Synthesis of Isocoumarins via Thallation-Olefination of Benzoic Acids

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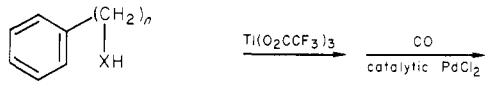
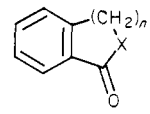
Abstract: Benzoic acid and substituted benzoic acids are readily thallated by thallium(III) trifluoroacetate and subsequently reacted with palladium chloride and simple olefins, allylic halides, vinyl halides, or vinyl esters to give isocoumarins. The organic halide reactions are catalytic in palladium. 1,2- and 1,3-dienes also react catalytically to afford 4-alkylidene- and 3-vinyl-3,4-dihydroisocoumarins, respectively. Vinylcyclopropanes also afford 3-vinyl-3,4-dihydroisocoumarins. This highly convenient thallation-olefination approach appears quite general for the synthesis of isocoumarins.

In recent years organothallium compounds have become increasingly useful as synthetic intermediates in organic synthesis.[1-3] The highly regiospecific electrophilic thallation of arenes[4,5] and subsequent synthetic transformations have afforded useful new routes to a variety of aromatic substrates. We recently reported that the heteroatom-directed ortho thallation and subsequent palladium-catalyzed carbonylation of benzylic and β-phenethyl alcohols, benzoic acid, phenylacetic acid, benzamide, acetanilide, phenylurea, and benzophenone provide a valuable new approach to aromatic carbonyl compounds (eq 1).[6] We now wish to report



$n = 0, 1, 2$; X = O, CO_2, CONH

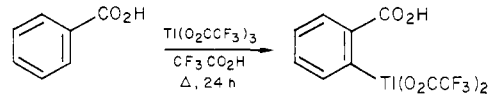


(1)

that the thallation-olefination of benzoic acids produces isocoumarins and 3,4-dihydroisocoumarins in one pot from readily available benzoic acids and a variety of simple olefins and dienes, greatly simplifying the synthesis of these important ring systems.

Results and Discussion

Alkene Reactions. Benzoic acid was converted to ortho-thallated benzoic acid **1** by the procedure of Taylor and McKillop (eq 2).[4,5]

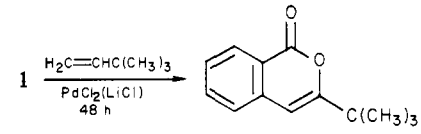


(2)

1

Removal of trifluoroacetic acid (TFA) afforded crude **1**, which could be used as such or recrystallized from TFA and washed with cold, dry methylene chloride. The latter material could be stored under nitrogen in the dark for several months and proved more convenient for our model studies.

For our initial work on the olefination reaction, we chose to study the effect of various solvents and the presence or absence of 2 equiv of lithium chloride on the reaction of **1**, $PdCl_2$, and 3,3-dimethyl-1-butene (eq 3). This reaction was observed to

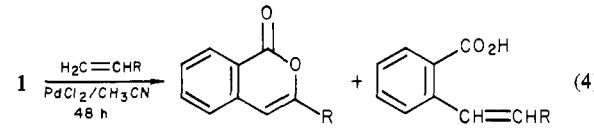


(3)

2

afford 3-*tert*-butylisocoumarin (**2**) in the following yields: HOAc/LiCl (0%), TFA/LiCl (0), DMSO/LiCl (5), HMPA/LiCl (16), CH_3OH (30), CH_3OH/LiCl (37), DME (37), THF/LiCl (39), CH_3CN (50), CH_3CN/LiCl (40), CH_2Cl_2 (56), CH_2Cl_2/LiCl (55). The addition of lithium chloride did not appear to significantly improve the yield of **2**, and work on the cyclization step to be discussed later indicated that LiCl can adversely affect the formation of the six-member ring isocoumarin. From this work CH_3CN and CH_2Cl_2 appeared to be the solvents of choice. Subsequent work has shown that these two solvents nicely complement each other.

During the course of this early work, it was observed that considerable amounts of uncyclized materials, **3**, were formed in these reactions (eq 4). We therefore examined reaction conditions

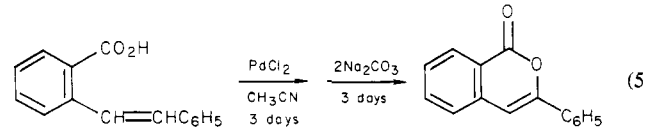


(4)

$R = CH_3$	30%	25%
$R = C_6H_5$	20%	49%

3

which might effect the cyclization of **3** ($R = C_6H_5$). Indeed, the simple, sequential addition of $PdCl_2$ and 2 equiv of Na_2CO_3 affords the desired isocoumarin in 80% yield (eq 5). The addition of 2



(5)

80%

equiv of LiCl to this reaction produced ~40% of the five-member ring alkylidene phthalide product as well as the isocoumarin. Additional LiCl failed to noticeably change the relative ratio of the two lactones. The reaction completely failed in the presence of dimethyl sulfide or trimethyl phosphite, and other solvents had little effect on the yield.

These new findings were then applied to the direct olefination of **1**. It was observed that addition of the base (either Et_3N or Na_2CO_3) alongside the olefin decreased the yield of isocoumarin, but if the base was added later, after the initial olefination step has had a chance to proceed to completion, high yields of isocoumarin product could be obtained. The addition of 2 equiv of

(1) Taylor, E. C.; McKillop, A. *Acc. Chem. Res.* **1970**, *3*, 338.
(2) McKillop, A.; Taylor, E. C. *Chem. Br.* **1973**, *9*, 4.
(3) McKillop, A.; Taylor, E. C. *Adv. Organomet. Chem.* **1973**, *11*, 147.
(4) McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fowler, J. S.; Taylor, E. C.; McGillivray, G.; Kienzle, F. *J. Am. Chem. Soc.* **1971**, *93*, 4841.
(5) Taylor, E. C.; Kienzle, F.; Robey, R. L.; McKillop, A.; Hunt, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 4845.
(6) Larock, R. C.; Fellows, C. A. *J. Am. Chem. Soc.* **1982**, *104*, 1900.

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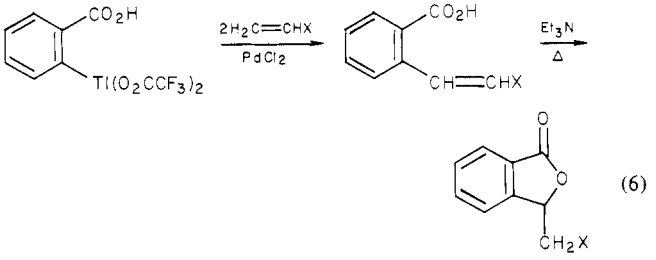
Et_3N, as well as 2 equiv of Na_2CO_3, was found to give still cleaner products, and by refluxing (80 °C) the reaction mixture, the reaction time for cyclization could be reduced to 5 h. Using this basic procedure, the reaction of a number of different olefins and benzoic acids was examined. The results are summarized in Table I.

The reaction of simple terminal olefins was examined initially. Unfortunately, ethylene (excess) gave a mixture of products including *o*-ethylbenzoic acid, the five-member ring methylenephthalide, and isocoumarin (Table I, entry 1). This reaction proved very sensitive to reaction conditions. Switching to *N,N*-dimethylformamide as the solvent gave the phthalide product almost exclusively (entry 2). 1-Hexene (entry 3) and other straight-chain olefins gave mixtures of products and only low yields of the desired isocoumarins. It is possible that palladium chloride is causing isomerization of these olefins to internal olefins which then undergo olefination. Terminal olefins not containing allyl hydrogens, such as styrene and 3,3-dimethyl-1-butene, were much more successful (entries 4 and 5). Olefins bearing electron-withdrawing groups, such as methyl acrylate and acrylonitrile, initially afford the corresponding substituted styrene derivative, which cyclizes to the corresponding phthalide upon refluxing with triethylamine (entries 6 and 7) (eq 6).



(6)

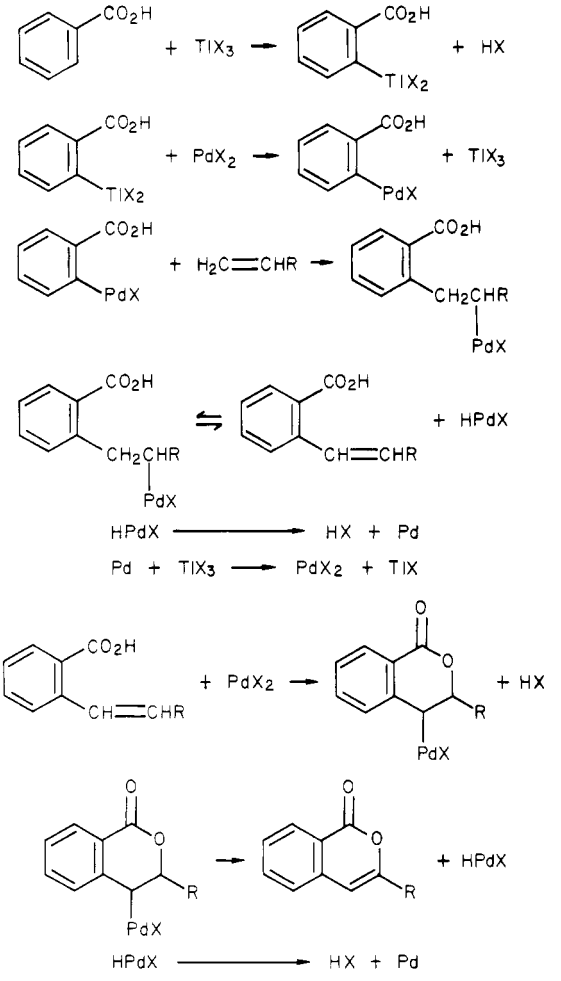
X = CO_2CH_3, CN

Internal olefins can also be employed in these reactions. *cis*-2-Butene affords the desired 3,4-dimethylisocoumarin plus 3-ethylisocoumarin, which apparently arises via isomerization of 2-butene to 1-butene and subsequent olefination (entry 8). Cyclohexene yields an unexpected spiro phthalide product and what appears to be small amounts of the corresponding isocoumarin (entry 9).

The regiochemistry of the thallation–olefination of substituted benzoic acids has proven quite interesting (entries 10–12). *m*-Chloro- and *m*-methylbenzoic acid undergo thallation predominantly at the less hindered site para to the substituent and afford the corresponding 7-substituted isocoumarins. On the other hand, *m*-methoxybenzoic acid undergoes thallation predominantly at the more hindered position between the two substituents resulting in 5-methoxyisocoumarin as the major product. The reason for the reversal in regiochemistry is unclear. One might argue that the bulky thallium electrophile normally prefers to react at the less hindered position, but coordination of the oxygen of the methoxy group becomes an overriding factor. We have observed earlier, however, that thallation–carbonylation of *m*-methoxybenzyl alcohol affords exclusively the product of thallation para to the methoxy group.[6] The relative ratios of the two possible thallation–olefination products were determined by NMR analysis and found to vary with the time of thallation as shown in Table II.

