (<2 h). Preliminary attempts to cyclize **39** with $Pd(OAc)_2$ using *p*-benzoquinone as a reoxidant for palladium failed. The amide nitrogen can apparently not act as a nucleophile under the slightly acidic conditions employed here. This contrast to previous results obtained and reported by our group, where nitrogen nucleophiles were used in an intramolecular 1,4-oxidation of 1,3-dienes.[13c]

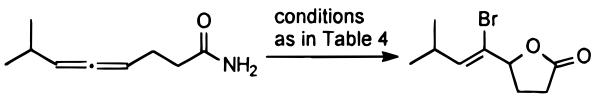
During the optimization of the allenic oxidation reactions, it was shown that $CuCl_2$, which is the most common Cu(II) oxidant for Pd(0),[2a] gave 4−5% of a byproduct, in which a chloride from $CuCl_2$ had attacked the middle allene carbon instead of the bromide. To suppress this side reaction, other Cu(II) salts were screened, of which $Cu(OAc)_2$ turned out to

Table 4. Palladium-Catalyzed Intramolecular Bromoamidation of Various *N*-Substituted Allenic Amides Employing $Cu(II)/O_2$ as an Oxidant[a]

entry	allenic amide	product	yield[b]	*Z*/*E*[c]
1	 **45**	 **74**	78%	76/24
2	 **46**	 **75**	69%	89/11
3	 **47**	 **76**	80%	79/21
4	 **48**	 **77**	28%	52/48

[a] Unless otherwise noted in the experimental part the reactions were carried out at room temperature in acetonitrile (0.15 M) employing 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.2 equiv of K_2CO_3 under an atmospheric pressure of O_2. The reaction times varied from 1 to 24 h. [b] Isolated yield after flash chromatography. [c] Determined by means of NOE measurements and the *Z*/*E* ratio was determined by ^1H NMR.

Scheme 8



78 **55**

be best. For the 6,6-disubstituted allenes **42** and **43**, $CuCl_2$ gave the most efficient reaction, and pyrrolidines **71** and **72** were obtained in 68% and 71% yield, respectively. The terminally unsubstituted allenic amide **44** worked better in the presence of $Cu(OTf)_2$ as an oxidant.

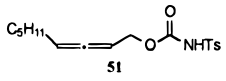
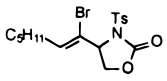
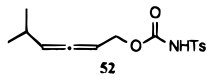
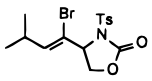
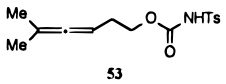
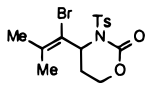
It was also of interest to compare these results with the NBS-promoted cyclizations. Thus, reaction of **39**, **40**, and **43** in the presence of NBS in CH_2Cl_2/THF afforded the corresponding pyrrolidines **68**, **69**, and **72**. The yields and selectivity of these compounds were in the same range as for the products obtained from the palladium-catalyzed version.

The intramolecular amidation reaction also worked well with benzyl ureas and carbamates (Table 4). The ureas **45** and **46** cyclized rapidly in 1 and 4 h, respectively, to give compounds **74** and **75** in 78% and 69% yield, respectively. Interestingly, the stereoselectivity for the isopropyl-substituted pyrrolidine was higher (*Z*/*E* = 89:11) than that of the pentyl-substituted pyrrolidine (*Z*/*E* = 76:24). This is in contrast to all other reported examples. The reaction of the carbamate **47** also performed well, and the product **76** was isolated in 80% yield after 24 h. The reaction of benzylamine **48** on the other hand was more sluggish, and pyrrolidine **77** could only be isolated in 28% yield. This observation can be rationalized by a strong coordination of the amine to palladium retarding the cyclization.[35]

Dienic amides **78**,[36] with a carbonyl carbon located within the tether, did not give the desired lactam product but produced lactone **55**, which was isolated in 70% yield (Scheme 8). Apparently, the keto function in **78** acts as the nucleophile, and the resulting iminoester is hydrolyzed under the reaction conditions to afford the lactone **55** as the sole product.

Encouraged by the results obtained for the palladium-catalyzed cyclizations of *N*-substituted allenic amides we tried

Table 5. Palladium-Catalyzed Intramolecular Cyclizations of Carbamates[a]

entry	allenic carbamate	product	yield[b]	*Z*/*E*[c]
1	 **51**	 **79**	68%	52/48
2	 **52**	 **80**	70%	49/51
3	 **53**	 **81**	22%	-

[a] Unless otherwise noted, the reactions were carried out at room temperature in acetonitrile (0.15M) employing 10 mol % of $Pd(OAc)_2$, 5 equiv of LiBr, 2.1 equiv of $Cu(OAc)_2 \cdot H_2O$, and 1.2 equiv of K_2CO_3 under an atmospheric pressure of O_2. Reaction times varied from 1 to 3 h. [b] Isolated yield after flash chromatography. [c] Determined by means of NOE measurements and the *Z*/*E* ratio was determined by ^1H NMR.

