Arylation of 8-Acetoxyoctalenone in a Nickel-Catalyzed Coupling Reaction with Lithium Arylborates

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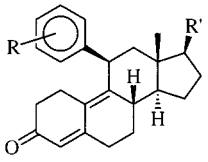
Keywords: Arylation / Borates / C−C coupling / Nickel / Steroids

In order to find a suitable organometallic compound and a catalyst for the arylation of 8-acetoxyoctalenone **4** (a stereoisomeric mixture of **4α** and **4β**), phenylation was first investigated with PhZnX (**7**: X = Cl; **8**: X = Br)/Pd or Ni cat., $PhSnBu_3$ (**9**)/Pd cat. and LiCl, and [PhB(Bu)(OCHMeCHMeO)]Li (**10a**)/Ni cat. Borate **10a** provided the desired product **11a** with high stereoselectivity. The stereochemical outcome was irrespective of the stereochemistry of the acetoxy group in **4**. Four more aryl groups, *p*-R-C_6H_4 (R = Me, MeO, Ph, and Me_2N), were installed stereoselectively with this method.

Introduction

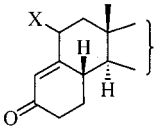
Since the Teutsch group reported the antiprogesterone activity of 11-aryl-19-nor steroids,[1] they have attracted much interest in the field of pharmaceutical chemistry,[2] and in addition their biological activity as a fertility control drug has prompted urgent elucidation of the biological role of natural 11-substituted steroids (i.e., those possessing the 19-methyl group).



11-Aryl-19-nor steroids

The 11-substituted-19-nor steroids have been prepared from 19-nor steroidal dienes by epoxidation followed by reaction with an organometallic such as copper compounds, and this methodology is now well established.[1,3] The method is, however, limited to synthesis of the 19-nor steroids. In order to develop a method for synthesis of natural 11-substituted steroids, we were interested in a substitution reaction of 8-hydroxyoctalenone derivatives **2** (X = leaving group) as a model compound of the A-ring-nor enone **1**.[4] The parent alcohol **2** (X = OH) is prepared by *m*-CPBA oxidation of the dienol acetate derived from octalenone **3**.[5]

However, the oxidation affords a stereoisomeric mixture of **2** (X = OH; α-OH/β-OH = 3:7), though the stereoisomers can be separated by chromatography. Consequently, it



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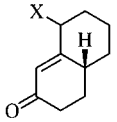

2: X = OH, Leaving group
3: X = H

is desirable to find a reaction by which a substrate derived from each stereoisomer of **2** (X = OH) conveniently furnishes the installation of an aryl group at the β side of the octalenone framework. This stereochemical requirement is of utmost importance. To this end, we studied a transition metal catalyzed coupling reaction of 8-hydroxyoctalenone derivatives with organometallics as illustrated in Equation 1. We expected that the π-allyl intermediate of the undesired stereochemistry (the metal center projected to the α side of the molecule) would be transformed into the desired intermediate or remain unchanged. Results along this line are described below.

Results and Discussion

Initially, installation of a phenyl group was examined using several organometallic compounds based on Zn,[6] Sn,[7] and B,[8] which are highly reactive toward allylic esters in the presence of appropriate catalysts, and the results are summarized in Table 1. When PhZnCl (**7**), prepared from PhLi and $ZnCl_2$, was allowed to react with a stereoisomeric mixture of acetate **4α** (α-OAc) and **4β** (β-OAc) (**4α/4β** = 1:3) in the presence of a palladium or a nickel catalyst under Negishi's conditions,[6] a mixture of unidentified products (Entry 1) or the reduction compound **3** was obtained as a major product (Entry 2), respectively.[9,10] Reactions with PhZnCl (**7**), prepared from PhMgBr and $ZnCl_2$, or PhZnBr (**8**) from PhLi and $ZnBr_2$ furnished similar results (data not shown). Next, a phenylstannane was examined. Hegedus carried out the coupling reaction between allylic

