



Pinacol versus Para Coupling of Aromatic Ketones

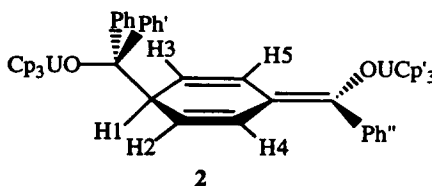
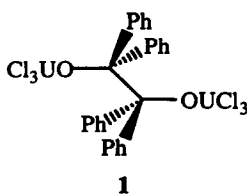
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Abstract : Aromatic ketones PhCOR were coupled with uranium complexes to give, after deuteroanalysis, the pinacol **3** and the keto-alcohol **4** resulting respectively from the pinacol and para coupling of the carbonyl substrate. The organometallic precursors of **3** and **4** were in equilibrium. Pinacols were obtained in higher yields by using the less sterically hindered complexes. © 1997 Elsevier Science Ltd.

The pinacolization of ketones is an important reaction for the formation of C-C bonds that found extensive use in organic synthesis¹. The reductive coupling of the carbonyl substrate is often mediated by Sm(II) or Ti(II) complexes. Samarium diiodide proved to be particularly efficient in such conversion of aromatic aldehydes and ketones², but addition of hexamethylphosphoramide to the reaction mixture led to different products; benzaldehyde was not coupled into hydrobenzoin but was converted into a keto-alcohol molecule³. We examined the reactions of aromatic ketones with a variety of uranium complexes; these compounds exhibit strong analogies in reactivity with those of titanium and the lanthanides^{4,5}.

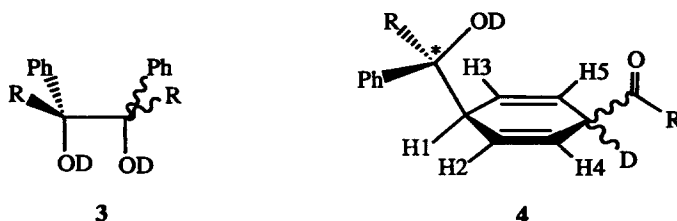
Benzophenone reacted with UCl₃ [or UCl₄ and Na(Hg)] to give the metalopinacol **1** as the initial product; this latter rearranged into the cyclic pinacolate UCl₂(O₂C₂Ph₄)⁵. In contrast, treatment of Ph₂CO with 1 mol. equiv. of Cp₃U(THF) [or Cp₃UCl and Na(Hg)] in THF (Cp = η-C₅H₅, THF = tetrahydrofuran) afforded complex **2** in almost quantitative yield⁶. The synthesis and structure of **2** are similar to those of the titanium compound [(silox)₃Ti(OCPh₂)₂], isolated from the reaction of Ph₂CO with (silox)₃Ti (silox = Bu^t₃SiO)⁷. Pinacol coupling of the ketyl radical [M-OCPh₂], produced by electron transfer from U(III) or Ti(III) to the carbonyl



group, would be sterically prohibited by the bulky Cp or silox ligands, thus favouring the para phenyl / carbonyl carbon coupling, reminiscent of the coupling of trityl radicals ⁸. Complex **2** was alternatively synthesized by treating $\text{Cp}_3\text{U}(\text{NEt}_2)$ with benzopinacol (eq. 1); this reaction implied homolytic cleavage of the pinacolic C-C bond of the likely intermediate $\text{Cp}_3\text{UOCPh}_2\text{CPh}_2\text{OUCp}_3$, followed by para coupling of the ketyl radical.



Benzaldehyde and aromatic ketones PhCOR ($\text{R} = \text{H}, \text{Me}, \text{Pr}^i$ and Bu^i) also reacted with $\text{Cp}_3\text{U}(\text{THF})$ to give the analogues of **2**, which were not isolated; anaerobic deuteryolysis of the reaction mixture afforded the keto-alcohol **4** in almost quantitative yield and the pinacol **3** was not detected. However, a mixture of **3** and **4** was obtained when PhCOR was similarly treated with UCl_4 and $\text{Li}(\text{Hg})$ (1 mol. equiv. each); the relative proportions of **4** increased from 5% ($\text{R} = \text{H}, \text{Me}$) to 12% ($\text{R} = \text{Pr}^i$) and 95% ($\text{R} = \text{Bu}^i$). This trend is clearly related to the growing steric bulk of the ketone which would impede the symmetric pinacol coupling for the benefit of the dissymmetric dimerization.