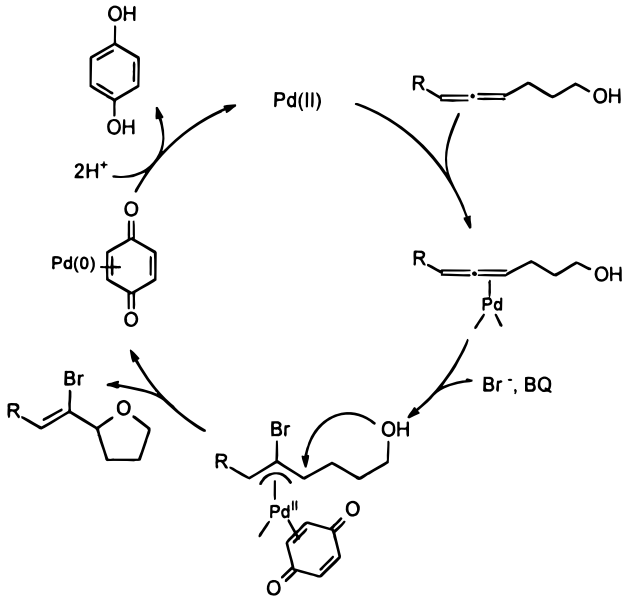
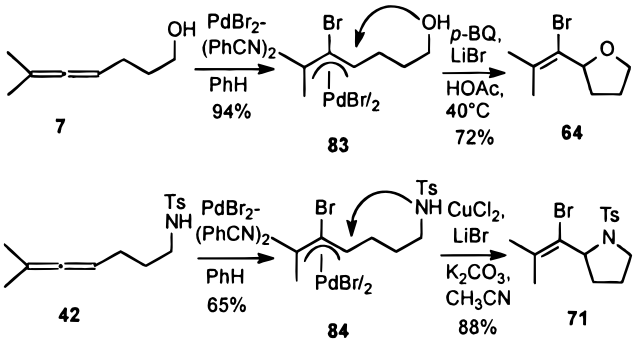


Figure 1.

to extend this methodology to include *N*-tosyl allenic carbamates. Thus carbamate **51** was prepared according to Scheme 6 and subjected to the Pd/Cu(II) conditions, which afforded oxazolidinone **79** after 2 h in 68% yield (Table 5). Similarly, treatment of carbamate **52** under the latter conditions afforded **80** in equally good yield (70%). Interestingly, the stereoselectivity in these reactions was low, giving (*E*)- and (*Z*)-isomers in nearly equal amounts, as was the case when γ-allenic acids were treated under the Pd/Cu(II) conditions (Table 1, method B). The one-carbon-higher homologue **53** was also cyclized to give the six-membered oxazolidinone **81**, albeit in low yield (22%).

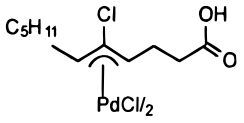
D. Mechanism. A likely mechanism for the palladium-catalyzed 1,2-oxidation is given in Figure 1. This mechanism is reminiscent of that of the corresponding 1,4-oxidation of conjugated dienes[12,13] and involves a (π-allyl)palladium intermediate. Nucleophilic attack on the initially formed (allene)-palladium complex produces a σ-allylpalladium intermediate, which rapidly equilibrates to the corresponding (π-allyl)-palladium intermediate. Attack by halides on allenes coordinated

Scheme 9



to palladium to give (π-allyl)palladium complexes is well precedented in the literature.[37] Coordination of *p*-benzoquinone to palladium in this π-allyl complex induces an intramolecular nucleophilic attack to give the tetrahydrofuran product.[38] In this process a Pd(0)−benzoquinone complex is formed,[39] which immediately undergoes an intramolecular redox reaction in the presence of acid to give Pd(II) and hydroquinone.[40]

The mechanism for the intramolecular lactonization reaction starting from allenic acids involves a similar catalytic cycle. An intermediate (π-allyl)palladium complex for the lactonization reaction has previously been isolated as a chloro dimer.[18a] The γ-allenic acid **22** was then reacted with a stoichiometric amount of $Pd(PhCN)_2Cl_2$ in benzene, which afforded (π-allyl)palladium complex **82**. Complex **82** was isolated and characterized and

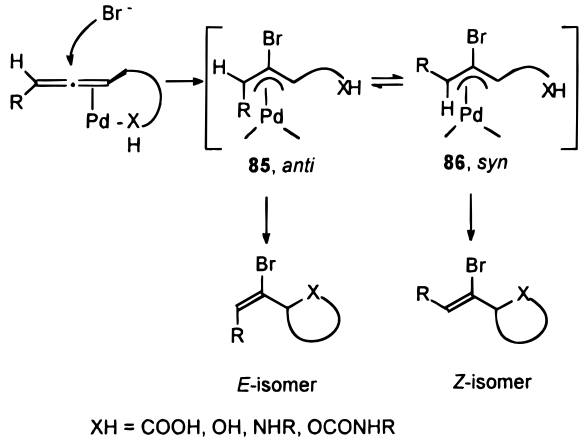


82

subsequently treated with *p*-benzoquinone, LiBr, and LiOAc in acetic acid, which resulted in a fast intramolecular cyclization to give the chloro-analogue of lactone **54** (Table 1).

The π-allyl intermediates from the oxybromination reaction and the intramolecular amidation reaction have now also been isolated as the more relevant intermediates. Thus, complexes **83** and **84** were obtained as yellow crystalline compounds from the reaction of allenes **7** and **42**, with $PdBr_2(PhCN)_2$[37](Scheme 9). They were fully characterized by spectroscopic methods. When complex **83** was subjected to the conditions of the catalytic reaction employing benzoquinone as the oxidant, tetrahydrofuran **64** was obtained in 72% yield after 12 h.[41] Similarly, when compound **84** was allowed to react under the catalytic conditions, but with $CuCl_2$ as the oxidant, pyrrolidine **71** was produced in 88% yield after 1 h.

