Palladium-mediated intramolecular acylation reaction in the attempted phosphinylation of a sterically hindered trifluoromethylsulfonyloxybiaryl carboxylic ester†

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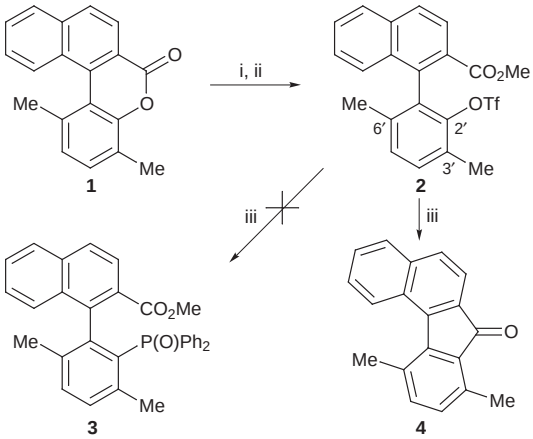
The unexpected palladium-assisted cyclization reaction of a sterically hindered *o*-methoxycarbonyl-*o′*-trifluoromethylsulfonyloxybiaryl gives fluorenone 4, *via* intramolecular acylation instead of the attempted phosphinylation.

Chiral phosphine ligands, mostly bisphosphines, constitute versatile tools for efficient transition metal catalyzed asymmetric reactions.[1] For some types of reactions, however, the use of bisphosphine transition metal complexes is hampered by their lack of reactivity and selectivity towards the desired reaction pathway. These problems can be overcome by the use of monodentate phosphine ligands ('MOP' ligands) introduced by Hayashi *et al*., who have demonstrated the efficiency of such ligands in enantioselective hydrosilylation and allylic alkylations.[2,3]

A promising novel MOP ligand with a biaryl backbone would be **3**, which, in contrast to related axially chiral binaphthyl derivatives previously prepared,[2,3] should exhibit a distinctly higher steric hindrance—and thus stereo-differentiation—in the proximity of the phosphorous part. Its *O*-trifluromethylsulfonyl activated synthetic precursor **2** should easily be synthesized in an enantiomerically pure form, with either configuration at the biaryl axis, by atropisomer-selective ring cleavage[4] of the configuratively unstable[5] lactone-bridged biaryl **1**. Here we report on the preparation and attempted phosphinylation of **2** (here still in racemic form), leading to a novel palladium-mediated ring closure to give fluorenone **4**.

Triflate **2**§ was synthesized from lactone **1**¶ by ring cleavage with $MeOH–K_2CO_3$ and esterification of the resulting free phenolic oxygen function with Tf_2O (Scheme 1). Reaction of **2** with $HP(O)Ph_2$ in the presence of $Pd(OAc)_2$ (10 mol%) and Hünig's base ($EtNPr^i_2$) according to Hayashi's method[6] gave no detectable amount of the anticipated phosphine oxide **3**, the most conspicuous product being a yellow nonpolar compound (28% isolated yield‖), which turned out to be the unexpected fluorenone **4**.**



Scheme 1 *Reagents and conditions*: i, MeOH, K_2CO_3, THF, room temp., 1 h; ii, Tf_2O, DABCO, CH_2Cl_2, 0 °C, 12 h; iii, $Pd(OAc)_2$, dppp, $HP(O)Ph_2$, $EtNPr^i_2$, Me_2SO, 100 °C, 6 d

Its structure was elucidated mainly *via* NMR, mass and combustion analytical data and confirmed by an X-ray structure analysis of single crystals obtained from light petroleum–Et_2O (2 : 1) (see Fig. 1), which unambiguously proves the unexpected tetracyclic constitution.†† Due to the steric hindrance in the C(5)–C(4c)– C(4b)–C(4a))–C(4) 'bay' with the adjacent methyl group at C(4), the molecule is not flat, but helically twisted, giving rise to two enantiomers. These are both found in the crystal, Fig. 1 arbitrarily showing the *M*-helical enantiomer. The overall molecular distortion of the 'inner spiral loop',[7] *i.e.* the sum of the dihedral angles α [C(13)– C(4)–C(4a)–C(4b), 5.6(9)°], β [C(4)–C(4a)–C(4b)–C(4c), 23.7(9)°] and γ [C(4a)–C(4b)–C(4c)–C(5), 10.4(8)°], is distinctly smaller (39.7°) than for comparably substituted lactones related to **1** (> 60°).[7]

