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Palladium(II)-Catalyzed Intramolecular 1,4-Oxyacyloxylation of Conjugated Dienes. A Stereocontrolled Route to Fused Six-Membered Lactones and Pyrans

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Received December 3, 2003

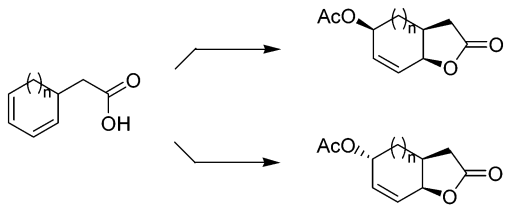
Stereocontrolled palladium(II)-catalyzed intramolecular 1,4-oxidations of dienyl acids and alcohols proceed under mild conditions to give fused δ-lactones and pyrans, respectively, in good yields. The stereo- and regioselectivity was affected by the presence of LiCl and solvent composition (HOAc/acetone). The products obtained were used for further functionalizations using copper(I)-mediated reactions. Stoichiometric reactions of preformed dibutylcyanocuprates with pyrans containing an allylic acetate gave *cis*- and *trans*-fused ring systems with high γ-selectivity and in high yields.

Introduction

The preparation of lactones from alkenoic acids is an important synthetic transformation that is commonly achieved by the iodo- or selenolactonization reactions.[1,2] Efficient methods for lactonization of alkenes, allenes, and dienes via metal activation have also been developed.[3−6]

Palladium(II)-catalyzed 1,4-oxidation of conjugated dienes has proven to be a useful tool in organic synthesis.[7] Stereoselective inter- as well as intramolecular reactions with a variety of nucleophiles have been developed.[8,9] We have previously reported on the efficient 1,4-acetoxylactonization of 1,3-dienes giving five-membered lactones with a dual stereocontrol (Scheme 1).[5,6]

SCHEME 1



Attempts to extend this lactonization reaction to six-membered lactones were unsuccessful and led mainly to 1,4-diacetoxylation of the diene due to a competing intermolecular reaction.[5,10] Intramolecular 1,4-functionalizations of 1,3-dienes having a hydroxyalkyl chain in the 2-position of the diene have been developed in our group during the past years.[11] We were therefore interested in whether the corresponding 2-substituted 1,3-dienes with a carboxylic nucleophile in the side chain would be able to compete with the intermolecular reaction, thereby providing six-membered lactones (eq 1).

In this paper, we report on intramolecular 1,4-oxidations involving different nucleophiles (−COOH and −OH) in the first step of the reaction. The δ-lactones and pyrans

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(1) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev*. **1979**, *8*, 171 and references therein.

(2) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*, CIS, Inc.: Philadelphia, 1994.

(3) For a review on reactions of metal-activated alkenes with heteroatom nucleophiles, see: Hegedus, L. S. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; pp 551−583.

(4) (a) Larock, R. C.; Harrison, L. W.; Hsu, M. H. *J. Org. Chem*. **1984**, *49*, 3662. (b) Pearson, A. J.; Kole, S. L.; Ray, T. *J. Am. Chem. Soc*. **1984**, *106*, 6060. (c) Pearson, A. J.; Khan, M. N. I. *J. Org. Chem*. **1985**, *50*, 5276. (d) Pearson, A. J.; Ray, T. *Tetrahedron* **1985**, *41*, 5765. (e) Ma, S.; Shi, Z. *J. Org. Chem*. **1998**, *63*, 6387. (f) Zenner, J. M.; Larock, R. C. *J. Org. Chem*. **1999**, *64*, 7312.

(5) (a) Bäckvall, J.-E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett*. **1989**, *30*, 137. (b) Bäckvall, J.-E.; Granberg, K. L.; Andersson, P. G.; Gatti, R.; Gogoll, A. *J. Org. Chem*. **1993**, *58*, 5445.

(6) This reaction has also been applied to the synthesis of the natural products paeonilactone A and B: (a) Rönn, M.; Andersson, P. G.; Bäckvall, J.-E. *Acta Chem. Scand*. **1998**, *52*, 524. (b) Jonasson, C.; Rönn, M.; Bäckvall, J.-E. *J. Org. Chem*. **2000**, *65*, 2122.

(7) (a) Bäckvall, J. E. In *Metal-catalyzed Cross-Coupling Reactions*; Stang, P., Diederich, F., Eds.; VCH: Weinheim, 1998; pp 339−385. (b) Harrington, P. J. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, G. A., Wilkinson, G., Eds. (Hegedus, L. S., Vol. Ed.); Pergamon: New York, 1995; Vol. 12, pp 797−904.

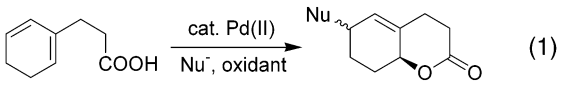
(8) (a) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem*. **1984**, *49*, 4619. (b) Bäckvall, J.-E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc*. **1985**, *107*, 3676. (c) Bäckvall, J.-E.; Vågberg, J. O. *J. Org. Chem*. **1988**, *53*, 5695.

(9) (a) Bäckvall, J.-E.; Andersson, P. G. *J. Am. Chem. Soc*. **1990**, *112*, 3683. (b) Bäckvall, J.-E.; Andersson, P. G. *J. Org. Chem*. **1991**, *56*, 2274. (c) Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **1992**, *114*, 8696. (d) Bäckvall, J.-E.; Andersson, P. G. *J. Am. Chem. Soc*. **1992**, *114*, 6374. (e) Bäckvall, J.-E.; Nilsson, Y. I. M.; Andersson, P. G.; Gatti, R. G. P.; Wu, J. *Tetrahedron Lett*. **1994**, *35*, 5713. (f) Castaño, A. M.; Bäckvall, J.-E. *J. Am. Chem. Soc*. **1995**, *117*, 560. (g) Nilsson, Y. I. M.; Gatti, R. G. P.; Andersson, P. G.; Bäckvall, J.-E. *Tetrahedron* **1996**, *52*, 7511. (h) Castaño, A. M.; Persson, B. A.; Bäckvall, J.-E. *Chem. Eur. J*. **1997**, *3*, 482. (i) Löfstedt, J.; Franzén, J.; Bäckvall, J.-E. *J. Org. Chem*. **2001**, *66*, 8015. (j) Dorange, I.; Löfstedt, J.; Närhi, K.; Franzén, J.; Bäckvall, J.-E. *Chem. Eur. J*. **2003**, *9*, 577.

(10) The increased flexibility of the acid-functionalized tether rendered the lactonization reaction too slow compared to the intermolecular reaction.

(11) (a) Koroleva, E. B.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett*. **1995**, *36*, 5397. (b) Itami, K.; Palmgren, A.; Bäckvall, J.-E. *Tetrahedron Lett*. **1998**, *39*, 1223.

10.1021/jo0357667 CCC: $27.50
Published on Web 04/02/2004



(1)

obtained are highly stereodefined products and are interesting intermediates for further functionalization reactions. Transition-metal-catalyzed reactions of these allylic substrates can lead to *cis*- or *trans*-fused heterocyclic ring systems. Pd(0)-catalyzed hydrogenolysis and Cu(I)-catalyzed S_N2' substitution reactions of the 1,4-oxidation products provide access to stereodefined *cis*- and *trans*-fused ring systems, with the concomitant introduction of a hydrogen or an extra carbon substituent at the bridgehead position.

Results and Discussion

The requisite starting materials were prepared by a palladium-catalyzed Negishi cross-coupling[12a] of the diene triflates[13] **1a**−**c** with the zinc reagents from ethyl 3-iodopropionate or ethyl 4-iodobutyrate, followed by either hydrolysis or reduction. This afforded the corresponding carboxylic acids **3a**−**c** or alcohols **4a**−**c**, respectively (Scheme 2).