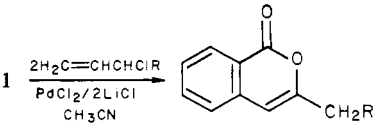
The overall transformation from benzoic acid to isocoumarin is readily understood by the sequence of well-established organometallic reactions outlined in Scheme I. Aromatic thallation is a well-known reaction extensively employed by Taylor and McKillop.[4,5] Transmetalation of organothallium compounds by palladium[6-8] is known to provide organopalladium compounds that react with olefins by addition and subsequent palladium hydride elimination to afford vinyl hydrogen substitution products.[9] In

Scheme I



our reaction with electron-deficient olefins, these styrene derivatives become the major product. During this process, palladium(II) is reduced to palladium(0), but the thallium(III) salt formed in the initial transmetalation step apparently reoxidizes the palladium(0) to palladium(II), which then promotes intramolecular (acyloxy)palladation of the styrene derivative. A second palladium hydride elimination affords the isocoumarin. At this stage, the palladium has once again been reduced to palladium(0) and all of the reoxidant has also been used up. The overall reaction therefore requires one palladium per arene. So far we have been unsuccessful in making these reactions catalytically efficient in palladium. Hegedus has reported the analogous palladium-promoted cyclization of *o*-vinylbenzoic acid to isocoumarin and methylene phthalide, but he did not offer a convenient route to the requisite alkenylbenzoic acids.[10]

Allylic Halides. There are several disadvantages to the reaction with simple olefins. An equimolar amount of palladium chloride is required, and olefins bearing allylic hydrogens generally afford mixtures of products usually containing only low yields of the desired isocoumarin. Fortunately, these difficulties are overcome by employing allylic halides (eq 7). In this case yields of iso-



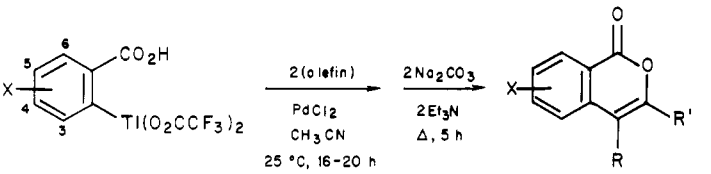
(7)

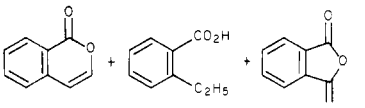
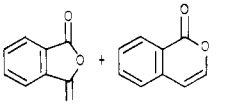
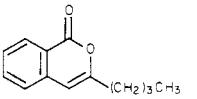
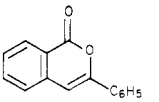
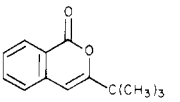
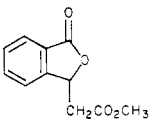
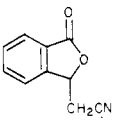
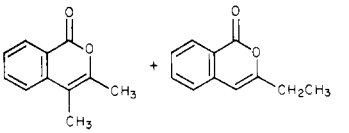
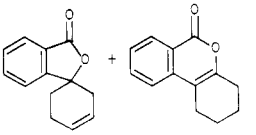
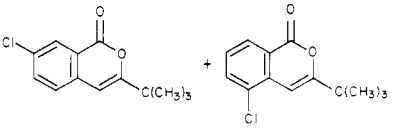
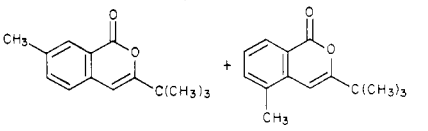
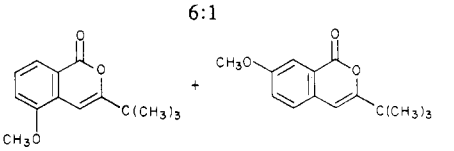
4

coumarins if only 10% $PdCl_2$ is used (**4**, R = H, 66%; R = CH_3, 48%) are as high as those obtained by using an equimolar amount

(7) Spencer, T.; Thorpe, F. G. *J. Organomet. Chem.* **1975**, *99*, C8.
(8) Uemura, S.: Miyoshi, H.; Wakasugi, M.; Okano, M.; Itoh, O.; Izumi, T.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 553.
(9) Heck, R. F. "Organic Reactions"; Wiley: New York, 1982; Vol. 27, Chapter 2, pp 345–390.
(10) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem.* **1977**, *42*, 1329.

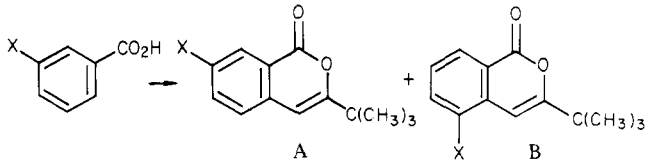
Table I. Olefination of Thallated Benzoic Acids Using Simple Alkenes



entry	olefin	X	product(s)	isolated yield, %[a]
1	$H_2C{=}CH_2$	H	 5:5:1	80[b]
2	$H_2C{=}CH_2$	H	 92:8	60[c]
3	$H_2C{=}CH(CH_2)_3CH_3$	H		40
4	$H_2C{=}CHC_6H_5$	H		79
5	$H_2C{=}CHC(CH_3)_3$	H		73
6	$H_2C{=}CHCO_2CH_3$	H		56[d]
7	$H_2C{=}CHCN$	H		55[d]
8	*cis*-$CH_3CH{=}CHCH_3$	H	 3:1	(73)[e]
9		H	 5:1	(61)[e]
10	$H_2C{=}CHC(CH_3)_3$	5-Cl	 9:1	65[e]
11	$H_2C{=}CHC(CH_3)_3$	5-CH_3	 6:1	41 (50)[e]
12	$H_2C{=}CHC(CH_3)_3$	3-OCH_3	 10:1	66[e]

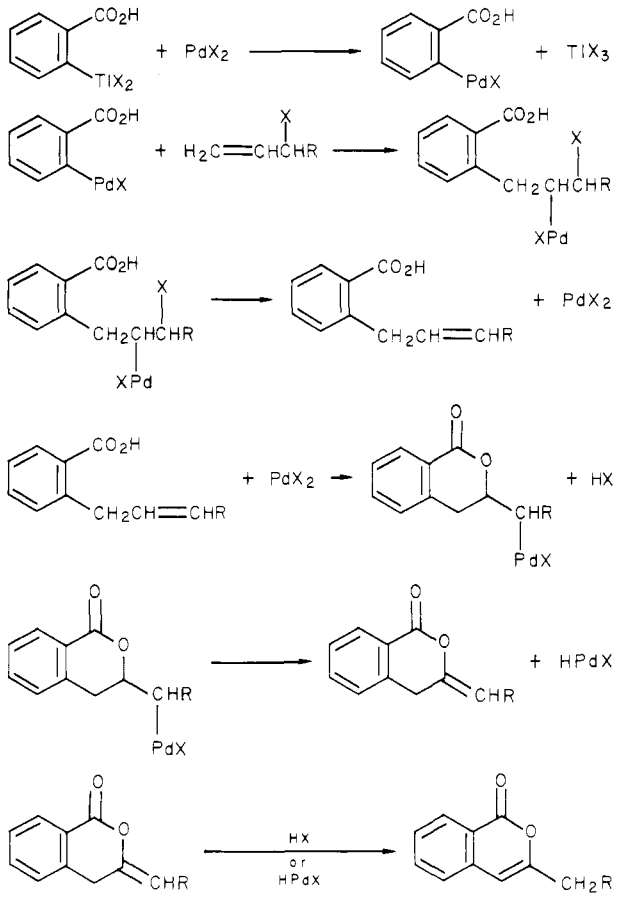
[a] Yields determined by gas chromatography are in parentheses. [b] 10 equiv of LiCl were added to the reaction. [c] DMF was used as the solvent. [d] This reaction was run with 10% $PdCl_2$ for 2 days at room temperature and then 2 equiv of Et_3N were added and refluxed for 20 h. [e] The reaction was run at room temperature for 2 days with 2 equiv of LiCl added (no bases added).

Table II. Regiochemistry of Thallation-Olefination of Substituted Benzoic Acids



X	thallation time, h	ratio A:B
Cl	41	5:2
	96	7:1
CH_3	19	4:1
	40	6:1
OCH_3	1	1:2
	14	1:10

Scheme II

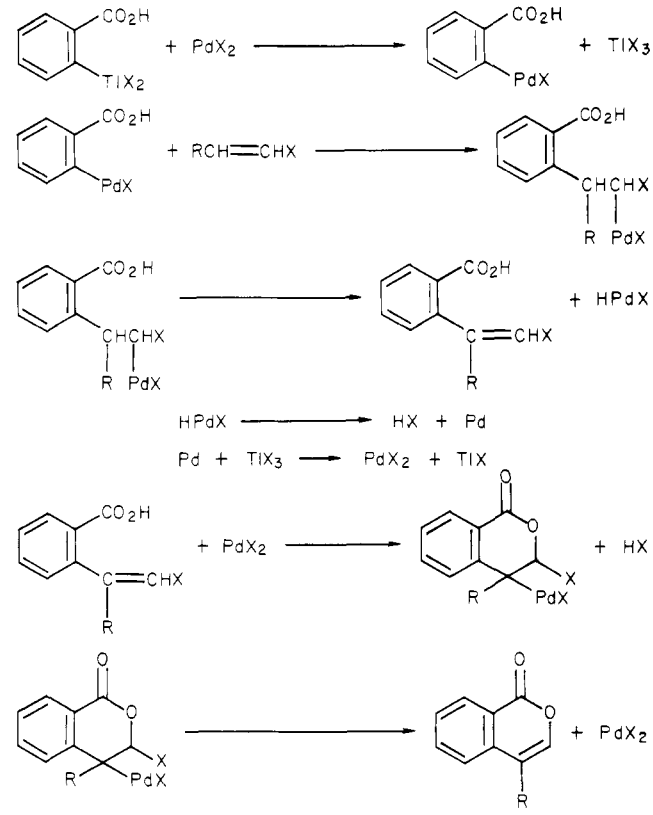


of $PdCl_2$ (**4**, R = H, 51%; R = CH_3, 52%). This reaction proceeds in higher yield when LiCl is added, and bases need not be added to complete the cyclization. Unlike the reaction of simple olefins containing allylic hydrogens, this reaction gives only one major product free of isomers in fair to good yield.

This reaction apparently proceeds by palladium-promoted allylation of the arene[11] and subsequent palladium(II)-promoted cyclization of the resulting *o*-allylic benzoic acid as reported previously by Hegedus[10] (Scheme II). In the allylation step, the palladium(II) species is not reduced, so that the reaction becomes catalytic in palladium. The thallium(III) remains available for reoxidation of the palladium(0) produced in the final palladium hydride elimination. Our procedure greatly simplifies the Hegedus approach[10] to isocoumarins in that simple allylic halides and benzoic acids are employed, instead of *o*-halobenzoic acids and π-allylnickel halides.

(11) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5531.

