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A Stereoselective Synthesis of cis- and trans-Fused Lactones via the Palladium(II)-Catalyzed Carbonylation of Organomercurials

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Abstract: Organomercurials **2a-c**, obtained by the regioselective, Hg(II)-mediated cleavage of cyclopropyl alcohols **1a-c**, are converted into the corresponding 5-membered *cis*-annulated lactones **3a-c** via the Pd(II)-catalyzed carbonylation in the presence of *p*-benzoquinone. Isomeric, *trans*-fused lactones can be synthesized in a similar way (**6** → **7**). The carbonylation occurs under an atmospheric pressure of CO.

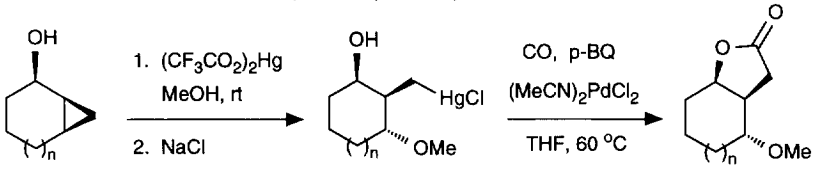
The five-membered lactone, annulated to another ring in a *cis*- or *trans*-fashion, is a typical structural motif encountered in a number of natural products.[1] Whereas the stereoselective synthesis of *cis*-lactones is usually accomplished via halolactonization and related reactions,[2] *trans*-isomers are more difficult to obtain.[3] The frequent requirement for the presence of another substituent in a stereo-defined position may present additional synthetic problems. Herein, we wish to report on a versatile method for the stereoselective construction of either *cis*- or *trans*-annulated 5-membered lactones with three adjacent chiral centers on the parent ring.

Recently, we have reported on the stereoselective "corner" opening of cyclopropane rings with mercury(II)[4,5] and thallium(III)[6] reagents. Whereas the resulting organothallium species are unstable and immediately undergo subsequent *in situ* reactions,[6] the corresponding organomercurials can be isolated and handled as stable compounds.[4,5,7] Thus, the *cis*-cyclopropyl alcohols **1a-c**, obtained via the stereoselective Simmons-Smith cyclopropanation of the corresponding allylic alcohols, are regioselectively opened with $(CF_3CO_2)_2Hg$ in MeOH[5,9] to give, after quenching with aq. NaCl, the organomercurials **2a-c** as the sole (**2a** and **2b**) or major (**2c**) products (Scheme 1).[5]

Carbonylation[10] of **2a** under an atmosphere of carbon monoxide was first explored in the presence of stoichiometric quantities of palladium(II) salts, namely $(AcO)_2Pd$, $(CF_3CO_2)_2Pd$, $PdCl_2$, $(Ph_3P)_2PdCl_2$, or $(MeCN)_2PdCl_2$.[11] The latter complex was the most promising one, mediating an essentially quantitative conversion of **2a** into the lactone **3a** (rt, 24 h);[12] it has, therefore, been selected for the development of a catalytic cycle.

Since Pd(II) is converted into Pd(0) in the carbonylation reaction, a successful catalytic cycle would require that an efficient oxidant be employed in a stoichiometric amount. Among mild oxidants that are known to serve this purpose, copper(II) salts seem to play a prominent role, as documented by their successful use in methoxycarbonylation reactions.[10b,13] However, after numerous experiments, we found *p*-benzoquinone to be superior to $CuCl_2$, $(AcO)_2Cu$, or $Cu(NO_3)_2$ with our system.[14] Thus, on heating at 60 °C with $(MeCN)_2PdCl_2$ (10 mol%) and *p*-benzoquinone (2.0 equiv) in THF under an atmosphere of CO for 4 days, the organomercurial **2a** has been almost quantitatively converted into the lactone **3a** as an essentially pure product in 60% isolated yield.[15,16] Similarly, organomercurials **2b** and **2c** showed practically quantitative conversions, affording the respective lactones **3b** (59%) and **3c** (52%).