The corresponding aromatic derivatives **3d**,**e** were prepared in a similar way (Scheme 3). Palladium-catalyzed coupling of diene triflates **1a**,**b** with the zinc derivative **5**, obtained from the methyl ester of 2-bromobenzoic acid and activated zinc,[12b,c] gave **2e**,**f**, which after hydrolysis afforded **3d**,**e**.

Triflate **1d** was prepared from (*R*)-(−)-carvone and then used to prepare diene acid **3f** employing the aforementioned procedure (Scheme 4). A direct pathway to **4d**[11b] would be by reduction of ester **2e**. Due to the relative instability of **2e**, another method was chosen. The benzylic diene alcohol **4d** was prepared instead by a nickel-catalyzed cross-coupling[14] of 2-cyclohexadienyl diphenyl phosphate **6**[15] with the Grignard reagent **7**, derived from (2-bromobenzyl)-*tert*-butyldimethylsilyl ether, and subsequent hydrolysis of silyl ether **8** with TBAF (Scheme 5).

A. Palladium(II)-Catalyzed Intramolecular 1,4-Diacyloxylation Reactions. Palladium-catalyzed oxidation of diene acid **3a** in acetic acid/acetone 1:4 in the presence of LiOAc and LiCl, using catalytic *p*-benzoquinone (BQ) and stoichiometric MnO_2 as the oxidant, afforded the fused lactone **9** in 90% yield and with a high degree of stereocontrol in the addition across the diene (Table 1, entry 1).[16] Surprisingly, the regioselectivity was poor, and a 75:25 mixture of 1,4- and 1,2-addition products **9a** and **9b** was obtained.[17]

The palladium(II)-catalyzed oxidation of 1,3-dienes is usually highly regioselective toward formation of 1,4-addition product.[5,7−9,18] Factors such as the electronic nature of the first nucleophile and the conformation of the (π-allyl)palladium intermediate have been shown to be important for this selectivity.[18] The choice of solvent has also been demonstrated to affect the regioselectivity in related cyclizations.[19] To investigate if the latter factor would also influence the regioselectivity in this system, a short solvent study was made using **3a** as a model substrate.[20] By varying the solvent composition from 100% HOAc to HOAc/acetone 1:6,[21] a trend in regioselectivity was observed. The best selectivity favoring formation of the 1,4-addition product was obtained with HOAc/acetone 1:4. Therefore, this solvent system was used for all reactions.

It is well documented that the role of the chloride ion is to block the coordination of acetate to palladium and thereby favor external attack of acetate.[7] When the reaction was carried out without added LiOAc and LiCl, *trans*-product **9c** was produced as a single isomer (entry 2).[16,22] Thus, the internal acetate migration is more selective toward 1,4-addition product than the external attack by the acetate nucleophile (Figure 1, **A**). It is known that this *cis* migration occurs via a σ-allyl intermediate.[7,8a,23] There would be release of strain in the (σ-allyl)palladium intermediate **B** (Figure 1), which has a more flexible double bond compared to the other possible σ-allyl (with the double bond connected to the bridgehead position). Thus, formation of intermediate **B** would favor the 1,4-addition product.

Lactonization of the seven-membered ring **3b**, in the presence of LiOAc and LiCl, gave results similar to those for the six-membered ring but with lower regioselectivity, providing regioisomeric lactones **10a** and **10b** in a ratio of 63:37 in 90% combined yield.[16] When the reaction was run in the absence of LiCl and with only 1 equiv of LiOAc, the regioselectivity was much improved and **10a** and **10b** were obtained in a ratio 91:9 in 98% combined yield (entry 3). When the reaction was carried out without added LiOAc and LiCl to obtain the *trans*-1,4-addition product, the *cis*/*trans* selectivity was not so good, and a mixture of four isomers of **10** (*cis* and *trans*; 1,2- and 1,4-addition) was obtained with >90% overall *cis* selectivity.[16] A lower *trans* selectivity for seven-membered rings compared to six-membered rings has previously been observed in the 1,4-diacetoxylation of dienes and was explained by conformational differences in the (σ-allyl)-palladium intermediates, with *cis* migration being unfavored for the seven-membered ring.[8a] Upon addition of 2.5 mol % sulfuric acid, to slow the rate of the external attack, and with *p*-benzoquinone as the stoichiometric

(12) (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (b) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (c) Palmgren, A.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 3764.

(13) (a) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979. (b) Karlström, A. S. E.; Rönn, M.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 2517.

(14) Karlström, A. S. E.; Itami, K.; Bäckvall, J.-E. *J. Org. Chem.* **1999**, *64*, 1745.

(15) Blotny, G.; Pollack, R. M. *Synthesis* **1988**, 109.

(16) The relative configuration of compounds **9a**, **10a**, **11a**, **12**, **13a**, **16a**, and **18a** were unambiguously assigned by NOE experiments. On the basis of these data, the relative stereochemistry of the remaining compounds (**9b**,**c**, **10b**, **11b**,**c**, **13b**,**c**, **16b**, and **18b**) were readily assigned from their ^{1}H NMR spectra.

(17) This is one of the rare exceptions to the very high 1,4-regioselectivity usually obtained in the palladium-catalyzed oxidations of conjugated dienes; see refs 5b and 11a.

(18) (a) Szabó, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7818. (b) Szabó, K. J. *Chem. Eur. J.* **1997**, *3*, 592.

(19) Andersson, P. G.; Aranyos, A. *Tetrahedron Lett.* **1994**, *35*, 4441.

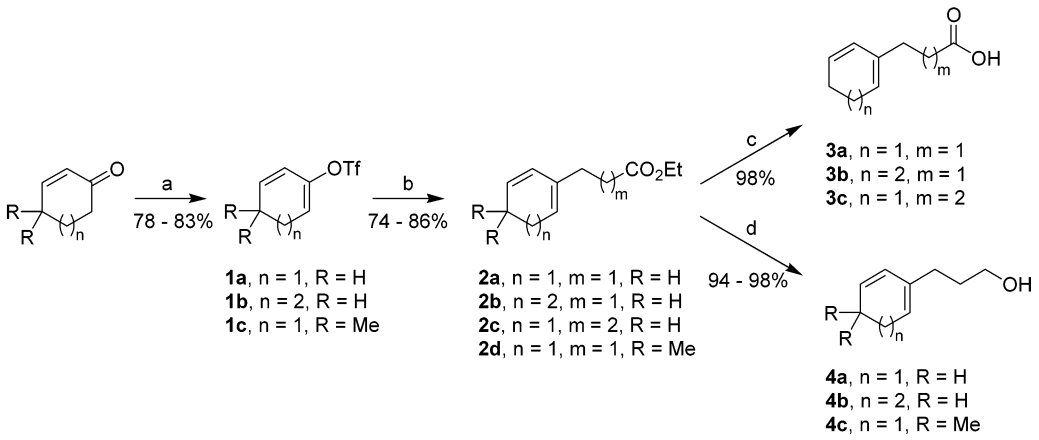
(20) Control experiments showed that no allylic transposition in the products occurred under the reaction conditions; see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

(21) This corresponds to 7.5 equiv of HOAc to substrate.

(22) For a mechanistic discussion, and an explanation of the stereoselectivity, see refs 5b and 8a.

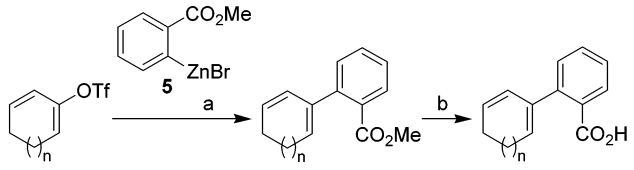
(23) Grennberg, H.; Langer, V.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1190.