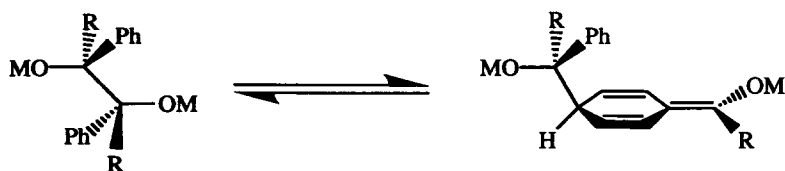


We studied in more details the coupling reactions of isobutyrophenone; for $\text{R} = \text{Pr}^i$, the products **3** (*dl* and *meso*) and **4** (*cis* and *trans*) were more easily distinguishable by NMR ⁹. The ketone was reduced with $\text{Li}(\text{Hg})$ in the presence of a variety of uranium (IV) compounds (Table 1) ¹⁰; these were derived from UCl_4 either by substitution of Cl groups with cyclopentadienyl ligands (entries 2 and 6) or addition of chloride ions (entry 3) or Lewis bases (entries 4 and 5).

Table 1. Relative Proportions of **3** and **4** Obtained by Reductive Coupling of PhCOPr^i with $\text{Li}(\text{Hg})$ in the Presence of Various Uranium (IV) Complexes.

Entry	Uranium (IV) complex	3 (%) (<i>dl/meso</i>)	4 (%)
1	$\text{UCl}_4(\text{THF})_2$	88 (5.2)	12
2	$(\text{C}_5\text{Me}_5)\text{UCl}_3(\text{THF})_2$	48 (3.0)	52
3	Li_2UCl_6	40 (2.3)	60
4	$\text{UCl}_4(\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2)_2$	35 (1.5)	65
5	$\text{UCl}_4(\text{Me}_2\text{NCH}_2\text{CH}_2\text{NMe}_2)_2$	30 (2.5)	70
6	$(\text{C}_5\text{H}_4\text{SiMe}_3)_3\text{UCl}$	< 1	99

The results confirmed that symmetric pinacol coupling of the aromatic ketone was disfavoured by steric constraints. It was interesting to note that when 2 equiv. of LiCl were added, before deuteration, to the reaction mixture corresponding to entry 1, the relative proportions of 3 and 4 were not 88 : 12 but were instead 40 : 60, exactly the same as those observed when LiCl was present from the very beginning of the reaction (giving Li_2UCl_6 , entry 3). This fact suggested that the organometallic precursors of 3 and 4 (Scheme 1) were not formed under kinetic control but were in equilibrium, presumably *via* the ketyl radical $[\text{M}-\text{OCPhR}]$.



Scheme 1. Equilibrium between the symmetric and dissymmetric coupling complexes of aromatic ketones

While the *dl* isomer was preponderant¹¹, lower *threo*-selectivity of the pinacols (*dl* / *meso* < 3) was observed with the more sterically demanding complexes. This trend could also be caused by steric constraints; the increasing quantities of the *meso* isomer would result from the bimetallic pinacolate compound in which nonbonded interactions between like groups were avoided (as shown in Scheme 1)¹².

In conclusion, the *para* coupling of aromatic ketones is a reaction which appears to be more general than might be previously have been expected^{3,7}. This reaction, which could be in competition with the McMurry type synthesis of pinacols and alkenes, should be avoided by using the less sterically demanding coupling agents.

References and Notes

1. Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 61-63; Barden, C. M.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484-5485; Balu, N.; Nayak, S. K.; Banerji, A. *J. Am. Chem. Soc.* **1996**, *118*, 5932-5937; Nicolaou, K. C.; Guy, R. K. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2079-2090; Bogdanovic, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109-121; Robertson, G. M. in *Comprehensive Organic Chemistry*; Trost, B. M.; Fleming I. Eds., Pergamon, Oxford, **1991**, vol. 3, pp. 563-610; Fürstner, A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729-1734; Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260-265.
2. Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765-766.
3. Shiue, J. S.; Lin, C. C.; Fang, J. M. *Tetrahedron Lett.* **1993**, *34*, 335-338.
4. Maury, O.; Villiers, C.; Ephritikhine, M. *New J. Chem.* **1997**, *21*, 137-139; Maury, O.; Villiers, C.; Ephritikhine, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1129-1130; Adam, R.; Villiers, C.; Ephritikhine, M. *Tetrahedron Lett.* **1994**, *35*, 573-574.
5. Villiers, C.; Adam, R.; Lance, M.; Nierlich, M.; Vigner, J.; Ephritikhine, M. *J. Chem. Soc. Chem. Comm.* **1991**, 1144-1145.