Scheme 10



The mechanism for the reaction with Cu(II) as the reoxidant is probably similar to that shown for the catalytic cycle in Figure 1. The use of $CuCl_2/O_2$ as the oxidant has previously been used in palladium-catalyzed intramolecular 1,4-oxidations of conjugated dienes, even though the reaction was less stereoselective than the corresponding reaction with *p*-benzoquinone.[12b,13c,14a,42]

E. Stereoselectivity. The stereoselectivity of the reaction seems to be related mainly to the relative abundance of the two *anti*- and *syn*-intermediate (π-allyl)palladium complexes **85** and **86** (Scheme 10). The *anti* complex **85** is predicted to be the kinetic intermediate, since the bromide will preferentially add to the sterically less hindered face (anti to R) of the allenic double bond closest to the tether. The *anti* complex **85** can then isomerize to the corresponding *syn*-complex **86** via a η^3-η^1-η^3-rearrangement.[43] The thermodynamic stability of a π-allyl complex is partly dependent on the steric interaction between the Pd atom and the substituent in the *anti* position, and 1,3-disubstituted (π-allyl)palladium complexes are known to be more stable in a *syn,syn* configuration.[43b,44] However, when the central position of the π-allyl is substituted, substantial amounts of the *anti* conformer have been observed.[45,3a,b,e,10c,e] It is the relative stability of these two complexes, the *syn* and the *anti*, as well as their reactivity and rate of isomerization that will determine the stereochemistry of the resulting products. Several factors, such as steric effects in the (π-allyl)palladium intermediates exerted by substituents at the allene group, the number of atoms located between the internal nucleophile and the π-allyl moiety, the nature of the nucleophile, and the choice of reoxidant (BQ or Cu(II)) will influence the ratio of the *syn* and *anti* complexes in the catalytic reaction.

When R is a medium-sized group, e.g., a primary alkyl, the (*Z*)-isomer is the predominantly formed isomer, via the *syn*-intermediate **86**. On the other hand if R is a larger group, the *E/Z* ratio increases, which indicates a slightly higher amount of the *anti*-intermediate **85** in the catalytic reaction. An explanation for these observations is that the rate of isomerization of the kinetically favored *anti* complex **85** to the *syn*

(35) (a) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 3994 (b) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

(36) The allenic amide **78** was prepared from the corresponding allenic ester **13** by a cyanide-catalyzed aminolysis. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.* **1987**, *52*, 5020.

(37) (a) Schultz, R. G. *Tetrahedron* **1964**, *20*, 2809. (b) Lupin, M. S.; Shaw, B. L. *Tetrahedron Lett.* **1964**, 883. (c) Lupin, M. S.; Powell, J.; Shaw, B. L. *J. Chem. Soc.* **1966**, 1687.

(38) Bäckvall, J.-E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243.

(39) Minematsu, H.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1975**, 466.

(40) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790.

(41) This makes the alternative mechanism of the 1,2-oxidation via oxypalladation or aminopalladation—to give a vinylpalladium species—followed by reductive elimination to form the vinyl bromide bond, less likely.

(42) Nilsson, Y. I. M.; Aranyos, A.; Andersson, P. G.; Bäckvall, J.-E.; Parrain, J. L.; Ploteau, C.; Quintard, J. P. *J. Org. Chem.* **1996**, *61*, 1825. (d) Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 8696.

(43) Corradini, P.; Maglio, A.; Musco, A.; Paiaro, G. *J. Chem. Soc., Chem. Commun.* **1966**, 618. (b) Faller, J. W.; Thomsen, M. E.; Mattina, M. J. *J. Am. Soc. Chem.* **1971**, *93*, 2642. (c) Faller, J. W.; Tully, M. T. *J. Am. Soc. Chem.* **1972**, *94*, 2676.

(44) (a) Trost, B.; Strege, P. E.; Weber, L.; Fullerton, T.; Dietsche, T. J, *J. Am. Chem. Soc.* **1978**, *100*, 3407. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

(45) Lukas, J.; Ramakers-Blom, J. E.; Hewitt, T. G.; De Boer, J. J. *J. Organomet. Chem.* **1972**, *46*, 167.

complex **86** decreases with the size of the R group.[45] This explains the observed results in the lactonization and oxybromination reaction when BQ was used as the oxidant. When R is a pentyl group, (**22** (Table 1, entry 1) and **28** (Table 2, entry 1)), the stereoselectivity is high (*Z*/*E* = 92:8 and 94:6) due to an almost total isomerization to the *syn*-complex **86**, which produces the (*Z*)-isomer. However, when R is an isopropyl group (**23** (Table 1, entry 4) and **29** (Table 2, entry 4)), the *syn*−*anti* isomerization is slower, which results in decreased selectivity (*Z*/*E* = 76:24 and 88:12).

Interestingly, the choice of reaction conditions had a dramatic effect on the stereoselectivity in the lactonization reaction. A change of reoxidant from BQ to $Cu(OAc)_2$ in the cyclization of γ-allenic acid **22** (Table 1, entry 2) resulted in total loss of alkene stereochemistry, and an almost equal mixture of (*E*)- and (*Z*)-isomers (*Z*/*E* = 54:46) was observed. The same effect on the *Z*/*E* ratio, by the change of oxidant, was observed also for the γ-allenic acid **23** (Table 1, entry 5), and here even a reversed selectivity (*Z*/*E* = 37:63) was observed with Cu(II). These observations can be rationalized, if one assumes that reaction under the Cu(II) conditions leads to a much faster intramolecular attack on the intermediate π-allyl complexes, with less time for the *anti*-complex **85** to isomerize to the more stable *syn*-complex **86**, than for reactions under the BQ conditions. This is a reasonable assumption since BQ is known to be a rather slow oxidant for the π-allyl complexes in these reactions.[46] Furthermore, the experiment on stoichiometric complexes (Scheme 9) showed that the internal nucleophile reacted more slowly (12 h) in the presence of BQ than with $Cu(OAc)_2$ (1 h).

