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Palladium-catalyzed intramolecular 1,4-additions to conjugated dienes

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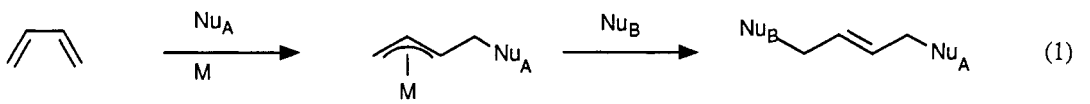
Abstract - Palladium-catalyzed intramolecular 1,4-additions to conjugated dienes have been developed. The reactions were performed in acetone - acetic acid (4 : 1) employing $Pd(OAc)_2$ as the catalyst and *p*-benzoquinone as the oxidant. Intramolecular attack by a heteronucleophile on a (π-diene)palladium intermediate leads to a heterocyclic (π-allyl)palladium species. Attack by a second nucleophile on the π-allyl complex leads to the product. The stereochemistry of the second nucleophilic attack can be controlled by the ligand environment to give overall either cis or trans 1,4-addition across the diene. Two approaches with cyclic dienes were used; one leading to an annulation and another leading to a spirocylization. In the former reaction amides, carboxylic acids and alcohols were used as nucleophiles in the intramolecular reaction. This led to fused pyrrolidines, lactones, and tetrahydrofurans or tetrahydropyrans, respectively. The intramolecular oxyacetoxylation was used for the synthesis of marmeloxides A and B and the intramolecular oxyamination was applied to the synthesis of α- and γ-lycorane. In the spirocyclization, alcohols served as nucleophiles in the intramolecular attack, resulting in stereoselective oxaspirocyclizations.

Regioselective metal-mediated additions to conjugated dienes have attracted considerable interest recently.[1] One advantage with the metal-promoted reactions over classical electrophilic additions to conjugated dienes[2] is that they usually can be directed towards a high 1,2- or 1,4-selectivity. With transition metals a 1,4-selectivity is often obtained and the reason for this selectivity is that the addition to the conjugated diene proceeds via a (π-allyl)metal complex (eq. 1).

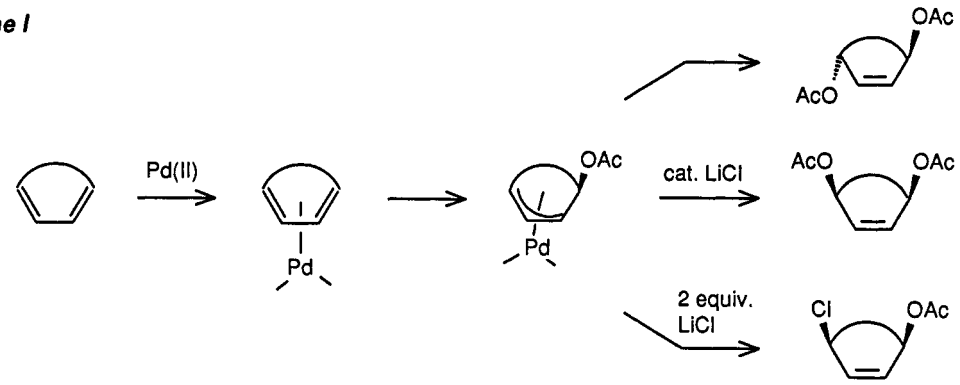


(1)

The aim of our research in this field has been to develop efficient palladium-catalyzed stereo- and regioselective additions to conjugated dienes and to extend these reactions to intramolecular reactions. These reactions are of importance in organic synthesis since the corresponding transformations are difficult to perform by classical methods. In this review I will summarize our recent work on the intramolecular palladium-catalyzed 1,4-oxidations of conjugated dienes. Some applications of these reactions in organic synthesis will also be given.

Our interest in this area emerged from our mechanistic studies on nucleophilic addition to (π-olefin)- and (π-allyl)-palladium complexes.[3] Based on our mechanistic knowledge we were able to develop a number of synthetically important intermolecular 1,4-oxidations of conjugated dienes. These reactions proceed via nucleophilic attack on (π-diene)- and (π-allyl)-palladium complexes. In a number of cases it is possible to control the stereochemistry of the attack by the second nucleophile (Scheme I). Thus, efficient 1,4-diacetoxylations (cis or trans)[4] and 1,4-chloroacetoxylations[5] were developed. These additions have found a number of synthetic applications. In particular, the chloroacetoxylation is synthetically useful since the chloride in the chloroacetates can be substituted either with retention (Pd-catalysis) or with inversion (S_N2 or copper-catalyzed S_N2'). In a subsequent reaction the acetate can serve as a leaving group. Some recent applications include annulation reactions,[6] synthesis of perhydrohistrionicotoxin,[7] pyrrolidinic ant-venom alkaloids,[8] and tropane alkaloids (scopine and pseudoscopine).[9]