Scheme III



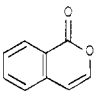
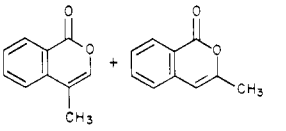
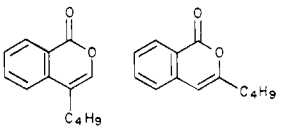
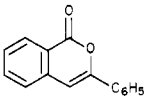
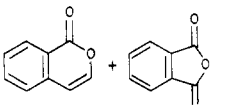
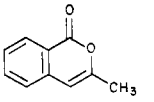
Vinyl Halides and Acetates. There remain, however, major disadvantages to the preceding approaches. Neither approach discussed so far effectively generates either the parent isocoumarin system or simple 4-substituted isocoumarins. We have observed that both of these objectives can be accomplished by using vinyl halides under exactly the same reaction conditions as applied to simple olefins (Table III). Thus, excess vinyl bromide affords isocoumarin in high yield uncontaminated by methylenephthalide (Table III, entry 1). This reaction can be effected in 51% yield by using only 10% $PdCl_2$ and requires no base to effect cyclization.

This isocoumarin synthesis appears to be fairly general. Both 1- and 2-halo-1-alkenes can be employed. The former give predominantly 4-substituted isocoumarins and the latter exclusively the 3-substituted product. No five-member ring phthalides are observed in any of these reactions. Little difference in yields is observed using either cis or trans vinyl halides (compare entries 3 and 4) or bromo vs. iodo alkenes (entries 3 and 5), although the latter appear to be a little more regioselective perhaps for steric reasons. 1-Halo-1-alkenes appear to give higher yields when the reaction is refluxed for some time. Increasing substitution or steric hindrance about the carbon–carbon double bond tends to lower the yield as seen by comparing entries 1, 2, 3, and 6.

The vinyl halide reactions appear to proceed as shown in Scheme III. Arylpalladium addition to the alkene occurs with the aryl group adding preferentially to the carbon β to the halogen. A series of steps analogous to those of Scheme I ensue with the sole difference being the elimination of palladium halide in the final step, instead of palladium hydride. This mechanism accounts for both the regiochemistry and the catalytic nature of the reaction. An alternative scheme in which arylpalladium addition to the alkene occurs with the opposite regiochemistry followed by palladium *halide* elimination and subsequent cyclization of the resulting styrene derivative can be ruled out on two grounds. First, the formation of 4-substituted isocoumarins from 1-halo-1-alkenes speaks against this mechanism. Second, vinyl bromide gives only isocoumarin and no methylene phthalide, suggesting that *o*-vinylbenzoic acid is not an intermediate in this reaction.

Enol acetates can also be employed in the olefination reaction, but they appear to offer no advantages over vinyl halides (Table III, entries 7 and 8). Vinyl acetate affords a mixture of iso-

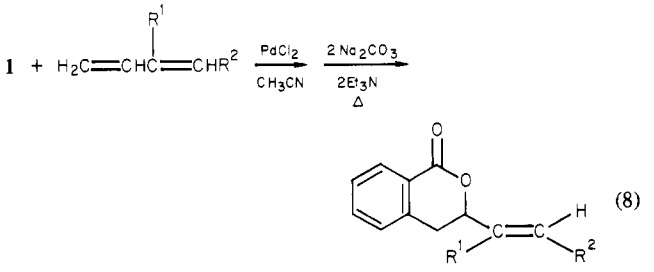
Table III. Olefination Using Vinyl Halides or Acetates

entry	vinyl halide or acetate	product(s)	isolated yield, %
1	$H_2C{=}CHBr$		71
2	*cis*-$CH_3CH{=}CHBr$	 9:2 	69
3	*cis*-*n*-$C_4H_9CH{=}CHBr$	6:1	32, 35[a]
4	*trans*-*n*-$C_4H_9CH{=}CHBr$	4:1	41, 58[a]
5	*cis*-*n*-$C_4H_9CH{=}CHI$	10:1	35, 45[a]
6	$C_6H_5CBr{=}CH_2$		31
7	$H_2C{=}CHOAc$	 2:1	68
8	$H_2C{=}C(OAc)CH_3$		38

[a] Reaction was refluxed 20 h.

coumarin and methylenephthalide suggesting that this reaction proceeds at least in part through *o*-vinylbenzoic acid. Isopropenyl acetate yields only 3-methylisocoumarin, but the yield is low and allyl chloride gives superior results.

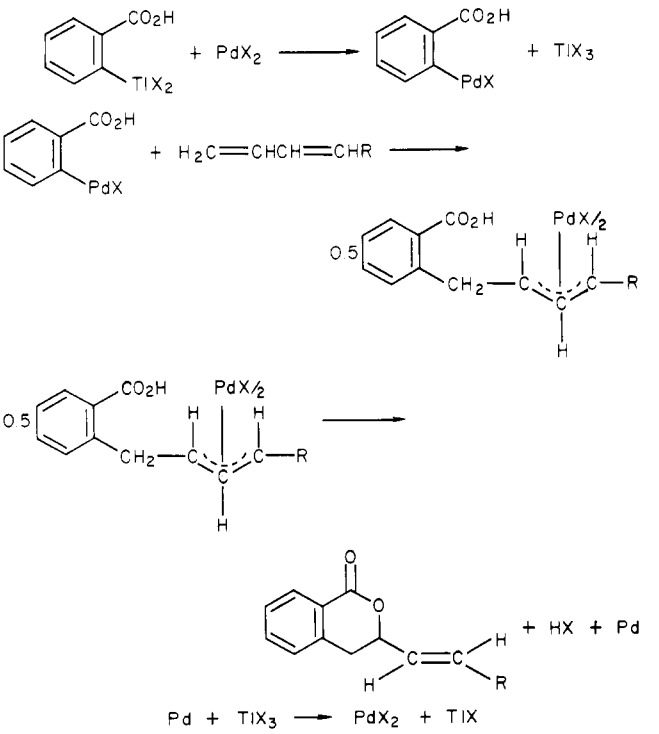
1,2-, 1,3-, and 1,4-Dienes. Thallation–olefination using 1,2-, 1,3-, and 1,4-dienes has been examined. Using a procedure identical with that of simple olefins, the reaction of 1,3-dienes provides an excellent route to 3-alkenyl-3,4-dihydroisocoumarins (eq 8). Some representative yields are indicated in Table IV entries 1–5.



(8)

This reaction is believed to proceed as shown in Scheme IV. Arylpalladium addition to 1,3-dienes is known to generate π-allylpalladium compounds.[12] The addition to both *cis*- and *trans*-1,3-pentadiene apparently proceeds regioselectively to afford only the more stable syn π-allylpalladium compound, which eventually provides the *trans*-propenyl product. Unlike earlier work with isoprene which proved regioselective,[12] we observe products of addition of **1** to each of the double bonds of isoprene. The resulting π-allylpalladium species is unstable under the reaction conditions and undergoes intramolecular displacement by

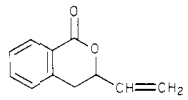
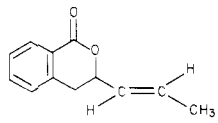
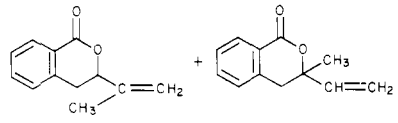
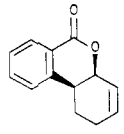
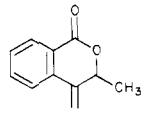
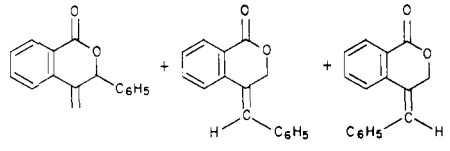
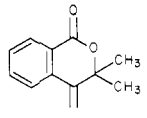
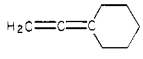
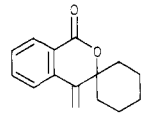
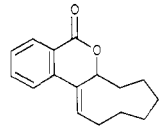
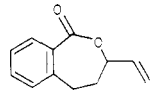
Scheme IV



the neighboring carboxy group. This reaction apparently proceeds with retention, since 1,3-cyclohexadiene affords the cis product. Intermolecular thermal displacement of palladium in π-allylpalladium compounds by carboxylates is a known reaction.[13] There is no evidence for eight-member ring formation in our

(12) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5542.

Table IV. Olefination Using Dienes

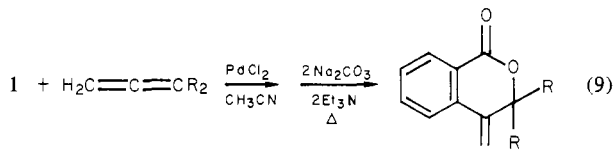
entry	diene	product(s)	isolated yield, %
1	$H_2C{=}CHCH{=}CH_2$		87
2	*trans*-$H_2C{=}CHCH{=}CHCH_3$		71
3	*cis*-$H_2C{=}CHCH{=}CHCH_3$		78
4	$H_2C{=}CHC(CH_3){=}CH_2$	 9:4	70
5			45
6	$H_2C{=}C{=}CHCH_3$		39[a]
7	$H_2C{=}C{=}CHC_6H_5$	 5:1:1	54[a]
8	$H_2C{=}C{=}C(CH_3)_2$		67[a]
9			70[b]
10			56[b]
11	$H_2C{=}CHCH_2CH{=}CH_2$		34[b]

[a] Procedure A (see Experimental Section). [b] Procedure B.

reaction. The resulting palladium metal can once again be re-oxidized by the thallium(III) salt generated during the initial transmetalation step.

Consistent with this mechanism is the observed palladium catalysis of this reaction. If the solvent is changed to methylene chloride from the usual acetonitrile and the bases are omitted, one can obtain a 56% yield of 3-vinyl-3,4-dihydroisocoumarin from 1,3-butadiene and 10% $PdCl_2$. The addition of 2 equiv of lithium chloride to this reaction had little effect on the yield (51% yield).

1,2-Dienes can also be effectively employed in these reactions (eq 9). Modest to good yields of 4-alkylidene-3,4-dihydroisocoumarins are obtained (Table IV, entries 6–10), presumably through a mechanism identical with that of Scheme IV except


(9)

that the arylpalladium intermediate adds to the central carbon of the allene to generate a π-allylpalladium intermediate, which upon intramolecular carboxylate displacement affords the observed product. Organopalladium additions to allenes are known to proceed by formation of π-allylpalladium compounds.[14] This olefination reaction appears to be highly regioselective since only one regioisomer is observed in all reactions except that of phenylallene, which afforded 4-methylene-3-phenyl-3,4-dihydroiso-

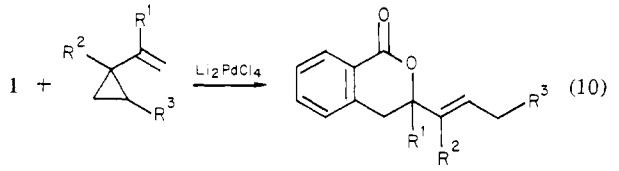
(13) Tsuji, J.; Sakai, K.; Nagashima, H.; Shimizu, I. *Tetrahedron Lett.* **1981**, *22*, 131.

(14) Stevens, S. R.; Shier, G. D. *J. Organomet. Chem.* **1970**, *21*, 495.

coumarin and two isomeric 4-benzylidene-3,4-dihydroisocoumarins in the ratio 5:1:1 (entry 7). The structures of the products were established by ^{13}C off-resonance NMR techniques. Carboxylate displacement at the more highly substituted terminus of π-allylpalladium compounds has been observed previously.[12,15] Preliminary attempts to employ only catalytic amounts of palladium chloride in these reactions have led to only low yields of the desired products.

