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Regiocontrolled, Palladium-Catalyzed Bisfunctionalization of Allenyl Esters. Multicomponent Coupling Approaches to Highly Substituted α,β-Unsaturated δ-Lactones

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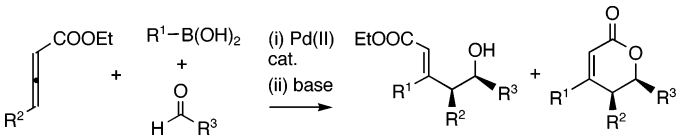

A palladium-catalyzed regioselective bisfunctionalization of allenyl esters with boronic acids (nucleophiles) and aldehydes (electrophiles) was demonstrated. The three-component coupling afforded α,β-unsaturated δ-lactones under mild conditions and with excellent chemo-, regio-, and diastereoselectivity. Aromatic, heteroaromatic and vinylic boronic acids ($R^1B(OH)_2$) reacted with ethyl 2,3-butadienoate and benzaldehyde to afford the corresponding 4-R^1,6-Ph-disubstituted α,β-unsaturated δ-lactones in 62−78% yields. Lactones derived from aromatic, heteroaromatic, and vinylic aldehydes were isolated in 51−58% yields, while aliphatic aldehydes were less reactive. The regiochemistry of bisfunctionalization of allenyl ester homologues remained controlled by the ester substituent, and the reactions afforded *cis*-4,5,6-trisubstituted α,β-unsaturated δ-lactones and esters of (*Z*)-*syn*-3,4,5-trisubstituted-5-hydroxy-2-pentenoic acids in combined 47−65% yields. The superior performance of a π-allylpalladium(II) dimer catalyst featuring an auxiliary allyl ligand derived from β-pinene, among diverse palladium(II) catalysts, was demonstrated. A catalytic cycle involving an unsymmetrical bis-π-allylpalladium complex as the key intermediate was proposed, and the communication highlights the synthetic potential of such intermediates. However, the efficiency of asymmetry transfer remained low (<20%).

Introduction

In the past two decades, the development of palladium-catalyzed multicomponent and cascade reactions opened up new, more efficient routes to synthesis of complex medicinally relevant targets.[1] Allenes have served as versatile substrates in these transformations.[2] In most cases, the processes exploit an attack of a nucleophile on an electrophilic π-allylpalladium(II) intermediate, constructed in situ from the allene.[3] The polarity of the π-allylpalladium(II) intermediates could be reversed via reductive transmetalation with electropositive metals or their compounds (Zn, In, InI, SmI_2, $SnCl_2$, $ZnEt_2$)[4] or transmetalation with main group metal reagents (R_2AlSnR_3, R_6Sn_2, R_6Si_2 or $(RO)_6B_2$),[5] to afford main group metal allyls capable of reacting with electrophiles. The palladium-catalyzed indium-mediated three-component coupling of aryl iodides, allenes, and aldehydes or imines providing an access to complex homoallylic alcohols or amines underscores the utility of this strategy.[6] Relying on a mechanistically distinct pathway, related carbon−carbon bond constructions were achieved via a nickel-

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catalyzed tandem coupling of alkynes or dienes with alkyl or aryl metals (B, Zn) and aldehydes, imines, or epoxides.[7] The protocol was successfully used in total syntheses of complex natural products.[8] However, its applications to bisfunctionalization of allenes have remained limited to a few intramolecular processes.[9] The "π-allylpalladium umpolung" has been also realized by exploiting the reactivity of bis-π-allylpalladium complexes[10] and allylpalladium(II) complexes with three-coordinate pincer ligands.[11] η^1-Bonded allyl ligands in these complexes reacted with aldehydes or imines at the terminal vinylic carbon, providing branched homoallylic alcohols or amines.[10,11] Unsymmetrical bis-π-allylpalladium complexes bearing a chiral nonracemic β-pinene-derived auxiliary allyl ligand were proposed as catalytic intermediates in asymmetric syntheses of homoallylic amines (up to 91% ee).[12]

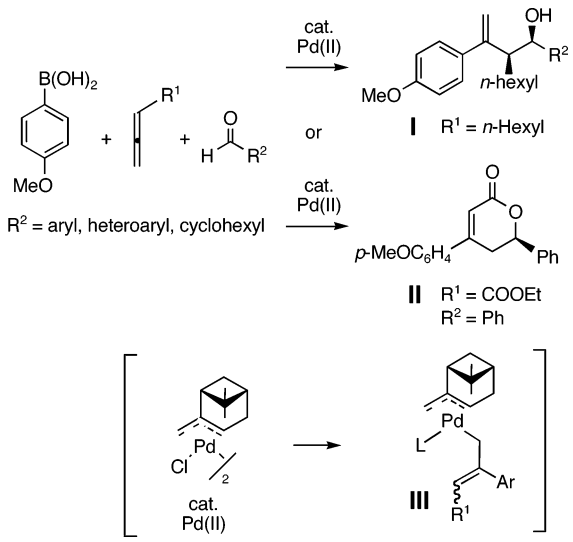

FIGURE 1. Methodology for the synthesis of homoallylic alcohols.

Inspired by these studies, we envisioned a new synthetic protocol, in which a single palladium catalyst would combine two building blocks to form an unsymmetrical bis-π-allylpalladium complex, which would subsequently mediate a selective allyl transfer to electrophiles. Recently, we have reported a methodology for a regioselective preparation of branched homoallylic alcohols **I** via palladium(II)-catalyzed coupling of a boronic acid and 1,2-nonadiene (R^1 = *n*-hexyl) with aldehydes (Figure 1).[13] A catalytic cycle featuring the generation of an unsymmetrical bis-π-allylpalladium complex **III** (R^1 = *n*-hexyl, Ar = *p*-methoxyphenyl) followed by a chemoselective transfer of the "preassembled" allyl fragment to aldehydes[14] was proposed for the new process. Unexpectedly, an experiment utilizing ethyl 2,3-butadienoate (R^1 = COOEt) instead of 1,2-nonadiene (R^1 = *n*-hexyl) afforded a low yield of lactone **II** (Figure 1). The lactone **II** apparently originated from a selective attachment of the aldehyde to the unsubstituted carbon of the allene, corresponding to a reversal of the expected[15] regiochemistry.

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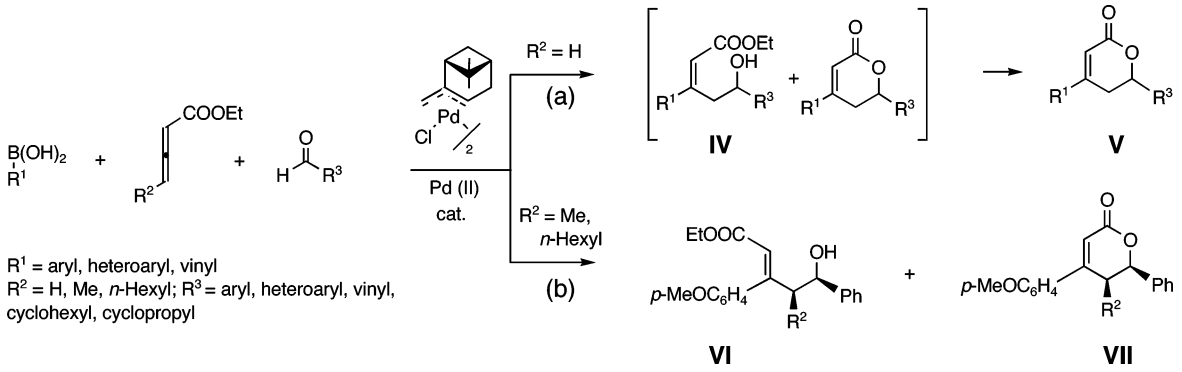

FIGURE 2. New applications to the synthesis of α,β-unsaturated δ-lactones.

α,β-Unsaturated δ-lactones constitute valuable building blocks offering multiple opportunities for elaboration to complex synthetic targets,[16] and the δ-lactone core is found in biologically significant natural products.[17] A method that would allow for a one-pot regio- and stereoselective construction of highly substituted δ-lactones via a tandem bisfunctionalization of allenyl esters (Figure 1) would notably improve the efficiency of traditional synthetic schemes.[18]

Herein we describe a new protocol for the synthesis of substituted α,β-unsaturated δ-lactones via a palladium-catalyzed three-component coupling of boronic acids, allenyl esters, and aldehydes (Figure 2). The method includes an in situ lactonization of (*E*)-alcohols **IV** affording lactones **V** as the sole products of the three-component coupling (reaction (a), Figure 2). Aromatic, heteroaromatic, and vinylic boronic acids reacted with ethyl 2,3-butadienoate (R^2 = H) and benzaldehyde to afford lactones **V** (R^3 = Ph) in 62−78% yields (Figure 2). Lactones **V** derived from aromatic, heteroaromatic, and vinylic aldehydes were isolated in 51−58% yields, whereas aliphatic aldehydes (R^3 = cyclohexyl, cyclopropyl) afforded the corresponding lactones **V** in diminished yields (32−44%). Lactone **V** (R^1 = *p*-methoxyphenyl, R^3 = phenyl) was obtained in 20% enantiomeric excess, and optimization of the stereoinduction has not been the subject of the present study. The reactions proceeded under neutral conditions at room temperature and tolerated the presence of potentially reactive functionalities (aryl bromides and ketones). Remarkably, the regiochemistry of the bisfunctionalization of allenyl ester homologues (R^2 = Me, *n*-hexyl) remained exclusively controlled by the ester substituent, yielding lactones **VII** (R^2 = Me, *n*-hexyl), as well as (*Z*)-alcohols **VI** (R^2 = Me, *n*-hexyl) in combined yields 47−65% (reaction (b), Figure 2). A survey of diverse Pd(II) and Pd(0) catalysts demonstrated a superior performance of π-allylpalladium(II) complexes bearing bridged bicyclic "auxiliary" allyl ligands in the absence of phosphines. These results highlight the synthetic potential of rarely studied unsymmetrical bis-π-allylpalladium complexes[19] and motivate our ongoing investigations on the structure−activity properties of the "nontransferable" allyl ligands.

Results and Discussion

Method Development. The reported protocol for the preparation of a single lactone **II** (Figure 1) required a high load of the palladium catalyst (20 mol % Pd) to afford lactone **II** in 65% yield.[13] In an initial series of experiments, molar ratios of reagents (boronic acid/allene/aldehyde = 2:5:1) and allylpalladium(II) dimer catalyst **1a** (10 mol % Pd), previously utilized in the preparation of homoallylic alcohols,[13] were employed. The effects of auxiliary phoshine ligands and solvents on the stability of catalytic intermediates, as manifested by the extent of precipitation of palladium(0),[13] were evaluated. Application of relatively strong phosphine donors led to low yields and complex reaction mixtures,[20] whereas weak ligands did not affect the yields, selectivity, or catalyst

(15) Computational studies showed that in η^3,η^1-bis-π-allylpalladium complex the *unsubstituted* terminus of the η^1-bonded allyl ligand was preferentially bonded to palladium as a result of steric factors and that d_σ-π^* hyperconjugative interaction was responsible for the nucleophilic reactivity of the terminal and often *substituted* vinylic carbon, rationalizing the regioselective formation of branched organic products. See references 10a,b.