The reason why no phosphine oxide **3** was formed must be seen in the unusually high steric hindrance at the substitution site, C-2′, which is bounded (as in other cases) by the bulky

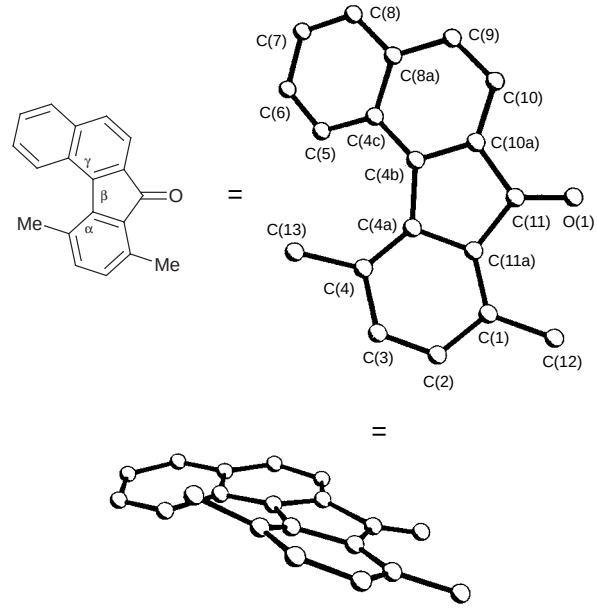
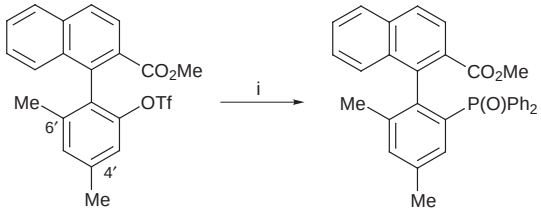


Fig. 1 Molecular structure of fluorenone **4** in the crystal. All hydrogen atoms are omitted for clarity. Selected bond length (Å) and angles (°): O(1)–C(11) 1.238(6), C(11)–C(11a) 1.470(7), C(10a)–C(4b) 1.390(7), C(10)–C(9) 1.372(6), C(9)–C(8a) 1.410(7), C(4c)–C(4b) 1.431(6), C(11)–C(10a) 1.479(6), C(8a)–C(4c) 1.426(6), C(4b)–C(4a) 1.501(6), C(4a)–C(11a) 1.427(6), C(4)–C(13) 1.514(7), C(1)–C(12) 1.495(7); O(1)–C(11)–C(10a) 124.9(5), O(1)–C(11)–C(11a) 128.2(4), C(4b)–C(10a)–C(10) 123.6(4), C(9)– C(8a)–C(8) 120.8(5), C(5)–C(4c)–C(4b) 123.8(5), C(4c)–C(4b)–C(4a) 133.8(5), C(4)–C(4a)–C(4b) 132.5(5), C(4a)–C(4)–C(13) 127.1(4), C(11a)–C(1)–C(12) 123.0(5), C(4a)–C(11a)–C(11) 107.6(4), C(4b)–C(10a)–C(11) 109.1(5), C(11a)–C(11)–C(10a) 106.9(5), C(11a)–C(4a)–C(4b) 107.9(4).



5 **6**

Scheme 2 *Reagents and conditions*: i, $Pd(OAc)_2$, dppp, $HP(O)Ph_2$, $EtNPr^i_2$, Me_2SO, 100 °C, 6 d

substituted naphthyl residue at C-1′ *and* by the unprecedented additional methyl group at C-3′ (Scheme 1). That this extra steric hindrance is responsible for the failure of the introduction of the sterically demanding phosphorus substituent was demonstrated by successfully performing the desired substitution on the regioisomeric compound **5**,‡‡ in which the methyl group is located at C-4′ (Scheme 2). Under the same reaction conditions as applied above, this triflate smoothly gave the desired phosphine oxide **6**,§ in high yields (74% of isolated pure material) and within the 'normal'[6] reaction time of about 12 h. The much slower fluorenone formation from the 3′-methyl isomer **2**, apparently by C–C bond formation of the presumed 2′-palladated intermediate§§ with the methoxycarbonyl substituent on the naphthalene part, took about a week.

