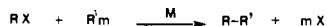# Palladium-Catalyzed Cross Coupling of Allyl Halides with Organotin Reagents: A Method of Joining Highly Functionalized Partners Regioselectively and Stereospecifically

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Abstract: The palladium-catalyzed reaction of allyl halides with aryl- and vinyltin reagents gives high yields of cross-coupled products. In the presence of 1–3 atm of carbon monoxide, ketones are obtained, resulting from cross coupling accompanied by carbon monoxide insertion. The reaction is mild and tolerant of a wide variety of functionalities (OH, OR, CN, CO_2R, CHO) on either the allyl chloride or the tin reagent. Coupling at the allyl halide partner proceeds with inversion of configuration at the carbon bearing the halide, with retention of geometry at the allylic double bond, and with a regioselectivity for the least-substituted carbon in the allylic framework. Retention of double-bond geometry is observed in the vinyltin partner.

Of the relatively few basic reaction types that generate a new carbon–carbon bond, the transition-metal-catalyzed reactions of various organic partners, specifically the cross-coupling reaction of organometallic reagents with organic halides and related electrophiles, is one of the most straightforward.[1–7] In order for the coupling reaction to be useful, it should be highly catalytic, and the reaction conditions and the reagents, including the organometallic partner, should tolerate a wide variety of functional groups so that tedious protection–deprotection reactions of the functional groups carried into the coupling product are not necessary.

$$RX \ + \ R'm \ \xrightarrow{\ M\ } \ R{-}R' \ + \ mX$$

A distinctly valuable electrophilic organic partner is an allyl halide or other similar electrophile, particularly if it undergoes the coupling regiospecifically and without *E–Z* double-bond isomerization. The palladium-catalyzed coupling of allylic acetates with stabilized enolates has been especially useful in the synthesis of elaborate, highly functionalized organic molecules.[8,9] However, the general structure required of the enolate coupling partner in this reaction limits, to an extent, the framework and functionality that can be brought into the product.

Various organometallic reagents, R^1m, have been utilized in coupling reactions with disparate success. High conversions often are not obtained with lithium or Grignard reagents, neither will tolerate a wide variety of functionality on either coupling partner,[3,4] and often homocoupling of the organic halide is observed. The copper-promoted coupling of different vinyl or aryl groups is more successful, but it often results in extensive homocoupling.[10] In addition, the methods of synthesis of copper reagents do not always allow the presence of a more reactive functionality on the organocopper partner.

The use of metals of intermediate electronegativity for the organometallic reagent generally leads to higher yields of coupled products with fewer side reactions. Many of these organometals tolerate a wide range of functionality in either or both of the coupling partners. Organozinc compounds are particularly good in this regard, although the methods of synthesis are limited to the extent that a wide variety of structures are not always available in the organic portion of the organozinc reagent. Organomercurials also tolerate functionality, but the methods for their synthesis are somewhat limited, and unfortunately, methods for the alkylation of organomercurials are limited to a few examples with organic halides.[11,12] Other organometallic partners in which the metal is boron or aluminum often are not conveniently synthesized or the structure of the organic portion is limited by the methods of synthesis available, usually hydroboration or hydroalumination.[5,8] Organozirconium reagents have the advantage that they will tolerate ether or acetal groups in the hydrozirconation reaction as well as carbonyl and ester functions in the vinyl halide partner.[13] The functionality on the zirconium reagent is limited, however, and low turnovers of catalyst are observed.

One of the most versatile organometallic reagents is the organotin reagent. Organotins containing a variety of reactive functional groups can be prepared by a number of different reaction types, and these reagents are not particularly oxygen or moisture sensitive.[14–16] In fact, organotin reagents can be purified by silica column chromatography or distillation without decomposition.

The palladium-catalyzed cross-coupling reaction of acid chlorides with organotin reagents takes place under mild conditions in high yields.[17–25] Most importantly, the reaction tolerates a wide variety of functional groups, including ester, nitro, nitrile, methyl ketone, and even aldehyde.[18,23–25] Organotin reagents that couple efficiently can contain acetylenic, vinyl, aryl, allyl, benzyl,

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and alkyl groups bound to tin. The tetraorganotin reagent transfers the first group rapidly, but the second leaves about 100 times slower. Fortunately, different types of groups transfer selectively from tin, the simple alkyl groups (usually methyl or *n*-butyl) having the slowest transfer rate.[23] Thus, a single acetylenic, vinyl, aryl, allyl, or benzyl group transfers exclusively with the other three alkyl anchoring groups remaining on tin. Acid chlorides and vinyltin reagents couple with retention of geometry at the double bond.[25]

The palladium-catalyzed coupling reaction of allyl acetates with allyltin reagents is not general, since cinnamyl acetate appears to be one of the few allylic acetates that undergoes the reaction.[26] The palladium-catalyzed coupling of allyl bromides with allyltins takes place under mild reaction conditions, but the yields of 1,5-dienes are moderate, and allylic transposition predominates in the allyltin partner.[27] In a preliminary report[28] we had shown that a regioselective palladium-catalyzed cross-coupling reaction of allyl halides with vinyl or phenyl stannanes could be carried out in which reactive functional groups could be present in either partner.

Results and Discussion

Two basic types of cross-coupling reactions have been explored, the direct coupling of allyl halides with vinyl- or phenyltins and the coupling of these reagents in the presence of carbon monoxide. Schematically, in the direct coupling reaction, the sequence of catalytic events includes oxidative addition of the allylic halide to the palladium(0) catalyst to give an allylpalladium(II) halide (**1**)[29,30] which undergoes transmetalation with the organotin reagent to yield the diorganopalladium complex **2** that undergoes reductive elimination,[30-36] generating the coupled product **3**. Alternatively, if carbon monoxide is present, CO insertion takes place with **1** to yield acylpalladium species **4** prior to transmetalation and reductive elimination.
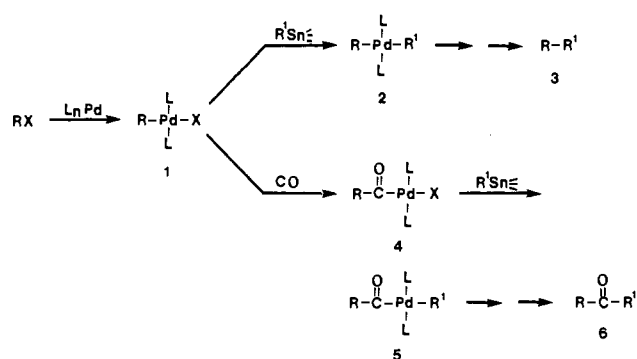

