Tandem Intramolecular Carbolithiation-Lithium/Zinc Transmetallation and Applications to Carbon−Carbon Bond-Forming Reactions

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Dedicated to Professor Armin de Meijere on the occasion of his 65th birthday

Keywords: Alkylation and acylation / Intramolecular carbolithiation / Lithium−zinc transmetallation / Michael reaction / Negishi reaction

Lithium/zinc transmetallation with the cyclic organolithium intermediate **3** (prepared by intramolecular carbolithiation of the initially formed organolithium **2**) gives the corresponding organozinc intermediate **5**. Copper- or palladium-promoted S_N2' reactions between compound **5** and allylic or propargylic halides, as well as arylation, vinylation, benzylation, acylation, and conjugate addition to α,β-unsaturated carbonyl compounds, afford (after hydrolysis) the expected compounds **7**–**15**, which are not accessible directly from the organolithium precursor **3** even with transition metal catalysis.

Introduction

Organolithium compounds are very useful intermediates in synthetic organic chemistry, since because of the high polarity of the carbon-lithium bond they are potential carbanions capable of reacting with different electrophiles under mild reaction conditions (low temperatures).[1] A special class of organolithium intermediates are those bearing a functionality,[2] as they are able to transfer the functionality to the electrophilic reagent in their reactions with electrophiles, so polyfunctionalized molecules can be prepared in only one synthetic operation. One problem associated with the generation of very reactive organolithium intermediates is that the lithiation step should be carried out at low temperature in order to avoid decomposition of the carbanionic intermediate. For that purpose, we have over the last few years been developing a methodology consisting of the use of lithium powder and a catalytic amount of an arene, with the most used electron-transfer agents being naphthalene and 4,4′-di-*tert*-butylbiphenyl (DTBB).[3,4] We have recently introduced a polymer-supported version of this arene-catalyzed lithiation, which allows us to reuse the polymer several times without losing any efficiency.[5] In our group we have used this methodology for: (a) generation of organolithium compounds starting from nonhalogenated materials,[6] (b) preparation of functionalized organolithium compounds by carbon-heteroatom bond cleavage,[2] including heterocyclic compounds,[7] (c) generation of polylithium synthons, mainly by halogen-lithium exchange from polychlorinated materials,[8] and (d) activation of other metals[9] such as nickel, and their use in reduction reactions.[10] In some cases, when the organolithium intermediate is too unstable, it is necessary to perform the lithiation in the presence of the electrophile (Barbier-type reaction conditions)[11] in order to avoid its decomposition. A very recent application of the arene-catalyzed lithiation was the generation of an unsaturated organolithium compound **2**, which can undergo intramolecular carbolithiation[12] to yield a new organolithium compound **3**. Further treatment of this intermediate with typical electrophiles, such as carbonyl compounds, affords the expected compounds **4**.[13] However, other processes such as S_N2' reactions, arylation, acylation, or conjugate addition are not possible, either with no reaction taking place or with the production of mixtures of compounds being observed. For these reasons we considered the possibility of transforming the intermediate **3** into an organozinc compound **5**[14] in order to study such reactions and to produce a new family of cyclopentane-derived compounds of type **6** (Scheme 1). Thus, in this paper we combine intramolecular carbolithiation with a lithium/zinc transmetallation to extend the reactivity of intermediate **3**.[15]

Results and Discussion

Once intermediate **3** had been generated by DTBB-catalyzed lithiation of 6-chlorohex-1-ene (**1**),[13] the excess of lithium powder was filtered off, and the resulting solution containing the intermediate **3** was added at 0 °C to a solu-

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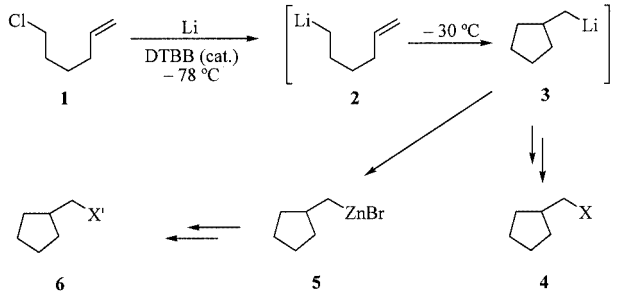
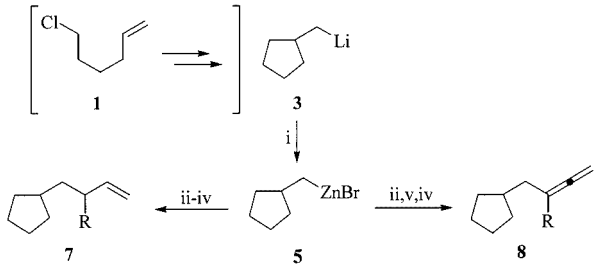
 DOI: 10.1002/ejoc.200400349



Scheme 1

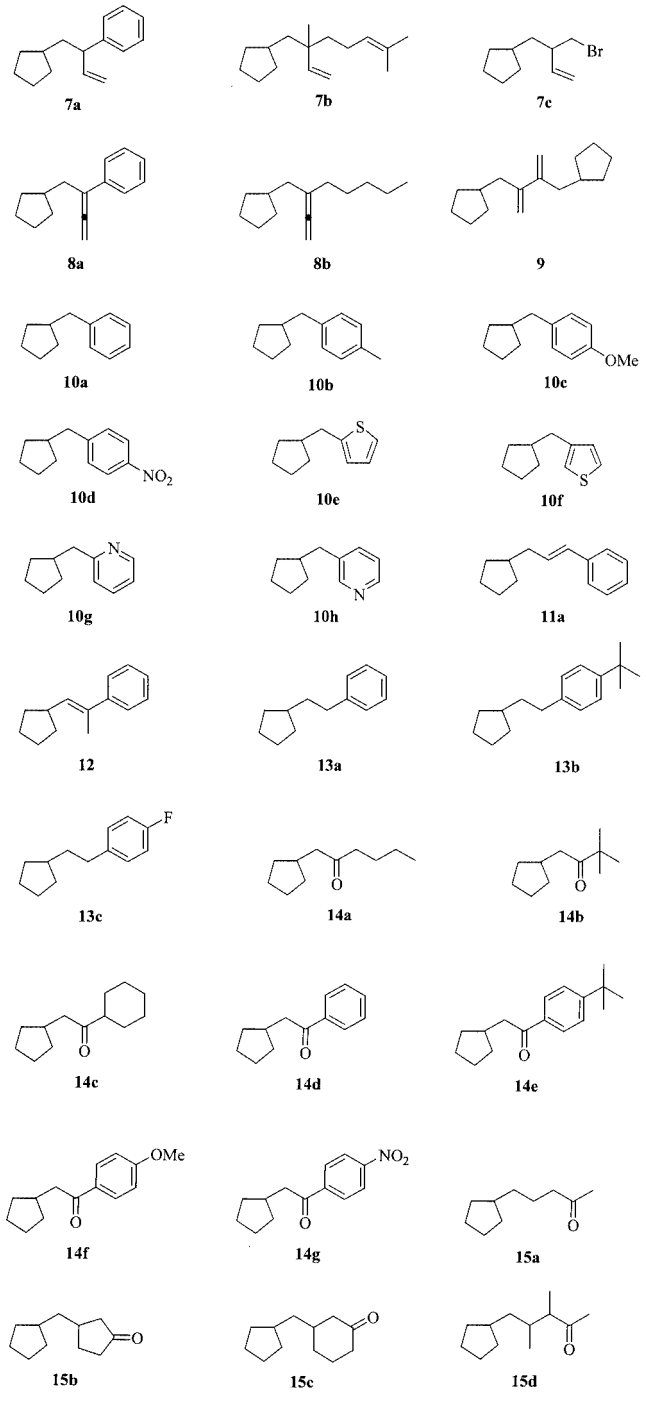
tion of zinc bromide (1.1 equiv.). After 15 min, copper(I) cyanide (1.1 equiv.) was added at the same temperature to the resulting solution of compound **5**, and the mixture was then treated with an allylic chloride or bromide, giving, after hydrolysis with 2 M hydrochloric acid, the corresponding product **7**, as the outcome of a clean S_N2' process (Scheme 2 and Scheme 3, Table 1, entries 1−3). The corresponding S_N2 products, which are the only ones obtained on direct treatment of intermediate **3** with the same electrophiles,[16] were never observed (GLC-MS) in the reaction crude mixtures.