We have also examined the olefination of one 1,4-diene, namely, 1,4-pentadiene (entry 11, Table IV). Since we earlier observed that organopalladium additions to nonconjugated dienes results in π-allylpalladium formation by remote palladium migration,[16] it appeared that this diene might also provide the expected π-allylpalladium product when reacted with **1** and palladium chlorde in acetonitrile, and subsequent treatment with base ought to provide the corresponding lactone. This indeed turned out to be the case, although the yield of lactone was low.

Vinylcyclopropanes. We have also recently observed that the addition of organopalladium compounds to vinylcyclopropanes results in the formation of π-allylpalladium compounds.[17] It therefore appeared that the olefination of vinylcyclopropanes ought to lead, by intramolecular π-allylpalladium displacement, to the 3-vinyl-3,4-dihydroisocoumarin ring system (eq 10). This is



(10)

indeed the case as seen in Table V. These results are most easily explained by the mechanism outlined in Scheme V. Note that the cyclopropane ring opening of the phenyl-substituted cyclopropane occurs so as to place the palladium in the benzylic position. No product arising from ring opening toward the methylene is observed. This reaction, while catalytic in palladium chloride [10% $PdCl_2$ gave a 16% yield of 3-(*trans*-1′-propenyl)-3,4-dihydroisocoumarin], is not very efficient.

Conclusion

By the simple process of thallation and subsequent palladium-promoted olefination of benzoic acids, we have at hand an efficient, highly convenient route to the biologically important[15] iscoumarin and 3,4-dihydroisocoumarin ring systems. The sequence requires only inexpensive, readily available starting materials and is flexible enough to afford a variety of substitution patterns. The fact that this reaction can be made catalytic with respect to palladium makes this approach an especially attractive one. Furthermore, preliminary studies indicate that the thallation–olefination process can be successfully employed on a variety of other aromatic substrates to provide a novel, new approach to a number of other important heterocyclic ring systems.

Experimental Section

Equipment. Melting points were taken on a Thomas Hoover Uni-Melt melting point apparatus and are reported uncorrected. Infrared (IR) spectra were recorded on a Beckman Model 4250 spectrophotometer. Proton NMR spectra were determined on either a Nicolet NT-300-NB $^{13}C/^{1}H$ FT-NMR or Varian A-60 or EM360A/L spectrometers. All the chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Exact mass spectra were recorded on a Varian MS-9 mass spectrometer. Vapor pressure chromatographic analysis was carried out using a Varian 3700 gas chromatograph. Flash column chromatography was performed using Kieselgel 60, 230–400 mesh silica gel. Elemental analyses were performed by Galbraith Laboratories Inc.

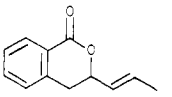
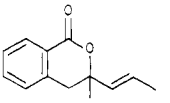
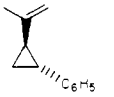
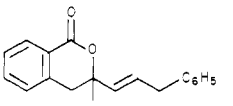
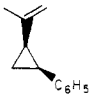
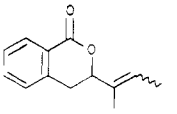
Reagents. All commercially available reagents were used as such without purification. The following chemicals were obtained from Aldrich: 3,3-dimethyl-1-butene, styrene, acrylonitrile, methyl acrylate, *m*-chlorobenzoic acid, *m*-methoxybenzoic acid, *m*-methylbenzoic acid, 3-chloro-1-butene, isoprene, 1,3-cyclohexadiene, vinyl bromide, 1-bromo-1-propene, vinyl acetate, and isopropenyl acetate. Benzoic acid and trifluoroacetic acid were purchased from Fisher. 1-Hexene was obtained from Phillips Petroleum. Ethylene, *cis*-2-butene, and 1,3-butadiene were obtained from Matheson. Cyclohexene and allyl chloride were purchased from Eastman. *cis*-1,3-Pentadiene was available from Chemical Samples (now Wiley Organics), and *trans*-1,3-pentadiene was purchased from Fluka. Dr. R. P. Johnson of this department kindly provided the 1-phenyl-1,2-propadiene and 1,2-cyclononadiene.

Pure, dried, distilled solvents were used for all reactions. Tetrahydrofuran was obtained by distillation from calcium hydride, while acetonitrile and methylene chloride were distilled from phosphorus pentoxide. Dimethylformamide (DMF) was distilled over calcium hydride under reduced pressure. Dimethoxyethane (DME) and triethylamine (Et_3N) were distilled from lithium aluminum hydride (LAH).

Thallium(III) trifluoroacetate was prepared according to the literature procedure[4] and handled in a nitrogen-filled glovebag while transferring into the reaction flask.

General Procedure for the Thallation of Benzoic Acids. Thallium(III) trifluoroacetate (11.3 g, 0.02 mol) was dissolved in argon-saturated tri-

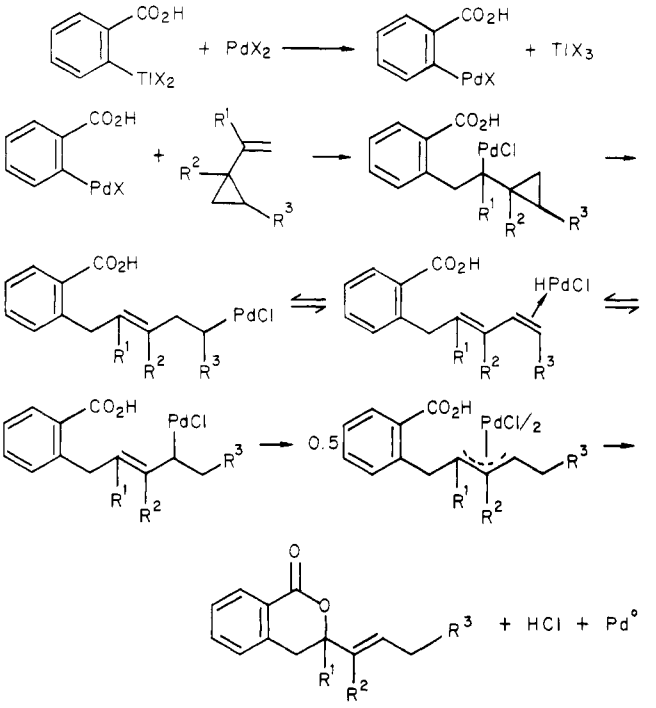
Table V. Olefination Using Vinylcyclopropanes

entry	vinylcyclopropane	product	isolated yield, %[a]
1			64
2			40 (50)
3			32 (42)
4			26
5			(65)

$E:Z = 90:10$

[a] Procedure A (procedure B); see Experimental Section.

Scheme V



(15) Takahashi, Y.; Tsukiyama, K.; Sakai, S.; Ishii, Y. *Tetrahedron Lett.* **1970**, 1913.
(16) Larock, R. C.; Takagi, K. *Tetrahedron Lett.* **1983**, *24*, 3457.
(17) Larock, R. C.; Varaprath, S., *J. Org. Chem.*, in press.

fluoroacetic acid (40 mL). Benzoic acid (2.5 g, 0.02 mol) was added, and the contents were stirred and gently refluxed in an 80 °C oil bath for 24 h. The flask was cooled to room temperature, and the white crystals that precipitated were collected by filtration and washed with cold, dry methylene chloride. The yield of the ortho-thallated benzoic acid ranges from 90% to 95%.

m-Methoxybenzoic acid was thallated as described above with the following modifications: The mixture was heated at reflux temperature for a shorter reaction time (14 h). The crystals that settled on cooling were collected by a quick filtration into a round-bottom flask and dried by using a vacuum pump. The off-white solid was not washed with methylene chloride because of its solubility in this solvent.

m-Chlorobenzoic acid and *m*-methylbenzoic acid were thallated as described for *m*-methoxybenzoic acid (thallation times 40 and 96 h, respectively).

Caution! Organothallium compounds are toxic and should be handled with extreme care.

Reaction of Thallated Benzoic Acids with Simple Olefins. The thallated benzoic acid (5 mmol) and palladium(II) chloride (5 mmol) were weighed into a round-bottom flask. For reactions with certain olefins, lithium chloride (10 mmol) was also added to the reaction flask. The solvent (10 mL) was added followed by addition of the appropriate olefin (10 mmol). The contents were stirred at room temperature for 20 h. Triethylamine (10 mmol) and anhydrous sodium carbonate (10 mmol) were then added in that order. The contents were gently heated at reflux temperature for 5 h. After cooling to room temperature, ether (20 mL) was added and the solution was filtered through Celite. The residue was washed with ether (100 mL). The combined ether solutions were washed with 2 × 15 mL of saturated ammonium chloride solution, dried over anhydrous $MgSO_4$, and concentrated to an oil using a rotary evaporator. The crude products were purified by distillation, recrystallization, or flash chromatographic separation on silica gel using a hexane/ethyl acetate solvent mixture as eluant. The following compounds were prepared by using this basic procedure.

Synthesis of Isocoumarin. Reaction of thallium compound **1** (0.28 g, 0.5 mmol) with $PdCl_2$ (89 mg, 0.5 mmol) and excess ethylene (a balloon full) in acetonitrile as the solvent followed by treatment with triethylamine (0.14 mL, 1.0 mmol) and anhydrous sodium carbonate (106 mg, 1.0 mmol) as described above gave a crude mixture containing several products. Isocoumarin was separated by flash chromatography on silica gel using hexane/ethyl acetate (19:1) as the eluant. It was further purified by recrystallization from hexane to obtain the pure product: yield 54 mg, 37%; mp 46–47 °C (lit.[18] mp 47 °C); ^1H NMR ($CDCl_3$) δ 6.3 (d, 1 H, C_4 H, J = 6 Hz), 7.2 (d, 1 H, C_3 H, J = 6 Hz), 7.2–8.25 (m, 4 H, Ar H); IR (CCl_4) 1750, 1730 (C=O), 1700 (C=C) cm^{-1}.

3-*tert*-Butylisocoumarin. Reaction of 3,3-dimethyl-1-butene (84 mg, 1.0 mmol) with thallium compound **1** (0.5 mmol) and $PdCl_2$ (0.5 mmol) in the manner described above gave after flash chromatography on silica gel (4:1 hexane/ethyl acetate) the title product as a white solid in 73% yield: mp 61 °C; ^1H NMR ($CDCl_3$) δ 1.3 (s, 9 H, *t*-Bu), 6.1 (s, 1 H, C_4 H), 7.1–7.8 (m, 3 H, Ar H), 8.0–8.2 (dd, 1 H, C_8 H, J = 7 and 2 Hz); IR (CCl_4) 1745 (C=O), 1645 (C=C) cm^{-1}; mass spectrum, m/e 202.098 88 (calcd, 202.099 38). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.94; H, 7.15.

3-*n*-Butylisocoumarin. Reaction of 1-hexene (1.0 mmol) with thallium compound **1** (0.5 mmol) and $PdCl_2$ (0.5 mmol) in the manner described above gave after routine workup followed by chromatographic separation (silica gel, 4:1 hexane/ethyl acetate) the title compound in 40% yield: mp 44 °C (lit.[19] mp 45–46 °C); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3, J = 7 Hz), 1.1–1.7 (m, 4 H, CH_2's), 2.5 (t, 2 H, CH_2, J = 7 Hz), 6.07 (s, 1 H, C_4 H), 7.1–7.8 (m, 3 H, Ar H), 8.0–8.2 (dd, 1 H, C_8 H, J = 7 and 2 Hz); IR (CCl_4) 1735 (C=O), 1650 (C=C) cm^{-1}; mass spectrum, m/e 202.098 88 (calcd for $C_{13}H_{14}O_2$, 202.099 38). Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.23; H, 7.04.

