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Journal of Organometallic Chemistry 692 (2007) 4528–4534
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Acylzirconocene chloride: Formation of carbocycles by palladium-catalyzed cascade reaction

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Received 28 February 2007; received in revised form 25 April 2007; accepted 26 April 2007
Available online 1 May 2007

Abstract

Acylzirconocene chloride complex as an acyl group donor reacts with ω-carbonyl α,β-enones or with bis-enones to give carbocyclic compounds under 10 mol% $Pd(OAc)_2$-catalyzed conditions, and each reaction was accelerated by the addition of a stoichiometric amount of Me_2Zn. The formation of the carbocycles from ω-carbonyl α,β-enones was considered to be a result of a series of reactions; (i) the formation of Pd(II)-intermediate by an electron transfer from the Pd(0)-catalyst to an α,β-enone function in an initial step, (ii) an acyl group transfer from the acylzirconocene complex to the Pd(II)-intermediate (transmetalation), (iii) the reductive elimination of Pd(0)-metal, and (iv) an intramolecular addition of metal enolate to ω-carbonyl group. On the other hand, the reaction of bis-enones with acylzirconocene chloride under the identical condition afforded reductive cyclization product, bicyclo[3.3.0] octane derivatives, in which acyl group from acylzirconocene complex was not incorporated.
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Keywords: Acylzirconocene chloride; Palladium catalyst; Cascade reaction; Reductive cyclization

1. Introduction

The search for carbon–carbon bond formations by the metal-catalyzed addition of acylzirconocene chloride complex **1** to unsaturated bonds is the current focus of our investigation. The stable acylzirconocene chloride complex **1** can be easily prepared through the hydrozirconation of 1-alkenes or -alkynes followed by an insertion of carbon monoxide by treating with carbon monoxide under atmospheric pressure (Scheme 1) [1].

On the basis of the described motive, we have reported on carbon–carbon forming reactions of **1** [2] since our first report on the reaction of **1** with aldehydes giving α-ketols has been published [2h]. Among the reactions we reported, it is worth commenting that $Pd(OAc)_2$-catalyzed reactions of **1** with α,β-enone derivative **2** brought about 1,2- or 1,4-selective nucleophilic addition of acyl group of **1** (Scheme 1) [2e,2f]. The siteselective addition of **1** to α,β-enone derivative **2** is considered to be catalyzed by a low valent palladium metal, presumably Pd(0), which is generated *in situ* through the reaction of **1** and $Pd(OAc)_2$ giving bisacylated Pd(II) followed by reductive elimination [3]. In these reactions, we speculated on the initial formation of Pd(II) intermediate species **A** by an electron transfer from Pd(0) to the α,β-enone function (Scheme 2) [2e,2f,4]. Thus, the catalytic cycle for the nucleophilic addition of **1** to α,β-enone derivative **2** was suggested to consist of the following two consecutive reactions: (i) the transfer of an acyl group from **1** to the Pd(II) intermediate **A** (transmetalation) and (ii) subsequent reductive elimination of palladium metal.

On the basis of the catalytic cycle shown in Scheme 2, we examined the palladium-catalyzed reaction of **1** with α,β-enone **3**, which is tethered to ω-unsaturated chain, and reported the formation of a cyclization/acylation product, bicyclo[3.3.0] compound **4**, by the cyclization of Pd(II) intermediate **B** to ω-unsaturated chain and the following acyl group transfer from **1** (Scheme 3) [5].

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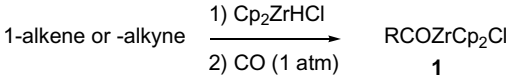
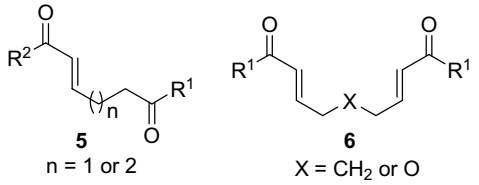
doi:10.1016/j.jorganchem.2007.04.033

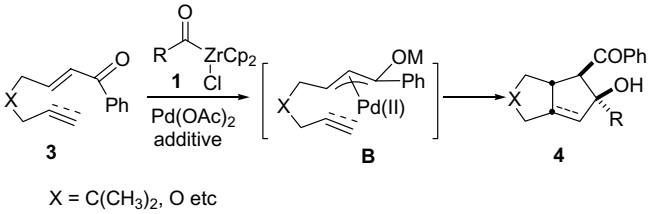


Scheme 1. Formation of **1**.

Transition metal-catalyzed cyclization reactions of the aldehyde or α,β-enone, which is tethered to an ω-unsaturated carbon–carbon bond functional group, attracted much attention for the preparation of cyclic compounds [6]. In particular, $Ni(COD)_2$-catalyzed reaction of ω-alkynyl-tethered α,β-enone compounds in the presence of organozinc and electrophile giving bicyclo[3.3.0] compounds is noteworthy, and the reaction has been reported to proceed through a π-allylic nickel complex followed by the formation of metallacycle [7]. In the nickel-catalyzed reaction of 1,6-ynals, vinylzirconocene chloride has been reported to be an efficient organometalic reagent for the formation of cyclopentanol derivatives [8]. Recently, the nickel-catalyzed reaction of ω-allenyl aldehydes in the presence of organozinc were also shown to give stereochemically defined cyclopentanol derivatives [6a]. Palladium-catalyzed reactions of ω-allenyl aldehydes in the presence of organotin and electrophile are also reported to undergo cyclizations to generate cyclopentanols stereoselectively [9].

