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A Practical Method For Stabilizing Lithiated Halogenated Aromatic Compounds

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Abstract:

An exothermic decomposition was observed during a metalation/acylation of 3,4-difluoroanisole (5), resulting in a significant thermal hazard. The lithiated anion 6 was found to decompose exothermically at temperatures above −47 °C showing an adiabatic temperature rise at a peak rate of 120 °C/min. A literature search revealed similar observations for metalation/acylation in analogous aromatic difluoro compounds. This sequence of reactions was evaluated thermochemically. Control experiments at −55 °C over 2 h indicated anion 6 was stable at temperatures below −55 °C under dilute reaction concentrations. This runaway hazard could be addressed using $MgCl_2$ to stabilize the reactive species and thereby decrease its decomposition rate. Thermochemical experiments suggested $MgCl_2$ forms a weak interaction with lithiated species 6, rather than *via* complete lithium−magnesium exchange. The process was successfully piloted on a multikilo scale by use of $MgCl_2$ as an additive.

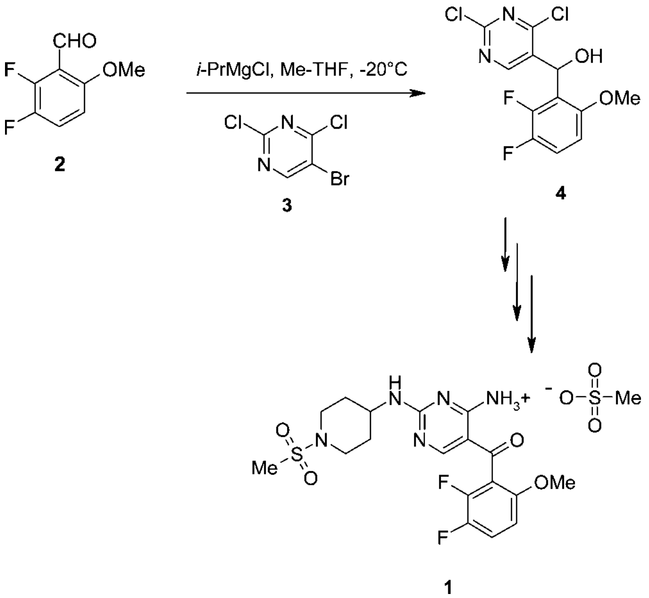
Introduction

6-Methoxy-2,3-difluorobenzaldehyde (**2**) is an important intermediate for the preparation of [4-amino-2-(1-methanesulfonylpiperidin-4-ylamino)pyrimidin-5-yl]-(2,3-difluoro-6-methoxyphenyl)methanone (**1**), a potent and selective CDK4 inhibitor.[1] Compound **1** can be prepared *via* dichloropyrimidine intermediate **4**, which in turn is available through the coupling of 6-methoxy-2,3-difluorobenzaldehyde (**2**) and 5-bromo-2,4-dichloropyrimidine (**3**) (Scheme 1).

The synthetic route for preparing 6-methoxy-2,3-difluorobenzaldehyde (**2**) has been disclosed[2] and involves a low temperature (−78 °C) metalation/formylation of 3,4-difluoroanisole (**5**) (Scheme 2).

After treatment of 3,4-difluoroanisole (**5**) with 1.3 equiv of *n*-BuLi (2.5 M in hexanes) at −78 °C in 2-methyltetrahydrofuran (Me-THF) (0.86 M), the mixture was allowed to stir for an additional hour. Following the slow addition of anhydrous DMF to the reaction mixture at −78 °C, the contents were warmed to 0 °C over 2 h. After quenching with aqueous citric acid and layer separation the crude aldehyde was isolated.

Scheme 1. **Overall synthesis of CDK4 inhibitor**



Scheme 2. **Formylation of 3,4-difluoroanisole**

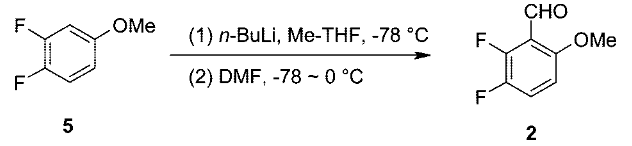


Table 1. **Formylation of 3, 4-difluoroanisole (5)**

entry	base	solvent	temp (°C)	*A*% purity (HPLC)	% yield
1	LDA	THF	−50	99.9	71[a]
2	*n*-BuLi	THF	−65	98.3	>95[b]
4	*n*-BuLi	Me-THF	−65	99.7	>95[b]
5	*n*-BuLi	Me-THF	−78	99.7	90[c]
6	*n*-BuLi	Me-THF	−78	99.8	92[c]

[a] Crystallized from heptane/TBME. [b] Isolated as crude product. [c] Crystallized from petroleum ether and toluene.

Aldehyde (**5**) (95% HPLC purity) can be carried directly into the next reaction or crystallized from heptanes. Crystallization from *n*-heptane gave a light-yellow solid (>99% HPLC purity). Lithiation of 3,4-difluoroanisole (**5**) could be also accomplished using LDA (Table 1) but required dilution (0.54 M).

Stability of 2-Lithio-3,4-Difluoroanisole Intermediate (6). Low-temperature ortho-lithiation of **5** has safety issues because of the formation of the highly energetic and unstable benzyne intermediate **7** (Scheme 3). Low-temperature ortho-lithiation of halogenated aromatics is well-known to have exothermic safety

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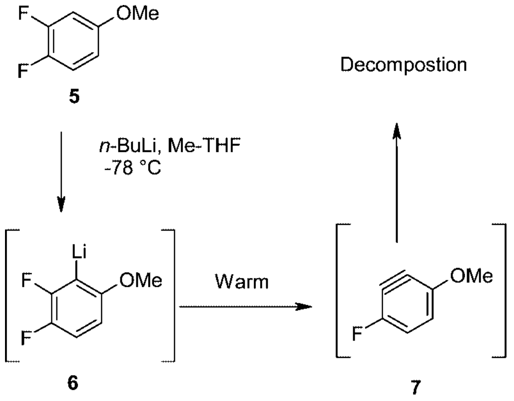
(1) Chu, Xin-Jie; DePinto, W.; Bartkovitz, D.; So, S.-S.; Vu, T.; Packman, K.; Lukacs, C.; Ding, Q.; Jiang, N.; Wang, K.; Goelzer, P.; Yin, X.; Smith, A. M.; Higgins, B. X.; Chen, Y.; Xiang, Q.; Moliterni, J.; Kaplan, G.; Graves, B.; Lovey, A.; Fotouhi, N. *J. Med. Chem.* **2006**, *49*, 6549–6560.

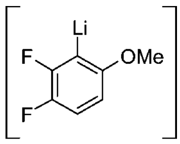
(2) Boot, J. R.; Brace, G.; Delatour, C. L.; Dezutter, N.; Fairhurst, J.; Findlay, J.; Gallagher, P. T.; Hoes, I.; Mahadevan, S.; Mitchell, S. N.; Rathmell, R. E.; Richards, S. J.; Simmonds, R. G.; Wallace, L.; Whatton, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5395–5399.

10.1021/op8001596 CCC: $40.75

Scheme 3. **Postulated mechanism for decomposition of 2-lithio-3,4-difluoroanisole**



issues.[3] In the event of lost cooling and/or a high charging rate of *n*-BuLi, the rate of formation of this unstable benzyne intermediate increases substantially; this may result in thermal shock, equipment damage and loss of containment from a runaway reaction. As such, our initial approach was to determine the thermal stability of the 2-lithio-3,4-difluoroanisole (**6**).



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The thermal characteristics of this reaction were studied using an HEL Simular reaction calorimeter which was equipped with a double-jacketed, 0.8-L, glass reactor rated for operating pressures up to 6 bar. The inner jacket contained heat-transfer fluid with an evacuated outer jacket for system insulation. Anion **6** was generated by the addition of 2.5 M *n*-BuLi in hexanes (1.3 equiv) to a Me-THF solution of 3,4-difluoroanisole (**2**) (0.86 M final concentration, 30 g scale of difluroansiole, 270.7 mL total volume of reaction mixture) while maintaining the batch temperature below −60 °C. The calorimeter was operated in power compensation mode, maintaining the jacket at a fixed temperature below the batch temperature setpoint (in this study, 12 °C below the setpoint) using a coil heater inserted into the batch to compensate for the heat removed by the jacket to maintain the batch temperature setpoint. After completing the *n*-BuLi addition, the batch was heated at 2 °C/min (see Figure 1). A maximum power input in the power compensation mode was measured at a batch temperature of −50 °C. The power input needed to heat the batch declined steadily when the release of energy *via* decomposition increased. The batch temperature could no longer be controlled at −30 °C (jacket −42 °C), and the batch temperature increased at an accelerating rate, peaking at 50 °C, and was accompanied by darkening of the reaction mixture. The maximum self-heating rate (d*T*/d*t*) observed was 120 °C/min (jacket at −40 °C), and the maximum deviation from the setpoint was 70 °C.

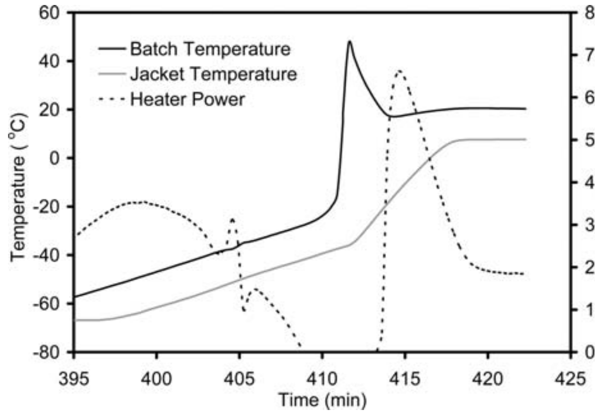
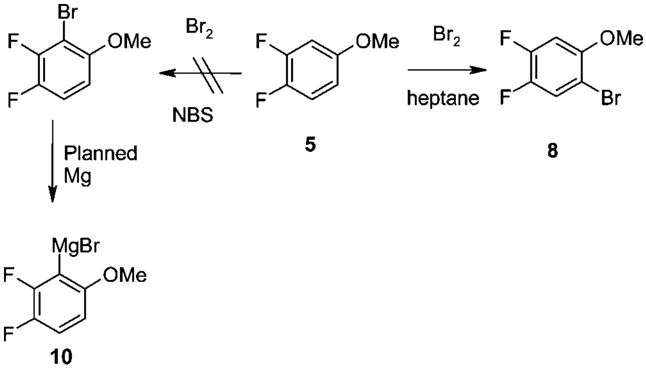


Figure 1. **Decomposition profile of 2-lithio-3,4-difluoroanisole (6) (0.86 M).**

Scheme 4. **Bromination of 3,4-difluoroanisole**



Halogenated aromatic lithium anions are known[3] to decompose via energetic benzyne intermediates such as **7** (Scheme 3). Further support for benzyne intermediates comes from trapping studies with various nucleophiles.[3b]

After this initial experiment revealed the thermal hazard present in this process, the rapid development of a robust and safely scalable process was of utmost importance to our Clinical Supply Program. Experiments were made to find alternative routes to the desired intermediate and also to find methods for improving the safety of the current process.

Results and Discussions

To avoid the thermal instability of the lithiated intermediate **6** in the ortho-lithiation method, alternate reaction pathways were explored with a plan of Grignard reagent in mind. Regioselective bromination of 3,4-difluoroanisole (**5**) to produce 2-bromo-3,4-difluoroanisole (Scheme 4) with bromine gave the undesired regioisomer, 2-bromo-4,5-difluoro-anisole (**8**), whereas bromination with *N*-bromosuccinimide was too slow to be practical.

In a more direct approach to formylation, reaction of 3,4-difluoroanisole (**5**) with α,α-dichloromethyl methyl ether in the presence of titanium tetrachloride[4] (Scheme 5), after acidic workup, also produced the undesired regioisomer, 2-methoxy-4,5-difluorobenzaldehyde (**9**).

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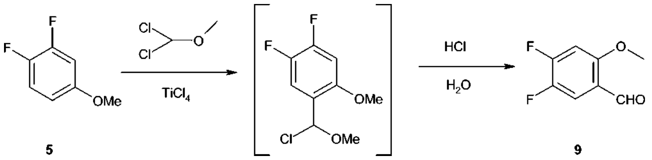
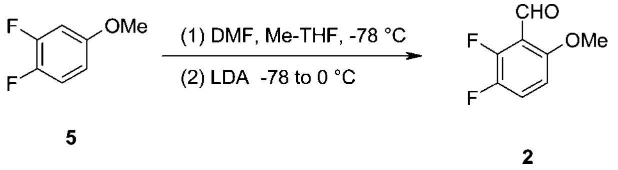
(3) For example, in difluoro series: (a) Rodney, L. P., Jr. *Curr. Opin. Drug Discovery Dev.* **2000**, *3* (6), 783–792. (b) For discussion of chlorobromophenyllithium and trapping studies, see: Hickey, R. M.; Allwein, P. S.; Nelson, D. T.; Kress, H. K.; Sudah, S. O.; Moment, J. A.; Rodgers, D. S.; Kaba, M.; Fernandez, P. *Org. Process Res. Dev.* **2005**, *9*, 764–767. (c) 2,6-Dibromophenyllithium: Lulinski, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384. (d) Fluorine as an ortho-directing group: Bridges, J. A.; Lee, A.; Maduakor, C. E.; Schwartz, E. *Tetrahedron Lett.* **1992**, *33* (49), 7499–7502. (e) Lithiation of fluoroanisoles: Furlano, C. D.; Calderon, N. S.; Chen, G.; Kirk, L. K. *J. Org. Chem.* **1988**, *53*, 3145–1347. (f) Ladd, L. D.; Weinstock, J. *J. Org. Chem.* **1981**, *46*, 203–206.