3-Phenylisocoumarin. Treatment of thallium compound **1** (0.5 mmol) with $PdCl_2$ (0.5 mmol) and styrene (1.0 mmol) in acetonitrile as the solvent followed by triethylamine (1 mmol) and sodium carbonate (1 mmol) as bases as described above gave an impure solid. Separation by chromatography on silica gel (4:1 hexane/ethyl acetate) followed by recrystallation from hexane yielded the title compound as a white solid: yield 87.7 mg, 79%; mp 87–88 °C (lit.[20] mp 89–90 °C); ^1H NMR ($CDCl_3$) δ 6.85 (s, 1 H, C_4 H), 7.1–7.5 (m, 5 H, Ar H), 7.6–7.9 (m, 3 H, Ar H), 8.1–8.3 (m, 1 H, C_8 H); IR (CCl_4) 1735 (C=O), 1655 (C=C) cm^{-1}; mass spectrum, m/e 222.067 76 (calcd for $C_{15}H_{10}O_2$ 222.068 08).

3,4-Dimethylisocoumarin. The general procedure described above was modified for this compound. A stirred suspension of thallium compound **1** (0.5 mmol), $PdCl_2$ (0.5 mmol), and lithium chloride (1.0 mmol) in acetonitrile was exposed to a balloon filled with *cis*-2-butene, and the contents were stirred at room temperature for 48 h. The usual isolation, followed by chromatographic separation on silica gel (19:1 hexane/ethyl acetate, R_f 0.1), gave the title compound[21] in 54% yield. It could be recrystallized from hexane: mp 129 °C; ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H, CH_3), 2.27 (s, 3 H, CH_3), 7.15–7.8 (m, 3 H, Ar H), 8.05–8.25 (m, 1 H, C_8 H); IR (CCl_4) 1740 (C=O), 1660 (C=C) cm^{-1}; mass spectrum, m/e 174.067 98 (calcd for $C_{11}H_{10}O_2$, 174.068 08).

The compound 3-ethylisocoumarin was obtained as a minor product (19%) in the above reaction (separation on silica gel, 19:1 hexane/ethyl acetate, R_f 0.15). For ^1H NMR and IR data on this minor isomer, see the later procedure employing allylic chlorides.

1,3-Dihydrospiro[isobenzofuran-1-one-3,1′-cyclohex-3′-ene]. The title compound was obtained as a major product by reacting cyclohexene (1.0 mmol) with thallium compound **1** (0.5 mmol), $PdCl_2$ (0.5 mmol), and LiCl (1.0 mmol) in acetonitrile by the modified procedure described above for the synthesis of 3,4-dimethylisocoumarin. The product was separated by flash chromatography on silica gel (19:1 hexane/ethyl acetate, R_f 0.05–0.10) and recrystallized from hexane: yield 51%; mp 112–114 °C; 300-MHz ^1H NMR ($CDCl_3$) δ 2.0 (m, 2 H, C'_6 H), 2.3–2.7 (m, 4 H, C'_2 H and C'_5 H), 7.4, 7.55, and 7.65 (3 m, 3 H, C_4 H, C_5 H, C_6 H), 7.9 (m, 1 H, C_7 H); IR (CCl_4) 1770 (C=O), 1640 (C=C) cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.77; H, 6.19.

The compound 1,2,3,4-tetrahydro-4*H*-dibenzo[*b*,*d*]pyran-6-one was obtained as a minor product (10%) during chromatographic separation on silica gel (19:1 hexane/ethyl acetate, R_f 0.12–0.16): ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, CH_2's), 2.3–2.6 (m, 4 H, $=CCH_2$), 7.15–7.7 (m, 3 H, Ar H), 8.1–8.3 (m, 1 H, C_7 H); IR (CCl_4) 1740 (C=O), 1655 (C=C) cm^{-1}.

3-*tert*-Butyl-7-chloroisocoumarin. Method A: The reaction was carried out without prior isolation of the arylthallium compound. *m*-Chlorobenzoic acid (184.5 mg, 1.17 mol) and thallium trifluoroacetate (641 mg, 1.17 mmol) were dissolved in argon-saturated trifluoroacetic acid (3 mL) and heated at reflux temperature for 40 h. The solvent TFA was removed on a rotary evaporator and replaced with acetonitrile (10 mL). Palladium chloride (21 mg, 1.17 mmol) and 3,3-dimethyl-1-butene (0.25 mL, 2.35 mmol) were added, and the mixture was stirred at room temperature for 16 h. This was followed by the addition of 2 equiv each of triethylamine and sodium carbonate and refluxing for 5 h as described above. The usual workup yielded a crude mixture, which was purified by flash chromatography on silica gel (4:1 hexane/ethyl acetate) to obtain a white solid (53%) containing the title compound as the major isomer. Recrystallization from hexane resulted in the isolation of the pure product: mp 121–123 °C; ^1H NMR (CCl_4) δ 1.3 (s, 9 H, *t*-Bu), 6.08 (s, 1 H, C_4 H), 7.15–7.5 (m, 2 H, Ar H), 7.85–8.0 (br s, 1 H, C_8 H); IR (CCl_4) 1740 (C=O), 1650 (C=C) cm^{-1}; mass spectrum, m/e 236.060 63 (calcd for $C_{13}H_{13}ClO_2$, 236.060 41). Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54. Found: C, 65.87; H, 5.66.

The minor isomer, 3-*tert*-butyl-5-chloroisocoumarin was detected in the ^1H NMR spectrum of the crude reaction mixture by the presence of a signal at δ 6.6 for the C_4 hydrogen.

Method B: This procedure was essentially the same as method A except that the ortho-thallated *m*-chlorobenzoic acid was isolated as an off-white dry solid before subjecting it to subsequent reactions, yield 65% (based on thallium compound) of a mixture containing the two regioisomers in a 9:1 ratio with the title compound predominating.

3-*tert*-Butyl-5-methoxyisocoumarin. Reaction of *m*-methoxybenzoic acid (153.2 mg, 1.0 mmol) with thallium trifluoroacetate (547.2 mg, 1.0 mmol) in TFA (3 mL, 14 h) followed by treatment with $PdCl_2$, 3,3-dimethyl-1-butene, triethylamine, and sodium carbonate in acetonitrile as outlined in method A above gave a crude product mixture. Routine workup and purification by chromatography on silica gel (4:1 hexane/ethyl acetate) gave a product mixture in 58% yield containing the title compound as the major isomer (10:1). The compound 3-*tert*-butyl-7-methoxyisocoumarin is present as a minor isomer. Recrystallization in hexane gave the pure 5-methoxy compound: mp 133 °C; ^1H NMR ($CDCl_3$) δ 1.45 (s, 9 H, *t*-Bu), 3.92 (s, 3 H, OCH_3), 6.68 (s, 1 H, C_4 H), 7.0–7.6 (m, 2, Ar H), 7.7–7.9 (m, 1 H, C_8 H); IR (CCl_4) 1750 (C=O), 1650 (C=C) cm^{-1}. The minor isomer could be identified by an absorption in the ^1H NMR spectrum at δ 6.25.

3-*tert*-Butyl-7-methylisocoumarin. The reaction of *m*-methylbenzoic acid (0.68 g, 5 mmol) with thallium trifluoroacetate (5 mmol), $PdCl_2$ (5 mmol), LiCl (10 mmol), and 3,3-dimethyl-1-butene (10 mmol) following method A described above, but in the absence of any base, yielded a crude product mixture. Separation on a silica gel column eluting with 4:1 hexane/ethyl acetate followed by recrystallization (hexane) afforded the pure product in 41% yield: mp 67–68 °C; ^1H NMR (CCl_4) δ 1.35

(18) Bamberger, E.; Frew, W. *Chem. Ber.* **1894**, *27*, 207.
(19) Batu, G.; Stevenson, R. *J. Org. Chem.* **1980**, *45*, 1532.
(20) Charubala, R.; Guggisberg, A.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1096.
(21) Heller, G. *Chem. Ber.* **1935**, *68*, 1085, 1089.

(s, 9 H, *t*-Bu), 2.42 (s, 3 H, Ar CH_3), 6.07 (s, 1 H, C_4 H), 7.0–7.5 (m, 2 H, Ar H), 7.9 (br s, 1 H, C_8 H); IR (CCl_4) 1740 (C=O), 1650 (C=C) cm^{-1}; mass spectrum, *m/e* 216.114 87 (calcd for $C_{14}H_{16}O_2$, 216.115 03). Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.78; H, 7.52.

Reactions with Electron-Deficient Olefins: 3-(Carbomethoxymethyl)phthalide. The thallated benzoic acid obtained from 0.61 g (5 mmol) of benzoic acid and 1.37 g (5 mmol) of thallium trifluoroacetate was stirred at room temperature for 2 days with $PdCl_2$ (0.5 mmol) and methyl acrylate (10 mmol) in acetonitrile solvent. Triethylamine (10 mmol) was added and the mixture heated at reflux temperature for 20 h. Routine isolation followed by distillation afforded the pure product in 56% yield: bp 175 °C (0.3 mmHg); ^1H NMR ($CDCl_3$) δ 2.92 (d, 2 H, CH_2, J = 7 Hz), 3.78 (s, 3 H, OCH_3), 5.9 (t, 1 H, CHAr, J = 7 Hz), 7.4–7.8 (m, 3, Ar H), 7.85–8.1 (m, 1 H, C_7 H); IR (CCl_4) 1775 (C=O, lactone), 1750 (C=O, ester) cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.22; H, 4.87.

3-(Cyanomethyl)phthalide. With 0.53 g (10 mmol) of acrylonitrile and by the procedure outlined above for the preparation of 3-(carbomethoxymethyl)phthalide, the title compound was obtained as an impure solid. Recrystallization from hexane afforded the pure product in 55% yield: mp 116 °C; ^1H NMR ($CDCl_3$) δ 3.05 (d, 2 H, CH_2, J = 7 Hz), 5.66 (t, 1 H, CHAr, J = 7 Hz), 7.3–8.0 (m, 4 H, Ar H); IR (CCl_4) 2240 (C≡N), 1775 (C=O) cm^{-1}. Anal. Calcd for $C_{10}H_7NO_2$: C, 69.35; H, 4.07. Found: C, 69.13; H, 4.04.