Scheme 2. (i) $ZnBr_2$, THF, 0 °C, 15 min; (ii) CuCN·2LiCl, THF, 0 °C, 15 min; (iii) $RCH{=}CHCH_2X$ (X = Cl, Br), 0 °C, 2 h; (iv) 2 M HCl; (v) $RC{\equiv}CCH_2Cl$

An S_N2' process was also the only one observed when propargyl chlorides were used, compounds **8** being isolated under the same reaction conditions (Schemes 2 and 3, Table 1, entries 4 and 5). In the case of 1,4-dichlorobut-2-yne as electrophile (1:0.5 molar ratio), the obtained allene **8c** underwent a second S_N2' addition to give the corresponding 1,3-diene **9**[17] (Scheme 2 and Scheme 4, Table 1, entry 6). The same result was obtained with use of a stoichiometric amount of the electrophile, the excess of the starting compound being isolated unchanged after workup. On the other hand, intermediate **3** also mainly gives acetylene derivatives through S_N2 reactions when propargyl chlorides are used as electrophiles.[18,19]

We next studied the palladium-catalyzed arylation of the zinc intermediate **5**, the so-called Negishi-type reaction.[20,21] Thus, once compound **5** had been generated as shown above, it was treated with a catalytic amount (5 mol %) of the complex of palladium(II) acetate and tri-*tert*-butylphosphane in THF at room temperature, and the corresponding aryl bromide was then added, the resulting mixture being heated at reflux to give, after hydrolysis, the expected coupling products **10** (Scheme 3 and Scheme 5, Table 1, entries 7 and 9−11). No significant difference in yield was observed when phenyl iodide was used instead of phenyl bromide (Table 1, entries 7 and 8). Brominated heterocycles were also suitable electrophiles for the Negishi-type reaction, and the expected coupling products **10** were easily obtained under similar reaction conditions (Scheme 3 and Table 1, entries 12−15). Arylation of the lithium intermediate **3** also failed here, even in the presence of the palladium catalyst, so the presence of both the zinc and the

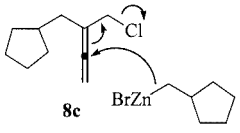


Scheme 3. Structures of compounds **7**−**15**

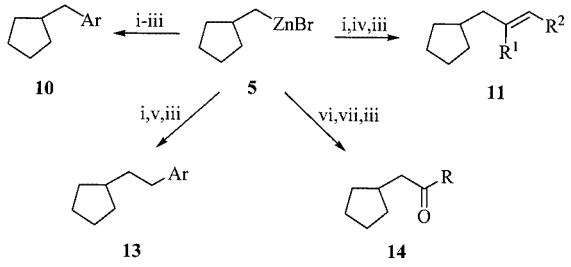
Table 1. Preparation of compounds **7**−**15**

Entry	Electrophile E	Additive (equiv.)	Reaction conditions T (°C)	time (h)	Product[a] No.	Yield (%)[b]
1	(*E*)-PhCH=CHCH$_2$Cl	CuCN·2LiCl (1.1)	0	2	**7a**	54
2	geranyl chloride	CuCN·2LiCl (1.1)	0	2	**7b**	53
3	(*E*)-BrCH$_2$CH=CHCH$_2$Br	CuCN·2LiCl (1.1)	0	2	**7c**	66
4	PhC≡CCH$_2$Cl	CuCN·2LiCl (1.1)	0	2	**8a**	45
5	C$_5$H$_{11}$C≡CCH$_2$Cl	CuCN·2LiCl (1.1)	0	2	**8b**	61
6	ClCH$_2$C≡CCH$_2$Cl	CuCN·2LiCl (1.1)	0	2	**9**	59[c]
7	PhBr	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10a**	46
8	PhI	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10a**	53
9	4-MeC$_6$H$_4$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10b**	52
10	4-MeOC$_6$H$_4$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10c**	60
11	4-O$_2$NC$_6$H$_4$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10d**	62
12	2-bromothiophene	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10e**	46
13	3-bromothiophene	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10f**	66
14	2-bromopyridine	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10g**	48
15	3-bromopyridine	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**10h**	53
16	(*E*)-PhCH=CHBr	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**11a**	39
17	CH$_2$=CPhBr	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**12**	56
18	PhCH$_2$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**13a**	44
19	4-*t*BuC$_6$H$_4$CH$_2$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**13b**	46
20	4-FC$_6$H$_4$CH$_2$Br	Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (0.05)	65	6	**13c**	30
21	BuCOCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14a**	54
22	*t*BuCOCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14b**	74
23	*c*-C$_6$H$_{11}$COCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14c**	82
24	PhCOCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14d**	60
25	4-*t*BuC$_6$H$_4$COCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14e**	54
26	4-MeOC$_6$H$_4$COCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14f**	61
27	4-O$_2$NC$_6$H$_4$COCl	PdCl$_2$(PPh$_3$)$_2$ (0.05)	0	3	**14g**	45
28	CH$_2$=CHCOMe	CuCN·2LiCl (1.1)[d]	0	3	**15a**	63
29	cyclopent-2-enone	CuCN·2LiCl (1.1)[d]	0	3	**15b**	62
30	cyclohex-2-enone	CuCN·2LiCl (1.1)[d]	0	3	**15c**	66
31	(*E*)-MeCH=CMeCOMe	CuCN·2LiCl (1.1)[d]	0	3	**15d**	31[e]

[a] All products were >95% pure (GLC and/or ^{1}H NMR). [b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on 6-chlorohex-1-ene (**1**) used as starting material for the generation of intermediates **3** and **5**. [c] Only 0.5 equiv. of the electrophile were used. [d] BF_3·OEt_2 (1.1 equiv.) was also used as additive. [e] A ca. 1:1 mixture of diastereomers was obtained (300 MHz ^{1}H NMR).