Direct Coupling. Although the cross-coupling reaction of allyl halides with allyltins gave only moderate yields of product and was not regioselective,[27] the palladium-catalyzed reaction of allyl chlorides or bromides with vinyl- or aryltin reagents gave cross-coupling products in uniformly high isolated yields (Tables I and II). Several features of this reaction make it especially synthetically valuable. First, the reaction can be carried out at moderate reaction temperatures in solvents such as THF or CHCl₃. Thus, unlike other transition-metal-catalyzed cross-coupling reactions with main-group organometallics, this palladium-catalyzed reaction involving organotin reagents is tolerant of a wide variety

of reactive functional groups, including ester in the allyl halide (examples 3, 4, 6–8, and 10, Table I, and 6 and 7, Table II) and in the tin reagent (examples 9 and 10, Table I), nitrile in either partner (examples 5, Table I, and 7, Table II), alcohol (example 8, Table I), and even aldehyde (example 5, Table 2). The reaction also proceeds with retention of double-bond geometry in the vinyltin partner (see particularly examples 7, 9, and 10, Table I). In the allyl halide, retention of the *Z*-olefin geometry in neryl chloride (example 4, Table II) as well as retention of the *E* geometry in geranyl chloride (example 3, Table II) is observed. Coupling shows regioselectivity for a primary allylic carbon rather than a secondary (example 5, Table II), and coupling takes place without allylic transposition in reactions of primary allyl halides (examples 2, 3, 5, 6, and 7, Table I, and 3 and 4, Table II; primary vs. secondary or tertiary).

A variety of palladium catalysts can be introduced; palladium(II) complexes were reduced to a palladium(0) complex by the organotin reagent.[23] Which palladium catalyst is used does not appear to make an appreciable difference in the yield of product. For example, when catalyst A, (CH₃CN)₂PdCl₂ + 0.5 PPh₃, was present (example 3, Table I, X = Br) a 74% yield of coupled product was obtained vs. a 70% yield when the catalyst was benzylchlorobis(triphenylphosphine)palladium(II), B. Similarly, 94% and 85% yields were obtained respectively, in example 4, with catalysts A and B. In examples 2 and 3, however, the ligands on palladium apparently are important, since running the reaction under 1 atm of carbon monoxide, which leads to a palladium catalyst having carbonyl ligands, improved the yields from 53 to 81% and 87 to 100%, respectively. In no other examples was the yield increased in the presence of carbon monoxide.

Carbonylative Coupling. When the coupling reaction was run in the presence of carbon monoxide, usually 3 atm or greater, product resulting from cross coupling accompanied by carbon monoxide insertion was obtained. The reaction introduces a ketone function at the coupling juncture of the two partners and serves as a synthesis of unsymmetrical ketones. The yields of ketones are uneven and are accompanied, in some reactions, by the direct coupling product, the relative amounts of the two products being dependent on the carbon monoxide pressure. In the carbonylative coupling reaction of allyl chloride and trimethyl-2-methylpropenyltin, both lower temperatures and higher carbon monoxide pressure favored the carbonylative coupling.
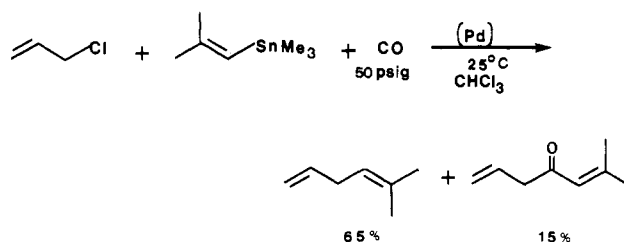

The carbonylative coupling of allyl bromide **7** and the vinyltin reagent (**8**), however, gave the carbonylative coupling product **9** in a 74% yield.
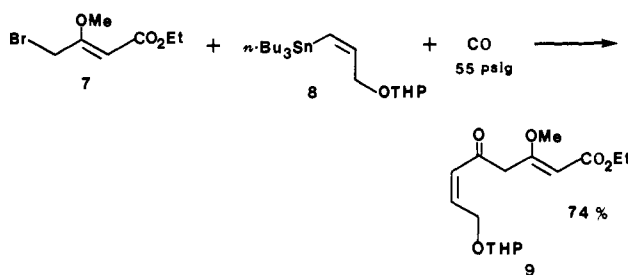

Similarly, the coupling of allyl halides and aryltin reagents in the presence of carbon monoxide generates the aryl ketone, higher carbon monoxide pressures giving higher yields of ketone at the expense of the direct coupling product.

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45 psig

450 psig

1 : 4.5

8.3 : 1
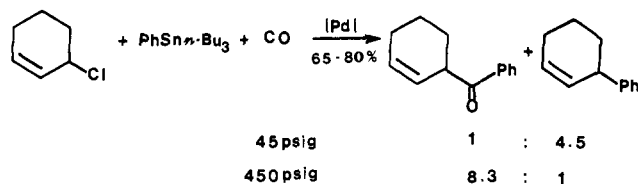
The carbonylative coupling reactions of 3-furanyltrimethyltin (10) and prenyl chloride (11) or geranyl chloride (12) led, in high yields, to egomaketone (13) and a precursor (14) to dendrolasin (15), a major constituent of a mandibular gland secretion of the Formicine ant, *Lasius faliginosis* Latr.[37] This method of synthesis of these products circumvents the tedious, low-yield routes previously reported.[38,39]

75% isolated

92% nmr

69% isolated
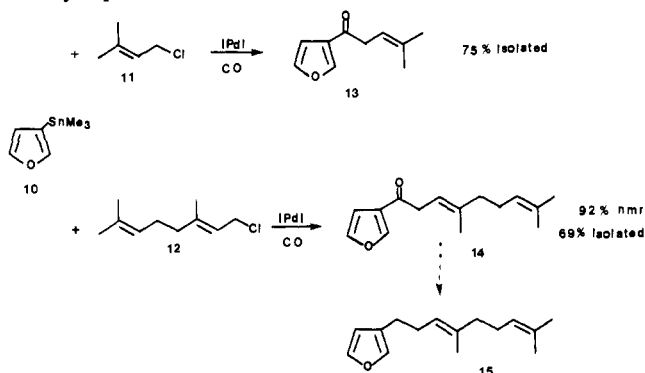
Stereochemistry and Mechanisms. In an effort to determine the stereochemistry of the coupling reaction at the allyl partner, the reactions with *cis*- and *trans*-3-chloro-5-carbomethoxycyclohexene (18) were examined. The chlorides were obtained from the lactone (16).[40] Methanolysis of 16 at ambient temperature[41] gave isomerically pure *cis*-3-hydroxy-5-carbomethoxycyclohexene (*cis*-17). Alcohol 17 was converted to the allylic chloride (18) with triphenylphosphine/carbon tetrachloride[42] with predominate inversion of configuration at carbon. In addition, chloride 18 enriched in the cis isomer was obtained by methanolysis of 16 in refluxing methanol to yield 57% *trans*-17, which on conversion to the chloride gave 42/58 *cis*/*trans*-18.