Reaction with Allylic Chlorides: 3-Methylisocoumarin. Procedure A (catalytic $PdCl_2$): palladium chloride (0.09 g, 0.5 mmol), LiCl (0.04 g, 1 mmol), and allyl chloride (0.77 g, 10 mmol) were added to the thallated benzoic acid **1** (5 mmol) prepared from 0.61 g (5 mmol) of benzoic acid and 1.37 g (5 mmol) of thallium trifluoroacetate in acetonitrile as solvent. After it was stirred at room temperature for 2 days, the reaction was worked up by the standard isolation procedure. The crude product was recrystallized from hexane to obtain 48% of the pure product; mp 71 °C (lit.[22] mp 73–74 °C); ^1H NMR (CCl_4) δ 2.2 (s, 3 H, CH_3), 6.1 (s, 1 H, C_4 H), 7.25–7.6 (m, 3 H, Ar H), 8.0–8.2 (m, 1 H, C_8 H); IR (CCl_4) 1740 (C=O), 1670 (C=C) cm^{-1}. Procedure B (stoichiometric $PdCl_2$): procedure B was carried out in a manner identical with procedure A except that an equivalent amount of palladium chloride with respect to the thallated benzoic acid was employed. By use of the standard isolation procedure, the product yield was estimated to be 59% by using gas chromatography with tetradecane as the internal standard.

3-Ethylisocoumarin. Procedure A described above was followed using 3-chloro-1-butene as the allylic halide and 10 mol % of $PdCl_2$. After routine isolation, the pure product[22] was obtained by recrystallization from hexane: mp 69 °C; ^1H NMR (CCl_4) δ 1.3 (t, 3 H, CH_3, J = 7 Hz), 2.55 (q, 2 H, CH_2, J = 7 Hz), 6.15 (s, 1 H, C_4 H), 7.15–7.7 (m, 3 H, Ar H), 8.0–8.2 (m, 1 H, C_8 H); IR (CCl_4) 1735 (C=O), 1650 (C=C) cm^{-1}; mass spectrum, *m/e* 174.067 40 (calcd for $C_{11}H_{10}O_2$, 174.068 08).

Preparation of Vinyl Halides. Vinyl bromide and vinyl acetate are commercially available. *cis*-1-Bromo-1-propene was purified by distillation of the commercially available mixture by spinning band column.

***trans*-1-Bromo-1-hexene.** This compound was obtained in 31% overall yield by hydroalumination of 1-hexyne with diisobutylaluminum hydride followed by quenching with bromine according to the published procedure.[23]

***cis*-1-Bromo-1-hexene.** This compound was prepared according to the published procedure.[24] 1-Hexyne was hydroborated by catecholborane (Aldrich) in 65% yield [bp 110 °C (0.3 mmHg)] and subsequently reacted with bromine to afford the *cis*-vinyl bromide[25] in 74% yield [bp 41 °C (15 mmHg)].

1-Iodo-1-Hexyne. To 1-hexyne (10 g, 0.12 mol) dissolved in argon-saturated THF (30 mL) and cooled to −78 °C was added *n*-butyl lithium (61 mL of 2 M solution in hexane) dropwise from an addition funnel. The contents were warmed to 0 °C and cooled back down to −78 °C, and iodine (30.9 g) dissolved in argon-saturated THF (20 mL) was added from an addition funnel. After the addition was complete, the contents were warmed to room temperature, and the solution was extracted with ether (100 mL), and the ether extract was washed with water and brine solution. After it was dried over anhydrous $MgSO_4$, the solution was concentrated on a rotary evaporator and the product distilled [bp 73 °C (17 mmHg)] to yield 73% of 1-iodo-1-hexyne.

***cis*-1-Iodo-1-hexene.** This compound was synthesized according to the published procedure.[26] To a freshly prepared THF solution of dicyclohexylborane was added 1-iodo-1-hexyne at 0 °C. After quenching the reaction mixture with glacial acetic acid, the product was extracted with ether, concentrated, and distilled [bp 70 °C (18 mmHg)] in 60% yield.

α-Bromostyrene. This compound was synthesized according to the published procedure[27] in 66% yield [37 °C (0.25 mmHg)] by dehydrohalogenation of 1-phenyl-1,2-dibromoethane with KOH. The latter compound in turn was synthesized in quantitative yield by the addition of bromine to styrene.

Reaction with Vinyl Halides: Isocoumarin. Following the general procedure for simple olefins described earlier, the reaction of vinyl bromide (excess) with isolated thallated benzoic acid **1** (0.5 mmol) and $PdCl_2$ (0.5 mmol) in acetonitrile was carried out in the presence of Et_3N and Na_2CO_3. The product isocoumarin was isolated in the usual manner and purified as outlined before (yield 71%). The ^1H NMR data are identical with those reported earlier.

4- and 3-Methylisocoumarin. Reaction of 1-bromo-1-propene (a mixture containing both the cis and the trans isomers, 1.0 mmol) by the usual procedure gave a crude product, which was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate): 60% yield, with 4-methylisocoumarin present as the major component (4:1); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H, CH_3), 7.06 (s, 1 H, C_3 H), 7.15–7.86 (m, 3 H, Ar H), 8.0–8.3 (m, 1 H, C_8 H).

The presence of the minor isomer 3-methylisocoumarin is indicated by a CH_3 absorption at δ 2.21 and a C_4 H absorption at δ 6.15 in the NMR spectrum. Using pure *cis*-1-bromo-1-propene one obtains a 69% yield (9:2 ratio of 4- to 3-methylisocoumarin with 4-methylisocoumarin as the major product).

4- and 3-*n*-Butylisocoumarin. With pure *trans*-1-bromo-1-hexene as the vinylic halide substrate and by the general procedure described above, a crude product mixture was obtained. Purification by chromatographic separation (silica gel, 4:1 hexane/ethyl acetate) gave a 41% yield of the product mixture (4:1) containing 4-*n*-butylisocoumarin as the major isomer: ^1H NMR ($CDCl_3$) δ 0.7–1.13 (distorted t, 3 H, CH_3, J = 6 Hz), 1.2–1.9 (m, 4 H, CH_2), 2.3–2.7 (t, 2 H, allylic CH_2, J = 6 Hz), 7.1 (s, 1 H, C_3 H), 7.23–7.9 (m, 3 H, Ar H), 8.23–8.45 (m, 1 H, C_8 H). The minor isomer was identified by the absorption of C_4 H at δ 6.23 as a singlet.

The above procedure has been modified slightly to improve the yield. After the addition of Et_3N and Na_2CO_3, the reaction mixture was heated at reflux temperature for 20 h: yield 58% (5:1 ratio with 4-*n*-butylisocoumarin as the major product).

The reaction of *cis*-1-iodo-1-hexene was carried out in a similar manner to obtain the same isomers in a total yield of 45% (10:1 ratio with 4-*n*-butylisocoumarin as the major product).

3-Phenylisocoumarin. Reaction using α-bromostyrene under the usual conditions and chromatographic separation on silica gel (4:1 hexane/ethyl acetate) gave the pure product in 31% yield. Physical data on this compound have been reported earlier.

Reaction with Vinyl Acetates: Isocoumarin. Vinyl acetate reacted under conditions similar to those described for vinyl halides to give a 68% yield of a mixture containing isocoumarin as the major product (2:1). The minor product, methylenephthalide, is identified by a singlet absorption at δ 5.2 in the ^1H NMR spectrum.

3-Methylisocoumarin. Isopropenyl acetate reacted under the conditions described above to give, after purification on silica gel (4:1 hexane/ethyl acetate), pure 3-methylisocoumarin in 38% yield.

Reaction with 1,3-Dienes: 3-Vinyl-3,4-dihydroisocoumarin. The general olefin procedure described earlier was employed using 1,3-butadiene (excess), thallium compound **1** (0.5 mmol), and $PdCl_2$ (0.5 mmol) in the presence of Et_3N and Na_2CO_3. Following routine isolation and purification (silica gel, 4:1 hexane/ethyl acetate) the pure product is obtained in 87% yield: ^1H NMR ($CDCl_3$) δ 3.0 (d, 2 H, C_4 H, J = 7 Hz), 4.8–6.2 (m, 4 H, CH=CH_2 and C_3 H), 7.0–7.6 (m, 3 H, Ar H), 7.85–8.2 (m, 1 H, C_8 H); mass spectrum, *m/e* 174 (M^+, parent ion).

3-(*trans*-1′-Propenyl)-3,4-dihydroisocoumarin. Following the general procedure using 1.0 mmol of *cis*-1,3-pentadiene and 0.5 mmol each of the thallium compound **1** and $PdCl_2$, in acetonitrile as solvent with Et_3N and Na_2CO_3 (2.0 mmol each) as bases, the pure product was obtained after isolation and purification in the usual manner (silica gel, 4:1 hexane/ethyl acetate, R_f 0.3) in 78% yield: 300-MHz ^1H NMR ($CDCl_3$) δ 1.75 (dd, 3 H, CH_3, J = 6 and 1.5 Hz), 3.02 (m, 2 H, C_4 H), 4.96 (m, 1 H, C_3 H), 5.63 (m, 1 H, C_2 H, J = 15 Hz), 5.91 (m, 1 H, C_1' H, J = 15 Hz), 7.24–7.56 (m, 3 H, Ar H), 8.05–8.1 (m, 1 H, C_8 H); IR (CCl_4) 1725 (C=O), 1610 (C=C) cm^{-1}; mass spectrum, *m/e* 188.084 39 (calcd for $C_{12}H_{12}O_2$, 188.08373). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.58; H, 6.43. Found: C, 75.51; H, 6.42.

Reaction with *trans*-1,3-pentadiene under conditions similar to that of *cis*-1,3-pentadiene gave the same cyclized product in 71% yield.

3-Isopropenyl-3,4-dihydro- and 3-Methyl-1-vinyl-3,4-dihydroisocoumarins. Reaction with isoprene under conditions similar to that of 1,3-pentadiene gave following chromatographic separation (silica gel, 4:1

(22) Nagami, H. *J. Pharm. Soc. Jpn.* **1941**, *61*, 46, 49.
(23) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.
(24) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370.
(25) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456.
(26) Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* **1967**, *89*, 5086.
(27) Ashworth, F.; Burkhardt, G. N. *J. Chem. Soc.* **1928**, 1801.

hexane/ethyl acetate), a product mixture containing the title compounds (9:4, respectively) in a combined yield of 70%: ^{1}H NMR ($CDCl_3$) of 3-isopropenyl-3,4-dihydroisocoumarin δ 1.9 (s, 3 H, CH_3), 3.1 (m, 2 H, C_4 H), 4.75–5.36 (m, 2 H, $=CH_2$), 7.1–7.7 (m, 3 H, Ar H), 7.9–8.2 (m, 1 H, C_8 H); ^{1}H NMR ($CDCl_3$) of 3-methyl-3-vinyl-3,4-dihydroisocoumarin δ 1.55 (s, 3 H, CH_3), 3.1 (m, 2 H, C_4 H), 4.75–5.36 (m, 2 H, $=CH_2$), 5.9 (dd, 1 H, CH=, J = 16 and 10 Hz), 7.1–7.7 (m, 3 H, Ar H), 7.9–8.2 (m, 1 H, C_8 H).

***cis*-1,2,4a,10b-Tetrahydro-4*H*-dibenzo[*b*,*d*]pyran-6-one.** Reaction with 1,3-cyclohexadiene under conditions similar to that of 1,3-pentadiene gave, following chromatographic separation (silica gel, 3:1 hexane/ethyl acetate), the title compound in 29% yield: bp 170 °C (0.4 mmHg); 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.8–2.0 (m, 2 H, CH_2), 2.25–2.30 (m, 2 H, CH_2C=), 3.1 (m, 1 H, C_{10b} H), 5.0 (t, 1 H, C_{4a} H, J = 4 Hz); 6.0–6.2 (m, 2 H, CH=CH), 7.2-7.6 (m, 3 H, Ar H), 8.0–8.1 (m, 1 H, C_7 H); IR (CCl_4) 1720 (C=O), 1610 (C=C) cm^{-1}; mass spectrum, m/e 200.083 68 (calcd for $C_{13}H_{12}O_2$, 200.083 73). By addition of 2 equiv of LiCl to the $PdCl_2$ in acetonitrile and stirring of the solution until all salts are dissolved prior to addition of the organothallium compound, the yield of lactone could be increased to 45%.

