The Palladium-Catalyzed Hydroarylation and Hydrovinylation of Tertiary 3-(*o*-Acetoxyaryl)- and 3-(*o*-Benzoyloxyaryl)propynols − A Route to 4-Aryl- and 4-Vinyl-2,2-Dimethyl-3-chromenes

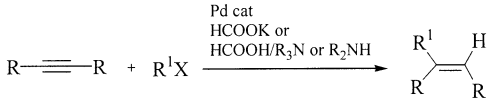
Antonio Arcadi,[a] Sandro Cacchi,*[b] Giancarlo Fabrizi,[b] Fabio Marinelli,*[a] and Paola Pace[b]

Keywords: Alkynes / Palladium / Cyclizations / Chromenes / Hydroarylation(hydrovinylation)

The palladium-catalyzed hydroarylation and hydrovinylation of tertiary 3-(*o*-acetoxyaryl)- and 3-(*o*-benzoyloxyaryl)propynols provides a regio- and stereoselective route to allylic alcohols with aryl and vinyl substituents which can be readily converted into the corresponding chromene derivatives. The hydroarylation and hydrovinylation reaction is believed to proceed through a carbopalladation step whose regiochemistry is primarily controlled by the directing effect of the tertiary hydroxy group.

Introduction

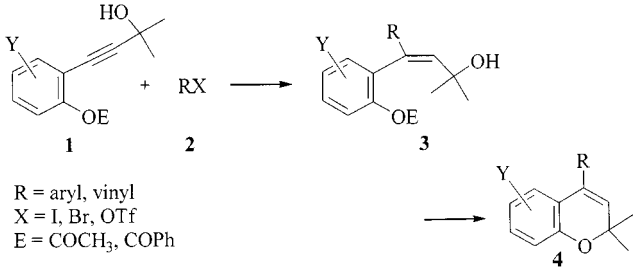
The palladium-catalyzed hydroarylation and hydrovinylation of disubstituted alkynes with aryl and vinyl halides or triflates represents a valuable tool for the addition of a C_{sp^2} unit and a hydrogen to the carbon−carbon triple bond (Scheme 1).[1] Though the formation of overall *trans*-addition derivatives has been observed in some cases,[2] the reaction is usually stereoselective, and overall *cis*-addition products are the main olefin derivatives. Therefore, the addition reaction of alkynes with suitable nucleophilic and electrophilic centers close to the acetylenic system can be followed by a cyclization step. On the basis of this strategy, useful new routes to substituted butenolides,[2,3] quinolines,[4] chromanols, and coumarins[5] have been developed by this group.



R^1 = aryl, vinyl
X = I, Br, OTf

Scheme 1. The palladium-catalyzed hydroarylation and hydrovinylation reaction of alkynes

Recent interest in the 2,2-dimethyl-3-chromene ring as a common moiety in a novel class of potassium channel activators, with smooth-muscle relaxant activity in a variety of cardiovascular and bronchopulmonary diseases (cromakalim,[6] Ro 31-6930,[7] and several other compounds with the 2,2-dimethyl-3-chromene moiety have been tested[8]) and a recent report that chromenes with an aromatic substituent at the C-4 may act as potent retinoic acid receptor α-selective antagonists[9] prompted us to investigate the possible utilization of this chemistry in the preparation of 4-substituted 2,2-dimethyl-3-chromenes. On the basis of our previous work on the regioselective hydroarylation and hydrovinylation of tertiary propargylic alcohols,[2,3,10] we envisioned the hydroarylation(hydrovinylation)/cyclization sequence reported in the Scheme 2 as a viable route to 4-aryl- and 4-vinyl-2,2-dimethyl-3-chromenes **4**, and a study was undertaken to evaluate its feasibility. Herein we report the results of this study.



Scheme 2. The preparation of 4-aryl- and 4-vinylchromenes by the palladium-catalyzed hydroarylation(hydrovinylation)

Results and Discussion

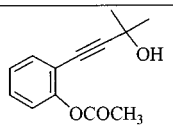
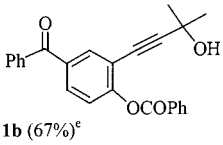
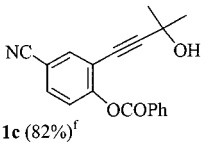
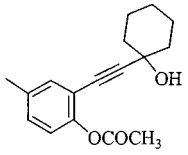
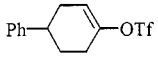
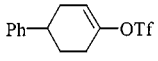
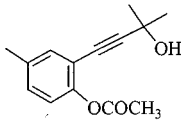
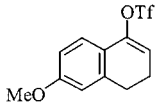
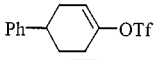
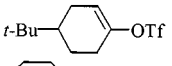
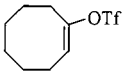
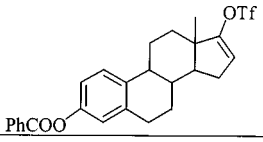
Palladium-Catalyzed Hydroarylation and Hydrovinylation of 3-(*o*-Acetoxyaryl)- and 3-(*o*-Benzoyloxyaryl)propynols 1

Hydroarylation and hydrovinylation reactions have been carried out using 3-(*o*-acetoxyaryl)- or 3-(*o*-benzoyloxyaryl)-propynols (**1**) as the starting alkynes instead of the corresponding *o*-alkynylphenols because of the tendency of the latter to cyclize to benzo[*b*]furans under basic conditions (vide infra).[11] Compounds **1** were prepared in good to high yields through the palladium-catalyzed coupling of *o*-acetoxy- or *o*-benzoyloxyaryl iodides with terminal alkynes[12] (Table 1).

[a] Dipartimento di Chimica, Ingegneria Chimica e Materiali, Via Vetoio, 67100 L'Aquila, Italy
[b] Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P. le A. Moro 5, 00185 Roma, Italy

  1434−193X/00/1224−4099 $ 17.50+.50/0

Table 1. Palladium-catalyzed hydroarylation and hydrovinylation of 3-(*o*-acetoxyaryl)- and 3-(*o*-benzoyloxyaryl)propynols (**1**)[a]

entry	alkyne **1**[b]	aryl iodide or vinyl triflate **2**	procedure, rxn time	hydroarylation and hydrovinylation products **3**, yield %[c]
1		*p*-MeO-C_6H_4-I	A, 4.5 h	**a** (85)[d]
2		*m*-F-C_6H_4-I	A, 26 h	**b** (40)[d]
3		*m*-Me-C_6H_4-I	A, 15 h	**c** (88)[d]
4		*p*-MeCONH-C_6H_4-I	A, 3.5 h	**d** (90)
5		*o*-MeO-C_6H_4-I	A, 6 h	**e** (74)[d]
	1a (81%)			
6		*m*-MeCONH-C_6H_4-I	A, 6.5 h	**f** traces
7		*m*-MeCONH-C_6H_4-I	B, 6.5 h	**f** (67)[d]
	1b (67%)[e]			
8		*p*-MeO-C_6H_4-I	B, 8 h	**g** (40)[e]
	1c (82%)[f]			
9		*m*-Me-C_6H_4-I	A, 17 h	**h** (34)
10		*m*-Me-C_6H_4-I	B, 55 h	**h** (66)
11		*p*-MeO-C_6H_4-I	A, 4 h	**i** (70)
12		*p*-Cl-C_6H_4-I	A, 24 h	**j** (22)
13		*p*-Cl-C_6H_4-I	B, 22 h	**j** (52)
14		*p*-MeOOC-C_6H_4-I	B, 15 h	**k** (64)
	1d (86%)			
15			B, 23 h	**l** (75)[g]
16			C, 72 h	**l** (25)
17			C, 6 h	**m** (70)
	1e (69%)			
18			C, 22 h	**n** (64)
19			C, 18 h	**o** (83)
20			C, 24 h	**p** (50)
21			B, 48 h	**q** (46)[g]

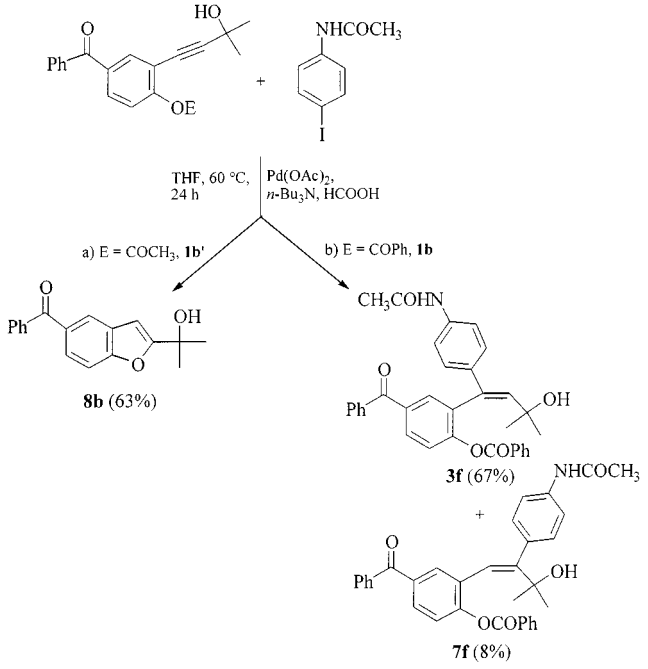
[a] Unless otherwise stated, reactions were carried out at 60 °C using the following molar ratios: procedure A: **1/2**/$n$$Bu_3N$/HCOOH/$Pd(OAc)_2$/P(*o*-tol)$_3$ = 1:2.4:3.6:2.6:0.05:0.1, DMF; procedure B: **1/2**/$n$$Bu_3N$/HCOOH/$n$$Bu_4NCl$/$Pd(OAc)_2$ = 1:2.4:3.6:2.6:1:0.05, THF; procedure C: **1/2**/HCOOK/$Pd(OAc)_2$ = 1.2:1:2:0.05, DMF. – [b] Figures in parentheses refer to the isolated yield of **1**, prepared through the palladium-catalyzed coupling of terminal alkynes with *o*-acetoxy- or *o*-benzoyloxyaryl iodides as described in the reference 11. – [c] Yields refer to single runs and are given for isolated products. – [d] The regioisomeric allylic alcohol was detected in less than 8% yield. – [e] **7g** was isolated in 23% yield. – [f] In the presence of 2 mol-% of CuI. – [g] Carried out in the presence of 0.05 equiv. of dppp using the following molar ratio: **1:2** = 1.2:1.