Scheme I

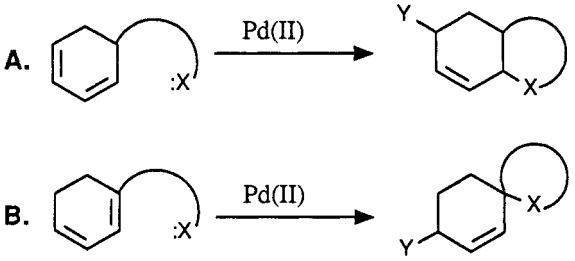


About three years ago we set up some new goals with the aim of extending the palladium-catalyzed 1,4-oxidations of conjugated dienes into an intramolecular variant. We considered two main approaches (Fig. 1). In both cases a nucleophile in a side chain will participate in the oxidation reaction. In the first approach (A) the side chain with the nucleophile is situated in the 5-position of the diene and this leads to a

Fig. 1

NEW GOALS:

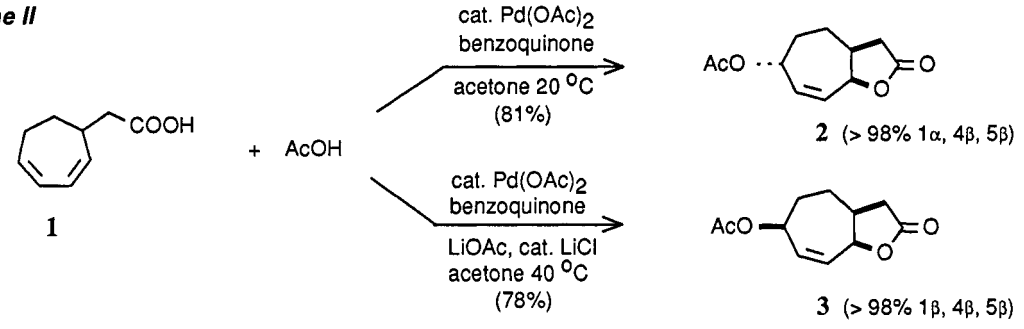
Extend the Pd-catalyzed 1,4-oxidations to intramolecular reactions



type of annulation. In the second approach (B) the side chain is situated in the 1-position of the conjugated diene and this would lead to synthetically useful spirocyclizations.

We first studied the annulation approach using cycloheptadiene derivative **1** with a carboxylic group in the side chain.[10] Palladium-catalyzed oxidation of this diene in acetone-acetic acid (4:1) employing p-benzoquinone as the oxidant afforded lactone **2** in which the addition of the oxygen functions has occurred trans (Scheme II). Now, when the same reaction was performed in the presence of LiOAc and a catalytic

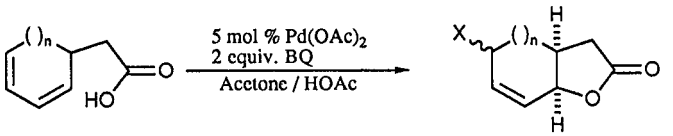
Scheme II



amount of LiCl, an overall cis acetoxylactonization to give **3** took place. The stereoselectivity towards either trans or cis acetoxylactonization was high in each case. It was shown that the reaction proceeds via a lactonic (π-allyl)palladium intermediate[10] and the attack by acetate either cis or trans to this intermediate determines the stereochemistry of the product (*vide infra*). Such a dual stereocontrol in lactonization reactions is unprecedented in the literature and usually only one of the stereochemical pathways can be obtained via a given method.[11]

The reaction works well with cyclohexadiene and cycloheptadiene derivatives (Table 1). At an increased chloride concentration it is also possible to obtain a highly stereoselective cis chlorolactonization. The resulting chlorolactones are synthetically useful since the chloride can be substituted with either retention or inversion by various nucleophiles.[5]