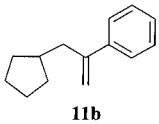
Scheme 4



Scheme 5. (i) Pd(OAc)$_2$(P*t*Bu$_3$)$_2$ (5%), THF, room temp., 10 min; (ii) ArX (X = Br, I), THF reflux, 6 h; (iii) 2 M HCl; (iv) BrR^{1}C=CHR^2, THF reflux, 6 h; (v) ArCH$_2$Br, THF reflux, 6 h; (vi) PdCl$_2$(PPh$_3$)$_2$, THF, 0 °C, 15 min; (vii) RCOCl, 0 °C to room temp., 2 h

palladium components is necessary for the reaction to take place.[21]

When a vinyl bromide was used under the same reaction conditions as employed for the Negishi reaction, the expected coupling products **11** were obtained (Schemes 3 and 5, Table 1, entry 16). With treatment with α-bromostyrene, however, the initially formed olefin **11b** underwent spontaneous isomerization under the reaction conditions, giving the corresponding product **12** (Scheme 3 and Table 1, entry 17).

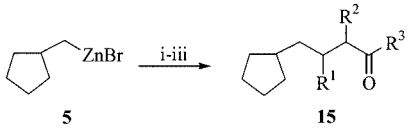


Palladium-promoted benzylation of the zinc intermediate **5** under the same reaction conditions as described above for the Negishi-type reaction gave the expected coupling products **13** (Schemes 3 and 5, and Table 1, entries 18−20). It is noteworthy that significant amounts of the corresponding dimers (dibenzylic products), resulting from self-coupling of the electrophile used, were obtained in these cases. These dimers were the only reaction products isolated for α-substi-

tuted benzylic bromides, such as α-methyl- and α-phenylbenzyl bromides, as well as for fluorenyl bromide.

We next studied the palladium-catalyzed acylation of intermediate **5** with different alkyl and aryl acyl chlorides at temperatures ranging between 0 °C and room temperature, in order to prepare the expected ketones **14** (Schemes 3 and 5, and Table 1, entries 21−27). In this case the palladium(II) chloride/triphenylphosphane (5%) complex was active enough for the reaction to take place. In no case the corresponding alcohol resulting from over-addition to the ketone **14** was detected. As is well known, this is the normal process when an alkyllithium, such as compound **3**, is treated with an acyl chloride, even under favorable stoichiometric conditions.[22]

In the final part of this study we investigated reactions between intermediate **5** and α,β-unsaturated ketones.[23] In this case it was not only necessary to use a stoichiometric amount of copper(I) cyanide to activate the organometallic reagent, but we also needed to activate the carbonyl compound with the boron trifluoride/diethyl ether complex.[24] Under these reaction conditions the expected 1,4-addition products **15** were isolated (Scheme 3 and Scheme 6, Table 1, entries 28−31) without any contamination with the corresponding 1,2-addition adducts, which were the main products when intermediate **3** was used in the absence of the copper and boron partners.[25]



5 **15**

Scheme 6. (i) CuCN·2LiCl, THF, 0 °C, 15 min; (ii) E = $R^1CHCR^2COR^3$, BF_3·OEt_2, THF, 0 °C; (iii) HCl/H_2O

Conclusion

Lithium/zinc transmetallation, after intramolecular carbolithiation, allows the reactivity of the corresponding cyclic organolithium intermediates to be expanded, to afford new reactions not possible through lithium chemistry alone, including S_N2' reactions, arylation, vinylation, benzylation, acylation, and conjugate addition. In all these processes the organozinc reagent **5** is activated with a transition metal such as copper or palladium. It is noteworthy that all yields given in this paper are relative to the starting chlorinated material **1**, and so include the processes of (a) lithiation, (b) carbolithiation, (c) lithium-zinc transmetallation, (d) transition metal-promoted coupling, and (e) final hydrolysis, suggesting that they can be considered rather good, this route being convenient for the generation of cyclopentane derivatives. In all cases variable amounts of methylcyclopentane, the result of metal-hydrogen exchange from intermediates **3** and/or **5**, are obtained as by-product (GLC), this compound being easily removable thanks to its high volatility.

Experimental Section

General: All reactions were carried out under argon. FT-IR spectra were obtained with a Nicolet Impact 400D spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker AC 300 instrument in $CDCl_3$ as solvent and with TMS as internal standard; chemical shifts (δ) are given in ppm, and coupling constants (*J*) are given in Hz. Low-resolution mass spectra (EI) were obtained at 70 eV with an Agilent 5973 Network spectrometer, fragment ions in *m*/*z* with relative intensities (%) in parentheses. High-resolution mass spectra were obtained by the service at the University of Alicante on a Finnigan MAT 95 S apparatus. The purities of volatile products and chromatographic analyses (GLC) were determined on an Agilent 6890 Series instrument equipped with a flame ionization detector and a 30 m capillary column (0.32 mm diam., 0.25 μm film thickness), with nitrogen (2 mL/min) as carrier gas, $T_{injector}$ = 275 °C, $T_{detector}$ = 300 °C, T_{column} = 60 °C (3 min) and 60−270 °C (15 °C/min). Thin layer chromatography (TLC) was carried out on Merck plastic sheets coated with 60 F_{254} silica gel. Column chromatography was carried out on Merck 63−200 μm silica gel. All starting materials and solvents were commercially available (Acros, Aldrich, Fluka) and were used as the best grade without further purification. Lithium powder was prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as already reported by us.[26] Zinc bromide was dried with a heating gun under reduced pressure (0.1 Torr) for 15 h before use. 3-Phenylpropargyl chloride was prepared by the reported procedure.[27]

S_N2' Reactions between Intermediate 5 and Allylic and Propargylic Halides. Isolation of Compounds 7−9. General Procedure: 6-Chlorohex-1-ene (0.138 mL, 1.0 mmol) was added at −30 °C under an argon atmosphere to a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL). The color disappeared after the substrate addition, the reaction mixture was stirred until the green color was regenerated (40 min), and the excess lithium was then filtered off under inert conditions. The resulting solution was added at 0 °C to a solution of zinc bromide (260 mg, 1.1 mmol) in THF (5 mL) and the color of the mixture changed to brown. A solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (100 mg, 1.1 mmol) and lithium chloride (93 mg, 2.2 mmol) in THF (5 mL)] was added to the resulting mixture, which then turned black. The solution was stirred for 10 min at 0 °C and the corresponding allylic or propargylic halide (1.1 mmol) was added. After 2 h stirring, the reaction mixture was hydrolyzed with water (10 mL), acidified (2 M HCl, 10 mL), and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NH_4Cl solution (2 × 15 mL) and dried over $MgSO_4$, and the solvents were evaporated (15 Torr) to yield a residue, which was purified by column chromatography (silica gel, hexane) to give compounds **7**−**9**. Structures and yields are given in Scheme 3 and Table 1; physical, spectroscopic and analytical data follow.

4-Cyclopentyl-3-phenyl-1-butene (7a): R_f = 0.69 (hexane). IR (film): $\tilde{\nu}$ = 3080, 3061, 3026 (C=CH), 1636, 1600, 1492 cm^{-1} (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (m, 11 H, 5 × CH_2, CH), 3.29 (m, 1 H, C*H*CH=), 5.01 (m, 2 H, CH_2=), 5.95 (ddd, *J* = 7.7, 10.2, 17.1 Hz, 1 H, CH=), 7.23 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 25.2, 32.6, 32.7 (4 × CH_2), 37.6 (CH), 42.1 (CH*C*H_2CH), 49.0 (*C*HCH=), 113.6 (CH_2=), 126.0, 127.6, 128.4, 144.8 (ArC), 142.7 (CH=) ppm. GC-LRMS: *m*/*z* (%) = 201 (1.0) [M^+ +1], 200 (6.0) [M^+], 118 (36), 117 (100), 115 (29), 104 (14), 91 (16), 55 (14). HRMS for $C_{15}H_{20}$: calcd. 200.1565; found 200.1574 [M^+].