6. A 50 ml round bottom flask was charged with $\text{Cp}_3\text{U}(\text{THF})$ (252 mg, 0.5 mmol) and Ph_2CO (91 mg, 0.5 mmol) and THF (50 ml) was condensed under vacuum at -78°C . The reaction mixture was stirred for 15 h at 20°C . After filtration, the solution was evaporated to dryness and the red microcrystalline powder of **2** was washed with pentane and dried under vacuum (260 mg, 85 %). Analysis. Found : C, 54.32; H, 4.07. $\text{C}_{56}\text{H}_{50}\text{O}_2\text{U}_2$ requires : C, 54.63; H, 3.92. Complex **2** was characterized by its NMR spectra (COSY and NOESY) (for attribution, see the formula). δ ppm (THF, 30°C , 200 MHz) : 9.92 (2 H, d, $J = 7.2$ Hz, ortho-Ph), 9.52 (2 H, d, $J = 7.5$ Hz, ortho-Ph'), 9.5 (1 H, br, H2), 8.97 (1 H, br, H1), 7.91 (2 H, t, $J = 7.2$ Hz, meta-Ph), 7.80 (1 H, t, $J = 7.2$ Hz, para-Ph), 7.30 (2 H, t, $J = 7.5$ Hz, meta-Ph'), 7.18 (1 H, t, $J = 7.2$ Hz, para-Ph'), 6.70 (1 H, br, H3), 5.60 (1 H, t, $J = 7.3$ Hz, para-Ph''), 5.02 (2 H, t, $J = 7.5$ Hz, meta-Ph'') 3.29 (1 H, br, H4), -0.07 (1 H, br, H5), -2.61 (2 H, d, $J = 7.5$ Hz, ortho-Ph''), -7.82 (15 H, s, Cp'), -16.14 (15 H, s, Cp).
7. Covert, K. J.; Wolczanski, P. T.; Hill, S. A.; Krusic, P. J. *Inorg. Chem.* **1992**, *31*, 66-78.
8. Neumann, W. P.; Uzick, W.; Zarkadis, A. K. *J. Am. Chem. Soc.* **1986**, *108*, 3762-3770.
9. An NMR tube was charged with one of the uranium (IV) complexes listed in Table 1 (44.7 μmol) in THF d_8 (0.4 ml); PhCOPr^i (6.7 ml, 44.7 μmol) was introduced via a microsyringe and $\text{Li}(\text{Hg})$ (1 % Li, 37.3 mg, 44.7 μmol) was added. The reaction mixture was stirred for 12 h at 20°C and hydrolyzed with D_2O (10 μl). Compounds **3** and **4** were characterized by their NMR spectra (for attribution, see the formula). δ ppm (THF, 30°C , 200 MHz). **3** ($\text{R} = \text{Pr}^i, dl$)¹³ : 7.5-7.2 (10 H, m, Ph), 1.80 (2 H, hept, $J = 6.5$ Hz, CHMe_2), 1.23 and 0.36 (6 H + 6 H, d, $J = 6.5$ Hz, CHMe_2); **3** ($\text{R} = \text{Pr}^i, meso$) : 7.5-7.2 (10 H, m, Ph), 2.15 (2 H, hept, $J = 6.5$ Hz, CHMe_2), 0.67 and 0.45 (6 H + 6 H, d, $J = 6.5$ Hz, CHMe_2); **4** ($\text{R} = \text{Pr}^i, cis$ or $trans$ isomer) : 7.1-7.6 (5 H, m, Ph), 6.45 and 6.35 (1 H + 1 H, m, H4 and H5), 5.63 and 5.26 (1 H + 1 H, d of d of d, $J_{\text{H2(3)-H4(5)}} = 10.5$ Hz, $J_{\text{H2(3)-H1}} = 4.0$ Hz, $J_{\text{H2(3)-H3(2)}} = 2.0$ Hz, H2 and H3), 3.7 (1 H, m, H1), 2.8 (1 H, m, CHMe_2), 2.3 (1 H, m, CHMe_2), 0.80 and 0.70 (3 H + 3 H, d, $J = 6.5$ Hz, CHMe_2), 0.96 (6 H, m, CHMe_2); **4** ($\text{R} = \text{Pr}^i, other$ isomer): 7.1-7.6 (5 H, m, Ph), 6.59 and 6.25 (1 H + 1 H, m, H4 and H5), 5.54 and 5.31 (1 H + 1 H, d of d of d, $J_{\text{H2(3)-H4(5)}} = 10.5$ Hz, $J_{\text{H2(3)-H1}} = 4.0$ Hz, $J_{\text{H2(3)-H3(2)}} = 2.0$ Hz, H2 and H3), 3.7 (1 H, m, H1), 2.8 (1 H, m, CHMe_2), 2.3 (1 H, m, CHMe_2), 0.80 and 0.73 (3 H + 3 H, d, $J = 6.5$ Hz, CHMe_2), 0.96 (6 H, m, CHMe_2). The relative proportions of the two isomers of **4** are *ca* 50 : 50.
10. Reaction of PhCOPr^i with $\text{Li}(\text{Hg})$ gave, after hydrolysis, a mixture of the starting carbonyl substrate (19 %), **3** (53 %, $dl / meso = 19$), **4** (5 %) and $\text{PhCH}(\text{OH})\text{Pr}^i$ (23 %).
11. Handa, Y.; Inanaga, J. *Tetrahedron Lett.* **1987**, *28*, 5717-5718.
12. Clerici, A.; Porta, O. *J. Org. Chem.* **1985**, *50*, 76-81.
13. Leimner, J.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 3697-3705.

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