As an extension of the transition metal-catalyzed cyclization chemistry using **1**, we report herein the formation of carbocycles by treating ω-carbonyl α,β-enones **5** or bis-enone compounds **6** with acylzirconocene chloride complex **1** in the presence of a catalytic amount of $Pd(OAc)_2$.





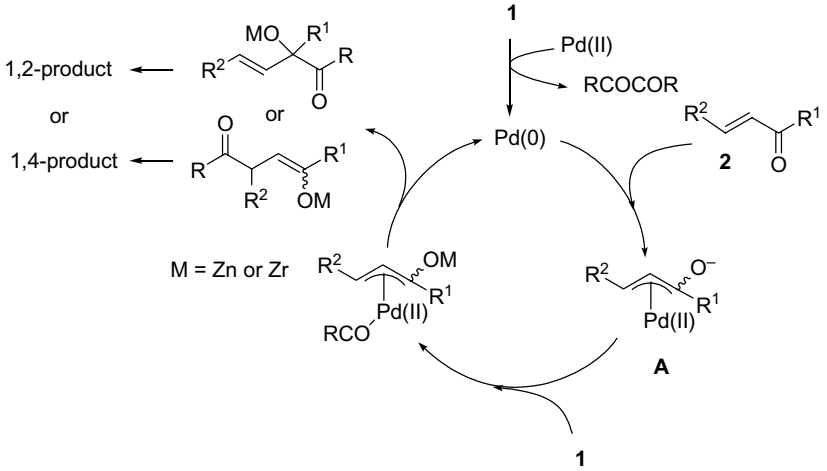
Scheme 3. Acylation/cyclization of **3**.

2. Results and discussion

At the outset, we examined the reaction of ω-carbonyl α,β-enone **5** with *n*-nonanoylzirconocene chloride (**1a**) under the catalytic conditions employed for the addition of **1** to α,β-enone **2** (10 mol% $Pd(OAc)_2$ in THF/ether (1/2) at ambient temperature) [2f], and the reaction of **1a** with **5** afforded carbocycles **7** as a mixture of two stereoisomers in moderate yields. The results are shown in Table 1. Other possible stereoisomers or a product derived from 1,4-addition of acylzirconocene to the α,β-enone function of **5** could not be detected in the reaction mixture.

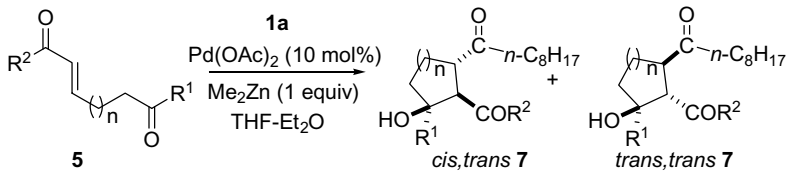
The addition of an equivalent amount of Me_2Zn is important for the acceleration of the reaction, and the use of less than 1 equiv. amount of Me_2Zn reduced the yield of **7** (entry 4). Without the addition of Me_2Zn the reaction was very slow, and a trace amount of **7** was observed by TLC. The use of BF_3OEt_2 (1 equiv.) or Me_2AlCl, which is known to be an efficient additive for the conjugate addition of **1** to α,β-enones **2**, was less efficient in the present reaction. It turned out that the use of Pd catalysts such as $Pd(PPh_3)_4$, $Pd(acac)_2$ or $PdCl_2(PPh_3)_2$ did not improve the yield of **7**, and nickel catalysts such as $Ni(COD)_2$ or $Ni(acac)_2$, gave a complex mixture which contains a trace amount of **7** (by TLC). It should be mentioned that the stereoselectivity of the present reaction was disappointingly low.

The formation of carbocycles **7** would be brought about through 1,4-conjugate addition and subsequent addition of



Scheme 2. A catalytic cycle for the regioselective addition of **1** to **2**.

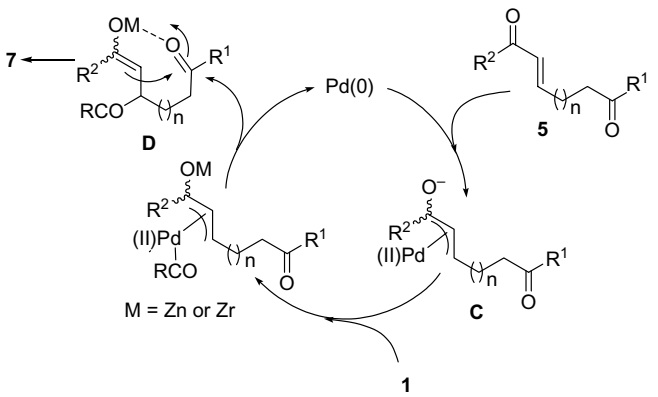
Table 1
Cascade reaction of **5**



Entry	R^1	R^2	**5**	*n*	**7**	Yield (%)[a]	*cis*/*trans*[b]
1	H	C_6H_5	**5a**	1	**7a**	34	2.4
2	CH_3	CH_3	**5b**	1	**7b**	55	10
3	CH_3	C_6H_5	**5c**	1	**7c**	65	2
4						14[c]	2
5	H	C_6H_5	**5d**	2	**7d**	81	2
6	CH_3	C_6H_5	**5e**	2	**7e**	51	1
7	H	CH_3	**5e**	2	**7f**	83	1.1
8[d]	CH_3	C_6H_5	**5f**	1	**7g**	57	1.1