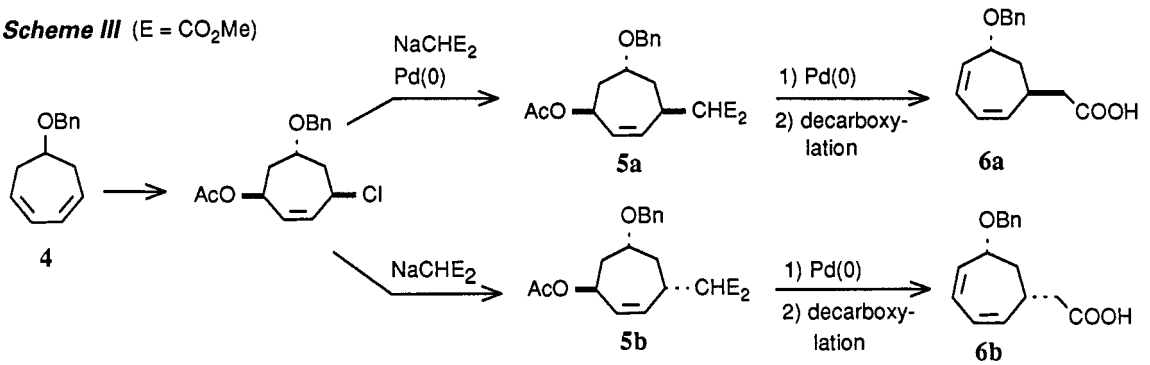
Table I



n =	Cl^-	X =	isol. yield	*cis / trans*
1	-----	AcO	88 %	< 2 / 98
1	0.2 equiv.	AcO	69 %	76 / 24
1	2 equiv.	Cl	85 %	> 98 / 2
2	-----	AcO	81 %	< 2 / 98
2	0.2 equiv.	AcO	78 %	> 98 / 2
2	2 equiv.	Cl	76 %	> 98 / 2

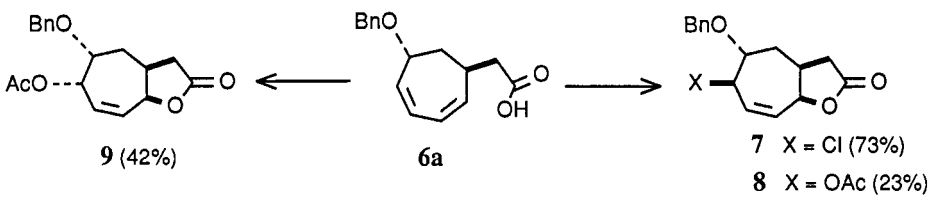
The lactonization reactions were also applied to more substituted systems.[10b] Introduction of a $-CH_2COOH$ group in a substituted diene such as **4** was done by the chloroacetoxylation approach (Scheme III). This allows the preparation of both the *trans*- and *cis*-stereoisomers **6a** and **6b.** Palladium-catalyzed

Scheme III (E = CO_2Me)

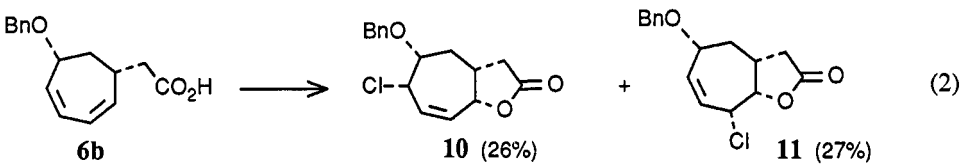


chloroacetoxylation of diene **4** was highly diastereoselective[5,8] and subsequent substitution of the chloride with either retention (Pd(0)) or inversion (S_N2) afforded isomers **5a** and **5b**. Palladium-catalyzed elimination of acetic acid[12] and decarboxylation afforded the requisite starting materials (**6a** and **6b**) for the lactonization reaction.

Scheme IV



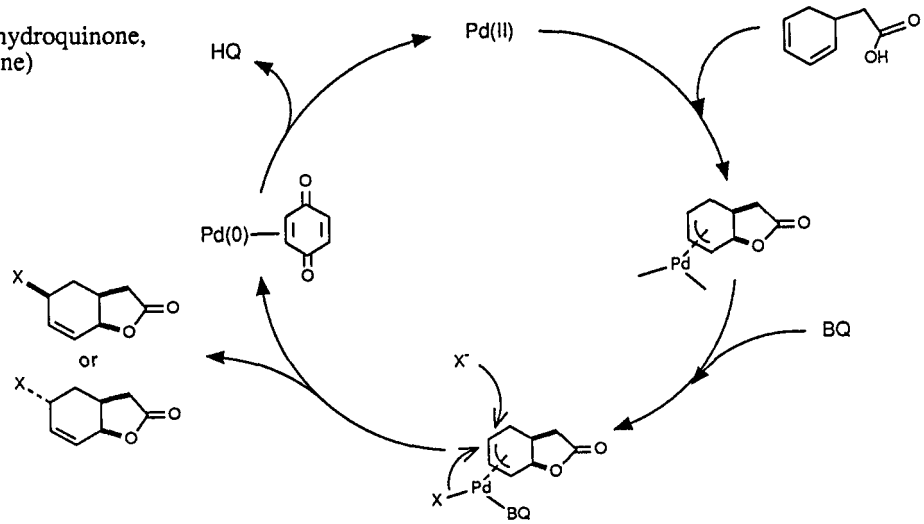
The palladium-catalyzed lactonization reaction of **6a** and **6b** proceeded in moderate to good yield. The chlorolactonization of **6a** afforded **7** in 73% yield (Scheme IV). The corresponding cis acetoxylactonization afforded **8** in low yield. In the absence of any lithium salts the *trans*-acetoxylactonization product was isolated in 42% yield. The corresponding lactonization reaction of **6b** was less regioselective. Thus, cis chlorolactonization of **6b** afforded a 1:1 mixture between lactones **10** and **11** (equation 2).