(4) Furlano, C. D.; Kirk, L. K. *J. Org. Chem.* **1986**, *51*, 4073–4075.

Scheme 5. **Alkylation of 3,4-difluoroanisole**



Scheme 6. **Formylation of 3,4-difluoroanisole**



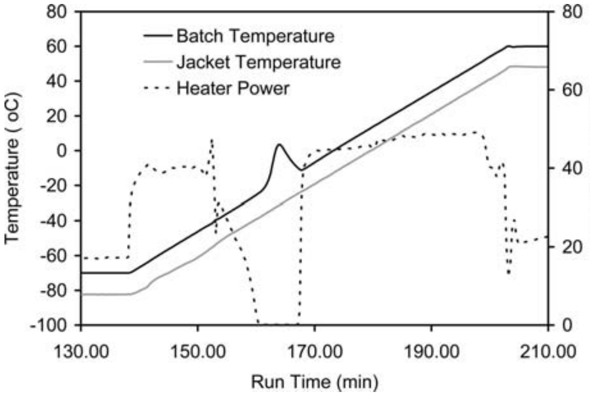


Figure 2. **Decomposition profile of 2-lithio-3,4-difluoroanisole 6 (0.47 M).**

Lithiation of 3,4-difluoroanisole (**5**) with 1.1 equiv of LDA in the presence of DMF in order to minimize the accumulation of the unstable anion **6** gave only 30% conversion to the desired product (**2**) (Scheme 6).

Ortho-lithiation under more dilute conditions (0.47 M) was examined by doubling the original amount of Me-THF. After lithiation below −70 °C, the batch was heated at 2 °C/min to 40 °C. Similarly, an exothermic degradation began at about −43 °C, and the batch temperature increased to a maximum of 21 °C above the setpoint, along with the development of a dark coloration. As expected, the increased heat capacity of the system better absorbed the heat, thereby slowing the formation of unstable benzyne intermediate **7**; however, the decomposition still occurred under the more dilute reaction conditions, although the maximum temperature and temperature rate were lower as compared to the higher concentration (Figure 2).

Although diluting the reaction provided a temporary solution, it reduced the capacity and would increase waste disposal costs from additional solvent usage.

A preferred solution to the reaction runaway hazard was through the use of anhydrous $MgCl_2$ as an additive. If complete Li−Mg exchange occurs, then the resulting ArMgCl intermediate could be less reactive.[5] Alternatively, $MgCl_2$ was thought to complex with intermediate **6** and thereby stabilize to slow the rate of benzyne formation. While initially observed and studied with 3,4-difluoroanisole (**5**) as substrate, this phenomenon could be extended to other halogenated aromatic compounds. A standard procedure involved the addition of anhydrous magnesium chloride to a solution of 3,4-difluoroanisole in 2-methyltetrahydrofuran and stirring the slurry for 20 h at 20 °C, followed by cooling to −78 °C and adding *n*-BuLi (1.3 equiv). Warming the resulting mixture at a rate of 2 °C/min from −70 to 40 °C did not cause a runaway reaction (Figure 3).

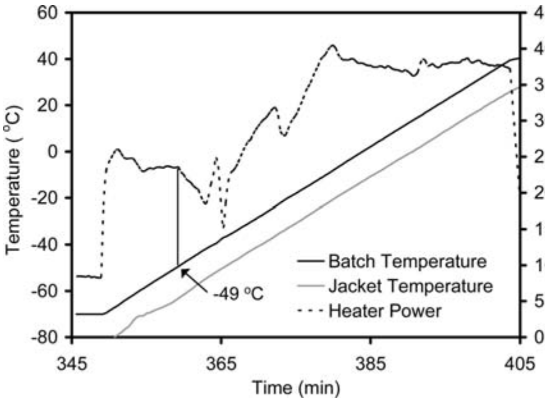
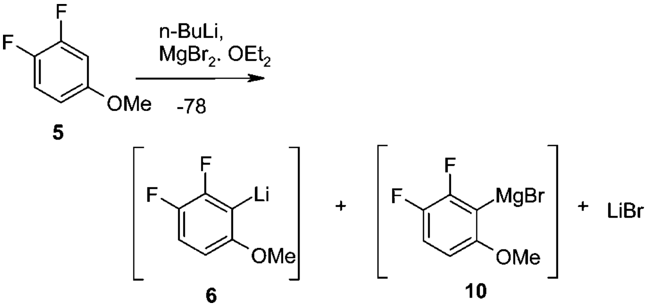


Figure 3. **Reaction profile of 2-lithio-3,4-difluoroanisole (6) with $MgCl_2$.**

Scheme 7. **Preparation of 2-methoxy-5,6-difluorophenyl magnesium bromide**



An exothermic reaction was observed starting at −49 °C; however, the rate of decomposition was not sufficient to cause a runaway as compared to the cases without $MgCl_2$. At all times during the heating phase, the power input into the reactor was greater than either of the baselines, resulting in a system that was more conservative than adiabatic.