[a] Isolated yield.
[b] Determined by ^1H NMR.
[c] *Reaction conditions*: 0.5 equiv. of Me_2Zn, at ambient temperature for 3 h.
[d] 5-Phenyl-*n*-pentanoylzirconocene chloride was used.

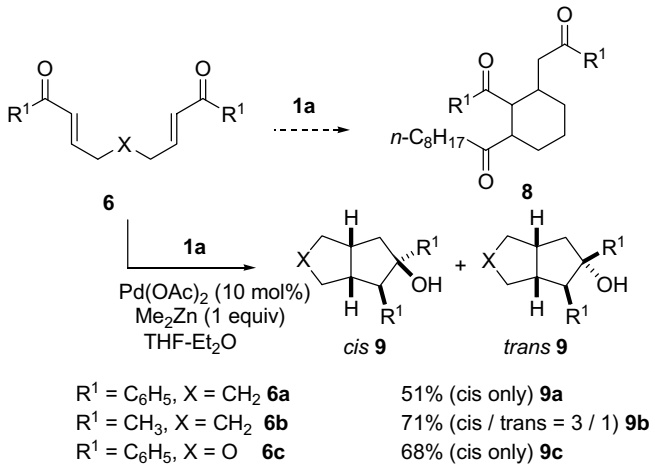
the metal enolate intermediate to ω-carbonyl function (intramolecular aldol reaction). Although the exact role of Me_2Zn for the acceleration of the present reaction was unclear, the additive might take part in the generation of the metal enolate **D** or in the addition of the metal enolate **D** to ω-carbonyl group (Scheme 4) [10]. We assume that the present acylation/cyclization reactions of **5** could be brought about by the initial formation of Pd-complex **C** by (i) an initial electron transfer from *in situ* generated Pd(0) to the α,β-unsaturated functional group, (ii) formation of Pd(II) complex **C**, and (iii) transfer of the acyl group from **1** to Pd(II)-complex **C** (transmetalation), (iv) subsequent reductive elimination of Pd(0), and (v) intramolecular addition of metal enolate **D** to ω-carbonyl group albeit the metal species of the enolate **D** generated *in situ* is unclear (Scheme 4) [11].



Scheme 4. A catalytic cycle for the formation of **7**.

It should be noted that the attempted $Pd(OAc)_2$-catalyzed reaction of **1a** with an 1,6-ynal or ω-allenyl aldehyde compound, which has no α,β-enone functional group, did not give cyclization/acylation products [12]. This observation indicates that the α,β-enone functional group in **5** is necessary for bringing about the present Pd-catalyzed acylation/cyclization. The α,β-unsaturated ester group, instead of the α,β-enone in **5**, did not afford the corresponding product. The length of the tethering chain in **5** is also an important factor for the reaction; that is, the 4-carbon tethering chain ($n = 3$) did not give the corresponding 7-membered ring product but gave a mixture of 1,2- and 1,4-addition products. Thus, the present reaction is restricted to the formation of a cyclopentane or cyclohexane framework.

Based on the described reactions of the ω-carbonyl α,β-enones **5** with **1a**, we examined the reaction of **1a** with bis-enone compounds **6**, which are expected to afford carbocycles **8** through tandem 1,4-conjugate addition (Scheme 5). The reaction of bis-enone **6**, however, with **1a** under the identical condition to that of **5** gave unexpectedly reductive cyclization product **9** and the acyl group of **1** was not incorporated in the bicyclo[3.3.0] products **9**. The similar observation have been reported in the $Ni(COD)_2$-catalyzed reactions of bis-enone **6** with $BuLi/ZnCl_2$ [6b]. Thus, the formation of **9** would be the result of the reductive coupling and subsequent aldol reaction. However, little is known about the precise mechanism of the bis-enone reductive cyclizations. It should be mentioned that the reaction of **6** without the use of acylzirconocene chloride complex **1a** did not afford **9**. The use of alkyl- or alkenylzirconocene chloride complex in place of acylzirconocene chloride complex **1** also gave **9** albeit the reaction was less efficient.



Scheme 5. Reductive cyclization of bis-enones **6**.

