Palladium Catalyzed Coupling Reactions of Diiodoarenes with Allylic and Homoallylic Alcohols

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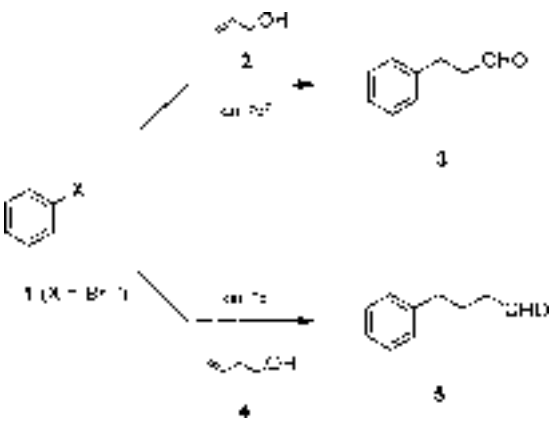
Abstract. A sequential transformation consisting of a twofold Heck reaction of 1,2-diiodobenzene (**14**) with allyl alcohol (**2**) followed by an intramolecular aldol condensation is suitable for the construction of the benzocyclohept-2-ene-2-carboxaldehyde (**15**). Under the same reaction conditions 1,8-diiodonaphthalene (**7**) leads to 1-acenaphthenyl-methanol (**6**), 2-(1-acenaphthenyl)-ethanol (**8**), 1-(1-acenaphthenyl)-ethanol (**11**), 5-(1,8-naphthalena)-nonan-2,8-dione (**12**) and 5-(1-naphthyl)-3-methylpentan-2-on (**13**) mainly.

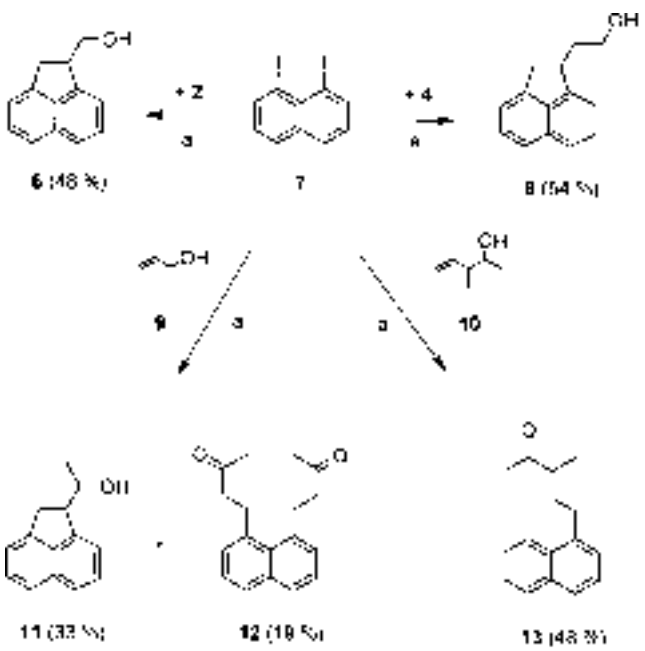
The palladium catalyzed coupling reaction of aryl halides with allylic and homoallylic alcohols represents a special type of Heck reaction [1]: the olefinic double bond migrates into conjugation with the hydroxyl group through a mechanism of β-hydrogen elimination and readdition of the intermediary hydrido palladium species. Decomplexation and tautomerization finally lead to ketones or to aldehydes [2] such as **3** and **5** (Scheme 1). This facile entry to carbonyl compounds opens up opportunities for sequential transformations [3] combining the Heck reaction with classical carbonyl reactions [4]. In this paper we report on our attempts to use dihaloarenes such as 1,8-diiodonaphthalene (**7**) and 1,2-diiodobenzene (**14**) as coupling components in order to achieve twofold Heck reactions [5] to dicarbonyl compounds suitable for intramolecular aldol reactions.

The coupling reaction of **7** with an excess of allyl alcohol (**2**) (10 equivalents) leads to the formation of the acenaphthene derivative **6**, a 1:1 product (Scheme 2). The anticipated 1:2 product could not be detected.