The observation that γ-allenic acid **23** gave the reversed stereochemistry also supports the theory that the *anti*-complex is the kinetically observed intermediate. This reaction was also performed in the absence of K_2CO_3 (Table 1, method B) in an attempt to slow the nucleophilic attack on the π-allyl intermediate and allow more time for isomerization of the *anti*- to the *syn*-isomer. The observed increase of the relative amount of the (*Z*)-isomer from *Z*/*E* = 37:62 to *Z*/*E* = 52:48 in this case supports the mechanism in Scheme 10.

The number of carbon atoms between the nucleophilic group and the π-allyl system and the nature of the nucleophile also influenced the selectivity. In contrast to the poor selectivity observed, when γ-allenic acids **22** and **23** (Table 1, entries 2 and 5) were cyclized under the Pd/Cu(II) conditions, the one-carbon-higher homologue δ-allenic acids **25** and **26** (Table 1, entries 11 and 13) and the *N*-tosyl-substituted allenic amides **39**−**44** (Table 3) worked excellently, with high stereoselectivity. Evidently, cyclization to furnish six-membered rings was slower than the analogous five-membered ring cyclization, and the intramolecular nucleophilic attack by *N*-tosyl allenic amines was slower compared to nucleophilic attack by carboxylic groups. The slower intramolecular attack favors formation of the *syn*-complex **86** (Table 3 and Table 1, entries 11 and 13). In one of the cyclizations we observed a higher *Z*-selectivity for R = isopropyl than for R = pentyl (**46** → **75** and **45** → **74**, respectively, Table 4). In this case the nucleophile is a urea, and coordination of the terminal nitrogen to palladium would also allow π-olefin complex formation with the double bond further away from the tether (Figure 2). In this case the *syn/anti* selectivity will be different from that discussed in Scheme 10.

The stereochemical outcome of the NBS-promoted cyclization can be explained from previous studies by Friesen et al.[31b] on iodocyclizations of trichloroacetimidate derivatives of primary α-allenic alcohols. The mechanism involves an intramolecular attack of the nucleophilic group on a rapidly equilibrating mixture of the bromonium species **87** and **88** (Scheme 11). The steric interaction between the attacking nucleophile and the R group on the olefin will disfavor transition-state **88**, which leads to the *E* isomer. This explanation fits well with our observations. Treating γ-allenic acid **22** with NBS gave lactone **54** with a *Z*/*E* ratio of 88/12.

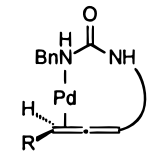
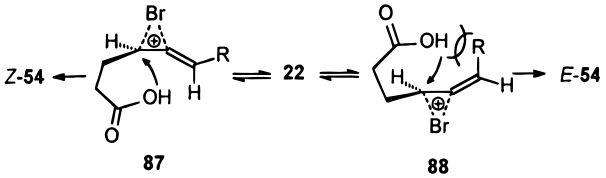
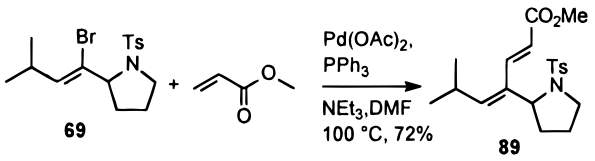


Figure 2.

Scheme 11

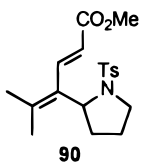


Scheme 12



F. Synthetic Applications. The present palladium-catalyzed method allows a mild preparation of various five- and six-membered heterocycles. The products obtained from the intramolecular palladium-catalyzed 1,2-addition to allenes should be useful synthetic intermediates for further selective functionalization. The vinyl bromides obtained can undergo a number of transformations, such as metal-catalyzed carbonylation,[47] palladium-catalyzed coupling reactions,[48] or coupling with a cuprate.[49] To demonstrate the synthetic utility of the reaction a Heck-coupling with methyl acrylate was carried out. Subjecting **69** to the Heck-coupling conditions afforded product **89** in 72% yield (Scheme 12).

This should be compared with the corresponding Pd(0)-catalyzed cyclization/Heck process reaction developed by Gallagher et al.[7b] Cyclization of *N*-tosyl-substituted allenic amide **42** using $PdCl_2$ in the presence of methyl acrylate and NEt_3 in DMF at 100 °C afforded the Heck product **90** in only 32% yield together with a substantial amount of dimeric products.



Conclusion

A palladium(II)-catalyzed intramolecular 1,2-functionalization of allenes has been developed. The reaction, which is a two-

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(47) Reference 2, pp 188−209.

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(49) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.

electron oxidation reaction, is reminiscent of the corresponding Pd(II)-catalyzed 1,4-functionalization of 1,3-dienes. As in the latter reaction, this new reaction proceeds via a π-allyl intermediate formed from attack by a first nucleophile, followed by an intramolecular nucleophilic attack on the π-allyl moiety. The new intramolecular 1,2-oxidation utilizes mild oxidants such as *p*-benzoquinone or copper(II) salts and should therefore tolerate various functionalities. The reaction provides access to a variety of oxygen- and nitrogen-containing five- and six-membered heterocycles. Furthermore, these latter compounds are useful intermediates for further selective functionalizations.