Pearson's methodology for stereoselective functionalization of 1,3-cycloheptadiene based on (π-dienyl)iron chemistry allows access to *cis*-5,7-disubstituted 1,3-cycloheptadienes (*e.g.* **6b**). These compound were used for lactonization reactions to prepare synthetic intermediates for the synthesis of tylosin and carbomycin[13b,c]. Thus, only lactones corresponding to **10** were obtained. With our methdology the corresponding lactones **8** and **9** are also available.

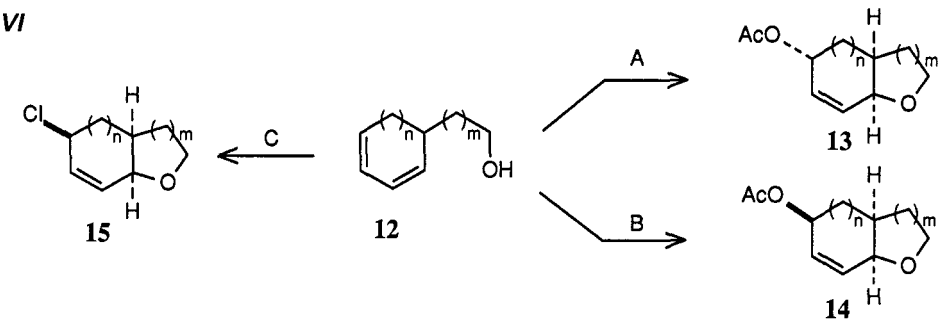
The catalytic cycle for these intramolecular 1,4-oxidations of cyclic dienes is shown in Scheme V. This scheme is also valid for the other palladium-catalyzed intramolecular 1,4-additions described in this review (*vide infra*).

Scheme V (HQ = hydroquinone, BQ = *p*-benzoquinone)



The palladium-catalyzed intramolecular 1,4-additions also worked well with an alcohol in the side chain. In this way fused tetrahydrofurans and tetrahydropyrans were prepared in stereoselective reactions from dienols **12** (Scheme VI).[14] The reactions were performed under three different ligand environments: A (no

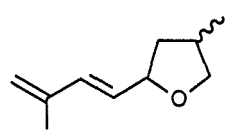
Scheme VI



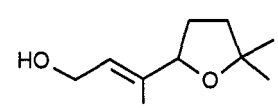
LiCl), B (0.2 equiv. of LiCl) and C (2 equiv. of LiCl). By this slight variation of the LiCl concentration it was possible to direct the reaction towards either trans oxyacetoxylation (**13**), cis oxyacetoxylation (**14**) or cis oxychlorination (**15**). Results from these reactions are given in Tables II and III. These new procedures allow the preparation of fused [6,5], [7,5], [6,6] and [7,6] tetrahydrofurans and tetrahydropyrans. In most cases it was possible to obtain a dual stereocontrol in the intramolecular 1,4-oxyacetoxylation (Table II). In the formation of [6,5] [6,6] and [7,5] fused systems the absence of chloride gave a >98% trans addition. In the presence of chloride a cis addition took place. The preparation of tetrahydrofurans fused to the seven-membered ring proceeded with a very high dual stereocontrol. Thus, oxidation of the diene in the absence of LiCl afforded the cyclized product in 90% yield with >98% trans addition. In the presence of chloride ligands the same diene gave the fused tetrahydrofuran in 87% yield with >98% cis addition.

As can be seen in Table III the cis 1,4-oxychlorination proceeds in good yield and high stereoselectivity for the formation of these ring systems. However, attempts to prepare 4- and 7-membered oxacycles failed. In these cases the intermolecular 1,4-addition was faster than the desired intramolecular reaction.

The intramolecular reaction with alcohols as nucleophiles also works nicely with acyclic dienes. This was demonstrated by applications to the synthesis of naturally occurring tetrahydrofurans. Thus, Marmeloxides A and B and a terpene alcohol from peppermint oil was prepared from acyclic precursors.[15]

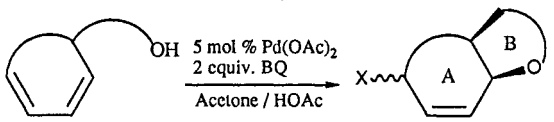


Marmelooxide A(cis) and B(trans)



