

Novel Alkali Metal-Induced H–D Atom Exchange Reaction of Diaryl Ketones with THF-*d*₈: Unexpectedly High D Atom-Incorporation at Meta Position of Benzophenone

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This paper describes the hitherto unknown atom-exchange reaction between hydrogens of diaryl ketones and α -deuteriums of THF-*d*₈ oxygen, which proceeds under ordinary conditions during the preparation of absolute THF.

Sodium and potassium benzophenone ketyls (anion radicals) are widely used in many laboratories as an indicator for the preparation of absolute THF because of their characteristic deep blue color which is highly sensitive to moisture and oxygen.¹ In connection with our recent study on the samarium(II) triflate-promoted pinacol-coupling reaction,² we attempted to prepare samarium(III) benzophenone ketyl by the transmetalation of sodium benzophenone ketyl with Sm(OTf)₃ in THF-*d*₈,³ in which we observed a novel H–D atom-exchange reaction. Further investigation revealed that the reaction is highly sodium-selective and proceeds through the formation of a benzophenone dianion.⁴ Thus, when a deep blue solution of sodium benzophenone ketyl in THF-*d*₈ was heated at 120 °C with sodium metal in a sealed tube and then the resulting red-purple solution was treated with oxygen, partially deuterated benzophenone was obtained (Table 1).⁵

(1) Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth-Heinemann: Oxford, 1996; p 334.

(2) Hanamoto, T.; Sugimoto, Y.; Sugino, A.; Inanaga, J. *Synlett* **1994**, 377.

(3) For a recent study of lanthanide ketyl complexes, see: Hou, Z.; Fujita, A.; Zhang, Y.; Miyano, T.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 754.

(4) For recent studies on the formation and reactivity of metal diaryl ketone dianions, see: (a) Yoshimura, T.; Hou, Z.; Wakatsuki, Y. *Organometallics* **1995**, *14*, 5382. (b) Hou, Z.; Yoshimura, T.; Wakatsuki, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11169. (c) Hou, Z.; Yamazaki, H.; Fujiwara, Y.; Taniguchi, H. *Organometallics* **1992**, *11*, 2711. (d) Hou, Z.; Yamazaki, H.; Kobayashi, K.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1992**, 722. (e) Pons, J. M.; Santelli, M. *Tetrahedron* **1990**, *46*, 513. (f) Olivier, H.; Chauvin, Y.; Saussine, L. *Tetrahedron* **1989**, *45*, 165. (g) Hou, Z.; Takamine, K.; Aoki, O.; Shiraiishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.* **1988**, *53*, 6077. (h) Hirayama, M.; Ohhata, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2751. (i) Honzl, J.; Lovy, J. *Tetrahedron* **1984**, *40*, 1885. (j) Trzupke, L. S.; Newirth, T. L.; Kelly, E. G.; Sbartati, N. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1973**, *95*, 8118 and references therein.

(5) Typical experimental procedure follows (run 5 in Table 1): In a glovebox, a solution of benzophenone (36.4 mg, 0.2 mmol) in THF-*d*₈ (1 mL) was mixed with sodium (171 mg, 7.4 mmol) at room temperature. The reaction tube was removed from the glovebox and then flame-sealed under reduced pressure. The mixture was heated at 120 °C for 48 h. After cooling, the sealed tube was opened in an oxygen bag, and the solution was aspirated with an oxygen-containing gastight syringe. The reaction tube was washed with a small amount of THF, and the combined solution was passed through a short column of silica gel. After evaporation of the solvent, the crude product was subjected to preparative TLC with hexanes–ethyl acetate (6:1) as an eluent to give partially deuterated benzophenone (18.7 mg, 50%). A solid: IR (KBr) $\nu = 2269$ (C–D), 1650 cm⁻¹ (C=O); ¹H NMR (500 MHz, CDCl₃, 25 °C, TMS) $\delta = 7.78$ –7.84 (m, 1.08 H, ortho-H), 7.56–7.62 (m, 1.50 H, para-H), 7.46–7.52 (m, 2.36 H, meta-H). The intensities are determined by the comparison with 1,4-dimethoxybenzene [$\delta = 6.84$ (s, 4 H, aromatic H)] as an internal standard. ¹³C NMR (125 Hz, CDCl₃, 25 °C, TMS) $\delta = 196.70$, 137.60, 137.51, 137.43, 132.38, 132.28, 132.17, 130.02, 130.01, 129.90, 129.73 [t, J (C–D) = 23.8 Hz], 129.63 [t, J (C–D) = 24.8 Hz], 128.25, 128.14, 128.03, 127.98, 127.85 [t, J (C–D) = 24.8 Hz]; MS (FAB) *m/z* (relative %) 194 (8), 193 (31), 192 (20), 191 (30), 190 (49), 189 (70), 188 (88), 187 (100), 186 (95), 185 (66), 184 (34), 183 (18), 182 (7). Partially deuterated benzhydrol (ca. 23%) and benzopinacol (ca. 9%) were also isolated. When the reaction was carried out in THF in a small sealed tube, 1,1-diphenyl-1-propanol (ca. 15%) was isolated as an additional byproduct, which must be formed by the coupling reaction of the benzophenone dianion with ethylene, one of the decomposition products of the THF anion.⁶

