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On the Mechanism of the Directed *ortho* and Remote Metalation Reactions of *N*,*N*-Dialkylbiphenyl 2-carboxamides[§]

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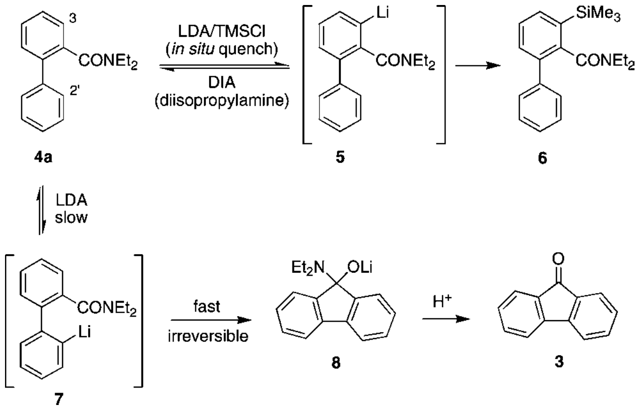
ABSTRACT



A study concerning the mechanism of the LDA-mediated *ortho* and remote metalation of *N*,*N*-dialkyl-2-biphenyl carboxamides (e.g., 4a) is reported. On the basis of site-selective lithiation/electrophile quench experiments, including deuteration, the LDA metalation of 4 is proposed to involve initial amide-base complexation (CIPE) and equilibrium formation of 5, whose fast reaction with an *in situ* electrophile (TMSCl) to afford 6 prevents its equilibration with 7. In the absence of an electrophile, 5 undergoes equilibration via 4a with 7, whose fate is instantaneous cyclization to a stable tetrahedral carbinolamine oxide 8 which, only upon hydrolysis, affords fluorenone (3).

Combined directed *ortho* (DoM) and remote (DreM) metalation−cross-coupling strategies have allowed the development of new synthetically useful methodologies for general and regioselective routes to fluorenones, dibenzo[*b*,*d*]pyranones, 9-phenanthrols, 9-aminophenanthrenes, acridones, and related heterocycles[1] and have acted as a conduit for the synthesis of natural products.[2] In the original prototype study in this area concerning *N*,*N*-diethyl 2-biphenyl carboxamides (Scheme 1), metalation of **2a** with *s*-BuLi/TMEDA (1.1 equiv) in THF at −78 °C followed by the addition of an electrophile was shown to afford C3-substituted derivatives **1**[3] (DoM process), whereas, in distinct contrast, when **2a** was subjected to LDA (1.1 equiv) at 0 °C−rt, cyclization was observed to give fluorenone **3** (84%)[4] (DreM process).

[§] To Peter Stanetty, a Laudatio for the 60th Birthday: for dedicated heterocyclic chemistry including new metalation directions, for joie de vivre, and for friendship.

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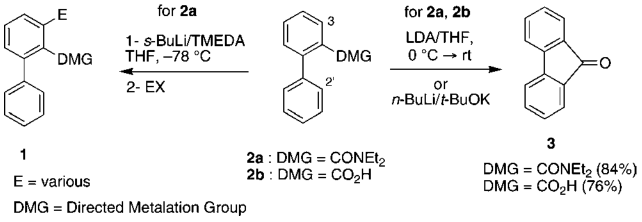
(1) For leading references, see: MacNeil, S. L.; Wilson, B. J.; Snieckus, V. *Org. Lett.* **2006**, *8*, 1133.

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

(3) (a) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5093. (b) Cheng, W.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 5097.