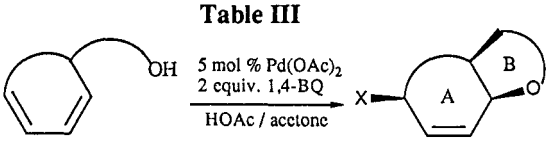
Peppermint oil component

Table II



Ring size A	B	Cl⁻	X =	isol. yield	*cis / trans*
6	5	-------	AcO	87 %	< 2 / 98
6	5	0.2 equiv.	AcO	82 %	91 / 9
6	6	-------	AcO	87 %	< 2 / 98
6	6	0.2 equiv.	AcO	85 %	91 / 9
7	5	-------	AcO	90 %	< 2 / 98
7	5	0.2 equiv.	AcO	87 %	> 98 / 2
7	6	-------	AcO	86 %	25 / 75
7	6	0.2 equiv.	AcO	84 %	> 98 / 2

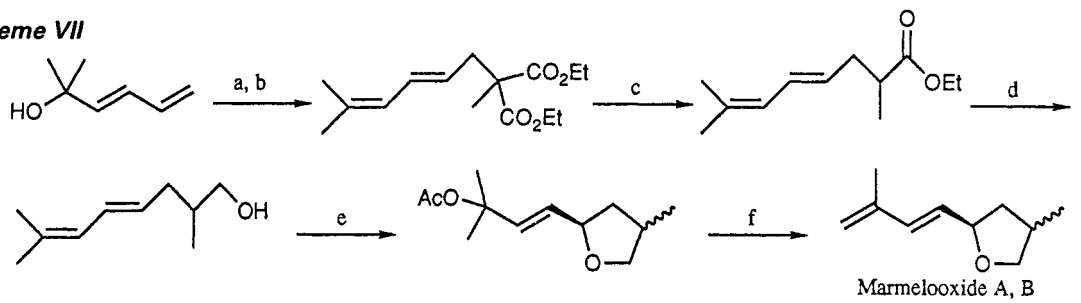
Table III



Ringsize A	B	Cl⁻	X =	isol. yield	*cis / trans*
6	4	2 equiv.	----	-------	-------
6	5	2 equiv.	Cl	91 %	> 98 / 2
6	6	2 equiv.	Cl	89 %	> 98 / 2
6	7	2 equiv.	----	-------	-------
7	5	2 equiv.	Cl	87 %	> 98 / 2
7	6	2 equiv.	Cl	81 %	> 98 / 2

The synthesis of the Marmeloxide A and B is outlined in Scheme VII.

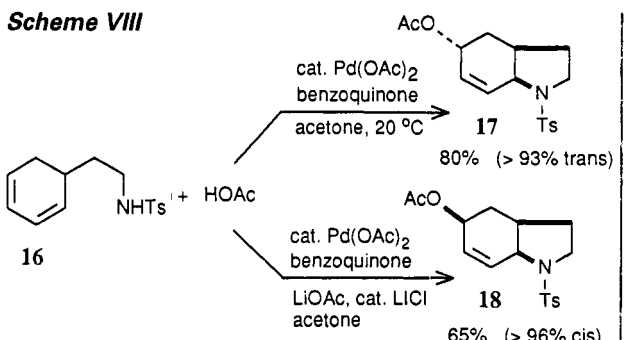
Scheme VII



a. Ac_2O, Pyridine, DMAP, 87 %; b. $NaCHMe(CO_2Et)_2$, $Pd(OAc)_2$, PBu_3, 83 %; c. NaCN, H_2O, 82 %; d. DIBALH, 94 %; e. $Pd(OAc)_2$, 1,4-benzoquinone, 74 %; f. *i*-Bu_3N, $Pd(dba)_2$, dppe, 84 %.

The intramolecular palladium-catalyzed 1,4-oxidations of conjugated dienes were recently extended to the use of amides as nucleophiles.[16] Thus, dienamide **16** underwent stereoselective palladium-catalyzed intramolecular oxyaminations to give hexahydroindole derivatives **17** and **18**. (Scheme VIII). By the usual ligand control it was possible to obtain a dual stereocontrol. The effect of chloride, as previously discussed, is to block the coordination of acetate to the metal in the intermediate (π-allyl)palladium complex (Scheme IX). In the presence of chloride external attack by acetate takes place; in the absence of chloride cis migration of coordinated acetate preferentially occurs. A further increase of the chloride concentration 2 equiv. of LiCl) resulted in a highly stereoselective cis 1,4-chloroamidation. Results of some intramolecular chloroamidation reactions are given in Table IV.