The yields of the palladium-catalyzed hydroarylation and hydrovinylation of **1** have been proved to be highly dependent on the nature of the palladium/formate system, the ligand, the C_{sp^2} donor, and the alkyne component. Reactions have been carried out at 60 °C and three basic procedures have been developed: procedure A, 2.4 equiv. of RX, 2.6 equiv. of HCOOH, 3.6 equiv. of $n$$Bu_3N$, 5 mol-% $Pd(OAc)_2$, and 10 mol-% of P(*o*-tol)$_3$, DMF; procedure B, 2.4 equiv. of RX, 2.6 equiv. of HCOOH, 3.6 equiv. of $n$$Bu_3N$, 1 equiv. of $n$$Bu_4NCl$, 5 mol-% $Pd(OAc)_2$, THF; procedure C, 1

equiv. of RX, 1.2 equiv. of alkyne, 2 equiv. of HCOOK, 5 mol-% of $Pd(OAc)_2$, DMF. Usually procedures A and B have been employed with aryl iodides. Although in some cases procedure B has been found to give higher yields than procedure A, no systematic study has been carried out in order to establish when procedure B provides better results than procedure A (and vice versa). Procedure C has been usually employed with vinyl triflates.[13]

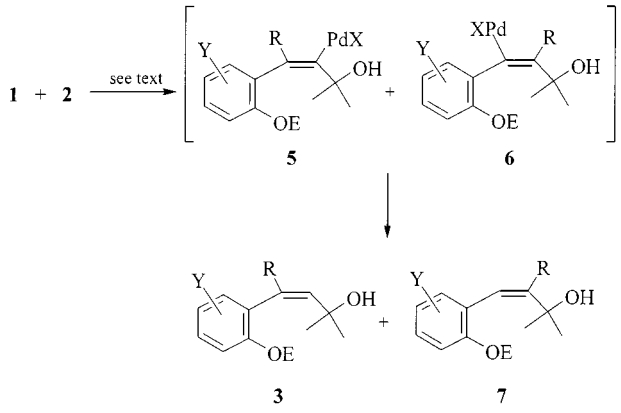
Using these procedures, a variety of alkynes have been successfully converted into the corresponding hydroarylation or hydrovinylation derivatives **3** (Table 1). Aryl iodides with electron-donating and electron-withdrawing groups and vinyl triflates can be employed. Even aryl iodides with *ortho* substituents give good results (Table 1, entry 5).

Of the acyl protecting groups studied with alkynes bearing electron-withdrawing substituents on the aromatic ring, PhCO− appears to be the group of choice. Indeed, under hydroarylation conditions the acetyl esters of these alkynes tend to generate benzo[*b*]furan derivatives, most probably through the intermediacy of phenolic compounds derived from the hydrolysis of the ester function.[10] For example, the acetyl derivative **1b′** under conditions B in the presence of *m*-acetamidophenyl iodide leads to the isolation of the benzo[*b*]furan product **8b** in 63% yield (Scheme 3a) whereas the employment of the benzoyl derivative **1b**, which is less prone to free phenolic group under the reaction conditions, affords the hydroarylation product **3f** in 67% yield along with minor amounts of its regioisomer **7f** (Scheme 3b).



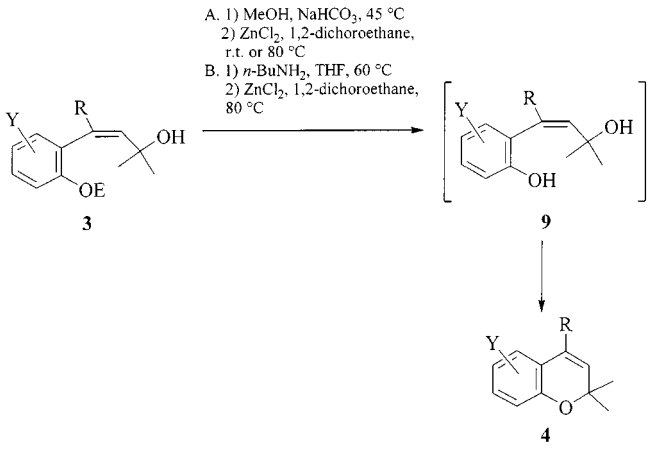
Scheme 3. The reaction of **1b′** and **1b** with *m*-acetamidophenyl iodide under hydroarylation conditions

The reaction is quite regioselective. Only with **1c** was the regioisomeric derivative **7g** isolated in significant yield (Table 1, entry 8). As found in our previous work on the hydroarylation and hydrovinylation of propargylic alcohols,[2,3,10] the carbopalladation step appears to be primarily controlled by the pronounced directing effect of the tertiary hydroxy group. The strong directive effect of this group probably involves coordination of the oxygen to the incoming palladium during the addition step. Coordination of the neighboring hydroxy group has also been implicated in the high regioselectivity observed in related addition chemistry of propargyl alcohols.[14] The net result is the preferential formation of the carbopalladation intermediate **5** and, consequently, of the hydroarylation or hydrovinylation product **3** (Scheme 4). The regiochemistry of the latter has been indirectly assigned on the basis of NOE experiments on the cyclization products. For example, irradiation of the methyl groups of **4a**, **e**, **g**, **m**, **o**, **p** leads to the enhancement of the neighboring vinyl proton. In order to confirm the regiochemical assignment of the addition products, the regioisomeric hydroarylation derivatives **7a** and **7g** were cyclized, and the corresponding chromene derivatives **10a** and **10g** produced (Table 2, entries 2 and 9) which upon irradiation of the methyl groups do not show any effect on the vinyl proton.



Scheme 4. The formation of hydroarylation and hydrovinylation products from the propargylic alcohols **1**

All our previous work on this type of addition reaction has demonstrated that the *cis* adduct is usually the main product, and therefore, the hydroarylation and hydrovinylation derivatives **3**, isolated as single isomers are also assumed to be *cis*. A NOE study on the hydrovinylation derivative **3n** confirmed this assignment, at least in this case.



Scheme 5. The cyclization of the allylic alcohols **3** to 4-aryl- and 4-vinylchromenes **4**

Table 2. The cyclization of hydroarylation and hydrovinylation products to substituted chromenes[a]

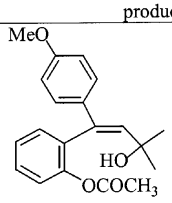
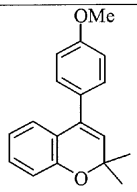
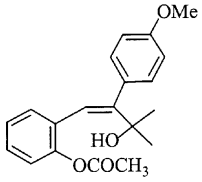
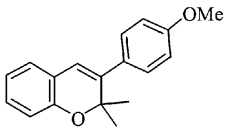
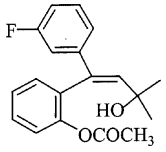
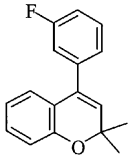
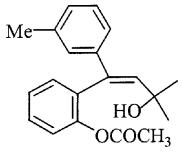
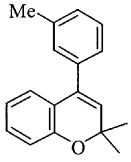
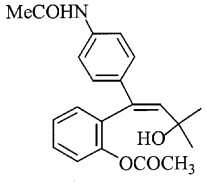
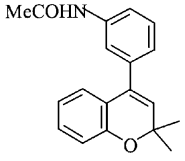
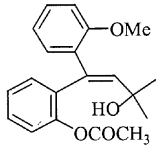
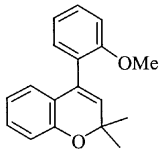
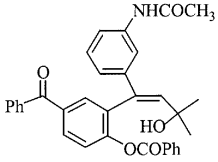
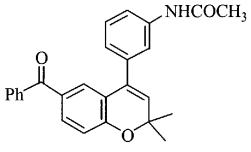
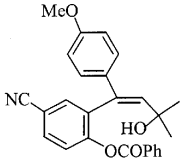
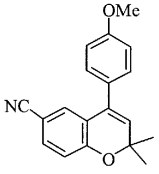
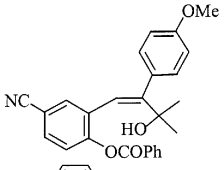
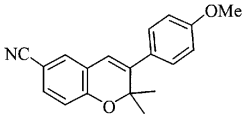
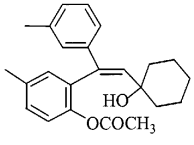
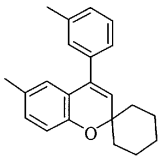
entry	hydroarylation and hydrovinylation products		4-aryl- and 4-vinylchromenes		procedure, yield[b]
1		**3a**		**4a**	A,[c] 90%
2		**7a**		**10a**	A,[c] 50%
3		**3b**		**4b**	A,[c] 72%
4		**3c**		**4c**	A,[c] 70%
5		**3d**		**4d**	A,[c] 71%
6		**3e**		**4e**	A,[c] 85%
7		**3f**		**4f**	B, 60%
8		**3g**		**4g**	B, 57%
9		**7g**		**10g**	B, 30%
10		**3h**		**4h**	A,[c] 57%