Slight variations of the reaction conditions, for instance changing the base from triethyl amine to potassium carbonate, has only a minor influence on the yields. The homoallylic alcohol **4** reacts in the same way, leading to the homologous product **8**. These annulation reactions proceed by a carbopalladation of the olefinic



Scheme 1 Heck reaction with simple allylic and homoallylic alcohols



Scheme 2 Palladium catalyzed coupling reactions of 1,8-diiodonaphthalene **7** with allylic and homoallylic alcohols; reaction conditions a: excess of unsaturated alcohol, 5 mol-% palladium acetate in DMF in the presence of an appropriate base at 80–90 °C for 2 d.

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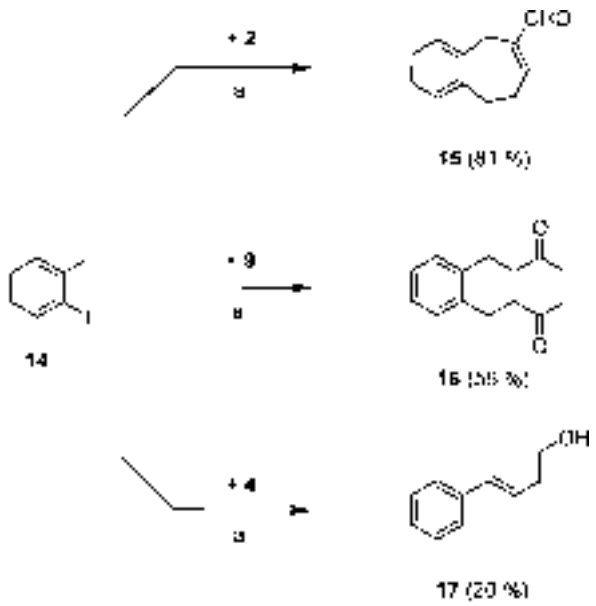
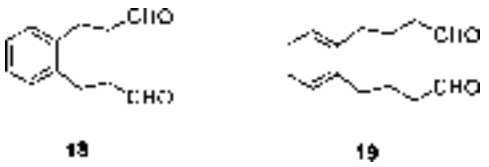
component followed by an Ullmann type ring closure. We have described this type of reactions previously with unfunctionalized olefins such as norbornene and styrene and with various disubstituted alkynes as coupling components [6]. In contrast, with the sterically more demanding unsaturated alcohols **9** and **10** the annulation reaction is less facile. In the case of the allylic alcohol **9** a significant amount of the symmetrical 1:2 product **12** is observed besides a 63:17 mixture of the diastereoisomers of **11**. The hydrodehalogenated compound **13** is the only isolated coupling product of the relatively bulky homoallylic alcohol **10**. In summary, the formation of acenaphthene derivatives represents the typical pathway for Pd-catalyzed coupling reactions of 1,8-diiodonaphthalene (**7**) with simple allylic and homoallylic alcohols; on the other hand this annulation reaction is strongly inhibited by moderate steric hindrance.

With 1,2-diiodobenzene (**14**) and allyl alcohol (**2**) as coupling components the twofold Heck reaction is successful (Scheme 3): the functionalized benzocycloheptadiene **15** is obtained in good yield. In this domino process the intermediate biscarbaldehyde **18** cyclizes *via* an intramolecular aldol condensation to give the 7-membered ring. In the case of the homoallylic alcohol **4** exclusively the hydrodehalogenated Heck product **17** was detected besides polymeric material. Presumably for the intermediate biscarbaldehyde **19** the intramolecular aldol condensation resulting in a 9-membered ring is unfavoured, and therefore polycondensation is the main reaction pathway. The Heck reaction with the secondary allylic alcohol **9** gives the diketone **16** as the main product, which is obviously not reactive enough to cyclize under the reaction conditions.



Scheme 3 Palladium catalyzed coupling reactions of 1,2-diiodobenzene **14** with allylic and homoallylic alcohols; reaction conditions a: excess of unsaturated alcohol, 5 mol-% palladium acetate in DMF in the presence of an appropriate base at 80–100 °C for 2–3 d.



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Although limited to special cases our investigation shows that the Heck reaction of vicinal dihaloarenes with allylic alcohols is a pathway to some interesting structures difficult to synthesize by other methods.