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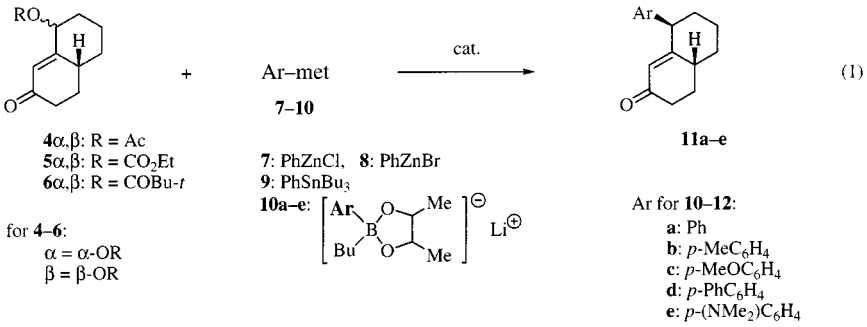


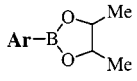
Table 1. Coupling reaction of substrates **4**, **5**, and **6** with phenylmetal compounds

Entry[a]	Substrate No.	α-/β-OR	Ph-met[b]	Catalyst[c]	Product ratio (%) **11a** (Yield,[d] β-/α-Ph[e])	**3**
1	**4**	mixture[f]	**7**[g]	$Pd(tpp)_4$	0	0
2	**4**	mixture	**7**[g]	$NiCl_2(tpp)_2$	5 (nd)[h]	32[i]
3	**4**	mixture	**9**	$Pd_2(dba)_3{\cdot}CHCl_3$	0	major[j]
4	**4**	mixture	**10a**	$NiCl_2$(dppf)	82 (75%, 96:4)	18
5	**4**	mixture	**10a**	$NiCl_2$(dppp)	59 (nd,[h] 96:4)	41
6	**4**	mixture	**10a**	$NiCl_2(tpp)_2$	63 (nd,[h] 93:7)	37
7	**5**	mixture	**10a**	$NiCl_2$(dppf)	64 (nd,[h] 93:7)	36
8	**6**	mixture	**10a**	$NiCl_2$(dppf)	82 (63%, 95:5)	18
9	**4β**	β-OAc	**10a**	$NiCl_2$(dppf)	89 (80%, 96:4)	11
10	**4α**	α-OAc	**10a**	$NiCl_2$(dppf)	84 (76%, 94:6)	16

[a] Reactions were carried out in THF at 60 °C overnight. – [b] 1.5–1.8 equiv. – [c] 5–10 mol-%. – [d] Isolated yield by chromatography. – [e] Determined by ^1H NMR spectroscopy. – [f] α-OR/β-OR = 1:2 to 1:4. – [g] Prepared from PhLi and $ZnCl_2$. – [h] Isolated yield and/or ratio was not determined. – [i] Substrate **4** was recovered in 55% yield. – [j] Enone **3** was obtained as a major product.

acetates and organostannanes under forcing conditions [$Pd(dba)_2$, LiCl, DMF].[7] However, reaction of acetate **4** and $PhSnBu_3$ (**9**) under these conditions afforded a mixture of products, in which **3** was the major product (Entry 3).

Finally, the borate reagent was examined, which is reactive toward allylic esters only in the presence of a nickel catalyst.[8] Reaction of phenylboronate ester **12a** (Ar = Ph) and *n*BuLi[11] at room temperature for 15 min generated lithium phenylborate **10a** in situ, and further reaction with acetate **4** at 60 °C afforded **11a** (Ar = Ph) as a major product, for the first time (Entries 4–6).