3-(Cyclopentylmethyl)-3,7-dimethylocta-1,6-diene (7b): R_f = 0.81 (hexane). IR (film): $\tilde{\nu}$ = 3080, 3056 (C=CH), 1636 cm^{-1} (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.98 (s, 3 H, CH_2CCH_3), 1.02 (m, 2 H, CH_2), 1.29 (m, 2 H, CH_2), 1.49 (m with s at 1.58, 9 H, CH_3CCH_3, 3 × CH_2), 1.85 (m with s at 1.67, 8 H, CH_3CCH_3, 2 × CH_2, CH), 4.88 (dd, *J* = 1.4, 17.5 Hz, 1 H, CHH=), 4.95 (dd, *J* = 1.4, 10.8 Hz, 1 H, CHH=), 5.08 [def. t, *J* = 7.1 Hz, 1 H, $(CH_3)_2C=CH$], 5.73 (dd, *J* = 10.8, 17.5 Hz, 1 H, $CH_2=CH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 22.7 [$(CH_3)_2C=$], 22.9, 25.1 (3 × CH_2), 25.7 (CH_3CHCH_2), 35.0, 35.1 (2 × CH_2), 36.5 (CH_2CHCH_2), 40.1 (CH_2CCH_3), 41.6, 47.8 (2 × CH_2), 111.1 (=CH_2), 125.2 [$(CH_3)_2C=CH$], 130.9 [$(CH_3)_2C=CH$], 148.0 ($CH_2=CH$) ppm. GC-LRMS: *m*/*z* (%) = 220 (3.0) [M^+], 138 (13), 137 (12), 109 (70), 96 (13), 95 (83), 83 (43), 82 (61), 81 (69), 79 (10), 70 (12), 69 (100), 68 (21), 67 (52), 55 (78), 53 (16). HRMS for $C_{16}H_{28}$: calcd. 220.2191; found 220.2199 [M^+].

4-Bromo-3-(cyclopentylmethyl)-1-butene (7c): R_f = 0.67 (hexane). IR (film): $\tilde{\nu}$ = 3076 (C=CH), 1641 cm^{-1} (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (m, 11 H, 5 × CH_2, CH_2CHCH_2), 2.41 (m, 1 H, $CHCH_2Br$), 3.35 (d, *J* = 2.8 Hz, 1 H, BrCHH), 3.37 (d, *J* = 2.3 Hz, 1 H, BrCHH), 5.10 (m, 2 H, CH_2=), 5.62 (m, 1 H, CH=) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.06, 25.09, 32.1, 33.1 (4 × CH_2), 37.3 (CH_2CHCH_2), 38.6, 39.5 (2 × CH_2), 44.9 ($CHCH_2Br$), 116.5 (CH_2=), 139.8 (CH=) ppm. GC-LRMS: *m*/*z* (%) = 189 (1.3) [$M^+ - (CH=CH_2)$], 137 (12), 123 (19), 109 (11), 95 (33), 83 (55), 82 (68), 81 (68), 79 (15), 69 (28), 68 (19), 67 (87), 55 (100), 54 (46), 53 (37). HRMS for $C_8H_{12}Br$: calcd. 189.0279; found 189.0067 [$M^+ - (CH=CH_2)$].

4-Cyclopentyl-3-phenyl-1,2-butadiene (8a): R_f = 0.70 (hexane). IR (film): $\tilde{\nu}$ = 3059, 3027 (C=C=C−H), 1940 cm^{-1} (C=C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (m, 2 H, CH_2), 1.56 (m, 4 H, 2 × CH_2), 1.81 (m, 2 H, CH_2), 2.10 (sept, *J* = 7.6 Hz, 1 H, CH), 2.41 (t, *J* = 3.2 Hz, 1 H, CHHC=C=), 2.43 (t, *J* = 3.5 Hz, 1 H, CHHC=C=), 5.04 (d, *J* = 3.0 Hz, 1 H, CHH=), 5.05 (d, *J* = 3.1 Hz, 1 H, CHH=), 7.18 (t, *J* = 7.3 Hz, 1 H, ArH), 7.30 (m, 2 H, ArH), 7.40 (d, *J* = 7.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 32.7, 36.4 (5 × CH_2), 38.2 (CH), 77.6 (CH_2=), 104.6 ($CH_2=C=C$), 126.0, 126.5, 128.3, 136.6 (ArC), 209.2 ($CH_2=C=C$) ppm. GC-LRMS: *m*/*z* (%) = 199 (0.7) [M^+ +1], 198 (4.1) [M^+], 131 (14), 130 (100), 129 (72), 128 (28), 127 (11), 115 (49), 91 (11). HRMS for $C_{15}H_{18}$: calcd. 198.1409; found 198.1406 [M^+].

3-(Cyclopentylmethyl)-1,2-octadiene (8b): R_f = 0.88 (hexane). IR (film): $\tilde{\nu}$ = 3046 (C=C=C−H), 1957 cm^{-1} (C=C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 3 H, CH_3), 1.56 (m, 19 H, 9 × CH_2, CH), 4.62 (m, 2 H, $=CH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.6, 25.3, 27.3, 31.6, 32.2, 32.7, 39.1 (9 × CH_2), 38.1 (CH), 74.8 ($C=C=CH_2$), 102.9 ($C=C=CH_2$), 206.3 ($C=C=CH_2$) ppm. GC-LRMS: *m*/*z* (%) = 192 (0.7) [M^+], 121 (43), 109 (15), 107 (24), 95 (42), 94 (18), 93 (35), 91 (18), 82 (12), 81 (34), 80 (14), 79 (39), 77 (16), 69 (31), 68 (100), 67 (69), 55 (23), 53 (14). HRMS for $C_{14}H_{24}$: calcd. 192.1878; found 192.1860 [M^+].

2,3-Bis(cyclopentylmethyl)-1,3-butadiene (9):[17] R_f = 0.85 (hexane). IR (film): $\tilde{\nu}$ = 3088 (C=CH), 1629, 1592 cm^{-1} (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13, 1.60, 1.98 (3 m, 18 H, 8 × CH_2, 2 × CH), 2.22 (d, *J* = 7.3 Hz, 4 H, 2 × CH_2C=), 4.88 (s, 2 H, =CH_2), 5.03 (s, 2 H, =CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 32.5, 40.9 (10 × CH_2), 38.4 (2 × CH), 112.0 (2 × =CH_2), 147.7 (2 × C=CH_2) ppm. GC-LRMS: *m*/*z* (%) = 219 (1.2) [M^+ +1], 218 (5.5) [M^+], 150 (30), 149 (44), 136 (28), 135 (83), 121 (48), 109 (16), 108 (53), 107 (91), 104 (13), 95 (33), 94 (23), 93 (55), 91 (38), 84 (30), 83 (35), 82 (99), 81 (43), 80 (19), 79 (54), 77 (26), 69 (54), 68 (28), 67 (100), 66 (20), 65 (15), 55 (31), 53 (25). HRMS for $C_{16}H_{26}$: calcd. 218.2035; found 218.2035 [M^+].