Table 2. *(Continued)*

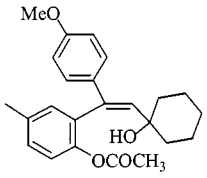
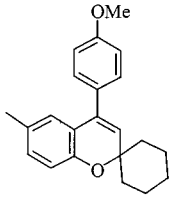
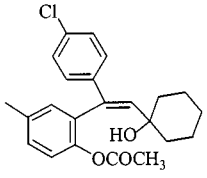
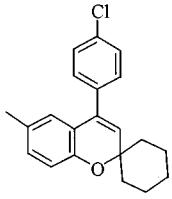
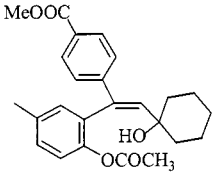
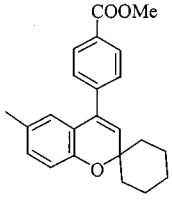
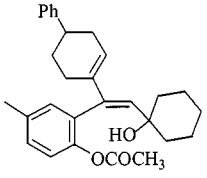
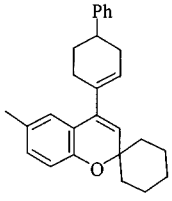
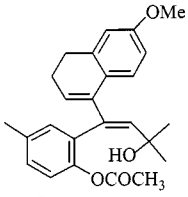
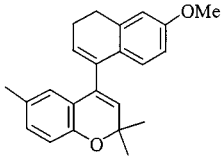
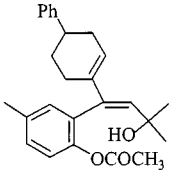
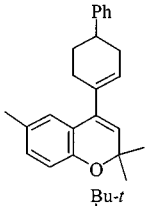
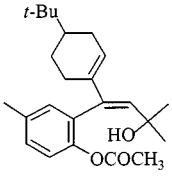
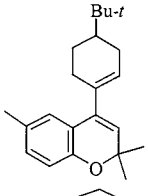
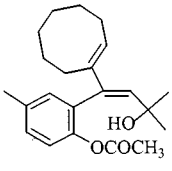
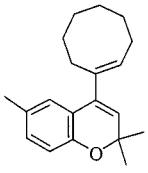
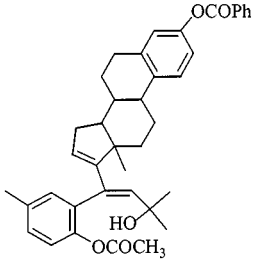
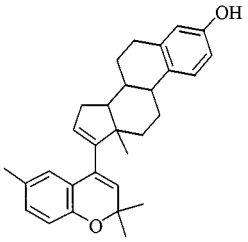
entry	hydroarylation and hydrovinylation products		4-aryl- and 4-vinylchromenes		procedure,[a] yield[b]
11		**3i**		**4i**	A,[c] 83%
12		**3j**		**4j**	A,[c] 75%
13		**3k**		**4k**	A,[c] 76
14		**3l**		**4l**	A,[d] 80%
15		**3m**		**4m**	A,[c] 63%
16		**3n**		**4n**	A,[d] 79%
17		**3o**		**4o**	A,[d] 72%
18		**3p**		**4p**	A,[d] 62%

Table 2. *(Continued)*

entry	hydroarylation and hydrovinylation products	4-aryl- and 4-vinylchromenes	procedure,[a] yield[b]
19	 **3q**	 **4q**	A,[d,e] 65%

[a] Procedure A: 1) Saturated $NaHCO_3$ 2.5 mL/mmol, MeOH, 45 °C, 1−1.5 h; 2) $ZnCl_2$ (1 equiv.), 1,2-dichloroethane, room temp. or 80 °C, 1.5−2 h. Procedure B: 1) nBuNH$_2$ (12 equiv.), THF, 60 °C, overnight; 2) $ZnCl_2$ (1 equiv.), 1,2-dichloroethane, 80 °C, 1 h. − [b] Yields refer to single runs and are given for isolated products. − [c] Step 2 at 80 °C. − [d] Step 2 at room temperature. − [e] The step 1 was carried out in MeOH/Me_2CO 80:20.

The most significant effect observed upon irradiation of the vinyl proton close to the tertiary alcoholic group was the enhancement of the vinyl proton of the neighboring cyclohexenyl group

Conversion of Hydroarylation and Hydrovinylation Products 3 into 4-Aryl- and 4-Vinylchromenes 4

Compounds **3** were converted into the corresponding chromene derivatives **4** through a sequential *cleavage of the ester group/zinc chloride mediated cyclization* process, which has been conducted as a one-pot procedure without the isolation of the phenolic intermediates **9** (procedures A and B; Scheme 5). The cyclization step was carried out according to literature procedures.[15]

Our preparative results are summarized in Table 2. Phenolic derivatives generated from the hydrovinylation products **3l−q** showed a strong tendency to cyclize and were partially converted into the corresponding chromene derivatives when the evaporation of the solvent (after the hydrolysis step and workup) was carried out at 45 °C. In these cases, conversion into cyclic derivatives was completed by addition of zinc chloride. Evaporation of the solvent at room temperature, however, allowed us to prevent cyclization during the evaporation of the solvent and to obtain cleaner reaction mixtures, which were subsequently subjected to cyclization conditions, at room temperature, to afford chromene products usually in higher yield.

Conclusion

The chemistry outlined here provides a versatile, new approach to the synthesis of 4-aryl- and 4-vinyl-2,2-dimethyl-3-chromenes through palladium-catalyzed hydroarylation or hydrovinylation of aryl iodides or vinyl triflates and substituted propargylic alcohols followed by the one-pot hydrolysis/cyclization of the resultant addition products. The generality of the process − demonstrated by the employment of a variety of alkynes and aryl iodides and vinyl triflates − as well as the high regioselectivity usually observed makes the methodology an attractive route to this class of compounds.

Experimental Section

Melting points were determined with a Büchi apparatus and are uncorrected. − Alkynes **1a−e** were prepared through coupling reactions of *o*-acetoxy- or *o*-benzoyloxyphenyl iodides with alk-1-ynes according to the procedure given in ref.[12] Vinyl triflates were prepared according to ref.[13] All of the other reagents and the catalyst are commercially available and were used as purchased, without further purification. − Reaction products were purified on axially compressed columns, packed with SiO_2 25−40 μm (Macherey−Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. − ^{1}H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) spectra (TMS as internal standard; $CDCl_3$, unless otherwise stated) were recorded with a Bruker AM 200 spectrometer. − IR spectra were recorded with a Nicolet 5DX FT/IR spectrometer. − MS spectra were recorded with a Hewlett−Packard HP 5980A spectrometer equipped with a Data System 5934A.

Spectral Data for Alkynes 1a−e

1a: Oil. − IR (neat): $\tilde{\nu}$ = 3320 cm^{-1}, 1760. − ^{1}H NMR: δ = 1.60 (s, 6 H); 2.26 (br. s, 1 H); 2.34 (s, 3 H); 7.08 (d, J = 8.0 Hz, 1 H), 7.15−7.34 (m, 2 H); 7.46 (dd, J = 7.5 Hz, J = 1.3 Hz, 1 H). − ^{13}C NMR: δ = 20.4, 30.9, 64.8, 76.3, 99.0, 116.7, 121.7, 125.5 129.0, 132.5, 151.2, 166.8. − MS *m*/*z* (relative intensity): 218 [M$^+$] (2.9), 200 (3.3), 158 (100). − $C_{13}H_{14}O_3$ (218.3): calcd. C 71.54, H 6.67; found C 71.42; H 6.68.

1b: M.p. 79−81 °C. −IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1}, 1760, 1650. − ^{1}H NMR δ = 1.35 (s, 6 H), 2.03 (br. s, 1 H), 7.37−7.55 (m, 7 H), 7.77−7.93 (m, 2 H), 8.24−8.29 (m, 4 H). − ^{13}C NMR: δ = 31.0, 65.3, 76.3, 100.2, 117.3, 122.5, 128.5, 128.7, 128.9, 130.0, 130.3, 131.2, 132.7, 134.1, 134.8, 135.2, 137.1, 155.0, 164.2, 195.0. − MS *m*/*z* (relative intensity): 384 [M$^+$] (0.8), 366 (3.2), 262 (36). − $C_{25}H_{20}O_4$ (384.4): calcd. C 78.11, H 5.24; found C 78.22, H 5.22.

1c: M.p. 111−113 °C. − IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1}, 2220, 1760. − ^{1}H NMR: 1.36 (s, 6 H), 2.90 (br. s, 1 H), 7.41 (d, J = 8.4 Hz, 1 H), 7.49−7.75 (m, 5 H), 8.21−8.25 (m, 2 H). − ^{13}C NMR: δ = 30.6, 65.0, 74.8, 101.6, 109.8, 117.3, 118.7, 123.5, 128.3, 128.6, 130.2, 132.7, 134.1, 136.3, 154.9, 163.6. − MS *m*/*z* (relative intens-

ity): 305 [M$^+$] (0.9), 288 (4.6), 183 (21.3). −$C_{19}H_{15}NO_3$ (305.3): calcd. C 74.74, N 4.59, H, 4.95; found C 74.81, N 4.55, H 4.93.