Reduction of *cis*-1,2,4a,10b-Tetrahydro-4*H*-dibenzo[*b*,*d*]-pyran-6-one. The above compound was dissolved in absolute ethanol (0.5 mmol/20 mL). Raney nickel was added, and the contents were shaken for 24 h under 60 psi of hydrogen pressure. Ethanol was evaporated and the residue dissolved in ether, filtered, and concentrated. The crude product was purified by column chromatography (silica gel, 4:1 hexane/ethyl acetate). The proton NMR spectra obtained is identical with that reported[6] earlier by us for *cis*-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b*,*d*]-pyran-6-one confirming the cis ring junction in the compound prepared by olefination using 1,3-cyclohexadiene.

Preparation of 1,2-Dienes and Precursors: **3-Chloro-3-methyl-1-butyne.** This compound was prepared following a published literature procedure:[28] yield 50%; ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 6 H, CH_3), 2.6 (s, 1 H, C≡CH).

3-Methyl-1,2-butadiene. This allene was prepared by reduction of 3-chloro-3-methyl-1-butyne with Zn/Cu couple according to the literature procedure:[29] yield 60%; bp 41 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (t, 6 H, CH_3, J = 3 Hz), 4.5 (heptet, 2 H, $=CH_2$, J = 3 Hz).

3-(*p*-Tosyloxy)-1-butyne. This compound was prepared from the commerically available 1-butyn-3-ol (Farchan) according to the literature procedure:[30] yield 91%; ^{1}H NMR ($CDCl_3$) δ 1.55 (d, 3 H, CH_3, J = 6 Hz), 2.43 (s, 3 H, Ar CH_3), 2.45 (d, 1 H, C≡CH, J = 2 Hz), 5.15 (dq, 1 H, OCH, J = 6 and 2 Hz), 7.33 and 7.8 (two d, 4 H, Ar H, J = 8 Hz).

3-Chloro-1-butyne. This compound was prepared from the corresponding tosylate by displacement with lithium chloride according to the literature procedure:[31] yield 98%; bp 74 °C; ^{1}H NMR ($CDCl_3$) δ 1.75 (d, 3 H, CH_3, J = 7 Hz), 2.56 (d, 1 H C≡CH, J = 2 Hz), 4.6 (dq, 1 H, CHCl, J = 7 and 2 Hz).

1,2-Butadiene. This compound was prepared from 3-chloro-1-butyne according to the literature procedure:[29] yield 61%; bp 24 °C; ^{1}H NMR ($CDCl_3$) δ 1.5–1.65 (m, 3 H, CH_3), 4.6 (m, 2 H, $=CH_2$), 5.0 (m, 1 H, =CH).

1-Chloro-1-ethynylcyclohexane. This compound was prepared from the corresponding commerically available acetylenic alcohol (Farchan) according to the published procedure:[28] yield 80%; bp 30 °C (0.25 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.3–2.4 (m, 10 H, CH_2's), 2.65 (s, 1 H, ≡CH).

Vinylidenecyclohexane. This compound was prepared from 1-chloro-1-ethynylcyclohexane according to the literature procedure:[29] yield 86%; bp 36 °C (17 mmHg); ^{1}H NMR ($CDCl_3$) δ 1.4–1.85 (m, 6 H, CH_2's), 1.85–2.3 (m, 4 H, $=CCH_2$), 4.4–4.6 (m, 2 H, $=CH_2$).

Reactions with 1,2-Dienes: **4-Methylene-3-phenyl-3,4-dihydroisocoumarin.** Procedure A: the general procedure described earlier for reactions with olefins was employed. Accordingly, 1-phenyl-1,2-propadiene (1.0 mmol) was treated with thallium compound **1** (0.5 mmol) and $PdCl_2$ (0.5 mmol) in acetonitrile as solvent. After stirring at room temperature for 16 h, triethylamine (1.0 mmol) and sodium carbonate (1.0 mmol) were added and the contents heated at reflux temperature for 5 h. Following the usual isolation procedure, the crude product obtained was purified by chromatographic separation (silica gel, 4:1 hexane/ethyl acetate): yield 54%; ^{1}H NMR ($CDCl_3$) δ 5.13 (d, 1 H, =CH, J = 2 Hz), 5.8 (d, 1 H, =CH, J = 2 Hz), 6.03 (br s, 1 H, C_3 H), 7.1–7.7 (m, 3 H, Ar H), 8.0–8.2 (m, 1 H, C_5 H); mass spectrum, m/e 236 (M^+, parent ion). Procedure B involves addition of 2 equiv of LiCl to the $PdCl_2$ in acetonitrile and stirring of the solution until all salts are dissolved before adding the thallium compound.

3,3-Dimethyl-4-methylene-3,4-dihydroisocoumarin. The reaction using 3-methyl-1,2-butadiene was performed following the general procedure A described above: yield 67%; ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 6 H, CH_3), 5.43 (s, 1 H, =CH), 5.7 (s, 1 H, =CH), 7.25–7.7 (m, 3 H, Ar H), 8.0–8.23 (m, 1 H, C_8 H); ^{13}C NMR ($CDCl_3$) δ 164.0, 143.7, 136.4, 133.8, 129.5, 128.8, 124.2, 123.5, 111.6, 82.3, 27.5; ^{13}C NMR (off-resonance) δ 82.2 (s, OC≡), 111.7 (t, $=CH_2$); mass spectrum, m/e 188 (M^+, parent ion).

3-Methyl-4-methylene-3,4-dihydroisocoumarin. Procedure A using 1,2-butadiene afforded the title compound in 39% yield: ^{1}H NMR ($CDCl_3$) δ 1.56 (d, 3 H, CH_3, J = 6 Hz), 5.05–5.33 (tq, 1 H, C_3 H, J = 6 and 1 Hz), 5.36 (d, 1 H, =CH, J = 2 Hz), 5.7 (d, 1 H, =CH, J = 2 Hz), 7.25–7.7 (m, 3 H, Ar H), 8.0–8.2 (m, 1 H, C_8 H); mass spectrum, m/e 174 (M^+, parent ion).

4-Methylenespiro[1*H*-2-benzopyran-1-one-3(4*H*),1′-cyclohexane]. With vinylidenecyclohexane as the allenic substrate and by use of procedure B outlined above, the title compound was obtained in 70% yield: ^{1}H NMR ($CDCl_3$) δ 0.7–2.0 (m, 10 H, CH_2's), 5.4 (s, 1 H, =CH), 5.66 (s, 1 H, =CH), 7.2–7.65 (m, 3 H, Ar H), 8.0–8.2 (m, 1 H, C_8 H); mass spectrum, m/e 228 (M^+, parent ion).

2a*H*-3,4,5,6,7,8-Hexahydrocyclonona[2,3-*c*]-1*H*-2-benzopyran-1-one. Following procedure B above, the reaction with 1,2-cyclononadiene gave the title compound in 56% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.1-2.5 (m, 12 H, CH_2's), 5.59 (dd, 1H, J = 11.2 Hz, J = 4.9 Hz, -CH-O-), 6.4 (t, 1 H, J = 8.7 Hz, C=CH-), 7.3-8.02 (m, 4 H, Ar H); mass spectrum, m/e 242.130 68 (calcd for $C_{16}H_{18}O_2$, 242.130 92).

Reaction with 1,4-Pentadiene: **4,5-Dihydro-3-vinyl-2-benzoxepin-1-(3*H*)-one.** Following routine isolation and purification (silica gel, 4:1 hexane/ethyl acetate), the reaction with 1,4-pentadiene in acetonitrile, according to procedure B above, gave the title compound as a colorless oil in 34% yield: ^{1}H NMR ($CDCl_3$) δ 1.9–2.36 (m, 2 H, CH_2), 2.83–3.43 (m, 2 H, Ar CH_2), 4.53–4.96 (m, 1 H, OCH), 5.3–5.76 (m, 2 H, $=CH_2$), 6.0–6.5 (m, 1 H, CH=), 7.5–8.26 (m, 4 H, Ar H); mass spectrum m/e 188.084 11 (calcd for $C_{12}H_{12}O_2$, 188.083 73).

Preparation of Vinylcyclopropanes. Vinylcyclopropane was synthesized from 3-vinylpyrazoline according to the published procedure.[32] Isopropenylcyclopropane,[33] 1-methyl-1-vinylcyclopropane,[34] and *cis*- and *trans*-1-phenyl-2-isopropenylcyclopropanes were synthesized by modifying the literature procedures.[17]

Reactions with Vinylcyclopropanes: **3-Methyl-3-(1′-propenyl)-3,4-dihydroisocoumarin.** To an argon-saturated solution of $PdCl_2$ (0.5 mmol) and LiCl (1.0 mmol) in acetonitrile (15 mL) cooled to 0 °C was added thallium compound **1** followed immediately by an excess of isopropenylcyclopropane (0.2 mL). The mixture was warmed to room temperature and stirred overnight. Triethylamine (1.0 mmol) and K_2CO_3 (1.0 mmol) were added and the mixture was heated at reflux temperature for 5 h. Routine isolation and separation by flash chromatography on silica gel (4:1 hexane/ethyl acetate; Rf 0.30) gave the title compound in 50% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3 H, CH_3), 1.60 (dd, 3 H, $=CCH_3$, J = 6.5 and 1.5 Hz), 3.09 (s, 1 H, Ar CH), 3.11 (s, 1 H, Ar CH), 5.51 (dq, 1 H, OCCH=, J = 15.5 and 1.5 Hz), 5.70 (dq, 1 H, $=CHCH_3$, J = 15.5 and 6.5 Hz), 7.20 (d, 1 H, C_5 H, J = 7.5 Hz), 7.35 (t, 1 H, C_6 H, J = 7.5 Hz), 7.52 (t, 1 H, C_7 H, J = 7.6 Hz), 8.06 (d, 1 H, C_8 H, J = 7.6 Hz); mass spectrum, m/e 202.09861 (calcd for $C_{13}H_{14}O_2$, 202.099 38).

3-Methyl-3-(3′-phenylprop-1′-enyl)-3,4-dihydroisocoumarin. Following the procedure described above, the reaction with *trans*-(2-phenylisopropenyl)cyclopropane gave, after routine isolation and purification (silica gel, 4:1 hexane/ethyl acetate), the title compound in 42% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3 H, CH_3), 3.09 (d, 1 H, C_4 H, J = 16.1 Hz), 3.17 (d, 1 H, C_4 H, J = 16.1 Hz), 3.25 (d, 2 H, $C_{3'}$ H, J = 6.35 Hz), 5.56 (d, 1 H, $C_{1'}$ H, J = 15.6 Hz), 5.78 (dt, 1 H, C_2 H, J = 15.6 Hz), 6.85–7.54 (m, 4 H, Ar H), 8.05 (dd, 1 H, C_8 H, J = 1 Hz); mass spectrum, m/e 278.131 15 (calcd for $C_{19}H_{18}O_2$, 278.130 68). Starting with the corresponding *cis*-cyclopropane, a 26% yield of the same product was obtained.