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Experimental

IR: Perkin Elmer 983. – NMR spectra are recorded at 500.13 MHz using $CDCl_3$ as solvent and TMS as internal standard. ^{13}C NMR spectra are measured at 125.76 MHz using $CDCl_3$ as solvent and as internal standard (δ/ppm = 77.05). – MS: MAT 311 A and AMD 604. Mass spectra are recorded at an ionizing voltage of 70 eV by electron impact. – For analytical TLC precoated plastic sheets "POLYGRAM SIL G/UV_{254}" from Macherey-Nagel are used. – The substrates **7** [7] and **10** [8] were synthesized according to literature procedures.

Palladium Catalyzed Coupling Reactions of Diiodoarenes with Allylic and Homoallylic Aalcohols (General Procedure)

A mixture of 0.5 to 1 mmol of the diiodoarene, 2 to 15 equiv. of the unsaturated alcohol, 8 equiv. of an appropriate base, palladium acetate (5 mol-%) and 10 ml of dry DMF is stirred under nitrogen in a screw-capped tube at 80–100 °C for 2–3 d. After the addition of 50 ml of water the solution is extracted three times with 30 ml of diethyl ether. The combined organic layers are filtered through silica and concentrated *in vacuo*. The residue is purified by flash-chromatography and destillation or crystallization.

1-Acenaphthenyl-methanol (**6**)

From 190 mg (0.500 mmol) of 1,8-diiodonaphthalene (**7**), 290 mg (5.00 mmol) of allylic alcohol (**2**), 404 mg (4.00 mmol) of triethyl amine and 5.61 mg (25 μmol) of palladium acetate at 80 °C for 55 h according to the general procedure (see above). By flash-chromatography (TLC: silica/diethyl ether; R_f = 0.67) and distillation *in vacuo* (150 °C; 0.02 mbar) 44 mg (48%) of **6** are isolated as a yellow oil. When K_2CO_3 (8 equiv.) was applied as base in the presence of *n*-Bu_4NBr (2 equiv.) the yield of **6** was 33%. – IR (film): ν/cm^{-1} = 3360 (s, br, OH), 3038 (m), 2925 (s), 2872 (m), 1604 (m), 1595

(m), 1494 (m), 1426 (m), 1368 (m), 1069 (s, br), 1025 (s, br), 802 (s), 776 (s). – ^{1}H NMR: δ/ppm = 1.70 (s, br, 1H), 3.22 (m, 1H), 3.53 (m, 1H), 3.85 (m, 1H), 3.87 (m, 2H), 7.24 (d, 1H), 7.30 (d, 1H), 7.44 (t, J = 6.8 Hz, 2H), 7.61 (q, J = 8.3 Hz, 2H). – ^{13}C NMR: δ/ppm = 34.49 (t), 46.03 (d), 66.56 (t), 119.37, 119.56, 122.42, 123.38, 127.74, 128.04 (all d), 131.59, 139.12, 144.33, 145.64 (all s). – MS: *m/z* (%) = 184 (29) [M^+], 165 (12), 154 (17), 153 (100) [$C_{12}H_9^+$], 152 (36), 151 (10).

$C_{13}H_{12}O$	calcd.:	C 84.75 H 6.56
(184.2)	found:	C 84.59 H 6.60.

2-(1-Acenaphthenyl)-ethanol (**8**)