1d: Oil. − IR (neat): $\tilde{\nu}$ = 3350 cm^{-1}, 1760. − ^{1}H NMR: δ = 2.29 (s, 3 H), 2.31 (s, 3 H), 2.80 (br. s, 1 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 7.12 (d, *J* = 8.2 Hz, 1 H), 7.27 (s, 1 H). − ^{13}C NMR: δ = 20.7, 20.8, 23.4, 25.2, 39.9, 69.1, 79.3, 97.5, 116.6, 121.8, 130.1, 133.5, 135.6, 149.3, 169.3. − MS *m*/*z* (relative intensity): 272 [M$^+$] (2), 254 (6.5), 212 (100). − $C_{17}H_{20}O_3$ (272.3): calcd. C 74.97, H 7.40; found C 75.06, H 7.38.

1e: Oil. − IR (neat) $\tilde{\nu}$ = 3360, 1760 cm^{-1}. − ^{1}H NMR: δ = 1.57 (s, 6 H), 2.27 (s, 3 H), 2.29 (s, 3 H), 3.10 (br. s, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 7.06−7.12 (m, 1 H), 7.23−7.25 (m, 1 H). − ^{13}C NMR: δ = 20.6, 20.8, 31.3, 65.3, 77.0, 98.8, 116.5, 121.7, 130.1, 133.3, 135.6, 149.4, 169.3. − MS *m*/*z* (relative intensity): 232 [M$^+$] (2.1), 214 (3.7), 172 (100). − $C_{14}H_{16}O_3$ (232.3): calcd. C 72.39, H 6.94; found C 72.26, H 6.96.

Palladium-Catalyzed Hydroarylation and Hydrovinylation of 3-(*o*-Acetoxy-) and 3-(*o*-Benzoyloxyphenyl)propynols 1. − Procedure A: To a stirred solution of **1a** (0.366 g, 1.67 mmol) and *p*-iodoanisole (0.942 g, 4.03 mmol) in DMF (2 mL) were added tri-*n*-butylamine (1.44 mL, 6.04 mmol), $Pd(OAc)_2$ (0.019 g, 0.08 mmol), and tri(*o*-tolyl)phosphane (0.051 g, 0.17 mmol). The solution was stirred under nitrogen for 3 min. Then, formic acid (0.165 mL, 4.36 mmol) was added. The reaction mixture was stirred at 60 °C under nitrogen for 4.5 h and, after cooling, poured into a separating funnel containing ethyl acetate and HCl (0.1 N). The organic layer was separated, washed with 10% NaCl, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with an 85:15 v/v *n*-hexane/EtOAc mixture to give, in the order, **7a** (0.037 g, 7% yield) and **3a** (0.465 g, 85% yield).

7a: M.p. 76−78 °C. − IR (KBr) $\tilde{\nu}$ = 3500 cm^{-1}, 1750, 1610. − ^{1}H NMR: δ = 1.34 (s, 6 H), 2.34 (s, 3 H), 3.82 (s, 3 H), 6.13 (s, 1 H), 6.87 (BB′ part of an AA′BB′ system, *J* = 8.6 Hz, 2 H), 6.96−7.01 (m, 1 H), 7.13−7.26 (m, 5 H). − ^{13}C NMR: δ = 21.0, 30.4, 55.3, 74.3, 113.2, 121.2, 123.5, 125.7, 127.9, 129.8, 131.4, 132.9, 135.9, 147.4, 153.2, 158.5, 170.2. − MS *m*/*z* (%): 326 [M$^+$] (16), 308 (23), 251 (100). − $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.66, H 6.81.

3a: M.p. 68−69 °C. − IR (KBr) $\tilde{\nu}$ = 3450 cm^{-1}, 1750, 1610. − ^{1}H NMR: δ = 1.32 (s, 6 H), 2.04 (s, 3 H), 3.73 (s, 3 H), 6.06 (s, 1 H), 6.78 (BB′ part of an AA′BB′ system, *J* = 8.9 Hz, 2 H), 6.97−7.09 (m, 3 H), 7.21 −7.40 (m, 3 H). − ^{13}C NMR: δ = 20.6, 55.1, 71.4, 113.4, 122.1, 125.7, 127.3, 128.5, 132.4, 133.3, 133.5, 134.5, 137.4, 147.7, 158.8, 170.4. − MS *m*/*z* (%): 326 (6.5) [M$^+$], 308 (26.8), 265 (100). − $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.69, H 6.77.

Procedure B: To a stirred solution of **1d** (0.154 g, 0.57 mmol) and methyl *p*-iodobenzoate (0.356 g, 1.36 mmol) in THF (5 mL) were added tri-*n*-butylamine (0.483 mL, 2.04 mmol), *n*BuN_4Cl (0.167 g, 0.57 mmol), and $Pd(OAc)_2$ (0.006 g, 0.027 mmol). The solution was stirred under nitrogen for 3 min. Then, formic acid (0.056 mL, 1.47 mmol) was added. The reaction mixture was stirred at 60 °C under nitrogen for 15 h and, after cooling, worked-up as described for the procedure A. Purification by chromatography on silica gel, eluting with an 85:15 v/v *n*-hexane/EtOAc mixture afforded **3k** (0.148 g, 64% yield): M.p. 105−107 °C. − IR (KBr) $\tilde{\nu}$ = 3530 cm^{-1}, 1740, 1620. − ^{1}H NMR: δ = 1.45−1.71 (m, 10 H), 2.02 (s, 3 H), 2.40 (s, 3 H), 3.89 (s, 3 H), 6.21 (s, 1 H), 6.90 (d, *J* = 8.8 Hz, 1 H), 7.13−7.23 (m, 4 H), 7.91 (AA′ part of an AA′BB′ system, *J* = 8.2 Hz, 2 H), − ^{13}C NMR: δ = 20.7, 21.1, 21.6, 25.5, 52.1, 72.5, 121.8, 126.3, 128.7, 129.5, 129.6, 132.6, 132.9, 134.0, 135.6, 141.1, 145.5, 146.9, 166.9, 170.7. − MS *m*/*z* (%): 408 (11.2) [M$^+$], 390 (24), 331(92). − $C_{25}H_{28}O_5$ (408.5): calcd. C 73.51, H 6.91; found C 73.43, H 6.94.

Procedure C: To a stirred solution of **1e** (0.154 g, 0.66 mmol) and 6-methoxy-3,4-dihydro-1-naphthyl triflate (0.170 g, 0.55 mmol) in DMF (2 mL) was added $Pd(OAc)_2$ (0.006 g, 0.027 mmol). The solution was stirred under nitrogen for 3 min. Then, potassium formate (0.093 g, 1.1 mmol) was added. The reaction mixture was stirred at 40 °C under nitrogen for 6 h and, after cooling, worked-up as described for the procedure A. Purification by chromatography on silica gel, eluting with a 90:10 v/v *n*-hexane/EtOAc mixture gave **3m** (0.152 g, 70% yield): M.p. 101−103 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3500 cm^{-1}, 1760, 1610. − ^{1}H NMR: δ = 1.33 (s, 6 H), 2.10 (s, 3 H), 2.36 (s, 3 H), 3.90 (s, 3 H), 5.50 (t, *J* = 4.8 Hz, 1 H), 5.90 (s, 1 H), 6.74−6.71 (m, 2 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 7.04−7.09 (m, 1 H), 7.18 (d, *J* = 2.0 Hz, 1 H), 7.41 (d, *J* = 9.3 Hz, 1 H), − ^{13}C NMR: δ = 21.0, 21.1, 23.4, 28.8, 31.1 (broad), 55.2, 71.5, 110.6, 113.7, 121.9, 125.7, 126.4, 127.6, 128.9, 132.2, 133.2, 133.4, 134.9, 139.5, 139.7, 145.5, 158.2, 170.5. − MS *m*/*z* (%): 392 (15) [M$^+$], 374 (100); 331(35). − $C_{25}H_{28}O_4$ (392.5): calcd. C 76.50, H 7.19; found C 76.61, H 7.21.

3b: Oil. − IR (neat) $\tilde{\nu}$ = 3500 cm^{-1}, 1750, 1610. − ^{1}H NMR: δ = 1.34 (s, 6 H), 2.06 (s, 3 H), 6.17 (s, 1 H), 6.79−7.04 (m, 4 H), 7.16−7.41 (m, 4 H). − ^{13}C NMR: δ = 20.6, 71.6, 113.2 (d, *J* = 22 Hz), 114.0 (d, *J* = 21 Hz), 122.0, 122.2, 126.0, 128.9, 129.5, 129.7, 132.6, 132.9, 140.2, 144.5, 147.8, 162.8 (d, *J* = 245 Hz), 170.5. − MS *m*/*z* (%): 314 (3) [M$^+$], 253 (38.1), 239 (100). − $C_{19}H_{19}FO_3$ (314.4): calcd. C 72.60, H 6.09; found C 72.66, H 6.11.

3c: M.p. 56−57 °C. − IR (KBr) $\tilde{\nu}$ = 3500 cm^{-1}, 1750, 1600. − ^{1}H NMR: δ = 1.34 (s, 6 H), 2.06 (s, 3 H), 2.29 (s, 3 H), 6.11 (s, 1 H), 6.95−7.15 (m, 5 H), 7.30−7.37 (m, 3 H). − ^{13}C NMR: δ = 20.7, 21.5, 71.6, 122.2, 123.6, 125.8, 127.1, 120.0, 128.1, 128.7, 132.6, 133.5, 134.1, 137.7, 139.1, 142.1, 147.8, 170.5. − MS *m*/*z* (%): 310 (5) [M$^+$], 292 (16), 249 (100). − $C_{20}H_{22}O_3$ (310.4): calcd. C 77.39, H 7.14; found C 73.47, H 7.12.