10.1021/ol902268h

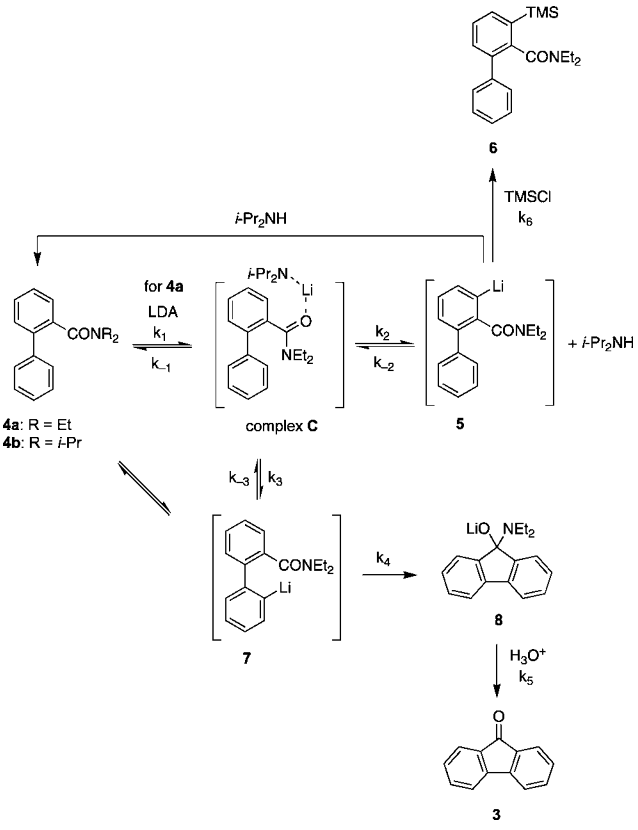
Scheme 1



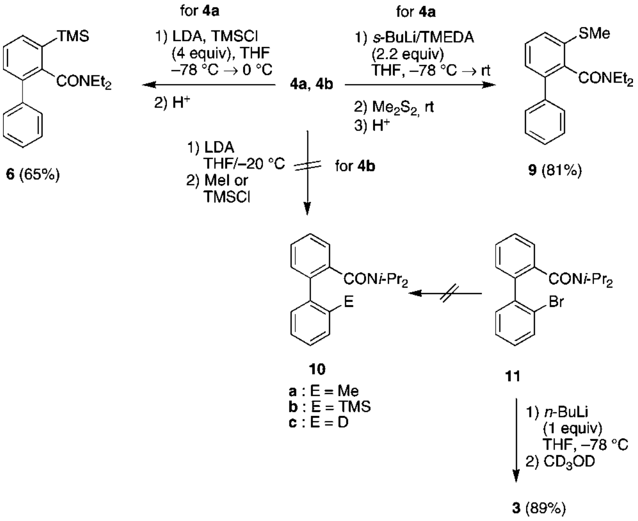
In a parallel study aimed to enhance the synthetic utility of the metalation chemistry of unprotected benzoic acids,[5] reaction of 2-biphenyl carboxylic acid (**2b**) with *n*-BuLi/*t*-BuOK (Lochmann−Schlosser base) was shown to occur in a nonregioselective fashion to also give **3**.[6] To expand practical synthetic utility for this important anionic aromatic chemistry,[1,7] we have aimed at understanding and controlling the DoM/DreM regioselectivity of these processes. Herein we report results that lead to the first mechanistic proposal concerning the metalation of *N*,*N*-dialkyl-2-biphenyl carboxamides.