Experimental Section

7-Methyl-octa-4,5-dienoic Acid Ethyl Ester (13). General Procedure for the Preparation of Allenic Esters 12−17 and Allenic Nitriles 18−21. A suspension of zinc (3.89 g, 59.4 mmol) in THF (5 mL) containing 1,2-dibromoethane (0.39 g, 2.1 mmol) was heated with a heat gun for 30 s and allowed to cool to room temperature. Chlorotrimethylsilane (0.22 mL, 1.8 mmol) was then added, and the mixture was allowed to stir for 15 min before a THF solution (25 mL) of the functionalized alkyl iodide, ethyl-3-iodopropionate **8a** (13.1 g, 57.4 mmol), was slowly added with a syringe. After the end of the addition, the reaction was stirred for 12 h at 35 °C. The solution was then cooled to −10 °C, and a solution of CuCN (3.68 g, 41.4 mmol) and predried LiCl (3.53 g, 83.0 mmol) in THF (50 mL) was added. The resulting green-gray solution was stirred at 0 °C for 30 min. The solution was then cooled to −40 °C, and the corresponding propargylic tosylate **11b** (10 g, 39.7 mmol) was slowly added. The reaction mixture was allowed to slowly warm to room temperature. After the addition of water, the reaction mixture was extracted with ether three times. The combined extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was then filtered through silica to give **13** in 93% yield (8.06 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.18 (m, 1H), 5.14 (m, 1H), 4.10 (q, J = 7.2 Hz, 2H), 2.39 (m, 2H), 2.32−2.20 (m, 3H), 1.24 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 172.8, 99.8, 90.8, 60.3, 33.5, 27.9, 24.0, 22.6, 22.5, 14.4. IR ($CHCl_3$): 1960, 1743 cm^{-1}.

Undeca-4,5-dienoic Acid (22). General Procedure for the Preparation of Acids 23−27. A mixture of ester **12** (0.94 g, 4.5 mmol) and NaOH (2.85 g, 71.6 mmol) in ethanol (10 mL) and H_2O (3.8 mL) was stirred and heated under reflux overnight. The mixture was concentrated in vacuo, and the residue was diluted with water. The aqueous solution was extracted with ether to remove neutral impurities. The aqueous layer was then acidified with concentrated HCl to pH 1 and extracted with ether. The ether solution was washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by flash chromatography (pentane/ether 2:1) gave **22** in 81% yield (0.71 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.6 (br s, COOH), 5.16 (m, 2H), 2.48 (distorted t, J = 7.4 Hz, 2H), 2.30 (m, 2H), 1.96 (m, 2H), 1.38 (m, 2H), 1.29 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 179.3, 92.8, 89.2, 33.2, 31.5, 28.92, 28.90, 23.6, 22.6, 14.2. IR (neat): 1964, 1712 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95; Found: C,72.31; H, 9.99.

Undeca-4,5-dien-1-ol (28). General Procedure for the Preparation of Alcohols 29−32. To an ice-cold suspension of $LiAlH_4$ (87.8 mg, 2.3 mmol) in dry ether (2 mL) under argon was added **12** (0.44 g, 2.1 mmol) in ether (2 mL). After 30 min the mixture was allowed to warm to room temperature, and the reaction mixture was quenched by the addition of EtOAc and water. The resulting suspension was diluted with 1 M HCl and extracted with ether. The combined organic phases were washed with $NaHCO_3$ and brine, dried, and concentrated. The residue was purified with silica gel chromatography (pentane/ether 3:1) to give 0.29 g of **28** (83%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (m, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.06 (m, 2H), 1.96 (m, 2H), 1.72 (tt, J = 7.6, 6.5 Hz, 2H), 1.38 (m, 2H), 1.32 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 91.5, 90.1, 62.5, 32.0, 31.4, 28.99, 28.96, 25.3, 22.6, 14.2. IR ($CHCl_3$): 2326, 1961 cm^{-1}.

***N*-(*p*-Tolylsulfonyl)-hexa-4,5-dienylamine. (44). General Procedure for the Preparation of Amine 33−37.** To a suspension of $LiAlH_4$ (1.62 g, 42.5 mmol) in diethyl ether (10 mL) under nitrogen at −20 °C was added hexa-4,5-diene nitrile **21** (3.3 g, 35.5 mmol) in ether (1 mL) over 5 min. After 30 min, the mixture was allowed to warm to room temperature, and the stirring was continued for 2 h. The mixture was then diluted with CH_2Cl_2 and quenched by the dropwise addition of saturated aqueous NaOH (2 M). The mixture was filtered, and the solids were washed with CH_2Cl_2. The combined filtrate and washings were then evaporated to give hexa-4,5-dienylamine **38** as pale yellow oil (2.69 g, 78%) which was used without further purification. The ^{1}H NMR data are in accordance to those previously reported.[50]

General Procedure for Sulfonamide Preparation (39−43). To an ice-cold solution of the crude amine **38** (2.69 g, 27 mmol) in pyridine (33 mL) was added tosyl chloride (6.30 g, 33 mmol). The mixture was stirred for 2h at 0 °C and then allowed to stand at −15 °C overnight. The suspension was then diluted with ether and washed with aqueous HCl (2 M). The aqueous washings were then back-extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by flash chromatography (pentane /ether 3:2) to afford compound **44** as a pale yellow oil (4.5 g, 65%). The ^{1}H NMR data are in accordance to those previously reported.[50]

