

Contribution to the Study of the Mechanism of Directed Remote-Metalation. Evidence for the Intermediacy of a Geminal Dimetallo Dialkoxide $C(OM)_2$ ($M = Li, K$), First Doubly Charged Director of Ortho Metalation

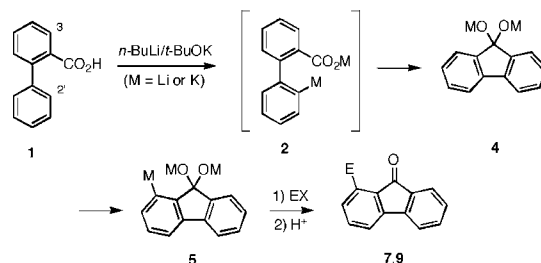
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ABSTRACT



The mechanism of the metalation of 2-biphenyl carboxylic acid (1) with the Lochmann–Schlosser superbase was determined by deuteriolysis. Both ortho (C_3) and remote (C_2) positions are metalated. The C_2 -metalated species 2 cyclizes instantaneously. Under suitable conditions, the doubly charged geminal dimetallo dialkoxide group $C(OM)_2$ 4 directs metalation in the adjacent position (C_1), affording a stable 1-metallo-9H-fluorene-9,9-dimetallo dialkoxide 5 that can be trapped by diverse electrophiles to give 1-substituted 9H-fluorene-9-ones 7 and 9 after acidic workup.

Although the CO_2Li group does activate neighboring positions toward metalation, its effect remains fairly weak.¹ This enables regioflexibility, as most other electronegative substituents outperform a competing carboxylate group by their superior ortho-directing power.²

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(1) (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2003**, 5, 1919.
(b) Gohier, F.; Mortier, J. *J. Org. Chem.* **2003**, 68, 2030 and references therein.

We recently communicated³ that 2-biphenyl carboxylic acid (1) readily undergoes metalation in the immediate vicinity of the carboxylate substituent (C_3) when treated with *s*-butyllithium (*s*-BuLi) in THF at -78°C . A strong interaction between the highly electron-rich π -system of the

(2) Hartung, C. G.; Snieckus, V. *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; p 330.

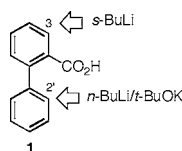
(3) Tilly, T.; Samanta, S. S.; Faigl, F.; Mortier, J. *Tetrahedron Lett.* **2002**, 43, 8347.

Table 1. Metalations of 2-Biphenyl Carboxylic Acid (**1**)^{a,b}

entry	acid	conditions ^c	% 7 (1 <i>d</i> ₁ :1 <i>d</i> ₀)	% 1 ^d (3 <i>d</i> ₁ :3 <i>d</i> ₀)
1	1	LICKOR (3.5 equiv), benzene, 60 °C, 1 h	76 (41:59)	10 (20:80)
2	1	(1) LICKOR (3.5 equiv), benzene, 60 °C, 1 h (2) <i>t</i> -BuLi (2 equiv), 60 °C, 2 h	72 (74:26)	0
3	1	(1) LICKOR (3.5 equiv), benzene, 60 °C, 1 h (2) <i>n</i> -BuLi (2 equiv), 60 °C, 2 h	70 (100:0)	0
4	1	LICKOR (5 equiv), benzene, 60 °C, 3 h	60 (100:0)	0
5	1	LICKOR (2 equiv), benzene, 60 °C, 5 h	9 (25:75)	85 (10:90)
6	8	<i>n</i> -BuLi (2 equiv), Et ₂ O, –78 °C, 2 h	86 (0:100)	0
7	8	(1) <i>n</i> -BuLi (2 equiv), Et ₂ O, –78 °C, 2 h (2) <i>n</i> -BuLi (3 equiv), Et ₂ O, –78 °C, 2 h	90 (60:40)	0
8	8	(1) <i>n</i> -BuLi (2 equiv), Et ₂ O, –78 °C, 2 h (2) <i>s</i> -BuLi/TMEDA (3 equiv), Et ₂ O, –78 °C → rt, 2 h	61 (100:0)	0
9	1	(1) <i>s</i> -BuLi (2.2 equiv), THF, –78 °C, 2 h (2) LICKOR (3.5 equiv), –78 °C, 2 h	71 (77:23)	28 (71:29)