SCHEME 2[a]



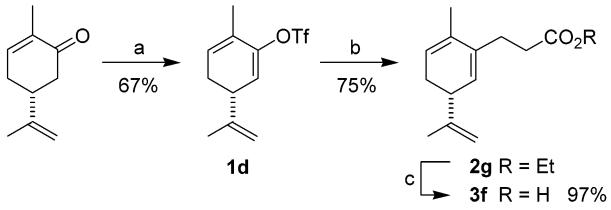
[a] Reagents and conditions: (a) LDA, −78 °C, then $PhNTf_2$; (b) $IZn(CH_2)_{m+1}CO_2Et$, 5% $Pd(PPh_3)_4$, benzene−DMA, 60 °C; (c) LiOH, $THF-H_2O$ 4:1, rt; (d) $LiAlH_4$, Et_2O, 0 °C → rt.

SCHEME 3[a]



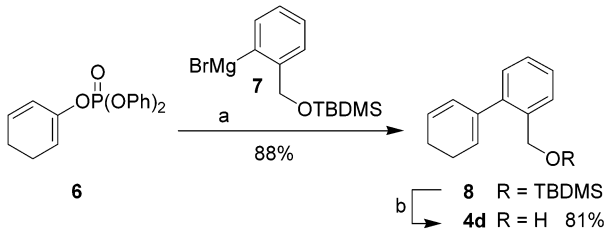
[a] Reagents and conditions: (a) **5**, 5% $Pd(PPh_3)_4$, THF, 55 °C; (b) NaOH, $MeOH-H_2O$ 4:1, reflux.

SCHEME 4[a]



[a] Reagents and conditions: (a) LDA, −78 °C, then $PhNTf_2$; (b) $IZn(CH_2)_2CO_2Et$, 5% $Pd(PPh_3)_4$, benzene−DMA, 60 °C; (c) LiOH, $THF-H_2O$ 4:1, rt.

SCHEME 5[a]



[a] Reagents and conditions: (a) **7**, $NiCl_2$(dppe), Et_2O, 0 °C; (b) TBAF, THF, rt.

oxidant, slightly improved results were obtained. A mixture of only three isomers was isolated, containing not more than 30% of the *trans*-1,4-addition product.

In contrast to substrates **3a** and **3b**, the aromatic derivative **3d** gave a completely regioselective *cis* addition with formation of the 1,4-addition product only (entry 4). However, a significant amount of hydrolyzed product **11b** was also formed under the reaction conditions. This is not a crucial problem, as the alcohol easily can be transformed into the acetate **11a**. Hydrolysis did not occur when the reaction was performed without LiOAc and LiCl, and the *trans* product **11c**[16] was isolated as a single isomer in 47% yield (entry 5). Substrate **3d** is slightly unstable and aromatizes easily during the reaction, which accounts for the low yields. The seven-membered aromatic analogue **3e** gave the *cis*-1,4-addition product **12** only and in 63% yield when the reaction was run chloride-free and with a 2 M LiOAc concentration (entry 6).

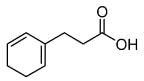
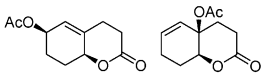
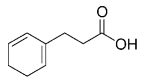
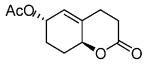
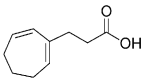
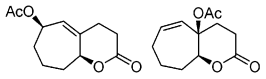
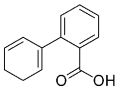
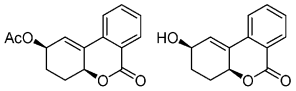
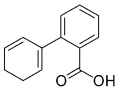
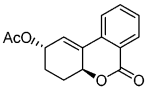
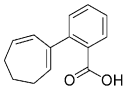
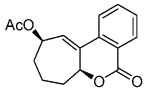
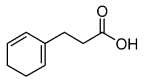
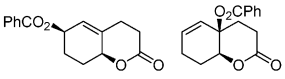
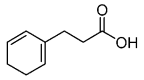
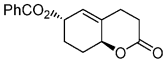
Applying the chloride- and acetate-free conditions to substrate **3c,** with a longer carbon chain, led to no ring-closed product, but instead, the diacetate was formed. This shows that the formation of a seven-membered lactone ring by intramolecular attack of the carboxylic acid on the diene is slower than intermolecular attack by acetate.

Carboxylic acids other than acetic acid can also be used as the external nucleophile, as is illustrated in entries 7 and 8. Cyclization of substrate **3a** in the presence of 1 equiv of benzoic acid and 4 equiv of lithium benzoate and a catalytic amount of LiCl in acetone resulted in the formation of *cis*-1,4-product **13a**, together with a small amount of the corresponding *cis*-1,2-product **13b** (ratio 81:19, 58% yield). The use of 5 equiv of benzoic acid in the absence of any lithium salts afforded the *trans*-1,4-product **13c** as the only isomer in 56% yield.

Cyclization of the carvone derivative **3f** gave a complex mixture of isomers and aromatized byproducts from which lactone **14** was isolated in 23% yield (Scheme 6).[16] It is interesting to note, however, that the *cis*-1,4-addition occurs on the same face as that of the isopropenyl group, giving an *all-cis* relative configuration of the substituents on the cyclohexenyl ring. This indicates that palladium is primarily coordinating to the less sterically hindered face of the diene. Carrying out the reaction under chloride- and acetate-free conditions gave lactone **14** in a mixture with (at least) three isomers in 11% combined yield.

Interestingly, when **3a** was cyclized without LiOAc but with an excess of LiCl (2.0 equiv), a complex mixture of

TABLE 1. Intramolecular 1,4-Oxidations with Carboxylic Acids[a]

entry	diene	LiOAc (equiv.)	LiCl (equiv.)	time (h)[b]	product	yield (%)[c]	Stereo-chem.[d]
1	 **3a**	2	0.2	12+24	 **9a** **9b** (75 : 25)	90	>98% *cis*
2	 **3a**	-	-	12+24	 **9c**	53	>98% *trans*
3[e]	 **3b**	1	-	36	 **10a** **10b** (91 : 9)	98	>98% *cis*
4[f]	 **3d**	2	0.5	12+12	 **11a** **11b** (55 : 45)	50	*cis/trans* 97:3
5[f]	 **3d**	-	-	12+12	 **11c**	47	>98% *trans*
6[e]	 **3e**	8.6 (2M)	-	36	 **12**	63	>98% *cis*
7[g]	 **3a**	-	0.2	12+48	 **13a** **13b** (81 : 19)	58	>98% *cis*
8[h]	 **3a**	-	-	12+12	 **13c**	56	>98% *trans*

[a] All reactions were performed on a 100 mg scale. Reaction conditions: the substrate was dissolved in 0.5 mL of HOAc/acetone 1:4 and added during 12 h to a solution of $Pd(OAc)_2$ (5 mol %), BQ (20−25 mol %), LiOAc and LiCl (if necessary), and MnO_2 (1.2 equiv) in 1.5 mL of HOAc/ acetone 1:4 at rt. After complete addition, the reaction mixture was stirred for an additional time. [b] Addition time of the substrate and additional stirring time. [c] Isolated yields. [d] Determined by ^1H NMR spectroscopy. [e] Reaction was performed at 40 °C. The substrate was added at once. [f] With 10 mol % $Pd(OAc)_2$ and 2 equiv of BQ instead of MnO_2. [g] With 1 equiv of $PhCO_2H$ and 4 equiv of $PhCO_2Li$ in 3 mL of acetone. [h] With 5 equiv of $PhCO_2H$ in 3 mL of acetone.

isomers was obtained where the main product came from external attack by acetate. None of the expected allylic chloride from external nucleophilic attack by chloride[5b,8b] on the (π-allyl)palladium intermediate was observed. The same result was also obtained with the seven-membered ring **3b**.

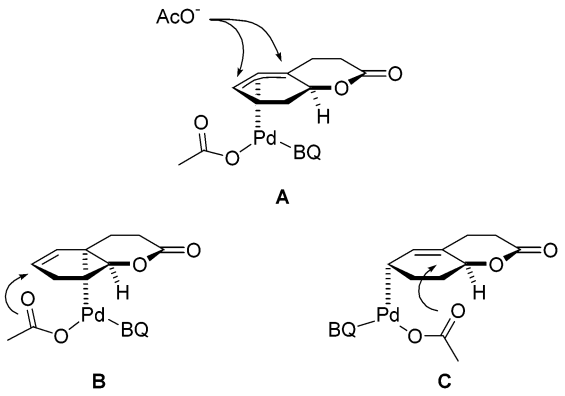
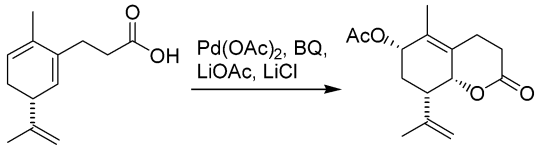


FIGURE 1.

SCHEME 6. Cyclization of Carvone Derivative 3f



B. Palladium(II)-Catalyzed Intramolecular 1,4-Alkoxyacyloxylation Reactions. Intramolecular 1,4-oxidation reactions, with a hydroxyalkyl chain in the 2-position of a 1,3-diene, have recently been reported.[11] The oxidation of diene alcohol **4a**[11a] was difficult to reproduce, and the previously published results could not be obtained. The reaction proved sensitive to the acetate concentration, and both **15a** and **15b** were formed with small amounts of the other diastereomer. For that reason, stoichiometric BQ was used as the oxidant instead of MnO_2, thereby avoiding the formation of $Mn(OAc)_2$ under the acetate-free reaction conditions that are necessary for the *trans* products. To obtain *cis*-addition product **15a**, a high acetate concentration was needed, and running the reaction with LiCl and 3 M LiOAc afforded **15a** as the major product (*cis*/*trans* = 80:20) (Table 2, entry 1). In the absence of chloride and acetate, *trans*-addition product **15b** was obtained in good selectivity (*cis*/*trans* = 5:95) (entry 2). For these reactions, the use of HOAc as the solvent proved superior to mixtures of HOAc and acetone.

Diene alcohol **4c** reacted much slower than **4a**. Without added LiOAc, a very slow reaction (reaction time 3 days) gave regioisomers **16a** and **16b** in a ratio 46:54 (entry 3). Acetic acid/acetone 1:4 had to be used as the solvent here to obtain the best selectivity toward 1,4-addition product. The addition of chloride and acetate did not lead to the formation of the 1,4-*cis*-addition product, and the diacetate was isolated instead. In the presence of a catalytic amount of LiCl and without LiOAc, small amounts of the diacetate and the Diels−Alder product were observed.

Oxidation of the seven-membered ring **4b** gave compound **17** in 69% yield with high stereoselectivity (>98% 1,4-*cis*-addition) when the reaction was run with 2 M LiOAc, at 40 °C. The seven-membered ring substrate **4b** gave *cis* addition over the diene even at lower concentrations of LiOAc (cf. lactone **10a**, entry 3 in Table 1), but the high concentration was needed to suppress formation of the 1,2-oxidation product (entry 4).

The aromatic six-membered ring analogue **4d**[11b] cyclized in 90% yield to selectively give the 1,4-*cis*-addition product **18a** (*cis*/*trans* = 88:12) with LiCl and 2.5 M LiOAc (entry 5). Under chloride- and acetate-free conditions, **4d** cyclized in 80% yield to predominantly give 1,4-*trans*-addition product **18b** (*cis*/*trans* = 20:80) (entry 6). In both cases only the 1,4-oxidation product was observed.

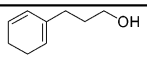
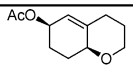
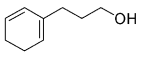
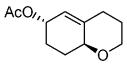
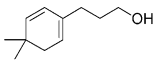
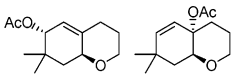
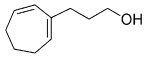
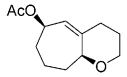
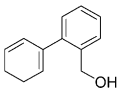
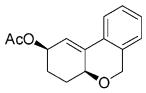
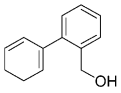
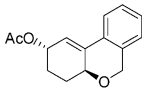
The stereoselectivity for the intramolecular alkoxyacyloxylation reactions was slightly lower compared to the analogous diacyloxylation reactions (vide supra) as all products (except for the seven-membered rings) were obtained together with small amounts of the other stereoisomer. A possible explanation could be that the methylene hydrogen atoms next to the oxygen interfere with palladium and thereby hinder the *cis* migration. The external attack, leading to the *cis* product, would then compete with the retarded *cis* migration and give the unwanted stereoisomer. This, on the other hand, would not explain why the *trans* product is formed even in the presence of LiCl, which usually efficiently blocks the *cis* migration.

C. Attempted Palladium(II)-Catalyzed 1,4-Amidoacetoxylation Reactions. Amides **19** and **20** were prepared in a few steps from dienyl alcohol **4b** (Scheme 7). Mesylation of alcohol **4b** followed by reaction with sodium tosylamide gave tosylamide **19**. Mesylation of **4b** followed by Gabriel synthesis gave the primary amine, which was acylated with benzylchloroformate to give carbamate **20**. Substrates **19** and **20** were subjected to the oxidation conditions as used for the alcohols, but the ring-closed products **21** and **22** were not formed (Scheme 7). Instead, products from intermolecular attack were observed, indicating that amides are very weak nucleophiles and cannot compete with acetate in this reaction. This result is surprising when compared to earlier related work on 1,4-oxidation reactions: with an amide functionality on a tether in the 5-position of the 1,3-diene, the ring-closed products could be obtained in usually more than 85% yield using the same reaction conditions.[9a] In those reactions, five-membered rings were formed, however, with the nucleophile in closer proximity to the diene. In the reaction discussed here, the formation of the diacetate products when using amide nucleophiles is remarkable, since only traces of these products are formed in the oxidation reactions with carboxylic acids and alcohols forming six-membered rings (vide supra).

D. Synthetic Applications: Palladium(0)-Catalyzed Hydrogenolysis Reactions. The stereodefined allylic products, obtained by intramolecular 1,4-oxidation reactions as shown before, are interesting substrates from a synthetic point of view. Tsuji et al. have reported on the Pd(0)-catalyzed hydrogenolysis of allylic formate or acetate esters[24] and applied this to the synthesis of *cis*- or *trans*-fused hydrindan and decalin systems, as well as the synthesis of steroids.[25] The reaction is usually highly regio- and stereospecific. Formation of a (π-allyl)-palladium formate complex from a formate ester proceeds with inversion of configuration. After rearrangement to a (σ-allyl)palladium formate complex, a concerted process

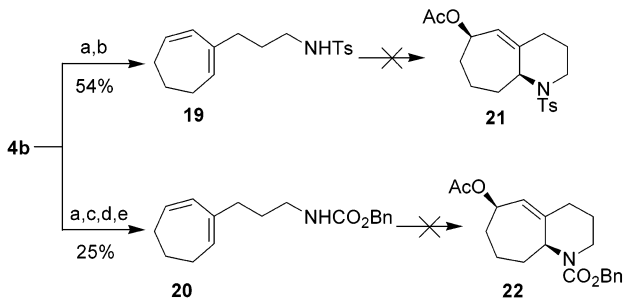
(24) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.
(25) (a) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1993**, *49*, 5483.