In examination of the overall proposed general mechanism, delineated in Scheme 2, we posed a number of questions. To answer the question of relative stabilities and potential interconversion of the *ortho*- and remote lithiated species **5** and **7**, formed from **4** via complex **C** as generally accepted (complex induced proximity effect, CIPE),[8,9] the following experiments were carried out (Scheme 3). First, it was demonstrated that carboxamide **4a** does not undergo deprotonation at −78 °C, as evidenced by its recovery upon *sequential* treatment at −78 °C with 1.1 equiv of LDA in THF and MeI or TMSCl (external quench).[4] However, when LDA (4 equiv) and TMSCl (4 equiv) were premixed in THF solution (−78 °C) prior to addition of **4a** (*in situ* quench conditions),[10] *N*,*N*-diethyl 3-(trimethylsilyl)biphenyl-2-carboxamide (**6**) was formed exclusively (65%).[11] This experiment suggests greater kinetic over thermodynamic acidity of C-3 H compared to C-2′ H in **4a**. The reaction of **5** with TMSCl leading to **6** is faster than its equilibration to **7**, which if it had occurred, should have been evidenced in the cyclization to **3** ($k_4 > k_3$). To fortify this result, a second experiment was carried out in which the anion **5**, prepared by reaction of **4a** with *s*-BuLi/TMEDA (2.2 equiv) at −78 °C,[3] was allowed to warm to rt (Scheme 3). Addition of dimethyl disulfide (external quench experiment) at this temperature afforded *N*,*N*-diethyl 3-(methylthio)biphenyl-2-carboxamide (**9**) as the sole product in 81% yield.

Scheme 2



Scheme 3



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(5) (a) Gohier, F.; Castanet, A.-S.; Mortier, J. *J. Org. Chem.* **2005**, *70*, 1501. (b) Nguyen, T. H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445. (c) Nguyen, T. H.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765.

(6) (a) Tilly, D.; Samanta, S. S.; De, A.; Castanet, A.-S.; Mortier, J. *Org. Lett.* **2005**, *7*, 827. (b) Tilly, D.; Samanta, S. S.; Castanet, A.-S.; De, A.; Mortier, J. *Eur. J. Org. Chem.* **2006**, 174.

(7) Substituted biaryls are of high current interest in the development of ligands for transition metal catalyzed reactions. For a superb comprehensive review, see: Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(8) (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.

(9) Riggs, J. C.; Singh, K. J.; Yun, M.; Collum, D. B. *J. Am. Chem. Soc.* **2008**, *130*, 13709, and references therein.

(10) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(11) When this reaction was carried out between 0 °C and rt with 2 equiv of LDA/TMSCl, the yield of **6** decreased to 11% yield with 85% recovery of starting material. At 0 °C, LDA partly destroys *in situ* TMSCl. However, even at this temperature, metalation of **4a** leading to **5** by the remaining LDA is competitive in rate.

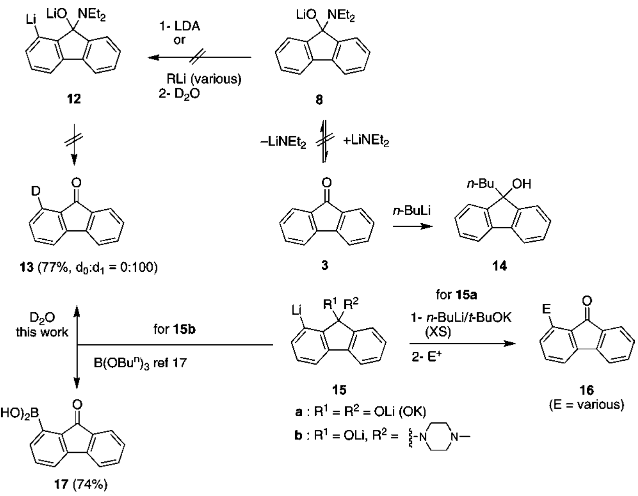
These experiments allow the conclusion that the *ortho*-lithiated species **5** generated under these conditions is formed efficiently, does not undergo self-condensation with starting **4a** to form a benzophenone product as is the case for the *ortho*-lithiated *N*,*N*-dialkyl benzamide[12] and, significantly, *is stable to room temperature* and does not equilibrate with **7** ($k_2 > k_3$).