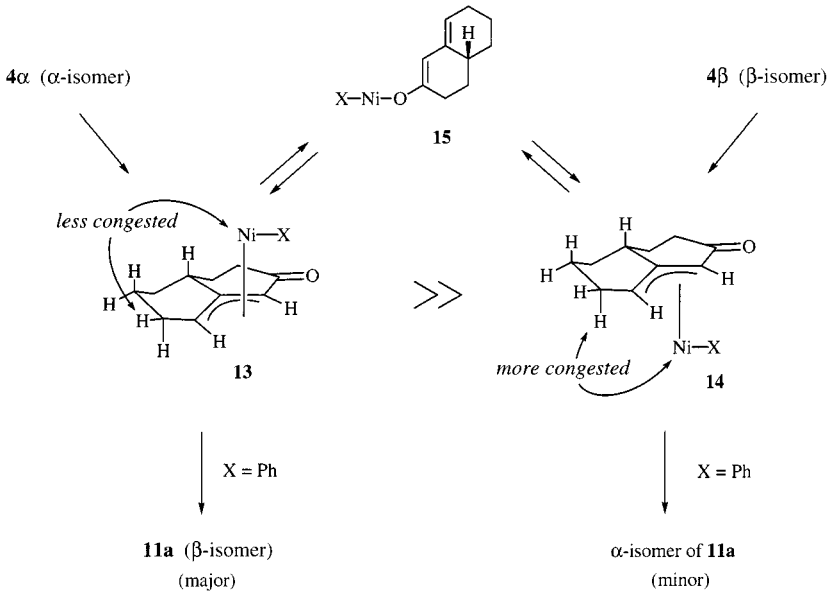
12a–e

The stereochemical purity of **11a** was higher than 93%, and the stereochemistry of the major product was assigned as depicted in **11a**, with the phenyl group on the desired β side of the ring, as determined by the ^1H NMR coupling constant of the proton at C-8 in the stable chair-like conformer: δ = 3.80 (t, *J* = 3 Hz).[12] The signal at δ = 3.38 (dd, *J* = 12, 4 Hz) was assigned to the same proton of the minor product with the α-Ph group.[12] Although **3** was produced as a by-product, use of dppf as a ligand suppressed its formation (Entry 4; cf. Entries 5 and 6), and the products were separated easily by chromatography on silica gel.

Leaving groups other than the acetoxy group were tested under the reaction conditions used in Entry 4. Reactions of carbonate **5** (**5α/5β** = 1:2) and pivaloate **6** (**6α/6β** = 1:4) resulted in worse and similar product ratios, respectively (Entries 7 and 8).

The stereochemistry of the reaction was studied under the conditions of Entry 4 by using the pure stereoisomers, **4α** and **4β**, which were prepared by separation of the stereoisomers of alcohol **2** (X = OH) followed by acetylation. The stereochemistry of the product was *independent* of that of the acetoxy group of **4**, and the same stereoisomer **11a** was obtained in the same ratio from both isomers (Table 1, Entries 9 and 10). Since the allylic coupling with hard nucleophiles generally proceeds with inversion, the present result is an exceptional case and is probably explained by the nickel enolate **15** of the half-chair conformation as illustrated in Scheme 1.[13] Thus, the reaction involves: (1) formation of the nickel enolate **15** (X = OAc) from acetates **4α** and **4β** through the initially formed π-allyl complexes **13** and **14**; (2) transmetalation of **15** (X = OAc) with borate **10a** to generate **15** (X = Ph); (3) peripheral change to the stable π-allyl complexes **13** (X = Ph), in which the Ni–Ph part is located on the less congested β side of the octalenone plane; (4) reductive elimination affording the coupling product **11a**.

The optimized conditions summarized in Entry 4 of Table 1 were applied to install other aryl groups onto the octalenone by using borates **10b–e**. The boronate esters **12d,e** [*p*-PhC_6H_4, *p*-$N(Me_2)C_6H_4$] were prepared in 94 and 50% yields, respectively, by the method[8] for synthesis of **12b,c** (Ar = *p*-MeC_6H_4, *p*-$MeOC_6H_4$) through lithiation of the corresponding aryl bromides followed by reaction with $B(OiPr)_3$ and esterification with 2,3-butanediol. As sum-



Scheme 1. Plausible pathway for formation of **11a**

Table 2. Reaction between acetate **4** and borates **10b**−**e**

Entry[a]	Ar	No.	Product **11** Yield (%)[b]	β-/α-Ar[c]	Yield of **3** (%)
1	*p*-MeC_6H_4	**11b**	69	94:6	17
2	*p*-$MeOC_6H_4$	**11c**	63	93:7	20
3	*p*-PhC_6H_4	**11d**	80	94:6	15
4	*p*-$(NMe_2)C_6H_4$	**11e**	54	90:10	22

[a] A 3:7 ratio of **4α/4β** was used; reactions were carried out in the presence of $NiCl_2$(dppf) (5−10 mol-%) at 60 °C for 12−16 h. − [b] Isolated yield by chromatography. − [c] Determined by ^{1}H NMR spectroscopy.

marized in Table 2, reaction of **4** (**4α/4β** = 3:7) with borates **10b**−**e** derived from the corresponding boronate esters **12b**−**e** and *n*BuLi afforded the corresponding products **11b**−**e** in good to moderate yields with high stereoselectivity (> 90%).[14] Among them, the substituent of Ar = *p*-$(NMe_2)C_6H_4$ is that used for UR 38 486.[2]

Conclusion

We have succeeded in the installation of aryl groups at C-8 of the octalenone **4**, a model enone for the synthesis of 11-aryl-substituted steroids through the intermediate **1**. High stereoselectivity was observed in the installation of the five aryl groups and is irrespective of that of acetate **4**. We are now carrying out the full scale synthesis of 11-aryl-substituted steroids.