The isomers of 18 can be readily distinguished on the basis of their high-field ¹H NMR spectra.[41] Typical one-bond coupling constants for the the upfield absorption corresponding to an H_4 proton in cis isomers are $J = 12.6$, 12.6, and 12.8 Hz, while the trans isomers show $J = 4.3$, 12.3, and 12.4 Hz.
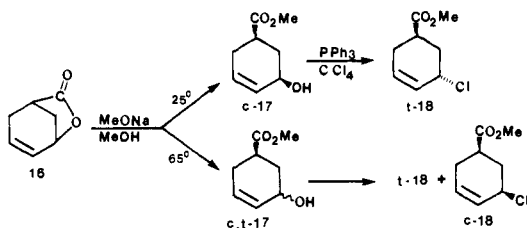
The reaction between chloride 18 and phenyl- and vinyltri-*n*-butylstannane, catalyzed by benzylchlorobis(triphenylphosphine)palladium(II), yielded the cross-coupled product, 19. In the presence of carbon monoxide, carbonylated cross-coupled product, 20, was also obtained (Table III). The reactions were not permitted to proceed to completion in order to permit recovery of unreacted starting chloride. In most cases, the theoretical amount of unreacted organotin and chloride 18 was recovered. Only at 750 psig of carbon monoxide pressure (entry 4, Table III) was significant decomposition of starting material observed. The

Scheme I
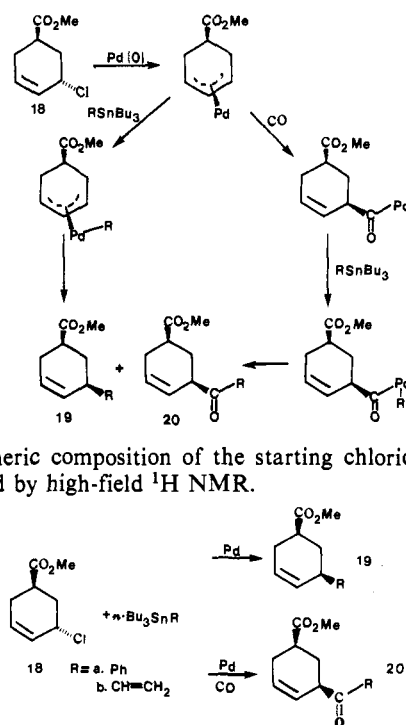
diastereomeric composition of the starting chloride (18) was determined by high-field ¹H NMR.

18   R = a. Ph
     b. CH=CH₂

The diastereomeric compositions of both the cross-coupled and carbonylated cross-coupled products indicate that these reactions proceed with essentially complete inversion of configuration at the carbon bearing the allylic chloride. Not only was the unreacted chloride recovered in each reaction, unepimerized, but also different diastereomeric mixtures of starting chloride, 18, gave products whose composition was dependent only upon the composition of the starting chloride (entries 2 and 3, Table III).

The synthetic versatility of this reaction is evidenced by the ability to obtain either direct cross coupling or cross coupling with carbon monoxide insertion by simple modification of reaction conditions. Thus, reaction of phenyltri-*n*-butylstannane with chloride 18 under 750 psig of carbon monoxide produced ketone 20a as the exclusive product (entry 4); while the similar reaction performed in the absence of carbon monoxide yielded only the cross-coupled product 19a (entry 1). Intermediate carbon monoxide pressures produced both coupled product, 19, and ketone, 20 (entries 2, 3, and 6).

These stereochemical results suggest a sequence of steps outlined in Scheme I. The active catalyst is probably Pd(PPh₃)₂, formed by reduction of PhCH₂Pd(PPh₃)₂Cl by organostannane.[23,32] Oxidative addition to Pd(0), which has been shown to proceed with inversion with allylic esters[43] and benzyl chloride,[44,45] probably occurs to yield an allyl–palladium(II) complex whose structure is undetermined. The presence of carbon monoxide in the reaction mixture does not modify the stereochemistry of this complex, since both directly cross-coupled products 19 and ketone 20 are produced at intermediate carbon monoxide pressures and the cis/trans ratio of the directly cross-coupled product 19 is unaffected by the presence of carbon monoxide (Table III). Carbon monoxide appears to simply divert the allyl–palladium(II) complex toward formation of ketone 20.

Since CO insertion into a palladium–carbon bond is known to proceed with retention of configuration at carbon,[46] the overall inversion of stereochemistry observed in formation of ketone 20 requires that the oxidative addition of palladium(0) to the chloride proceeds with inversion at carbon. Thus, in the formation of the cross-coupled product 19 the subsequent steps of transmetalation

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Table I. Palladium-Catalyzed Coupling of Allyl Halides with Vinyltin Reagents

Example	Allyl Halide	Tin Reagent	Solv./Cat.[a]	Product	%Yield[b]
1	⌇⌇⌇-Br	n-Bu₃Sn⌇⌇	CHCl₃/ A	⌇⌇⌇⌇	80*
2	⌇⌇⌇-Cl	Me₃Sn⌇⌇		⌇⌇⌇⌇	53–81*
3	X⌇⌇⌇-CO₂Me (X=Cl)	n-Bu₃Sn⌇⌇		⌇⌇⌇-CO₂Me	87–100*
	(X=Br)				74*
4	Br⌇⌇ with CO₂Me			⌇⌇ with CO₂Me	94*
5	Br⌇⌇⌇-CN		CHCl₃/ B	⌇⌇⌇-CN	65*
6	Br⌇⌇ OMe ⌇CO₂Me			⌇⌇ OMe ⌇CO₂Me	56
7		n-Bu₃Sn⌇⌇	THF/ C	⌇⌇ OMe ⌇CO₂Me	86
8		n-Bu₃Sn⌇⌇⌇-OH		HO⌇⌇ OMe ⌇CO₂Me	82
9	cyclohexenyl-Cl	n-Bu₃Sn⌇⌇-CO₂Bn		cyclohexenyl⌇⌇-CO₂Bn	72
10	cyclohexenyl (CO₂Me),Cl	n-Bu₃Sn⌇⌇-CO₂Bn		cyclohexenyl (CO₂Me)⌇⌇-CO₂Bn	87

[a] A = $(CH_3CN)_2PdCl_2$ + $0.5PPh_3$; B = $PhCH_2Pd(PPh_3)_2Cl$; C = $Pd(dba)_2$ + $2.0PPh_3$. Reactions were carried out in chloroform at 65 °C for 48 h (procedure 1) or in THF at 50 °C (procedure 2) as indicated. [b] Yields are isolated yields, except a ☆ indicates NMR yields. [c] Higher yields were obtained when the reaction was performed under 1 atm of CO.

and reductive elimination must proceed with net retention, either by double inversion or double retention at the allylic carbon center. Since reductive elimination from palladium has been shown[31,32] to proceed with retention at carbon, double retention seems the most likely pathway.

Although the oxidative addition takes place with inversion at the carbon bearing the allylic chloride, a number of different types of palladium(II) complexes may be generated, one or more of which may lead ultimately to the coupled product via the transmetalation reaction. The ability of the palladium-catalyzed coupling reaction with organotin reagents to undergo regioselective coupling (entry 5, Table II) requires that an allylic transposition pathway be available. This could occur by several different reactions or intermediates, two possible intermediates being a rapidly equilibrating σ-complex and a π-allyl complex.