Because a colored impurity had been an issue in the downstream process, an additional advantage in the use of $MgCl_2$ was that it afforded higher-quality product which was white in color, as opposed to a light-yellow to yellow product. The higher-purity profile of **2** in the presence of $MgCl_2$ can be attributed to fewer side reactions due to stabilization of intermediate **6**.

In order to explore the role of $MgCl_2$, we evaluated the stability and reactivity of the aryl-magnesium intermediate **10**. Aryl-MgBr intermediate **10** was prepared[5] by treating the lithiated anion **6** with the more reactive $MgBr_2 \cdot OEt_2$ at −78 °C (Scheme 7).

After aging the reaction mixture for 1 h, a sample was quenched into a Me-THF solution containing excess DMF at −70 °C. Based on the HPLC area % analysis 29% of product (**2**) and 71% of starting material (**5**) were observed. Obviously, DMF is very slow in reacting with the aryl-MgBr intermediate **10**. Warming the batch from −70 to 0 °C did not cause any

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(5) (a) Gilman, H.; Arntez, C. E. *J. Am. Chem. Soc.* **1950**, *72*, 3823. (b) Patten, D. A.; Nguyen, H. H; Danishefsky, S. J. *J. Org. Chem.* **1998**, *53*, 1003–1007.

Table 2. **Reactivity of aryl-MgBr intermediate 10 with DMF**

quench temp[a] °C	product **2** (% HPLC)	starting material **5** (% HPLC)
−70	29	71
−50	39	61
−30	43	56
0	48	51
20	58	42
20 (18 h)	89	10

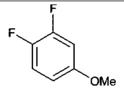
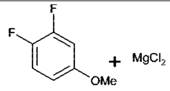
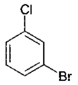
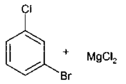
[a] After quenching with DMF the sample was held for 30 min.

color changes, indicating no decomposition; hence, extensive Li−Mg exchange may be occurring below approximately −50 °C, as lithiated intermediate **6** is unstable above −50 °C without $MgCl_2$. The colorless batch was cooled back to −78 °C, and samples were quenched into a Me−THF solution containing excess DMF at various temperatures (Table 2).

Quenching the batch after 18 h at 20 °C showed 89% conversion to **2** which suggests efficient Li−Mg exchange having occurred below −50 °C and that the aryl-MgBr intermediate **10** is stable at 0 °C. These results also suggest that **10** reacts slowly with DMF at −50 °C since only 39% conversion to **2** was observed. Preparing the desired aldehyde (**2**) via aryl-MgBr intermediate **10** is not practical. In contrast to the aryl-MgBr intermediate **10**, the lithiated anion **6** in the presence of $MgCl_2$, when heated with a steady ramp of 2 °C/min from −70 to 0 °C, resulted in a dark-brown solution due to decomposition *via* benzyne formation, although the rate of decomposition was not sufficient to cause a runaway reaction. This observation suggests Li−Mg exchange does not occur in the presence of $MgCl_2$. These experimental results suggest that $MgCl_2$ acts by forming a weak interaction with the lithiated species, rather than by a complete magnesium−lithium exchange.[6]

The thermal characteristics of these reactions were studied further using the HEL similar reaction calorimeter mentioned previously. Experimental reaction concentrations, shown in Table 3, were chosen to ensure that the runaway reactions did not approach refluxing conditions. The energy balance used for calculating the reaction power is shown in eq 1. The values for mc_p and UA are the lumped (reactor + contents) values for mass × heat capacity and heat transfer coefficient × surface area, respectively. These values were estimated using isothermal hold points and defined temperature ramps that were observed before and after the reaction. The values for Q_{heater} and T are observed heater power input and reactor temperature, respectively. When the batch of lithiated 3,4-difluoroanisole (**6**) was allowed to warm at a rate of 2 °C/min, the degradation generated heat at an onset temperature of −47 °C and reached a peak power output of 753 W/L at −2 °C. The maximum self-heating rate, calculated adiabatically, was 31 °C/min. In comparison, when $MgCl_2$ was present, the onset temperature was −45 °C with peak power output reduced to 298 W/L at −10 °C. In this case, the maximum adiabatic self-heating rate was 12 °C/min. The cumulative heat of reaction was −274 kJ/mol with and without $MgCl_2$. Clearly, the addition of $MgCl_2$ slows the decomposition of the lithiated species, lessening the maximum heat output, but does not affect the total energy released. This information further suggests that $MgCl_2$ may act by forming a weak interaction with the lithiated species, rather than by a complete exchange with the Li ion. This is supported by the observation that a complete exchange would be expected to lower the total reaction energy, as the initial state would have been a lower energy state. Similar results were found when investigating lithiated 3-bromochlorobenzene (Table 3 and Figures 4, 5, 6, and 7).