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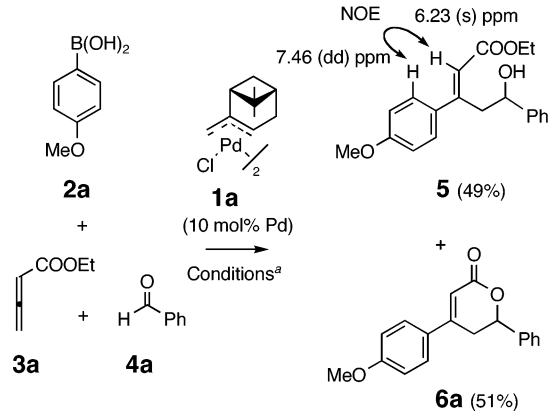
SCHEME 1. Optimized Protocol for Synthesis of the (*E*)-Alcohol and Lactone[a]



[a] Conditions: molar ratio of boronic acid/allene/aldehyde = 2:5:1, 0.05 mol % **1a** (10 mol % Pd), CsF (4.0 mol), THF, rt, 24 h.

stability.[21] Two products arising from the three-component coupling process, alcohol **5** and lactone **6a**, were isolated from these reactions (Scheme 1), and the best yields were surprisingly achieved in the absence of auxiliary phosphine ligands, without detection of precipitation of palladium(0). Reactions run in THF or 1,2-dichloroethane afforded the three-component coupling products **5** and **6** in good yields, whereas intractable mixtures were obtained in polar aprotic solvents (DMF, MeCN). Under the optimized conditions (complex **1a**, 10 mol % Pd in THF, CsF, 4.0 equiv, 24 h, rt), the coupling of boronic acid **2a** (2 equiv), allenyl ester **3a** (5 equiv), and aldehyde **4a** (1 equiv) provided alcohol **5** (49%) and lactone **6a** (51%) in a quantitative combined yield (Scheme 1). The excess of the allenyl ester and the boronic acid remained unreacted in the crude reaction mixtures, and a biaryl arising via a homocoupling of the boronic acid could not be isolated. Data acquired in ^{1}H NMR NOE experiments[22] confirmed the assignment of the (*E*) double bond geometry in alcohol **5** (Scheme 1). Although a slow lactonization of alcohol **5** was found to occur under the reaction conditions,[23] reagents that could be added to crude reaction mixtures to afford lactone **6a** as a single product, were sought. Lactonization mediated by an acid ($TsOH\cdot H_2O$ at 50 °C in THF)[24] required elevated temperatures, and appeared to be poorly reproducible on crude mixtures. A milder, base-mediated protocol (K_2CO_3, 2.0 equiv, EtOH, rt, 3.5 h)[25] proved to be satisfactory, providing lactone **6a** in 75% yield from the one-pot three-component coupling-lactonization (addition of K_2CO_3, 2.0 equiv, and EtOH, 1.0 mL, per 1.0 mL of THF, 3.5 h, rt) (entry 1, Table 1).

In a second series of optimization studies, the reagent ratios, and the nature and loading of the palladium catalysts employed in the one-pot two-step coupling-lactonization protocol were varied (Table 1). A reduction in the loading of catalyst **1a** from 10 to 5 mol % Pd resulted in the decrease in the yield of lactone **6a** from 75% to 41% (compare entries 1 and 2, Table 1). To favor the electrophilic attack, the reagent ratios were modified, limiting the excess of the allenyl ester[26] to 1:2.5 molar ratio of boronic acid/allene, and by increasing the excess of aldehyde to 1:1.6 molar ratio allene/aldehyde (e.g. 1:4 molar ratio of boronic acid/aldehyde). Under these conditions the yield of lactone **6a** rose to 63% (entry 3, Table 1), and a further improvement to 69% resulted from a reduction of the allenyl ester excess to a 1:1.5 ratio of boronic acid/allene (entry 4, Table 1). However, a decrease in the excess of aldehyde to a 1:2 molar ratio of boronic acid/aldehyde limited the yield of lactone **6a** to 57% (entry 5, Table 1). The protocol described in entry 5 may prove well-suited for larger scale syntheses due to a better substrate and catalyst economy (entry 5, Table 1). In analogy to our previous study,[13] the catalytic cycle of the reaction providing lactone **6a** is believed to involve exclusively intermediates with palladium in oxidation state Pd(II) (vide infra). Thus, the performance of alternate palladium(II) complexes **1b** (R = Me), complex **1c**, $Pd(OAc)_2$ with PCy_3 ligand (Pd/P = 1:1), and $Pd(OAc)_2$ with 1,2-bis(diphenylphosphino)ethane ligand (Pd/P = 1:2) as catalysts for the coupling process was evaluated (10 mol % Pd, boronic acid/allene/aldehyde ratio 2:5:1, entries 6−9, Table 1). Catalysts **1a** and **1b** showed essentially identical reactivity (compare entries 1 and 6, Table 1), indicating that the substitution at both the allylic termini of the β-pinene-derived auxiliary ligand was not critical to the catalyst performance.[14] The poor results achieved with other palladium(II) catalysts, reflected by the low (11−39%) yields of lactone **6a**, and the precipitation of palladium(0) (entries 6−9, Table 1), highlighted the importance of the "nontransferable" auxiliary allyl ligand for stabilizing the catalytic intermediates and mediating an efficient allyl transfer. An initial oxidative cyclization of allenyl ester **3a** mediated by the palladium(0) complex (Pd_2dba_3) giving rise to a metalacycle with palladium in oxidation state Pd(II),[27] could rationalize the formation of small quantities of lactone **6a** (23%, entry 10, Table 1). Lactone **6a** was obtained in 20% and 23% enantiomeric excess from reactions catalyzed by nonracemic complexes **1a** and **1b**, respectively (entries 1 and 6, Table 1). At present, optimization of the efficiency of asymmetry transfer was deemed premature, and subsequent studies aimed at

(20) The reaction outlined in Scheme 1 was run under the indicated conditions, except for the addition of 10 mol % of a monodentate phosphine ligand added as its HBF_4 salt. Ligands $H[PPh_2Me]BF_4$, $H[P(i\text{-}Pr)_3]BF_4$, $H[PCy_3]BF_4$ and $H[PPh(t\text{-}Bu)_2]BF_4$ were used and afforded the alcohol **5** and lactone **6a** in combined isolated yields 30%, 40%, 44%, and 48%, respectively. Furthermore, the ^{1}H NMR spectrum recorded on crude reaction mixtures indicated the presence of multiple byproducts that could not be characterized.

(21) Repeating the experiments as described in Scheme 1 and ref 20 in the presence of a weak phosphine donor ligand $P(o\text{-}Tol)_3$ afforded the alcohol **5** and lactone **6a** in a combined 88% yield, and ^{1}H NMR spectrum recorded on the crude reaction mixture did not reveal the presence of significant quantities of byproducts.

(22) ^{1}H NMR NOE experiment on alcohol **5** revealed that irradiation of the signal for the vinylic proton at δ 6.23 (s) led to the NOE enhancement of the signal at δ 7.46 (dd) corresponding to a proton in the *p*-methoxyphenyl substituent, as expected for the assigned structure of alcohol **5** with the (*E*) double bond geometry.

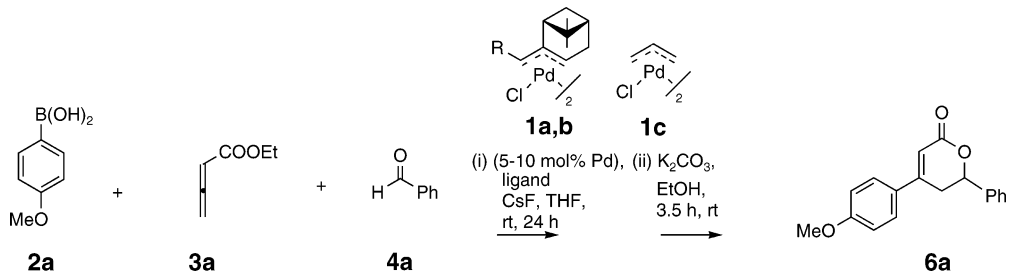
(23) Isolated alcohol **5** (1.0 equiv) was treated with boronic acid **2a** (2.0 equiv), catalyst **1a** (10 mol % Pd), and CsF (4.0 equiv) under the reaction conditions (THF, rt) in the absence of the aldehyde and allene components for 2 days to afford 45% yield of lactone **6a**.

(24) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947−5955.

(25) Smith, T. E.; Djang, M.; Velander, A. J.; Downey, C. W.; Carroll, K. A.; van Alphen, S. *Org. Lett.* **2004**, *6*, 2317−2320.

(26) In comparison to the aliphatic allene (1,2-nonadiene) used in our prior work, the allenyl ester **3a** would be expected to operate as a stronger ligand for palladium(II) complexes. For the discussion of binding of olefins to palladium complexes, see: Hartley, F. R. *Chem. Rev.* **1969**, *69*, 799−844.

TABLE 1. Evaluation of Choice of Catalyst and Effect of Reagent Ratios



2a **3a** **4a** **6a**

				molar ratio of reagents				
entry	catalyst	Pd (mol %)	ligand (mol %)	boronic acid	allene	aldehyde	yield (%)	ee[a] (%)
1	**1a** (R = H)	10	NA	2	5	1	75	20
2	**1a** (R = H)	5	NA	2	5	1	41	*b*
3	**1a** (R = H)	5	NA	1	2.5	4	63	*b*
4	**1a** (R = H)	5	NA	1	1.5	4	69	*b*
5	**1a** (R = H)	5	NA	1	1.5	2	57	*b*
6	**1b** (R = Me)	10	NA	2	5	1	76	23
7	**1c**	10	NA	2	5	1	33	
8	$Pd(OAc)_2$	10	PCy_3 (10)	2	5	1	39	
9	$Pd(OAc)_2$	10	dppe (10)	2	5	1	11	
10	Pd_2dba_3	10	PCy_3 (10)	2	5	1	23	

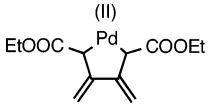
[a] Measured by chiral phase HPLC. [b] The enantiomeric excess of the product was not measured.

exploration of the reaction scope were performed with catalyst **1a** (10 mol % Pd), employing alternatively molar ratios of reagents, boronic acid/allene/aldehyde, 2:5:1 or 1:2.5:4.

Scope and Limitations of the Reaction with Ethyl 2,3-Butadienoate. The treatment of boronic acids **2**, ethyl 2,3-butadienoate **3a**, and benzaldehyde **4a** with catalyst **1a** (10 mol % Pd) under the conditions of the one-pot coupling-lactonization protocol (Method A; molar ratios of boronic acid/allene/aldehyde, 2:5:1, Table 2) afforded the corresponding lactones **6a**−**g** in good yields (55−78%) (Table 2). In two instances, olefins **7a** and **7b** were isolated in 46% and 43% yields, calculated per the boronic acid as the limiting reagent, respectively, (entries 2 and 4, Table 2). Moderate to small increases in the yields of lactones **6b** (from 57% to 78%) and **6c** (from 55% to 59%) were achieved with an excess of benzaldehyde (molar ratios of boronic acid/allene/aldehyde, 1:2.5:4; Method B, Table 2), limiting the formation of the olefinic byproducts **7a** (16%) and **7b** (14%) (calculated per boronic acid as the limiting reagent, entries 3 and 5, Table 2). Increasing the reaction times (48 h) did not improve the yields of lactones **6a**−**g**. Electron-rich and electron-deficient boronic acids (entries 1−6), olefinic boronic acids (*trans*-cinnamyl[28] or *trans*-1-octenyl, entries 7 and 8) and a heteroaromatic acid (3-furyl, entry 9) performed with an equal success in the new synthetic protocol. Steric hindrance in the proximity of the reaction site in the boronic acid proved detrimental, and only traces of the corresponding lactone were isolated from the coupling of *o*-tolylboronic acid. Attempts to couple aliphatic boronic acids using Method A (Table 2) were unsuccessful. The tolerance of reactive functional groups was notable. No byproducts arising from allylation of the unprotected ketone group were detected in the synthesis of lactone **6c** (entries 4 and 5, Table 2). Furthermore, the aryl bromide group in *m*-bromophenylboronic acid was preserved in lactone **6d** (entry 6, Table 2),[29] supporting the proposed exclusive involvement of palladium(II) intermediates (vide infra). Surprisingly, the coupling-lactonization with *N*-Boc-protected 5-bromo-2-indolylboronic acid **2b** afforded inseparable mixtures of products consisting of alcohol (*E*)-**8** and lactone **6o** in 65% combined yield, and ratios of alcohol **8** to lactone **6o** varying from 1:4 to 1:0.5 (Scheme 2), as elucidated by ^{1}H NMR analysis. The ^{1}H NMR NOE experiment performed on the mixture of products **8** and **6o** confirmed the assignment of (*E*) double bond geometry in alcohol **8**.[30] However, a complete lactonization of alcohol **8** could not be accomplished by a prolonged treatment with K_2CO_3 (EtOH) at elevated temperatures, and an attempted O-acetylation of alcohol **8** (Ac_2O, DMAP) was unsuccessful. A single fully characterized product was isolated following the treatment of the mixture of alcohol **8** and lactone **6o** (1:4 ratio of **8**/**6o**) with TFA/methylene chloride mixture (1:1)[31] providing the *N*-deprotected lactone **6p** in an excellent yield (Scheme 2).