3d: Oil. − IR ($CHCl_3$): $\tilde{\nu}$ = 3510 cm^{-1}, 3440, 1750, 1700, 1600. − ^{1}H NMR: δ = 1.34 (s, 6 H), 2.05 (s, 3 H), 2.08 (s, 3 H), 7.88 (br. s, 1 H), 6.10 (s, 1 H), 6.97−7.07 (m, 3 H), 7.26−7.40 (m, 5 H). − ^{13}C NMR: δ = 20.7, 24.4, 71.7, 119.6, 122.2, 125.9, 126.8, 128.7, 132.5, 133.3, 133.5, 137.3, 137.8, 138.3, 147.8, 168.7, 170.6. − MS *m*/*z* (%): 353 (3) [M$^+$], 335 (22), 292 (53), 278 (100). − $C_{21}H_{23}NO_4$ (353.4): calcd. C 71.37, N 3.96, H 6.56; found C 71.45, H 6.54.

3e: Oil. − IR (neat) $\tilde{\nu}$ = 3500 cm^{-1}, 1760. − ^{1}H NMR: δ = 1.34 (s, 6 H), 2.15 (s, 3 H), 3.64 (s, 3 H), 5.96 (s, 1 H), 6.80−6.93 (m, 3 H), 6.99−7.04 (m, 1 H), 7.15−7.27 (m, 3 H), 7.49−7.55 (m, 1 H). − ^{13}C NMR: δ = 20.9, 31.0, 55.3, 71.6, 111.5, 120.3, 121.7, 125.1, 128.1, 128.4, 130.3, 130.8, 132.0, 133.3, 134.1, 142.1, 147.5, 156.7, 170.4. − MS *m*/*z* (%): 326 (6) [M$^+$], 265 (67), 251 (100). − $C_{20}H_{22}O_4$ (326.4): calcd. C 73.60, H 6.79; found C 73.69, H 6.77.

3f: M.p. 183−184 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3520 cm^{-1}, 3480, 1750, 1720, 1690, 1620. − ^{1}H NMR: δ = 1.34 (br. s, 3 H), 1.39 (br. s, 3 H), 2.15 (s, 3 H), 6.00 (s, 1 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 7.23−7.60 (m, 10 H), 7.80−8.00 (m, 6 H). − ^{13}C NMR: δ = 24.6, 30.3, 31.7, 71.9, 119.4, 122.7, 127.1, 128.3, 128.6, 130.3, 130.5, 132.5, 132.7, 133.7, 134.1, 135.0, 135.3, 137.3, 137.4, 139.6, 151.3, 166.2, 168.3, 195.9. − MS *m*/*z* (%): 501 (1), 396 (8). − $C_{33}H_{29}NO_5$ (519.6): calcd. C 76.28, N 2.70, H 5.63; found C 76.39, N 2.69, H 5.64.

3g: M.p. 101−103 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3530 cm^{-1}, 2240, 1740, 1620. − ^1H NMR: δ = 1.30 (br. s, 3 H), 1.36 (br. s, 3 H), 3.78 (s, 3 H), 6.01 (s, 1 H), 6.89 (AA′ part of an AA′BB′ system, *J* = 8.7 Hz, 2 H), 6.73 (BB′ part of an AA′BB′ system, *J* = 8.7 Hz, 2 H), 7.23 (BB′ part of an AA′BB′ system, *J* = 8.1 Hz, 1 H), 7.44 (AA′ part of an AA′BB′ system, *J* = 8.1 Hz, 1 H), 7.62−7.83 (m, 8 H). − ^{13}C NMR: δ = 55.3, 71.7, 110.1, 113.6, 118.4, 123.6, 127.7, 128.1, 128.6, 130.3, 131.6, 132.4, 133.6, 134.3, 136.2, 136.4, 139.1, 151.5, 159.2, 165.7. − MS *m/z* (%): 413 (5) [M^+], 395 (23), 290 (63). − $C_{26}H_{23}NO_4$ (413.5): calcd. C 75.53, N 3.39, H 5.61; found C 75.43, N 3.40, H 5.59.

7g: M.p. 126−128 °C. − IR (KBr) $\tilde{\nu}$ = 3470 cm^{-1}, 2200, 1720, 1610. − ^1H NMR: δ = 1.30 (s, 6 H), 3.75 (s, 3 H), 6.04 (s, 1 H), 6.66 (BB′ part of an AA′BB′ system, *J* = 8.7 Hz, 2 H), 6.80 (AA′ part of an AA′BB′ system, *J* = 8.7 Hz, 2 H), 7.23 (d, *J* = 8.3 Hz, 1 H), 7.58−7.76 (m, 5 H), 8.19−8.24 (m, 2 H). − ^{13}C NMR: δ = 30.2, 55.2, 74.6, 113.1, 121.2, 122.6, 129.0, 129.4, 130.4, 131.5, 134.5, 135.8, 151.0, 155.3, 158.5, 165.5. −MS *m/z* (%): 413 (45) [M^+], 395 (9.7). − $C_{26}H_{23}NO_4$ (413.5): calcd. C 75.53, N 3.39, H 5.61; found C 75.43, N 3.41, H 5.58.

3h: M.p. 54−56 °C. − IR (KBr) $\tilde{\nu}$ = 3510 cm^{-1}, 1750, 1600. − ^1H NMR: δ = 1.40−1.70 (m, 10 H), 2.03 (s, 3 H), 2.28 (s, 3 H), 2.37 (s, 3 H), 6.07 (s, 1 H), 6.85−6.92 (m, 2 H), 6.95 (s, 1 H), 7.00−7.08 (m, 2 H), 7.14 (br. s, 2 H). − ^{13}C NMR: δ = 25.6, 30.2, 72.3, 121.8, 123.8, 127.1, 128.0, 128.1, 129.2, 132.9, 133.4, 134.9, 135.3, 137.6, 139.0, 142.5, 145.6, 170.6. − MS *m/z* (%): 364 (8) [M^+], 346 (22.5), 303 (94.2). − $C_{24}H_{28}O_3$ (364.5): calcd. C 79.09, H 7.74; found C 79.16, H 7.72.

3i: Oil. − IR (neat) $\tilde{\nu}$ = 3500 cm^{-1}, 1760, 1600. − ^1H NMR: δ = 1.40−1.70 (m, 10 H), 2.02 (s, 3 H), 2.36 (s, 3 H), 3.73 (s, 3 H), 6.02 (s, 1 H), 6.87 (d, *J* = 8 Hz, 1 H), 7.04−7.13 (m, 4 H), 6.76 (BB′ part of an AA′BB′ system, *J* = 8.6 Hz, 2 H). − ^{13}C NMR: δ = 55.1, 72.2, 113.5, 121.8, 127.5, 129.2, 132.8, 133.5, 134.2, 135.0, 135.3, 137.4, 145.6, 158.9, 170.5. − MS *m/z* (%): 362 (19), 319 (47). − $C_{24}H_{28}O_4$ (380.5): calcd. C 75.76, H 7.42; found C 75.69, H 7.40.

3j: M.p. 28−30 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3500 cm^{-1}, 1760, 1600. − ^1H NMR: δ = 1.43−1.66 (m, 10 H), 2.05 (s, 3 H), 2.38 (s, 3 H), 6.09 (s, 1 H), 6.89 (d, *J* = 8.7 Hz, 1 H), 7.04−7.27 (m, 6 H). − ^{13}C NMR: δ = 20.7, 21.1, 21.7, 25.5, 72.4, 121.9, 127.7, 128.3, 129.5, 132.9, 133.0, 133.7, 135.5, 139.5, 140.9, 145.5, 170.6. − MS *m/z* (%): 384 (8) [M+], 368 (6), 366 (17), 326 (18), 324 (52). − $C_{23}H_{25}ClO_3$ (384.9): calcd. C 71.77, H 6.55; found C 71.69, H 6.56.

3l: M.p. 95−96 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3470 cm^{-1}, 1750, 1600. − ^1H NMR ([D_6]DMSO, 70 °C): δ = 2.29 (s, 3 H), 2.49 (s, 3 H), 5.21 (br. s, 1 H), 5.77 (s, 1 H), 6.94−6.99 (m, 2 H), 7.07−7.23 (m, 6 H). − ^{13}C NMR ([D_6]DMSO, 70 °C): δ = 70.2, 121.6, 125.1, 125.4, 126.2, 127.7, 131.9, 133.2, 134.6, 135.2, 137.1, 145.3, 145.9, 168.5. − MS *m/z* (%): 430 (2) [M^+], 412 (25), 370 (16). − $C_{29}H_{34}O_3$ (430.6): calcd. C 80.89, H 7.96; found C 80.81, H 7.97.

3n: Oil. − IR ($CHCl_3$) $\tilde{\nu}$ = 3460 cm^{-1}, 1760, 1610. − ^1H NMR ([D_6]DMSO, 80 °C): δ = 1.06 (s, 6 H), 2.12 (s, 3 H), 2.30 (s, 3 H), 2.64−2.80 (m, 1 H), 5.28 (br. s, 1 H), 5.86 (s, 1 H), 6.95−6.99 (m, 2 H), 7.06−7.21 (m, 6 H). − ^{13}C NMR ([D_6]DMSO, 80 °C): δ = 19.6, 19.8, 25.8, 29.3, 28.8, 32.6, 38.4, 69.3, 121.3, 124.9, 125.0, 125.8, 127.4, 131.3, 131.5, 133.1, 134.2, 134.9, 136.7, 145.4, 145.7, 167.9. − MS *m/z* (%): 372 (35), 329 (22), 91 (100). − $C_{26}H_{30}O_3$ (390.5): calcd. C 79.97, H 7.74; found C 79.89, H 7.75.