Table 3. **Evaluation of $MgCl_2$ in halogenated aromatic compounds**

Substrate	Concentration (M)	Adiabatic Temp. Rise (°C)	$(dT/dt)_{max}$ (°C/min)	$\triangle H_{rxn}$ (kJ/gmol)
	0.49	90	31	-274
	0.49	85	12	-274
	0.49	49	52	-151
	0.49	45	15	-144

$$mc_p\frac{dT}{dt} = UA\Delta T + Q_{rxn} + Q_{htr} \tag{1}$$

In Situ Reaction Monitoring. To shed more light on the role of $MgCl_2$ we explored the use of *in situ* reaction monitoring. The lithiation and formylation reactions were monitored *in situ* using an IR probe (ReactIR, Mettler-Toledo Autochem).

As shown Figure 8, during both *n*-BuLi and DMF additions, a number of peaks in real-time IR spectra can be chosen to monitor the progress of the reaction.

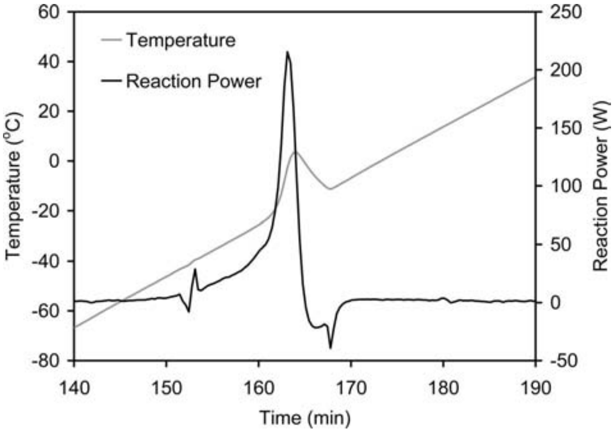


Figure 4. **Reaction profile of 2-lithio-3,4-difluoroanisole (6) without $MgCl_2$.**

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(6) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed* **2004**, *43*, 3333–3336.

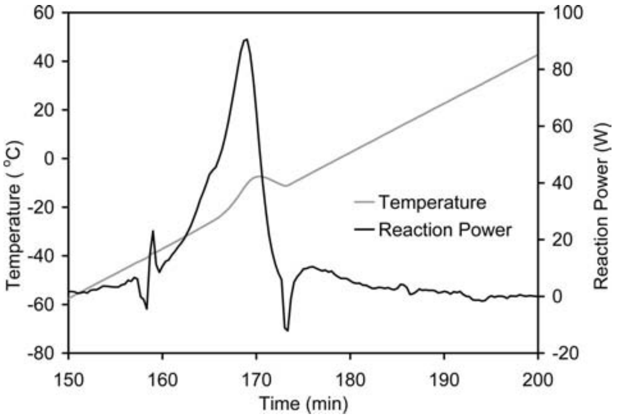

Figure 5. **Reaction profile of 2-litho-3,4-difluoroanisole 6 with $MgCl_2$.**

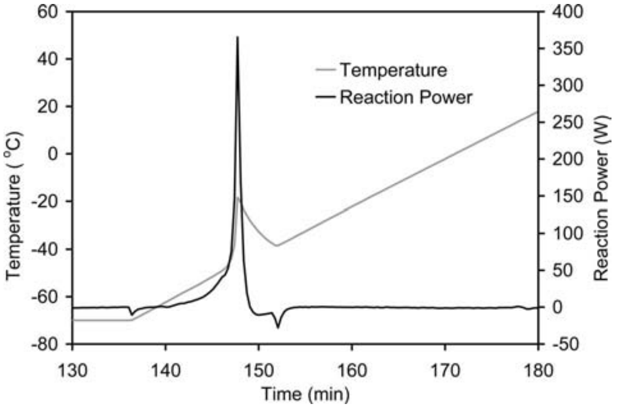

Figure 6. **Reaction profile of lithiated 3-bromochlorobenzene without $MgCl_2$.**

