Controlling Chemoselectivity in Reactions of Unprotected Naphthalene-1-carboxylic Acid with Strong Bases

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Whereas treatment of unprotected naphthalene-1-carboxylic acid with alkyllithiums (RLi) affords 1,4-addition products, the reaction with LTMP/Me_3SiCl under in situ quench conditions provides the arylsilane arising out from the substitution of lithium 2-lithionaphthalene carboxylate with Me_3SiCl. With the Lochmann–Schlosser superbase (*n*-BuLi/*t*-BuOK), metalation occurs preferentially in the position adjacent to CO_2Li although the peri and *ortho*, peri-dilithiated species are also formed.

Naphthalenes may undergo nucleophilic attack by organolithium compounds,[1] though dearomatisation of a naphthalene ring requires additional activation by an electron-withdrawing substituent. Naphthalenimines,[2] naphthyloxazolines[3] and very bulky 2,6-di-*tert*-butylphenyl esters of naphthalenecarboxylic acids[4] all accept nucleophiles, losing aromaticity in one ring thus providing valuable synthetic intermediates. The substituent withdraws sufficient electron density to allow dearomatising nucleophilic attack to take place.

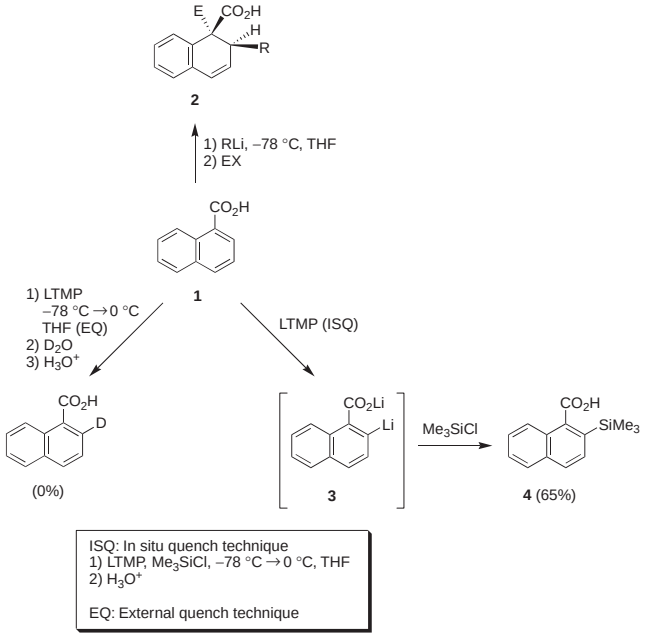
We have reported that naphthalene-1-carboxylic acid (**1**) undergoes predominantly conjugate addition with alkyllithiums (RLi) at low temperature (−78 °C) in THF and leads to various 1,1,2-trisubstituted-1,2-dihydronaphthalenes **2** after quenching with electrophiles (EX) (Scheme 1).[5,6] Entry of the electrophile proceeds exclusively from the more accessible opposite face to that carrying the alkyl group.

Ortho- and peri-lithiations of naphthalenecarboxylic acid derivatives have received so far less attention.[7] The best peri-lithiation-directing groups are those which coordinate to the incoming organolithium but do not acidify nearby protons, thereby disfavoring directed *ortho*-lithiation. Typical peri-lithiation substrates are therefore naphthalenes bearing electron-rich oxygen or nitrogen-based substituents (e.g. OMe, NMe_2, or CH_2NMe_2).[7] With the electron withdrawing tertiary amide substituent $CONR_2$—only group able to direct metalation in its adjacent position in the naphthalene series—, the *ortho*-substituted product becomes kinetically and thermodynamically favored.[7,8]

Although the CO_2Li group does activate neighboring positions towards metalation, the effect remains fairly weak.[9,10] This enables regioflexibility as most other electronegative substituents outperform a competing carboxylate group by their superior *ortho*-directing power.[11,12] For instance, whereas 4-fluoro benzoic acid is metalated preferentially in the position adjacent to the carboxylate by treatment with *s*-BuLi, *s*-BuLi/TMEDA or *t*-BuLi at ≈−78 °C, a complete reversal in regioselectivity is observed with LTMP at −50 °C.[13]

We decided to explore metalation conditions using sterically hindered lithium amides (LDA and LTMP) and the Lochmann–Schlosser base (*n*-butyllithium/*t*-BuOK)[14,15] with the intention of obtaining good chemo- and regiocontrol. It was not only of theoretical, but also of practical interest to test conditions for selective lithiation in *ortho*- or peri-position to the carboxylate, since the amide counterpart ($CONR_2$) is recalcitrant to hydrolysis.[16,17] There is also a real lack of methods for transformation of this group to other useful functionalities.

Acid **1** did not react upon treatment with LDA or LTMP (2.2 equiv.) in THF followed by a D_2O quench in the interval of temperature −78 °C → 0 °C [External quench (EQ)]. When LTMP and chlorotrimethylsilane were premixed prior to the addition of **1** [in situ quench (ISQ) technique],[18] 2-(trimethylsilyl)-naphthalene-1-carboxylic acid (**4**) was isolated in 65% yield.