In contrast, when LDA deprotonation of **4b** was carried out at −20 °C,[13] followed by addition of MeI or TMSCl at this temperature, **10a** and **10b** were not formed and only fluorenone (**3**) was isolated. This experiment suggests a slow remote deprotonation step occurs to give **7**, which has a short lifetime and undergoes cyclization to **3** in a fast and irreversible step. To corroborate this proposal and determine the behavior of anion **7** directly, *N*,*N*-diisopropyl 2-(2′-bromophenyl)benzamide (**11**) was subjected to metal−halogen exchange (1.1 equiv of *n*-BuLi, THF, −78 °C, 5 min) followed by CD_3OD quench. Formation of 2′-deuterated **10c** was not observed and undeuterated fluorenone (**3**) was obtained exclusively (89% yield).[14] Combined, the above results show that (1) the conversion of **5** to **7** does not occur under the RLi/TMEDA and *in situ* LDA/TMSCl conditions and (2) the LDA-mediated cyclization of independently generated **7** to **3** is faster than the isomerization of **7** to **5** ($k_4 > k_{-3}$).

To demonstrate that the kinetically deprotonated anion **5** may be converted into the thermodynamically favored carbinolamine oxide **8** through proton transfer involving DIA/LDA, we adopted the poignant experiments of Seebach.[15] Thus, biarylamide **4a** was treated first with *s*-BuLi/TMEDA (1.1 equiv) at −78 °C to form the stable *ortho*-lithiated species **5** (*vide supra*). Stirring at −78 °C was maintained for 1 h, and 10 mol % of DIA was then added. After warming to room temperature and normal workup, **3** was isolated in 30% yield with 70% recovery of starting material. This result is consistent with reprotonation of **5** by DIA affording **4a**, which in turn can be deprotonated by the generated residual LDA and give, either directly or via the postulated complex **C**, remote metalated species **7**. The subsequent cyclization of **7** leading to **8** is fast and irreversible, and the LDA-mediated equilibrium **5** ⇌ **7** is shifted toward the formation of **7**.

We now sought to address the nature of the organometallic species in the reaction mixture prior to hydrolysis. The carbinolamine oxide **8** is potentially present in equilibrium with fluorenone (**3**) by addition−elimination of $LiNEt_2$ (Scheme 4). If this is the case, the formation of 9-butyl-9*H*-fluoren-9-ol (**14**) is expected to some extent by the addition of alkyllithium bases to the generated **3**.[16] If, however, only **8** is present in solution, expectation that *peri*-metalated species **12** will be formed with excess base is inferred from our previous observations of the formation of the analogous trianion **15a** arising from 2-biphenyl carboxylic acid (**2b**) using an excess of *n*-BuLi/*t*-BuOK[6] to give products **16** and, from the results of Demeter, for the closer related carbinolamine oxide **15b** resulting from sequential reaction of **3** with lithio *N*-methylpiperazide and *n*-BuLi followed by quench with $B(OBu^n)_3$ to afford **17** (Scheme 4).[17] In the event, reaction of **4a** with 3 equiv of LDA at 0 °C followed by addition of D_2O provided the *undeuterated* fluorenone **3** in an improved yield (92%) compared with that obtained in the original experiments.[4] Furthermore, when 2−4 equiv of *n*-BuLi, *s*-BuLi, or *s*-BuLi/TMEDA were added to the reaction mixture *following* the treatment with LDA, undeuterated fluorenone was also obtained in >90% yields.

Scheme 4



The modest DMG power of the carbinolamine oxide $C(OLi)(NR_2)$,[18] as suggested by the vigorous conditions (refluxing benzene) necessary to generate the analogous species **15b**, was considered to be the reason for the lack of formation of *peri*-deuterated fluorenone **13** under our conditions (3 equiv of LDA/0 °C/D_2O quench). To provide further evidence for the intermediacy of **15b** and thus indirect evidence for **12**, the metalation conditions of Demeter were reproduced, but the reaction was quenched with D_2O. 1-Deutero-9*H*-fluoren-9-one (**13**) was obtained in 77% yield and >95% d_1-incorporation.[14b] Although conclusive evidence has not been obtained here, we note that corroborative support for carbinol amine intermediates in these DreM

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(12) Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *42*, 1823.

(13) Tilly, D. Ph.D. thesis, Université du Maine, 2004.