From 190 mg (0.500 mmol) of 1,8-diiodonaphthalene (**7**), 290 mg (5.00 mmol) of homoallylic alcohol **4**, 404 mg (4.00 mmol) of triethyl amine and 5.61 mg (25 μmol) of palladium acetate at 80 °C for 43 h according to the general procedure. The product is isolated by flash-chromatography (TLC: silica/diethyl ether; R_f = 0.60) and distillation *in vacuo* (150 °C; 0.15 mbar) to afford 54 mg (54%) of **8** as a yellow oil. – IR (film): ν/cm^{-1} = 3349 (s, br, OH), 3038 (m), 2930 (s), 2880 (s), 1603 (m), 1403 (m), 1425 (m), 1368 (m), 1049 (s), 803 (s), 779 (s). – ^{1}H NMR: δ/ppm = 1.64 (s, 1H), 1.87 (m, 1H), 2.19 (m, 1H), 3.06 (dd, J = 17.1 Hz, J = 3.8 Hz, 1H), 3.58 (dd, J = 17.2 Hz, J = 8.1 Hz, 1H), 3.81 (m, 1H), 3.83 (m, 2H), 7.25 (m, 2H), 7.44 (m, 2H), 7.60 (m, 2H). – ^{13}C NMR: δ/ppm = 37.58 (t), 39.43 (t), 40.06 (d), 61.26 (t), 118.87, 119.29, 122.40, 122.80, 127.84, 127.93 (all d), 131.53, 138.52, 144.39, 148.98 (all s). – MS: *m/z* (%) = 198 (57) [M^+], 179 (11), 167 (38), 166 (11), 165 (60), 154 (38), 153 (100) [$C_{12}H_9^+$], 152 (65), 151 (12).

$C_{14}H_{14}O$	calcd.:	C 84.81 H 7.12
(198.3)	found:	C 84.60 H 7.14.

1-(1-Acenaphthenyl)-ethanol (**11**)*; 5-(1,8-Naphthalena)-nonan-2,8-dione* (**12**)

From 380 mg (1.00 mmol) of 1,8-diiodonaphthalene (**7**), 720 mg (5.00 mmol) of allylic alcohol **9**, 1.03 g (8.00 mmol) of *N*,*N*-diisopropylethylamine and 11.2 mg (50 μmol) of palladium acetate at 90 °C for 2.5 d according to general procedure. By flash-chromatography the crude product is fractionated (TLC: silica/diethyl ether/petrol ether 1:1; R_f = 0.41 (**11,** diastereo-isomer **a**), 0.36 (**11**, diastereoisomer **b**), 0.26 (**12**), 0.17). First fraction (R_f = 0.36–0.41): After destillation *in vacuo* (120 °C, 0.25 mbar) 66 mg (33%) of **11** as a yellow oil were obtained (mixture of diastereoisomers in the ratio 63(**a**):37(**b**)). Second fraction (R_f = 0.26): After crystallization from petrol ether51 mg (19%) of **12** were obtained as colorless needles with *m.p.* 72–74 °C. – **11**: IR (Film): ν/cm^{-1} = 3404 (br, m, OH), 3037 (m), 2970 (m), 2927 (m), 1708 (m), 1603 (m), 1370 (m), 1172 (m), 1104 (m), 1047 (m), 823 (m), 785 (s). – ^{1}H NMR (diastereoisomer **a**): δ/ppm = 1.30 (d, J = 6.3 Hz, 3H), 3.40 (m, 2H), 3.77 (m, 1H), 4.36 (qd, J = 6.3 Hz, J = 3.6 Hz, 1H), 7.29 (d, J = 6.2 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.46 (dd, J = 10.1 Hz, J = 1.3 Hz, 1H), 7.46 (dd, J = 15.1 Hz, J = 10.1 Hz, 1H), 7.60 (dd, J = 8.2 Hz, J = 0.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H). – ^{13}C NMR (diastereoisomer **a**): δ/ppm = 20.44 (q, CH_3), 31.74 (t), 50.76 (d), 70.01 (d), 119.46, 119.48, 122.35, 123.50, 127.78, 128.09 (all d), 131.52, 139.60, 144.63, 145.61 (all s). – ^{1}H NMR (diastereomer **b**): δ/ppm = 1.23 (d, J = 6.3 Hz, 3H), 3.22 (dd, J = 17.4 Hz, J = 3.2 Hz, 1H), 3.49 (dd, J = 17.3 Hz, J = 8.2 Hz, 1H), 3.77 (m, 1H), 4.01 (m, 1H), 7.29 (d, J = 6.2 Hz, 1H), 7.37 (d, J = 6.8 Hz, 1H), 7.46 (dd, J = 15.1 Hz, J = 11.0 Hz, 1H), 7.46 (dd, J = 11.0 Hz, J = 1.2 Hz, 1H), 7.60 (dd, J = 8.2 Hz, J = 0.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H). – ^{13}C NMR (diastereomer **b**): δ/ppm = 20.63 (q, CH_3), 34.00 (t), 51.02 (d), 71.41 (d), 119.53, 120.59, 122.64, 123.63, 127.93, 128.16 (all d), 131.70, 144.56, 145.94 (all s). – MS: *m/z* (%) = 198 (33) [M^+], 180 (7), 179 (8), 165 (17), 155 (16), 154 (100), 153 (87), 152 (46), 151 (13).