Table 1. H–D Exchange Reaction of Benzophenone with THF-*d*₈

run	metal/equiv	time (h)	D content (%) ^a	ortho/meta/para	yield (%) ^b
1 ^c	Na/38.1	2	24/0/0		90
2	Na/37.5	24	55/15/7		74
3 ^c	Na/38.4	48	71/11/7		76
4	Na/1.0	48	<i>d</i>		67
5	Na/37.2	48	73/41/25		50 ^e
6	Na/37.6	240	77/42/23		48
7	K/32.6	48	<i>d</i>		76
8	Li/35.1	48	<i>d</i>		1 ^f
9	Sm/20.3	48	2/0/0		13 ^g

^a Determined by ¹H NMR analysis. ^b Isolated yield of benzophenone. Benzhydrol [13% (run 2), 11% (run 3), 5% (run 4), 23% (run 5), 24% (run 6)] and benzopinacol [11% (run 4), 9% (run 5), 7% (run 6)] were also isolated. ^c The reaction was conducted at 95 °C. ^d No deuterated benzophenone was detected. ^e See ref 5. ^f 1,1-Diphenyl(pentane-*d*₈)-1,5-diol was obtained in 76% yield. ^g Others are a complex mixture.

Careful analysis of the crude products by means of capillary GC–MS and FT-IR and ¹H and ¹³C NMR revealed that a significant amount of the D atom was incorporated at the ortho, meta, and para positions in this order of magnitude. When the reaction time was short, the D atom was incorporated only at the ortho position (run 1). These results are in sharp contrast to the case of the samarium benzophenone dianion which was selectively protonated at the para position when aromatic alcohols were used as the proton source.^{4a} The present atom-exchange reaction took place at 95 °C (runs 1 and 3) or even at the boiling point of THF. A prolonged reaction increased the D atom-incorporation affording up to a decadeuterated product as one of the isotopic isomers (run 6) (Figure 1).

A relatively high D content at the meta position is remarkable because the electron density of the benzophenone dianion is expected to be high at the ortho and para positions.⁴ The D atom-incorporation appears to reach a maximum in ca. 48 h at 120 °C (cf. runs 5 vs 6). When 1 equiv of sodium was used, no isotopic exchange reaction occurred (run 4), which indicates that the atom-exchange reaction does not take place via the ketyl intermediate but proceeds through the formation of a dianion followed by the dedeuteration from THF-*d*₈.^{6,7} Figure 2 shows the ¹H NMR spectrum of the reaction mixture obtained after 48 h of refluxing at 66 °C in a sealed NMR tube. The formation of the benzophenone dianion and its deuterated monoanion [Ph(D_m)-CD(O⁻)-Ph(D_n)] is apparent.⁸ Based on the integral ratio of the signals, the ortho, meta, and para hydrogens of the intermediates can be unambiguously assigned as indicated.

Interestingly, the use of potassium or lithium in place of sodium did not afford any deuterated benzophenone. In the former case, the starting benzophenone was recovered (run 7), although the reaction mixture turned red-purple and its ¹H NMR spectrum evidenced the generation of the dianion species. On the other hand, in the latter case, a color change (blue → red-purple → colorless) was observed, and a benzophenone-THF adduct, 1,1-diphenyl(pentane-*d*₈)-1,5-diol,⁹ was isolated as the major product (run 8).

(6) For the deprotonation reaction of THF, see Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **1984**, 25, 745 and references therein.