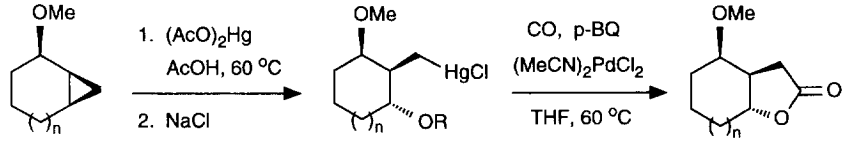
Scheme 1: **a**, n = 1; **b**, n = 2; **c**, n = 0; p-BQ = p-benzoquinone



1a - c **2a - c** **3a - c**

The isomeric organomercurials required for the synthesis of *trans*-fused lactones were prepared as follows. The cyclopropyl alcohol **1a** was first protected by methylation (MeI, NaH, THF, 40 °C, 1 h) and the resulting methyl ether **4a** (69%) was treated with $(AcO)_2Hg$ in AcOH (60 °C, 2 h), followed by quenching with aq. NaCl (Scheme 2). The chloromercurio acetate **5a** thus obtained was then hydrolyzed (NaOH, MeOH, rt) to furnish the chloromercurio alcohol **6a**. Note that, in contrast to Scheme 1, where $(CF_3CO_2)_2Hg$ in MeOH was used to introduce the MeO group, it was now the acetate anion that served as a nucleophile in the cyclopropane ring-opening;[17] this reversal of reactivity enabled us to eventually prepare **6a** with the desired *trans*-configuration. The seven-membered ring analogue **6b** was prepared from **1b** via **4b** in a similar manner. The two organomercurials **6a** and **6b** have been converted into the *trans*-lactones **7a** (63%)[18] and **7b** (58%), respectively, under the same conditions used for their *cis* counterparts.[19] Thus, these experiments have demonstrated that even the *trans*-fused lactones can be synthesized using this methodology.

Scheme 2: p-BQ = p-benzoquinone



4a, n = 1
4b, n = 2

5a, R = Ac, n = 1
5b, R = Ac, n = 2
6a, R = H, n = 1
6b, R = H, n = 2

7a, n = 1
7b, n = 2

In summary: We have developed an efficient method for the annulation of 5-membered lactone rings, in which three consecutive chiral centers are introduced. The method relies on the cleavage of an annulated cyclopropane ring with Hg(II) (**1** → **2** and **4** → **5**), followed by the Pd(II)-catalyzed carbonylation (**2** → **3** and **6** → **7**), and works with comparable efficiency for the construction of either *cis*- or *trans*-fused lactone rings (**5** or **7**). The choice of the Hg(II) reagent, in conjunction with selective protection, controls the final stereochemistry of the lactone annulation.

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References and Notes

1. Nakanishi, K.; Goto, T.; Itô, S.; Natori, S.; Nozoe, S. *Natural Product Chemistry*; Kodansha: Tokyo, 1974; Vol. I-III.
2. (a) Bartlett, P. A. in "Olefin Cyclization Processes that form Carbon-Heteroatom Bonds" *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p. 411. For a recent, Pd-catalyzed procedure, see: (b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.
3. Kočovský, P.; Tureček, F.; Hájíček, J. *Synthesis of Natural Products: Problems of Stereoselectivity*; CRC: Boca Raton, FL, 1986; Vol. I and II.
4. (a) Kočovský, P.; Šrogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* **1994**, *116*, 186. (b) Kočovský, P.; Šrogl, J. *Org. Chem.* **1992**, *57*, 4565.
5. Kočovský, P.; Grech, J. M.; Mitchell, W. L. *J. Org. Chem.* **1995**, *60*, 1482.
6. Kočovský, P.; Pour, M.; Gogoll, A.; Hanuš, V.; Smrčina, M. *J. Am. Chem. Soc.* **1990**, *112*, 6735.
7. We have also shown that the organomercurials can be transmetalated with Cu[4,5] and Pd.[8]
8. Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086.
9. (a) Collum, D. B.; Mohamadi, F.; Hallock, J. H. *J. Am. Chem. Soc.* **1983**, *105*, 6882. (b) Collum, D. B.; Still, W. C.; Mohamadi, F. *J. Am. Chem. Soc.* **1986**, *108*, 2094.
10. Low yields have usually been obtained for those carbonylations, which required the Hg → Pd transmetalation at an sp^3 carbon: (a) Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 335. (b) Kočovský, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580. By contrast, much better results have been obtained when the transmetalation occurred at an sp^2 carbon: (c) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505 and *ibid.* **1987**, *28*, 1023. See also: (d) Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009. (e) Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597.
11. For elucidation of the Hg → Pd transmetalation, see ref 8 and: (a) Heumann, A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 207. For general aspects of organomercury chemistry, see: (b) Larock, R. C. *Organomercury Compounds in Organic Synthesis*; Springer: Berlin, 1985. (c)