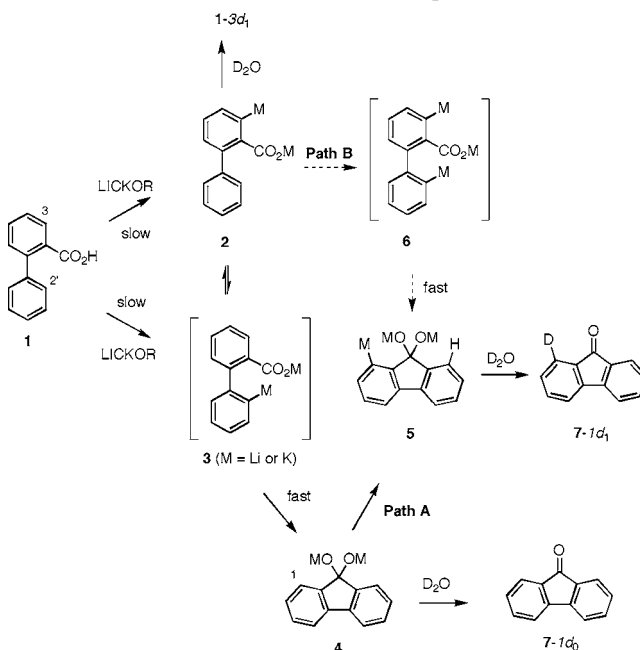
^a Isotope ratios were determined by ¹H NMR and FIMS. The error is taken to be ±5%. ^b Isolated yields (%). ^c Base was allowed to react with the substrate before D₂O was added at room temperature. ^d Recovered starting product.

carboxylate and the reagent places *s*-BuLi in the proximity of the *ortho*-carbon, prior to necessarily intramolecular deprotonation into the *ortho* position (complex-induced proximity effect (CIPE) process).⁴ We now report that **1**, by treatment with the Lochmann–Schlosser superbases (*n*-butyllithium/*t*-BuOK) (LICKOR), affords the fluorenone skeleton that arises from the metalation of the remote C_{2'} site. The mechanism is studied by deuteriolysis to identify the intermediates of the reaction. Strong evidence for the intermediacy of a geminal dimetallo dialkoxide function C(OM)₂ (M = Li, K) as a new director of *ortho* metalation is provided.



2-Biphenyl carboxylic acid (**1**) was submitted to a series of strong bases under the conditions depicted in Table 1. Scheme 1 diagrams the manner in which the products are formed. We initially discovered³ that addition of **1** to 3.5 equiv of preformed LICKOR superbases made of equimolecular amounts of *n*-butyllithium and potassium *tert*-butoxide,⁵ followed by acidic hydrolysis (2 M HCl) at room temperature, produced the fluorenone-9-one **7** in 57% yield in THF at 45 °C and 76% yield in benzene at 60 °C.

Treatment of **1** (100% *d*₀) with 3.5 equiv of LICKOR for 1 h at 60 °C in benzene, followed by quench with an excess of D₂O at room temperature, provided the fluorenone **7** (41% 1*d*₁, 59% 1*d*₀) in 76% yield after separation from unreacted

Scheme 1. Metalation of 2-Biphenyl Carboxylic Acid (**1**) with the Lochmann–Schlosser Superbase

1 (20% 3*d*₁, 80% 3*d*₀) (entry 1 and Scheme 1).⁶ The straightforward interpretation of this result is that 7-1*d*₁ arises from exposure of a *stable* trianion **5** (M = Li or K) to D₂O, whereas 7-1*d*₀ is formed via the tetrahedral dialkoxide **4**.^{7,8} The trianion **5** arises either from metalation of **4** directed by the *gem*-dimetallo dialkoxide group [C(OM)₂] (path A) or, more unlikely, from the cyclization of the trianion **6** formed

(4) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Whisler, M. N.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.