Experimental Section

General: The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0) and the center line of $CDCl_3$ triplet (δ = 77.1) as internal standards, respectively. − The nickel catalysts $NiCl_2(tpp)_2$, $NiCl_2$(dppf) were prepared according to the literature methods.[15,16] Boronate esters **12a**−**c** of Ar = Ph, *p*-MeC_6H_4, and *p*-$MeOC_6H_4$ were prepared by the literature procedures,[8] while **12d**,**e** were prepared by the procedure described below. $\Delta^{1(9)}$-Octalone-2 (**3**) was prepared by the literature method.[17] Routinely, an organic extract was dried with $MgSO_4$ and concentrated by using a rotary evaporator to leave a residue, which was purified by chromatography on silica gel.

8α- and 8β-Acetoxy-$\Delta^{1(9)}$-octalone-2 (4α,β). − I: 8-Hydroxy-$\Delta^{1(9)}$-octalone-2 (**2**) (X = OH) was prepared by a literature method[5a] with modification. In summary, concentrated H_2SO_4 (0.4 mL) was added to a mixture of $\Delta^{1(9)}$-octalone-2 (**3**) (6.15 g, 40.9 mmol) and isopropenyl acetate (20 mL, 182 mmol), and the resulting solution was stirred at room temperature for 15 min. After addition of saturated $NaHCO_3$, the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried, and concentrated under reduced pressure to afford the corresponding dienol acetate, which was used for further reaction without purification. On a ice-cold solution of the above acetate in 95% EtOH (100 mL) was added *m*-CPBA (8.82 g, 80% purity, 40.9 mmol) portionwise, and the resulting mixture was stirred at room temperature overnight. Methyl sulfide (1 mL, 14 mmol) was added to the mixture, and the mixture was stirred at room temperature for 2 h and concentrated. Saturated $NaHCO_3$ was added to the residue and the mixture was extracted with EtOAc repeatedly. The combined extracts were dried and concentrated to leave alcohol **2** (X = OH) with a 3:7 ratio of α-/β-OH isomer by ^{1}H NMR spectroscopy. These stereoisomers were separated by chromatography. The combined stereoisomers (4.74 g) or each of the stereoisomers was used for the next acetylation. − **II:** To an ice-cold stereoisomeric mixture of the hydroxyoctalenone **2** (X = OH) (4.74 g) in pyridine (6.0 mL, 74.2 mmol) was added Ac_2O (3.2 mL, 33.9 mmol). The reaction mixture was stirred at room temperature overnight and diluted with EtOAc. The resulting solution was washed with 3 N HCl and then with saturated $NaHCO_3$, dried, and concentrated to give an oil, which was purified by chromatography to furnish acetate **4** (4.63 g, 54% from octalenone **3**) as a mixture of **4α** and **4β** (3:7). − Bp 150 °C (< 1 Torr). **III:** In a similar way, each of the stereoisomeric alcohols **2** (X = OH) was transformed into the acetates **4α** and **4β**, respectively. − **4α**: IR (neat): $\tilde{\nu}$ = 1736, 1676, 1237 cm^{-1}. − ^{1}H NMR δ = 1.29 (dq, *J* = 4, 13 Hz, 1 H), 1.43−1.80 (m, 3 H),