2,3-Nonadienyl Tosylcarbamate (51). General Procedure for Tosylcarbamate Preparation (52 and 53). To a solution of the alcohol **49** (0.8 g, 5.71 mmol) in THF (12 mL) was added *p*-toluenesulfonyl isocyanate (1.23 g, 6.28 mmol). The resulting solution was stirred at room temperature for 30 min. The mixture was then diluted with ether and washed with water and brine. The organic phase was dried and concentrated. The residue was purified by silica gel chromatography (pentane/ether 3:1) to give **51** in 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, J = 8.4 Hz, 2H), 7.77 (br s, NH), 7.33 (d, J = 8.4 Hz, 2H), 5.20 (m, 1H), 5.15 (m, 1H), 4.53 (dd, J = 6.8, 2.3 Hz, 2H), 2.44, (s, 3H), 1.95 (dtd, J = 7.3, 6.8, 2.9 Hz, 2H), 1.35 (m, 2H), 1.27 (m, 4H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5, 150.0, 144.9, 135.3, 129.5, 128.3, 93.3, 85.8, 65.4, 31.3, 28.6, 28.2, 22.4, 21.7, 14.1. IR (neat): 3242, 1966, 1752, 1349, 1162 cm^{-1}.

5-(1-Bromo-1-heptenyl)-tetrahydro-2-furanone (54). General Procedure for Palladium(II)-Catalyzed Cyclization of γ-Allenic Acids (Method A, Table 1, 54−58). The allenic acid **22** (40 mg, 0.22 mmol) in acetic acid (0.4 mL, 0.55 M) was added during 18 h with a syringe pump to a stirred solution of $Pd(OAc)_2$ (2.5 mg, 0.011 mmol), 1,4-benzoquinone (142 mg, 1.31 mmol), $LiOAc{\cdot}2H_2O$ (134 mg, 1.31 mmol), and LiBr (114 mg, 1.31 mmol) in acetic acid (2.4 mL, 0.1 M) at 40 °C. After the reaction was complete (20 h), water and ether were added. The phases were separated, and the aqueous phase was extracted two times with ether. The combined organic extracts were washed with aqueous NaOH (2 M) (until the organic layer was pale yellow), brine and dried ($MgSO_4$). Evaporation of the solvent and silica gel chromatography using pentane/ether (3:2) afforded **54** (48.2 mg, 84%) as a mixture of *Z*- and *E*-isomers in a ratio of 92:8; colorless oil. Pure samples of the *E* and *Z* isomers were obtained by preparative HPLC (pentane /EtOAc; 4:1) (*Z*)-**54**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.12 (t, J = 7.3 Hz, 1H), 5.01 (dd, J = 7.1, 6.3 Hz, 1H), 2.68 (ddd, J = 17.8, 10.0, 6.0 Hz, 1H), 2.53 (ddd, J = 17.8, 9.7, 7.2 Hz, 1H), 2.43 (m, 1H), 2.27 (m, 1H), 2.20 (q, J = 7.3 Hz, 2H), 1.42 (quintet, J = 7.3 Hz, 2H), 1.30 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 132.6, 124.6, 82.3, 31.3, 30.7, 27.9, 27.7, 27.2, 22.4, 13.9. (*E*)-**54**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.13 (t, J = 8.2 Hz, 1H), 5.39 (dd, J = 8.0, 6.3 Hz, 1H), 2.75 (ddd, J = 17.8, 10.3, 5.6 Hz, 1H), 2.54 (ddd, J = 17.8, 10.3, 8.0 Hz, 1H), 2.32 (m, 2H), 2.16 (m, 1H), 1.42 (m, 2H), 1.30 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 138.1, 123.0, 75.9, 31.1, 29.7, 28.7, 28.2, 26.8, 22.3, 13.9. (*Z*+*E* mixture):EIMS *m*/*z* 260 [M$^+$ (^{79}Br), 2.8], 262 [M$^+$ (^{81}Br), 3.3], 111 (100). IR ($CDCl_3$): 1795 cm^{-1}. Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56; Found: C, 50.73; H, 6.47.

6-(1-Bromo-1-heptenyl)-tetrahydro-2*H*-2-pyranone (59). General Procedure for Palladium(II)-Catalyzed Cyclization of δ-Allenic Acids (Method B, Table 1, 59 and 60). A suspension of δ-allenic acid **25**, (108 mg, 0.55 mmol), $Pd(OAc)_2$ (12.3 mg, 0.055 mmol), LiBr

(50) Shaw, R. W.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, *24*, 3549.