3. Conclusions

In summary, palladium-catalyzed reactions of acylzirconocene chloride with α,β-enones which are tethered to the ω-carbonyl side chain provided a new entry of the reaction of acylzirconocene chloride complex as an acyl group donor. The preparation of carbocycles through cascade 1,4-conjugate addition of acylzirconocene chloride and the subsequent intramolecular aldol process indicates further utility of acylzirconocene complex as an acyl anion donor. The reductive formation of bicyclo[3.3.0] compounds from bis-enones without the introduction of acyl group of acylzirconocene chloride could be the result of the intervention of the electron transfer, which is proposed in the initial step for the reactions of acylzirconocene chloride with α,β-enones. Further study on the reactivity of acylzirconocene chloride, as an acyl group donor, is in progress.

4. Experimental

Infrared (IR) spectra were recorded on a FT-IR spectrophotometer, ν_{max} in cm^{-1}. ^1H NMR spectra were recorded on a 300 MHz or 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as internal standard ($CHCl_3$: δ 7.26 ppm). ^{13}C NMR spectra were recorded on a 75.5 MHz or 100 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as internal standard ($CDCl_3$: δ 77.0 ppm). High resolution MS data were obtained by ESI MS and/or EI MS, and $[M+Na]^+$ ion peaks are shown for each ESI MS. Thin-layer chromatography (TLC) was performed using precoated plates (0.25 mm) with a UV lamp, PMA or basic $KMnO_4$ for detection. Column chromatography was performed on silica gel (100–210 mm particle size), or on a flash silica gel (40–50 mm particle size). Medium-pressure liquid chromatography (MPLC) was performed on a 40×300 mm ID prepacked column with a UV detector. Moisture sensitive reactions were performed under an argon atmosphere in flame-dried glassware equipped with a magnetic stirring bar. Tetrahydrofuran (THF), diethyl ether, and dichloromethane were purchased as dehydrated solvents, and used without further purification.

4.1. General procedure for the preparation of a solution of n-nonanoylzirconocene chloride complex (*1a*) in THF

To a suspension of $Cp_2Zr(H)Cl$ (1 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added 1-octene (2.0 mmol) and the mixture was stirred at ambient temperature for 0.5 h. The reaction mixture was further stirred under CO atmosphere (1 atm) for 2 h at ambient temperature. The clear solution was concentrated to dryness *in vacuo* by using vacuum pump (10^{-3} mmHg) to give acylzirconocene chloride powder. After the powder was further subjected to vacuum for 2 h, a solution of **1** in THF was prepared by the addition of anhydrous THF (6 mL) to the powder, and the solution was directly used as a 1 mmol solution for the next step.

4.2. General procedure for the reactions of *5* or *6* with *1a*

To a solution of **1a** (0.5–1.5 mmol) in THF (6 mL) was added successively a solution of starting material **5** or **6** (0.5 mmol) in ether (12 mL), 1 M solution of Me_2Zn in hexane (0.5–1.5 mmol) and $Pd(OAc)_2$ (0.05 mmol) at 0 °C, and the mixture was stirred at ambient temperature for 3 h. The reaction mixture darkened and became turbid. After being quenched with aqueous $NaHCO_3$ under ice cooling, the mixture was extracted with ethyl acetate and dried over $MgSO_4$. The filtered solution was concentrated to dryness *in vacuo*, providing a crude product. Purification by silica gel column chromatography (hexanes/ethyl acetate) afforded product.

4.2.1. 1-(2-Benzoyl-3-hydroxycyclopentyl)-1-nonanone (*7a*)

According to the general procedure **7a** (28.1 mg, 34%) was obtained as a mixture of diastereomers by the reaction of **1a** (0.50 mmol) with **5a** (47.0 mg, 0.25 mmol). The mixture was separated by silica gel column chromatography (hexanes/ethyl acetate = 10:1) to give 1*R**-isomer (*trans* **7a**) (oil, first fraction) and 1*S**-isomer (*cis* **7a**) (oil, second fraction).

4.2.2. 1-[(1*R**,2*S**,3*S**)-2-Benzoyl-3-hydroxycyclopentyl]-1-nonanone (trans,trans *7a*)

^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, $J = 6.8$ Hz), 1.24–1.29 (m, 12H), 1.53–1.95 (m, 3H), 2.13–2.22 (m, 1H), 2.41–2.58 (m, 3H), 3.57 (m, 1H, C*H*–$COCH_2$–), 4.14 (dd, 1H, $J = 3.5$, 5.3 Hz, C*H*–COPh), 4.43 (bs, 1H, C*H*–OH), 7.46–8.07 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.7, 27.9, 29.1, 29.2, 29.3, 31.8, 35.2, 42.2, 52.3, 57.0, 76.7, 128.7, 128.8, 133.4, 136.2, 199.9, 213.0; IR (neat) ν 3413, 1706, 1675 cm^{-1}; ESI-MS *m/z* 353 $(M+Na)^+$; HRMS Calcd for $C_{21}H_{30}O_3Na^+$: 353.2093. Found: 353.2072.

