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Macrocycles from simple building blocks by a multifold Heck-type coupling reaction

Gerald Dyker,[a,]* Daniel Kadzimirsz[a] and Gerald Henkel[b]

[a]*Fakultät für Chemie, Ruhr-Universität Bochum, Universitätsstraße 150, D-44780 Bochum, Germany*
[b]*Fachbereich 13-Chemie und Chemietechnik, Universität Paderborn, Warburger Str. 100, 33098 Paderborn, Germany*

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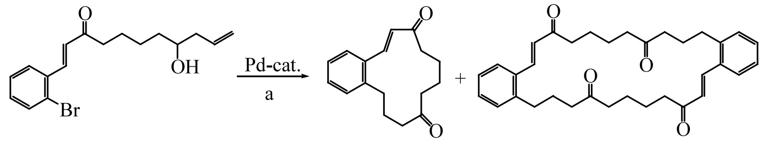
Abstract—Diiodobenzenes and bisallylic alcohols—two equivalents of each—were coupled under palladium catalysis to give oxofunctionalized macrocycles as 2:2 products. The 1:1 products as medium sized rings were disfavoured and not observed.

The intramolecular Heck reaction is a well-established method for the construction of carbocyclic as well as heterocyclic ring systems.[1] For macrocyclizations the reaction conditions of course have to be adjusted. In one of the first reported macrocyclizations via a Heck reaction one equivalent of the Pd-catalyst[2] was applied, but major improvements were achieved by using Jeffery's conditions,[3] using high dilution or working on solid support.[4] Thus, the Heck reaction became an efficient tool for the synthesis of macrocycles.[5]

In the examples reported for Heck-type macrocyclizations the precursors are rather tedious to prepare, especially when the target macrocycles are highly functionalized. This prompted us to evaluate allylic and homoallylic alcohols as building blocks, anticipating the formation of oxo-functionalized products. Recently, we tested the homoallylic alcohol **1** in a successful approach to the steroid framework via coupling product **2** and surprisingly found substantial amounts of by-product **3**, which was obviously derived from a twofold coupling reaction of **1**, initially by intermolecular C–C bond formation followed by a cyclization step.[6]

This encouraging result motivated us to test the scope of macrocyclizations making use of the coupling reaction of aryl halides with allylic and homoallylic alcohols. The generalized pictograms outlined in Scheme 2 map out two types of these processes: for type A both functionalities involved are present in a single starting material **4**, in fact, this is a generalization of the reaction in Scheme 1; for macrocyclizations of type B two different bifunctional starting materials **7** and **8** with corresponding functionality are utilized. In this case the first intermolecular coupling reaction gives rise to intermediate **9**, an extended analogue of **4**, which in principle has again the potential to directly cyclize to give **10**. When the cyclization to **10** is hindered by geometric or steric requirements the formation of extended macrocycles **11** should be favoured, either by a cyclization of two equivalents of intermediate **9** or, and even more likely, by stepwise reaction of **9** with **7** and **8**.



1 **2** (61%) **3** (17%)

Scheme 1. Pd-catalyzed macrocyclization of functionalized homoallylic alcohol **1**; a: 5 mol% Pd(OAc)$_2$, *N*-ethyldiisopropylamine, LiCl, DMF, 80°C, 2 days, high dilution.

Keywords: domino processes; Heck reaction; ketones; macrocycles; palladium catalysis.

* Corresponding author.

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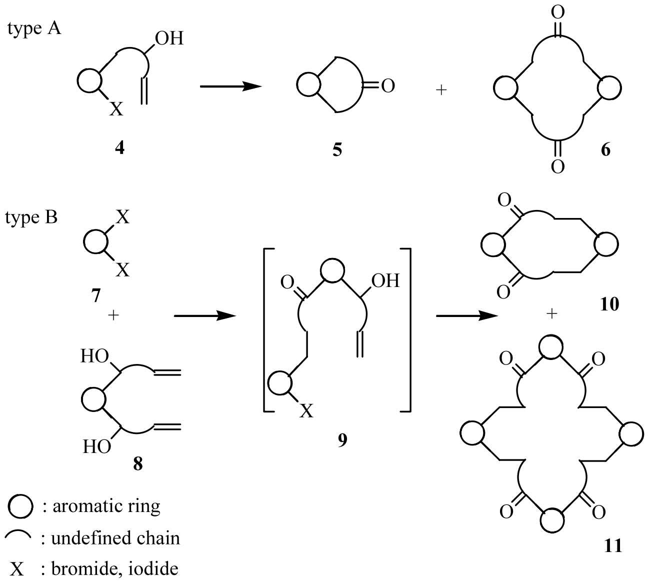

Scheme 2. Pictogram for macrocyclizations by coupling reactions of aryl halides with allylic and homoallylic alcohols.