Arylation, Vinylation, and Benzylation of Intermediate 5. Isolation of Compounds 10−13. General Procedure: 6-Chlorohex-1-ene (0.138 mL, 1.0 mmol) was added at −30 °C under an argon atmosphere to a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL). The color disappeared after the substrate addition, the reaction mixture was stirred until the green color was regenerated (40 min), and the lithium excess was then filtered off under inert conditions. The resulting solution was added at room temperature to a solution of zinc bromide (260 mg, 1.1 mmol) in THF (5 mL), and the color of the mixture changed to brown. A solution of $Pd(OAc)_2(PtBu_3)_2$ [prepared by dissolving palladium(II) acetate (11.3 mg, 0.05 mmol) and tri-*tert*-butylphosphane (22 mg, 0.1 mmol) in THF (7 mL)] was added to the resulting mixture, and the corresponding aryl halide (1.1 mmol) was then added. The mixture was heated at reflux for 6 h and was then hydrolyzed with water (10 mL), acidified (2 M HCl, 10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NH_4Cl solution (2 × 15 mL) and dried over $MgSO_4$. The solvents were evaporated (15 Torr) to yield a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **10−13**. Structures and yields are given in Scheme 3 and Table 1; physical, spectroscopic and analytical data follow.

(Cyclopentylmethyl)benzene (10a):[28] R_f = 0.62 (hexane). IR (film): $\tilde{\nu}$ = 3084, 3062, 3026 (ArC−H), 1603, 1495 cm^{-1} (ArC−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (m, 2 H, CH_2), 1.60 (m, 6 H, 3 × CH_2), 2.08 (def. sept, *J* = 7.6 Hz, 1 H, CH), 2.60 (d, *J* = 7.3 Hz, 2 H, $ArCH_2$), 7.21 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 32.4 (4 × CH_2), 42.0 (CH), 42.1 (CH_2), 125.5, 128.1, 128.8, 142.4 (ArC) ppm. GC-LRMS: *m*/*z* (%) = 161 (2.9) [M^+ + 1], 160 (20.2) [M^+], 92 (100), 91 (52), 69 (19), 65 (10). HRMS for $C_{12}H_{16}$: calcd. 160.1252; found 160.1260 [M^+].

***p*-(Cyclopentylmethyl)toluene (10b):** R_f = 0.71 (hexane). IR (film): $\tilde{\nu}$ = 3047, 3018, 3003 (ArC−H), 1514 cm^{-1} (ArC−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (m, 2 H, CH_2), 1.59 (m, 6 H, 3 × CH_2), 2.05 (sept, *J* = 7.6 Hz, 1 H, $CHCH_2$), 2.30 (s, 3 H, CH_3), 2.55 (d, *J* = 7.5 Hz, 2 H, $ArCH_2$), 7.06 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0 (CH_3), 24.9, 32.4, 41.6 (5 × CH_2), 42.1 ($CHCH_2$), 128.6, 128.8, 134.8, 139.3 (ArC) ppm. GC-LRMS: *m*/*z* (%) = 175 (2.6) [M^+ +1], 174 (26.8) [M^+], 106 (86), 105 (100), 91 (23). HRMS for $C_{13}H_{18}$: calcd. 174.1409; found 174.1406 [M^+].

***p*-(Cyclopentylmethyl)anisole (10c):**[29] R_f = 0.26 (hexane). IR (film): $\tilde{\nu}$ = 3060, 3030 (ArC−H), 1612, 1583, 1512 (ArC−C), 1246, 1040 cm^{-1} (C−O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (m, 2 H, CH_2), 1.53 (m, 2 H, CH_2), 1.67 (m, 4 H, 2 × CH_2), 2.04 (def. sept, *J* = 7.5 Hz, 1 H, CH_2CH), 2.54 (d, *J* = 7.5 Hz, 2 H, $ArCH_2$), 3.78 (s, 3 H, OCH_3), 6.81 (d, *J* = 8.6 Hz, 2 H, 2 × ArH), 7.08 (d, *J* = 8.4 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 32.4 (4 × CH_2), 41.1 ($ArCH_2$), 42.2 (CH), 55.2 (CH_3), 113.5, 129.6, 134.5, 157.5 (6 × ArC) ppm. GC-LRMS: *m*/*z* (%) = 191 (1.2) [M^+ + 1], 190 (8.6) [M^+], 122 (13), 121 (100).

1-(Cyclopentylmethyl)-*p*-nitrobenzene (10d):[30] R_f = 0.35 (hexane). IR (film): $\tilde{\nu}$ = 3103, 3077, 3048 (C=CH), 1597 (C=C), 1517, 1345 cm^{-1} (NO_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (m, 2 H, CH_2), 1.63 (m, 6 H, 3 × CH_2), 2.10 (def. sept, *J* = 7.7 Hz, 1 H, CH), 2.72 (d, *J* = 7.5 Hz, 2 H, $ArCH_2$), 7.32 (d, *J* = 8.7 Hz, 2 H, ArH),

8.13 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 32.4, 41.6 (5 × CH_2), 41.9 (CH), 123.4, 129.4, 146.1, 150.3 (ArC) ppm. GC-LRMS: m/z (%) = 206 (0.77) [M^+ +1], 205 (5.62) [M^+], 137 (100), 115 (10), 107 (17), 91 (11), 90 (13), 69 (40). HRMS for $C_{12}H_{15}NO_2$: calcd. 205.1103; found 205.1110 [M^+].

2-(Cyclopentylmethyl)thiophene (10e):[31] R_f = 0.66 (hexane). IR (film): $\tilde{\nu}$ = 3106, 3070, 3045 cm^{-1} (ArC−H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (m, 2 H, CH_2), 1.57 (m, 4 H, 2 × CH_2), 1.78 (m, 2 H, CH_2), 2.14 (sept, J = 7.6 Hz, 1 H, CH), 2.81 (d, J = 7.3 Hz, 2 H, ArCH_2), 6.77 (d, J = 3.4 Hz, 1 H, ArH), 6.91 (dd, J = 3.4, 5.1 Hz, 1 H, ArH), 7.10 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 32.4, 36.1 (5 × CH_2), 42.1 (CH), 122.8, 124.3, 126.5, 145.2 (4 × ArC) ppm. GC-LRMS: m/z (%) = 167 (3.2) [M^+ +1], 166 (24.5) [M^+], 98 (60), 97 (100), 69 (10).

3-(Cyclopentylmethyl)thiophene (10f): R_f = 0.81 (hexane). IR (film): $\tilde{\nu}$ = 3104, 3072, 3048, 1536 cm^{-1} (ArC−H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (m, 2 H, CH_2), 1.62 (m, 6 H, 3 × CH_2), 2.10 (sept, J = 7.6 Hz, 1 H, CHCH$_2$), 2.62 (d, J = 7.4 Hz, 2 H, CHCH_2), 6.92 (m, 2 H, SCH=CCH), 7.21 (dd, J = 3.0, 4.8 Hz, 1 H, SCH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 32.6, 36.4 (5 × CH_2), 41.1 (CH_2CH), 120.2, 124.8, 128.6, 142.7 (ArC). GC-LRMS: m/z (%) = 167 (1.3) [M^+ +1], 166 (11.7) [M^+], 98 (100), 97 (66). HRMS for $C_{10}H_{14}S$: calcd. 166.0816; found 166.0823 [M^+].