Subsequently, the scope of the three-component coupling reaction with ethyl 2,3-butadienoate **3a** with respect

(27) A structure of one possible regioisomer of the oxidative cyclization product is shown below (additional ligands on palladium were omitted for clarity).

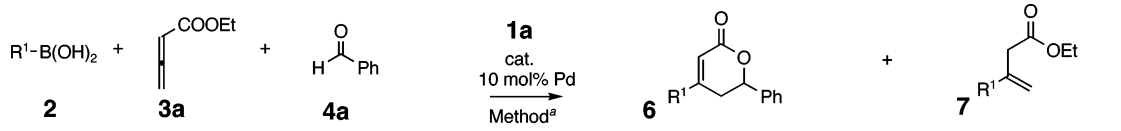


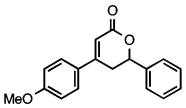
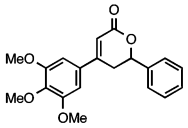
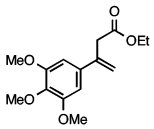
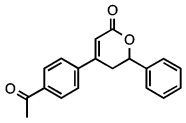
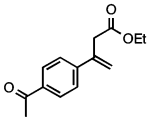
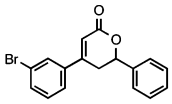
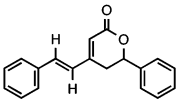
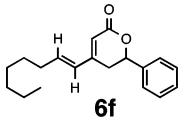
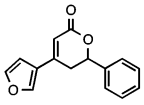
Oxidative homocoupling of allenes mediated by Pt(0) complexes providing corresponding Pt(II) metalacycles is known; see: (a) Stephan, C.; Munz, C.; Dieck, T. *J. Organomet. Chem.* **1994**, *468*, 273−278. (b) Barker, G. K.; Green, M.; Howard, J. A. K.; Spencer, J. L.; Stone, F. G. A. *J. Am. Chem. Soc.* **1976**, *98*, 3373−3374.

(28) Due to the overlap of the indicative signals in ^{1}H NMR spectra, the *trans* geometry of the olefin in lactone **6e** was confirmed by X-ray crystallographic analysis.

(29) Thus, the presented methodology provides an opportunity for further elaboration and diversification of the lactones via a subsequent palladium(0)-catalyzed cross-coupling or a Heck-type protocol initiated by an in situ addition of palladium(0) catalyst and suitable reagents. See ref 1a.

TABLE 2. Synthesis of 4,6-Disubstituted Lactones; Diversity in the Boronic Acid Component



	R^1	method[a]	reagent ratios[b] (mol equiv)	lactone **6**	yield (%)	olefin **7**	yield (%)[c]
1	*p*-methoxyphenyl	A	2 : 5 : 1	 **6a**	75	-	-
2	3,4,5-trimethoxyphenyl	A	2 : 5 : 1	 **6b**	57	 **7a**	46[c]
3		B	1 : 2.5 : 4		78		16[c]
4	*p*-methylcarbonyphenyl	A	2 : 5 : 1	 **6c**	55	 **7b**	43[c]
5		B	1 : 2.5 : 4		59		14[c]
6	*m*-bromophenyl	A	2 : 5 : 1	 **6d**	58	-	-
7	*trans*-2-phenylvinyl	A	2 : 5 : 1	 **6e**	78	-	-
8	*trans*-1-octenyl	A	2 : 5 : 1	 **6f**	64	-	-
9	3-furyl	A	2 : 5 : 1	 **6g**	62	-	-

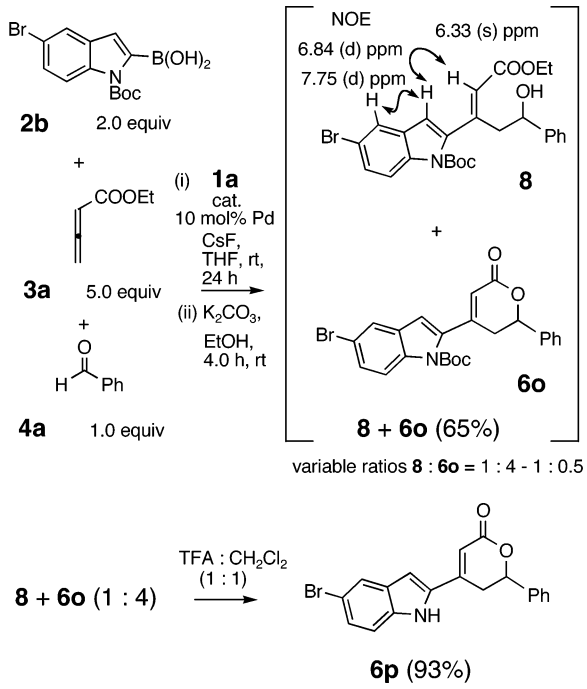
[a] Method A: (i) molar ratio of boronic acid/allene/aldehyde = 2:5:1, CsF (4.0 equiv), THF, rt, 24 h; (ii) K_2CO_3 (2.0 equiv), EtOH, 3−7 h, rt. Method B: same as method A except for molar ratio of boronic acid/allene/aldehyde = 1:2.5:4. [b] Molar ratio of boronic acid/allene/aldehyde. [c] Molar % yield calculated per the boronic acid as the limiting reagent (100 mol %).

to the aldehyde component was studied (Table 3). *p*-Methoxyphenylboronic acid (entries 1, 3, 4, 5, and 7, Table 3) and 3,4,5-trimethoxyphenylboronic acid (entries 2 and 6, Table 3) were employed. Electron-rich (entries 1 and 2) and electron-deficient (enry 3) aromatic aldehydes, as well as a vinylic *trans*-cinnamylaldehyde (entry 4) and a heterocyclic 2-furaldehyde (entry 5) afforded the corresponding lactones **6h**−**l** in moderate yields 51−58% that were nevertheless competitive with alternative multistep protocols.[18] Only in reactions with *p*-methoxy benzaldehyde (entry 1) and *trans*-cinnamylaldehyde (entry 4) improved yields of lactones **6h** (by 10%) and **6k** (by 8%) were obtained by employing an excess of aldehyde (Method B, Table 3). Aliphatic aldehydes proved to be less reactive, and lower yields of lactones **6m** (44%) and **6n** (32%) arising from the coupling to cyclohexanecarboxaldehyde and cyclopropanecarboxaldehyde were obtained (entries 6 and 7, Table 3). The olefinic byproduct **7a** was isolated from reactions described in entries 2 and 6 (Table 3) in 55% and 28% yields calculated per the boronic acid as the limiting reagent, respectively. The results summarized in Tables 2 and 3 and Scheme 2

(30) ^{1}H NMR NOE experiments on the inseparable mixture of alcohol **8** and lactone **6o** revealed that irradiation of the signal for the vinylic proton in alcohol **8** at δ 6.33 (s) led to the NOE enhancement of the signal at δ 6.84 (d) corresponding to the H-3 proton in the 5-bromo-2-indolyl substituent. Furthermore, irradiation of the H-3 proton in the indolyl ring at δ 6.84 led to the NOE enhancement of the signals at δ 6.33 (s) and at δ 7.75 (d), corresponding to the vinylic proton, and a proton in the aromatic ring of the indolyl substituent, respectively, as expected for the assigned structure of alcohol **8** with the (*E*) double bond geometry.

(31) Amat, M.; Perez, M.; Llor, N.; Bosh, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611−614.

SCHEME 2. Lactonization Accompanied by *N*-Boc-Deprotection

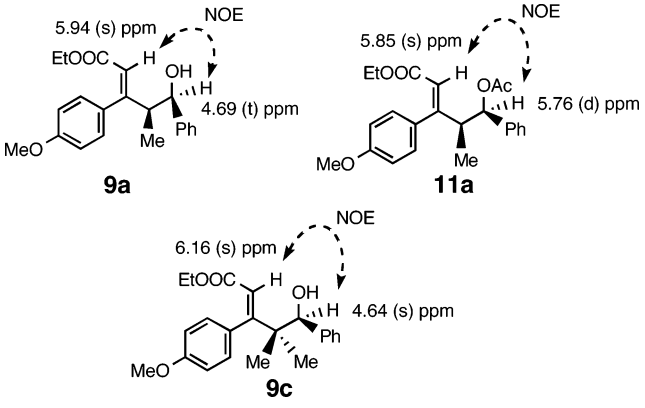


demonstrate that a synthetically attractive range of functionalized boronic acids and aldehydes can be employed in the novel regiocontrolled elaboration of ethyl 2,3-butadienoate **3a** to afford diverse 4,6-disubstituted α,β-unsaturated δ-lactones **6**.

Reactivity of Allenyl Ester Homologues. A potential extension of the new methodology to functionalization of substituted allenyl esters, and particularly those that would give rise to bis-π-allylpalladium intermediates **III** (Figure 1) substituted at both termini of the "preassembled" η^1-bonded allyl ligand, presents concerns about both chemoselectivity[14] and regioselectivity[15] of the allyl-transfer event. To explore these issues, the reactivity of allenyl ester homologues was studied (Table 4). Allenyl ester **3b** disubstituted at one allene terminus (Table 4) failed to provide the expected coupling products in reactions with boronic acid **2a** and benzaldehyde **4a** under the standard coupling-lactonization conditions (Method A, Table 4). For the first time in reactions with allenyl esters catalyzed by complex **1a**, catalyst instability, revealed by precipitation of palladium(0), appeared responsible for the failure of the synthetic protocol. Remarkably, reactions with allenyl esters **3c**−**e**[32] substituted at both allene termini proceeded with an excellent regioselectivity, providing only the products arising from the attachment of benzaldehyde to the allene carbon possessing one or two alkyl substituents (Methods A or C, entries 1−3, Table 4). However, the effectiveness of the control of the double bond geometry suffered, and alcohols **9a**−**c** isolated following the treatment of crude reaction mixtures with K_2CO_3 (Methods A and C, Table 4) were shown to possess the (*Z*) double bond geometry by the ^{1}H NMR NOE analyses performed on both the alcohols **9a**−**c** and the corresponding acetates **11a**−**b**.[33] Single diastereomers of alcohols **9a**−**b** and lactones **10a**−**b** were obtained. Alcohols **9a**−**b** were isolated in 95−98% purity (by ^{1}H NMR) after column chromatography and were completely characterized as acetates **11a**−**b** (Table 4). The relative stereochemistry in alcohols **9a**−**b** and acetates **11a**−**b** was tentatively assigned as *syn*.[34] Only *cis*-diastereomers of 4,5,6-trisubstituted lactones **10a**−**b** were formed.[35] Steric hindrance introduced by the additional substitution in allenyl ester homologues **3c**−**e** negatively affected the overall yields. Alcohol **9a** (39% with 95% purity) and lactone **10a** (26%) bearing a methyl substituent at C-5 were isolated in a 65% combined yield (Method A, reagent ratios of boronic acid/allene/aldehyde, 2:5:1; entry 1, Table 4). However, alcohol **9b** (18% with 95% purity) and lactone **10b** (29%) with a *n*-hexyl substituent at C-5 could only be obtained in a combined yield 47% (Method C, reagent ratios of boronic acid/allene/aldehyde, 1:1.5:4; entry 2, Table 4). In this case, treatment with an excess of aldehyde (Method C, Table 4) afforded about 10% improvement in the overall yield of products **9b** and **10b**, in comparison to the yields of the reaction performed with an excess of allene (Method A, Table 4). Disubstitution at the terminal carbon in allene **3e** reduced the yield of alcohol (*Z*)-**9c** to 28% (Method A, reagent ratios of boronic acid/allene/aldehyde, 2:5:1; entry 3, Table 4). Notably, no regioisomeric products arising from an electrophilic attack at the carbon bearing the ester substituent could be isolated from the crude reaction mixtures (entries 1−3, Table 4). The optimization of the asymmetry transfer was not pursued as a part of the present study.[36] The described three-component coupling protocol could not, however,

(32) In this protocol, racemic allenes **3c** and **3d** were employed, and no attempts were made to investigate whether a single enantiomer of each allenyl ester may have reacted preferentially in the coupling catalyzed by a nonracemic palladium(II) complex **1a**.

(33) ^{1}H NMR NOE experiments on the alcohols **9a**−**c** and acetates **11a**−**b** revealed that the irradiation of the signal for the vinylic proton at C-2 led to the NOE enhancement of the signal for the proton at C-5 as indicated in the examples below. Alternatively, irradiation of the signal for the proton at C-5 led to the NOE enhancement of the signal for the vinylic proton at C-2.