Specifically labeled 1-deuterio-2-cyclohexenol (21) was obtained by the lithium aluminum deuteride reduction of 2-cyclohexenone[47] (Scheme II). Conversion of the alcohol to the labeled 3-chlorocyclohexene (22) was accomplished with triphenylphosphine/carbon tetrachloride to give a product in which the

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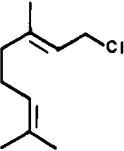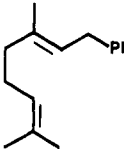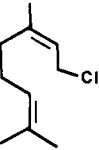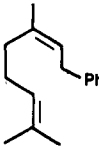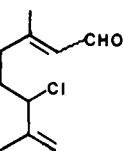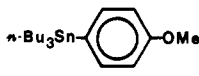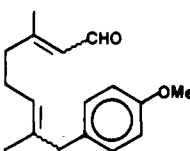
Scheme II
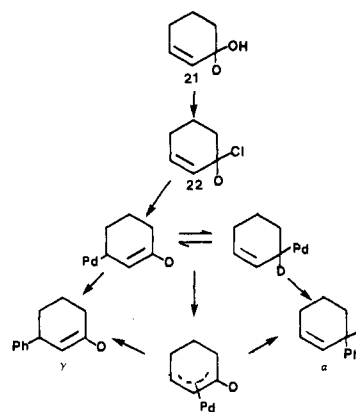
deuterium distribution was determined by ¹H NMR to be 74% α-D:26% γ-D. Reaction of this labeled allylic chloride under the standard conditions with phenyltributyltin gave 3-phenylcyclohexene in which the deuterium distribution was essentially equal (50:50 α-D:γ-D ± 2%). The reaction was not allowed to proceed

Table II. Palladium-Catalyzed Coupling of Allyl Halides with Aryltin Reagents[a]

Example	Allyl Halide	Tin Reagent	Product	% Yield
1		Me_3SnPh		72
2		$n\text{-}Bu_3SnPh$		62
3				82
4				90
5		$n\text{-}Bu_3Sn$—〈 〉—OMe		87
6		$n\text{-}Bu_3SnPh$		69
7		$n\text{-}Bu_3Sn$—〈 〉—CH_2CN		81

[a] The reactions were carried out in dry THF at 50 °C for 24 h (procedure 2), with equimolar amounts of the allyl halide and aryltin reagent in the presence of 3 mol % $Pd(dba)_2$ and 6 mol % PPh_3. Yields are isolated yields.

to completion, and unreacted allyl chloride maintained its original labeled integrity, demonstrating that no allylic transposition of the starting chloride took place under the reaction conditions.

These results suggest that when equivalent allylic carbons are available (2°), oxidative addition takes place to give either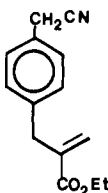 rapidly equilibrating σ-complexes or a symmetrical π-allyl complex that produce equal amounts of the α- and γ-σ-palladium complex as a result of the transmetalation reaction. Subsequent reductive elimination yields, therefore, the observed 50:50 mixture of α- and γ-products.

Experimental Section

Tetrahydrofuran was freshly distilled under nitrogen from sodium–benzophenone prior to use. Chloroform was passed through a short basic alumina column just prior to use in coupling reactions. Preparative gas chromatography analyses were carried out on a Varian Model 1520. The ¹H NMR spectra were obtained on Varian EM-360, JEOL FX100, and Nicolet NT 360 spectrometers; ¹³C NMR were obtained on the JEOL FX-100 spectrometer.

Tin Reagents. The following tin reagents were prepared according to the literature methods: tributylvinyltin,[48] (Z)-1-propenyltributyltin,[23,49] (Z)-2-butenyl-2-tributyltin,[23] benzyl (Z)- and (E)-3-(tributylstannyl)-propenoate,[23] (Z)-1-(tributylstannyl)-1-propenyl 3-tetrahydropyranyl

ether,[50] phenyltrimethyltin,[51] phenyltributyltin,[52] (4-methoxyphenyl)tributyltin,[53] and 4-(tributylstannyl)benzonitrile.[54]

Isobutenyltrimethyltin. To 2.75 g (0.11 g-atom) of magnesium turnings in 50 mL of THF was added 15.24 g (0.11 mol) of isobutenyl bromide. The mixture was heated just below the reflux temperature for 7 h and cooled, 10 g (50 mmol) of trimethyltin chloride in 20 mL of THF was added, and the mixture was heated to reflux for 14 h. The mixture was then cooled to −20 °C, and the excess Grignard reagent was quenched with 10% aqueous ammonium chloride. The aqueous layer was separated and extracted with ether. The combined organic fractions were dried ($MgSO_4$), and the solvent was removed by distillation. The residue was then distilled to yield 8.9 g (81%) of isobutenyltrimethyltin: ¹H NMR ($CDCl_3$) δ 0.13 (s, 9 H), 1.78 (s, 3 H), 1.88 (d, 3 H, $J = 1.4$ Hz), 5.44 (br s, 1 H); ¹³C NMR ($CDCl_3$) δ 8.76, 25.56, 28.60, 123.62, 151.40; bp 135–140 °C; HRMS calcd for $C_6H_7{}^{120}Sn$ (M − CH_3) 205.0036, found 205.0016.

3-(Trimethylstannyl)furan (10). To a solution of 34.0 mmol of 3-lithiofuran[55] in 80 mL of ether at −78 °C was added a solution of 6.77

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Table III. Palladium-Catalyzed Reactions of Organostannanes with Chloride 18[a]

entry no.	$(n\text{-Bu})_3$-SnR, R	18 cis/trans	P_{CO}, psig	cis/trans (yield)	
				19	**20[b]**
1	Ph	27/73	0	75/25 (57)	
2	Ph	16/84	40–45	79/21 (47)	100/0 (5)
3	Ph	42/58	40–45	59/41 (42)	52/48 (17)
4	Ph	26/74	750[c]	d	70/30 (37)
5	CH=CH$_2$	27/73	0	71/29 (70)	
6	CH=CH$_2$	12/88	40–45	86/14 (15)	64/36 (38)[e]

[a] The reactions were carried out at 40 °C with 5.7 mmol of chloride, 6.3 mmol of organostannane, and 0.5 mol % PhCH$_2$Pd(PPh$_3$)$_2$Cl in 10 mL of dry THF. Unreacted starting materials were recovered in the theoretical amount. [b] The yields reported are isolated yields; all compounds gave satisfactory analyses and spectral data. [c] Unreacted organostannane (17%) and chloride (14%) were recovered in this reaction. [d] None of this product was detected. [e] This product was found to epimerize upon standing.

g (34.0 mmol) of trimethyltin chloride in 40 mL of ether. After the addition was complete, the mixture was stirred at –78 °C for 24 h. The mixture was then allowed to warm to room temperature and was poured into 100 mL of water. The aqueous layer was extracted with ether. The combined organic fractions were dried (MgSO$_4$), and the solvent was removed in vacuo. The residue was vacuum distilled to yield 6.17 g (79%) of **10**: ^{1}H NMR (CDCl$_3$) δ 0.26 (s, 9 H), 6.37 (m, 1 H), 7.24 (m, 1 H), 7.54 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 9.24, 114.31, 114.60, 142.51, 146.89; bp 66–68 °C (24 mmHg). Anal. Calcd for C$_7$H$_{12}$OSn: C, 36.42; H, 5.24. Found: C, 36.04; H, 5.18.