(7) THF-*d*₈ with 99.5 atom % D was used. The ¹H NMR spectrum shows two multiplets at around $\delta = 1.7$ and 3.6 with a 1:0.8 integral ratio. After the reaction, the ratio changed, in the case of run 5 in Table 1, to 1:2.1 indicating that the D–H atom-exchange reaction occurred selectively at the α position.

(8) The ¹H NMR spectrum of the ytterbium benzophenone dianion has been reported.^{4a} The formation of the α -deuterated benzhydroxide anion was confirmed by comparing its ¹H NMR spectrum with that of the authentic diphenylmethoxide prepared from benzhydrol and NaH, in the presence of the freshly prepared sodium benzophenone dianion.

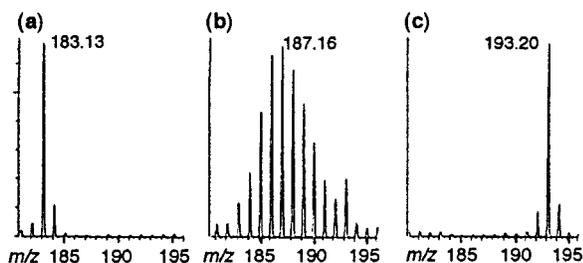


Figure 1. Mass spectra (FAB) of benzophenone (a), partially deuterated benzophenone (b, run 6 in Table 1), and benzophenone-*d*₁₀ (c).

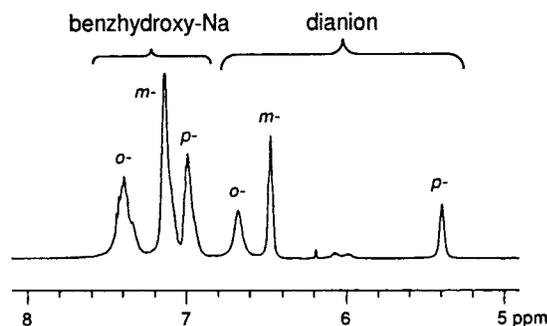


Figure 2. Phenyl part of the ¹H NMR spectrum of the reaction intermediates (PhCOPh-excess Na, THF-*d*₈, 66 °C, 48 h).

The reaction seems to proceed through the formation of the lithium benzophenone dianion^{4i,j,10} followed by its alkylative opening of THF-*d*₈ with the aid of a Lewis acidic lithium ion.¹¹ Surprisingly, to the best of our knowledge, there has been no report concerning such a reductive coupling reaction.

The opposite D–H exchange reaction of benzophenone-*d*₁₀¹² with THF was also realized under the same conditions as above (cf. run 5 in Table 1) but with less efficiency [H content (%): ortho/meta/para 16:4:1]. The observed isotope effect has been estimated to be ca. 6.

A possible reaction path for the H–D atom-exchange reaction of the sodium benzophenone dianion with THF-*d*₈ is shown in Scheme 1. Because the electron density is high at the ortho and para positions, the deuteriation from THF-*d*₈ would predominantly take place at the ortho and para positions to produce the corresponding *o*- and *p*-deuterated enolates (**1** and **2**)^{4a} and 2-tetrahydrofuryl-*d*₇ anion.⁶ Hydrogen-selective deprotonation from the former by the latter (or by any other dianion species) affords the *o*- and *p*-D-substituted dianions (**3** and **4**). On the other hand, the formation of the *m*-D-substituted dianion (**5**) would occur via 1,2-rearrangement of the *m*-metalated dienones (e.g., **6**), a resonance form of the *o*-D- and *p*-D-substituted trienolate (**1** and **2**), giving a thermodynamically more stable *o*-metalated dienones (e.g., **7**).^{10,13}

The metal-induced atom-exchange reaction of 9-fluorenone was also investigated (Table 2). The reaction with sodium exclusively afforded the 1(8)-D-substituted 9-fluorenone (run 2).¹⁴ Unlike the

(9) Alternatively, 1,1-diphenylpentane-1,5-diol was prepared in a similar manner using THF instead of THF-*d*₈ and fully identified with an authentic sample which was prepared according to a literature method: Lehmann, J.; Marquardt, N. *Liebigs. Ann. Chem.* **1988**, 827.

(10) For the X-ray structural analysis of lithium benzophenone dianion, see: Bogdanovic, B.; Krüger, C.; Wermecckes, B. *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 817. One of the lithium ions is shown to interact with the ortho carbon.