Scheme VIII



Scheme IX

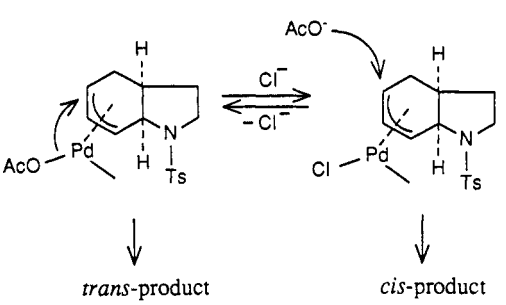
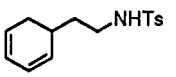
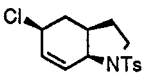
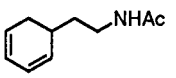
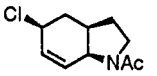
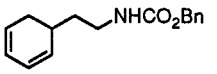
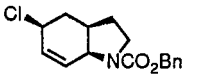
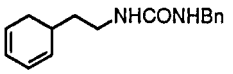
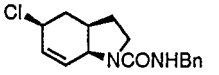
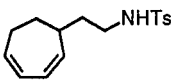
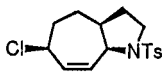


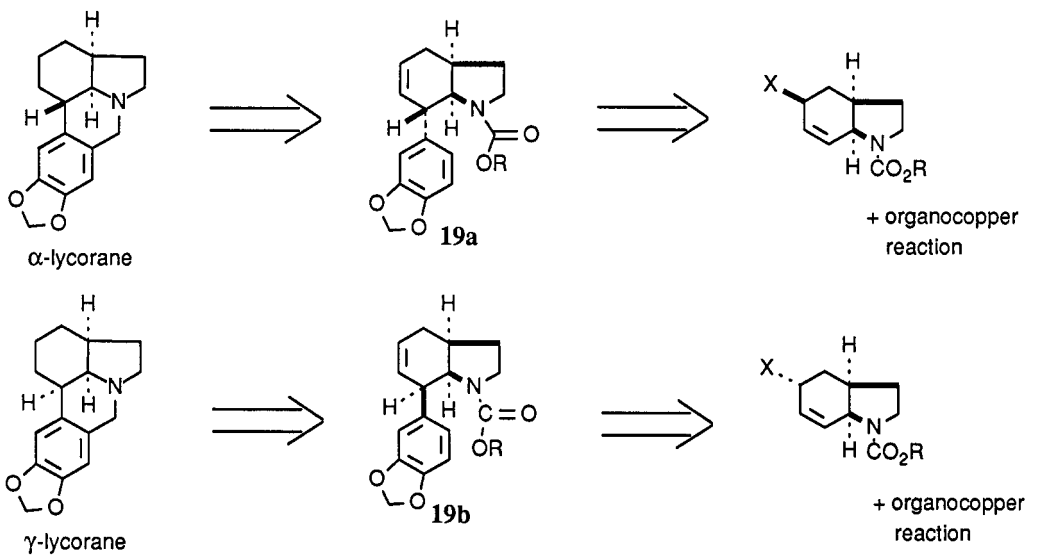
Table IV. Cyclizations of amides using chloride as external nucleophile.

entry	starting material	reaction time (h)	product	% 1,4-*cis* selectivity[a]	% yield
1		8		> 98	90
2		2		> 98	94
3		2		> 98	97
4		2		> 98	88
5		16		> 98	86

[a] Refers to the addition over the diene system. The bridgehead protons are always *cis* to one another.

It occurred to us that the hexahydroindol products formed from intramolecular chloroamidation would be particularly useful for the synthesis of amaryllidaceae alkaloids belonging to the lycorine class.[17] The α- and γ-lycoranes were chosen as synthetic targets and a retrosynthetic analysis of these epimeric alkaloids is shown in Scheme X. The lycoranes would be obtained by a Bischler-Napieralski cyclization of the

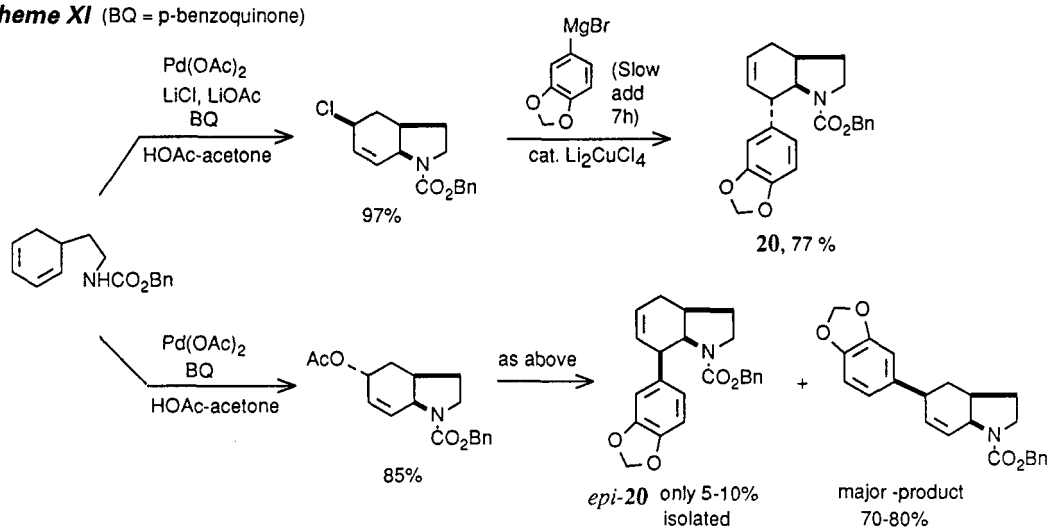
Scheme X Retrosynthetic analysis



stereodefined intermediates **19** followed by reduction of the unsaturated functions. The synthetic intermediates **19** would be available via an organocopper S_N2' displacement of the allylic leaving group in the hexahydroindole products. The latter reactions usually proceed with anti stereochemistry.[18]

The two hexahydroindole derivatives required for the planned synthesis of α- and γ-lycorane were prepared and reacted with the appropriate Grignard reagent in the presence of a copper catalyst (Scheme XI). The cis chloroamidation product reacted smoothly in this copper-catalyzed Grignard reaction, which was optimized towards S_N2' selectivity by slow addition of the Grignard reagent.[18c] Attempts to obtain a high S_N2'

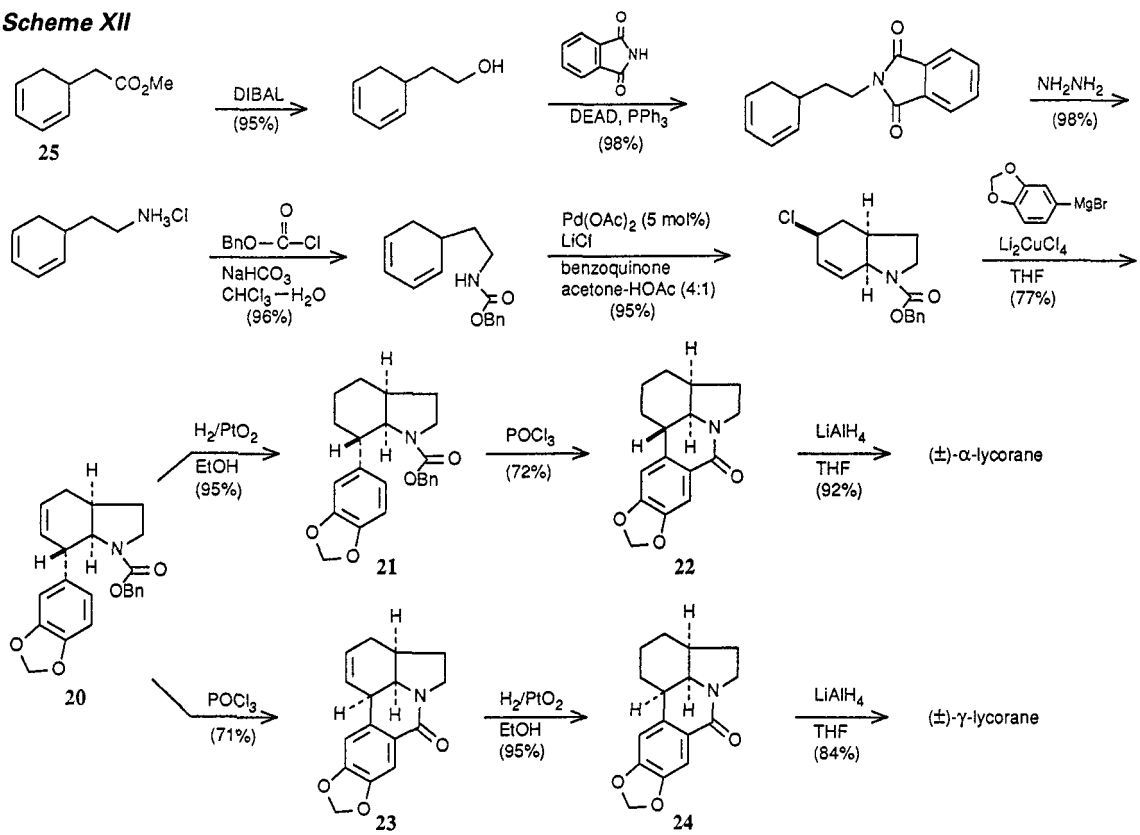
Scheme XI (BQ = p-benzoquinone)



selectivity in the corresponding reaction with the trans acetoxyamidation product were less successful. The major product under all reaction conditions tried were the S_N2-type substitution product. Only about 5-10% of the S_N2' product required for the synthesis of γ-lycorane could be obtained.

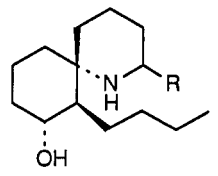
The double bond in **20** was hydrogenated to give **21** followed by a Bischler-Napieralski cyclization to **22**. The latter compound was transformed to α-lycorane via $LiAlH_4$ reduction (Scheme XII).