(5) For recent reviews on reaction of organolithium compounds with alkali metal alkoxides and reactions of superbases, see: (a) Lochmann, L. *Eur. J. Inorg. Chem.* **2000**, 1115. (b) Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975.

(6) Although it is generally admitted that LICKOR needs to be handled below –50 °C because of the rapid decomposition of the solvent (usually THF), this result shows that it is not necessarily the case if the base reacts faster with the substrate than with the solvent.

(7) ¹H NMR spectrum of the residue in THF-*d*₈ displays broad signals with poor resolution in the aromatic region that are probably due to the presence of aggregates that prevent a simple structural elucidation.

by metalation of **2** at the remote C_{2'} site (path B). The organometallic species **2** and **3** are formed by metalation, necessarily irreversible, of **1** by the superbase in positions C₃ and C_{2'}, respectively. The carboxylate group of **3** acts as an in situ trap for the arylanion thus formed, and the system cyclizes to give the dialkoxide **4**. **2** has a sufficient lifetime to be quenched by D₂O to give **1-3d₁**.

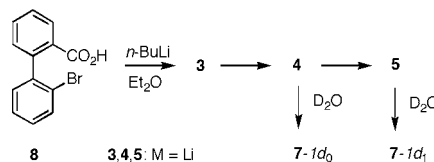
To demonstrate that the trianion **5** is formed by metalation of **4** directed by the *gem*-dialkoxide group rather than by cyclization of **6**, the following experiments have been done. After introduction of LICKOR (3.5 equiv) at 60 °C into a benzene solution containing the acid **1**, 2 equiv of *t*-BuLi was further added (entry 2). A quench by D₂O provided the fluorenone **7** containing 74% deuterium incorporation (72%). When *n*-BuLi (2 equiv) and LICKOR (5 equiv) were allowed to react under the conditions depicted (entries 3 and 4), isotopically pure **7-d₁** (100% *d₁*) was produced.

From the distribution products obtained (run 5) with 2 equiv of LICKOR, it can be deduced that the directing ortho metalation (DoM) of **4** leading to **5** (path A) is competitive in rate with the initial directed remote-metalation (DreM) of the acid **1** leading to **7**. This result explains why 3 equiv of LICKOR at least is required for optimal conversion of **1** to **7**.

The nature of the cations M involved in the stable organometallic species **4** and **5** is not known with certainty. In the literature, *gem*-dialkoxides were reported to be much more stable when the counterions were lithium rather than potassium. Whereas Ph₂C(OLi)₂ can be heated for hours in refluxing ether without an appreciable decomposition,⁹ the corresponding dipotassium salt (or the incipient salt) is an intermediate in the cleavage of benzophenone by potassium *t*-butoxide to give phenylpotassium and potassium benzoate.¹⁰ From the fact that C₆H₅K¹¹ is also present in the mixture, the structure of the organometallic species might be more complex than observed in the case of metalations carried out in THF or hydrocarbons with the LICKOR superbase itself. Both the structure of superbases in solution and the nature of the actual reactive species have been the objects of controversial discussions.¹²

Bromine–lithium exchange by treatment of 2'-bromobiphenyl carboxylic (**8**) with *n*-BuLi (2 equiv) in ether (–78

Scheme 2. Formation of Fluorenones **7-1d₀** and **7-1d₁** from **8** by a Bromine–Lithium Exchange Reaction



°C → rt) followed by D₂O afforded unlabeled **7** (100% *d₀*) exclusively (86%, entry 6) (Scheme 2). Since 2'-deuterio-2-biphenyl carboxylic acid (**1-2'd₁**) was not detected under these conditions, the dianion **3** is unstable and cyclizes instantaneously to give the dilithio *gem*-dialkoxide **4** (M = Li).¹³

We note that the control experiments carried out with **8** may not be perfect mimics of the DreM reaction carried out with the LICKOR superbase. The organometallic species that is produced from 2-biphenyl carboxylic acid (**1**) and the LICKOR superbase could be part of aggregates that could have different reactivity than exogenous lithium 2'-lithio biphenyl carboxylate (**3**) obtained from 2'-bromobiphenyl carboxylic acid (**8**) by bromine–lithium exchange.