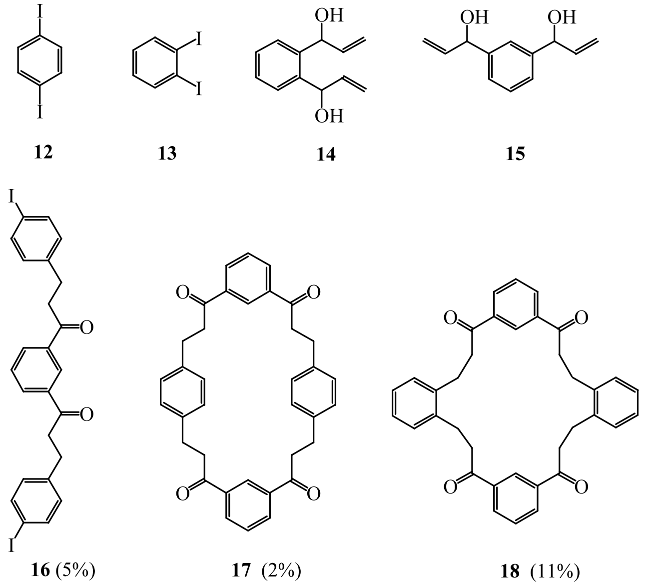

Figure 1. Starting materials and products of the Heck-type coupling reactions.

The latter type of cyclization seemed especially attractive, since it represents the synthesis of multifunctionalized macrocycles from simple precursors in a single preparative step. As model coupling components we chose commercially available diiodobenzenes **12** and **13** and the bisallylic alcohols **14** and **15**, easily accessible from the corresponding dicarboxaldehydes (Fig. 1). Since initial tests of the *ortho*-isomer **14** with both diiodobenzenes **12** and **13** did not seem to yield any macrocycles under high dilution conditions (0.025 M–0.008 M) even though complete consumption of the starting material took place, we anticipated that the *meta*-substituted bis(alcohol) **15** would be the most promising candidate. Heating a mixture of **15** with 1 equivalent of 1,4-diiodobenzene **12** in DMF (0.013 M) for 2 days at 100°C in the presence of 5% $Pd(OAc)_2$ and 8 equivalents of NEt_3 gave a 5% yield of the twofold coupling product **16** and 2% of the desired macrocycle **17**. Due to the C_{2V}-symmetry of **17** the ring size could not be determined by NMR, but was proven by mass spectroscopy ($m/z = 512$).

Further experiments showed that the formation of the 26-membered ring in **17** is rather independent of the various parameters of the reaction conditions. Changing the solvent (e.g. to DMSO) or the base (e.g. Hünig's base or Na_2CO_3) as well as using Jeffery's conditions,[3] and even high dilution conditions did not increase the yield of the macrocycle. Obviously, the geometries of the starting materials are more important for the