Larock, R. C. *Solvomercuration - Demercuration Reactions in Organic Synthesis*; Springer: Berlin 1986.

12. All new compounds were characterized by spectral and analytical methods.
13. For reviews on the Pd(II)-catalyzed alkoxycarbonylations, see: (a) Hosokawa, T.; Murahashi, S. *Acc. Chem. Res.* **1990**, *23*, 49. (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. See also: (c) Semmelhack, M. F.; Cheung, A. W. H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 7455.
14. For other Pd-catalyzed reactions that use *p*-BQ, see: (a) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335. (b) Bäckvall, J.-E. *Pure Appl. Chem.* **1983**, *55*, 1669. (c) Bäckvall, J.-E. *New J. Chem.* **1990**, *14*, 447. (d) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, *64*, 429. (d) McMurry, J. E.; Kočovský, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (e) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975 and references therein. (f) Grennberg, H.; Gogoll, A.; Bäckvall, J.-E. *Organometallics* **1993**, *12*, 1790. (g) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749.
15. All yields refer to isolated (preparative) yields of the often volatile compounds. The genuine yields (e.g., the "GC yields") were, in most cases, much higher.
16. ***Typical experiment:*** In a 10 mL flask, fitted with a condenser connected to a balloon containing carbon monoxide, was stirred a solution of the organomercurial **2a**[5] (200 mg; 0.52 mmol), *p*-benzoquinone (113 mg; 1.0 mmol), and $(CH_3CN)_2PdCl_2$ (13 mg; 0.052 mmol) in THF (3 mL) at 60 °C for 4 days. The reaction was then quenched with sodium dithionite, the product was taken up into ether, and the ethereal solution was successively washed with water, 5% aqueous HCl (3x), water, 5% aqueous $KHCO_3$ (3x), and water, and dried with Na_2SO_4. The solvent was evaporated and the residue was chromatographed on silica gel (21 g) with a petroleum ether-acetone mixture (98:2) to give the pure lactone **3a** (54 mg; 60%): ^{1}H NMR δ 1.04 (m, 1 H), 1.27-1.65 (m, 3 H), 2.00 (m, 2 H), 2.13 (m, 1 H), 2.47 (dd, 1 H, *J* = 15.5 and 7.8 Hz, CH_2-CO_2), 2.56 (dd, 1 H, *J* = 17.5 and 6.0 Hz, CH_2'-CO_2), 2.93 (ddd, 1 H, *J* = 10.6, 9.1, and 3.8 Hz, C*H*-OCH_3), 3.26 (s, 3 H, CH_3O), 4.60 (dd, 1 H, *J* = 7.0 and 3.5 Hz, CH-OCO); ^{13}C NMR δ 18.5 (t), 27.6 (t), 27.8 (t), 36.1 (t), 42.3 (d), 57.0 (q), 79.7 (d), 80.5 (d), 177.5; IR ν 1772 cm^{-1}; HRMS *m/z* (%) 170 ($M^{+\bullet}$, 14).
17. Note, that the less reactive $(AcO)_2Hg$ required higher temperature than did the more electrophilic[5] $(CF_3CO_2)_2Hg$.
18. **7a:** IR ν(C=O) 1777 cm^{-1}; ^{13}C NMR δ 176.9 ppm.
19. The five-membered derivative **1c** gives a 2:1 mixture of regioisomers on the cyclopropane cleavage.[5] Therefore, it was omitted in the *trans* series.

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