(*E*,*Z*)-3-(2′-Butenyl)-3,4-dihydroisocoumarin. By use of 1-methyl-1-vinylcyclopropane and the procedure outlined above, the title compound was obtained as a yellow oil. Purification (silica gel, 4:1 hexane/ethyl acetate) afforded the pure products as a mixture of *E* and *Z* isomers (90:10, respectively) in 65% yield: 300-MHz ^{1}H NMR ($CDCl_3$) δ 1.67 (d, 3 H, CH_3, J = 6.5 Hz), 1.77 (s, 3 H, CH_3), 2.84 (dd, 1 H, C_4 H, J = 16.2 and 2.9 Hz), 3.21 (dd, 1 H, C_4 H, J = 16.2 and 12.2 Hz), 4.86 (dd, 1 H, C_3 H, J = 12.1 and 2.9 Hz), 5.67 (q, 1 H, C_2 H, J = 6.5 Hz); mass spectrum, m/e 202.099 14 (calcd for $C_{13}H_{14}O_2$, 202.099 38).

3-(*trans*-1′-Propenyl)-3,4-dihydroisocoumarin. Following the proce-

(28) Hennion, G. F.; Nelson, K. W. *J. Am. Chem. Soc.* **1957**, *79*, 2142.
(29) Hennion, G. F.; Sheenan, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 1964.
(30) Brandsma, L.; Verkruijsse "Synthesis of Acetylenes, Allenes and Cumulenes"; Elsevier: New York, 1981; p 223.
(31) Reference 30, p 217.
(32) Traas, P. C.; Boelens, H.; Takken, H. J. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 57.
(33) Teraji, T.; Moritani, I.; Tsuda, E.; Nishida, S. *J. Chem. Soc. C* **1971**, 3252.
(34) Orchin, M.; Herrick, E. C. *J. Org. Chem.* **1959**, *24*, 139.

dure described above, the reaction with vinylcyclopropane gave, after routine isolation and purification (silica gel, 4:1 hexane/ethyl acetate), the title compound in 64% yield. The ^{1}H NMR spectrum obtained was identical with that reported above.

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Registry No. 1, 23649-17-4; **2**, 90991-96-1; ethene, 74-85-1; 1-hexene, 592-41-6; styrene, 100-42-5; 3,3-dimethyl-1-butene, 558-37-2; methyl acrylate, 96-33-3; acrylonitrile, 107-13-1; *cis*-2-butene, 590-18-1; cyclohexene, 110-83-8; (2-carboxy-5-chlorophenyl)bis(trifluoroacetate)thallium, 90991-93-8; (2-carboxy-5-methylphenyl)bis(trifluoroacetate)thallium, 90991-94-9; (2-carboxy-3-methoxyphenyl)bis(trifluoroacetate)-thallium, 90991-95-0; isocoumarin, 491-31-6; 2-ethylbenzoic acid, 612-19-1; methylenephthalide, 3453-63-2; 3-*n*-butylisocoumarin, 30531-69-2; 3-phenylisocoumarin, 4809-08-9; 3-(carbomethoxymethyl)phthalide, 3453-60-9; 3-(cyanomethyl)phthalide, 18327-98-5; 3,4-dimethylisocoumarin, 20281-09-8; 3-ethylisocoumarin, 26477-57-6; 1,3-dihydrospiro[isobenzofuran-1-one-3,1′-cyclohex-3′-ene], 90991-97-2; 1,2,3,4-tetrahydro-4*H*-dibenzo[*b*,*d*]pyran-6-one, 90991-98-3; 3-*tert*-butyl-7-chloroisocoumarin, 90991-99-4; 3-*tert*-butyl-5-chloroisocoumarin, 90992-00-0; 3-*tert*-butyl-7-methylisocoumarin, 90992-01-1; 3-*tert*-butyl-5-methylisocoumarin, 90992-02-2; 3-*tert*-butyl-5-methoxyisocoumarin, 90992-03-3; 3-*tert*-butyl-7-methoxyisocoumarin, 90992-04-4; vinyl bromide, 593-60-2; *cis*-1-bromo-1-propene, 590-13-6; *cis*-1-bromo-1-hexene, 13154-12-6; *trans*-1-bromo-1-hexene, 13154-13-7; *cis*-1-iodo-1-hexene, 16538-47-9; α-bromostyrene, 98-81-7; vinyl acetate, 108-05-4; isopropenyl acetate, 108-22-5; 4-methylisocoumarin, 68944-81-0; 3-methylisocoumarin, 29539-21-7; 4-*n*-butylisocoumarin, 90992-05-5; 1,3-butadiene, 106-99-0; *trans*-1,3-pentadiene, 2004-70-8; *cis*-1,3-pentadiene, 1574-41-0; isoprene, 78-79-5; 1,3-cyclohexadiene, 592-57-4; 1,2-butadiene, 590-19-2; 3-vinyl-3,4-dihydroisocoumarin, 90992-06-6; 3-(*trans*-1′-propenyl)-3,4-dihydroisocoumarin, 90992-07-7; 3-isopropenyl-3,4-dihydroisocoumarin, 90992-08-8; 3-methyl-1-vinyl-3,4-dihydroisocoumarin, 90992-09-9; *cis*-1,2,4a,10b-tetrahydro-4*H*-dibenzo-[*b*,*d*]pyran-6-one, 90992-10-2; 3-methyl-4-methylene-3,4-dihydroisocoumarin, 90992-11-3; 1-phenyl-1,2-propadiene, 2327-99-3; 3-methyl-1,2-butadiene, 598-25-4; vinylidenecyclohexane, 5664-20-0; 1,2-cyclononadiene, 1123-11-1; 1,4-pentadiene, 591-93-5; 4-methylene-3-phenyl-3,4-dihydroisocoumarin, 90992-12-4; *cis*-(4-phenylmethylene)-3,4-dihydroisocoumarin, 90992-13-5; *trans*-(4-phenylmethylene)-3,4-dihydroisocoumarin, 90992-14-6; 3,3-dimethyl-4-methylene-3,4-dihydroisocoumarin, 90992-15-7; 4-methylenespiro[1*H*-2-benzopyran-1-one-3,1′-cyclohexane], 90992-16-8; 2a*H*-3,4,5,6,7,8-hexahydrocyclonana[2,3-*c*]-1*H*-2-benzopyran-1-one, 90992-17-9; 4,5-dihydro-3-vinyl-2-benzoxepin-1(3*H*)-one, 90992-18-0; vinylcylcopropane, 693-86-7; isopropenylcyclopropane, 4663-22-3; *trans*-(2-phenylisopropenyl)cyclopropane, 41577-94-0; *cis*-(2-phenylisopropenyl)cyclopropane, 91050-50-9; 1-methyl-1-vinylcyclopropane, 16906-27-7; 3-methyl-3-(1′-propenyl)-3,4-dihydroisocoumarin, 90992-19-1; 3-methyl-3-(3′-phenylpropenyl)-3,4-dihydroisocoumarin, 90992-20-4; (*E*)-3-(2′-butenyl)-3,4-dihydroisocoumarin, 90992-21-5; (*Z*)-3-(2′-butenyl)-3,4-dihydroisocoumarin, 90992-22-6; thallium(III) trifluoroacetate, 23586-53-0; benzoic acid, 65-85-0; *m*-methoxybenzoic acid, 586-38-9; *m*-chlorobenzoic acid, 535-80-8; *m*-methylbenzoic acid, 99-04-7; allyl chloride, 107-05-1; 1-hexyne, 693-02-7; 1-iodo-1-hexyne, 1119-67-1; *trans*-1-bromo-1-propene, 590-15-8; *cis*-1,2,3,4,4a,10b-hexahydro-6*H*-dibenzo[*b*,*d*]pyran-6-one, 72331-10-3; 3-chloro-3-methyl-1-butyne, 1111-97-3; 3-butyn-2-ol 4-methylbenzenesulfonate, 53487-52-8; 3-chloro-1-butyne, 21020-24-6; 1-chloro-1-ethynylcyclohexane, 6209-75-2; acetylenic alcohol, 32038-79-2.

Friedel–Crafts Alkylation of Anisole and Its Comparison with Toluene. Predominant Ortho–Para Substitution under Kinetic Conditions and the Effect of Thermodynamic Isomerizations[1]

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Abstract: The $AlCl_3$ and BF_3, as well as 65% HPF_6, catalyzed Friedel–Crafts alkylation of anisole with alkyl halides and alcohols was investigated. The alkylation of anisole with lower catalyst concentrations under mild conditions shows predominant ortho/para directing effect generally with a ratio of ~2:1, with the amount of meta isomer uniformly less than 3%. With "swamping" catalyst conditions the amount of meta substitution in methylation and ethylation can substantially increase. The isomer distribution in tert-butylation changes with time due to rapid ortho–para interconversion. Consequently, the $AlCl_3$-catalyzed isomerization of isomeric alkylanisoles was also studied. In case of *tert*-butylanisoles, the ortho isomer shows relatively rapid conversion into para followed by much slower isomerization to meta. The para and meta isomers show isomerization to meta–para mixtures. Isomerization of ethyl-, isopropyl-, and benzylanisoles is generally slow whereas methylanisoles do not isomerize. Comparing results of the alkylation of anisole with toluene leads to the conclusion that the latter are readily affected by concurrent (and in some cases consecutive) isomerization. As the barrier for isomerization in the benzenium ion intermediates of the alkylations is higher in the case of CH_3O- than CH_3-substituted systems, anisole tends to give the kinetically controlled ortho–para alkylation products and the amount of meta isomer is low. Study of alkylation of 3,5-di- and 2,4,6-trideuteriated toluene and anisole and comparing retained deuterium contents with isomer distributions shows that alkylated product formation in case of toluene, but not of anisole, is proceeded by intramolecular, 1,2-alkyl, and hydrogen–deuterium shifting resulting also in increased meta substitution. This effect is most predominant in methylation and ethylation where the alkyl shifts are intramolecular but not in tert-butylation and benzylation, where alkyl transfer is intermolecular. Isopropylation is intermediate in nature. No simple selectivity–reactivity relationship is indicated in the studied alkylation reactions. As shown in benzylations with increasingly electron-donating and -withdrawing substituted benzyl chlorides overall rate (i.e., substrate selectivity) and isomer distributions (i.e., regioselectivity) are not determined in the same step as significantly decreased substrate selectivity is not accompanied by loss of positional selectivity. Previously reported alkylations showing high degree of meta substitution, therefore, must have been affected by thermodynamically controlled rearrangement processes, including intramolecular alkyl and hydrogen shifts in the arenium ion intermediates of the alkylation reactions. These are to be differentiated from possible subsequent product isomerizations. Under predominantly kinetic conditions anisole as well as toluene are substantially ortho–para directing in alkylations, as in other electrophilic aromatic substitutions.

Until the 1950s, it was generally accepted that electron-donor substituents, such as a methyl group on the benzene ring, lead to predominant ortho–para substitution.[2] Extending the Hammett $\rho\sigma$ relationship to aromatic substitutions and introducing a new

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