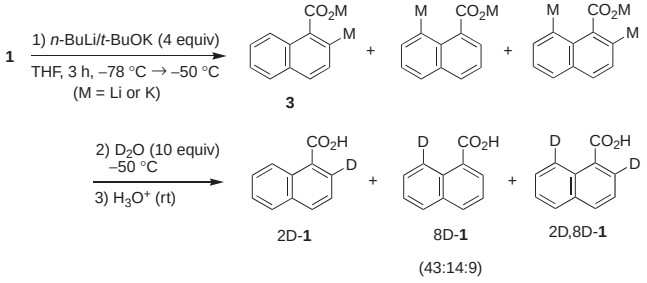


Scheme 1.

Chlorotrimethylsilane is known to react slowly with bulky bases such as lithium diisopropylamide (LDA) and LTMP,[18,19] and with *tert*-butyllithium and *n*-butyllithium.[20] Nevertheless, *s*-BuLi and *s*-BuLi:TMEDA destroy Me_3SiCl at −85 °C in THF.[11] The deprotonation of **1** by LTMP which produces a small concentration of the trappable aryllithium **3**, is sufficiently rapid to make the process competitive in rate with reaction of the hindered base with Me_3SiCl. Deuterium oxide destroys the excess LTMP under EQ conditions. Although triisopropyl borate is known to be an effective in situ-trap in the presence of LTMP,[21] it did not react under the previous ISQ conditions.

With the *n*-butyllithium/*t*-BuOK mixture (LICKOR), initial results from our laboratories were interesting though not synthetically useful. After much experimental manipulation, the best

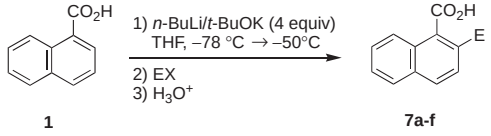
conditions involved forming the metalated species with LICKOR (4 equiv.) in THF at −78 °C (Scheme 2). The reaction was allowed to warm up to −50 °C, quenched with deuterium oxide (10 equiv.), and acidified at rt with 6 M HCl until pH reached 1. The deuterated products 2D-**1**, 8D-**1** and 2D, 8D-**1** were formed in a 43:14:9 ratio, via the intermediacy of the organometallic species **3**, **5**, and **6** (M = Li or K) resulting from the metalation of the substrate in ortho, peri, and *ortho*-peri positions, respectively.[22] The nature of the cations M involved in these species is not known with certainty. Both the structure of bases in solution as well as the nature of the actual reactive species have been the objects of controversial discussions.[23] To the best of our knowledge, aromatic dianionic carboxylates of the type **6** have never been reported so far.



Scheme 2.

With these optimized conditions in hand, we proceeded to evaluate the scope of the process. Since the separation of the major *ortho*-substituted products was readily accomplished by fractional recrystallization, the reported method provides an easy access to very simple 2-substituted naphthalene-1-carboxylic acids (Table 1).[24]

Table 1. Synthesis of 2-substituted naphthalene-1-carboxylic acids (**7a–f**)



Entry	EX	E	Product/%[a]	mp/°C
1	MeI	Me	**7a** (48)	125–127
2	EtI	Et	**7b** (38)	118–119
3	C_2Cl_6	Cl	**7c** (29)	148–150
4	$C_2Br_2Cl_4$	Br	**7d** (32)	136–139
5	I_2	I	**7e** (30)	185–187
6	Me_2S_2	MeS	**7f** (34)	105–109

[a]Isolated (recrystallized) yields.

Reaction with iodomethane and iodoethane gave the anticipated products (Entries 1 and 2). Quenching with such electrophiles as hexachloroethane, 1,2-dibromotetrachloroethane, and iodine provided the *ortho*-halogenated benzoic acids **7c–e** (Entries 3–5). Addition of dimethyl disulfide afforded the methylsulfenylated derivative **7f** (Entry 6). In each entry, the ortho, peri, and *ortho*-peri product distribution was similar to that observed with D_2O (Scheme 2).

The results reported in this letter corroborate the recent concept of how to achieve chemo or regiocontrol in hydrogen/metal exchange processes through mechanism-based matching of substituents and reagents.[11–13,15] Although the yields of 2-substituted naphthalene-1-carboxylic acids are modest, the present method is direct and does not require protection and deprotection of the CO_2H group. Extensions of the manipulation of carboxylic functional group are ongoing in our laboratories and will be reported upon in due course.

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24 General procedure: To a stirred solution of naphthalene-1-carboxylic acid (**1**) (300 mg, 1.74 mmol) in anhydrous THF (15 mL) at −78 °C, was added the precooled (−78 °C) THF solution (10 mL) of the LiCKOR base (6.96 mmol, 4 equiv.). The reaction mixture was allowed to warm up to −50 °C and stirred at this temperature for 3 h. The electrophile (6–10 equiv.) in THF (8 mL) was then added. The reaction mixture was allowed to warm to room temperature over a period of 2 h. Acidification and standard workup led to a residue which was purified by chromatography on silicagel using cyclohexane/ethyl acetate (90:10) followed by recrystallization (heptane/ethyl acetate).

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