TABLE 2. Intramolecular 1,4-Oxidations with Alcohols[a]

entry	diene	LiOAc (equiv.)	LiCl (equiv.)	time (h)[b]	product	yield (%)[c]	Stereo-chem.[d]
1	 **4a**	10.5 (3 *M*)	0.3	8+12	 **15a**	42	*cis/trans* 80:20
2	 **4a**	-	-	8+12	 **15b**	56	*cis/trans* 5:95
3[e]	 **4c**	-	-	8+72	 **16a 16b** (46 : 54)	70	>98% *trans*
4[f]	 **4b**	7.5 (2 *M*)	-	36	 **17**	69	>98% *cis*
5	 **4d**	14 (2.5 *M*)	0.3	8+8	 **18a**	90	*cis/trans* 88:12
6	 **4d**	-	-	8+8	 **18b**	80	*cis/trans* 20:80

[a] All reactions were performed on a 100 mg scale. Reaction conditions: the substrate was dissolved in 0.5 mL of HOAc and added during 8 h to a solution of $Pd(OAc)_2$ (10 mol %), BQ (2 equiv), and LiOAc and LiCl (if necessary) in 2.5 mL of HOAc at rt. After complete addition, the reaction mixture was stirred for an additional time. [b] Addition time of the substrate and additional stirring time. [c] Isolated yields. [d] Determined by ^1H NMR spectroscopy. [e] In 2.5 mL of HOAc/acetone 1:4. [f] Reaction was performed at 40 °C. The substrate was added at once.

SCHEME 7. Attempted 1,4-Oxidation Reactions with Dienyl Amides[a]

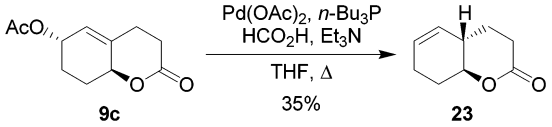


[a] Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, then rt; (b) TsNHNa, DMF, rt; (c) potassium phthalimide, KI, DMF, rt; (d) H_2NNH_2, EtOH, rt then 40 °C; (e) $BnCO_2Cl$, NaOH, THF−H_2O 2:1, 0 °C, then rt.

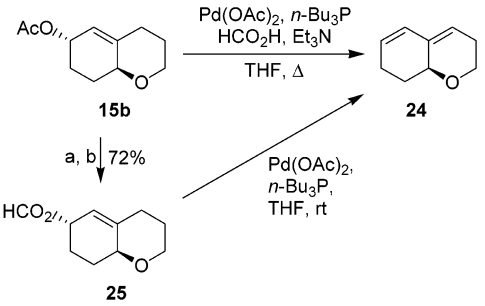
takes place with decarboxylation and hydride transfer to the most substituted side of the allyl system. The hydride attack comes from the same side as palladium and gives the final product with overall inversion. The same reaction can be done with an allylic acetate ester if formic acid is employed as the reducing agent. The use of an allylic formate ester or formic acid as the hydride source is essential for the high regioselectivity. Another factor influencing the regioselectivity is the choice of the ligand, where the use of tri-*n*-butylphosphine is reported to be superior to other phosphines.

In initial experiments, allylic lactone **9c** was used with ammonium formate as the reducing agent in refluxing THF. We found that 1 equiv of tri-*n*-butylphosphine, as reported by Tsuji, did not reduce $Pd(OAc)_2$ to render the active catalyst, and 4 equiv of phosphine was needed. Under these conditions, the desired *trans*-fused product **23** was obtained in only 35% yield (according ^1H NMR) together with products formed from opening of the lactone ring (Scheme 8). Since the two leaving groups apparently show similar reactivity, it was necessary to discriminate between them, and we planned to prepare the formate ester. However, during hydrolysis of the allylic acetate, the lactone was hydrolyzed too. Relacton-

SCHEME 8. Pd(0)-Catalyzed Hydrogenolysis Reaction on Lactone

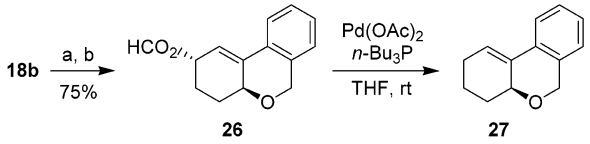


SCHEME 9[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, rt; (b) HCO_2H, Ac_2O, pyridine, 0 °C, then rt.

SCHEME 10[a]



[a] Reagents and conditions: (a) K_2CO_3, MeOH, rt; (b) HCO_2H, Ac_2O, pyridine, 0 °C, then rt.

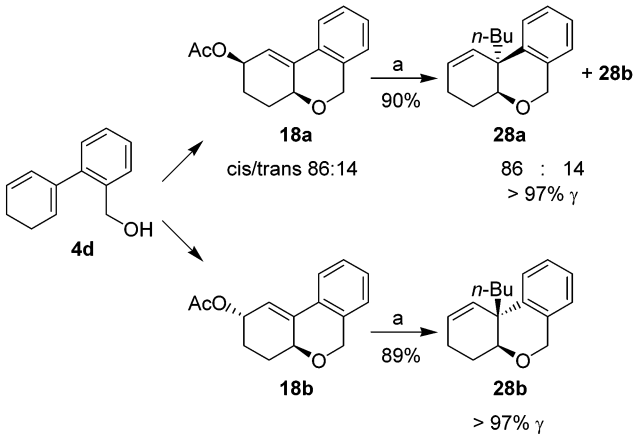
ization proved difficult and the formate ester could not be obtained.

We turned our attention to the allylic pyrans instead, which contain only one good leaving group (Scheme 9). Applying the same reaction conditions as before to pyran **15b** resulted in clean formation of the undesired product diene **24**, probably formed by β-hydride elimination from the more stable intermediate (σ-allyl)palladium complex with palladium attached to the higher substituted carbon. The more reactive formate ester **25** was then prepared and used as the substrate in THF at room temperature. Once more, the formation of diene **24** was observed.

Finally, the aromatic analogue **26**, prepared from **18b**, was subjected to the hydrogenolysis reaction. Unfortunately, formate ester **27** afforded the wrong regioisomer, olefin **27**, having the double bond conjugated with the aromatic ring (Scheme 10). This result indicates that the reaction also in this case proceeds via the more stable (σ-allyl)palladium complex, from which the hydride will be delivered to the least substituted side of the allyl system.

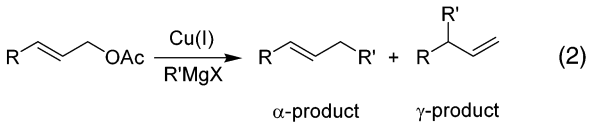
E. Synthetic Applications: Copper(I)-Mediated Substitution Reactions. Another way to functionalize the products from the 1,4-oxidation reactions discussed here is by organocopper S_N2'-substitution reactions using Grignard reagents. This type of reaction has previously been studied in our group.[26] By careful choice of the copper(I) catalyst, the reaction temperature, the solvent,

SCHEME 11. Copper(I)-Mediated Substitution Reactions on Acetates 18a,b[a]



[a] Reagents and conditions: (a) n-$Bu_2Cu(CN)(MgBr)_2$, Et_2O, 0 °C.

and the addition time of the Grignard reagent, the reaction can be directed to either α- or γ-product[26] (eq 2).



(2)

The reaction proceeds by γ-selective oxidative addition of the allylic acetate to the copper species with inversion of configuration, followed by a reductive elimination. Dependent on the reaction conditions, the reductive elimination can be either fast (formation of γ-product) or slow (formation of α-product). In this step, the configuration is retained, and the overall process hence takes place with inversion of the configuration. A regioselective γ-substitution reaction is most interesting with respect to our substrates, since it will give similar *cis*- or *trans*-fused ring systems as discussed before, but with an extra carbon substituent at the bridgehead position, thus generating highly defined chiral quaternary centers. Therefore, stoichiometric reactions with a preformed dialkyl cyanocuprate in ether at 0 °C should give the γ-product selectively.[27] Indeed, applying these conditions to allylic pyrans **18a**,**b** selectively gave the γ-products, and **28a**,**b** were obtained in high isolated yields (Scheme 11).