2-(Cyclopentylmethyl)pyridine (10g):[32] R_f = 0.16 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3065, 3007 (ArC−H), 1591, 1473 cm^{-1} (ArC−C and C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (m, 2 H, CH_2), 1.63 (m, 6 H, 3 × CH_2), 2.27 (sept, J = 7.7 Hz, 1 H, CH), 2.79 (d, J = 7.5 Hz, 2 H, ArCH_2), 7.10 (m, 2 H, 2 × ArH), 7.57 (def. t, J = 7.6 Hz, 1 H, ArH), 8.52 (d, J = 4.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 32.3 (4 × CH_2), 40.5 (CH), 44.2 (CH_2Ar), 120.7, 122.9, 136.0, 149.0, 161.9 (5 × ArC) ppm. GC-LRMS: m/z (%) = 161 (2.1) [M^+], 160 (6), 132 (9), 118 (7), 94 (9), 93 (100).

3-(Cyclopentylmethyl)pyridine (10h):[33] R_f = 0.10 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3081, 3050, 3027 (ArC−H), 1574, 1477 cm^{-1} (ArC−C and C=N). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (m, 2 H, CH_2), 1.62 (m, 6 H, 3 × CH_2), 2.07 (sept, J = 7.7 Hz, 1 H, CH), 2.60 (d, J = 7.5 Hz, 2 H, ArCH_2), 7.19 (dd, J = 4.8, 7.7 Hz, 1 H, ArH), 7.48 (def. d, J = 7.7 Hz, 1 H, ArH), 8.44 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 32.2 (4 × CH_2), 39.0 (CH_2Ar), 41.6 (CH), 123.1, 136.1, 137.4, 147.0, 150.0 (5 × ArC) ppm. GC-LRMS: m/z (%) = 161 (24.9) [M^+], 94 (14), 93 (100), 92 (12), 69 (14).

3-Cyclopentyl-1-phenyl-1-propene (11a):[34] R_f = 0.59 (hexane). IR (film): $\tilde{\nu}$ = 3081, 3059, 3024 (C=CH), 1598, 1496 cm^{-1} (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (m, 2 H, CH_2), 1.57 (m, 4 H, 2 × CH_2), 1.77 (m, 2 H, CH_2), 1.93 (sept, J = 7.5 Hz, 1 H, CH), 2.20 (t, J = 6.9 Hz, 2 H, CHCH_2), 6.22 (dt, J = 7.0, 15.8 Hz, 1 H, ArCH=CH), 6.36 (d, J = 15.8 Hz, 1 H, ArCH=CH), 7.17 (def. t, J = 7.0 Hz, 1 H, ArH), 7.30 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.1, 32.3, 39.4 (5 × CH_2), 40.0 (CHCH$_2$), 125.9, 126.7, 128.4, 130.1, 130.5, 137.9 (8C, ArCH=CH) ppm. GC-LRMS: m/z (%) = 186 (16.5) [M^+], 118 (32), 117 (100), 115 (35), 104 (85), 91 (19).

1-Cyclopentyl-2-phenyl-1-propene (12): R_f = 0.61 (hexane). IR (film): $\tilde{\nu}$ = 3080, 3056, 3023 (C=CH), 1599, 1493 cm^{-1} (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (m, 2 H, CH_2), 1.65 (m, 4 H, 2 × CH_2), 1.87 (m, 2 H, CH_2), 2.05 (s, 3 H, CH_3), 2.79 (sext, J = 8.3 Hz, 1 H, CH), 5.72 (d, J = 8.9 Hz, 1 H, CH=), 7.19, 7.32, 7.39 (3m, 2 H, 2H and 1H respectively, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.9 (CH_3), 25.4, 33.6 (4 × CH_2), 39.7 (CH), 125.5, 126.3, 128.1, 143.9 (ArC), 133.1 (C=), 134.2 (CH=) ppm. GC-LRMS: m/z (%) = 186 (42.8) [M^+], 171 (29), 157 (18), 144 (18), 143 (55), 142 (15), 141 (19), 130 (19), 129 (90), 128 (61), 127 (16), 119 (12), 118 (100), 117 (36), 115 (37), 105 (33), 103 (15), 91 (41), 78 (10), 77 (21), 51 (11). HRMS for $C_{14}H_{18}$: calcd. 186.1409; found 186.1404 [M^+].

(2-Cyclopentylethyl)benzene (13a):[35] R_f = 0.75 (hexane). IR (film): $\tilde{\nu}$ = 3085, 3062, 3026 (ArC−H), 1603, 1496 cm^{-1} (ArC−C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (m, 2 H, CH_2), 1.57 (m, 6 H, 3 × CH_2), 1.78 (m, 4 H, 2 × CH_2), 2.61 (t, J = 7.9 Hz, 2 H, PhCH_2), 7.16, 7.27 (2m, 3H and 2H respectively, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 32.6, 35.1, 38.1 (6 × CH_2), 39.6 (CHCH$_2$), 125.5, 128.2, 128.3, 143.1 (ArC) ppm. GC-LRMS: m/z (%) = 174 (16.9) [M^+], 92 (100), 91 (43), 83 (11), 55 (19). HRMS for $C_{13}H_{18}$: calcd. 174.1409; found 174.1406 [M^+].

1-*tert*-Butyl-4-(cyclopentylethyl)benzene (13b): R_f = 0.76 (hexane). IR (film): $\tilde{\nu}$ = 3091, 3054, 3022 cm^{-1} (ArC−H). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (m, 2 H, CH_2), 1.31 (s, 9 H, 3 × CH_3), 1.57 (m, 6 H, 3 × CH_2), 1.80 (m, 3 H, CH, CH_2), 2.59 (t, J = 8.0 Hz, 2 H, ArCH_2), 7.12 (d, J = 8.1 Hz, 2 H, 2 × ArH), 7.29 (d, J = 8.3 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (CH_2), 31.4 (3 × CH_3), 32.6 (CH_2), 34.3 [C(CH_3)$_3$], 34.6, 38.1 (2 × CH_2), 39.7 (CH), 125.1, 128.0, 140.0, 148.2 (6 × ArC) ppm. GC-LRMS: m/z (%) = 230 (12.6) [M^+], 216 (17), 215 (100), 147 (11), 117 (16), 91 (10), 55 (17). HRMS for $C_{17}H_{26}$: calcd. 230.2035; found 230.2010 [M^+].

1-(2-Cyclopentylethyl)-4-fluorobenzene (13c): R_f = 0.72 (hexane). IR (film): $\tilde{\nu}$ = 3069, 3039 (ArC−H), 1600, 1509 (ArC−C), 1222 cm^{-1} (ArC−F). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (m, 2 H, CH_2), 1.55 (m, 6 H, 3 × CH_2), 1.75 (m, 3 H, CH, CH_2), 2.58 (t, J = 8.0 Hz, 2 H, ArCH_2), 6.94 (tt, J = 2.1, 8.7 Hz, 2 H, 2 × ArH), 7.12 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 32.6, 34.3, 38.2 (6 × CH_2), 39.5 (CH), 114.7, 115.0, 129.5, 129.6, 138.55, 138.60, 159.5, 162.7 (6 × ArC) ppm. GC-LRMS: m/z (%) = 193 (3.3) [M^+ + 1], 192 (22.8) [M^+], 110 (97), 109 (100), 83 (47), 55 (37). HRMS for $C_{13}H_{17}F$: calcd. 192.1314; found 192.1325 [M^+].