(E)- and (Z)-1-(Tri-n-butylstannyl)-1-propen-3-ol. A mixture of the E and Z isomers was prepared by the reaction of tetra-n-butylammonium fluoride[56] with 1-(tri-n-butylstannyl)-3-(tert-butyldimethylsiloxy)-2-propene.[50] The isomeric alcohols were separated by medium-pressure liquid chromatography (silica gel, 19:1 hexane/isopropyl alcohol). The ^{1}H NMR spectra of the isomers matched those of the published[57] spectra.

Allyl Halides. Allyl chloride, allyl bromide, and prenyl chloride were obtained commercially and distilled before use. The following allyl halides were obtained by the literature procedure: methyl 4-chloro-2-butenoate,[58] methyl 4-bromo-2-butenoate,[59] ethyl 2-(bromomethyl)-propenoate,[60] 4-bromocrotononitrile,[61] ethyl 4-bromo-3-methoxy-2-butenoate,[62] 3-chlorocyclohexene,[63] and 6-chloro-3,7-dimethylocta-3,7-dienal.[67]

(E)-1-Chloro-3,7-dimethyl-2,6-octadiene. A solution of 2.0 g (13 mmol) of 3,7-dimethyl-2,6-octadienol in 40 mL of dichloromethane and 40 mL of carbon tetrachloride was treated with 3.7 g (14.3 mmol) of triphenylphosphine.[42] The resulting solution was stirred at room temperature for 6 h and concentrated. The resulting material was taken up in a minimum volume of 1:1 dichloromethane/carbon tetrachloride and purified by column chromatography (silica gel, dichloromethane/carbon tetrachloride 9:1) to yield 1.64 g (73%) of (E)-1-chloro-3,7-dimethyl-2,6-octadiene:[65] ^{1}H NMR (CDCl$_3$) δ 1.7 (m, 9 H), 2.1 (m, 4 H), 4.1 (d, 2 H), 5.2 (br s, 1 H), 5.5 (t, 1 H); ^{13}C NMR (CDCl$_3$) δ 15.9, 17.6, 25.6, 26.3, 39.4, 40.8, 120.3, 123.4, 131.5, 142.2.

(Z)-1-Chloro-3,7-dimethyl-2,6-octadiene. A solution of 2.0 g (13 mmol) of 3,7-dimethyl-2,6-octadienol in 25 mL of carbon tetrachloride and 5 mL of dichloromethane was treated with 3.7 g (14.3 mmol) of triphenylphosphine. The resulting solution was stirred at room temperature for 3 h and concentrated. The product was isolated by vacuum transfer, taken up in dichloromethane, dried (Na$_2$SO$_4$), and concentrated to yield 1.52 g (68%) of (Z)-1-chloro-3,7-dimethyl-2,6-octadiene: ^{1}H NMR (CDCl$_3$) δ 1.65 (m, 9 H), 2.1 (m, 4 H), 3.95 (d, 2 H), 4.8–5.5 (m,

2 H); ^{13}C NMR (CDCl$_3$) δ 17.6, 23.3, 25.6, 26.5, 31.8, 40.6, 121.1, 123.3, 131.8, 142.0.

cis-5-Carbomethoxy-2-cyclohexenol (17). This material was prepared by modification of the literature procedure.[41] A solution of 10.0 g (81 mmol) of 7-oxabicyclo[3.2.1]oct-2-en-6-one (16)[40] in 300 mL of anhydrous methanol was treated with 0.6 g (11 mmol) of sodium methoxide and stirred at room temperature for 12 h. The reaction solution was concentrated and partitioned between 100 mL of ether and 100 mL of 2% HCl. The ether layer was washed with half-saturated sodium bicarbonate, water, and brine, dried (MgSO$_4$), and concentrated to yield 12.6 g (100%) of product: ^{1}H NMR (CDCl$_3$) δ 1.4–3.1 (br m, 5 H), 3.55 (br s, 1 H), 3.8 (s, 3 H), 4.45 (br s, 1 H), 5.9 (s, 2 H).

cis- and trans-5-Carbomethoxy-2-cyclohexenol (17). A mixture of cis- and trans-5-carbomethoxy-2-cyclohexenol was prepared according to the procedure described for the cis isomer except that the reaction mixture was stirred at reflux for 12 h.

3-Chloro-5-carbomethoxycyclohexene (18). This compound was prepared from the corresponding alcohol **17** by the same method as for the preparation of (E)-1-chloro-3,7-dimethyl-2,6-octadiene: ^{1}H NMR (CDCl$_3$) δ 1.95–2.17 (m, 1 H), 2.20–2.50 (m, 3 H), 2.54–2.71 (dddd, H$_5$ cis), 2.95–3.05 (dddd, H$_5$ trans), 3.70 (s, CH$_3$ trans), 3.71 (s, CH$_3$ cis), 4.68 (br m, 1 H), 5.75–5.95 (m, 2 H); IR (neat) 1740 cm^{-1}; HRMS calcd for C$_8$H$_{11}$O$_2^{35}$Cl 174.0448, found 174.0453.

General Procedure for Palladium-Catalyzed Cross-Coupling Reactions of Allyl Halides and Organotins (Tables I and II). 1. In Chloroform: To a Schlenk tube was added 0.022 mmol of a palladium catalyst, either benzylchlorobis(triphenylphosphine)palladium(II)[66] or tetrakis(triphenylphosphine)palladium(0),[67] 1 mL of CHCl$_3$ (or CDCl$_3$ when the products were analyzed by NMR directly), 2.2 mmol of an allylic halide, and 2.2 mmol of a vinylic tin reagent in that order. The tube was capped, the contents were mixed well, and then the tube was placed in an oil bath maintained at 65 °C for 48 h. Usually, palladium black precipitated within 48 h. Benzene (75 μL, 0.84 mmol) was added as an internal standard, and the sample was analyzed by ^{1}H NMR to determine the yield of coupled product. In those reactions where the coupled products were volatile, the reaction mixture was vacuum transferred to separate the coupled products from palladium and tin residues. In those reactions where the coupled products were not volatile enough to vacuum transfer, the coupled products were separated from the palladium and tin residues by flash column chromatography. Analytically pure samples of the cross-coupled products were obtained by preparative gas chromatography.