The fluorenone arises from exposure of **4** to aqueous acid.¹⁴ Treatment of the species dilithio *gem*-dialkoxide **4** with 3 equiv of *n*-BuLi (–78 °C → rt) followed by D₂O, gave **7** in a yield of 90% (60% *d₁*, 40% *d₀*) via the trianion **5** (M = Li, entry 7). It is noteworthy that, when the same reaction was performed with the 1:1 complex *s*-BuLi/TMEDA (3 equiv), isotopically pure **7-1d₁** was obtained (61%, entry 8).

Remarkably, the *ortho*-lithio benzoate **2** (M = Li), prepared by treatment of **1** with *s*-BuLi in THF at –78 °C³ is stable over hours in THF at room temperature and does not give autocondensation products.¹⁵ Treatment of the preformed dianion **2** with LICKOR (3.5 equiv) (–78 °C → rt) (entry 9) led to **7** in 71% yield (77% deuterium incorporation), and **1** was recovered in both deuterated and nondeuterated forms (71% **3d₁**, 29% **3d₀**). An equilibrium between **2** and **3** most probably occurs via an intermolecular path as already observed in the sulfonate case.¹⁶ Accordingly, deprotonation of **1** with LICKOR is not site-selective.

Since the formation of **2** is a nonissue, cyclization of **3** leading to **4** is fast and irreversible and the equilibrium **2** ⇌ **3** is shifted toward the formation of **3** by Le Châtelier's Principle. Whereas **2** is stable at room temperature, a fast Li ⇌ K permutation presumably allows the equilibrium **2** (M = K) ⇌ **3** to be effective.

Under the optimized one-pot procedure found (entry 3, Table 1), trianion **5** was trapped with diverse electrophiles

(8) Dialkoxide **4** is not trappable by electrophiles: treatment of the species **4** with iodomethane or dimethyl sulfate gave the fluorenone **7** even when hydrolysis of the reaction mixture with water was omitted. The replacement of one atom of metal (M = Li or K) by an alkyl group gave an unstable salt C(OM)(OR) that lost alkoxide ion before a second substitution occurred to produce a ketal. See: (a) Bluhm, H. F.; Donn, H. V.; Zook, H. D. *J. Am. Chem. Soc.* **1955**, *77*, 4406. These results are consistent with the findings of the reaction of the diethyl amide corresponding to **1**: (b) Fu, J.-m. Ph.D. Thesis, University of Waterloo, 1990.

(9) (a) Hodge, P.; Perry, G. M.; Yates, P. *J. Chem. Soc., Perkin Trans. I* **1977**, 680. (b) Bluhm, H. F.; Donn, H. V.; Zook, H. D. *J. Am. Chem. Soc.* **1955**, *77*, 4406.

(10) (a) Rawson, G.; Wynberg, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 46. (b) Gassman, P. G.; Lumb, J. T.; Zalar, F. V. *J. Am. Chem. Soc.* **1967**, *89*, 946. (c) Davies, D. G.; Derenberg, M.; Hodge, P. *J. Chem. Soc. C* **1971**, 455.

(11) (a) Lochmann, L. *Collect. Czech. Chem. Commun.* **1987**, *52*, 2710. (b) Schlosser, M.; Choi, J. H.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633.

(12) (a) Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, *114*, 7482. (b) Kremer, T.; Harder, S.; Junge, M.; Schleyer, P. v. R. *Organometallics* **1996**, *15*, 585.

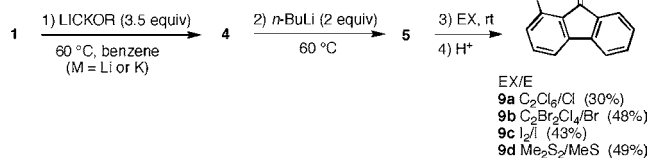
(13) Filler, R.; Fiebig, A. E.; Pelister, M. Y. *J. Org. Chem.* **1980**, *45*, 1290.