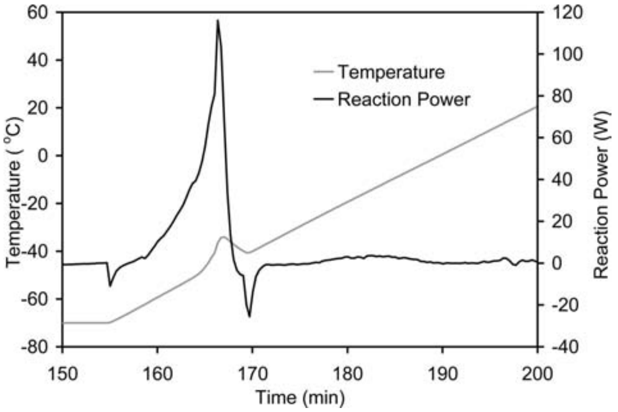

Figure 7. **Reaction profile of lithiated 3-bromochlorobenzene with $MgCl_2$.**

n-BuLi (2.5 M) in hexane was added (Figure 5, A) to a precooled solution (−78 °C) of 3,4-difluoroanisole (**5**) in Me−THF. The internal temperature was maintained between −70 and −76 °C. The formation of aryllithium intermediate **6** was indicated by an increase in the 1421 cm^{-1} peak absorbance, which corresponded well with the consumption of 3,4-difluoroanisole (**5**) (1517 cm^{-1} peak).

Similarly, during DMF addition (Figure 5, B), the disappearance of **6** (1420 cm^{-1} peak) was observed with a concomitant increase in the absorbance of the DMF-cyl intermediate (1497 cm^{-1} peak). These observations were supported by HPLC regarding the reaction completion. Interestingly, there were no notable ReactIR profiles differences observed between the reaction with or without $MgCl_2$.

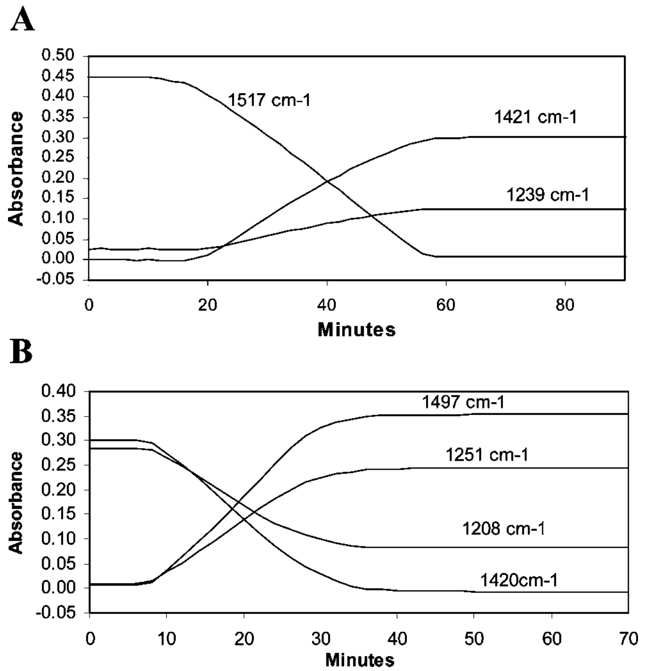

Figure 8. **ReactIR wave number profiles. (A) *n*-BuLi addition. (B) DMF addition.**

Summary

Low-temperature ortho-lithiation of halogenated aromatic compounds has been shown to present a significant thermal hazard, attributed to the formation of the highly unstable and energetic benzyne intermediate **7**. In the event of lost cooling or an excessive addition rate of *n*-butyllithium, the rate of benzyne formation and decomposition could lead to a thermal runaway. Such reactions were studied by reaction calorimetry and *in situ* IR analysis. The addition of $MgCl_2$ was shown to decrease the rate of decomposition and the resulting thermal hazard. While initially observed and studied with 3,4-difluoroanisole (**5**) as substrate, the phenomenon was also successfully extended to 3-bromochlorobenzene.

Experimental Section

Solvents and reagents were obtained from commercial sources and used without further purification. ^1H and ^{13}C NMR were performed on a Varian 400 MHz spectrometer.

HPLC Conditions: Agilent- Zorbox Eclipse XBD-phenyl column, 3.5 μm, 4.6 mm × 150 mm; mobile phase gradient 0.05% aqueous TFA/acetonitrile 75/25 over 15 min, then to 60/40 over 5 min, then to 25/75 over 5 min; 1.0 mL/min; 40 °C; detector 220 nm.