2. In THF: To a solution of 3.0 mol % of bis(dibenzylideneacetone)palladium(0)[68] in 5 mL of THF was added 6.0 mol % of triphenylphosphine, followed by allylic halide and 1.0 equiv of organotin. The reaction solution was stoppered and heated at 50 °C until palladium metal precipitated (24–48 h). The reaction was cooled, partitioned between 100 mL of ether and 100 mL of one-third saturated potassium fluoride, and vigorously stirred for 30 min. The resulting precipitate of tri-n-butylstannyl fluoride was removed by gravity filtration, and the organic layer was separated, washed with brine, and dried (MgSO$_4$). Products were isolated by medium-pressure liquid chromatography on a silica gel column.

Carbonylative Coupling. Typically, a solution of 3.0 mol % (based on the allyl halide) of bis(dibenzylideneacetone)palladium(0) in 5 mL of THF and 6.0 mol % of triphenylphosphine was introduced into a Fischer-Porter pressure tube (3 oz, obtained from Lab-Crest Scientific Division) under nitrogen, followed by 2–5 mmol each of allyl halide and tin reagent. The tube was fitted with a pressure gauge and pressurized to 50 psig with carbon monoxide, and the pressure was released. This was repeated two more times, and the tube was repressurized to the desired pressure, usually 45–55 psig. The tube was then placed in a constant temperature bath at 50 °C, and the contents were stirred with magnetic stirring for the designated time (usually 24 h). The reaction mixture was cooled and worked up as described above, procedure 2.

Coupling Products. The following known compounds were isolated according to the general procedure and identified by comparison to an authentic sample (allylbenzene) or the reported data: (Z)-3-methyl-2,5-hexadiene[69] (vacuum transfer followed by distillation), 3-phenylcyclohexene[70] (MPLC, hexane), 3-benzoylcyclohexene[71] (MPLC, hexane), (E)-1-phenyl-3,7-dimethyl-2,6-octadiene[72] (MPLC, hexane),

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(Z)-1-phenyl-3,7-dimethyl-2,6-octadiene[72] (MPLC, hexane), 5-methyl-1,4-hexadiene[69] (vacuum transfer followed by distillation), and 2-methyl-2,6-heptadien-4-one[73] (vacuum transfer followed by distillation).

2,6-Dimethyl-2,5-heptadiene (vacuum transfer followed by distillation): ^{1}H NMR (CDCl$_3$) δ 1.63 (s, 3 H), 1.68 (d, 3 H, J = 1 Hz), 2.66 (t, 2 H, J = 7 Hz), 5.10 (tm, 2 H, J = 7 Hz); ^{13}C NMR (CDCl$_3$) δ 17.74, 25.74, 27.26, 123.24, 131.07; HRMS calcd for C$_9$H$_{16}$ 124.1252, found 124.1254.

Methyl 2,5-Hexadienoate (column chromatography on silica, hexane followed by ether): ^{1}H NMR (CDCl$_3$) δ 2.95 (tm, 2 H), 3.72 (s, 3 H), 5.08 (m, 2 H), 5.83 (m, 2 H), 6.98 (dt, 1 H, J = 15.0, 6.6 Hz); ^{13}C NMR (CDCl$_3$) δ 35.90, 51.19, 116.94, 121.49, 133.52, 146.25, 166.39; HRMS calcd for C$_7$H$_{10}$O$_2$ 126.0680, found 126.0669.

Ethyl 2-Methylene-4-pentenoate (column chromatography on silica, hexane followed by ether): ^{1}H NMR (CDCl$_3$) δ 1.20 (t, 3 H, J = 7.1 Hz), 2.95 (d, 2 H, J = 6.6 Hz), 4.10 (q, 2 H, J = 7.1 Hz), 4.95 (m, 2 H), 5.7 (m, 3 H); ^{13}C NMR (CDCl$_3$) δ 13.94, 35.66, 60.24, 116.24, 124.47, 134.74, 138.89, 166.16. Anal. Calcd for C$_8$H$_{12}$O$_2$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.86.

2,5-Hexadienenitrile (preparative GC): ^{1}H NMR (CDCl$_3$) δ 3.16 (t of m, 2 H), 5.21 (m, 3 H), 5.7 (m, 1 H), 6.5 (dt, 1 H, J = 7, 11 Hz); ^{13}C NMR (CDCl$_3$) δ 35.55, 100.12, 115.42, 117.23, 132.52, 151.50; HRMS calcd for C$_6$H$_7$N 93.0578, found 93.0580.

Ethyl 3-Methoxy-2,5-hexadienoate (column chromatography with hexane, then ether, then chloroform): ^{1}H NMR (CDCl$_3$) δ 1.25 (t, 3 H, J = 7 Hz), 3.53 (m, 2 H), 3.62 (s, 3 H), 4.10 (q, 2 H, J = 7 Hz), 5.1 (m, 3 H), 5.8 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 14.00, 36.01, 55.05, 58.78, 116.12, 132.88, 166.45, 172.87; HRMS calcd for C$_9$H$_{14}$O$_3$ 170.0942, found 170.0940.

Ethyl 3-Methoxy-(2E,5Z)-heptadienoate (MPLC, 19:1 hexane/ethyl acetate): ^{1}H NMR (CDCl$_3$) δ 1.25 (t, 3 H), 1.60 (dd, 3 H), 3.58 (dd, 2 H), 3.63 (s, 3 H), 4.15 (q, 2 H), 5.01 (s, 1 H), 5.40–5.64 (m, 2 H, J_{56} = 12.8 Hz); IR (neat) 1720 cm^{-1}; HRMS calcd for C$_{10}$H$_{16}$O$_3$ 184.1100, found 184.1107.

Ethyl 7-Hydroxy-3-methoxy-(2E,5E)-heptadienoate (MPLC, 19:1 hexane/isopropyl alcohol): ^{1}H NMR (CDCl$_3$) δ 1.26 (t, 3 H), 1.90–2.15 (br s, 1 H), 3.52 (d, 2 H), 3.64 (s, 3 H), 4.09 (m, 2 H), 4.13 (q, 2 H), 5.02 (s, 1 H), 5.76 (m, 2 H); IR (neat) 3340, 1720 cm^{-1}. Anal. Calcd for C$_{10}$H$_{16}$O$_4$: C, 60.00; H, 8.00. Found: C, 59.42; H, 7.93.

Benzyl (E)-3-(2-Cyclohexenyl)propenoate (MPLC, 49:1 hexane/ethyl acetate): the ^{1}H NMR (CDCl$_3$) of this compound was compared with the known ethyl ester;[74] ^{1}H NMR (CDCl$_3$) δ 1.3–2.2 (m, 6 H), 3.8–4.3 (m, 1 H), 5.15 (s, 2 H, CH$_2$Ph), 5.3–6.2 (m, 4 H), 7.34 (s, 5 H, Ph); ^{13}C NMR (CDCl$_3$) δ 20.48, 24.80, 28.48, 34.96, 65.73, 118.10, 127.97, 128.22, 135.97, 153.78, 165.69; mass spectrum, m/e 151 (M – C$_6$H$_5$CH$_2$), 133, 105, 91, 77.