(239 mg, 2.75 mmol), $Cu(OAc)_2 \cdot H_2O$ (229 mg, 1.15 mmol), and K_2CO_3 (83.4 mg, 0.6 mmol) in acetonitrile (3.66 mL) was stirred at room temperature under an oxygen atmosphere for 1 h. The reaction was then diluted with brine/H_2O, and ether was added. The phases were separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were then washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography (pentane/ether 2:1) to afford **59** in 83% yield (0.13 mg) as a mixture of *Z*- and *E*-isomers (90:10). Pure samples of the *Z*-isomer was obtained by preparative HPLC (pentane/EtOAc; 4:1). (*Z*)-**59**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (dd, J = 6.9, 0.84 Hz, 1H), 4.83 (dd, J = 8.9, 3.9 Hz, 1H), 2.60 (ddd, J = 17.8, 8.8, 6.9 Hz, 1H), 2.50 (ddd, J = 17.8, 6.6, 5.6 Hz, 1H) 2.20 (app q, J = 2.7 Hz, 2H) 1.97 (m, 4H), 1.41 (m, 2H), 1.30 (m, 4H), 0.89 (t, J = 7.0, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 132.4, 124.3, 83.1, 31.4, 30.9, 29.7, 27.8, 27.5, 22.5, 18.1, 14.1. The following NMR data for the *E* isomer were taken from the mixture: (*E*)-**59**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16 (dd, J = 10.3, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 136.9, 124.3, 83.1, 31.2, 30.8, 29.7, 28.8, 27.5, 22.5, 18.7, 14.1. EIMS *m*/*z* 260 [M^+ (^{79}Br), 2.8], 262[M^+ (^{81}Br), 3.3], 111 (100). IR (neat): 1739 cm^{-1}. Anal. Calcd for $C_{12}H_{19}BrO_2$: C, 52.38; H, 6.96; Found: C, 52.28; H, 7.11.

2-(1-Bromo-3-methyl-1-butenyl)-tetrahydrofuran (62). General Procedure for Palladium(II)-Catalyzed Cyclization of γ-Allenic Alcohols (Method A, Table 2, 61−64). The allenic alcohol **29** (200 mg, 1.43 mmol) was added during 14 h with a syringe pump to a stirred solution of $Pd(OAc)_2$ (16.1 mg, 0.07 mmol), 1,4-benzoquinone (386 mg, 3.57 mmol), and LiBr (621 mg, 7.14 mmol) in acetic acid (5.2 mL) at 40 °C. After the reaction was complete (8 h), water and a mixture of ether/pentane (1:2) was added. The phases were separated, and the aqueous phase was extracted two times with ether/pentane (1:2). The combined organic extracts were washed with aqueous NaOH (2M) until the organic layer was pale yellow and then dried ($MgSO_4$). Evaporation of the solvent and silica gel chromatography using pentane/ether (95:5) afforded **62** (217 mg, 70%) as a inseparable mixture of *Z*- and *E*-isomers 88:12; colorless oil. (*Z*)-**62**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (dd, J = 8.9, 1.0 Hz, 1H), 4.41 (ddd, J = 6.9, 5.9, 1.0 Hz, 1H), 3.99 (m, 1H), 3.85 (m, 1H), 2.74 (d septet, J = 8.9, 6.7, Hz, 1H), 1.97 (m, 4H), 1.01 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 126.5, 82.6, 69.2, 31.5, 30.5, 25.8, 21.9, 21.8. The following NMR data for the *E*-isomer were taken from the mixture: (*E*)-**62**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (dd, J = 9.9, 0.5 Hz, 1H), 4.74 (br t, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 126.0, 76.0, 69.2, 31.5, 29.6, 26.7, 23.2, 22.9. EIMS *m*/*z* 218 [M^+ (^{79}Br), 2.1], 220 [M^+ (^{81}Br), 2.1], 139,(100). Anal. Calcd for $C_9H_{15}BrO$: C, 49.33; H, 6.90; Found: C,49.46; H, 7.05.

2-(1-Bromo-3-methyl-1-butenyl)tetrahydro-2*H*-pyran (66). General Procedure for Palladium(II)-Catalyzed Cyclization of δ-Allenic Alcohols (Method B, Table 2, 65-66). δ-Allenic alcohol **32**, (100 mg, 0.65 mmol) was added over 2 h to a suspension of $Pd(OAc)_2$ (14.6 mg, 0.065 mmol), LiBr, (282.3 mg, 3.24 mmol), $Cu(OAc)_2 \cdot H_2O$ (271.2, 1.36 mmol), and K_2CO_3 (107.5 mg, 0.78 mmol) in acetonitrile (4.21 mL) at room temperature under an oxygen atmosphere. The reaction was allowed to stir for an additional 1h and was then diluted with brine/H_2O and ether. The phases were separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were then washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography (pentane/ether 95:5) to afford 106 mg (70%) of **66** as a mixture of *Z*- and *E*-isomers (94:6); colorless oil. A pure sample of the *Z*-isomer was obtained by preparative HPLC (pentane /EtOAc 98:2). (*Z*)-**66**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82 (dd, J = 8.7, 0.9 Hz, 1H), 4.08 (m, 1H), 3.80 (ddd, J = 10.4, 2.1, 0.7 Hz, 1H), 3.51 (m, 1H), 2.75 (d septet, J = 8.7, 6.8 Hz, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.68−1.44 (m, 4H), 1.01 (d, J = 6.8 Hz, 3H) 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 125.6, 81.8, 68.7, 31.2, 30.6, 25.7, 23.4, 21.83, 21.82. The following NMR data for the *E*-isomer were taken from the mixture: (*E*)-**66**: ^{1}H NMR (400 MHz, $CDCl_3$): 4.14 (m, 1H), 3.52 (m, 1H). EIMS *m*/*z* 233 [$M^+ - 1$ (^{79}Br), 40.8], 235 [$M^+ - 1$ (^{81}Br), 33.8], 153 (100). Anal. Calcd for $C_{10}H_{17}BrO$: C, 51.52; H, 7.35; Found: C, 51.62; H, 7.51.