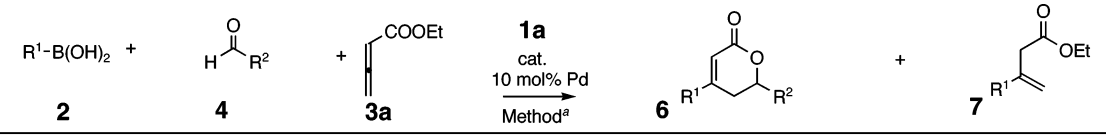


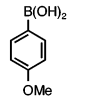
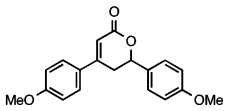
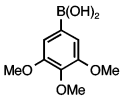
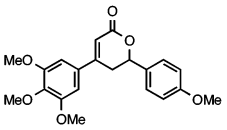
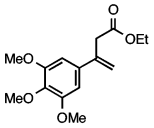
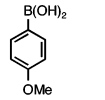
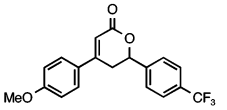
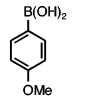
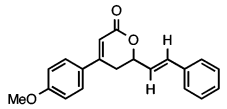
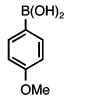
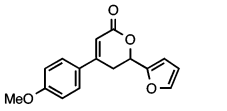
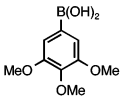
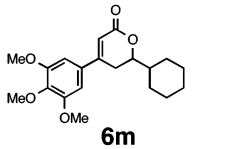
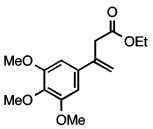
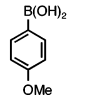
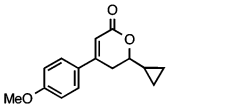
(34) Magnitudes of the *J* constants for coupling of protons H_4, H_5 (J_{H4-H5} = 3.6 Hz in alcohol **9a**, J_{H4-H5} = 3.9 Hz in alcohol **9b**, J_{H4-H5} = 5.3 Hz in acetate **11a**, J_{H4-H5} = 5.7 Hz in acetate **11b**) were consistent with dihedral angles anticipated in the most stable conformations of *syn* diastereomers of alcohols **9a**−**b** and acetates **11a**−**b**.

(35) Magnitudes of the *J* constants for coupling protons H_5, H_6 (J_{H5-H6} = 2.3 Hz in lactone **10a**, and J_{H5-H6} = 0 Hz in lactone **10b**) were consistent with dihedral angles anticipated for *cis* diastereomers of lactones **10a**−**b**.

(36) Chiral phase HPLC analysis indicated that the enantiomeric composition of lactone **10a** was close to a racemate. Racemic lactone **10a** was prepared by the method described in Table 4, but replacing the catalyst **1a** with commercially available achiral complex **1c** (Table 1).

TABLE 3. Synthesis of 4,6-Disubstituted Lactones; Diversity in the Aldehyde Component



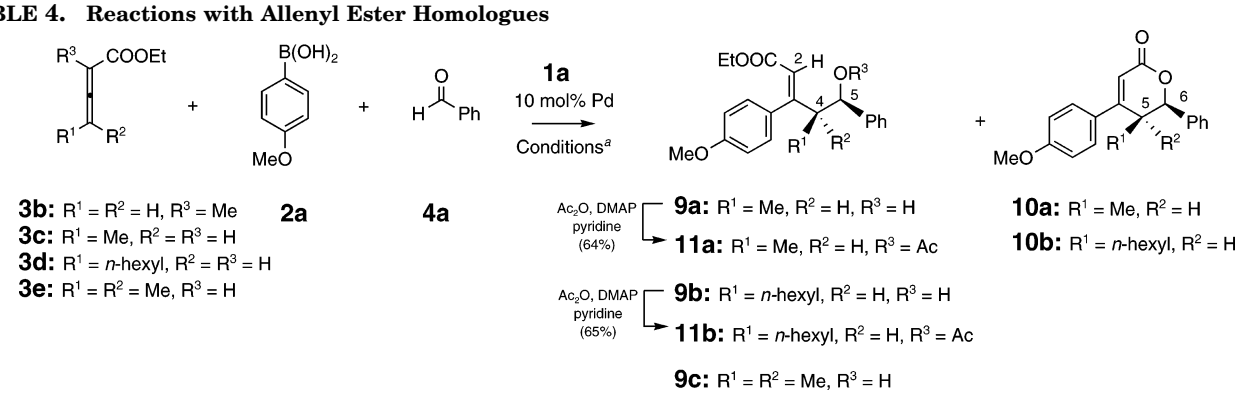
	R^1-B(OH)$_2$	R^2	method[a]	reagent ratios[b] (mol equiv)	lactone **6**	yield (%)	olefin **7**	yield (%)[c]
1		*p*-methoxyphenyl	B	1 : 2.5 : 4	 **6h**	58	-	-
2		*p*-methoxyphenyl	A	2 : 5 : 1	 **6i**	57	 **7a**	55[c]
3		*p*-trifluoromethyl--phenyl	A	2 : 5 : 1	 **6j**	51	-	-
4		*trans*-cinnamyl	B	1 : 2.5 : 4	 **6k**	51	-	-
5		2-furyl	A	2 : 5 : 1	 **6l**	51	-	-
6		cyclohexyl	A	2 : 5 : 1	 **6m**	44	 **7a**	28[c]
7		cyclopropyl	A	2 : 5 : 1	 **6n**	32	-	-

[a] Method A: (i) molar ratio of boronic acid/allene/aldehyde = 2:5:1, CsF (4.0 equiv), THF, rt, 24 h; (ii) K_2CO_3 (2.0 equiv), EtOH, 3−7 h, rt. Method B: same as method A except for molar ratio of boronic acid/allene/aldehyde = 1:2.5:4. [b] Molar ratio of boronic acid/allene/aldehyde. [c] Molar % yield calculated per the boronic acid as the limiting reagent (100 mol %).

be directly applied to other types of electron-deficient allenes of the general formula CH_2=C=CHX (X = SO_2-Ph, $CONMe_2$, CN, C(O)Me).[37]

Plausible Mechanism. A plausible catalytic cycle for a reaction mediated by complex **1a** involves transmetalation,[38] ligand exchange equilibrium, followed by migratory insertion of allenes[39] yielding unsymmetrical bis-π-allylpalladium intermediate **III** (compare Figure 3 and Figure 1).[12,13] Nucleophilic complex **III** then reacts with aldehydes,[10] providing the homoallylic products, and the aryl(allyl)palladium(II) complex is regenerated via transmetalation (Figure 3). Although a sensitivity of bis-π-allylpalladium complexes to protonation was reported,[40] our observations suggest that the olefinic byproducts **7** could also arise via a retro-allylation event competing with lactonization.[40] No alcohols formed by a direct attack of boronic acids on aldehydes were detected.[41] The effect of the reagent ratios on the yields of homoallylic products proved to be complex and dependent on the nature of the aldehyde and the allene[26] components and solvents, presumably affecting the position of the ligand exchange equilibrium (Tables 2-4). The regiochemical outcome of

TABLE 4. Reactions with Allenyl Ester Homologues



	allenes **3**				alcohols **9**				lactones **10**			
		R^1	R^2	method[a]		R^1	R^2	yield (%)		R^1	R^2	yield (%)
1	**3c**	Me	H	A	**9a**	Me	H	39[b]	**10a**	Me	H	26
2	**3d**	*n*-hexyl	H	C	**9b**	*n*-hexyl	H	18[b]	**10b**	*n*-hexyl	H	29
3	**3e**	Me	Me	A	**9c**	Me	Me	28				

[a] Conditions: Method A: (i) molar ratio of boronic acid/allene/aldehyde = 2:5:1, CsF (4.0 equiv), THF, rt, 24 h; (ii) K_2CO_3, (2.0 equiv), EtOH, 3−7 h, rt. Method C: (i) molar ratio of boronic acid/allene/aldehyde = 1:1.5:4, CsF (2.0 equiv), THF, rt, 24 h; (ii) K_2CO_3, (2.0 equiv), EtOH, 5.5 h, rt. [b] The yield is reported for a compound of 95% purity by ^{1}H NMR.

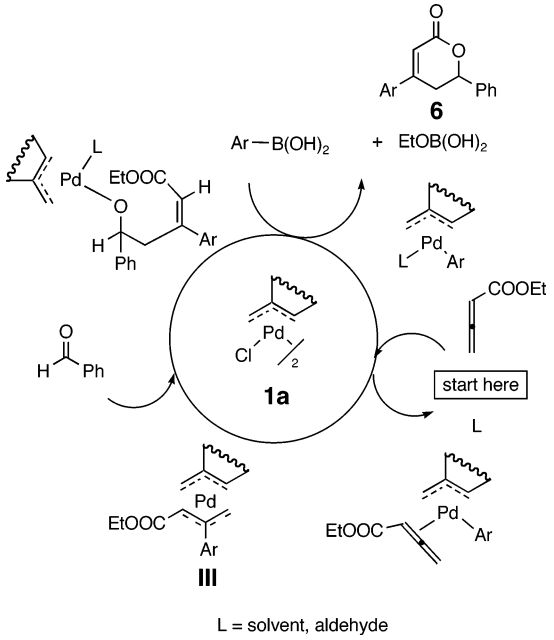


FIGURE 3. Proposed catalytic cycle.

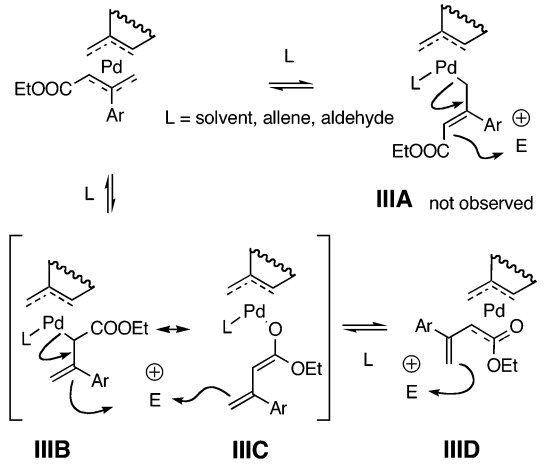
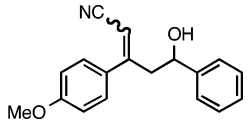


FIGURE 4. Proposed structures of nucleophilic allyl-transfer intermediates.

the described protocol revealed that the anticipated[15] attack of the aldehyde at the substituted vinylic terminus of the η^3,η^1-bonded complex **IIIA** did not occur (Figure 4). Instead, the results can be rationalized by the intervention of C- or O-bonded resonance forms of the palladium(II) ester enolate **IIIB** and **IIIC**,[42] respectively, or the η^3,η^3-bonded bis-π-oxoallylpalladium complex **IIID**,[43] which would be attacked by electrophiles selectively at the allene terminus lacking the ester substituent (Figure 4). In agreement with the experiment, the regiochemistry of the allylation via complexes **IIIB-D** would not be dependent on the presence of alkyl substituents at the vinylic terminus (see results in Table 4),

(37) Treatment of 1,2-propadienyl phenyl sulfone (X = SO_2Ph) or *N*,*N*-dimethyl 2,3-butadienamide (X = $CONMe_2$) with boronic acid **2a** and benzaldehyde **4a** under the standard coupling conditions (Scheme 1, no lactonization) did not afford the desired alcohols, and unreacted substrates along with small quantities (<10%) of olefinic byproducts arising from coupling of the allenes and the boronic acid were isolated. Under the same conditions, 3,4-pentadiene-2-one (X = C(O)Me) and 2,3-butadienenitrile (X = CN) afforded rather complex reaction mixtures containing several products of the three-component coupling. The alcohol shown below could be isolated in 22% yield.



(38) CsF additive activated the boronic acids for transmetalation; see: (a) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097. For selected reactions catalyzed by diverse transition metal complexes, which involve transmetalation from boronic acids to transition metals as the event that initiates the catalytic cycle, see: (b) Andeppan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218−219. (c) Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 169−171. (d) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231−2234. (e) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358−5359. (f) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313−3316.

although the increase in the steric hindrance would affect the reaction rates.

An alternative pathway involving allylation via free allylmetal species could not be rigorously ruled out. However, although a reductive transmetalation of mono-π-allylpalladium complexes with Et_3B yielding allyl boron reagents is known,[44] a transmetalation (an aryl-allyl exchange) between the nucleophilic bis-π-allylpalladium complexes and the cesium arylfluoroborates (ArFB-$(OH)_2Cs$) is not precedented and appears unlikely. Furthermore, the described three-component coupling reaction was successfully realized employing *p*-methoxyphenyl(trimethyl)stannane instead of the corresponding boronic acid.[45] Considering the differences in reactivity of free allylstannanes and allylboronic acids with aldehydes,[46] this experiment strengthens the proposed mechanistic rationale. The low efficiency of the asymmetry transfer in the presented work could arise from the involvement of an "open" transition state lacking the coordination of aldehyde to palladium,[13,47] in contrast to "closed" transition states proposed for Yamamoto's allylations of imines.[12] The relative magnitudes of steric hindrance between substituents at the "preassembled" allyl ligand (e.g., COOEt, Ar and H, Me or *n*-hexyl) would control the preference for formation of either (*E*)- or (*Z*)-homoallylic alcohols.[47] The generation of low yields of lactone **6a** from reactions catalyzed by other palladium(II) catalysts (see entries 7−10, Table 1) might proceed via symmetrical bis-π-allylpalladium(II) complex bearing 2 equiv of the "preassembled" allyl fragment[10,13] or by allylation via an η^1-bonded nucleophilic (η^1-allyl)(aryl)-Pd(II)L_2 complex.[48] These intermediates, however, suffer from a poor stability revealed by the precipitation of palladium(0) (entries 7−10, Table 1).

Conclusions

A new, convergent palladium-catalyzed method for a one-pot assembly of substituted α,β-unsaturated δ-lactones generating three new bonds in one synthetic operation has been demonstrated. Aromatic, vinylic, and heteroaromatic boronic acids and aldehydes reacted with ethyl 2,3-butadienoate and its homologues to afford di- and trisubstituted α,β-unsaturated δ-hydroxy esters and the corresponding δ-lactones in combined 47−78% yields, under mild conditions, and with excellent chemo-, regio-, and diastereoselectivity. The protocol relies on an exclusive regiocontrol by the ester substituent, and the regiochemical outcome is opposite to analogous transformations with alkyl-substituted allenes.[13] The reaction represents the first example of a tandem C-3 nucleophilic/C-4 electrophilic (RCH=C=CHCOOEt → (E)RCH−C(Nu)=CHCOOEt) bisfunctionalization of allenyl esters. Results described herein highlight the synthetic potential of unsymmetrical bis-π-allylpalladium complexes as catalytic intermediates in cascade and multicomponent sequences. Studies toward the extension of the new methodology to elaboration of imines and the development of an efficient asymmetric variant are in progress.

Experimental Section

(*E*)-Ethyl 5-hydroxy-3-(*p*-methoxyphenyl)-5-phenylpent-2-enoate (5) and 5,6-Dihydro-4-(*p*-methoxyphenyl)-6-phenyl-2*H*-pyran-2-one (6a).[13] To a solution of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (0.069 g, 0.452 mmol, 2.0 equiv), and CsF (0.137 g, 0.905 mmol, 4.0 equiv) in THF (5 mL) was simultaneously injected neat benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv) and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv). The solution was stirred for 24 h under argon. Water (20 mL) was

(39) For a palladium-catalyzed synthesis of dienes via a reaction of boronic acids with allenes, see: Oh, C. H.; Ahn, T. W.; Reddy, R. V. *Chem. Commun.* **2003**, 2622−2623.

(40) For a discussion on the sensitivity of bis-π-allylpalladium complexes to protonation by traces of water, see refs 10c,d,f. An experiment involving treatment of isolated alcohol **5** with K_2CO_3 in EtOH gave rise to small quantities of the corresponding olefinic byproduct of type **7**, suggesting that modifications to the lactonization procedure might be warranted, depending on the electronic properties of the boronic acids and aldehydes used. Alternative pathways providing the olefinic byproducts via palladium(0)-mediated steps appear unlikely, since precipitation of palladium(0) was not observed and the reaction remained catalytic in palladium.

(41) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450−4452.

(42) For a discussion of the different bonding modes available to palladium enolates, see: (a) Tian, G.; Boyle, P. D.; Novak, B. M. *Organometallics* **2002**, *21*, 1462−1465. (b) Albeniz, A. C.; Catalina, N. M.; Espinet, P.; Redon, R. *Organometallics* **1999**, *18*, 5571−5576.

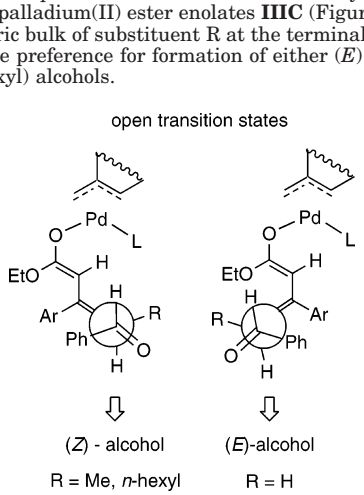
(43) For a discussion of the chemistry of η^3-oxoallylpalladium(II) complexes, see: (a) Lemke, F. R.; Kubiak, C. P. *J. Organomet. Chem.* **1989**, *373*, 391−400. (b) Yanase, N.; Nakamura, Y.; Kawaguchi, S. *Inorg. Chem.* **1980**, *19*, 1575−1581. (c) Yoshimura, N.; Murahashi, S.-I.; Moritani, I. *J. Organomet. Chem.* **1973**, *52*, C58−C60.

(44) In situ formation of allylboron reagents via reduction of mono-π-allylpalladium complexes with Et_3B (reduction failed with Ph_3B) is known, see: Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795−6798.

(45) Treatment of arylstannane (*p*-methoxyphenyl(trimethyl)tin, 1.2 equiv) with benzaldehyde **4a** (1.0 equiv), ethyl 2,3-butadienoate **3a** (5.0 equiv), and with catalyst **1a** (10 mol % Pd) in THF (60 °C, 24 h) followed by the standard (Table 1) lactonization conditions afforded lactone **6a** in 59% yield, and no regioisomeric products were detected in the crude reaction mixture. The elevated temperature was required to ensure an efficient transmetalation. In a control experiment reported in an earlier communication (ref 13), the addition of allyltributyltin to benzaldehyde at 60 °C failed to afford any homoallylic alcohol products. For a discussion of the mechanism of Pd(II)-catalyzed reactions of allylstannanes with aldehydes proposing the involvement of bis-π-allylpalladium complexes, see ref 10k.

(46) Allylboronic acids and allylboranes undergo facile uncatalyzed reactions with aldehydes; see: (a) Brown, H. C.; Racherla, Y. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1866−1874. (b) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5400−5403. The presence of a Lewis acid catalyst is required to enable the reactions between allylstannanes and aldehydes, see: (c) Maruyama, K.; Ishihara, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1981**, *22*, 4235−4238. For a general discussion, see: (d) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 3rd ed.; Plenum Press: New York, 1993; Chapter 9.

(47) Proposed "open" transition states for the allyl transfer from O-bonded allylpalladium(II) ester enolates **IIIC** (Figure 4) are shown below. The steric bulk of substituent R at the terminal vinylic carbon may control the preference for formation of either (*E*) (R = H) or (*Z*) (R = Me, *n*-hexyl) alcohols.



(48) Kurosawa, H.; Urabe, A. *Chem. Lett.* **1985**, 1839−1840.

added, and the mixture was extracted with ether (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford a crude product that was separated by flash chromatography over silica eluting with EtOAc/hexane (1:3), to afford alcohol **5** (0.037 g, 49%) as a clear colorless oil and lactone **6a** (0.032 g, 51%)[13] as a white solid.

Analytical data for alcohol 5: R_f = 0.49 (EtOAc/hexane, 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.8 Hz, 2.0 Hz, 2 H), 7.41 (d, J = 7.1 Hz, 2 H), 7.33 (t, J = 7.8 Hz, 2 H), 7.24 (t, J = 6.8 Hz, 1 H), 6.91 (dd, J = 8.8 Hz, 2.0 Hz, 2 H), 6.23 (s, 1 H), 4.76−4.73 (m, 1 H), 4.29−4.18 (m, 2 H), 3.91 (d, J = 6.3 Hz, 1 H), 3.84 (s, 3 H), 3.69 (dd, J = 13.5 Hz, 10.2 Hz, 1 H), 3.17 (dd, J = 13.5 Hz, 3.3 Hz, 1 H), 1.32 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 160.7, 156.2, 145.1, 132.6, 128.4 (2 carbons), 128.3 (2 carbons), 127.7, 125.5 (2 carbons), 118.0, 114.1 (2 carbons), 73.6, 61.1, 55.3, 41.2, 14.3; IR (neat, cm^{-1}) 3433 (m br), 1701 (s), 1683 (s), 1602 (s), 1027 (m); HRMS (ES$^+$) calcd for $C_{20}H_{23}O_4$ (M + H$^+$) 327.1596, found 327.1587.

Analytical data for lactone 6a: mp 126−127 °C (ether) [lit. 120−122 °C (EtOAc/hexane, 3:4)[13]].

General Procedures for the Preparation of α,β-Unsaturated-δ-Lactones 6. Method A. To a solution of (+)-(3,2,-10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), boronic acid **2** (2.0 equiv), and CsF (4.0 equiv) in THF (5 mL) was simultaneously injected neat aldehyde **4** (1.0 equiv) and ethyl 2,3-butadienoate **3a** (5.0 equiv). **Method B.** To a solution of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), boronic acid **2** (1.0 equiv), and CsF (2.0 equiv) in THF (5 mL) was simultaneously injected neat aldehyde **4** (4.0 equiv) and ethyl 2,3-butadienoate **3a** (2.5 equiv). A common protocol was subsequently used for both Method A and B. The reaction mixture was stirred for 24 h under argon followed by the addition of solid anhydrous K_2CO_3 (0.063 g, 0.455 mmol, 2.0 equiv) and EtOH (5 mL). The resulting suspension was stirred under argon for an additional 3−7 h. Water (20 mL) was added, and the mixture was extracted with ether (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford crude products that were separated by flash chromatography over silica, eluting with EtOAc/hexane mixtures to yield lactones **6** as white solids or colorless oils.

5,6-Dihydro-4-(*p*-methoxyphenyl)-6-phenyl-2*H*-pyran-2-one (6a).[13] Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 3.0 h, and eluting with EtOAc/hexane (1:3) afforded lactone **6a** (0.047 g, 75%) as a white solid.[13]

5,6-Dihydro-6-phenyl-4-(3,4,5-trimethoxyphenyl)-2*H*-pyran-2-one (6b) and Ethyl 3-(3,4,5-Trimethoxyphenyl)-but-3-enoate (7a). Method A. Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), 3,4,5-(trimethoxy)phenylboronic acid (0.096 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to the Method A, including the treatment with K_2CO_3 for 5.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6b** (0.043 g, 57%) as a white solid and olefin **7a** (0.058 g, 46% calculated per boronic acid as the limiting reagent) as a clear colorless oil. **Method B.** Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), 3,4,5-(trimethoxy)phenylboronic acid (0.056 g, 0.265 mmol, 1.0 equiv), CsF (0.080 g, 0.526 mmol, 2.0 equiv), benzaldehyde **4a** (0.112 g, 1.06 mmol, 108 μL, 4.0 equiv), and ethyl 2,3-butadienoate **3a** (0.074 g, 0.662 mmol, 77 μL, 2.5 equiv) according to Method B, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6b** (0.070 g, 78%) as a white solid and olefin **7a** (0.012 g, 16% calculated per boronic acid as the limiting reagent) as a clear colorless oil.

Analytical data for lactone 6b: mp 165−167 °C (ether); R_f = 0.49 (EtOAc/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2 H), 7.46−7.25 (m, 3 H), 6.75 (s, 2 H), 6.42 (d, J = 1.7 Hz, 1 H), 5.53 (dd, J = 10.6 Hz, 5.1 Hz, 1 H), 3.90 (s, 3 H), 3.89 (s, 6 H), 3.07−2.95 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 154.4, 153.5 (2 carbons), 140.5, 138.6, 131.3, 128.9, 128.8 (2 carbons), 126.2 (2 carbons), 114.5, 103.5 (2 carbons), 78.9, 61.0, 56.3 (2 carbons), 34.5; IR (neat, cm^{-1}) 1710 (s), 1240 (m), 1130 (m); HRMS (ES$^+$) calcd for $C_{20}H_{21}O_5$ (M + H$^+$) 341.1389, found 341.1370.

Analytical data for olefin 7a: R_f = 0.45 (EtOAc/hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 2 H), 5.49 (s, 1 H), 5.21 (d, J = 0.8 Hz, 1 H) 4.12 (q, J = 7.1 Hz, 2 H), 3.86 (s, 3 H), 3.84 (s, 6 H), 3.48 (d, J = 0.7 Hz, 2 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 152.9 (2 carbons), 140.9, 135.9, 135.7, 115.9, 103.2 (2 carbons), 60.9, 60.8, 56.1 (2 carbons), 41.6, 14.1; IR (neat, cm^{-1}) 1731 (s), 1581 (s), 1245 (m), 908 (m), 840 (m), 703 (s); HRMS (ES$^+$) calcd for $C_{15}H_{21}O_5$ (M + H$^+$) 281.1389, found 281.1373.

5,6-Dihydro-4-(*p*-methylcarbonylphenyl)-6-phenyl-2*H*-pyran-2-one (6c) and Ethyl 3-(*p*-Methylcarbonylphenyl)-but-3-enoate (7b). Method A. Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methylcarbonylphenylboronic acid (0.074 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6c** (0.037 g, 55%) as a white solid and olefin **7b** (0.045 g, 43% calculated per boronic acid as the limiting reagent) as a clear colorless oil. **Method B.** Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), *p*-methylcarbonylphenylboronic acid (0.043 g, 0.265 mmol, 1.0 equiv), CsF (0.080 g, 0.526 mmol, 2.0 equiv), benzaldehyde **4a** (0.112 g, 1.06 mmol, 108 μL, 4.0 equiv), and ethyl 2,3-butadienoate **3a** (0.074 g, 0.662 mmol, 77 μL, 2.5 equiv) according to the Method B, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6c** (0.045 g, 59%) as a white solid and olefin **7a** (0.009 g, 14% calculated per boronic acid as the limiting reagent) as a clear colorless oil.

Analytical data for lactone 6c: mp 133−136 °C (ether); R_f = 0.50 (EtOAc/hexane, 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.5 Hz, 2 H), 7.63 (d, J = 8.5 Hz, 2 H), 7.49−7.47 (m, 2 H), 7.45−7.36 (m, 3 H), 6.53 (d, J = 1.9 Hz, 1 H), 5.57 (dd, J = 11.1 Hz, 4.6 Hz, 1 H), 3.13−2.99 (m, 2 H), 2.63 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 164.7, 153.2, 140.2, 138.4, 138.3, 128.9 (2 carbons), 128.84, 128.80 (2 carbons), 126.3 (2 carbons), 126.1 (2 carbons), 116.9, 78.9, 34.2, 26.7; IR (neat, cm^{-1}) 1718 (s), 1685 (s); HRMS (ES$^+$) calcd for $C_{19}H_{17}O_3$ (M + H$^+$) 293.1178, found 293.1161.

Analytical data for olefin 7b: R_f = 0.40 (EtOAc/hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 2 H), 7.51 (d, J = 8.6 Hz, 2 H), 5.63 (s, 1 H), 5.34 (d, J = 0.5 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.53 (d, J = 0.8 Hz, 2 H), 2.59 (s, 3 H), 1.17 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 170.9, 144.4, 140.2, 136.2, 128.5 (2 carbon), 125.9 (2 carbon), 118.4, 60.9, 41.0, 26.6, 14.0; IR (neat, cm^{-1}) 1731 (s), 1681 (s); HRMS (ES$^+$) calcd for $C_{14}H_{17}O_3$ (M + H$^+$) 233.1178, found 233.1165.

4-(*m*-Bromophenyl)-5,6-dihydro-6-phenyl-2*H*-pyran-2-one (6d). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *m*-bromophenylboronic acid (0.091 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13

mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 6.0 h, and eluting with EtOAc/hexane (1:5) afforded lactone **6d** (0.043 g, 58%) as a white solid: mp 107−110 °C (ether); R_f = 0.39 (EtOAc/hexane 1:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 7.58 (d, J = 7.9 Hz, 1 H), 7.49−7.46 (m, 3 H), 7.44−7.37 (m, 3 H), 7.32 (t, J = 7.9 Hz, 1 H), 6.45 (d, J = 1.9 Hz, 1 H), 5.54 (dd, J = 11.3 Hz, 4.3 Hz, 1 H), 3.06−2.95 (m, 2 H);^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 152.9, 138.2, 138.0, 133.6, 130.5, 129.1, 128.8, 128.7 (2 carbons), 126.1 (2 carbons), 124.6, 123.3, 116.2, 78.8, 34.2; IR (neat, cm^{-1}) 1716 (s), 703 (m); HRMS (ES$^+$) calcd for $C_{17}H_{14}BrO_2$ (M + H$^+$) 329.0177, found 329.0154.

5,6-Dihydro-4-(*trans*-2-phenylethenyl)-6-phenyl-2*H*-pyran-2-one (6e). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *trans*-2-phenylvinylboronic acid (0.067 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 3.5 h, and eluting with EtOAc/hexane (1:5) afforded lactone **6e** (0.049 g, 78%) as a white solid: mp 138−141 °C (ether); R_f = 0.52 (EtOAc/hexane,1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 4 H), 7.45−7.43 (m, 2 H), 7.41−7.30 (m, 4 H), 6.95 (s, 2 H), 6.10 (d, J = 1.9 Hz, 1 H), 5.58 (dd, J = 11.9 Hz, 3.8 Hz, 1 H), 2.96 (dd, J = 17.2 Hz, 3.8 Hz, 1 H), 2.82 (ddd, J = 17.2 Hz, 11.9 Hz, 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 152.4, 138.7, 136.5, 135.3, 129.6, 128.9 (2 carbons), 128.7 (2 carbons), 128.6, 127.4 (2 carbons), 126.3, 126.1 (2 carbons), 117.6, 78.7, 31.8; IR (neat, cm^{-1}) 1708 (s), 1244 (m), 964 (m); HRMS (ES$^+$) calcd for $C_{19}H_{17}O_2$ (M + H$^+$) 277.1229, found 277.1227.

5,6-Dihydro-4-(*trans*-1-octenyl)-6-phenyl-2*H*-pyran-2-one (6f). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *trans*-1-octenylboronic acid (0.071 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 6.0 h, and eluting with EtOAc/hexane (1:7) afforded lactone **6f** (0.041 g, 64%) as a clear colorless oil: R_f = 0.53 (EtOAc/hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.33 (m, 5 H), 6.27−6.24 (m, 2 H), 5.89 (d, J = 1.7 Hz, 1 H), 5.40 (dd, J = 11.9 Hz, 3.9 Hz, 1 H), 2.78 (dd, J = 17.4 Hz, 3.9 Hz, 1 H), 2.66 (ddd, J = 17.3 Hz, 11.9 Hz, 1.9 Hz, 1 H), 2.20 (q, J = 7.2 Hz, 2 H), 1.45−1.36 (m, 2 H), 1.33−1.26 (m, 6 H), 0.88 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 152.9, 140.7, 138.8, 128.7, 128.6 (2 carbons), 128.6, 126.1 (2 carbons), 115.7, 78.6, 33.2, 31.8, 31.6, 28.8, 28.7, 22.5, 14.0; IR (neat, cm^{-1}) 1712 (s), 1639 (m), 700 (m); HRMS (ES$^+$) calcd for $C_{19}H_{25}O_2$ (M + H$^+$) 285.1855, found 285.1839.

5,6-Dihydro-4-(3-furyl)-6-phenyl-2*H*-pyran-2-one (6g). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), 3-furylboronic acid (0.051 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:4) afforded lactone **6g** (0.034 g, 62%) as a white solid: mp 104−107 °C (ether/hexane 1:4); R_f = 0.41 (EtOAc/hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s br, 1 H), 7.50 (t, J = 1.9 Hz, 1 H), 7.47−7.35 (m, 5 H), 6.65 (dd, J = 1.9 Hz, 0.4 Hz, 1 H), 6.24 (d, J = 2.1 Hz, 1 H), 5.51 (dd, J = 11.9 Hz, 3.9 Hz, 1 H), 2.94 (ddd, J = 17.4 Hz, 11.9 Hz, 2.2 Hz, 1 H), 2.82 (dd, J = 17.4 Hz, 3.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 146.5, 144.9, 142.5, 138.4, 128.7 (3 carbons), 126.1 (2 carbons), 123.9, 113.0, 107.3, 78.5, 33.8; IR (neat, cm^{-1}) 1712 (s), 1629 (m), 1164 (m); HRMS (ES$^+$) calcd for $C_{15}H_{13}O_3$ (M + H$^+$) 241.0865, found 241.0854.

5,6-Dihydro-4,6-bis(*p*-methoxyphenyl)-2*H*-pyran-2-one (6h). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid (0.040 g, 0.265 mmol, 1.0 equiv), CsF (0.080 g, 0.526 mmol, 2.0 equiv), *p*-methoxybenzaldehyde (0.144 g, 1.06 mmol, 128 μL, 4.0 equiv), and ethyl 2,3-butadienoate **3a** (0.074 g, 0.662 mmol, 77 μL, 2.5 equiv) according to Method B, including the treatment with K_2CO_3 for 6.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6h** (0.047 g, 58%) as a white solid: mp 116−118 °C (ether); R_f = 0.51 (EtOAc/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.9 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H), 6.93 (dd, J = 11.8 Hz, 2.9 Hz, 4 H), 6.39 (s, 1 H), 5.46 (dd, J = 8.8 Hz, 6.8 Hz, 1 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 2.99−2.95 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 161.7, 159.7, 153.9, 130.7, 127.9, 127.7 (2 carbons), 127.6 (2 carbons), 114.3 (2 carbons), 113.9 (2 carbons), 112.7, 78.5, 55.4, 55.3, 33.9; IR (neat, cm^{-1}) 1704 (s), 1604 (m), 1515 (m); HRMS (ES$^+$) calcd for $C_{19}H_{19}O_4$ (M + H$^+$) 311.1283, found 311.1280.

5,6-Dihydro-6-(*p*-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-2*H*-pyran-2-one (6i) and Ethyl 3-(3,4,5-Trimethoxyphenyl)-but-3-enoate (7a). Treatment of (+)-(3,2,10-η-pinene)-palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), 3,4,5-(trimethoxy)phenylboronic acid (0.096 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), *p*-methoxybenzaldehyde (0.031 g, 0.226 mmol, 28 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:2) afforded olefin **7a** (0.069 g, 55% calculated per boronic acid as the limiting reagent) as a clear colorless oil and lactone **6i** (0.048 g, 57%) as a white solid: mp 169−171 °C (ether); R_f = 0.37 (EtOAc/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.7 Hz, 2 H), 6.96 (d, J = 8.7 Hz, 2 H), 6.75 (s, 2 H), 6.41 (d, J = 2.0 Hz, 1 H), 5.48 (dd, J = 11.6 Hz, 4.1 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 6 H), 3.83 (s, 3 H), 3.03 (ddd, J = 17.6 Hz, 11.8 Hz, 2.2 Hz, 1 H), 2.93 (dd, J = 17.6 Hz, 4.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 159.9, 154.7, 153.5 (2 carbons), 140.4, 131.3, 130.6, 127.7 (2 carbons), 114.5, 114.0 (2 carbons), 103.4 (2 carbons), 78.7, 60.9, 56.3 (2 carbons), 55.3, 34.4; IR (neat, cm^{-1}) 1708 (s), 1130 (m), 833 (w); HRMS (ES$^+$) calcd for $C_{21}H_{23}O_6$ (M + H$^+$) 371.1495, found 371.1485.