4.2.3. 1-[(1S*,2R*,3S*)-2-Benzoyl-3-hydroxycyclopentyl]-1-nonanone (cis,trans 7a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J = 6.7$ Hz), 1.18–1.53 (m, 12H), 1.69–2.07 (m, 3H), 2.33–2.52 (m, 3H), 2.58 (d, 1H, $J = 2.4$ Hz), 3.72 (td, 1H, $J = 7.2$, 9.9 Hz, C*H*–$COCH_2$–), 4.21 (dd, 1H, $J = 4.6$, 9.2 Hz, C*H*–COPh), 4.63 (dt, 1H, $J = 4.5$, 6.6 Hz, C*H*–OH), 7.45–8.05 (m, 5H, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.6, 27.0, 29.1, 29.2, 29.3, 31.8, 35.2, 42.7, 51.5, 53.5, 75.5, 128.5, 128.7, 133.5, 137.1, 201.5, 212.0; IR (neat) ν 3855, 1705, 1682 cm^{-1}; ESI-MS m/z 353 $(M+Na)^+$; HRMS Calcd for $C_{21}H_{30}O_3Na^+$: 353.2093. Found: 353.2063.

4.2.4. 1-(2-Acetyl-3-hydroxy-3-methylcyclopentyl)-1-nonanone (7b)

According to the general procedure **7b** (77.6 mg, 55%) was obtained as a mixture of diastereomers by the reaction of **1a** (1.00 mmol) with **5b** (70.0 mg, 0.50 mmol). The mixture was separated by silica gel column chromatography (hexanes/ethyl acetate = 10:1) to give 1*S**-isomer (*cis* **7b**) (oil, first fraction) and 1*R**-isomer (*trans* **7b**) (oil, second fraction).

4.2.5. 1-[(1S*,2R*,3S*)-2-Acetyl-3-hydroxy-3-methylcyclopentyl]-1-nonanone (cis,trans 7b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 3H, $J = 6.7$ Hz, –CH_2–C*H*$_3$), 1.18–1.25 (m, 10H), 1.38 (s, 3H, C(OH)–*CH*$_3$), 1.45–1.80 (m, 5H), 2.20 (s, 3H, COC*H*$_3$), 2.30–2.50 (m, 3H), 3.26 (d, 1H, $J = 9.9$ Hz, C*H*–$COCH_3$), 3.36 (s, 1H, O*H*), 3.43 (td, 1H, $J = 6.6$, 10.1 Hz, C*H*-$COCH_2$–); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.0, 22.6, 23.7, 26.6, 26.7, 29.1, 29.2, 29.3, 31.7, 32.2, 40.3, 41.9, 54.0, 60.1, 80.7, 211.5, 212.6; IR (neat) ν 3483, 1702 cm^{-1}; ESI-MS m/z 305 $(M+Na)^+$. Anal. Calc. for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, 72.19; H, 10.52%.

4.2.6. 1-[(1R*,2S*,3S*)-2-Acetyl-3-hydroxy-3-methylcyclopentyl]-1-nonanone (trans,trans 7b)

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J = 6.7$ Hz, –CH_2-C*H*$_3$), 1.18 (s, 3H, C(OH)–*CH*$_3$), 1.20–1.29 (m, 10H), 1.53 (t, 2H, $J = 6.8$ Hz), 1.69–2.03 (m, 4H), 2.26 (s, 3H, COC*H*$_3$), 2.43 (ddt, 3H, $J = 7.5$, 17.0, 35.1 Hz), 3.34 (d, 1H, $J = 8.0$ Hz, C*H*–$COCH_3$), 3.39 (dt, 1H, $J = 7.8$, 15.3 Hz, C*H*–$COCH_2$–); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.0, 22.6, 23.6, 24.0, 25.3, 29.1, 29.2, 29.3, 31.5, 31.8, 41.8, 42.0, 50.7, 63.5, 80.8, 208.7, 212.5; IR (neat) ν 3464, 1702 cm^{-1}; ESI-MS m/z 305 $(M+Na)^+$; HRMS Calcd for $C_{17}H_{30}O_3(M + Na)^+$: 305.2093. Found: 305.2076.

4.2.7. 1-(2-Benzoyl-3-hydroxy-3-methylcyclopentyl)-1-nonanone (7c)

A reaction of **5c** (101.1 mg, 0.5 mmol) and **1a** (1.0 mmol) was carried out as described in typical reaction procedure to give a mixture of **7c** as a mixture of distereomers (112 mg, 65%). The mixture was separated by silica gel column chromatography (hexanes/ethyl acetate = 10:1) to give 1*S**-isomer (*cis* **7c**) as a first effluent and 1*R**-isomer (*trans* **7c)** as a second effluent.

4.2.8. 1-[(1S*,2R*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclopentyl]-1-nonanone (cis,trans 7c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J = 7.2$ Hz), 1.10–1.32 (m, 10H), 1.29 (s, 3H, C(OH)–C*H*$_3$), 1.39–1.50 (m, 2H), 1.68–1.82 (m, 2H), 1.90–1.99 (m, 1H), 2.24 (dt, 1H, $J = 16.9$, 7.6 Hz,), 2.34–2.47 (m, 2H), 3.59–3.67 (m, 1H, C*H*–$COCH_2$–), 3.80 (s, 1H, O*H*), 4.16 (d, 1H, $J = 9.7$ Hz, C*H*–COPh), 7.25–7.59 (m, 3H), 7.98–8.01 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.5, 26.6, 27.2, 29.0, 29.1, 29.3, 31.8, 40.7, 42.5, 128.7, 128.8, 133.8, 137.7, 205.1, 211.9; IR (neat) ν 3465, 1706, 1671 cm^{-1}; EIMS m/z 345 $(M^+ + 1)$; HRMS Calcd for $C_{22}H_{32}O_3$: 344.23514. Found: 344.23217.