3o: Oil. − IR ($CHCl_3$) $\tilde{\nu}$ = 3480 cm^{-1}, 1750, 1630. − ^1H NMR ([D_6]DMSO, 70 °C): δ = 0.82 (s, 9 H), 0.97 (s, 3 H), 0.98 (s, 3 H), 2.08 (s, 3 H), 2.29 (s, 3 H), 5.09 (br. s, 1 H), 5.80 (s, 1 H), 6.90 (br. s, 1 H), 6.96 (d, *J* = 8 Hz, 1 H), 7.07−7.12 (m, 1 H). − ^{13}C NMR ([D_6]DMSO, 70 °C): δ = 20.0, 20.2, 23.7, 26.6, 27.1, 30.0, 31.4, 43.3, 69.5, 121.8, 126.0, 127.8, 131.6, 131.7, 133.3, 134.3, 135.0, 136.8, 145.6, 168.3. − MS *m/z* (%): 370 (12) [M^+], 352 (85), 309 (24), 295 (100). − $C_{24}H_{34}O_3$ (370.5): calcd. C 77.80, H 9.25; found C 77.69, H 9.23.

3p: M.p. 99−100 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3500 cm^{-1}, 1750. − ^1H NMR: δ = 1.23 (s, 6 H), 2.17 (s, 3 H), 2.34 (s, 3 H), 5.20 (t, *J* = 8.4 Hz, 1 H), 5.81 (s, 1 H), 6.89 (d, *J* = 2.2 Hz, 1 H), 6.95 (d, *J* = 1.7 Hz, 1 H), 7.06−7.16 (m, 1 H). − ^{13}C NMR: δ = 71.2, 121.5, 128.8, 130.0, 132.5, 132.6, 134.3, 134.6, 135.0, 140.5, 145.8, 170.6. − MS *m/z* (%): 342 (7) [M^+], 324 (100), 282 (69). − $C_{22}H_{30}O_3$ (342.5): calcd. C 77.16, H 8.83; found C 77.26, H 8.85.

3q: M.p. 209−211 °C. − IR ($CHCl_3$) $\tilde{\nu}$ = 3480 cm^{-1}, 1730, 1600. ^1H NMR ([D_6]DMSO, 100 °C): δ = 0.99 (s, 3 H), 1.05 (s, 3 H), 1.06 (s, 3 H), 2.12 (s, 3 H), 2.30 (s, 3 H), 5.02 (m, 1 H), 6.05 (s, 1 H), 6.94−7.10 (m, 5 H), 7.32 (d, *J* = 8.5 Hz, 1 H), 7.52−7.70 (m, 3 H), 8.12−8.87 (m, 2 H). − ^{13}C NMR ([D_6]DMSO, 100 °C): δ = 69.4, 117.9, 120.6, 121.4, 125.1, 127.4, 128.1, 128.9, 128.9, 131.3, 131.9, 133.0, 133.1, 136.5, 137.3, 145.3, 148.0, 164.0, 167.8. − MS *m/z* (%): 590 (13) [M^+], 572 (9). − $C_{39}H_{42}O_5$ (590.8): calcd. C 79.29, H 7.17; found C 79.36, H 7.15.

Cyclization of Allylic Alcohols 3 and 7 to Substituted 2,2-Dimethyl-3-chromenes 4 and 10. − Procedure A: To a stirred solution of **3e** (0.236 g, 0.72 mmol) in MeOH (12 mL), saturated $NaHCO_3$ (1.8 mL) was added. The reaction mixture was stirred at 40 °C for 1 h and, after cooling, poured into a separating funnel containing ethyl acetate and water. The organic layer was separated, washed with 10% NaCl, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was dried under vacuum (1.5 Torr) for 0.5 h and then dissolved in 1,2-dichloroethane (12 mL). $ZnCl_2$ was added (0.099 g, 0.72 mmol), and the reaction mixture was stirred at 80 °C for 50 min. The reaction mixture was then cooled and extracted with $NaHCO_3$ (1 M) and EtOAc. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with an 85:15 v/v *n*-hexane/EtOAc mixture to give **4e** (0.164 g, 85% yield): M.p. 93−94 °C. − IR (KBr) $\tilde{\nu}$ = 1610 cm^{-1}, 1500. − ^1H NMR: 1.50 (s, 6 H), 3.69 (s, 3 H), 5.56 (s, 1 H), 6.69−6.74 (m, 2 H), 6.81−6.85 (m, 1 H), 6.90−7.01 (m, 2 H), 7.04−7.12 (m, 1 H), 7.18 (dd, *J* = 7.4 Hz, *J* = 1.9 Hz, 1 H), δ = 7.28−7.37 (m, 1 H), − ^{13}C NMR: δ = 27.8, 55.5, 75.8, 111.1, 116.4, 120.3, 120.7, 122.4, 125.4, 127.4, 128.7, 129.1, 129.8, 131.0, 131.9, 152.6, 157.3. − MS *m/z* (%): 266 (13) [M^+], 251 (100). − $C_{18}H_{18}O_2$ (266.3): calcd. C 81.17, H 6.81; found C 81.25, H 6.82.

Procedure B: To a stirred solution of **3g** (0.105 g, 0.25 mmol) in THF (8 mL), *n*-butylamine (0.55 mL, 3.06 mmol) was added. The reaction mixture was stirred at 60 °C for 18 h and, after cooling, poured into a separating funnel containing ethyl acetate and HCl (0.1 M). The organic layer was separated, washed with 10% NaCl, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was dried under vacuum (1.5 Torr) for 0.5 h and dissolved in 1,2-dichloroethane (5 mL). $ZnCl_2$ was added (0.035 g, 0.25 mmol) and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was then worked up as described in the procedure A. The residue was purified by chromatography on silica gel eluting with a 97:3 v/v *n*-hexane/EtOAc mixture to give **4g** (0.042 g, 57% yield): Oil. − IR (neat) $\tilde{\nu}$ = 2200 cm^{-1}, 1600, 1510. − ^1H NMR: δ = 1.51 (s, 6 H), 3.86 (s, 3 H), 5.64 (s, 1 H), 6.85−6.99 (m, 3 H), 7.22 (d, *J* = 8.5 Hz, 2 H), 7.31 (d, *J* = 1.8 Hz,

1 H), 7.42 (dd, J = 8.3 Hz, J = 2.0 Hz, 1 H). − ^{13}C NMR: δ = 28.0, 55.4, 77.5, 103.6, 113.7, 114.1, 117.8, 123.2, 129.19, 129.24, 129.6, 129.7, 132.8, 133.2, 157.3, 159.6. − MS *m/z* (%): 291 (8) [M$^+$], 276 (100). − $C_{19}H_{17}NO_2$ (291.3): calcd. C 78.33, N 4.81, H 5.88; found C 78.47, N 4.83, H 5.89.

4a: M.p. 93−94 °C. − IR (KBr) ṽ = 1620 cm^{-1}, 1530. − ^{1}H NMR: δ = 1.46 (s, 6 H), 3.80 (s, 3 H), 5.55 (s, 1 H), 6.92−6.76 (m, 4 H), 6.99−7.04 (m, 1 H), 7.08−7.17 (m, 1 H), 7.26 (AA′ part of an AA′BB′ system, J = 8.7 Hz, 2 H). − ^{13}C NMR: δ = 27.6, 55.3, 75.7, 113.7, 116.8, 120.5, 122.6, 125.6, 128.4, 129.1, 129.8, 130.7, 134.3, 153.4, 159.2. − MS *m/z* (%): 266 (10) [M$^+$], 251 (100). − $C_{18}H_{18}O_2$ (266.3): calcd. C 81.17, H 6.81; found C 81.09, H 6.80.

10a: M.p. 73−74 °C. − IR (KBr) ṽ = 1610 cm^{-1}, 1520. − ^{1}H NMR: 1.52 (s, 6 H), 3.83 (s, 3 H), 6.30 (s, 1 H), 6.82−6.90 (m, 4 H), 7.02−7.17 (m, 2 H), δ = 7.25 (AA′ part of an AA′BB′ system, J = 8.8 Hz, 2 H). − ^{13}C NMR: δ = 27.0, 55.3, 78.7, 113.5, 116.3, 121.0, 121.8, 123.0, 126.2, 128.8, 129.3, 131.9, 141.8, 152.3, 159.0. − MS *m/z* (%): 266 (23) [M$^+$], 251 (100). − $C_{18}H_{18}O_2$ (266.3): calcd. C 81.17, H 6.81; found C 81.05, H 6.84.

4b: M.p. 72−74 °C. − IR (KBr) ṽ = 1610 cm^{-1}, 1510. − ^{1}H NMR: δ = 1.48 (s, 6 H), 5.61 (s, 1 H), 6.78−6.90 (m, 2 H), 6.96−7.04 (m, 2 H), 7.07−7.18 (m, 3 H), 7.29−7.39 (m, 1 H). − ^{13}C NMR: δ = 27.5, 75.7, 114.5 (d, J = 21 Hz), 115.7 (d, J = 22 Hz), 117.0, 120.6, 121.8, 124.4, 125.3, 129.5, 129.8, 133.9, 133.9, 140.6, 153.3, 162.7 (d, J = 246 Hz). − MS *m/z* (%): 254 (9) [M$^+$], 239 (100). − $C_{17}H_{15}FO$ (254.3): calcd. C 80.29, H 5.95; found C 80.17, H 5.93.