Thus, a two-step reaction sequence applied to dienyl alcohols as demonstrated here gives easy access to fused ring systems with a highly defined configuration. The control of the stereoselectivity in the palladium-catalyzed oxidation reaction and the overall inversion in the copper-mediated S_N2' substitution reaction makes the synthesis of these ring systems possible with predictable stereochemistry. Allylic *cis*-acetates will lead to the *cis*-fused ring systems, while *trans*-acetates will lead to the *trans*-fused ring systems.

The stoichiometric reactions of a dialkylcyanocuprate with allylic lactone **9c** gave products formed by opening of the lactone ring. A leaving group more reactive than

(26) (a) Bäckvall, J.-E.; Sellén, M. *J. Chem. Soc., Chem. Commun.* **1987**, 827. (b) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615. (c) Persson, E. S. M.; van Klaveren, M.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Chem. Eur. J.* **1995**, *1*, 351.

(27) Persson, E. S: M.; Bäckvall, J.-E. *Acta Chem. Scand.* **1995**, *49*, 899.

the lactone ring is obviously needed. However, the replacement of acetate by a better leaving group was impossible due to problems with the hydrolysis and subsequent cyclization of **9c**.

Conclusions

We have synthesized a number of bicyclic ring systems by intramolecular palladium(II)-catalyzed 1,4-oxidation reactions of 1,3-dienes having a side chain, with a carboxylic or alcoholic nucleophile, in the 2-position of the diene. The δ-lactones and pyrans, respectively, were obtained in good yields, and both the *cis*- and *trans*-diastereomers could be obtained selectively by the presence or absence of catalytic amounts of LiCl. Six-membered rings can be formed efficiently by this method, but the formation of seven-membered rings is too slow to compete with the formation of the diacetate products. We have also shown that the regioselectivity for the oxidation of the dienyl carboxylic acids was affected by the solvent composition, with acetic acid/acetone 1:4 leading to mostly 1,4-oxidation product.

Furthermore, we have tried to use the products from the intramolecular oxidation reactions in transition metal-catalyzed functionalization reactions. The substrates were not easily compatible with a palladium(0)-catalyzed hydrogenolysis reaction and gave ring-opened products or wrong regioisomers instead of the expected *cis*- or *trans*-fused ring systems. On the other hand, stereo- and regioselective organocopper reactions of the allylic acetate provided access to the *cis*- and *trans*-fused ring systems via an anti S_N2'-substitution of the allylic acetate by an alkyl group. The products were obtained in high yields.

The combination of a stereoselective intramolecular 1,4-oxidation reaction and either hydrogenolysis or S_N2'-substitution reaction should be useful for obtaining *cis*- or *trans*-fused ring systems. The presence of such structures in nature makes the reactions discussed in this paper potentially useful in organic synthesis.

Experimental Section

3-(2-Cyclohexadienyl)propanoic Acid Ethyl Ester (2a). Following a literature procedure,[12a] triflate **1a** (3.33 g, 14.6 mmol) was allowed to react with $Pd(PPh_3)_4$ (843 mg, 0.73 mmol) and the zinc reagent (prepared from ethyl-3-iodopropionate (5.00 g, 21.9 mmol) and Zn(Cu) couple[28] (2.40 g, 36.7 mmol)) in 135 mL of benzene and 10 mL of DMA at 60 °C, and the reaction was stirred overnight. The mixture was cooled to rt and poured into a saturated solution of NH_4Cl (100 mL). The phases were separated, and the aqueous phase was extracted with ether (×3). The combined organic phases were washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography (pentane/Et_2O 95:5) gave 2.25 g (86%) of **2a** as a colorless oil. ^{1}H NMR δ: 5.86−5.77 (m, 2H), 5.51−5.46 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.43−2.28 (m, 4H), 2.08 (m, 4H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ: 173.4, 134.4, 127.3, 126.7, 120.8, 60.4, 33.6, 30.8, 22.4 (2C), 14.4. MS *m*/*z*; 180 (M^+, 24), 134 (24), 105 (34), 91 (100), 77 (23). IR (neat): 2824, 1735, 1439, 1372, 1288, 1176, 1042, 941, 809, 745 cm^{-1}.

2-(2-Cyclohexadienyl)benzoic Acid Methyl Ester (2e). The organozinc reagent **5** (1.5 mmol, 6 mL THF) from 2-bromobenzoic acid methyl ester[12b] was transferred via a cannula to a solution of **1a** (0.228 g, 1.0 mmol) and $Pd(PPh_3)_4$ (57 mg, 0.05 mmol) in 6 mL of THF. The mixture was heated and kept at 55 °C for 16 h. A saturated solution of NH_4Cl was added, and the aqueous phase was extracted with Et_2O (×3). The combined organic phases were washed with brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed (pentane (200 mL) and then pentane/Et_2O 9:1) to give 0.139 g (65%) of the title compound as a colorless oil. ^{1}H NMR δ: 7.75 (dd, J = 7.7, 1.5 Hz, 1H), 7.44 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 7.31 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.27 (dd, J = 7.6, 1.4 Hz, 1H), 5.90 (m, 2H), 5.79 (m, 1H), 3.82(s, 3H), 2.32 (m, 2H), 2.21 (m, 2H). ^{13}C NMR δ: 169.0, 142.6, 137.3, 131.4, 129.9, 129.6, 129.5, 127.2, 126.8, 125.8, 123.6, 51.9, 22.7, 21.8. MS *m*/*z*: 214 (M^+, 30), 182 (37), 181 (100), 153 (30). IR (neat): 2928, 1728, 1600, 1450, 1382, 1278, 1122, 965 cm^{-1}.

3-(2-Cyclohexadienyl)propanoic Acid (3a). Ethyl ester **2a** (2.25 g, 12.5 mmol) was dissolved in 125 mL of THF−H_2O 4:1. LiOH (900 mg, 37.5 mmol) was added, and the mixture was stirred at ambient temperature overnight. THF was removed in vacuo, and the aqueous phase was washed once with pentane/Et_2O. After acidification (concd HCl), the aqueous phase was extracted with EtOAc (×4) and the combined organic phases were dried (Na_2SO_4). After evaporation of the solvents, the residue was chromatographed through a short silica column (pentane/Et_2O 1:1) to give 1.88 g (99%) of **3a** as a colorless oil. ^{1}H NMR δ: 5.88−5.77 (m, 2H), 5.52 (m, 1H), 2.51−2.43 (m, 2H), 2.39−2.31 (m, 2H), 2.10 (m, 4H). ^{13}C NMR δ: 179.6, 133.9, 127.4, 126.4, 120.8, 33.1, 30.3, 22.2 (2C). MS *m*/*z*: 152 (M^+, 27), 134 (22), 91 (100), 77 (31). IR (neat): 2937, 1735, 1497, 1207, 1044, 985, 744 cm^{-1}.

2-(2-Cyclohexadienyl)benzoic Acid (3d). Hydrolysis of diene **2e** in MeOH−H_2O 4:1 with NaOH (3 equiv) and heating the mixture at reflux temperature gave **3d** as a colorless oil in 80% yield. ^{1}H NMR δ: 7.91 (dd, J = 7.7, 1.4 Hz, 1H), 7.50 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.35 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.30 (dd, J = 7.6, 1.3 Hz, 1H), 5.96 (m, 1H), 5.89 (m, 1H), 5.80 (m, 1H), 2.33 (m, 2H), 2.22 (m, 2H). ^{13}C NMR δ: 173.4, 143.7, 137.3, 132.3, 130.5, 130.2, 130.0, 127.1, 126.9, 126.0, 123.9, 22.7, 21.7. MS *m*/*z*: 200 (M^+, 13), 172 (100), 144 (82), 116 (29).