$C_{14}C_{14}O$	calcd.:	C 84.81 H 7.12
(199.3)	found:	C 84.72 H 7.08.

12: IR (KBr): ν/cm^{-1}= 3055 (w), 3002 (w), 2944 (w), 2895 (w), 1704 (s, C=O), 1413 (m), 1359 (m), 1287 (m), 1161 (m), 821 (m), 781 (m). – ^{1}H NMR: δ/ppm = 2.12 (s, 6H, CH_3), 2.77 (t, 4H), 3.37 (t, 4H), 7.33 (m, 4H), 7.71–7.73 (dd, 2H). – ^{13}C NMR: δ/ppm = 30.15 (q, CH_3), 31.01 (t), 46.26 (t), 125.18, 128.99, 129.69 (all d), 130.47, 136.10, 137.15 (all s), 207.49 (s, C=O). – MS: *m/z* (%) = 268 (14) [M^+], 250 (16), 193 (36), 192 (95), 179 (19), 167 (64), 166 (18), 165 (44), 153 (41), 152 (63), 43 (100).

$C_{18}H_{20}O_2$	calcd.:	C 80.57 H 7.51
(268.4)	found:	C 80.57 H 7.48.

5-(1-Naphthyl)-3-methylpentan-2-on (**13**)

From 380 mg (1.00 mmol) of **7**, 200 mg (2.00 mmol) of homoallylic alcohol **10**, 1.10 g (8.00 mmol) of K_2CO_3, 1.28 g (2.00 mmol) of *n*-Bu_4NBr, and 11.2 mg (50 μmol) of palladium acetate at 100 °C for 46 h according to the general procedure. By flash-chromatography (TLC: silica/diethyl ether/hexane 1:1; R_f = 0.91, 0.83, 0.71, 0.61) the fraction with R_f = 0.83 is isolated and distilled *in vacuo* (140 °C; 0.25 mbar) to afford 110 mg (48%) of **13** as a yellow oil. – IR (film): ν/cm^{-1} = 3052 (w), 2933 (m), 2874 (w), 1709 (s, C=O), 1510 (w), 1457 (w), 1356 (w), 1167 (w), 799 (s), 780 (s). – ^{1}H NMR: δ/ppm = 1.19 (d, J = 7.1 Hz, 3H), 1.77 (m, 1H), 2.15 (s, 3H), 2.15 (m, 1H), 2.63 (m, 1H), 3.03 (m, 2H), 7.29 (d, J = 6.7 Hz, 1H), 7.38 ("t", 1H), 7.48 (m, 2H), 7.71 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.5 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H). – ^{13}C NMR: δ/ppm = 16.54 (q, CH_3), 28.19 (q, CH_3), 30.63 (t), 33.70 (t), 46.87 (d), 123.67, 125.48, 125.87, 125.95, 126.75, 128.75 (all d), 131.73, 133.87, 137.90, 212.31 (all s). – MS: *m/z* (%) = 226 (14) [M^+], 155 (18), 154 (100), 153 (32), 152 (9), 141 (26), 115 (15), 43 (10).

$C_{16}H_{18}O$	calcd.:	C 84.91 H 8.02
(226.3)	found:	C 84.88 H 7.98.