Benzyl (Z)-3-(cis-5-Carbomethoxy-2-cyclohexenyl)propenoate (MPLC, 9:1 hexane/ethyl acetate): ^{1}H NMR (CDCl$_3$) δ 1.35–2.80 (m, 5 H), 3.68 (s, 3 H), 4.25 (br m, 1 H), 5.14 (s, 2 H), 5.73–6.04 (m, 4 H), 7.35 (m, 5 H); IR (neat) 1730, 1720 cm^{-1}. Anal. Calcd for C$_{18}$H$_{20}$O$_4$: C, 72.00; H, 6.67. Found: C, 71.38; H, 6.64.

8-(4-Methoxyphenyl)-3,7-dimethyl-2,6-octadienal (MPLC, 19:1 hexane/ethyl acetate): ^{1}H NMR (CDCl$_3$) δ 1.6 (s, 3 H), 2.0–2.45 (m, 7 H), 3.3 (s, 2 H), 3.8 (s, 3 H), 5.35 (br m, 1 H), 6.05 (d, 1 H), 7.1 (dd, 4 H), 10.3 (d, 1 H); IR (neat) 1690 cm^{-1}; HRMS calcd for C$_{17}$H$_{22}$O$_2$ 258.1621, found 258.1622.

Ethyl α-Methylene-(4-(cyanomethyl)phenyl)propanoate (MPLC, 17:3 hexane/ethyl acetate): ^{1}H NMR (CDCl$_3$) δ 1.2 (t, 3 H), 3.6 (s, 2 H), 3.7 (s, 2 H), 4.1 (q, 2 H), 5.5 (m, 1 H), 6.2 (s, 1 H), 7.2 (s, 4 H); IR (neat) 2245, 1725 cm^{-1}; HRMS calcd for C$_{14}$H$_{15}$NO$_2$ 229.1104, found 229.1103.

Ethyl 5-Oxo-3-methoxy-5-tetrahydropyranoxyl-(2E,6Z)-octadienoate (9) (MPLC, 9:1 hexane/ethyl acetate): ^{1}H NMR (CDCl$_3$) δ 1.05 (t, 3 H), 1.45 (br m, 6 H), 3.35–4.3 (m, 11 H), 4.5 (m, 1 H), 5.05 (s, 1 H), 6.35–6.8 (m, 2 H); IR (neat) 1720, 1680 cm^{-1}. Anal. Calcd for C$_{16}$H$_{24}$O$_6$: C, 61.54; H, 7.69. Found: C, 61.40; H, 7.68.

Egomaketone (13). The product of the carbonylation reaction (50 psig) between 0.92 mL (8.2 mmol) of prenyl chloride and 1.89 g (8.20 mmol) of 3-(trimethylstannyl)furan according to the general procedure was purified by column chromatography on silica gel with use of ether:hexane (1:1) as eluting solvent to give egomaketone in 75% yield: ^{1}H NMR (CDCl$_3$) δ 1.68 (s, 3 H), 1.75 (d, 3 H, J = 1.2 Hz), 3.46 (d, 2 H, J = 7 Hz), 5.39 (t, 1 H, J = 7 Hz), 6.77 (m, 1 H), 7.44 (m, 1 H), 8.06 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 18.10, 25.69, 40.29, 108.60, 115.95, 127.16, 135.34, 143.80, 147.02, 192.97; bp 104–106 °C (4.75 mmHg).

The ^{1}H and ^{13}C NMR data are consistent with those reported.[39]

3-Furanyl Geranyl Ketone (14). The carbonylation reaction (50 psig) between 1.4 g (8.2 mmol) of geranyl chloride and 1.89 g (8.2 mmol) of 3-(trimethylstannyl)furan according to the general procedure gave a 92% yield of product as determined by ^{1}H NMR with use of nitromethane as internal standard. The product was purified by column chromatography on silica gel with use of ether as eluting solvent followed by vacuum distillation to give 1.32 g (69%) of pure ketone: ^{1}H NMR (CDCl$_3$) δ 1.60–1.77 (S + M, 9 H), 2.07 (m, 4 H), 3.45 (d, 2 H, J = 7 Hz), 5.08 (br s, 1 H), 5.40 (t, 1 H, J = 7 Hz), 6.77 (m, 1 H), 7.42 (m, 1 H), 8.04 (m, 1 H); ^{13}C NMR (CDCl$_3$) δ 16.46, 17.57, 25.57, 26.39, 39.53, 40.34, 108.60, 115.84, 123.72, 127.10, 131.31, 138.78, 143.75, 147.02, 192.91; bp 100–102 °C (0.05 mmHg). The ^{1}H and ^{13}C NMR data are consistent with those reported.[39]

Procedure for the Cross-Coupling Reactions between 3-Chloro-5-carbomethoxycyclohexene and Phenyl- or Vinyltri-n-butyltin (Table III). To a solution of 0.5 mol % of benzylchlorobis(triphenylphosphine)palladium(II)[66] in 10 mL of dry THF was added chloride (5.7 mmol) and organotin (6.3 mmol). The reaction solution was stoppered and heated at 40 °C until palladium metal precipitated (24–36 h). The reaction was cooled, partitioned between 100 mL of ether and 100 mL of one-third saturated potassium fluoride, and vigorously stirred for 30 min. The resulting precipitate of tri-n-butylstannyl fluoride was removed by gravity filtration, and the organic layer was separated, washed with brine, and dried (MgSO$_4$). Products and unreacted starting materials were isolated by medium-pressure liquid chromatography (silica gel, 1:9 ethyl acetate/hexane).

Under Carbon Monoxide. Reactions under a carbon monoxide atmosphere were carried out in a Fisher-Porter tube at 40–45 psig or in a glass-lined stainless steel bomb at 750 psig by using a procedure identical with the above procedure.

3-Phenyl-5-carbomethoxycyclohexene (19a): ^{1}H NMR (CDCl$_3$) δ 1.58–1.68 (ddd, H$_4$ cis), 2.11–2.20 (ddd, H$_4$ trans), 2.20–2.40 (m, 3 H), 2.46–2.65 (dddd, H$_5$ trans), 2.72–2.82 (dddd, H$_5$ cis), 3.4–3.6 (br m, 1 H), 3.64 (s, CH$_3$ trans), 3.67 (s, CH$_3$ cis), 5.7–6.0 (m, 2 H), 7.15–7.35 (br s, 5 H); IR (neat) 1740 cm^{-1}; HRMS calcd for C$_{14}$H$_{16}$O$_2$ 216.1151, found 216.1157.

3-Benzoyl-5-carbomethoxycyclohexane (20a): ^{1}H NMR (CDCl$_3$) δ 1.87–1.97 (ddd, H$_4$ cis), 2.00–2.07 (ddd, H$_4$ trans), 2.25–2.45 (m, 3 H), 2.73–2.82 (dddd, H$_5$ cis), 2.92–2.98 (dddd, H$_5$ trans), 3.70 (s, CH$_3$ cis), 3.72 (s, CH$_3$ trans), 4.15–4.25 (br m, 1 H), 5.70–5.95 (m, 2 H), 7.40–7.60 (m, 3 H), 7.90–8.00 (m, 2 H); IR (neat) 1740, 1680 cm^{-1}; HRMS calcd for C$_{15}$H$_{16}$O$_3$ 244.1100, found 244.1102.