Scheme XII

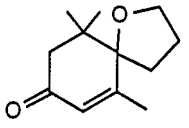


The original strategy to reach the epimeric alkaloid γ-lycorane involved the use of isomer *epi*-**20**. The low yield in the organocopper reaction made this pathway untenable. However, by chance we found a simple route to **23** via intermediate **20**. It turned out that if the order of hydrogenation and cyclization was reversed, a highly stereoselective isomerization took place in the Bischler-Napieralski cyclization. In this way γ-lycorane was obtained efficiently from **20** in a good overall yield. The whole total synthesis of α- and γ-lycorane from diene ester **25** is outlined in Scheme XII.[19] The overall yields of (±)-α- and (±)-γ-lycorane from diene ester **25** were 40 and 36 %, respectively.

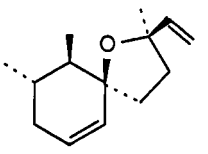
If the side chain containing the nucleophile is situated in the 1-position a synthetically important spirocyclization may occur (*cf.* Figure 1). Several natural products with heterospirocyclic structures are known *e.g.* histrionicotoxins,[20] theaspirone,[21] dihydrotheaspirane,[22] and dactyloxene B.[23] The 1-substituted dienes required for the oxaspirocyclization were prepared according to a recently developed procedure[24] as



histrionicotoxins



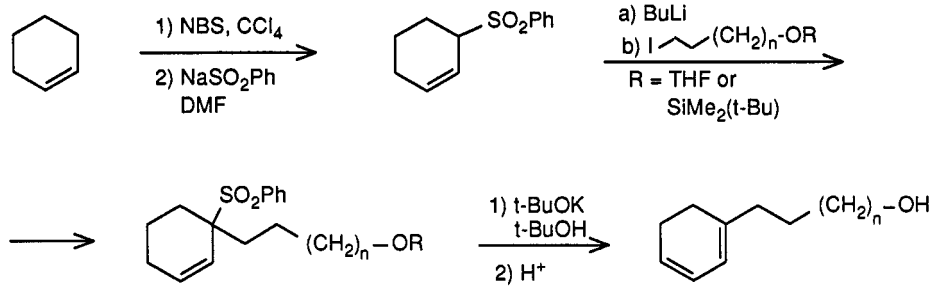
theaspirone



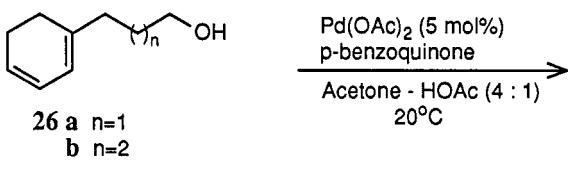
dactyloxene-B

outlined in Scheme XIII. The key step in this procedure is the highly regioselective 1,4-elimination of benzenesulfinic acid. By this procedure a number of 1-(ω-hydroxy)-1,3-cycloalkaldienes were prepared.

Scheme XIII



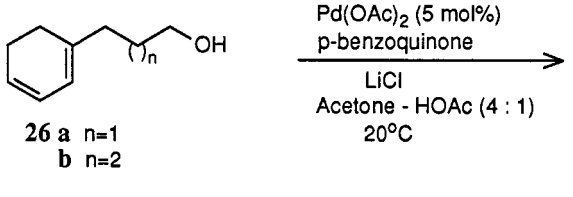
Palladium-catalyzed cyclization of diene alcohol **26a** using the usual reaction conditions in the absence of chloride ligands afforded spiroether **27a** in 86% yield with >98% trans stereochemistry (equation 3).[25] When the oxidation of **26a** was performed in the presence of 1.8 equiv. of LiCl a highly selective cis oxychlorination to give spiroether **28a** occurred (equation 4).



26 a n=1
b n=2

27 a 86% (> 98% trans)
b 82% (> 98% trans)

(3)



26 a n=1
b n=2

28 a 73% (> 99% cis)
b 70% (> 99% cis)

(4)

Extending the hydroxyalkyl chain by one carbon led to six-membered oxaspirocycles. Thus, spirocyclization of **26b** to **27b** and **28b** resulted in comparable yields and stereoselectivities. The corresponding spirocyclizations of cycloheptadiene derivatives were slower than for their six-membered analogues. However, by prolonging the reaction time acceptable yields of the corresponding spirocycles were obtained.

Conclusions. New methods for palladium-catalyzed intramolecular 1,4-additions to conjugated dienes have been developed. A dual stereocontrol in these regioselective additions allow the preparation of a variety of stereodefined heterocyclic compounds. The synthetic utility of these new reactions was demonstrated by the synthesis of several natural products. Recently, we have also developed procedures[26] for the preparation of enantiomerically pure starting materials (*e.g.* **1, 12, 16, 25**) for the intramolecular palladium-catalyzed reactions. Thus, enantiomerically pure products from the annulation reactions shown in the Schemes of this review are now readily available.

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