***N*-(*p*-Tolylsulfonyl)-2-(1-bromo-3-ethyl-hept-1-enyl)-pyrrolidine (70). General Procedure for Palladium(II)-Catalyzed Cyclization of γ-Allenic Amides (Method B, Table 3, 4, and 5, 68−81).** A suspension of γ-allenic tosylamide **41** (150 mg, 0.43 mmol), $Pd(OAc)_2$ (9.6 mg, 0.04 mmol), LiBr (186.9 mg, 2.14 mmol), $Cu(OAc)_2$ (179.6, 0.90 mmol), and K_2CO_3 (71.0 mg, 0.51 mmol) in acetonitrile (2.86 mL) was stirred at room temperature under an oxygen atmosphere for 2−5 h. The reaction was then diluted with brine/H_2O, and ether was added. The phases were separated, and the aqueous phase was extracted three times with ether. The combined organic extracts were then washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography (pentane/ether 3:1) to afford 146 mg (80%) of **70** as a mixture of *Z*- and *E*-isomers (89/11); colorless oil. Pure samples of the diastereomeric *E*- and *Z*-isomers were obtained by preparative HPLC (pentane /EtOAc 10:1). (*Z*)-**70**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4, 2H), 5.79 (dd, J = 9.5, 1.1 Hz, $^1/_2$ H), 5.76 (dd, J = 9.5, 1.1 Hz, $^1/_2$ H), 4.40 (m, 1H), 3.47 (m, 1H), 3.33 (m, 1H), 2.44 (m, 1H), 2.42 (s, 3H), 2.05 (m, 1H), 1.88 (m, 1H), 1.80−1.58 (m, 3H), 1.53−1.17 (m, 7H), 0.93−0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, (135.6, 135.5), (134.9, 134.8), 129.5 (2C), (127.9, 127.7, 2C), (127.29, 127.28), (66.1, 66.0), 49.4, 42.7, (34.29, 34.27), (32.14, 32.10), (29.45, 29.30), (27.81, 27.78), (23.9, 23.8), (22.91, 22.88), 21.6, 14.2, (11.8, 11.7). (*E*)-**70**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4, 2H), 5.69 (d, J = 10.6 Hz, $^1/_2$ H), 5.67 (d, J = 10.6 Hz, $^1/_2$ H), 4.75 (m, 1H), 3.60 (m, 1H), 3.39 (m, 1H), 2.44 (m, 1H), 2.42 (s, 3H), 2.05 (m, 1H), 1.88 (m, 1H), 1.80−1.58 (m, 3H), 1.53−1.17 (m, 7H), 0.98 (t, J = 6.9 Hz, $1^1/_2$H), 0.92 (t, J = 6.9 Hz, $1^1/_2$H), 0.87 (t, J = 6.9 Hz, $1^1/_2$H), 0.82 (t, J = 6.9 Hz, $1^1/_2$H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (143.0, 142.9), (139.6, 139.5) (136.6, 136.5), (129.33, 129,30, 2C), (127.9, 127.7), (127.2, 127.1, 2C), 59.4, 49.6, (42.1, 41.9) (34.8, 34.1), (32.8, 32.7), (29.8, 29.4), (28.1, 27.6), 25.27, 23.2, (22.91, 22.88), 21.6, 14.2, (12.0, 11.7). (*E*/*Z*-mixture): IR (neat): 1352, 1159 cm^{-1}. Anal. Calcd for $C_{20}H_{30}BrNO_2S$: C, 56.07; H, 7.06; N, 3.27. Found: C, 56.08; H, 7.23; N, 3.30.

2-Bromo-(π-allyl)palladium Complex (83). The complex **83** was prepared by adding **7** (20 mg, 0.16 mmol) to a red slurry of $PdBr_2(PhCN)_2$ (63 mg, 0.13 mmol) in benzene (5 mL). After 10 min the reaction mixture turned yellow, and the benzene was evaporated. The resulting oil was washed with ether/pentane (1:2) to get rid of benzonitrile. Evaporation of the solvent afforded **83** as a yellow powder in 94% yield (48.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 (t, J = 6.0 Hz, 1H), 3.75 (t, J = 6.0 Hz, 1H), 2.12 (m, 1H), 1.98 (m, 3H), 1.72 (s, 3H), 1.63 (br s, OH), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.1, 91.0, 81.2, 62.5, 31.5, 29.9, 28.3, 25.6.

Reaction of 83 under the Catalytic Conditions with BQ as the Reoxidant. The complex **83** (40 mg, 0.10 mmol) was dissolved in acetic acid (0.4 mL) and treated with LiBr (44.4 mg, 0.51 mmol) and benzoquinone (27.5 mg, 0.255 mmol). The reaction was stirred overnight at 40 °C to give tetrahydrofuran **64** in 72% yield after normal workup (see general procedure for γ-allenic alcohol cyclizations.)

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Supporting Information Available: Details for the preparation and spectroscopic data for compounds **2a**−**6a**, **2b**−**6b**, **7**, **12**, **14**−**21**, **23**−**27**, **29**−**32**, **39**−**43**, **45**−**50**, **52**, **53**, **55**−**58**, **60**, **61**, **63**−**65**, **68**, **69**, **71**−**81**, **84**, and **89**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **2b**, **6b**, **13-20**, **23-32**, **39**, **40**, **42**, **43**, **45**, **47**−**49**, **51**−**53**, **56**, **63**, **72**, **77**, **78**, **83**, **84**, and **89**. This material is available free of charge via the Internet at http://pubs.acs.org.

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