Acylation of Intermediate 5. Isolation of Ketones 14. General Procedure: 6-Chlorohex-1-ene (0.138 mL, 1.0 mmol) was added at −30 °C under an argon atmosphere to a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL). The color disappeared after the substrate addition, the reaction mixture was stirred until the green color was regenerated (40 min), and the excess lithium was then filtered off under inert conditions. The resulting solution was added at 0 °C to a solution of zinc bromide (300 mg, 1.3 mmol) in THF (5 mL), the color of the mixture changing to brown. A solution of $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) in THF (7 mL) was added to the resulting mixture, which was stirred for 10 min at 0 °C. The corresponding acid chloride (1.1 mmol) was then added. After 2 h stirring, the reaction mixture was hydrolyzed with water (10 mL), acidified (2 M HCl, 10 mL), and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NH_4Cl solution (2 × 15 mL) and dried over $MgSO_4$, and the solvents were evaporated (15 Torr) to yield a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate) to give compounds **14**. Structures and yields are given in Scheme 3 and Table 1; physical, spectroscopic and analytical data follow.

1-Cyclopentyl-2-pentanone (14a): R_f = 0.55 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1713 cm^{-1} (C=O). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.07 (m, 2 H, CH_2), 1.30 (sext, *J* = 7.4 Hz, 2 H, CH_3CH_2), 1.57 (m, 6 H, 3 × CH_2), 1.81 (m, 2 H, CH_2), 2.22 (sept, *J* = 7.7 Hz, 1 H, CH), 2.40 (m, 4 H, CH_2COCH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 22.3, 24.9, 25.9, 25.8, 32.6 (6 × CH_2), 35.6 (CH), 42.7, 49.1 (CH_2COCH_2), 211.5 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 169 (2.3) [M^+ + 1], 168 (17.4) [M^+], 111 (45), 101 (47), 100 (11), 85 (51), 83 (100), 67 (11), 59 (39), 58 (86), 57 (63), 55 (70). HRMS for $C_{11}H_{20}O$: calcd. 168.1514; found 168.1499 [M^+].

1-Cyclopentyl-3,3-dimethyl-2-butanone (14b):[36] R_f = 0.70 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1076 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (m, 2 H, CH_2), 1.12 (s, 9 H, 3 × CH_3), 1.58 (m, 4 H, 2 × CH_2), 1.82 (m, 2 H, CH_2), 2.26 (def. sept, *J* = 7.7 Hz, 1 H, CH), 2.51 (d, *J* = 6.9 Hz, 2 H, CH_2CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (2 × CH_2), 26.3 (3 × CH_3), 32.6 (2 × CH_2), 35.2 (CH), 42.7 (CH_2C=O), 43.9 [$C(CH_3)_3$], 215.9 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 168 (6.6) [M^+], 111 (59), 83 (100), 57 (57), 55 (39). HRMS for $C_{11}H_{20}O$: calcd. 168.1514; found 168.1507 [M^+].

Cyclohexyl Cyclopentylmethyl Ketone (14c): R_f = 0.57 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1708 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (m, 2 H, CH_2), 1.30 (m, 6 H, 3 × CH_2), 1.58 (m, 4 H, 2 × CH_2), 1.80 (m, 6 H, 3 × CH_2), 2.25 (m, 2 H, 2 × CH), 2.45 (d, *J* = 7.2 Hz, 2 H, CH_2CO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 25.6, 25.8, 28.4, 32.6 (9 × CH_2), 35.3 ($CHCH_2C$=O), 46.9 (CH_2C=O), 50.8 (CHC=O), 214.2 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 195 (1.4) [M^+ + 1], 194 (9.5) [M^+], 127 (14), 126 (15), 111 (48), 83 (100), 55 (50). HRMS for $C_{13}H_{22}O$: calcd. 194.1671; found 194.1671 [M^+].

α-Cyclopentylacetophenone (14d):[37] R_f = 0.69 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3063, 3027 (C=CH), 1599, (C=C), 1688 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18 (m, 2 H, CH_2), 1.60 (m, 4 H, 2 × CH_2), 1.88 (m, 2 H, CH_2), 2.39 (def. sept, *J* = 7.6 Hz, 1 H, CH), 2.99 (d, *J* = 7.0 Hz, 2 H, CH_2CO), 7.45, 7.55, 7.96 (3m, 2 H, 1 H and 2 H respectively, 5 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 32.7 (4 × CH_2), 36.0 (CH), 44.8 (CH_2C=O), 128.1, 128.5, 132.8, 137.2 (ArC), 200.4 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 189 (1.0) [M^+ +1], 188 (6.2) [M^+], 121 (17), 120 (87), 105 (100), 77 (45), 51 (11).

4-*tert*-Butyl-α-cyclopentylacetophenone (14e): R_f = 0.61 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3088, 3056, 3034 (C=CH), 1717, 1681 (C=O), 1606 cm^{-1} (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (m, 2 H, CH_2), 1.33 (s, 9 H, 3 × CH_3), 1.59 (m, 4 H, 2 × CH_2), 1.85 (m, 2 H, CH_2), 2.96 (d, *J* = 7.0 Hz, 2 H, $ArCOCH_2$), 7.46 (m, 2 H, 2 × ArH), 7.90 (m, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (2 × CH_2), 31.0 (3 × CH_3), 32.6 (2 × CH_2), 36.0 (CH_2CH), 44.6 ($ArCOCH_2$), 125.1, 128.0, 134.6, 166.6 (6 × ArC), 199.8 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 245 (0.2) [M^+ +1], 244 (0.1) [M^+], 187 (18), 176 (44), 162 (12), 161 (100), 118 (11). HRMS for $C_{16}H_{21}O$: calcd. 229.1592; found 229.1558 [M^+ − CH_3].

α-Cyclopentyl-4-methoxyacetophenone (14f):[38] R_f = 0.33 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3074, 3053 (C=CH), 1711, 1676 (C=O), 1258, 1031 cm^{-1} (ArC−O−C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (m, 2 H, CH_2), 1.58 (m, 4 H, 2 × CH_2), 1.86 (m, 2 H, CH_2), 2.37 (def. sept, *J* = 7.7 Hz, 1 H, CH), 2.93 (d, *J* = 7.2 Hz, 2 H, CH_2CO), 3.85 (s, 3 H, OCH_3), 6.92 (d, *J* = 8.9 Hz, 2 H, 2 × ArH), 7.94 (d, *J* = 8.9 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.8, 32.6 (4 × CH_2), 36.2 (CH), 44.3 (CH_2), 55.3 (OCH_3), 113.5, 130.2, 131.4, 163.1 (6C, ArC), 198.9 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 218 (1.0) [M^+], 150 (78), 135 (100), 92 (14), 77 (18). HRMS for $C_{14}H_{18}O_2$: calcd. 218.1307; found 218.1325 [M^+].