(11) For the alkylative opening of THF, see: Moret, E.; Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1991**, 409, 83 and references therein. An excellent review for organoalkali compounds, see: Schlosser, M. *Organometallic Reagents. In Organometallics in Synthesis: A Manual*; Schlosser, M., Ed.; John Wiley & Sons: New York, 1994; p 1.

(12) Benzophenone-*d*₁₀ was prepared according to a literature method by using benzene-*d*₆ (99.5 atom % D) instead of benzene: Marvel, C. S.; Sperry, W. M. in *Org. Synth.; Coll. Vol. 1* (Eds.: Gilman, H.; Blatt, A. H.), Wiley: New York, 1941; p 95.

(13) An attempt to trap the intermediates **6** and **7** directly with methyl iodide resulted in failure probably because of their instability and low concentration in the medium, cf.: Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, 98, 1520.

Scheme 1

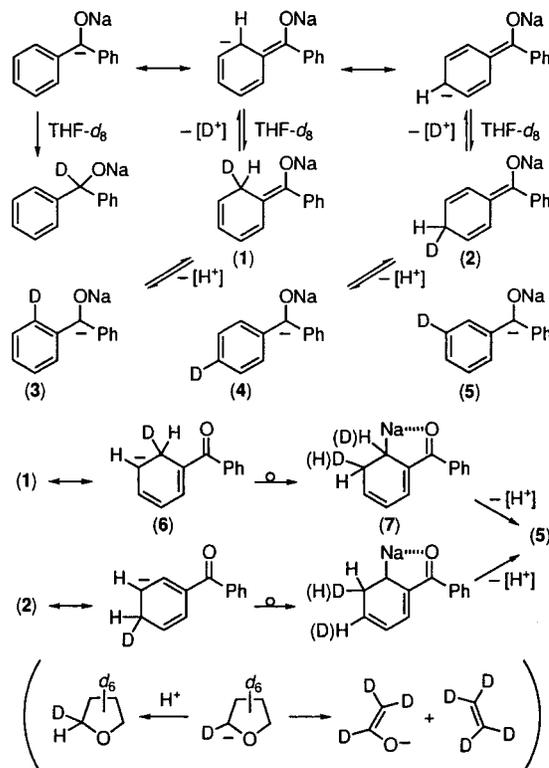
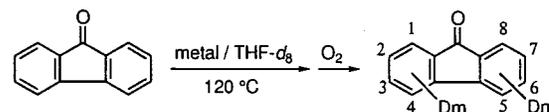


Table 2. H–D Exchange Reaction of 9-Fluorenone with THF-*d*₈



run	metal/equiv	time (h)	D content (%) ^a				yield (%) ^b
			1(8)	2(7)	3(6)	4(5)	
1	Na/38.9	48	27	0	0	0	100
2	Na/37.8	240	52	0	0	0	96
3	K/32.2	240	25	9	1	7	61 ^c
4	Li/35.2	240	51	7	1	8	6 ^d
5	Sm/20.3	240	9	0	0	0	23 ^e

^a Determined by ¹H NMR analysis. ^b Isolated yield. ^c 9-Hydroxyfluorenone (20%) and the THF-*d*₈ adduct (10%) were also isolated. ^d When the reaction was carried out in THF, 1,1-(9-fluorenylidene)-1,5-pentanediol was obtained in 55% yield. ^e Others are a complex mixture.

benzophenone case, potassium and lithium were found to promote the atom-exchange reaction to a considerable extent, although the recovery of 9-fluorenone was not always high.^{4h}

In conclusion, we disclosed hitherto unknown atom-exchange reactions of diaryl ketone dianions with THF, the reaction course of which is highly dependent on the counteranions employed. All protons of the sodium benzophenone dianion intermediate were unambiguously assigned by the D-incorporation experiment.

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Supporting Information Available: ¹H NMR (500 MHz) spectrum of sodium benzophenone dianion, ¹H and ¹³C NMR (125 MHz), IR, and mass spectra of partially deuterated benzophenone (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) Quite recently, an X-ray structural analysis of sodium 9-fluorenone dianion has been done, which indicates the definite interaction between the metal cation and aromatic ring, particularly with the ortho position. See, Hou, Z.; Fujita, A.; Yamazaki, H.; Wakatsuki, Y. *Chem. Commun.* **1998**, 669.