3-(2-Cyclohexadienyl)propanol (4a). $LiAlH_4$ (1.33 g, 35.0 mmol) was suspended in 30 mL of Et_2O and cooled to 0 °C. Ethyl ester **2a** (3.0 g, 16.7 mmol) was dissolved in 25 mL of Et_2O and added dropwise to the suspension. The solution was stirred for 45 min at 0 °C and then at rt for 1 h. A saturated Na_2SO_4 solution was carefully added to quench the reaction. Et_2O was added, and the phases were separated. The aqueous phase was extracted with Et_2O (×2), and the combined organic phases were washed with H_2O and brine and then dried ($MgSO_4$). After evaporation of the solvent, the residue was chromatographed (pentane/ Et_2O 1:1) to give 2.22 g (97%) of **4a** as a colorless oil. ^{1}H NMR δ: 5.88−5.76 (m, 2H), 5.54−5.49 (m, 1H), 3.67−3.62 (t, J = 6.6 Hz, 2H), 2.15−2.06 (m, 6H), 1.75−1.62 (m, 2H), 1.43 (br s, 1H). ^{13}C NMR δ: 135.4, 127.2, 127.1, 120.7, 62.7, 32.0, 31.3, 22.5, 22.4.

2-(2-Cyclohexadienyl)benzyl Alcohol (4d). Silyl ether **8**[14] (1.49 g, 4.97 mmol) was dissolved in 5 mL of THF and added to a solution of TBAF (3.13 g, 9.93 mmol) in 20 mL of THF under argon. The reaction was complete in 10 min. The solvent was evaporated, Et_2O was added, and the organic phase was washed with H_2O (×2) and brine and dried ($MgSO_4$). The solvent was carefully evaporated at reduced pressure and without heating. The residue was chromatographed (pentane/Et_2O 2:1) to give 745 mg (81%) of **4d** as a colorless oil. ^{1}H NMR δ: 7.47−7.43 (m, 1H), 7.33−7.23 (m, 2H), 7.19−7.15 (m, 1H), 6.02−5.90 (m, 2H), 5.80−5.75 (m, 1H), 4.69 (d, J = 4.8 Hz, 2H), 2.37−2.28 (m, 2H), 2.27−2.18 (m, 2H), 1.73 (br s, 1H). ^{13}C NMR δ: 141.3, 138.2, 136.2, 128.9, 128.3, 127.8, 127.5, 127.4, 127.0, 125.3, 63.4, 22.7, 21.9.

Compound 9a. General Procedure for Palladium(II)-Catalyzed 1,4-Diacyloxylation. To a solution of $Pd(OAc)_2$

(28) Smith, R. D.; Simmons, H. E. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 855.

(7.4 mg, 0.033 mmol), *p*-benzoquinone (17.8 mg, 0.164 mmol), MnO_2 (68.7 mg, 0.79 mmol), LiCl (5.6 mg, 0.132 mmol), and $LiOAc{\cdot}2H_2O$ (134 mg, 1.32 mmol) in 1.5 mL of HOAc/acetone 1:4 was added diene acid **3a** (100 mg, 0.66 mmol) in 0.5 mL of HOAc/acetone 1:4 over 12 h. After additional stirring for 24 h, saturated $NaHCO_3$ (aq) was added, and the aqueous phase was extracted with Et_2O (×4). The combined organic phases were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Column chromatography (pentane/Et_2O 1:3) gave 125 mg (90%) of lactones **9a** and **9b** in a 75:25 ratio. White solid. Mp: 90−91 °C. ^{1}H NMR δ: 5.75 (m, 1H), 5.18 (m, 1H), 4.75 (m, 1H), 2.72−2.47 (m, 4H), 2.06 (m, 1H), 2.03 (s, 3H), 2.00−1.86 (m, 2H), 1.78 (m, 1H). ^{13}C NMR δ: 171.6, 170.5, 136.9, 123.2, 75.2, 66.2, 29.7, 25.4, 25.3, 24.5, 21.2. MS *m/z*: 211 ([M + H]$^+$, 0.8), 168 (100), 150 (27), 122 (36), 108 (37), 95 (69), 79 (41). IR (KBr): 2922, 1731, 1435, 1363, 1241, 1021 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.05; H, 6.88.

Compound 9b. Colorless oil. ^{1}H NMR δ: 6.00 (ddd, J = 9.8, 4.5, 2.9 Hz, 1H), 5.58 (ddd, J = 9.8, 2.5, 1.8 Hz, 1H), 4.94 (dd, J = 11.2, 3.6 Hz, 1H), 2.60 (dd, J = 9.6, 1.3 Hz, 1H), 2.58 (d, J = 9.6 Hz, 1H), 2.34−2.08 (m, 4H), 2.09 (s, 3H), 1.98 (m, 1H), 1.87 (m, 1H). ^{13}C NMR δ: 176.3, 170.3, 133.5, 127.5, 82.3, 74.8, 31.8, 29.1, 24.3, 23.9, 21.2. MS *m/z*: 210 (M$^+$, 1.5), 167 (5), 139 (26), 124 (100), 96 (62), 81 (32).

Compound 13a. To a solution of $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), *p*-benzoquinone (17.8 mg, 0.164 mmol), MnO_2 (68.7 mg, 0.79 mmol), LiCl (5.6 mg, 0.132 mmol), benzoic acid (80.3 mg, 0.66 mmol), and $PhCO_2Li$ (337 mg, 2.63 mmol) in 2.5 mL of acetone was added diene acid **3a** (100 mg, 0.66 mmol) in 0.5 mL of acetone over 12 h. After additional stirring for 48 h and workup, chromatography (pentane/Et_2O 1:3) gave an inseparable mixture of two isomers **13a** and **13b** (81:19) in 58% yield. A pure sample of **13a** was obtained by recrystallization from pentane/Et_2O. ^{1}H NMR δ: 8.07−8.02 (m, 2H), 7.60−7.53 (m, 1H), 7.48−7.41 (m, 2H), 5.93−5.88 (m, 1H), 5.51−5.445 (m, 1H), 4.86−4.79 (m, 1H), 2.79−2.51 (m, 4H), 2.23−2.03 (m, 3H), 1.97−1.85 (m, 1H). ^{13}C NMR δ: 171.9, 166.2, 137.4, 133.2, 130.3, 129.8, 128.5, 123.5, 75.5, 66.9, 29.9, 25.7, 25.6, 24.9. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.34; H, 5.95. **Compound 13b.** ^{1}H NMR (distinguishable peaks in mixture of isomers) δ: 5.83−5.77 (m, 1H), 5.24−5.17 (m, 1H), 4.79−4.72 (m, 1H).

Compound 13c. To a solution of $Pd(OAc)_2$ (7.4 mg, 0.033 mmol), *p*-benzoquinone (14.2 mg, 0.132 mmol), MnO_2 (68.7 mg, 0.79 mmol), and benzoic acid (400 mg, 3.29 mmol) in 2.5 mL of acetone was added diene acid **3a** (100 mg, 0.66 mmol) in 0.5 mL of acetone over 12 h. After additional stirring for 12 h and workup, chromatography (pentane/Et_2O 1:3) gave **13c** as a colorless oil in 56% yield. ^{1}H NMR δ: 8.05−8.00 (m, 2H), 7.59−7.53 (m, 1H), 7.47−7.40 (m, 2H), 5.85−5.81 (m, 1H), 5.66−5.57 (m, 1H), 4.95−4.87 (m, 1H), 2.79−2.47 (m, 4H), 2.41−2.26 (m, 2H), 1.96−1.69 (m, 2H). ^{13}C NMR δ: 171.9, 166.1, 135.9, 133.2, 130.2, 129.7, 128.5, 125.3, 75.2, 69.5, 29.9, 27.4, 26.3, 25.5.