1.86−2.01 (m, 2 H), 2.14 (s, 3 H), 2.12−2.48 (m, 5 H), 5.31 (ddd, J = 11, 6, 2 Hz, 1 H), 5.95 (t, J = 2 Hz, 1 H). − ^{13}C NMR δ = 20.9, 23.0, 28.4, 33.2, 33.7, 35.8, 37.0, 72.6, 120.6, 162.9, 170.1, 199.7. − MS (EI); *m*/*z* (%): 208 [M$^+$] (15), 166 (100), 137 (24), 120 (13), 109 (12), 91 (27). − HRMS (EI) for $C_{12}H_{16}O_3$ [M$^+$]: calcd. 208.1099; found 208.1100. − **4β**: IR (nujol): ṽ = 1735, 1672, 1236 cm^{-1}. − ^{1}H NMR: δ = 1.29 (dq, J = 4, 13 Hz, 1 H), 1.54−1.76 (m, 3 H), 1.82 (tt, J = 13, 3 Hz, 1 H), 1.90−2.02 (m, 1 H), 2.07 (s, 3 H), 2.04−2.22 (m, 2 H), 2.28−2.49 (m, 2 H), 2.56−2.70 (m, 1 H), 5.43 (t, J = 3 Hz, 1 H), 5.99 (d, J = 2 Hz, 1 H). − ^{13}C NMR: δ = 19.8, 21.2, 28.7, 31.6, 33.5, 34.0, 36.1, 73.5, 127.1, 160.6, 170.0, 200.3. − MS (EI); *m*/*z* (%): 208 [M$^+$] (15), 166 (100), 148 (34), 138 (25), 137 (25), 120 (44), 91 (56). − HRMS (EI) for $C_{12}H_{16}O_3$ [M$^+$]: calcd. 208.1099; found 208.1109.

2-(4-Biphenylyl)-4,5-dimethyl-1,3,2-dioxaborolane (12d). − I: To a solution of 4-bromobiphenyl (2.47 g, 10.6 mmol) and bipyridine (ca. 5 mg) in THF (25 mL) was added *n*BuLi (4.2 mL, 2.53 M in hexane, 10.6 mmol) slowly at −78 °C. After 1 h of stirring at −78 °C, B(O*i*Pr)$_3$ (2.7 mL, 11.7 mmol) was added. The reaction mixture was stirred at the same temperature for 4 h and warmed up to room temperature over 2 h. Saturated NH_4Cl was added and the resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried, and concentrated to give the corresponding boronic acid, which was used for the next reaction without purification. − **II:** To a mixture of the above boronic acid and $MgSO_4$ (ca. 1 g) in EtOAc (20 mL) was added 2,3-butanediol (0.95 mL, 10.5 mmol, *meso*/*dl* isomer = 4:1). The resulting mixture was stirred at room temperature overnight. After filtration, the filtrate was concentrated to give a residue, which was purified by chromatography to furnish the boronate ester **12d** (2.51 g, 94%) as a 92:8 mixture of *meso*/*dl* isomers. − Bp 170 °C (< 1 Torr). − IR (nujol): ṽ = 1609, 1097 cm^{-1}. − ^{1}H NMR δ = 1.30 and 1.40 (2 d, J = 6 and 6 Hz, 5.52 and 0.48 H), 4.14−4.24 and 4.66−4.77 (2 m, 0.16 and 1.84 H), 7.35 (tt, J = 7, 1.5 Hz, 1 H), 7.44 (tt, J = 7, 1.5 Hz, 2 H), 7.62 (d, J = 8 Hz, 4 H), 7.89 (d, J = 7 Hz, 2 H). − $C_{16}H_{17}BO_2$ (252.1): calcd. C 76.22, H 6.80; found C 76.13, H 6.79.

2-[4-(Dimethylamino)phenyl]-4,5-dimethyl-1,3,2-dioxaborolane (12e): According to the procedure described above for the preparation of the boronate ester **12d**, 4-bromo-*N*,*N*-dimethylaniline (2.49 g, 12.4 mmol), *n*BuLi (5.5 mL, 2.26 M in hexane, 12.4 mmol), B(O*i*Pr)$_3$ (3.2 mL, 13.9 mmol), bipyridine (ca. 5 mg), and THF (40 mL) afforded the corresponding boronic acid after hydrolysis. The boronic acid was converted into the boronate ester **12e** (1.35 g, 50%, *meso*/*dl* isomer = 3:1) by using 2,3-butanediol (1.1 mL, 12.2 mmol, *meso*/*dl* isomer = 4:1), $MgSO_4$ (ca. 2 g), and EtOAc (20 mL). − Bp 150−160 °C (< 1 Torr). − IR (nujol): ṽ = 1604, 1094 cm^{-1}. − ^{1}H NMR δ = 1.27 and 1.37 (2d, J = 6 and 6 Hz, 4.5 and 1.5 H), 2.99 (s, 6 H), 4.07−4.17 and 4.59−4.70 (2m, 0.5 and 1.5 H), 6.69 (d, J = 9 Hz, 2 H), 7.69 (d, J = 9 Hz, 2 H). − $C_{12}H_{18}BNO_2$ (219.1): calcd. C 65.79, H 8.28; found C 65.94, H, 8.20.