(14) (a) Additionally, metalation of *N*,*N*-diethyl 3-deuterio-2-biphenyl carboxamide (d_0:d_1 1:99) with LDA (3 equiv) at 0 °C followed by quench with 2 M HCl furnished, in addition to unreacted starting material (8%, d_0:d_1 1:99), 1-d_1-fluorenone (d_0:d_1 78:22, 83% yield), indicative of some erosion of d_1-content due to a KIE. **4a**-3d_1 was prepared by amidation of 3-deutero-2-biphenyl carboxylic acid.[6b] (b) Isotope ratios were determined by ^1H NMR and FIMS. The error is approximated to be ±5%.

(15) (a) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. (b) For a review, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(16) In a separate experiment, treatment of **3** with *n*-BuLi (1.1 equiv) in THF at rt afforded **14** (51% yield) as expected.

(17) Demeter, A.; Timári, G.; Kotschy, A.; Bérces, T. *Tetrahedron Lett.* **1997**, *38*, 5219.

(18) (a) Comins, D. L. *Synlett* **1992**, 615. (b) For the complexity of lithio carbinolamine oxide solid-state structures, see: Clegg, W.; Liddle, S. T.; Snaith, R.; Wheatley, A. E. H. *New J. Chem.* **1998**, 1323, and references therein.

reactions for species of the type **8** has been achieved by a React IR study.[19]

In summary, the first study concerning the mechanism of the DoM and DreM reactions of biaryl-2-carboxamide derivatives has been carried out (Scheme 2), which allows the following comments and conclusions: (1) the initial generation of complex **C** in a fast process representative of the well accepted CIPE[8,20] is assumed; (2) *ortho*-lithiated species **5**, generated under *s*-BuLi/TMEDA or *in situ* LDA/TMSCl conditions, does not undergo equilibration with **7** as evidenced by the formation of 3-substituted products **6** and **9** (Scheme 3); remote-metalated species **7**, generated independently by metal−halogen exchange of **11**, does not undergo equilibration with **5** but rather rapid cyclization to give fluorenone (**3**) via the tetrahedral intermediate **8**; (3) the equilibrium between **5** and **7** via **4a** is established by generation of residual LDA (by addition of DIA) in the solution of independently generated **5**; (4) the inability to trap **7**, independently generated under typical LDA conditions, by electrophiles (including D_2O) and its resulting formation of fluorenone (**3**) is consistent with fast and irrevesible formation of carbinolamine oxide **8**, which constitutes the thermodynamic driving force and the basis for the success of the DreM reaction; (5) although direct evidence for **8**, most likely existing as a dimer or larger associated complex species,[21] was not obtained, the formation of this species bearing a weak DMG prior to hydrolysis was inferred by evidence for the generation of an analogous *peri*-metalated species **15b** and a React IR study on a related biaryl 2-amide.

We believe that this mechanistic study which leads to an advanced understanding of the *ortho* and remote metalation of birarylamides will warrant a reappraisal of other known analogous processes, provide a foundation for rational design of new DoM and DreM reactions, and thereby may contribute to further progress in the field of carbanionic synthetic aromatic chemistry.

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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] Treatment of *N*,*N*-diethyl 4-(3-methoxy-phenyl)-nicotinamide with LDA leads to the gradual disappearance of the amide absorption band (C═O, $\nu = 1632$ cm^{-1}) and, *only after quench with MeOH*, the appearance of the azafluorenone band (C═O, ν 1718 cm^{-1}); see: Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588.

[20] All reactions, whether conducted with RLi bases or LDA bases, may proceed via CIPE. The structures of the complexes will have different geometries and therefore different possible access to transition state deprotonation. For example, different stoichiometries of $(s\text{-BuLi})_n(\text{TMEDA})_m$ complexes can be involved in similar deprotonation reactions; see: Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.

[21] Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B. *J. Am. Chem. Soc.* **2004**, *126*, 3113.