4.2.9. 1-[(1R*,2R*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclopentyl]-1-nonanone (trans,trans 7c)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J = 7.2$ Hz), 1.13 (s, 3H, C(OH)–C*H*$_3$), 1.17–1.30 (m, 10H), 1.50–1.59 (m, 2H), 1.86–1.95 (m, 3H), 2.12–2.20 (m, 1H), 2.41 (dt, 1H,$J = 17.0$, 7.2 Hz), 2.47 (s, 1H), 2.52 (dt, 1H, $J = 17.0$, 7.2 Hz), 3.62–3.69 (m, 1H), 4.25 (d, 1H, $J = 6.7$ Hz C*H*–COPh), 7.45–7.60 (m, 3H), 8.05–8.08 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.6, 25.2, 26.9, 29.1, 29.2, 29.3, 31.8, 42.0, 42.1, 128.7, 129.0, 133.4, 137.7, 200.9, 213.0; IR (neat) ν 3483, 1705, 1671 cm^{-1}; EIMS m/z 344 (M^+); HRMS Calcd for $C_{22}H_{32}O_3$: 344.23514. Found: 344.23560.

4.2.10. 1-(2-Benzoyl-3-hydroxycyclohexyl)-1-nonanone (7d)

According to the general procedure **7d** (139 mg, 81%) was obtained as a mixture of diastereomers by the reaction of **1a** (1.00 mmol) with **5d** (100 mg, 0.50 mmol). The mixture was separated by silica gel column chromatography to give 1*S**-isomer (*cis* **7d**) (oil, first fraction) and 1*R**-isomer (*trans* **7d**) (oil, second fraction).

4.2.11. 1-[(1S*,2R*,3S*)-2-Benzoyl-3-hydroxycyclohexyl]-1-nonanone (cis,trans 7d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, $J = 6.7$ Hz), 1.22–1.28 (m, 11H), 1.47–2.08 (m, 7H), 2.20 (s, 1H), 2.50 (m, 2H), 3.40 (ddt, 1H, $J = 3.5$, 11.4, 12.7 Hz, C*H*–$COCH_2$-), 3.78 (dd, 1H, $J = 2.1$, 11.0 Hz, C*H*–COPh), 4.22 (d, 1H, $J = 2.0$ Hz, C*H*–OH), 7.42–7.46 (m, 3H, Ar-H), 7.92–7.95 (d, 2H, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.0, 19.2, 22.6, 23.4, 28.5, 29.1, 29.1, 29.3, 31.7, 32.0, 41.4, 46.5, 50.5, 66.4, 128.5, 128.6, 133.1, 136.3, 203.4, 213.5; IR (neat) ν 3485, 1704, 1682 cm^{-1}; ESI-MS m/z 367 $(M+Na)^+$. Anal. Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.66; H, 9.34%.

4.2.12. 1-[(1R*,2S*,3S*)-2-Benzoyl-3-hydroxycyclohexyl]-1-nonanone (trans,trans 7d)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, $J = 6.9$ Hz), 1.13–1.61 (m, 16H), 1.91 (m, 1H), 2.03 (dt, 2H, $J = 3.3$,

12.7 Hz), 2.37 (ddt, 2H, $J = 7.6$, 17.0, 52.1 Hz), 3.07 (ddd, 1H, $J = 3.6$, 10.6, 12.8 Hz, C*H*–$COCH_2$–), 3.72 (t, 1H, $J = 10.3$ Hz, C*H*–COPh), 3.83 (m, 1H), 7.42–7.55 (m, 3H, Ar-H), 8.03–8.06 (d, 2H, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.4, 23.9, 28.2, 29.1, 29.3, 31.8, 35.1, 41.6, 52.8, 53.1, 73.7, 77.3, 128.4, 128.7, 132.9, 138.7, 204.9, 211.9; IR (neat) ν 3457, 1707, 1671 cm^{-1}; ESI-MS m/z 367 $(M+Na)^+$. Anal. Calc. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.61; H, 9.15%.

4.2.13. 1-(2-Benzoyl-3-hydroxy-3-methylcyclohexyl)-1-nonanone (7e)

According to the general procedure **7e** (45.6 mg, 51%) was obtained as a mixture of diastereomers by the reaction of **1a** (0.50 mmol) with **5e** (54.0 mg, 0.25 mmol). The mixture was separated by silica gel column chromatography to give 1*S**-isomer (*cis* **7e**) (oil, first fraction) and 1*R**-isomer (*trans* **7e**) (oil, second fraction).