General Procedure of the Coupling Reaction: Synthesis of 8-phenyl-Δ$^{1(9)}$-octalone-2 (**11a**) is representative. To an ice-cold mixture of the boronate ester **12a** (132 mg, 0.75 mmol) and $NiCl_2$(dppf) (17 mg, 0.025 mmol) in THF (1.5 mL) was added *n*BuLi (0.30 mL, 2.53 M in hexane, 0.76 mmol) dropwise under argon. The mixture was stirred at 0 °C for 5 min and then at room temperature for 15 min. Acetate **4** (114 mg, 0.547 mmol, **4α**/**4β** = 3:7) was added to the mixture, and the resulting solution was stirred at 60 °C for 14 h. Saturated $NaHCO_3$ was added to the mixture and the product was extracted with hexane three times. The combined hexanes were dried and concentrated to give an oil, which was purified by chromatography to furnish the coupling product **11a** and its stereoisomer (92 mg, 75%, **11a**/isomer = 96:4) and the by-product **3** (13 mg, 16%). − **11a**: IR (neat): ṽ = 3025, 1671, 1617 cm^{-1}. − ^{1}H NMR: δ = 1.32−1.48 (m, 1 H), 1.62−1.76 (m, 3 H), 1.82−1.96 (m, 2 H), 2.11 (dq, J = 14, 6 Hz, 1 H), 2.30−2.53 (m, 4 H), 3.80 (t, J = 3 Hz, 1 H), 6.01 (d, J = 2 Hz, 1 H), 7.19−7.36 (m, 5 H). − ^{13}C NMR: δ = 20.9, 29.1, 30.4, 34.1, 35.1, 36.2, 47.3, 126.5, 127.1, 127.4, 128.8, 141.5, 168.7, 200.3. − MS (EI); *m*/*z* (%): 226 [M$^+$] (100), 208 (26), 170 (70), 141 (62), 128 (38), 115 (56), 91 (59). − HRMS (FAB) for $C_{16}H_{19}O$ [(M + H)$^+$]: calcd. 227.1436; found 227.1436.

8-(4-Methylphenyl)-Δ$^{1(9)}$-octalone-2 (11b): IR (nujol): ṽ = 1660, 1614 cm^{-1}. − ^{1}H NMR: δ = 1.31−1.47 (m, 1 H), 1.60−1.75 (m, 3 H), 1.80−1.94 (m, 2 H), 2.10 (dq, J = 14, 6 Hz, 1 H), 2.33 (s, 3 H), 2.26−2.52 (m, 4 H), 3.76 (t, J = 3 Hz, 1 H), 6.00 (d, J = 2 Hz, 1 H), 7.14 (s, 4 H). − ^{13}C NMR: δ = 20.8, 20.9, 29.0, 30.4, 34.1, 35.0, 36.2, 46.9, 127.0, 127.3, 129.5, 136.1, 138.4, 168.9, 200.4. − MS (EI); *m*/*z* (%): 240 [M$^+$] (100), 222 (21), 207 (30), 184 (57), 169 (32), 155 (30), 141 (37), 128 (31), 115 (34), 105 (28), 91 (42). − HRMS (EI) for $C_{17}H_{20}O$ [M$^+$]: calcd. 240.1514; found 240.1515.

8-(4-Methoxyphenyl)-Δ$^{1(9)}$-octalone-2 (11c): IR (neat): ṽ = 1670, 1616, 1509, 1250 cm^{-1}. − ^{1}H NMR: δ = 1.32−2.52 (m, 11 H), 3.74 (t, J = 3 Hz, 1 H), 3.80 (s, 3 H), 5.99 (d, J = 2 Hz, 1 H), 6.86 (d, J = 9 Hz, 2 H), 7.17 (dd, J = 9, 1 Hz, 2 H). − ^{13}C NMR: δ = 20.8, 29.0, 30.5, 34.1, 34.9, 36.2, 46.5, 55.3, 114.1, 126.8, 128.4, 133.3, 158.2, 169.0, 200.3. − MS (EI); *m*/*z* (%): 256 [M$^+$] (100), 238 (17), 210 (17), 200 (37), 199 (19), 121 (21), 91 (16). − HRMS (EI) for $C_{17}H_{20}O_2$ (M$^+$): calcd. 256.1463; found 256.1477.