4c: Oil. − IR (neat) ṽ = 1610 cm^{-1}, 1490. − ^{1}H NMR: δ = 1.48 (s, 6 H), 2.36 (s, 3 H), 5.59 (s, 1 H), 6.75−6.90 (m, 2 H), 7.01 (dd, J = 7.6 Hz, J = 1.5 Hz, 1 H), 7.09−7.18 (m, 4 H), 7.22−7.27 (m, 1 H). − ^{13}C NMR: δ = 21.4, 27.6, 75.7, 116.2, 116.8, 120.5, 122.4, 125.6, 125.8, 128.2, 128.4, 128.8, 129.1, 129.3, 134.8, 137.9, 138.3, 153.3. − MS *m/z* (%): 250 (9) [M$^+$], 235 (100). − $C_{18}H_{18}O$ (250.3): calcd. C 86.36, H 7.25; found C 86.27, H 7.22.

4d: M.p. 191−193 °C. − IR (KBr) ṽ = 3320 cm^{-1}, 1670, 1610, 1540. − ^{1}H NMR: δ = 1.48 (s, 6 H), 2.31 (s, 3 H), 5.58 (s, 1 H), 6.77−6.89 (m, 2 H), 6.99 (dd, J = 7.7, J = 1.6 Hz, 1 H), 7.11−7.19 (m, 1 H), 7.44 (br. s, 1 H), 7.30 (BB′ part of an AA′BB′ system, J = 8.6 Hz, 2 H), 7.53 (AA′ part of an AA′BB′ system, J = 8.6 Hz, 2 H). − ^{13}C NMR: δ = 24.6, 27.6, 75.7, 116.9, 119.7, 120.5, 122.3, 125.5, 128.9, 129.2, 129.3, 134.2, 137.4, 153.3, 166.5. − MS *m/z* (%): 293 (13) [M$^+$], 278 (100), 236 (27). − $C_{19}H_{19}NO_2$ (293.4): calcd. C 77.79, N 4.77, H 6.53; found C 77.68, N 4.75, H 6.54.

4f: M.p. 162−164 °C. − IR (KBr) ṽ = 1670 cm^{-1}, 1610, 1540. − ^{1}H NMR (acetone-d6): δ = 1.53 (s, 6 H), 2.09 (s, 3 H), 5.81 (s, 1 H), 6.99 (d, J = 8.5 Hz, 1 H), 7.33 (d, J = 8.6 Hz, 2 H), 7.50−7.58 (m, 4 H), 7.65−7.75 (m, 5 H), 9.26 (br. s, 1 H). − ^{13}C NMR ([D$_6$]acetone): δ = 24.6, 27.9, 77.2, 116.6, 119.8, 121.9, 127.9, 128.1, 129.1, 129.4, 129.8, 130.0, 132.0, 132.4, 133.4, 133.6, 137.8, 138.0, 157.7, 168.5, 195.7. − MS *m/z* (%): 397 (6) [M$^+$], 382 (100). − $C_{26}H_{23}NO_3$ (397.5): calcd. C 78.57, N 3.52, H 5.83; found C 78.49, N 3.50, H 5.84.

10g: M.p. 71−73 °C. − IR (KBr) ṽ = 2210 cm^{-1}, 1610, 1520, 1500. − ^{1}H NMR: δ = 1.54 (s, 6 H), 3.84 (s, 3 H), 6.26 (s, 1 H), 6.85−6.93 (m, 3 H), 7.20−7.31 (m, 3 H), 7.40 (dd, J = 8.3 Hz, J = 2.0 Hz, 1 H). − ^{13}C NMR: δ = 27.3, 55.3, 76.4, 80.4, 104.1, 113.7, 117.2, 119.2, 120.0, 123.5, 129.3, 130.0, 130.9, 132.9, 143.7, 156.1, 159.4. − MS *m/z* (%): 291 (22) [M$^+$], 276 (100). − $C_{19}H_{17}NO_2$ (291.3): calcd. C 78.33, N 4.81, H 5.88; found C 78.21, N 4.84, H 5.86.

4h: M.p. 101−103 °C. − IR (KBr) ṽ = 1610 cm^{-1}, 1490. − ^{1}H NMR: δ = 1.35−1.95 (m, 10 H), 2.18 (s, 3 H), 2.38 (s, 3 H), 5.61 (s, 1 H), 6.79−6.84 (m, 2 H), 6.92−6.96 (m, 1 H), 7.16−7.19 (m, 3 H), 7.24−7.27 (m, 1 H). − ^{13}C NMR: δ = 20.7, 21.4, 21.5, 25.5, 35.5, 76.1, 116.7, 123.1, 125.9, 126.0, 128.2, 128.3, 128.8, 129.4, 129.5, 129.6, 135.4, 137.9, 138.8, 150.9. − MS *m/z* (%): 304 (31) [M$^+$], 261 (100). − $C_{22}H_{24}O$ (304.4): calcd. C 86.80, H 7.95; found C 86.72, H 7.94.

4i: M.p. 84−86 °C. − IR (KBr) ṽ = 1610 cm^{-1}, 1510. − ^{1}H NMR: δ = 1.25−1.95 (m, 10 H), 3.84 (s, 3 H), 5.60 (s, 1 H), 6.77−6.85 (m, 1 H), 6.92 (d, J = 8.8 Hz, 2 H), 7.01 (dd, J = 7.7 Hz, J = 1.6 Hz, 1 H), 7.10−7.19 (m, 1 H), 7.28 (d, J = 8.8 Hz, 2 H). − ^{13}C NMR: δ = 20.5, 24.4, 34.4, 54.2, 75.0, 112.6, 115.6, 122.2, 125.0, 127.3, 128.4, 128.8, 128.9, 130.1, 133.7, 150.0, 158.1. − MS *m/z* (%): 320 (29) [M$^+$], 277 (100). − $C_{22}H_{24}O_2$ (320.4): calcd. C 82.46, H 7.55; found C 82.35, H 7.53.

4j: M.p.92−94 °C. − IR (KBr) ṽ = 1640 cm^{-1}, 1510. − ^{1}H NMR: δ = 1.31−2.01 (m, 10 H), 2.18 (s, 3 H), 5.61 (s, 1 H), 6.73 (d, J = 2 Hz, 1 H), 6.82 (d, J = 8.1 Hz, 1 H), 6.96 (dd, J = 8.2 Hz, J = 2.0 Hz, 1 H), 7.25−7.38 (m, 5 H). − ^{13}C NMR: δ = 20.7, 21.5, 25.4, 35.4, 76.1, 116.8, 122.6, 125.8, 128.5, 129.3, 129.8, 130.1, 133.4, 134.4, 137.2, 150.9. − MS *m/z* (%): 326 (7), 324 (21) [M$^+$]. − $C_{21}H_{21}ClO$ (324.8): calcd. C 77.65, H 6.52; found C 77.74, H 6.54.

4k: M.p. 93−95 °C. − IR (KBr): ṽ = 1750, 1630, 1510 cm^{-1}. − ^{1}H NMR: δ = 1.28−2.03 (m, 10 H), 2.18 (s, 3 H), 3.94 (s, 3 H), 5.68 (s, 1 H), 6.73 (d, J = 1.7 Hz, 1 H), 6.84 (d, J = 8.2 Hz, 1 H), 6.97 (dd, J = 8.2 Hz, J = 1.7 Hz, 1 H), 7.42 (d, J = 8.6 Hz, 2 H), 8.06 (d, J = 8.6 Hz, 2 H). − ^{13}C NMR: δ = 21.5, 25.4, 35.3, 52.1, 76.1, 116.9, 122.5, 125.8, 128.8, 129.3, 129.6, 129.83, 129.84, 129.9, 134.7, 143.6, 150.9, 166.9. − MS *m/z* (%): 348 (28) [M$^+$], 305 (100). − $C_{23}H_{24}O_3$ (348.4): calcd. C 79.28, H 6.94; found C 79.36, H 6.92.

4l: M.p. 78−80 °C. − IR ($CHCl_3$) ṽ = 1600 cm^{-1}, 1490. − ^{1}H NMR: δ = 2.27 (s, 3 H), 2.85−3.00 (m, 1 H), 5.51 (s, 1 H), 5.83 (br. s, 1 H), 6.77 (d, J = 8.7 Hz, 1 H), 6.90 (br. s, 2 H), 7.24−7.34 (m, 5 H). − ^{13}C NMR: δ = 20.9, 21.5, 25.4, 29.2, 30.0, 33.6, 35.3, 35.5, 39.8, 75.9, 116.7, 122.6, 125.6, 126.06, 126.09, 126.4, 126.9, 128.4, 129.1, 129.5, 135.9, 136.9, 146.8, 150.9. − MS *m/z* (%): 370 (42) [M$^+$], 327 (100). − $C_{27}H_{30}O$ (370.5): calcd. C 87.52, H 8.16; found C 87.64, H 8.15.

4m: M.p. 48−50 °C. − IR (KBr) ṽ = 1600 cm^{-1}, 1490. − ^{1}H NMR: δ = 1.47 (s, 6 H), 2.10 (s, 3 H), 2.33−2.43 (m, 2 H), 2.82−2.90 (m, 2 H), 3.77 (s, 3 H), 5.58 (s, 1 H), 5.92 (t, J = 4.5 Hz, 1 H), 6.54−6.65 (m, 2 H), 6.71−6.74 (m, 2 H), 6.91−6.85 (m, 2 H). − ^{13}C NMR: δ = 20.7, 23.2, 27.7, 28.6, 29.7, 55.2, 75.6, 110.9, 113.8, 116.3, 122.0, 125.78, 125.83, 126.2, 127.6, 129.5, 129.64, 129.69, 135.5, 135.9, 137.5, 150.6, 158.6. − MS *m/z* (%): 332 (21) [M$^+$], 317 (100). − $C_{23}H_{24}O_2$ (332.4): calcd. C 83.10, H 7.28; found C 83.17, H 7.26.