4.2.14. 1-[(1S*,2R*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclohexyl]-1-nonanone (cis,trans 7e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, $J = 6.8$ Hz), 1.02 (s, 3H, CH(OH)–C*H*$_3$), 1.11–1.40 (m, 14H), 1.61–1.71 (m, 1H), 1.80 (d, 1H, $J = 13.7$ Hz), 1.97 (qt, 1H, $J = 3.9$, 17.2 Hz), 2.10 (dd, 1H, $J = 3.2$, 13.0 Hz), 2.29 (dt, 1H, $J = 7.2$, 16.8 Hz), 2.43 (dt, 1H, $J = 7.5$, 16.9 Hz), 3.36 (d, 1H, $J = 2.3$ Hz, O*H*), 3.41 (ddd, 1H, $J = 3.5$, 11.0, 12.6 Hz, C*H*–$COCH_2$–), 3.73 (d, 1H, $J = 11.0$ Hz, C*H*–COPh), 7.45–8.06 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 20.9, 22.6, 23.4, 28.8, 29.1, 29.2, 30.3, 31.7, 38.5, 41.6, 51.0, 52.1, 70.3, 128.6, 128.8, 133.5, 138.3, 207.4, 213.3; IR (neat) ν 3500, 1706, 1654 cm^{-1}; ESI-MS m/z 381 $(M+Na)^+$. Anal. Calc. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.11; H, 9.45%.

4.2.15. 1-[(1R*,2S*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclohexyl]-1-nonanone (trans,trans 7e)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3H, $J = 6.6$ Hz), 1.19–1.54 (m, 18H), 1.63 (td, 1H, $J = 3.6$, 13.1 Hz), 1.78–2.08 (m, 3H), 2.44 (dt, 1H, $J = 7.1$, 17.1 Hz), 2.50 (dt, 1H, $J = 7.5$, 17.0 Hz), 3.16 (ddd, 1H, $J = 3.8$, 11.0, 12.7 Hz, C*H*–$COCH_2$–), 3.93 (d, 1H, $J = 11.0$ Hz, C*H*–COPh), 7.42–8.05 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.3, 23.4, 23.4, 28.5, 29.1, 29.2, 29.3, 31.8, 41.7, 41.8, 51.4, 55.2, 72.9, 128.4, 128.8, 132.8, 139.4, 203.7, 212.7; IR (neat) ν 3475, 1707, 1668 cm^{-1}; ESI-MS m/z 341 $(M-OH)^+$; HRMS Calcd for $C_{23}H_{32}O_2$-$(M-OH)^+$: 341.2481. Found: 341.2482.

4.2.16. 1-(2-Acetyl-3-hydroxycyclohexyl)-1-nonanone (7f)

According to the general procedure **7f** (117 mg, 83%) was obtained as a mixture of diastereomers by the reaction of **1a** (2.00 mmol) with **5f** (70.0 mg, 0.50 mmol). The mixture was separated by silica gel column chromatography to give 1*R**-isomer (*trans* **7f**) (oil, first fraction) and 1*S**-isomer (*cis* **7f**) (colorless crystals, second fraction).

4.2.17. 1-[(1R*,2S*,3S*)-2-Acetyl-3-hydroxycyclohexyl]-1-nonanone (trans,trans 7f)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, $J = 6.8$ Hz), 1.21–1.51 (m, 15H), 1.62 (d, 1H, $J = 4.7$ Hz), 1.85–2.00 (m, 3H), 2.34–2.47 (m, 5H), 2.81–2.84 (m, 2H), 3.64 (tt, 1H, $J = 4.9$, 10.0 Hz, C*H*-OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 22.6, 23.6, 23.9, 28.0, 29.1, 29.2, 29.3, 31.8, 33.8, 35.5, 41.2, 52.6, 57.6, 73.2, 212.1, 213.8; IR (neat) ν 3419, 1704 cm^{-1}; ESI-MS m/z 305 $(M+Na)^+$; HRMS Calcd for $C_{17}H_{30}O_3Na^+$: 305.2093. Found: 305.2057.

4.2.18. 1-[(1S*,2R*,3S*)-2-Acetyl-3-hydroxycyclohexyl]-1-nonanone (cis,trans 7f)

Mp 48.0–50.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3H, $J = 6.7$ Hz), 1.09–1.29 (m, 11H), 1.48–2.08 (m, 8H), 2.26 (s, 3H), 2.50 (t, 2H, $J = 7.3$ Hz), 2.94 (dd, 1H, $J = 2.2$, 11.2 Hz, C*H*–COPh), 3.12 (td, 1H, $J = 3.6$, 11.8 Hz, C*H*–$COCH_2$–), 4.35 (bs, 1H, C*H*–OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.1, 19.2, 22.6, 23.5, 28.3, 29.1, 29.2, 29.3, 29.4, 31.8, 32.3, 41.3, 46.2, 55.6, 65.9, 211.3, 213.7; IR (KBr) ν 3480, 1696 cm^{-1}; ESI-MS m/z 305 $(M+Na)^+$; HRMS Calcd for $C_{17}H_{30}O_3Na^+$: 305.2093. Found: 305.2065.