Compound 15a. General Procedure for Palladium(II)-Catalyzed 1,4-Alkoxyacyloxylation Reactions. To a solution of $Pd(OAc)_2$ (16.3 mg, 0.072 mmol), *p*-benzoquinone (156.5 mg, 1.45 mmol), LiCl (9.2 mg, 0.217 mmol), and $LiOAc{\cdot}2H_2O$ (765 mg, 7.5 mmol) in 2.0 mL of HOAc was added diene alcohol **4a** (100 mg, 0.725 mmol) in 0.5 mL of HOAc over 8 h. After additional stirring for 12 h, brine was added, and the aqueous phase was extracted with Et_2O (×3). The combined organic phases were washed with cold 2 M NaOH and brine. After drying ($MgSO_4$) and evaporation of the solvent, the residue was chromatographed (pentane/Et_2O 2:1) to give 60 mg (42%) of pyrans **15a** and **15b** in an 80:20 ratio. The ^{1}H and ^{13}C NMR data were in agreement with those reported in the literature.[11b]

Compound 15b. Using the same procedure and amounts as for **15a**, but without added LiCl and $LiOAc{\cdot}2H_2O$, pyrans **15a** and **15b** were isolated in a 5:95 ratio in 56% yield. The ^{1}H and ^{13}C NMR data were in agreement with those reported in the literature.[11b]

Compound 16a. Using the same procedure and amounts as for **15b**, but with 72 h of additional stirring time, pyrans **16a** and **16b** were isolated in a 46:54 ratio in 70% yield. The products were separated by column chromatography (pentane/Et_2O 2:1). Colorless oil. ^{1}H NMR δ: 5.24−5.21 (m, 1H), 5.14−5.09 (q, J = 2.4 Hz, 1H), 3.99−3.93 (m, 1H), 3.88−3.82 (app t, J = 7.2 Hz, 1H), 3.54−3.47 (dt, J = 11.6, 3.2 Hz, 1H), 2.33−2.26 (m, 1H), 2.23−2.12 (m, 1H), 2.05 (s, 3H), 1.86−1.80 (dd, J = 13.2, 6.0 Hz, 1H), 1.76−1.61 (m, 2H), 1.50−1.43 (dd, J = 13.2, 8.8 Hz, 1H), 0.96 (s, 3H), 0.89 (s, 3H). ^{13}C NMR δ: 171.1, 138.5, 120.8, 76.7, 73.3, 68.0, 41.7, 34.9, 31.1, 28.0, 27.9, 21.2, 20.7.

Compound 16b. Colorless oil. ^{1}H NMR δ: 5.83−5.79 (dd, J = 10.0, 1.2 Hz, 1H), 5.64−5.60 (d, J = 10.0 Hz, 1H), 3.85−3.76 (m, 2H), 3.44−3.37 (ddd, J = 11.2, 9.6, 3.2 Hz, 1H), 2.55−2.48 (dddd, J = 12.8, 4.8, 4.0, 1.6 Hz, 1H), 1.94 (s, 3H), 1.83−1.73 (m, 3H), 1.65−1.47 (m, 2H), 1.07 (s, 3H), 1.00 (s, 3H). ^{13}C NMR δ: 169.9, 142.2, 124.4, 76.1, 75.6, 66.2, 37.2, 33.0, 32.0, 31.2, 30.2, 23.5, 22.2.

Compound 17. Following the general procedure, **4b** was allowed to react in the presence of 2 M $LiOAc{\cdot}2H_2O$ but without added LiCl. The substrate was added at once, and the reaction was stirred at 40 °C for 36 h. Chromatography (pentane/Et_2O 2:1) gave **17** as a colorless oil.^{1}H NMR δ: 5.42−5.34 (m, 2H), 4.02−3.89 (m, 2H), 3.54−3.43 (m, 1H), 2.40−2.28 (m, 1H), 2.20−2.09 (m, 1H), 2.05 (s, 3H), 1.96−1.80 (m, 4H), 1.74−1.56 (m, 4H). ^{13}C NMR δ: 170.6, 141.5, 125.0, 79.1, 72.6, 65.4, 32.5, 31.9, 30.0, 25.2, 21.7, 21.5.

Compound 25. Allylic acetate **15b** (970 mg, 4.95 mmol) was dissolved in MeOH (10 mL), and K_2CO_3 (68.4 mg, 0.49 mmol) was added. The solution was stirred at rt for 3 h. After evaporation of the solvent, column chromatography (pentane/Et_2O 1:3) gave 623 mg (82%) of the corresponding alcohol as a colorless oil.

A solution of formic acid (1.16 mL, 29.6 mmol) and acetic anhydride (2.79 mL, 29.6 mmol) was stirred for 15 min and then cooled to 0 °C. The allylic alcohol (228 mg, 1.48 mmol), dissolved in pyridine (3.59 mL, 44.4 mmol), was slowly added, and the solution was stirred for 2 h at rt. Et_2O was added, and the solution was washed with water (×2) and aqueous $NaHCO_3$ (×2). The organic phase was dried ($MgSO_4$) and evaporated. Column chromatography (pentane/Et_2O 85:15) gave 238 mg (88%) of the allylic formate ester **25** as a colorless oil. ^{1}H NMR δ: 8.05 (s, 1H), 5.47−5.41 (m, 2H), 4.02−3.94 (m, 1H), 3.92−3.85 (m, 1H), 3.61−3.51 (dt, J = 11.4, 3.3 Hz, 1H), 2.39−2.30 (m, 1H), 2.30−2.17 (m, 1H), 2.17−2.04 (m, 2H), 1.83−1.64 (m, 2H), 1.62−1.53 (m, 2H). ^{13}C NMR δ: 160.9, 141.6, 121.0, 73.9, 69.6, 68.1, 31.7, 28.1, 27.1, 26.6.

Compound 28a. General Procedure for Cross-Coupling Reactions with Preformed Dibutylcuprates. *n*-BuMgBr (1.05 mL, 0.45 M in Et_2O, 0.471 mmol) was added dropwise to a slurry of CuCN (22 mg, 0.246 mmol) in Et_2O (1.5 mL) at −30 °C. The reaction mixture was stirred for 2 h while the temperature was allowed to rise to 0 °C. Allylic acetate **18a** (cis/trans 86:14; 50 mg, 0.205 mmol) was dissolved in Et_2O (1.0 mL) and added to the cuprate at 0 °C. The reaction mixture was stirred at that temperature for 2 h and then quenched with NH_4Cl. The two layers were separated, and the aqueous phase was extracted with Et_2O (×3). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Column chromatography (pentane/Et_2O 2:1) gave 44.6 mg (90%) of an inseparable mixture of compounds **28a** and **28b** in a 86:14 ratio as a colorless oil. ^{1}H NMR δ: 7.35−7.31 (dd, J = 7.8, 1.5 Hz, 1H), 7.26−7.20 (m, 1H), 7.16−7.09 (ddd, J = 7.8, 1.5 Hz, 1H), 6.98−6.94 (m, 1H), 5.76−5.65 (m, 2H), 4.81−4.78 (d, J = 3.6 Hz, 2H), 4.02−3.98 (app t, J = 4.8 Hz, 1H), 2.29−2.16 (m, 1H), 2.11−1.85 (m, 4H), 1.66−1.55 (ddd, J = 14.4, 12.3, 4.2 Hz, 1H), 1.28−1.12 (m, 3H), 1.06−0.94 (m, 1H), 0.86−0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR δ: 140.4,

134.5, 134.1, 127.1, 127.0, 125.5, 125.3, 124.2, 74.4, 66.4, 40.9, 40.7, 26.7, 24.2, 23.5, 22.0, 14.1.

Acknowledgment. Financial support from the Swedish Research Council and the Swedish Research Council for Engineering Sciences is gratefully acknowledged.

Supporting Information Available: Additional experimental and characterization data for starting material synthesis; reactions following general procedures; ^{1}H and ^{13}C NMR spectra of compounds **1c**,**d**, **2a**−**g**, **3a**−**f**, **4b**,**c**, **9b**−**c**, **11a**−**c**, **13c**, **14**, **16a**,**b**, **17**, **18a**, **19**, **20**, **25**, and **28a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0357667