3-Vinyl-5-carbomethoxycyclohexane (19b): ^{1}H NMR (CDCl$_3$) δ 1.20–2.95 (m, 6 H), 3.68 (s, CH$_3$ trans), 3.69 (s, CH$_3$ cis), 4.95–5.10 (m, 2 H), 5.55–5.90 (m, 3 H); IR (neat) 1740 cm^{-1}; HRMS calcd for C$_{10}$H$_{14}$O$_2$ 166.0994, found 166.0997.

3-(1-Oxo-2-propenyl)-5-carbomethoxycyclohexene (20b): ^{1}H NMR (CDCl$_3$) δ 1.72–1.83 (ddd, H$_4$ trans), 1.86–1.95 (ddd, H$_4$ cis), 2.00–2.50 (m, 3 H), 2.64–2.72 (dddd, H$_5$ trans), 2.72–2.86 (dddd, H$_5$ cis), 3.40–3.60 (br m, 1 H), 3.70 (s, 3 H), 5.60–5.95 (m, 3 H), 6.30–6.60 (m, 2 H); IR (neat) 1740, 1700 cm^{-1}; HRMS calcd for C$_{11}$H$_{14}$O$_3$ 194.0943, found 194.0948.

1-Deuterio-2-cyclohexenol (21) (obtained by lithium aluminum deuteride reduction of 2-cyclohexenone[47]): ^{1}H NMR (CDCl$_3$) δ 1.0–2.2 (m, 6 H), 3.25 (s, 1 H), 5.8 (s, 2 H); ^{2}H NMR (CHCl$_3$) δ 4.00 (s); mass spectrum, m/e 82 (M$^+$ – H$_2$O).

1-Deuterio- and 3-Deuterio-3-chlorocyclohexene (22). 1-Deuterio-2-cyclohexenol (1.5 g, 15.2 mmol) was dissolved in 40 mL of 1:1 dichloromethane:carbon tetrachloride, 4.4 g (16.7 mmol) of triphenylphosphine was added, and the solution was stirred at room temperature for 3 h. Solvents were removed under aspirator pressure, and 0.4 g (22%) of the product was isolated by vacuum transfer: ^{1}H NMR (CDCl$_3$) δ 1.5–2.5 (m, 6 H), 4.8 (br m, H 3), 6.1 (s, H 1, H 2); ^{2}H NMR (CHCl$_3$) δ 4.56 (s, d$_3$), 5.86 (s, d$_1$). Relative integration gave a composition of 74% α-d/26 γ-d.

1-Deuterio- and 3-Deuterio-3-phenylcyclohexene. A mixture of these compounds was prepared by the standard procedure. Purification was carried out by medium-pressure liquid chromatography (hexane:silica gel) to yield the cross-coupled product in 58% yield: ^{1}H NMR (CDCl$_3$) δ 1.5–2.3 (m, 6 H), 3.3 (br m, H 3), 5.7 (m, H 1, H 2), 7.2 (s, 5 H). Relative integration of the 3.3- and 5.7-ppm signals yielded a composition of 49% α-d/51% γ-d. ^{2}H NMR (CHCl$_3$) δ 3.39 (s, d$_3$), 5.95 (s, d$_1$). Relative integration gave a composition of 51% α-d/49% γ-d. Unreacted 3-chlorocyclohexene (32%) whose deuterium distribution was essentially identical (74% α-d/26% γ-d) with the starting chloride was also isolated.

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Theoretical and Experimental Evaluation of IFER for MSE (Interactive Free Energy Relationship for Multiple-Substituent Effects). Mechanistic Significance of the Reaction Constant and Cross-Interaction Constant[†]

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Abstract: Substituent–substituent interactions are quantitatively investigated by the interactive free energy relationship (IFER), $\log k_{XY}/k_{HH} = \rho_1{}^H\sigma_X + \rho_2{}^H\sigma_Y + q\sigma_X\sigma_Y$, which is theoretically derived on the reasonable assumption that the quadratic terms in $\sigma_X{}^2$ and $\sigma_Y{}^2$ are negligible compared to the cross term in $\sigma_X\sigma_Y$. The IFER equation is tested for different types of substituent effects on various classes of reactions involving one or two reagents and including all the possible behaviors with respect to RSP. This equation is applied to 35 data sets of multiple-substituent effects (MSE); the additive ($q = 0$) and nonadditive ($q \neq 0$) effects are accurately described provided that the elementary FER's, where only one substituent varies, are linear. With this condition, 32 values of the cross-interaction constant can be calculated, mainly from kinetic and thermodynamic data; q is found to vary markedly, from $+1$ to -8. As regards the kinetic effects, the IFER works regardless of the reactivity–selectivity dependence. The extensive survey of q values enables interactions to be compared in rates and equilibria: the interaction constant is systematically higher for kinetic than for thermodynamic data; ρ for rates is twice as sensitive to the structure as ρ for equilibria. This result, analyzed in terms of the thermodynamic and intrinsic kinetic contributions to the reactivity, suggests that the interaction constant q reflects at least in part a change in the transition-state position induced by the substituent. The constant q is a free energy relationship parameter, complementary to the reaction constant ρ for investigating the structure of the transition state.

According to the Hammond postulate[1] and to more recent theoretical developments[2,3] such as those of Marcus and Lewis–More O'Ferrall, free energy relationships (FER) should not be linear. This intriguing deduction is the subject of frequent debate since it casts doubt upon the very significance of the FER parameters usually considered as terms characteristic of the transition-state position. Experimental proofs of curvature in FER are not common. The situation is, moreover, quite different depending on whether Brønsted[4] rate–equilibrium relationships or Hammett[5] structure–reactivity relationships are concerned. While there is experimental[6] support for the theoretical prediction of curvature[7] in Brønsted relationships, very little has been done in connection with Hammett or Hammett–Brown equations.[8] More O'Ferrall has shown[9] from a study on rates and equilibria in five reactions that the Hammett ρ for one substituent could be a variable described by the following expression.

$$\rho = \rho_0 + 2m\sigma \qquad (1)$$

However the opposite theory, namely that structure–reactivity relationships are linear and that ρ is constant, has been upheld[10] on a pragmatic basis. This debate is of fundamental importance since the assumption of a constant ρ leads one to conclude, contrary to what is commonly agreed,[11] that ρ cannot be an index of the transition-state position. In fact linearity of reactivity–structure relationships means merely that the second derivative of the reactivity[12] is negligible compared to the first derivative ($m \ll \rho$).

$$(\partial \log k_X)/\partial \sigma_X = \rho \qquad (2)$$

$$(\partial^2 \log k_X)/\partial \sigma_X{}^2 = \partial\rho/\partial\sigma_X = m \qquad (3)$$

Several reasons, both experimental and theoretical,[13] can be invoked to explain the fact that no curvature has yet been detected

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