α-Cyclopentyl-4-nitroacetophenone (14g): R_f = 0.40 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 3108, 3077, 3049 (C=CH), 1736, 1693 (C=O), 1602 (C=C), 1526, 1346, 1318 cm^{-1} (NO_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (m, 2 H, CH_2), 1.62 (m, 4 H, 2 × CH_2), 1.89 (m, 2 H, CH_2), 2.39 (def. sept, *J* = 7.7 Hz, 1 H, CH), 3.05 (d, *J* = 7.0 Hz, 2 H, CH_2CO), 8.11 (d, *J* = 8.9 Hz, 2 H, 2 × ArH), 8.31 (d, *J* = 8.6 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 32.6 (4 × CH_2), 35.7 (CH), 45.3 (CH_2), 55.3 (OCH_3), 123.8, 129.0, 141.5, 150.1 (ArC), 198.6 (1C=O) ppm. GC-LRMS: *m*/*z* (%) = 233 (0.9) [M^+], 216 (13), 167 (24), 166 (32), 165 (100), 150 (71), 120 (10), 104 (43), 92 (17), 76 (25), 67 (16), 55 (19). HRMS for $C_{13}H_{15}NO_3$: calcd. 233.1052; found 233.1030 [M^+].

Conjugate Addition of Intermediate 5 to α,β-Unsaturated Ketones. Isolation of Compounds 15. General Procedure: 6-Chlorohex-1-ene (0.138 mL, 1.0 mmol) was added at −30 °C under an argon atmosphere to a stirred green suspension of lithium powder (40 mg, 5.8 mmol) and DTBB (13.3 mg, 0.05 mmol) in THF (4 mL). The color disappeared after the substrate addition, the reaction mixture was stirred until the green color was regenerated (40 min), and the excess lithium was then filtered off under inert conditions. The resulting solution was added at 0 °C to a solution of zinc bromide (260 mg, 1.1 mmol) in THF (5 mL), the color of the mixture changing to brown. A solution of CuCN·2LiCl [prepared by dissolving copper(I) cyanide (100 mg, 1.1 mmol) and lithium chloride (93 mg, 2.2 mmol) in THF (5 mL)] was added to the resulting mixture, which then changed to a black color. The solution was stirred at 0 °C for 10 min, and a mixture of the electrophile (1.1 mmol) and $BF_3·Et_2O$ (2.2 mmol) was added. After 2 h stirring the reaction mixture was hydrolyzed with water (10 mL), acidified (2 M HCl, 10 mL), and extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with saturated NH_4Cl solution (2 × 15 mL) and dried over $MgSO_4$. The solvents were evaporated (15 Torr) to yield a residue, which was purified by column chromatography (silica gel, hexane) to give compounds **15**. Structures and yields are given in Scheme 3 and Table 1; physical, spectroscopic and analytical data follow.

5-Cyclopentyl-2-pentanone (15a):[39] R_f = 0.35 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1717 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (m, 4 H, 2 × CH_2CH_2CH), 1.54 (m, 5 H, $CHCH_2CH_2CH_2C$=O), 1.73 (m, 4 H, 2 × CH_2CH_2CH), 2.14 (s, 3 H, CH_3), 2.42 (t, *J* = 7.4 Hz, 2 H, CH_2C=O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.1, 25.1 (3 × CH_2), 29.8 (CH_3), 32.6, 35.6 (3 × CH_2), 39.9 (CH), 44.0 (CH_2C=O), 209.5 (C=O). GC-LRMS: *m*/*z* (%) = 154 (1.8) [M^+], 121 (13), 97 (16), 96 (20), 94 (16), 71 (22), 69 (18), 67 (25), 59 (21), 58 (100), 55 (24).

3-(Cyclopentylmethyl)cyclopentan-1-one (15b):[40] R_f = 0.34 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09 (m, 2 H, CH_2), 1.54 (m, 8 H, 4 × CH_2), 1.80 (m, 4 H, 2 × CH_2), 2.20 (m, 4 H, 2 × CH, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.01, 25.04 (2 × CH_2CH_2CH), 29.8 (CH_2), 32.8, 32.9 (2 × CH_2CH_2CH), 36.4, 38.5 (2 × CH), 38.6, 42.2, 45.6 (3 × CH_2), 220.1 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 167 (1.6) [M^+ +1], 166 (13.3) [M^+], 137 (11), 125 (30), 122 (11), 83 (100), 81 (15), 69 (27), 68 (16), 67 (33), 56 (13), 55 (44). HRMS for $C_{11}H_{18}O$: calcd. 166.1358; found 166.1356 [M^+].

3-(Cyclopentylmethyl)cyclohexan-1-one (15c): R_f = 0.27 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1713 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.07 (m, 2 H, CH_2), 1.22−2.09 (m, 16 H,

8 × CH_2), 2.34 (m, 2 H, 2 × CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (2 × CH_2), 25.3 (CH_2), 31.5, 32.7, 32.8 (3 × CH_2), 37.0 (CH), 38.2 (*C*HCH_2C=O), 41.5 (CH*C*H_2CH), 43.2 (CH_2*C*H_2C=O), 48.4 (CH*C*H_2C=O), 212.3 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 180 (2.6) [M^+], 98 (10), 97 (100), 69 (14), 67 (16), 55 (26). HRMS for $C_{12}H_{20}O$: calcd. 180.1514; found 180.1509 [M^+].

5-Cyclopentyl-3,4-dimethylpentan-2-one (15d): (diastereomeric mixture ca. 1:1) R_f = 0.48 (hexane/ethyl acetate, 9:1). IR (film): $\tilde{\nu}$ = 1711 cm^{-1} (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.7 Hz, 3 H, CHCH_3), 0.92 (d, *J* = 6.7 Hz, 3 H, CHCH_3), 0.97 (d, *J* = 7.0 Hz, 3 H, CHCH_3), 1.01 (d, *J* = 6.9 Hz, 3 H, CHCH_3), 1.08 (m, 4 H, 2 × CH_2), 1.56 (m, 10 H, 4 × CH_2, 2 × CH), 1.81 (m, 10 H, 4 × CH_2, 2 × CH), 2.13 (s, 6 H, 2 × COCH_3), 2.42 (m, 2 H, 2 × CH cycle) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6, 12.1, 15.2, 17.9 (4 × CH_3), 25.0 (2 × CH_2), 28.4, 28.8 (2 × CO*C*H_3), 31.9, 32.3, 33.0, 33.7 (4 × CH_2), 33.2, 33.9, 37.4, 37.5 (4 × CH), 38.9, 41.7 (4 × CH_2), 51.7, 53.1 (2 × *C*HCO), 212.7, 212.8 (C=O) ppm. GC-LRMS: *m*/*z* (%) = 182 (0.2) [M^+], 99 (12), 83 (14), 72 (100), 69 (17), 57 (11), 55 (20). HRMS for $C_{12}H_{22}O$: calcd. 182.1671; found 182.1680 [M^+].

Acknowledgments

This work was generously supported by the Spanish Ministerio de Ciencia y Tecnología (grant no. BQU2001−0538) and the Generalitat Valenciana (grants nos. CTIDIB2002−310 and GRUPOS03/135). R. O. thanks the Spanish Ministerio de Educación, Cultura y Deporte for a scholarship.

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Received May 18, 2004