5,6-Dihydro-4-(*p*-methoxyphenyl)-6-(*p*-trifluoromethylphenyl)-2*H*-pyran-2-one (6j). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), *p*-trifluoromethylbenzaldehyde (0.040 g, 0.226 mmol, 31 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 6.0 h, and eluting with EtOAc/hexane (1:3) afforded lactone **6j** (0.041 g, 51%) as a white solid: mp 162−164 °C (ether); R_f = 0.51 (EtOAc/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.3 Hz, 2 H), 7.61 (d, J = 8.2 Hz, 2 H), 7.52 (d, J = 7.9 Hz, 2 H), 6.95 (d, J = 8.9 Hz, 2 H), 6.41 (d, J = 2.0 Hz, 1 H), 5.59 (dd, J = 11.8 Hz, 3.9 Hz, 1 H), 3.86 (s, 3 H), 3.05 (dd, J = 17.5 Hz, 4.0 Hz, 1 H), 2.95 (ddd, J = 17.4 Hz, 11.8 Hz, 2.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 161.9, 153.7, 142.7, 130.8 (q, J (^{31}C−^{19}F) = 32.4 Hz), 127.7 (2 carbons), 127.6, 126.4 (2 carbons), 125.7 (q, J (^{31}C−^{19}F) = 3.7 Hz, 2 carbons), 123.9 (q, J (^{31}C−^{19}F) = 270.5 Hz), 114.5 (2 carbons), 112.7, 77.8, 55.5, 34.0; IR (neat, cm^{-1}) 1710 (s), 1326 (s), 1247 (s), 1066 (m); HRMS (ES$^+$) calcd for $C_{19}H_{16}F_3O_3$ (M + H$^+$) 349.1052, found 349.1039.

5,6-Dihydro-4-(*p*-methoxyphenyl)-6-(*trans*-2-phenylethenyl)-2*H*-pyran-2-one (6k). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid (0.040 g, 0.265 mmol, 1.0 equiv), CsF (0.080 g, 0.526 mmol, 2.0 equiv), *trans*-cinnamylaldehyde (0.140 g, 1.06 mmol, 133 μL, 4.0 equiv), and ethyl 2,3-butadienoate **3a** (0.074 g, 0.066 mmol, 77 μL, 2.5 equiv) according to Method B, including the treatment with K_2CO_3

for 6.5 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6k** (0.041 g, 51%) as a white solid: mp 144−146 °C (ether); R_f = 0.38 (EtOAc/hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.9 Hz, 2 H), 7.41 (d, J = 7.4 Hz, 2 H), 7.34 (t, J = 7.1 Hz, 2 H), 7.29 (d, J = 7.3 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 15.9 Hz, 1 H), 6.36 (dd, J = 15.9 Hz, 6.3 Hz, 1 H), 6.34 (s, 1 H), 5.17 (pent, J = 5.3 Hz, 1 H), 3.86 (s, 3 H), 2.96 (dd, J = 17.4 Hz, 4.2 Hz, 1 H), 2.86 (ddd, J = 17.4 Hz, 10.7 Hz, 1.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 161.8, 153.7, 135.8, 133.2, 128.7 (2 carbons), 128.3, 128.0, 127.6 (2 carbons), 126.7 (2 carbons), 125.8, 114.4 (2 carbons), 112.8, 77.3, 55.5, 32.1; IR (neat, cm^{-1}) 1704 (s), 1604 (m), 1421 (m); HRMS (ES$^+$) calcd for $C_{20}H_{19}O_3$ (M + H$^+$) 307.1334, found 307.1322.

5,6-Dihydro-6-(furan-2-yl)-4-(*p*-methoxyphenyl)-2*H*-pyran-2-one (6l). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), 2-furaldehyde (0.022 g, 0.226 mmol, 19 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:2) afforded lactone **6l** (0.032 g, 51%) as a white solid: mp 114−115 °C (ether); R_f = 0.52 (EtOAc/hexane, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.9 Hz, 2 H), 7.44 (dd, J = 1.7 Hz, 0.8 Hz, 1 H), 6.96 (d, J = 8.9 Hz, 2 H), 6.47 (d, J = 3.3 Hz, 1 H), 6.40 (dd, J = 3.3 Hz, 1.8 Hz, 1 H), 6.35 (d, J = 1.7 Hz, 1 H), 5.57 (dd, J = 10.9 Hz, 4.1 Hz, 1 H), 3.86 (s, 3 H), 3.27 (ddd, J = 17.5 Hz, 10.9 Hz, 2.0 Hz, 1 H), 3.06 (dd, J = 17.5 Hz, 4.1 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 161.8, 153.6, 150.8, 143.0, 127.9, 127.7 (2 carbons), 114.4 (2 carbons), 112.6, 110.5, 108.9, 71.9, 55.5, 29.9; IR (neat, cm^{-1}) 1710 (s), 1604 (m), 1247 (s), 1031 (m), 1014 (m); HRMS (ES$^+$) calcd for $C_{16}H_{15}O_4$ (M + H$^+$) 271.0970, found 271.0960.

5,6-Dihydro-6-cyclohexyl-4-(3,4,5-trimethoxyphenyl)-2*H*-pyran-2-one (6m) and Ethyl 3-(3,4,5-Trimethoxyphenyl)-but-3-enoate (7a). Treatment of (+)-(3,2,10-η-pinene)-palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), 3,4,5-(trimethoxy)phenylboronic acid (0.096 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), cyclohexanecarboxaldehyde (0.025 g, 0.226 mmol, 27 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 6.5 h, and eluting with EtOAc/hexane (1:3) afforded olefin **7a** (0.036 g, 28% calculated per boronic acid as the limiting reagent) as a clear colorless oil and lactone **6m** (0.034 g, 44%) as a white solid: mp 132−133 °C (ether); R_f = 0.39 (EtOAc/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 2 H), 6.28 (d, J = 1.9 Hz, 1 H), 4.27 (pent, J = 5.5 Hz, 1 H), 3.90 (s, 6 H), 3.88 (s, 3 H), 2.73 (ddd, J = 17.4 Hz, 11.7 Hz, 2.1 Hz, 1 H), 2.65 (dd, J = 17.4 Hz, 4.2 Hz, 1 H), 2.00 (d, J = 12.2 Hz, 1 H), 1.83−1.69 (m, 5 H), 1.31−1.11 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 154.9, 153.4 (2 carbons), 140.3, 131.9, 114.7, 103.5 (2 carbons), 81.5, 60.9, 56.3 (2 carbons), 41.7, 29.1, 28.5, 28.2, 26.2, 25.9, 25.8; IR (neat, cm^{-1}) 1703 (s), 1419 (m), 1130 (m), 894 (m); HRMS (ES$^+$) calcd for $C_{20}H_{27}O_5$ (M + H$^+$) 347.1858, found 347.1843.

5,6-Dihydro-6-cyclopropyl-4-(*p*-methoxyphenyl)-2*H*-pyran-2-one (6n). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), cyclopropanecarboxaldehyde (0.016 g, 0.226 mmol, 17 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 6.0 h, and eluting with EtOAc/hexane (1:3) afforded lactone **6n** (0.018 g, 32%) as a white solid: mp 70−72 °C (ether/hexane 1:4); R_f = 0.43 (EtOAc/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 2 H), 6.95 (d, J = 8.7 Hz, 2 H), 6.28 (d, J = 1.8 Hz, 1 H), 3.85 (s, 3 H), 3.80−3.67 (m, 1 H), 2.91 (dd, J = 17.5 Hz, 4.3 Hz, 1 H), 2.83 (ddd, J = 17.5 Hz, 10.9 Hz, 1.8 Hz, 1 H), 1.36−1.19 (m, 1 H), 0.73−0.61 (m, 2 H), 0.6−0.5 (m, 1 H), 0.37−0.31 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 161.6, 153.9, 128.3, 127.6 (2 carbons), 114.3 (2 carbons), 112.7, 81.8, 55.4, 31.7, 14.9, 3.5, 2.2; IR (neat, cm^{-1}) 1701 (s), 1604 (m), 1182 (m), 1037 (m); HRMS (ES$^+$) calcd for $C_{15}H_{17}O_3$ (M + H$^+$) 245.1178, found 245.1178.

Synthesis of an Inseparable Mixture of 4-(*N*-*tert*-Butoxycarbonyl-5-bromoindol-2-yl)-5,6-dihydro-6-phenyl-2*H*-pyran-2-one (6o) and (*E*)-Ethyl 3-(*N*-*tert*-Butoxycarbonyl-5-bromoindol-2-yl)-5-hydroxy-5-phenylpent-2-enoate (8). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), (*N*-*t*-butoxycarbonyl-5-bromo-1*H*-indol-2-yl)boronic acid **2b** (0.154 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 2,3-butadienoate **3a** (0.127 g, 1.13 mmol, 131 μL, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 4.0 h, and eluting with EtOAc/hexane (1:5) afforded an inseparable mixture of alcohol **8** and lactone **6o** (0.075 g, combined yield 65%) as a white solid in a 1:0.7 molar ratio of **8**:**6o**, as indicated by ^{1}H NMR (in repeated experiments, the ratio of alcohol **8** to lactone **6o** was found to vary between 1:4 to 1:0.5).

Analytical data (^{1}H NMR) for the mixture of 8 and 6o in 1:0.7 ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 7.84 (d, J = 8.9 Hz, 0.7 H), 7.75 (d, J = 1.7 Hz, 1 H), 7.70 (d, J = 1.9 Hz, 0.7 H), 7.5−7.27 (m, 11.2 H), 6.84 (d, J = 1.5 Hz, 1 H), 6.65 (s, 0.7 H), 6.33 (s, 1 H), 6.25 (d, J = 1.8 Hz, 0.7 H), 5.86 (dd, J = 8.3 Hz, 4.9 Hz, 1 H), 5.68 (dd, J = 10.4 Hz, 5.5 Hz, 0.7 H), 4.01 (dd, J = 13.5 Hz, 4.9 Hz, 2 H), 3.98 (dd, J = 12.4 Hz, 4.9 Hz, 1 H), 3.20 (dd, J = 13.4 Hz, 8.4 Hz, 1 H), 2.91−2.80 (m, 1.4 H), 1.69 (s, 9 H), 1.32 (s, 6.3 H), 1.28 (t, J = 7.2 Hz, 3 H).

4-(5-Bromoindol-2-yl)-5,6-dihydro-6-phenyl-2*H*-pyran-2-one (6p). A mixture of alcohol **8** and lactone **6o** (**8**:**6o** = 1:4 molar ratio by ^{1}H NMR, 0.030 g) prepared as described above was dissolved in CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) and stirred at room temperature under argon for 2.5 h. Saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced pressure to afford lactone **6p** (0.021 g, 93%) as a white solid: mp 263−265 °C decomp (ether); R_f = 0.51 (EtOAc/hexane, 2:3); ^{1}H NMR (500 MHz, acetone-d_6) δ 7.79 (s, 1 H), 7.58 (d, J = 7.6 Hz, 2 H), 7.45 (t, J = 7.5 Hz, 2 H), 7.41−7.38 (m, 2 H), 7.33 (d, J = 8.7 Hz, 1 H), 7.09 (s, 1 H), 6.51 (d, J = 1.5 Hz, 1 H), 5.66 (dd, J = 11.9 Hz, 3.4 Hz, 1 H), 3.29 (dd, J = 17.4 Hz, 3.4 Hz, 1 H), 3.10 (ddd, J = 17.2 Hz, 11.9 Hz, 1.5 Hz, 1 H), 2.88 (s, 1 H); ^{13}C NMR (125 MHz, acetone-d_6) δ 165.5, 146.7, 140.6, 138.2, 136.5, 131.1, 129.7 (2 carbons), 129.5, 128.2, 127.5 (2 carbons), 124.8, 114.5, 113.9, 112.8, 106.9, 79.6, 33.4; IR (neat, cm^{-1}) 3299 (s), 1672 (s), 1620 (m), 1419 (m), 896 (m), 842 (m); HRMS (ES$^+$) calcd for $C_{19}H_{15}NBrO_2$ (M + H$^+$) 368.0286, found 368.0271.