To the best of our knowledge, the ring closure reaction of **2** to give **4** is the first intramolecular acylation mediated by $Pd(OAc)_2$ to give substituted fluorenone systems. Initial attempts to enhance the yield of **4** and decrease the reaction times, *e.g.* by using larger amounts of the palladium catalyst, gave improved yields of up to 42%, while in the absence of either $Pd(OAc)_2$, $EtNPr^i_2$ or $HP(O)Ph_2$, no reaction took place. Investigations to further optimize this new reaction, also with respect to the suppression of the likewise observed deoxygenation, and to investigate its possible application to natural product synthesis, are in progress.

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 347 'Selektive Reaktionen Metall-aktivierter Moleküle') and by the Fonds der Chemischen Industrie.

Notes and References

† Part 69 in the series 'Novel Concepts in Directed Biaryl Synthesis'; for Part 68, see W. A. Schenk, J. Kümmel, I. Reuther, N. Burzlaff, A. Wuzik, O. Schupp, G. Bringmann, submitted for publication in *Eur. J. Inorg. Chem.*

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§ All new compounds were fully characterized by spectroscopic and analytic methods.

¶ Prepared from the corresponding bromonaphthoic aryl ester, in analogy to ref. 7.

‖ In this reaction, likewise 25% of starting material **2** was recovered, along with its deoxygenation product (H instead of OTf, 29%).

** *Selected data* for **4**: ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H($CDCl_3$, 25 °C) 2.64 (s, 3 H, Me), 2.68 (s, 3 H, Me), 6.99, 7.20 (d × 2, 2 H, 2-H, 3-H, $^2J_{HH}$ 7.9), 7.47–7.57 (m, 2 H, Ph), 7.70–7.77 (m, 2 H, Ph), 7.81–7.88 (m, 1 H, Ph), 8.31–8.37 (m, 1 H, Ph); δ_C 194.8 (C=O), 145.5–119.3 (Ph), 23.7, 17.6 (Ph*Me*); *m/z* 258 (100%) $[M]^+$, 243 (10) $[M - CH_3]^+$, 230 (15) $[M - CO]^+$, 228 (18) $[243 - CH_3]^+$.

†† *Crystal data* for **4**: $C_{19}H_{14}O$, orange needles, crystal dimensions 0.3 × 0.3 × 0.3, M = 258.30, monoclinic, space group $P2_1/c$, a = 11.602(3), b = 14.641(2), c = 7.7016(14) Å, β = 102.914(8)°, V = 1275.1(4) Å^3, Z = 4, D_c = 1.345 g cm^{-3}, μ = 0.081 mm^{-1}, F(000) = 544, 2810 reflections collected ($3 \leqslant \theta \leqslant 23°$) at 173(2) K, 1664 independent (R_{int} = 0.1079), 1663 used in the structure refinement, $R1$ = 0.0652 [$I \geqslant 2\sigma(I)$], $wR2$ = 0.1665 [all data], gof = 0.974 for 184 parameters, largest difference peak/hole = 0.233/−0.307 e Å^{-3}. Data were collected from a shock-cooled crystal on an Enraf-Nonius CAD4 four circle diffractometer (graphite-monochromated Mo-Kα radiation, λ = 0.71073 Å) equipped with low temperature devices (ref. 8). The structure was solved by direct methods (SHELXS-96 (ref. 9) and refined by full-matrix least-squares methods against F^2 (SHELXL-96) (ref. 10). Anisotropic refinement of all non-H atoms. R values: $wR2 = [[w(F_o^2 - F_c^2)^2]/[w(F_o^2)^2]]^{1/2}$, $R1 = ||F_o| - |F_c||/|F_o|$. CCDC 182/859.

‡‡ The triflate **5** was synthesized analogously to compound **2**, starting from the corresponding *o*-methoxycarbonyl-*o*′-hydroxybiaryl, which had been prepared earlier (ref. 11).

§§ We suspect that the oxidative addition of the aryl triflate to the Pd reagent, comparable to the first reaction step of a Heck reaction, is the initiating step, leading to an Ar–Pd–OTf species, for which the deoxygenation product (see note ‖) constitutes a significant hint. This Pd intermediate should then further react with the ester functionality.

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Received in Liverpool, UK, 27th February 1998; 8/01674G