Benzocyclohept-2-ene-2-carboxaldehyde (**15**)

From 165 mg (0.500 mmol) of diiodide **14**, 1.45 g (2.50 mmol) of allylic alcohol **2**, 404 mg (4.00 mmol) of triethylamine and 5.61 mg (25 *m*mol) of palladium acetate at 80 °C for 44 h according to general procedure. By flash-chromatography (TLC: silica/diethyl ether/hexane 1:1; R_f = 0.60, 0.70) the product with R_f = 0.70 is isolated and destilled *in vacuo* (80 °C; 0.10 mbar) to yield 70 mg (81%) of colorless crystals with *m.p.* 73–76 °C. – IR (film): ν/cm^{-1} = 3347 (w), 3065 (w), 3022 (w), 2927 (m), 2884 (m), 1681 (s), 1637 (s), 1492 (m), 1453 (m), 1414 (m), 1232 (m), 1134 (s), 753 (s). – ^{1}H NMR: δ/ppm = 2.73 (m, 2H), 3.05 (t, 2H), 3.72 (s, 2H), 6.56 (t, J = 1.0 Hz, 1H), 7.13–7.18 (m, 4H), 9.31 (s, 1H). – ^{13}C NMR: δ/ppm = 28.17 (t), 30.76 (t), 31.14 (t), 126.55,

127.04, 128.37, 128.57 (all d), 140.14, 140.42, 140.90 (all s), 153.84 (d), 194.22 (d). – MS: *m/z* (%) = 172 (97) [M^+], 170 (27), 157 (24), 143 (79) [$C_{11}H_{11}^+$], 141 (49), 129 (73), 128 (100), 127 (24), 117 (66), 116 (95), 115 (80), 91 (29).
$C_{12}H_{12}O$ (172.2) calcd.: C 83.69 H 7.02 found: C 83.58 H 7.06.

1,2-Bis(3-oxobutyl)benzene (**16**)

From 330 mg (1.00 mmol) of 1,2-diiodobenzene (**14**), 1.45 g (15.0 mmol) of allylic alcohol **9**, 1.03 g (8.00 mmol) of *N*,*N*-diisopropylethylamine and 11.2 mg (50 μmol) of palladium acetate at 100 °C for 3 d according to the general procedure. By flash-chromatography (TLC: silica/diethyl ether/hexane 1:1; R_f = 0.33, 0.17) the product with R_f = 0.17 is isolated and distilled *in vacuo* (120 °C; 0.15 mbar) to give 122 mg (56%) of a colorless oil. – IR (film): ν/cm^{-1} = 3410 (w), 3061 (m), 3017 (m), 1713 (s), 1490 (m), 1411 (s), 1362 (s), 1283 (m), 1228 (m), 1162 (s), 759 (s). – ^{1}H NMR: δ/ppm = 2.15 (s, 6H), 2.73 (m, 4H), 2.88 (m, 4H), 7.12 (s, 4H). – ^{13}C NMR: δ/ppm = 26.29 (t), 30.10 (q, CH_3), 44.58 (t), 126.57 (d), 129.05 (d), 138.73 (s), 207.83 (s, C=O). – MS: *m/z* (%) = 218 (0.16) [M^+], 199 (45), 158 (10), 157 (18), 145 (44), 143 (13), 141 (35), 118 (19), 117 (73), 116 (16), 115 (18), 91 (12), 70 (14), 43 (100).
$C_{14}H_{18}O_2$ (218.3) calcd.: C 77.03 H 8.31 found: C 76.92 H 8.30.

(E)-4-Phenyl-but-3-en-1-ol (**17**)

From 165 mg (0.500 mmol) of diiodide **14**, 180 mg (2.50 mmol) of homoallylic alcohol **4**, 404 mg (4.00 mmol) of triethyl amine and 5.61 mg (25 *m*mol) of palladium acetate at 80 °C for 44 h according to general procedure. By flash-chromatography (TLC: silica/diethyl ether/hexane 1:1; R_f = 0.73, 0.27) the product with R_f = 0.27 is isolated; further purification by and distillation *in vacuo* (80 °C; 0.41 mbar) gives 15 mg (20%) of **17** as a colorless oil. – ^{1}H NMR- and ^{13}C NMR-spectra are in accord with reported data [9]. – ^{1}H NMR: δ/ppm = 2.50 (qd, 2H), 3.76 (t, J = 6.3 Hz, 2H), 6.21 (dt, J = 15.8 H, J = 7.2 Hz, 1H), 6.50 (d, J = 15.9 Hz, 1H), 7.20–7.37 (m, 5H). – ^{13}C NMR: δ/ppm = 36.44 (t), 62.06 (t), 126.11 (d), 126.38 (d), 127.30 (d), 128.57 (d), 132.84 (d), 137.30 (s).

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