4n: M.p. 62−64 °C. − IR (KBr) ṽ = 1610 cm^{-1}, 1490. − ^{1}H NMR: δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 2.26 (s, 3 H), 3.80−3.85 (m, 1 H), 5.46 (s, 1 H), 5.82 (br. s, 1 H), 6.73 (d, J = 8.6 Hz, 1 H), 6.89−6.91 (m, 2 H), 7.20−7.35 (m, 5 H). − ^{13}C NMR: δ = 20.9, 27.4, 27.5, 29.2, 30.0, 33.5, 39.8, 75.3, 116.6, 121.7, 125.5, 126.1, 126.7, 126.9, 128.4, 129.3, 129.6, 135.7, 136.5, 146.8, 151.0. − MS *m/z* (%): 330 (27) [M$^+$], 315 (100). − $C_{24}H_{26}O$ (330.5): calcd. C 87.23, H 7.93; found C 87.14, H 7.92.

4o: M.p. 63−65 °C. − IR ($CHCl_3$) ṽ = 1590 cm^{-1}, 1490. − ^{1}H NMR: δ = 0.91 (s, 9 H), 1.38 (s, 6 H), 2.26 (s, 3 H), 5.41 (s, 1 H), 5.74 (br. s, 1 H), 6.71 (d, J = 8.0 Hz, 1 H), 6.87−6.93 (m, 2 H). −

^{13}C NMR: δ = 20.8, 24.3, 27.1, 27.2, 27.40, 27.46, 30.2, 32.3, 43.9, 75.3, 116.5, 121.8, 125.6, 126.5, 126.8, 129.1, 129.5, 135.5, 136.5, 151.0. − MS *m/z* (%): 310 (14) [M$^+$], 295 (100). − $C_{22}H_{30}O$ (310.5): calcd. C 85.11, H 9.74; found C 85.02, H 9.71.

4p: Oil. − IR ($CHCl_3$) ṽ = 1610 cm^{-1}, 1490. − ^{1}H NMR: δ = 1.39 (s, 3 H), 1.40 (s, 3 H), 1.45−1.60 (m, 8 H), 2.24 (s, 3 H), 2.21−2.34 (m, 4 H), 5.38 (s, 1 H), 5.68 (t, *J* = 8.2 Hz, 1 H), 6.71 (d, *J* = 8.1 Hz, 1 H), 6.82 (d, *J* = 2.2 Hz, 1 H), 6.90 (dd, *J* = 8.1 Hz, *J* = 2.2 Hz, 1 H). − ^{13}C NMR: δ = 20.8, 26.3, 26.49, 26.54, 27.6, 28.4, 28.5, 30.0, 75.4, 116.4, 125.8, 127.2, 129.2, 129.3, 129.6, 136.7, 139.2, 151.0. − MS *m/z* (%): 282 (10) [M$^+$], 267 (100). − $C_{20}H_{26}O$ (282.4): calcd. C 85.06, H 9.28; found C 85.17, H 9.29.

4q: M.p. 64−66 °C. − IR (KBr) ṽ = 3400 cm^{-1}, 1610, 1490. − ^{1}H NMR: δ = 0.92 (s, 3 H), 1.40 (s, 3 H), 1.44 (s, 3 H), 2.25 (s, 3 H), 2.85−2.95 (m, 2 H), 5.45 (s, 1 H), 5.70 (br. s, 1 H), 6.58−6.64 (m, 2 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 6.88−6.98 (m, 2 H), 7.12 (d, *J* = 8.2 Hz, 1 H). − ^{13}C NMR: δ = 16.6, 20.9, 26.6, 27.4, 27.8, 27.9, 29.6, 29.7, 31.7, 35.1, 37.6, 44.2, 48.6, 56.3, 75.3, 112.6, 115.3, 116.4, 122.8, 126.2, 126.3, 128.1, 129.2, 129.3, 129.4, 129.7, 133.0, 138.3, 150.86, 150.83, 153.3. − MS *m/z* (%): 426 (16) [M$^+$], 411 (100). − $C_{30}H_{34}O_2$ (426.6): calcd. C 84.47, H 8.03; found C 84.38, H 8.01.

8b: Oil. − IR ($CHCl_3$) ṽ = 3440 cm^{-1}, 1660, 1610, 1600. − ^{1}H NMR: δ = 1.69 (s, 6 H), 6.64 (s, 1 H), 7.42−7.62 (m, 4 H), 7.74−7.78 (m, 3 H), 7.97−8.00 (m, 1 H). − ^{13}C NMR: δ = 28.7, 69.1, 100.8, 111.0, 124.2, 126.6, 128.2, 130.0, 132.2, 132.6, 138.2, 157.0, 162.8, 165.2, 196.7. − MS *m/z* (%): 280 (27) [M$^+$], 265 (100). − $C_{18}H_{16}O_3$ (280.3): calcd. C 77.12, H 5.75; found C 77.20, H 5.74.

Acknowledgments

Work carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni" supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome. The authors are also greatly indebted to Consiglio Nazionale delle Ricerche (CNR) and to the University "La Sapienza", Rome, for financial support of this research, and to Dr. Luciana Turchetto of the Istituto Superiore di Sanità for obtaining the mass spectra of isolated products.

[1] S. Cacchi, *J. Organomet. Chem.* **1999**, *576*, 42−64. − S. Cacchi, in: *Perspectives in Organopalladium Chemistry for the XXI Century* (Ed.: J. Tsuji), Elsevier, **1999**, pp. 42−64.
[2] A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, P. Pace, *Eur. J. Org. Chem.* **1999**, 3305−3313 and the references cited therein.
[3] A. Arcadi, E. Bernocchi, A. Burini, S. Cacchi, F. Marinelli, B. R. Pietroni, *Tetrahedron Lett.* **1989**, *30*, 3465−3468. − A. Arcadi, E. Bernocchi, A. Burini, S. Cacchi, F. Marinelli, B. R. Pietroni, *Tetrahedron* **1988**, *44*, 481−490.
[4] S. Cacchi, G. Fabrizi, F. Marinelli, L. Moro, P. Pace, *Tetrahedron* **1996**, *52*, 10225−10240.
[5] S. Cacchi, G. Fabrizi, L. Moro, P. Pace, *Synlett* **1997**, 1367−1370.
[6] J. M. Evans, G. Stemp, *Chem. Ber.* **1991**, *27*, 439−442.
[7] M. R. Attwood, P. S. Jones, P. B. Paciorek, S. Redshaw, *Life Sci.* **1991**, *48*, 803−810. − M. R. Attwood, I. Churcher, R. M. Dunsdon, D. N. Hurst, P. S. Jones, *Tetrahedron Lett.* **1991**, *32*, 811−814.
[8] See, for example: Y. Satoh, J. L Stanton, A. J. Hutchison, A. H. Libby, T. J. Kowalsky, W. H. Lee, D. H. White, E. F. Kimble, *J. Med. Chem.* **1993**, *36*, 3580−3594. − K. S. Atwal, G. J. Grover, S. Z. Ahmed, F. N. Ferrara, T. W. Harper, K. S. Kim, P. G. Sleph, S. Dzwonczyk, A. D. Russel, S. Moreland, J. R. McCullough, D. E. Normandin, *J. Med. Chem.* **1993**, *36*, 3971−3974. − F. Cassidy, J. M. Evans, M. S. Hadley, A. H. Haladij, P. E. Leach, G. Stemp, *J. Med. Chem.* **1992**, *35*, 1623−1627. − R. Gericke, G. Harting, I. Lues, C. Shittenhelm, *J. Med. Chem.* **1991**, *34*, 3074−3085. − D. R. Buckle, J. R. S. Arch, A. E. Fenwick, C. S. V. Houge-Frydrych, I. L. Pinto, D. G. Smith, S. G. Taylor, J. M. Tedder, *J. Med. Chem.* **1990**, *33*, 3028−3034. − R. Bergmann, V. Eiermann, R. Gericke, *J. Med. Chem.* **1990**, *33*, 2759−2767. − R. Bergmann, R. Gericke, *J. Med. Chem.* **1990**, *33*, 492−504.
[9] M. Teng, T. T. Duong, A. T. Johnson, E. S. Klein, L. Wang, B. Khalifa, R. A. S. Chandraratna, *J. Med. Chem.* **1997**, *40*, 2445−2451.
[10] A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron* **1985**, *41*, 5121−5131.
[11] A. Arcadi, S. Cacchi, M. Del Rosario, G. Fabrizi, F. Marinelli, *J. Org. Chem.* **1996**, *61*, 9280−9288.
[12] W. B. Austin, N. Bilow, W. J. Kelleghan, K. S. Y. Lau, *J. Org. Chem.* **1981**, *46*, 2280−2286.
[13] P. G. Stang, W. Treptow, *Synthesis* **1980**, 283−284.- P. G. Stang, M. Hanack, L. R. Subramanian, *Synthesis* **1982**, 85−126. − S. Cacchi, E. Morera, G. Ortar, *Org. Synth.* **1990**, *68*, 138−147.
[14] R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652−7662. − R. C. Larock, X. Han, M. J. Doty, *Tetrahedron Lett.* **1998**, *39*, 5713−5716. − R. C. Larock, Q. Tian, *J. Org. Chem.* **1998**, *63*, 2002−2009. − R. C. Larock, M. J. Doty, X. Han, *Tetrahedron Lett.* **1998**, *39*, 5143−5146. − R. C. Larock, E. K. Yum, M. J. Doty, K. K. C. Sham, *J. Org. Chem.* **1995**, *60*, 3270−3271.
[15] S. Kim, K. N. Chung, S. Yang, *J. Org. Chem.* **1987**, *52*, 3917−3919.

Received May 31, 2000
[O00278]