Synthesis of 2-Methoxy-5,6-difluorobenzaldehyde (2) in the Presence of Anhydrous $MgCl_2$. To a 500 mL round-bottom flask was added 3,4-difluoroanisole (**5**, 20.0 g, 139 mmol), 2-methyltetrahydrofuran (Me-THF, 100 mL) and anhydrous magnesium chloride (15.0 g, 153 mmol). The mixture was stirred at room temperature for 20 h and then cooled to −78 °C using dry ice/acetone bath. To the mixture was added *n*-BuLi (2.5 M in hexanes, 71.7 mL, 179 mmol) over 1 h, maintaining the internal temperature below −70 °C. After stirring 1 h *N,N*-dimethylformamide (DMF) (15.0 mL, 194 mmol) was added over 15 min, maintaining the batch temperature below −70 °C. After 1 h the batch warmed to 0 °C over an hour. To the batch was added 150 mL of aqueous citric acid (0.5 M) solution, and the phases were separated. The organic layer was concentrated to dryness to obtain (**2**) as a light-yellow solid in >95% yield and 98% purity (HPLC). Retention times: 10.66 min (3,4-difluoroanisole) and 7.84 min (2,3-difluoro-6-methoxy-benzaldehyde).

Synthesis of 2-Bromo-6-chlorobenzaldehyde in the Presence of Anhydrous $MgCl_2$. To a 500 mL round-bottom flask was added 1-bromo-3-chlorobenzene (26.5 g, 139 mmol), 2-methyltetrahydrofuran (Me-THF, 100 mL) and anhydrous magnesium chloride (15.0 g, 153 mmol). The mixture was stirred at room temperature for 20 h and then cooled to −78 °C using a dry ice/acetone bath. To the mixture was added LDA (2.0 M in hexanes/THF, 91.2 mL, 182 mmol) dropwise over 1 h, while maintaining the batch temperature below −70 °C. After 1 h *N,N*-dimethylformamide (DMF) (15.0 mL, 194 mmol) was added over 15 min by maintaining the batch temperature below −70 °C. After 1 h the batch was warmed to 0 °C over 1 h. To the batch was added 150 mL of aqueous citric acid (0.5 M), and the phases were separated. The organic layer was concentrated to dryness, and crude product was recrystallized from heptanes to obtain a light-yellow solid product in 80% yield. ^{1}H NMR 10.25 (s, 1H), 7.78 (dd, $J = 0.8, 0.8$, 1H), 7.65 (dd, $J = 0.6, 0.81$, 1H), 7.53 (t, $J = 8.1$, 1H). Retention times: 13.9 min (2-bromo-6-chlorobenzene) and 11.3 min (2-bromo-6-chlorobenzaldehyde).

Pilot-Plant Synthesis of 2-Methoxy-5,6-difluorobenzaldehyde (2). The vessel chosen for this process was a 200-L, Hastelloy C22, baffled vessel (Pfaudler) equipped with two diplegs for subsurface additions. The vessel and auxiliary equipment is rated for temperatures from −100 to 260 °C and pressures of 40 bar. The contents are agitated using a dual-impeller, pitched-blade turbine agitator with operation up to 350 rpm. The vessel is normally heated and cooled using its jacket, which is fed by a heat-transfer fluid loop with an electric heater and can be cooled to temperatures as low as −70 °C by heat exchange with liquid nitrogen. Additionally, a Praxair D-Cool direct-injection liquid nitrogen system, which injects liquid nitrogen directly into the batch, can be used to cool the contents to temperatures as low as −100 °C. The D-Cool unit can regulate the liquid nitrogen flow to maintain batch temperature to within ±2 °C under normal conditions. This system is capable of cooling loads in excess of 24 kW.

For each batch, 5.0 kg of $MgCl_2$ was charged to the nitrogen-inerted reactor, followed by 7.0 kg of 3,4-difluoroanisole (**5**) and 60 kg of 2-methyltetrahydrofuran. This mixture was cooled to about −25 °C using the jacket. The jacket was then drained of heat transfer fluid, and the batch was further cooled using the D-Cool system. Maximum agitator speed was maintained to effectively disperse the nitrogen through the batch. After stabilizing at −78 °C, 20.1 kg of 2.5 M *n*-butyllithium in hexanes was charged through the first dipleg. The batch was held for 1 h, followed by a charge of 7.2 kg of dimethylformamide through the second dipleg. After holding for 2 h, the D-Cool unit was deactivated, and the batch was heated to 5 °C using the jacket. The reaction was quenched with 90 kg of a 9 wt % aqueous citric acid solution. The layers were separated, and the product was precipitated by solvent exchange to *n*-heptane. Three batches were run, producing 14.6 kg (58% yield) with average assay of 98.5 area % (HPLC). The pilot-scale yield was lower than expected from laboratory experiments. Subsequent analysis of process streams indicated that reaction conversion was about 81% and the majority of product was lost during the isolation of the solid product.

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