4.2.19. 1-(2-Benzoyl-3-hydroxy-3-methylcyclopentyl)-5-phenyl-1-pentanone (7g)

5-Phenyl-*n*-pentanoylzirconocene chloride was generated from 4-phenyl-1-butene by the general procedure described for the formation of **1**. According to the general procedure **7g** (52.5 mg, 57 %) was obtained as a mixture of diastereomers by the reaction of 5-phenyl-*n*-pentanoylzirconocene chloride (0.50 mmol) with **5g** (50.5 mg, 0.25 mmol). The mixture was separated by silica gel column chromatography to give 1*S**-isomer (*cis* **7g**) (oil, first fraction) and 1*R**-isomer (*trans* **7g**) (oil, second fraction).

4.2.20. 1-[(1S*,2R*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclopentyl]-5-phenyl-1-pentanone (cis,trans 7g)

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (s, 3H, C*H*$_3$), 1.54–1.58 (m, 4H), 1.61–1.94 (m, 3H), 2.27 (dt, 1H, $J = 7.1$, 17.1 Hz), 2.37–2.54 (m, 4H), 3.62 (td, 1H, $J = 6.5$, 10.6 Hz, C*H*-$COCH_2$-), 3.78 (s, 1H, O*H*), 4.15 (d, 1H, $J = 9.7$ Hz, C*H*-COPh), 7.08–8.00 (m, 10H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.1, 26.6, 27.1, 30.8, 35.6, 40.7, 42.2, 54.8, 54.9, 81.8, 125.7, 128.3, 128.3, 128.8, 128.8, 133.8, 137.7, 142.0, 205.0, 211.6; IR (neat) ν 3474, 1705, 1673 cm^{-1}; ESI-MS m/z 365 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{29}O_3Na^+$: 365.2117. Found: 365.2096.

4.2.21. 1-[(1R*,2S*,3S*)-2-Benzoyl-3-hydroxy-3-methylcyclopentyl]-5-phenyl-1-pentanone (trans,trans 7g)

^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 3H), 1.57–1.60 (m, 4H), 1.88–2.17 (m, 4H), 2.42–2.60 (m, 5H), 3.64 (m, 1H, C*H*–$COCH_2$–), 4.25 (d, 1H, $J = 6.8$ Hz, C*H*–COPh), 7.12–8.07 (m, 10H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 23.2, 25.2, 26.8, 30.9, 35.7, 41.9, 41.9, 53.3, 58.3, 81.9,

125.7, 128.3, 128.3, 128.7, 129.0, 133.4, 137.6, 142.1, 200.8, 212.6; IR (neat) ν 3480, 1705, 1671 cm^{-1}; ESI-MS m/z 387 $(M+Na)^+$; HRMS Calcd for $C_{24}H_{28}O_3Na^+$: 387.1936. Found: 387.2097.

4.2.22. [(1S*,2R*,3aR*,6aR*)-2-Hydroxy-2-phenyl-octahydro-1-pentalenyl](phenyl)methanone (9a)

According to the general procedure, **9a** (77.5 mg, 51%) was obtained as colorless crystals by the reaction of **1a** (1.00 mmol) with **6a** (152 mg, 0.50 mmol). Spectral data of **9a** were identical to the authentic material [7d].

4.2.23. 1-[(1S*,2R*,3aR*,6aR*)-2-Hydroxy-2-methyl-octahydro-1-pentalenyl]-1-ethanone(cis 9b), 1-[(1S*,2S*,3aR*,6aR*)-2-hydroxy-2-methyloctahydro-1-pentalenyl]-1-ethanone(trans 9b)

According to the general procedure, **9b** (32.3 mg, 71%) was obtained as a mixture of diastereomers by the reaction of **1a** (0.50 mmol) with **6b** (45.0 mg, 0.25 mmol). The mixture was separated by silica gel column chromatography to give 2R^*-isomer (*cis* **9b**) (oil, first fraction) and 2S^*-isomer (*trans* **9b**) (oil, second fraction). Spectral data of **9b** were identical to the authentic sample [7d].

4.2.24. [(3aR*,4S*,5R*,6aR*)-5-Hydroxy-5-phenyl-hexahydro-1H-cyclopenta[c]furan-4-yl](phenyl)-methanone (9c)

According to the general procedure **9c** (52.4 mg, 68 %) was obtained as colorless crystals by the reaction of **1a** (0.50 mmol) with **6c** (76.5 mg, 0.25 mmol).

Mp 158.0–160.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, 1H, $J = 2.0$, 8.2, 13.0 Hz), 2.31 (dd, 1H, $J = 7.8$, 13.1 Hz), 3.03–3.16 (m, 2H), 3.31 (dd, 1H, $J = 5.5$, 9.7 Hz), 3.51 (dd, 1H, $J = 6.2$, 9.0 Hz), 3.71 (dd, 2H, $J = 9.2$, 13.4 Hz), 3.97 (dd, 1H, $J = 16.4$, 25.5 Hz), 5.19 (s, 1H), 7.02–7.81 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 43.7, 49.6, 50.6, 58.5, 72.0, 74.1, 87.4, 124.7, 127.0, 128.3, 128.5, 128.8, 134.0, 137.3, 143.5, 206.1; IR (KBr) ν 3398, 1671 cm^{-1}; ESI-MS m/z 331 $(M+Na)^+$; HRMS Calcd for $C_{20}H_{20}O_3Na^+$: 331.1310. Found: 331.1287.

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