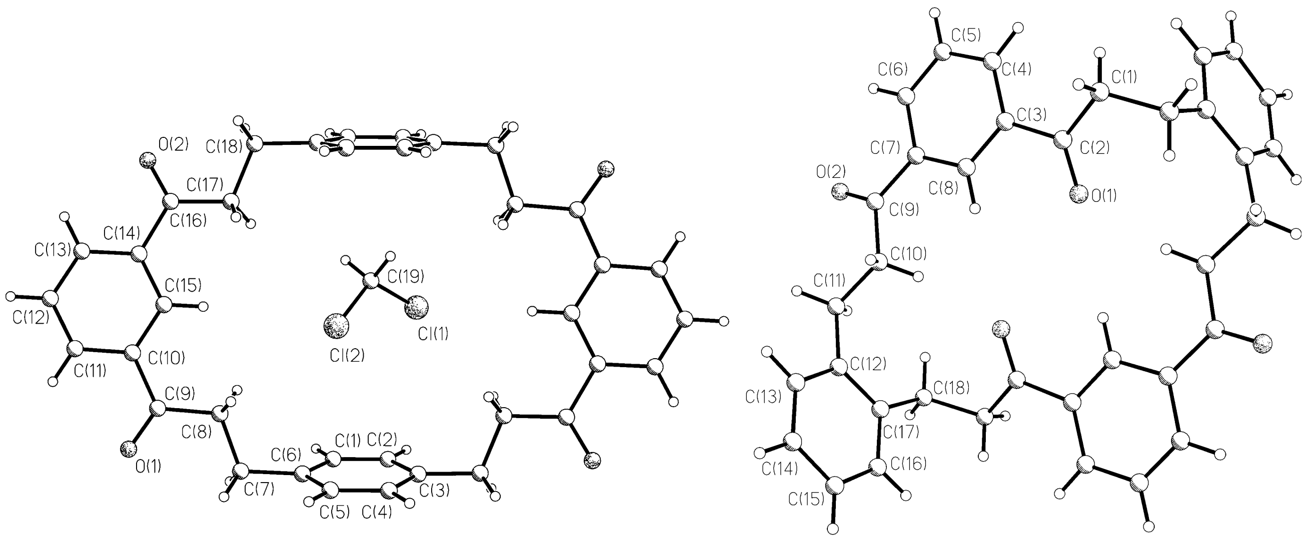

Figure 2. Crystal structures of macrocycles **17** and **18**.

achievable yield: upon changing to *ortho*-diiodobenzene **13** the yield of the corresponding macrocycle **18**, a 22-membered ring, increased to 11%, indicating that in this case each C–C bond forming step proceeds with an efficiency range of 60%.[7]

Both macrocycles **17** and **18** obtained by this method can be crystallized by slow evaporation of a CH_2Cl_2/2-propanol/MTBE solution. The resulting crystals were of sufficient quality for X-ray-structure analysis (Fig. 2).[8]

In summary the Heck-reaction using allylic and homoallylic alcohols can be used to construct large, symmetric macrocyclic rings from simple, readily available starting materials in a one-pot reaction. In particular, the oxo-functionalities might be useful for the construction of macrocyclic host molecules with selective binding properties.

Acknowledgements

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7. Selected physical and spectroscopic data; **17**: TLC, $R_f=0.28$ (silica, MTBE/pentane 1:2); mp 190–192°C (from isopropanol; single crystals for X-ray structure analysis from CH_2Cl_2/*i*-PrOH/MTBE); IR (KBr): $\nu=3019\ cm^{-1}$ (w), 2929 (m), 1678 (vs), 1599 (m), 1515 (m), 1373 (m), 1304 (s), 1193 (s), 981 (m), 808 (s), 685 (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.30$ (‘d’, $J=6.3$ Hz, 6H), 7.63 (‘t’, $J=6.3$ Hz, 2H), 7.20 (s, 8H), 3.29 (‘t’, $J=8.2$ Hz, 8H), 3.03 (‘t’, $J=8.2$ Hz, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=197.54$ (s), 139.24 (s), 136.82 (s), 132.35 (d), 129.55 (d), 128.89 (d), 127.66 (d), 41.81 (t), 29.52 (t); MS (70 eV, 250°C) *m*/*z* (%): 528 (67 M^+), 510 (7), 393 (26), 263 (35), 117 (74), 44 (100), HRMS: calcd. for $C_{36}H_{32}O_4$: 528.23006, found: 528.23084. **18**: TLC, $R_f=0.45$ (silica, MTBE/hexanes 1:1); m.p. 228°C (from CH_2Cl_2/*i*-PrOH); IR (KBr): $\nu=3061\ cm^{-1}$ (w), 2902 (w), 1681 (vs), 1595 (m), 1490 (m), 1165 (s), 803 (m), 755 (s), 685 (m); ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.61$ (t, $J=1.4$ Hz, 2H), 8.19 (dd, $J=7.8$, 1.6 Hz, 4H), 7.58 (t, $J=7.8$ Hz, 2H), 7.21 (dd, $J=5.6$, 3.5 Hz, 4H), 7.14 (dd, $J=5.8$, 3.4 Hz, 4H), 3.46 (t, $J=7.5$ Hz, 8H), 3.14 (t, $J=7.4$ Hz, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=198.50$ (s), 138.94 (s), 137.16 (s), 132.23 (d), 129.26 (d), 129.23 (d), 128.02 (d), 126.72 (d), 40.05 (t), 26.68 (t); MS (70 eV, 260°C) *m*/*z* (%): 528 (3, M^+), 510 (100), 492 (36), 231 (48), 147 (89), 77 (62); elemental analysis: $C_{36}H_{32}O_4$ (528.64); calcd. C 81.79, H 6.10, found C 81.53, H 6.06.
8. X-ray data have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC-214085 for **17** and CCDC-214084 for **18**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ [fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk].