Transmetallation with Palladium(II) of an Organomercurial arising from Mercury(II)-mediated Cyclopropane Cleavage. Tuning of the Palladium Reactivity and a Novel, Intramolecular Redox Reaction

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The cleavage of the fused-ring cyclopropane hydroxy derivative **1** by means of Hg^{II} is highly stereoselective and gives a rearranged organomercurial **3**, transmetallation of which with Pd^{II} can be controlled by ligands to afford either lactol **4** or acid **8**; the latter compound is formed *via* an intramolecular insertion of Pd into the C–H bond (**6** → **7**), as evidenced by isotopic labelling.

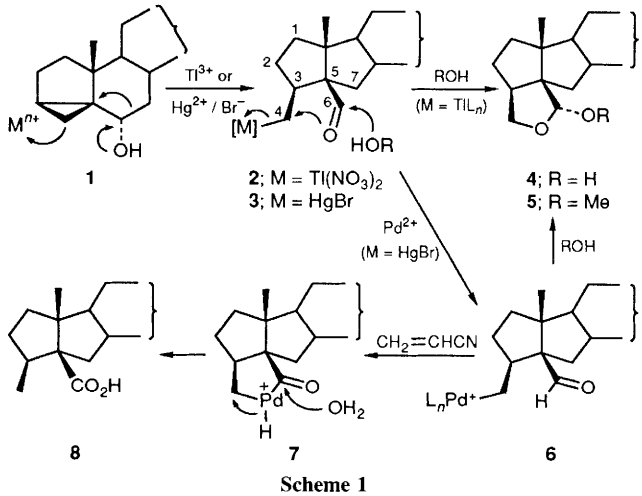
Transmetallation is a promising methodology that takes advantage of combining specific reactivities of different metals.[1] Recently, we have described a stereospecific, Tl^{III}-mediated cleavage of the steroidal cyclopropane derivative **1**, followed by a unique skeletal rearrangement that afforded lactone **4** *via* the thalliated intermediate **2** (Scheme 1).[2] Mercury(II) ion, isoelectronic with thallium(III), is also known to be capable of cleavage of cyclopropane.[3] Herein, we report the reaction of **1** with Hg^{II}, isolation of the organomercurial product, and its transmetallation with Pd.

Treatment of 3α,5-cyclo-5α-cholestan-6α-ol **1**[4] with $Hg(NO_3)_2.H_2O$ in 1,2-dimethoxyethane (DME)–MeCN (3 : 2) at room temperature for 1.5 h, followed by quenching with aqueous KBr, afforded the organomercurial **3** in 97% isolated yield (Scheme 1),† which, unlike the thalliated species **2**, was fairly stable.

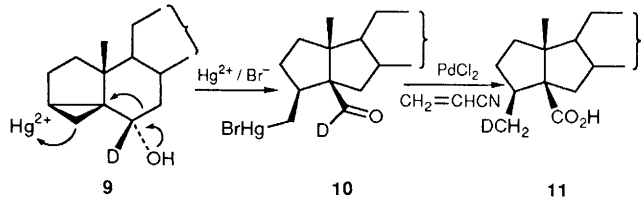
Catalytic reaction of **3** with Li_2PdCl_4 (5 mol %; generated *in situ* from $PdCl_2$ and LiCl) and $CuCl_2$ (3 equiv.) in DME–H_2O,[5] presumably proceeding *via* the organopalladium(II) species **6**, furnished lactol **4**; in the presence of MeOH, the corresponding methyl acetal **5** was formed. The same reaction was observed in the absence of $CuCl_2$, when a stoichiometric amount of Li_2PdCl_4 was used. Thus, similarly to thallium, in this instance palladium served as a good leaving group and enabled the transformation of **3** to **4** to take place employing the same mechanism.

When the transmetallation of the organomercurial **3** with Li_2PdCl_4 was attempted in the presence of a π-acid, such as maleic anhydride, acrylonitrile or cyclohex-2-enone, acid **8** was isolated as the sole or major product,‡ rather than the lactol **4**. Apparently, the coordination to a π-acid dramatically changed the reactivity of Pd.§ This rather unexpected reaction can be rationalized as follows. Instead of undergoing the $5(O)^{\pi,n}$-*exo-tet* ring closure[6] to **4**, in this instance the transient organopalladium **6** preferred an intramolecular insertion into the C–H bond of the aldehyde group.[7] This step generated palladacycle **7** (a highly unstable Pd^{IV} species), which collapsed to the acid **8** *via* a hydrogen transfer from Pd to C(4) (reductive elimination) followed by hydrolysis of the acyl–Pd bond (presumably *via* acyl chloride)[8] and formation of Pd^0.¶ In order to verify this mechanism, deuteriated aldehyde **10** was prepared from [6β-^{2}H]-alcohol **9** (Scheme 2), which in turn was synthesized by a highly stereoselective reduction of 3α,5-cyclo-5α-cholestan-6-one with $LiAl^2H_4$. Transmetallation of **10** under the same conditions as applied to its unlabelled counterpart (*i.e.* Li_2PdCl_4, CH_2=CHCN, DME, H_2O room temp.) resulted in the formation of acid **11** labelled in the methyl group. The mass and ^{13}C NMR spectra revealed an almost quantitative transfer of deuterium from the aldehyde group to the methyl,‖ which is in an excellent agreement with the proposed mechanism.

The observed behaviour of Hg^{2+} parallels the reactivity of Tl^{3+} in the cyclopropane ring-opening. The difference



Scheme 1



Scheme 2

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† ^1H NMR: δ 9.72 (s, 1 H, CHO); ^{13}C NMR: δ 34.78 (CH_2HgBr) and 206.22 (CHO); ^{199}Hg NMR: δ −1063 (indirectly referenced to $HgCl_2$ at δ −1501.6 and Ph_2Hg at δ −808.5). The full assignment of carbon signals in the ^{13}C NMR spectrum has been achieved.

‡ IR: $\nu_{C=O}$ 1683, ν_{COH} 2500–3100 cm^{-1}; ^{13}C NMR: δ 181.87.

§ This transformation occurs with a stoichiometric amount of Pd^{2+}. When attempted as a catalytic process with added $CuCl_2$ to reoxidize Pd^0, no reaction was observed. It was also found that addition of $CuCl_2$ to the stoichiometric experiment (still in the presence of a π-acid) dramatically slowed the rate; a 2 : 1 mixture of **4** and **8** was obtained. Hence, a different type of oxidant has to be sought in order to make this process catalytic.

¶ The reversed sequence may also be considered. However, this would first generate a nucleophilic CO_2H group which may be capable of S_N2 replacing of Pd^{II} at C(4) and forming a γ-lactone, in analogy to the conversion of **6** into **4**.

‖ In the proton-decoupled ^{13}C NMR spectrum of **8**, the C(4) (methyl) appeared at δ 13.97 as a singlet. This resonance was replaced by a triplet at δ 13.73 in the spectrum of deuteriated **11**. No trace of the signal corresponding to the unlabelled methyl was detected in the latter spectrum. The mass spectrum of **11** confirmed that ≥95% of deuterium had migrated to the methyl group. An authentic sample of **11** was prepared from **3** by reduction with $LiAl^2H_4$ followed by Jones' oxidation.

between Tl and Hg is only seen in the fate of the organometallics generated in this way; the organothallium intermediate **2** is highly unstable and only undergoes the S_N2 ring closure (**2** → **4**) which seriously limits the synthetic applicability. By contrast, the organomercurial **3** is fairly stable, and can be isolated in the pure state and utilized for subsequent transformations.** This divergence of behaviour can serve as a clear example of how a choice of metal can be used to delicately control the reactivity. The organopalladium intermediate **6** offers further opportunities for tuning; here, it is the ligands attached to the same metal that have the decisive influence. In the absence of added ligands, the Pd^{II} intermediate **6** undergoes a clean S_N2 reaction, while addition of π acids promotes its conversion into the Pd^{IV} species **7** *via* insertion into the C–H bond. We are confident that these findings are of a general nature and might be used as the key steps for construction of complex molecules, such as triquinanes. Furthermore, the intramolecular redox reaction of **6**, producing methyl acid **8**, is a novel, mild procedure (related to, *e.g.* the intramolecular Cannizzarro or Tishchenko reaction) of potential synthetic applicability.

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** Aside from the Pd-mediated conversion of **3** into **4**, **5**, or **8**, we have found that, *e.g.*, Wadsworth–Emmons alkenation can be performed with **3** without losing the –HgBr functionality. Furthermore, reaction of **3** with Me_2CuLi (−78 °C, 5 min) led to a ring closure producing the corresponding cyclobutanol in high yield.[9]

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