Pergamon

Tetrahedron, Vol. 53, No. 49, pp. 16711-16720, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)10116-8

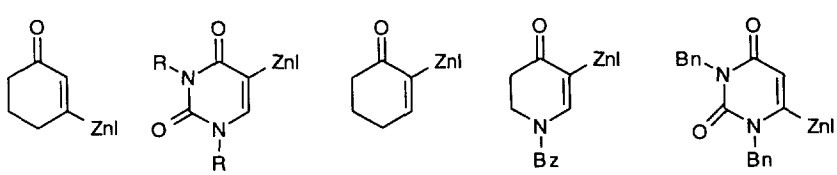
Preparation and Reactions of 2-Zincated 2-Cyclohexen-1-one and Related Heterocycles

A. S. Bhanu Prasad and Paul Knochel*
Fachbereich Chemie der Philipps-Universität Marburg,
Hans-Meerwein-Straße, 35032 Marburg, Germany

Keywords: functionalized organozinc compounds, palladium(0) catalysis, copper(I) catalysis, arylated uracils.

Abstract: The reaction of zinc dust in THF with 2-iodocyclohexenone **6**, 3-iodo-*N*-benzoyl-1-azacyclohex-2-en-4-one **8** provides the corresponding zinc organometallics **3** and **4** which react in the presence of a copper(I) catalyst or palladium(0) catalyst with an allylic bromide or alkenyl and aryl iodides in satisfactory to good yields. Several of these products can further be cyclized leading diastereoselectively to a polyfunctional decaline **12** or a pyrrole derivative **13**. A 6-zincated uracil reagent has also been prepared and reacted with aryl iodides in the presence of a palladium catalyst leading to new 6-arylated uracil derivatives **11**. © 1997 Elsevier Science Ltd.

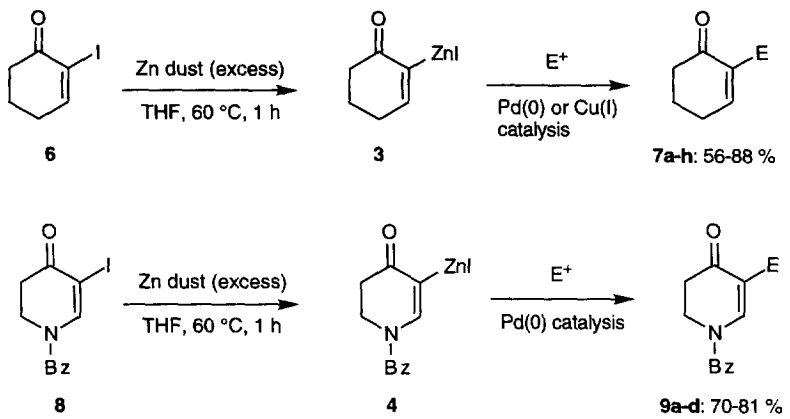
Organozincs tolerate most organic functional groups allowing the preparation of a wide range of polyfunctional organometallics.[1] We have reported the preparation of 3-oxocyclohexenylzinc iodide[2] **1** and the 5-zincated uracil[3] derivative **2** and have shown their utility for forming new carbon-carbon bonds in the presence of transition metal salts. Herein, we wish to report our results concerning the successful preparation of the 6-oxocyclohexenylzinc iodide **3**, the related heterocycle **4** and the 6-zincated uracil derivative **5** as well as their use in copper and palladium catalyzed reactions. Whereas unactivated alkenyl iodides require the use of a polar solvent like *N,N*-dimethylacetamide (DMAC)[4] or the use of highly active



1 **2**: R = Me, Bn **3** **4** **5**

zinc powder,[5] alkenyl iodides bearing electron-withdrawing substituents[2] or having an heteroatom in close proximity to the carbon-halogen react far more readily with zinc dust. Thus, the treatment of 2-iodocyclohexenone **6** with zinc dust (10 equiv) previously activated[7] with 1,2-dibromoethane (20 mol %) and TMSCl (ca. 2 mol %) in THF at 60 °C for 1 h leads to the complete conversion to the zinc reagent **3** (70 % estimated by iodolysis and hydrolysis of reaction aliquots and GC analysis). This zinc enolate displays a somewhat reduced reactivity compared to other alkenyl zinc reagents. However by using a two-fold excess of this reagent versus the electrophile, copper catalyzed reaction with ethyl (2-bromomethyl)acrylate and uncatalyzed reaction with trimethylstannyl chloride (entries 1 and 2 of Table 1) proceed in satisfactory

yields (72-56 %) leading to the expected 2-substituted cyclohexenones **7a-b** (Table 1 and Scheme 1). Similarly, palladium(0) catalyzed cross-coupling reactions[8] with various alkenyl and aryl iodides (entries 3-8 of Table 1) furnishes polyfunctional 2-alkenylated or arylated cyclohexenones **7c-h** in 60-88 % yield.



Scheme 1

We have also prepared the 3-iodo-*N*-benzoyl-1-azacyclohex-2-en-4-one **8** in two steps[6,9] starting from *N*-benzoyl-1-aza-4-cyclohexanone (see experimental section). The corresponding organozinc reagent **4** is obtained by direct insertion of zinc dust in THF (60 °C, 1 h) in ca. 80 % yield. Interestingly, this organozinc compound undergoes very rapidly cross-coupling reactions using the usual palladium catalyst *bis*(dibenzylideneacetone)palladium(0)[10] (Pd(dba)$_2$; ca. 1 mol %) and (*o*-furyl)$_3$P[11] (tfp, 4 mol %). These cross-coupling reactions are very fast and complete within 1 h at 25 °C which may be explained[3b] by the presence of the enamine functionality contained in the zinc reagent **4** (Scheme 2). This donor functionality may facilitate the transmetalation from zinc to palladium leading to the intermediate Ar^1-Pd-Ar^2 via an addition-elimination mechanism (Scheme 2). A reductive elimination will furnish the products **9a-d**.

Table 1. Reaction of the alkenylzinc iodides **3** and **4** with electrophiles in the presence of a copper catalyst (CuCN·2LiCl) or a palladium catalyst (Pd(dba)$_2$; tfp).

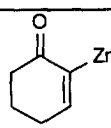
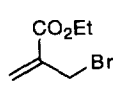
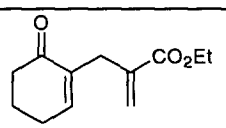
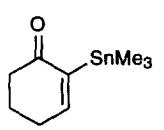
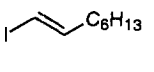
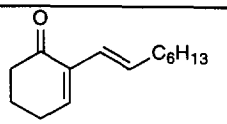
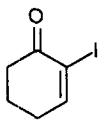
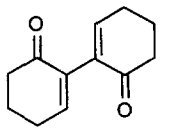
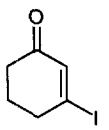
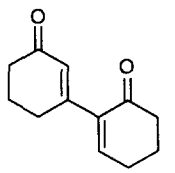
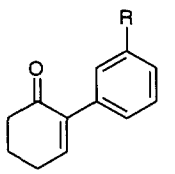
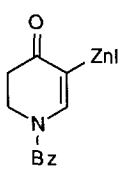
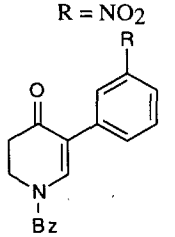
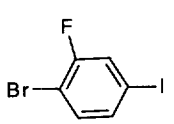
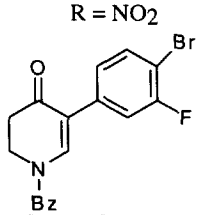
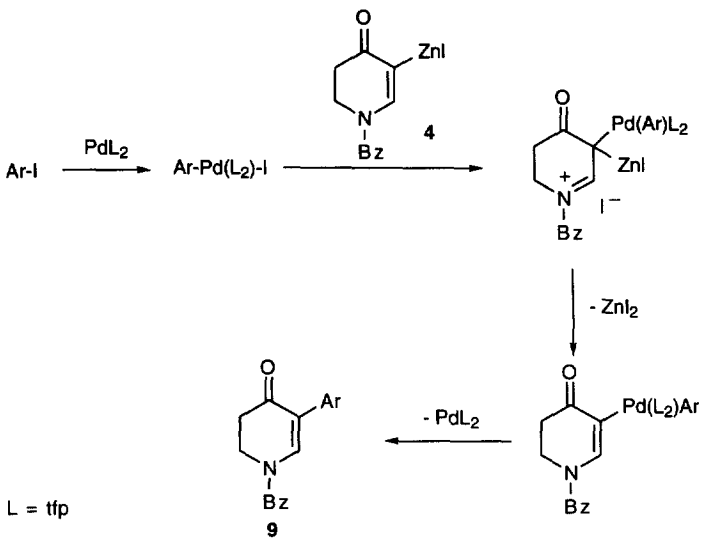
entry	zinc reagent	electrophile	products **7** or **9**	yield (%)[a]
1	 **3**		 **7a**	72
2	**3**	Me_3SnCl	 **7b**	56

Table 1 (continued).

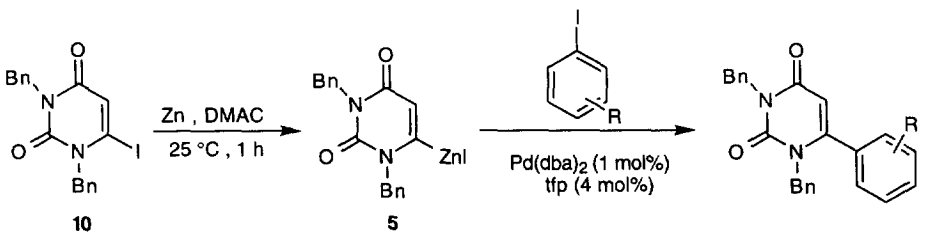
3	**3**			**7c**	80
4	**3**			**7d**	60
5	**3**			**7e**	71
					
6	**3**	*m*-CF_3-C_6H_4I	R = CF_3	**7f**	85
7	**3**	*m*-EtO_2C-C_6H_4I	R = CO_2Et	**7g**	78
8	**3**	*m*-O_2N-C_6H_4I	R = NO_2	**7h**	88
	 **4**				
9	**4**	*m*-CF_3-C_6H_4I	R = CF_3	**9a**	70
10	**4**	*m*-EtO_2C-C_6H_4I	R = CO_2Et	**9b**	81
11	**4**	*m*-O_2N-C_6H_4I	R = NO_2	**9c**	72
12	**4**			**9d**	73

[a]Isolated yields of analytically pure products.



Scheme 2

Finally, we have prepared 6-iodouracil derivative **10** starting from 6-chlorouracil.[12] Its conversion to the corresponding zinc reagent **5** is best performed using zinc dust in DMAC.[4] Under these conditions, the conversion to the zinc organometallic **5** is complete within 1 h at 25 °C (Scheme 3). The reaction of **5** with various aryl iodides in the presence of $Pd(dba)_2$ (1 mol %) and tfp (4 mol %) furnishes the 6-arylated uracil derivatives **11a-c** in 70-76 % (25 °C, 4h; Scheme 3).

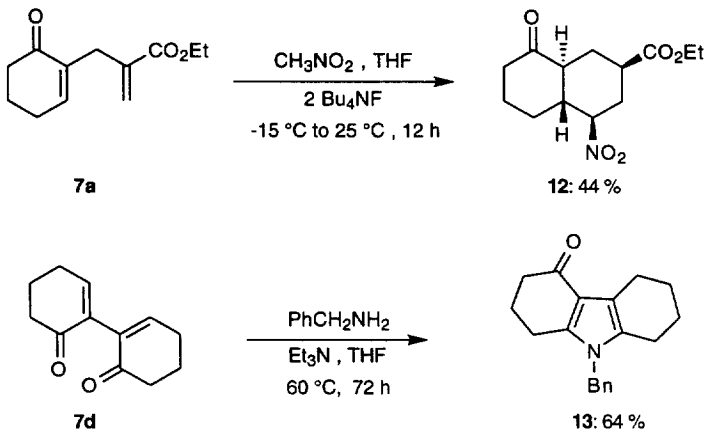


11a : R = *m*-CO_2Et, 76 %
11b : R = *p*-Cl, 70 %
11c : R = H, 72 %

Scheme 3

This method allows to prepare 6-arylated uracils **11a-c** which may be of pharmaceutical interest.[3] Some of the products **7** obtained by the reaction of **3** with electrophiles may undergo further cyclizations. Thus, the reaction of **7a** with nitromethane (1.1 equiv) in THF in the presence of Bu_4NF (2 equiv, -15 °C to 25 °C, 12

h) furnishes the polyfunctional decaline **12** as only one diastereoisomer in 44 % yield as proved by X-ray analysis (Figure 1). Also, the dimer **7d** provides after treatment with benzylamine and Et_3N in THF (60 °C, 72 h) the pyrrole **13** in 64 % yield.



Scheme 4

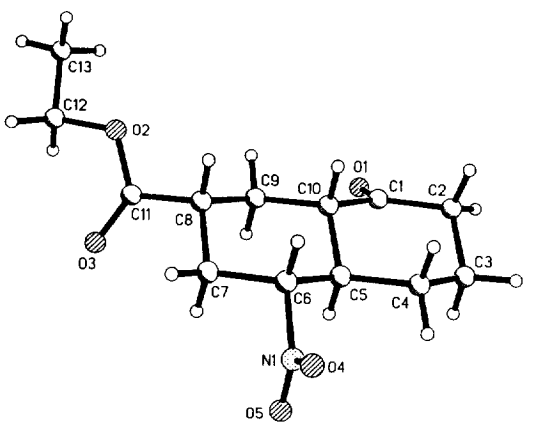


Figure 1. ORTEP representation of the structure of **12** determined by X-ray analysis.[13]

In summary, we have prepared several new functionalized cyclic and heterocyclic zinc compounds and have shown their use for preparing polyfunctional molecules like **7a-h**, **9a-d**, **11a-c**, **12** and **13**. Further applications of these reagents are currently underway.

Experimental Section

General methods. Unless otherwise indicated, all reactions were carried out under an argon atmosphere. Solvents (THF or DMAC) were dried and freshly distilled over respectively sodium/benzophenone and

CaH_2. Zinc dust (-325 mesh) was purchased from Aldrich or Riedel-de Haën (Germany). Reactions were monitored by gas chromatography (GC) analysis of worked up reaction aliquots. Unless otherwise indicated, the reaction mixtures were worked up as follows: the reaction mixture was poured into a mixture of ethyl acetate and sat. aq. NH_4Cl. The two phase mixture was filtered to remove insoluble salts and the two layers were separated. The combined organic extracts were washed with water (50 mL) and sat. aq. NaCl (20 mL), dried over $MgSO_4$ and filtered. The residue obtained after evaporation of the solvents was purified by flash chromatography. Fourier transform infrared spectra (FT-IR) were recorded on a Nicolet 5 DXB spectrometer. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Bruker AC-200 and AC-300 (200, 300 MHz (proton) and 50, 75.5 MHz (carbon)). Mass spectra (MS) and exact mass calculation were recorded on a VG-70-250 S mass spectrometer. The ionization methods used were desorption chemical ionization (CI) and electron impact ionization (EI, 70 eV).

Starting materials. The following starting materials were prepared according to literature procedures: 2-iodocyclohexenone (**6**),[6] tris(*o*-furyl)phosphine,[11] ethyl (2-bromomethyl)acrylate,[14] 3-iodo-2-cyclohexenone,[15] (*E*)-1-iodo-1-octene.[16]

Preparation of 3-iodo-*N*-benzoyl-1-azacyclohex-2-en-4-one (8).[6] *N*-benzoylazacyclohex-2-en-4-one[9] (200 mg, 1 mmol) was dissolved in CH_2Cl_2 (8 mL) and iodine (250 mg, 1 mmol) was added, followed by pyridinium dichromate (380 mg, 1 mmol). The reaction mixture was stirred overnight and worked up as usual affording pure **8** as a foam (200 mg, 61 % yield) after flash chromatography (EtOAc:hexanes 1:1). IR (KBr): 1673 (s), 1565 (s), 1335 (m), 1287 (s), 1133 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.1 (s, 1H), 7.54-7.45 (m, 5H), 4.15 (t, J = 7 Hz, 2H), 2.83 (t, J = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 186.3, 168.1, 148.9, 131.3, 130.9, 128.0, 127.7, 42.4, 33.8. MS (EI): 327 (M^+, 7), 105 (100), 77 (32), 51 (8). Exact mass calcd. for $C_{12}H_{10}INO_2$: 327.12. Observed: 326.98.

Preparation of 6-iodo-*N*,*N*-dibenzyluracil (10). 6-Iodouracil[12] (1.80 g, 2.34 mmol), K_2CO_3 (1.38 g, 10 mmol) was dissolved in dry DMF (10 mL). Benzyl chloride (630 mg, 5 mmol) was added and the reaction mixture was stirred at 25 °C for 3 days. The solvent was removed under vacuum (60 °C, 10^{-2} mm Hg), water was added and the product was extracted with ethyl acetate. After the usual workup, the crude product was purified by chromatography (EtOAc:hexanes 1:3) affording the pure uracil derivative **10** (730 mg, 75 % yield) as a foam. IR (KBr): 1705 (s), 1634 (s), 1431 (s), 1342 (w), 714 (m), 692 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.37-7.14 (m, 10 H), 6.40 (s, 1H), 5.18 (s, 2H), 4.98 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.3, 150.1, 136.8, 135.9, 129.5, 129.3, 128.9, 128.4, 128.3, 127.4, 116.1, 112.6, 57.3, 45.4. MS (EI): 418 (M^+, 20), 327 (2), 108 (2), 91 (100), 51 (14). Exact mass calcd. for $C_{18}H_{15}IN_2O_2$: 418.25. Observed: 418.02.

Typical procedure for the preparation of 2-(2-carboethoxy-2-propenyl)cyclohex-2-en-1-one (7a). A dry three-necked 25 mL flask equipped with an argon inlet, a magnetic stirring bar and a thermometer was charged with zinc dust (-325 mesh, Aldrich, 3.25 g, 50 mmol), 1,2-dibromoethane (0.82 mL, 9.5 mmol, ca. 20 mol %) in THF (2.5 mL). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred (ca. 30 s). This heating was repeated twice and the zinc suspension was allowed to reach 25 °C (5 min). TMSCl (ca. 0.15 mL) was added neat and the reaction mixture was allowed to stir for 5 min. A solution of 2-iodocyclohexenone **6** (1.1 g, 5 mmol) in THF (1.5 mL) was added and the reaction mixture was stirred for 1 h at 60 °C. The conversion was complete as judged by GC analysis. The zinc reagent was diluted with THF (4 mL) and the excess zinc powder was allowed to settle for 1 h. The supernatant liquid was transferred into a flask containing CuCN (450 mg, 5 mmol) and LiCl (420 mg, 10 mmol) in THF (5 mL) at –60 °C. The reaction mixture was allowed to warm to 0 °C and was cooled back to –60 °C after

stirring for 5 min. A THF solution of ethyl (2-bromomethyl)acrylate[14] (580 mg, 3 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm to 0 °C and was kept for 2 h at this temperature. After the usual workup, the crude product was purified by flash chromatography (ether:hexanes 2:3) affording the desired cyclohexenone derivative **7a** (450 mg, 72 % yield) as a colorless oil.

Typical procedure for the preparation of 3-(3-trifluoromethylphenyl)-*N*-benzoylazacyclohex-2-en-4-one (9a). A dry, three-necked flask equipped with an argon inlet, a magnetic stirring bar and a thermometer was charged with zinc dust (650 mg, 10 mmol) and 1,2-dibromoethane (0.16 mL, ca. 1.9 mmol) in THF (2 mL). 3-Iodo-N-benzoylazacyclohex-2-en-4-one **8** (327 mg, 1 mmol) was added as a solid and the reaction mixture was heated for 1 h at 60 °C. The conversion was complete as judged by GC analysis. The zinc reagent was diluted with THF (1 mL) and the excess zinc powder was allowed to settle for 1 h. The supernatant liquid was transferred into a flask containing $Pd(dba)_2$ (6 mg, 10 μmol), tfp (10 mg, 40 μmol), 3-iodotrifluoromethylbenzene (160 mg, 0.6 mmol) in THF (1 mL). The reaction mixture was allowed to stir for 0.5 h at rt and was worked up as usual. The crude product obtained after evaporation of the solvent was purified by flash chromatography (EtOAc:hexanes 1:3) and isolated as a solid (145 mg, 70 % yield, mp = 98-100 °C).

Analytical data of products 7a-h, 9a-d of Table 1:

2-(2-Carboethoxy-2-propenyl)cyclohex-2-en-1-one (7a): 450 mg, 72 % yield obtained by the reaction of ethyl (2-bromomethyl)acrylate (580 mg, 3 mmol) with **3** (5 mmol). Reaction conditions: -60 °C to 0 °C, 2 h. Purification by flash chromatography (ether:hexanes 2:3). IR (neat): 2939 (s), 1715 (s), 1674 (s), 1634 (m), 1382 (m), 1144 (s), 887 (w), 750 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.69 (s, 1H), 6.14 (s, 1H), 5.47 (s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.14 (s, 2H), 2.38-2.29 (m, 4H), 1.98-1.89 (m, 2H), 1.21 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.9, 167.2, 147.2, 138.8, 137.4, 126.8, 61.0, 38.8, 31.6, 26.4, 23.4, 14.5. MS (EI): 208 (M^+, 16), 163 (28), 162 (100), 135 (32), 79 (22). Exact mass calcd. for $C_{12}H_{16}O_3$: 208.26. Observed: 208.11.

2-(Trimethylstannyl)cyclohex-2-en-1-one (7b): 430 mg, 56 % yield obtained by the reaction of Me_3SnCl (597 mg, 3 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 12 h. Purification by flash chromatography (ether:hexanes 1:3). Solid (mp = 38 °C). IR (KBr): 2919 (m), 1713 (m), 1655 (m), 773 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.07 (dt, J_1 = 4 Hz, J_2 = 3.8 Hz, 1H), 2.36 (t, J = 7 Hz, 2H), 2.31-2.26 (m, 2H), 0.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 202.2, 159.2, 145.3, 38.1, 27.9, 23.0, (-) 9.34. MS (EI): 245 (100), 244 (32), 243 (77), 242 (27), 215 (30), 163 (5), 118 (3). Anal. calcd. for C: 41.75, H: 6.23. Found: C: 41.60, H: 6.27.

(*E*)-2-(1-Octenyl)cyclohex-2-en-1-one (7c): 400 mg, 80 % yield obtained by the reaction of (*E*)-1-iodooctene (595 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 1 h. Purification by flash chromatography (ether:hexanes 1:3). IR (neat): 2929 (s), 2858 (s), 1697 (s), 1636 (m), 938 (w), 725 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.85 (t, J = 4.4 Hz, 1H), 6.17-5.99 (m, 2H), 2.40-2.32 (m, 4H), 2.07-2.00 (m, 2H), 1.95-1.87 (m, 2H), 1.35-1.19 (m, 8 H), 0.82 (dt, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 198.7, 143.5, 136.7, 132.9, 123.9, 38.9, 33.3, 31.8, 29.3, 29.0, 26.4, 22.8, 22.7, 14.1. MS (EI): 206 (M^+, 42), 135 (100), 95 (1), 79 (15), 28 (88). Anal. calcd. for C: 81.48, H: 10.77. Found: C: 80.45, H: 10.66.

6,6'-Dioxo-1,1'-bicyclohexenyl (7d): 285 mg, 60 % yield obtained by the reaction of 2-iodocyclohex-2-en-1-one (555 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 4 h. Purified by flash chromatography (ether:hexanes 4:1). Solid (mp = 104 °C). IR (KBr): 2934 (w), 1684 (s), 1668 (s), 1614 (w), 779 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 6.73 (t, J = 4.1 Hz, 2H), 2.46-2.35 (m, 8H), 2.01-1.94 (m, 4H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.0, 148.6, 137.9, 38.7, 26.5, 23.3. MS (EI): 190 (M^+, 100), 162 (70), 134 (28), 67 (3), 55 (20), 28 (43). Anal. calcd. for C: 75.76, H: 7.42. Found: C: 75.46, H: 7.50.

6,3'-Dioxo-1,1'-bicyclohexenyl (7e): 340 mg, 71 % yield obtained by the reaction of 3-iodocyclohex-2-en-1-one (555 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 4 h. Purified by flash chromatogra-

phy (ether:hexanes 4:1). IR (neat): 2947 (m), 1673 (s), 1607 (w), 770 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.94 (t, J = 4.3 Hz, 1H), 5.96 (d, J = 1.1 Hz, 1H), 2.46-2.30 (m, 8H), 2.02-1.91 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.6, 196.9, 159.3, 148.1, 140.3, 127.4, 38.8, 37.2, 28.8, 26.1, 25.9, 22.7, 22.3. MS (EI): 190 (80), 162 (17), 134 (100), 67 (7), 55 (13). Anal. calcd. for C: 75.76, H: 7.42. Found: C: 75.36, H: 7.46.

2-(3-Trifluoromethylphenyl)cyclohex-2-en-1-one (7f): 510 mg, 85 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (680 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 16 h. Purification by flash chromatography (ether:hexanes 2:3). IR (neat): 1681 (s), 1331 (s), 1125 (s), 800 (s), 701 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.54-7.36 (m, 4H), 7.03 (t, J = 4.3 Hz, 1H), 2.56-2.46 (m, 4H), 2.09-2.01 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 197.4, 149.2, 139.3, 137.4, 132.2, 131.0, 130.6, 130.1, 129.7, 128.4, 126.1, 125.6, 125.5, 125.4, 125.4, 124.3, 124.3, 124.2, 124.2, 122.5, 38.9, 26.6, 22.8. MS (EI): 240 (M^+, 100), 221 (8), 183 (7), 171 (24). Anal. calcd. for C: 64.99, H: 4.62. Found: C: 64.99, H: 4.67.

2-(3-Carboethoxyphenyl)cyclohex-2-en-1-one (7g): 480 mg, 78 % yield obtained by the reaction of ethyl 3-iodobenzoate (698 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 16 h. Purification by flash chromatography (ether:hexanes 2:3). IR (neat): 1717 (s), 1679 (s), 1602 (w), 1254 (s), 757 (s). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.76-7.72 (m, 2H), 7.27-7.16 (m, 2H), 6.84 (t, J = 4.4 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.39-2.26 (m, 4H), 1.93-1.83 (m, 2H), 1.18-1.11 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 198.0, 166.9, 149.2, 140.0, 137.2, 133.6, 130.7, 130.0, 129.0, 128.3, 61.3, 39.3, 27.0, 23.3, 14.7. MS (EI): 244 (M^+, 100), 215 (9), 199 (59), 171 (13), 75 (3). Anal. calcd. for C: 73.75; H: 6.60. Found: C: 73.69, H: 6.56.

2-(3-Nitrophenyl)cyclohex-2-en-1-one (7h): 480 mg, 88 % yield obtained by the reaction of 1-iodo-3-nitrobenzene (620 mg, 2.5 mmol) with **3** (5 mmol). Reaction conditions: 25 °C, 16 h. Purification by flash chromatography (ether:hexanes 1:1). Solid (mp = 46 °C). IR (KBr): 1669 (s), 1526 (s), 1348 (s), 804 (m), 742 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 8.15-8.06 (m, 2H), 7.65-7.60 (m, 1H), 7.40 (dt, J_1 = 8.0 Hz, J_2 = 7.9 Hz, 1H), 7.12 (t, J = 3.9 Hz, 1H), 2.56-2.48 (m, 4H), 2.10-2.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 197.6, 150.5, 148.2, 138.6, 138.5, 135.3, 129.3, 124.0, 122.7, 39.1, 27.0, 23.1. MS (EI): 217 (M^+, 81), 189 (100), 171 (3). Anal. calcd. for C: 66.35, H: 5.10, N: 6.45. Found: C: 66.36, H: 5.15, N: 6.24.

3-(3-Trifluoromethylphenyl)-*N*-benzoylazacyclohex-2-en-4-one (9a): 145 mg, 70 % yield obtained by the reaction of 1-iodo-3-trifluoromethylbenzene (163 mg, 0.6 mmol) with **4** (1 mmol). Reaction conditions: 25 °C, 0.5 h. Purification by flash chromatography (EtOAc:hexanes 1:3). Solid (mp = 98-100 °C). IR (KBr): 1681 (s), 1666 (s), 1597 (s), 1301 (s), 719 (s), 702 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80 (s, 1H), 7.59-7.42 (m, 9H), 4.19 (t, J = 7.3 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 191.0, 170.1, 143.1, 134.6, 132.5, 132.1, 131.9, 130.8, 130.4, 128.9, 128.6, 128.5, 125.7, 125.4, 125.3, 124.2, 124.1, 122.1, 118.7, 43.4, 36.5. MS (EI): 345 (M^+, 21), 326 (2), 105 (100), 77 (40), 76 (1), 50 (1), 28 (4). Anal. calcd. for C: 66.08, H: 4.09, N: 4.06. Found: C: 65.86, H: 4.23, N: 3.98.

3-(3-Carboethoxyphenyl)-*N*-benzoylazacyclohex-2-en-4-one (9b): 170 mg, 81 % yield obtained by the reaction of ethyl 3-iodobenzoate (166 mg, 0.6 mmol) with **4** (1 mmol). Reaction conditions: 25 °C, 1 h. Purification by flash chromatography (EtOAc:hexanes 1:2). Solid (mp = 98-100 °C). IR (KBr): 1718 (s), 1663 (s), 1592 (s), 1309 (s), 707 (s), 654 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.82 (s, 1H), 7.79-7.22 (m, 9H), 4.23-4.16 (m, 2H), 4.12-4.07 (m, 2H), 2.66-2.62 (m, 2H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 191.3, 170.1, 166.2, 143.0, 134.4, 133.3, 132.7, 132.0, 130.6, 129.5, 128.8, 128.7, 128.5, 128.2, 119.0, 60.9, 43.4, 36.5, 14.3. MS (EI): 349 (M^+, 20) 304 (3), 105 (100), 77 (29), 28 (2). Exact mass calcd. for $C_{21}H_{19}NO_4$: 349.41. Observed: 349.13.

3-(3-Nitrophenyl)-*N*-benzoylazacyclohex-2-en-4-one (9c): 140 mg, 72 % yield obtained by the reaction of 1-iodo-3-nitrobenzene (149 mg, 0.6 mmol) with **4** (1 mmol). Reaction conditions: 25 °C, 1 h. Purification

by flash chromatography (EtOAc: hexanes 1:1). Solid (mp = 118-120 °C). IR (KBr): 1679 (s), 1657 (s),1600 (s), 1522 (s), 715 (m), 707 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.06 (s, 1H), 8.01-7.40 (m, 9H), 4.17 (t, J = 6.6 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 190.8, 170.0, 148.0, 143.6, 135.6, 134.6, 132.3, 132.1, 129.0, 128.9, 128.6, 123.4, 122.1, 117.5, 43.4, 36.3. MS (EI): 322 (M^+, 10), 105 (100), 77 (21), 28 (7). Anal. calcd. for C: 67.07, H: 4.39, N: 8.69. Found: C: 66.82, H: 4.32, N: 8.51.

3-(4-Bromo-3-fluorophenyl)-*N*-benzoylazacyclohex-2-en-4-one (9d): 160 mg, 73 % yield obtained by the reaction of 1-bromo-2-fluoro-4-iodobenzene (180 mg, 0.6 mmol) with **4** (1 mmol). Reaction conditions: 25 °C, 1 h. Purification by flash chromatography (EtOAc:hexanes 1:2). Solid (mp = 116-118 °C). IR (KBr): 1664 (s), 1591 (s), 878 (s), 720 (s), 649 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74 (s, 1H), 7.57-7.42 (m, 5H), 7.16-7.07 (m, 3H), 4.19 (t, J = 7.1 Hz, 2H), 2.76 (t, J = 7.1 Hz, 2H). ^{13}C NMR (^{13}C NMR, 75.5 MHz): δ 190.3, 170.0, 161.4, 158.1, 144.6, 132.9, 132.9, 132.3, 132.0, 128.8, 128.7, 127.2, 127.1, 121.7, 121.6, 120.7, 120.5, 119.4, 119.1, 113.1, 43.1, 36.1. MS (EI): 375 (M^+, 15), 374 (M^+, 2), 373 (M^+, 11), 105 (100), 77 (36), 28 (7). Anal. calcd. for C: 57.78, H: 3.50, N: 3.74. Found: C: 57.87, H: 3.43, N: 3.80.

Typical procedure for the preparation of 6-iodozincio-*N,N*-dibenzyluracil and its palladium catalyzed cross-coupling with an aryl iodide. Preparation of 6-(3-carboethoxyphenyl)-*N,N*-dibenzyluracil (11a). A dry three-necked 25 mL flask equipped with an argon inlet, a magnetic stirring bar and a thermometer was charged with zinc dust (195 mg, 3 mmol) in DMAC (1 mL). After activation with 1,2-dibromoethane and TMSCl as described previously[4], 6-iodo-*N,N*-dibenzyluracil **10** (418 mg, 1 mmol) in THF (1 mL) was added and the reaction mixture was stirred 1 h at rt. The reaction temperature rose to ca. 40 °C during the addition. DMAC (2 mL) was added and the zinc dust was allowed to settle. The zinc reagent **5** was added to $Pd(dba)_2$ (6 mg, 10 μmol) and tfp (10 mg, 40 μmol) in THF (1 mL) at 0 °C and was treated with ethyl 3-iodobenzoate (166 mg, 0.6 mmol). After 4 h of stirring at rt, the reaction mixture was worked up with EtOAc. The crude reaction product was purified by flash chromatography (EtOAc: hexanes 1:2) affording the desired product **11a** as a foam (200 mg, 76 % yield). IR (KBr): 1705 (s), 1663 (s), 825 (m), 696 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.90 (d, J = 7.8 Hz, 1H), 7.62 (s, 1H), 7.33-6.63 (m, 12H), 5.52 (s, 1H), 5.02 (s, 2H), 4.70 (s, 2H), 4.13 (q, J = 7 Hz, 2H), 1.15 (t, J = 7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 167.4, 163.9, 155.9, 154.6, 138.9, 138.4, 135.3, 134.1, 133.2, 133.1, 131.2, 131.1, 130.9, 130.7, 130.5, 129.8, 129.7, 128.7, 105.9, 63.5, 51.0, 46.8, 16.4. MS (EI): 440 (M^+, 100), 349 (5), 244 (50), 198 (18), 91 (93). Exact mass calcd. for $C_{27}H_{24}N_2O_4$: 440.50. Observed: 440.18.

6-(4-Chlorophenyl)-*N,N*-dibenzyluracil (11b): 170 mg, 70 % yield obtained by the reaction of 1-chloro-4-iodobenzene (143 mg, 0.6 mmol) with **5** (1 mmol). Reaction conditions: 25 °C, 4 h. Purification by flash chromatography (ether:hexanes 1:2) affords **11b** as a foam. IR (KBr): 1708 (s), 1663 (s), 1619 (w), 825 (m), 696 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.43-6.76 (m, 14H), 5.59 (s, 1H), 5.12 (s, 2H), 4.81 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.8, 152.6, 151.4, 135.8, 135.3, 130.3, 128.3, 128.1, 127.9, 127.7, 127.4, 126.6, 125.5, 102.7, 48.4, 43.6. MS (EI): 404 (M^+, 15), 402 (M^+, 66), 311 (10), 268 (13), 206 (30), 132 (22), 91 (100), 77 (9). Exact mass calcd. for $C_{24}H_{19}Cl^{35}N_2O_2$: 402.88. Observed: 402.11.

6-Phenyl-*N,N*-dibenzyluracil (11c): 160 mg, 72 % yield obtained by the reaction of iodobenzene (122 mg, 0.6 mmol) with **5** (1 mmol). Reaction conditions: 25 °C, 4 h. Purification by flash chromatography (ether:hexanes 1:2) affords **11c** as a foam. IR (KBr): 1697 (s), 1659 (s) 1623 (m), 717 (m), 705 (m) cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.43-6.77 (m, 15 H), 5.61 (s, 1H), 5.32 (s, 2H), 4.98 (s, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 162.6, 155.4, 153.1, 137.5, 137.1, 133.6, 130.6, 129.7, 129.2, 129.1, 129.0, 128.5, 128.2, 128.1, 127.3, 104.0, 50.0, 45.2. MS (EI): 368 (M^+, 60), 277 (12), 172 (66), 116 (7), 91 (100), 77 (10). Exact mass calcd. for $C_{24}H_{20}N_2O_2$: 368.44. Observed: 368.15.

Preparation of (4a*S, 5*S**, 7*S**, 8a*R**)-7-carboethoxy-5-nitro-decahydro-1-naphthalenone (12).** A mixture of **7a** (210 mg, 1 mmol) and nitromethane (67 mg, 1.1 mmol) in THF (2 mL) was cooled to –15 °C, Bu_4NF (2 mL, 1 M in THF, 2 mmol) was slowly added. The reaction mixture was allowed to warm to rt

and was stirred for 12 h and worked up as usual. The crude reaction mixture was purified by flash chromatography (EtOAc:hexanes 2:3) furnishing the bicyclic product **12** as a white solid (mp = 68 °C, 120 mg, 44 % yield). IR (KBr): 2962 (w), 1732 (s), 1714 (s), 1549 (s). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.42-4.35 (m, 1H), 4.08 (q, J = 7 Hz, 2H), 2.46-1.14 (m, 8H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 208.5, 173.2, 90.0, 61.5, 51.2, 46.2, 41.3, 40.2, 33.1, 28.3, 27.5, 25.3, 14.5. MS (EI): 269 (M^+, 1), 177 (79), 149 (62), 131 (100), 93 (19), 79 (24). Exact mass calcd. for $C_{13}H_{19}NO_5$: 269.30. Observed: 269.13.

Preparation of 1H, 2H, 3H, 5H, 6H, 7H, 8H-9-benzyl-4-oxocarbazole (13). The dienone **7d** (190 mg, 1 mmol), benzylamine (214 mg, 2 mmol) and Et_3N (330 mg, 3 mmol) mixture was heated in THF (2 mL) at 60 °C for 3 days. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc:hexanes 2:3) affording the carbazol **13** (180 mg, 64 % yield) as a foam. IR (KBr): 2938 (m), 1641 (s), 1476 (s), 1093 (m), 909 (s), 737 (s), 698 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.31-7.22 (m, 3H), 6.93-6.91 (d, J = 6.8 Hz, 2H), 4.94 (s, 2H), 2.79-2.75 (m, 2H), 2.40-2.33 (m, 4H), 2.08-1.99 (m, 2H), 1.75-1.66 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.6, 142.7, 137.1, 129.3, 128.9, 127.5, 125.9, 118.1, 117.0, 46.8, 38.3, 23.8, 23.2, 22.9, 22.8, 22.7, 22.0, 21.5, 21.4. MS (EI): 279 (M^+, 100), 188 (51), 91 (89). Exact mass calcd. for $C_{19}H_{21}NO$: 279.41. Observed: 279.16.

Acknowledgments: We thank the DFG (SFB 260 and Leibniz program) for generous support and BASF AG, Witco (Bergkamen), Chemetall (Frankfurt), Sipsy (Avrillé, France) and Bayer AG for the generous gift of chemicals. B.P. thanks the Alexander von Humboldt-Stiftung for a fellowship.

References and Notes

1. (a) Knochel, P.; Singer R. D. *Chem. Rev.* **1993**, *93*, 2117; (b) Knochel, P. *Synlett* **1995**, 393.
2. (a) Rao, C. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 4593; (b) Knochel, P.; Rao, C. J. *Tetrahedron* **1993**, *49*, 29.
3. (a) Stevenson, T. M.; Prasad, A. S. B.; Citineni, J. R.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375; (b) Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237.
4. Majid, T. N.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 4413.
5. (a) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445; (b) Rieke, R. D. *Science* **1989**, *246*, 1260.
6. Bovonsombat, P.; Angara, G. J.; Mc Nelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787.
7. Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.
8. (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (e) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573.
9. Cameron, T. S.; Cordes, R. E.; Pinto, B. M.; Szarek, W. *A. Can. J. Chem.* **1981**, *59*, 3136.
10. Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134.
11. (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585; (b) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
12. Horwitz, J. P.; Tomson, A. J. *J. Org. Chem.* **1961**, *26*, 3392.
13. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB1 1EW.
14. Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
15. Piers, E.; Nagakura, I. *Synth. Commun.* **1975**, *5*, 193.
16. Brandsma, L. *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, **1971**, p. 99.

(*Received in Germany* 28 *August* 1997; *accepted* 18 *September* 1997)