General Procedures for the Preparation of Substituted α,β-Unsaturated δ-Lactones 10a−b, Alcohols 9a−c, and Acetates 11a−b. Method A. To a solution of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (2.0 equiv), CsF (4.0 equiv), and allene **3** (5.0 equiv) in THF (5 mL) was injected neat benzaldehyde **4a** (1.0 equiv). **Method C.** To a solution of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (1.0 equiv), CsF (2.0 equiv), and allene **3** (1.5 equiv) in THF (5 mL) was injected neat benzaldehyde **4a** (4.0 equiv). A common protocol was subsequently used for both Method A and C. The reaction mixture was stirred for 24 h under argon followed by the addition of solid anhydrous K_2CO_3 (0.063 g, 0.455 mmol, 2.0 equiv) and EtOH (5 mL). The resulting suspension was stirred under argon for an additional 3−7 h. Water (20 mL) was added, and the mixture was extracted with ether (2 × 20 mL) and CH_2Cl_2 (2 × 20 mL). Organic extracts were dried ($MgSO_4$), and the solvents were removed under reduced

pressure to afford crude products that were separated by flash chromatography over silica, eluting with EtOAc/hexane mixtures, to yield alcohols **9a**−**c** as colorless oils and lactones **10a**−**c** as white solids or oils. Alcohols **9a**−**b** were isolated in approximately 95% purity (^{1}H NMR), and their complete characterization was accomplished after conversion[49] into *O*-acetates **11a**−**b** as described below.

(±)-(*Z*)-(4*S*,5*R*)-Ethyl 5-Acetoxy-3-(*p*-methoxyphenyl)-4-methyl-5-phenylpent-2-enoate (11a) and (±)-(5*S*,6*R*)-5,6-Dihydro-4-(*p*-methoxyphenyl)-5-methyl-6-phenyl-2*H*-pyran-2-one (10a). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and (±)-ethyl penta-2,3-dienoate **3c** (0.143 g, 1.13 mmol, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 5.0 h, and eluting with EtOAc/hexane (1:3) afforded alcohol **9a** (0.028 g, 39%) in 95% purity by ^{1}H NMR as a clear colorless oil and lactone **10a** (0.017 g, 26%) as a white solid.

To a solution of alcohol **9a** (95% purity by ^{1}H NMR) (0.019 g, 0.059 mmol) in pyridine (3 mL) was added acetic anhydride (0.012 g, 0.118 mmol, 11 μL) and DMAP (0.001 g, 0.012 mmol). The solution was stirred at 60 °C under argon for 20 h. The crude reaction mixture was poured into 10% HCl (20 mL) and extracted with diethyl ether (3 × 20 mL). Organic extracts were dried ($MgSO_4$), and solvents were removed under reduced pressure to afford a crude product that was purified by flash chromatography over silica eluting with EtOAc/hexane (1:4) to yield acetate **11a** (0.014 g, 64%) as a clear colorless oil.

Analytical data for lactone 10a: mp 109−112 °C (ether/hexane, 1:4); R_f = 0.46 (EtOAc/hexane, 2:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 6.9 Hz, 1.9 Hz, 2 H), 7.33−7.32 (m, 4 H), 7.29−7.27 (m, 1 H), 6.92 (dd, J = 6.9 Hz, 1.9 Hz, 2 H), 6.20 (s, 1 H), 5.52 (d, J = 2.3 Hz, 1 H), 3.83 (s, 3 H), 3.42 (qd, J = 7.0 Hz, 2.3 Hz, 1 H), 1.43 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 161.6, 158.0, 139.1, 128.6 (2 carbons), 128.0, 127.8 (2 carbons), 127.6, 125.9 (2 carbons), 114.4 (2 carbons), 112.8, 83.1, 55.4, 35.6, 19.1; IR (neat, cm^{-1}) 1716 (s), 1604 (m), 1514 (m); HRMS (ES$^+$) calcd for $C_{19}H_{19}O_3$ (M + H$^+$) 295.1334, found 295.1320.

Analytical data (^{1}H NMR) for alcohol 9a: R_f = 0.44 (EtOAc/hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.23 (m, 5 H), 7.06 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 5.94 (s, 1 H), 4.69 (t, J = 3.6 Hz, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), 3.82 (s, 3 H), 2.92−2.86 (m, 1 H), 1.80 (d, J = 2.5 Hz, 1 H),1.12 (d, J = 6.9 Hz, 3 H), 1.10 (t, J = 7.1 Hz, 3 H).

Analytical data for Acetate 11a: R_f = 0.38 (EtOAc/hexane, 2:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.22 (m, 3 H), 7.16 (d, J = 7.2 Hz, 2 H), 6.95 (d, J = 8.5 Hz, 2 H), 6.84 (d, J = 8.6 Hz, 2 H), 5.85 (s, 1 H), 5.76 (d, J = 5.3 Hz, 1 H), 3.98 (qd, J = 7.1 Hz, 2.2 Hz, 2 H), 3.81 (s, 3 H), 3.00 (pent, J = 6.2 Hz, 1 H), 2.07 (s, 3 H), 1.20 (d, J = 6.9 Hz, 3 H), 1.08 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 166.2, 159.3, 159.2, 139.1, 132.1, 128.8 (2 carbons), 128.2 (2 carbons), 127.7, 126.5 (2 carbons), 118.8, 113.3 (2 carbons), 76.2, 59.9, 55.2, 48.4, 20.9, 14.1, 13.9; IR (neat, cm^{-1}) 1741 (s), 1726 (s), 1606 (m), 1510 (m), 1232 (m); HRMS (ES$^+$) calcd for $C_{23}H_{27}O_5$ (M + H$^+$) 383.1858, found 383.1845.

(±)-(*Z*)-(4*S*,5*R*)-Ethyl 5-Acetoxy-4-(1-*n*-hexyl)-3-(*p*-methoxyphenyl)-5-phenylpent-2-enoate (11b) and (±)-(5*S*,6*R*)-5,6-Dihydro-5-(1-*n*-hexyl)-4-(*p*-methoxyphenyl)-6-phenyl-2*H*-pyran-2-one (10b). Treatment of (+)-(3,2,10-η-pinene)-palladium(II) chloride **1a** (0.007 g, 0.013 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (0.040 g, 0.263 mmol, 1.0 equiv), CsF (0.080 g, 0.526 mmol, 2.0 equiv), benzaldehyde **4a** (0.112 g, 1.05 mmol, 107 μL, 4.0 equiv), and (±)-ethyl deca-2,3-dienoate **3d** (0.078 g, 0.395 mmol, 1.5 equiv) according to Method C, including the treatment with K_2CO_3 for 5.5 h, and eluting with EtOAc/hexane (1:5) afforded alcohol **9b** (0.020 g, 18%) in 95% purity by ^{1}H NMR as a clear colorless oil and lactone **10b** (0.028 g, 29%) as a clear colorless oil.

To a solution of alcohol **9b** (95% purity by ^{1}H NMR) (0.014 g, 0.034 mmol) in pyridine (2 mL) was added acetic anhydride (0.007 g, 0.068 mmol, 6 μL) and DMAP (0.0008 g, 0.007 mmol). The solution was stirred at 60 °C under argon for 33 h. The crude reaction mixture was poured into 10% HCl (20 mL) and extracted with diethyl ether (3 × 20 mL). Organic extracts were dried ($MgSO_4$) and solvents removed under reduced pressure to afford a crude product that was purified by flash chromatography over silica eluting with EtOAc/hexane (1:4) to yield acetate **11b** (0.010 g, 65%) as a clear colorless oil.

Analytical data for lactone 10b: R_f = 0.42 (EtOAc/hexane, 1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 6.9 Hz, 2 H), 7.37−7.31 (m, 4 H), 7.30−7.26 (m, 1 H), 6.91 (d, J = 7.9 Hz, 2 H), 6.20 (s, 1 H), 5.72 (s, 1 H), 3.83 (s, 3 H), 3.23 (dd, J = 9.1 Hz, 3.3 Hz, 1 H), 1.90−1.80 (m, 1 H), 1.69−1.64 (m, 1 H), 1.56−1.27 (m, 8 H), 0.87 (t, J = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 161.6, 156.9, 139.5, 128.5 (2 carbons), 127.9, 127.8, 127.7 (2 carbons), 125.6 (2 carbons), 114.5 (2 carbons), 112.8, 79.8, 55.4, 41.0, 32.8, 31.6, 29.1, 27.5, 22.6, 14.0; IR (KBr, cm^{-1}) 1710 (s), 1604 (m), 1514 (m); HRMS (ES$^+$) calcd for $C_{24}H_{29}O_3$ (M + H$^+$) 365.2116, found 365.2110.

Analytical data (^{1}H NMR) for alcohol 9b: R_f = 0.49 (EtOAc/hexane, 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 5 H), 6.89 (d, J = 6.7 Hz, 2 H), 6.81 (d, J = 6.8 Hz, 2 H), 5.87 (s, 1 H), 4.67 (d br, J = 3.9 Hz, 1 H), 3.99 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 2.75 (pent, J = 4.8 Hz, 1 H), 1.81 (d, J = 2.5 Hz, 1 H), 1.69−1.56 (m, 2 H), 1.43−1.17 (m, 8 H), 1.10 (t, J = 7.1 Hz, 3 H), 0.85 (t, J = 6.7 Hz, 3 H).

Analytical data for Acetate 11b: R_f = 0.41 (EtOAc/hexane, 2:7); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.20 (m, 3 H), 7.17 (d, J = 6.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 8.7 Hz, 2 H), 5.79 (d, J = 5.7 Hz, 1 H), 5.78 (s, 1 H), 3.97 (q, J = 7.1 Hz, 2 H), 3.79 (s, 3 H), 2.88 (q, J = 7.5 Hz, 1 H), 2.02 (s, 3 H), 1.65−1.62 (m, 1 H), 1.49−1.41 (m, 2 H), 1.17−1.08 (m, 7 H), 1.06 (t, J = 7.1 Hz, 3 H), 0.85 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 166.1, 159.1, 157.3, 138.7, 132.9, 128.8 (2 carbons), 128.2 (2 carbons), 127.8, 126.9 (2 carbons), 119.6, 113.2 (2 carbons), 76.7, 59.8, 55.2, 54.2, 31.6, 29.4, 28.7, 27.3, 22.6, 20.9, 14.1, 14.0; IR (neat, cm^{-1}) 1741 (s), 1728 (s), 1606 (m), 1230 (s); HRMS (ES$^+$) calcd for $C_{28}H_{37}O_5$ (M + H$^+$) 453.2641, found 453.2652.

(*Z*)-Ethyl 4,4-Dimethyl-5-hydroxy-3-(*p*-methoxyphenyl)-5-phenylpent-2-enoate (9c). Treatment of (+)-(3,2,10-η-pinene)palladium(II) chloride **1a** (0.006 g, 0.011 mmol, 0.05 equiv), *p*-methoxyphenylboronic acid **2a** (0.069 g, 0.452 mmol, 2.0 equiv), CsF (0.137 g, 0.905 mmol, 4.0 equiv), benzaldehyde **4a** (0.024 g, 0.226 mmol, 23 μL, 1.0 equiv), and ethyl 4-methyl-penta-2,3-dienoate **3e** (0.159 g, 1.13 mmol, 5.0 equiv) according to Method A, including the treatment with K_2CO_3 for 7.0 h, and eluting with EtOAc/hexane (1:4) afforded alcohol **9c** (0.023 g, 28%) as a clear colorless oil: R_f = 0.38 (EtOAc/hexane 1:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−7.25 (m, 5 H), 7.08 (s br, 2 H). 6.91 (d, J = 8.6 Hz, 2 H), 6.16 (s, 1 H), 4.64 (s, 1 H), 3.94 (q, J = 7.1 Hz, 2 H), 3.83 (s, 3 H), 1.95 (s br, 1 H), 1.13 (s, 3 H), 1.07 (t, J = 7.1 Hz, 3 H), 0.86 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 164.6, 158.6, 140.4, 130.4, 129.2 (br, 2 carbons),128.1 (2 carbons), 127.6, 127.5 (2 carbons), 119.7, 112.9, 76.9, 59.8, 55.0, 45.7, 29.7, 25.1, 19.5, 14.0; IR (neat, cm^{-1}) 3589 (s), 1720 (s), 1606 (m), 1508 (s); HRMS (ES$^+$) calcd for $C_{22}H_{27}O_4$ (M + H$^+$) 355.1909, found 355.1898.

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Supporting Information Available: Description of general experimental procedures, analytical methods for determination of the enantiomeric composition of lactones **6a** and **10a**, experimental protocols for reactions reported in entries 8−10 of Table 1, photocopies of ^{1}H and ^{13}C NMR spectra of all new compounds prepared in this study, including the ^{1}H NOE difference spectra for alcohols **5**, **8**, **9a**−**c** and acetates **11a** and **11b**, and X-ray crystallographic studies on lactone **6e** (in CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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