(14) Reaction of the isolated fluorenone **7** with LICKOR (3.5 equiv) in benzene at 60 °C led to the 1,2-addition product 9-butyl-9H-fluoren-9-ol (75%).

(15) Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2051.

(16) Alo, B. I.; Familoni, O. B. *J. Chem. Soc., Perkin Trans. I* **1990**, 1611.

Scheme 3. Synthesis of 1-Substituted Fluorenones **9a–d**



(C₂Cl₆, C₂Br₂Cl₄, I₂, Me₂S₂) to give the corresponding fluorenones **9a–d**.^{17,18} This work complements and extends previous research by Snieckus, Quéguiner, Mongin, and

(17) **General Procedure.** *n*-Butyllithium (4.5 mL, 7.8 mmol) was added to a suspension of potassium *tert*-butoxide (792 mg, 7.07 mmol) in benzene (10 mL) at ambient temperature. After the mixture was stirred for 5 min, LICKOR was transferred into a round flask containing 2-biphenyl carboxylic acid (**1**) (400 mg, 2.02 mmol) in benzene (5 mL). Stirring was maintained for 1 h at 60 °C, and the temperature was allowed to cool to room temperature. *n*-Butyllithium (2.5 mL, 4.05 mmol) was added dropwise, and the mixture was stirred at 60 °C for an additional 2 h. After the reaction mixture was warmed to room temperature gradually, the reaction was quenched with the electrophile (40.4 mmol) in benzene (6 mL). Standard workup provided the desired fluorenone, which was purified by chromatography on silica gel (cyclohexane/ethyl acetate 90:10).

(18) (Trimethylsilyl)-9*H*-fluoren-9-one that is produced by trapping the intermediate with chlorotrimethylsilane is not stable under these conditions. The silyl group is presumably metalated. See inter alia: (a) Wang, G.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424. (b) Brough, P. A.; Fisher, S.; Zhao, B.-P.; Thomas, R. C.; Snieckus, V. *Tetrahedron Lett.* **1996**, *37*, 2915. (c) Mohri, S.-I.; Stefinovic, M.; Snieckus, V. *J. Org. Chem.* **1997**, *62*, 7072 and references therein.

others on the mechanism of directed remote-metalations that are followed by intramolecular trapping.¹⁹ Our results suggest that delivery of the alkyllithium by prior coordination to the chelating atom assists a metalation that takes place in a nonregiospecific fashion. Evidence for the intermediacy of a geminal dimetallo dialkoxide C(OM)₂ (M = Li, K), the first doubly charged director of ortho metalation, is also provided. Extensions of the manipulation of other *gem*-dimetallo dialkoxides are ongoing in our laboratories and will be reported upon in due course.

Acknowledgment. This research was supported by the CNRS, Université du Maine, and Institut Universitaire de France.

Supporting Information Available: Details of compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(19) These include, inter alia, reactions of 2-, 3-, and 4-pyridylbenzoates: (a) Rebstock, A.-S.; Mongin, F.; Trécourt, F.; Quéguiner, G. *Tetrahedron* **2003**, *59*, 4973. 2-Biphenyl diethylamide: (b) Fu, J.-M.; Zhao, B.-P.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683. (c) Fu, J.-m.; Snieckus, V. *Can. J. Chem.* **2000**, *78*, 905. (d) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424. 2-Aminobiphenyl: (e) Narasimhan, N. S.; Alurhar, R. H. *Indian J. Chem.* **1969**, *7*, 1280. (f) Narasimhan, N. S.; Chandrachood, P. S. *Synthesis* **1979**, 589. (g) Narasimhan, N. S.; Chandrachood, P. S.; Shete, N. R. *Tetrahedron* **1981**, *37*, 825. 1-(2'-Carboxyphenyl)pyrrole: (h) Cartoon, M. E. K.; Cheeseman, G. W. H. *J. Organomet. Chem.* **1981**, *212*, 1.