8-(4-Biphenylyl)-Δ$^{1(9)}$-octalone-2 (11d): IR (neat): ṽ = 3029, 1670 cm^{-1}. − ^{1}H NMR: δ = 1.34−1.50 (m, 1 H), 1.63−1.79 (m, 3 H), 1.85−2.00 (m, 2 H), 2.13 (dq, J = 14, 6 Hz, 1 H), 2.30−2.58 (m, 4 H), 3.83 (t, J = 3 Hz, 1 H), 6.04 (d, J = 2 Hz, 1 H), 7.30−7.61 (m, 9 H). − ^{13}C NMR: δ = 20.9, 29.1, 30.4, 34.1, 35.1, 36.2, 47.1, 127.1, 127.42, 127.45, 127.9, 128.9, 139.5, 140.5, 140.8, 168.6, 200.3. − $C_{22}H_{22}O$ (302.4): calcd. C 87.38, H 7.33; found C 87.71, H 7.33.

8-[4-(Dimethylamino)phenyl]-Δ$^{1(9)}$-octalone-2 (11e): IR (neat): ṽ = 1669, 1616, 1521 cm^{-1}. − ^{1}H NMR: δ = 1.37 (dq, J = 6, 12 Hz, 1 H), 1.59−1.93 (m, 5 H), 2.09 (dq, J = 14, 6 Hz, 1 H), 2.27−2.53 (m, 4 H), 2.93 (s, 6 H), 3.71 (t, J = 3.5 Hz, 1 H), 6.00 (d, J = 2 Hz, 1 H), 6.70 (d, J = 9 Hz, 2 H), 7.12 (dd, J = 9, 1 Hz, 2 H). − ^{13}C NMR: δ = 20.9, 29.0, 30.4, 34.3, 34.9, 36.2, 40.6, 46.4, 112.8, 126.6, 128.0, 129.0, 149.2, 169.6, 200.5. − $C_{18}H_{23}NO$ (269.4): calcd. C 80.26, H 8.61; found C 80.42, H 8.54.

Acknowledgments

This research was financially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Government of Japan. The high resolution mass spectra were measured by Mr. Yasumasa Tashiro of Nippon Chemiphar.

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[9] To check reactivity of the catalytic system, reaction of acetate [PhCH=CH−CH(OAc)Me] with PhZnCl in the presence of $Pd(tpp)_4$ (see ref.[6b]) was tested to give the product [PhCH=CH−CH(Ph)Me] in 86% yield.

[10] Formation of a reduction product was reported in the attempted palladium-catalyzed coupling reaction of the cepham acetate and $PhSnMe_3$.[7]

[11] The original phenylborate prepared from **12a** and MeLi gave a 57:43 mixture of **11a** and **3** under the best conditions (Table 1, Entry 4).

[12] Coupling constants of the proton attached to C-8 for the major and minor product were almost same as those of acetate **4β** and **4α**, respectively (for ^{1}H NMR spectra, see Experimental Section).

[13] Recently, Trost reported a palladium-catalyzed allylic coupling reaction involving the palladium enolate: B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1999**, *121*, 3543−3544.

[14] Stereochemistry of the products **11b**−**e** was determined by comparison of the coupling constants for the proton at C-8 with those of **11a**. The ^{1}H NMR spectroscopic data of the protons for α-Ar isomers of **11b**−**e** were as follows. − Isomer of **11b**: δ = 3.34 (dd, *J* = 12, 4 Hz, 1 H). − Isomer of **11c**: δ = 3.33 (dd, *J* = 11, 4 Hz, 1 H). − Isomer of **11d**: δ = 3.42 (dd, *J* = 12, 4 Hz, 1 H), − Isomer of **11e**: δ = 3.28 (dd, *J* = 13, 4 Hz, 1 H).

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Received March 13, 2000
[O00121]