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Use of lithium *N,O*-dimethylhydroxylamide as an efficient in situ protecting agent for aromatic aldehydes

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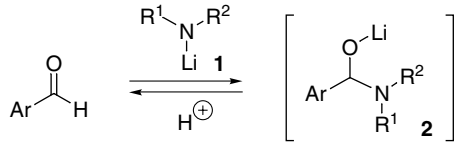
Abstract—The use of lithium *N,O*-dimethylhydroxylamide as an alternative in situ protecting agent for aryl aldehydes with low *ortho*-directing properties has been evaluated and subsequently applied to two practical multi-step one-pot syntheses of developmental drug candidate intermediates.

1. Introduction

The synthetic potential of α-amino lithium alkoxides **2** as protecting groups, metalation-directing groups and synthetic intermediates has been investigated and reviewed (Scheme 1).[1]



Scheme 1.

Comins pioneered the strategy of forming α-amino alkoxides by addition of lithium dialkylamides **1** to aromatic[2] and heteroaromatic aldehydes,[3] and demonstrated that mild acidic treatment unveils the masked formyl moiety. He introduced, amongst others, lithium 1-methylpiperazide (LNMP; **5**), lithium morpholide (**7**), the weakly basic lithium *N*-methyl-*N*-(2-pyridinyl)amide (LMPA; **4**), as well as the strongly *ortho*-metal directing lithium amide of *N,N,N′*-trimethylethylenediamine (LTMDA; **6**) (Fig. 1). Alternative in situ protection of aldehyde carbonyls was achieved by use of titanium tetrakis(dialkylamides).[4]

Curiously, the readily available lithium *N,O*-dimethylhydroxylamide (LDHA; **3**) has not been investigated as an in situ protecting group for aromatic aldehydes, although the use of Weinreb amides has found widespread application for ketone syntheses.[5] In these reactions, the lack of over-addition products was rationalized by a stable, metal-chelated intermediate similar to **2**. Lipshutz recently exploited the stability of α-amino lithium alkoxide complexes such as **2** for clean formylations of carbanions with methoxy(methyl)formamide.[6]

Although the potential existed for a novel and potentially useful application of lithium *N,O*-dimethylhydroxylamide (**3**), our primary interest in the in situ aldehyde masking methodology derived from the need to develop short and cost-efficient routes to synthetic intermediates **10** and **11** of *GlaxoSmithKline* drug candidates in preclinical development (Fig. 2).

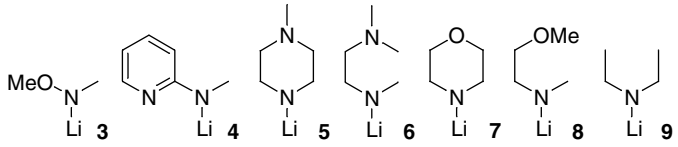


Figure 1.

Keywords: *N,O*-dimethylhydroxylamine; α-amino lithium alkoxides; in situ protection of aromatic aldehydes.

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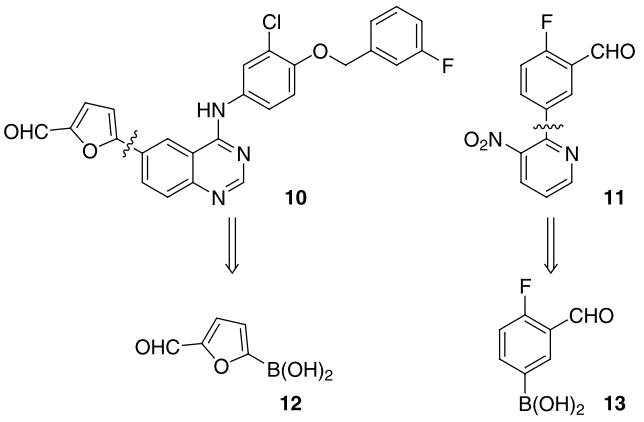


Figure 2.

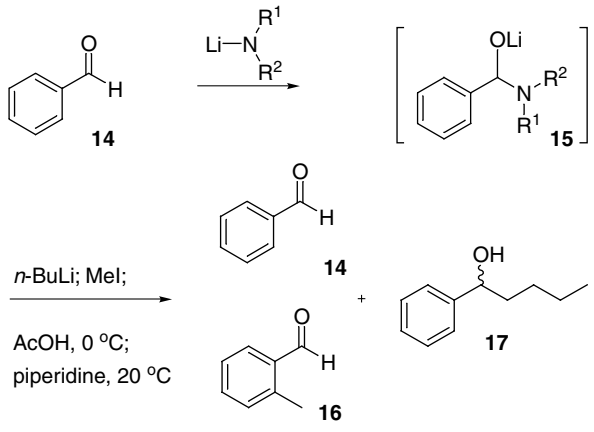
Both compounds should be accessible by Suzuki coupling[7] of boronic acids **12** and **13**, respectively, with their corresponding heteroaryl halide coupling partners. We intended to use latent α-amino alkoxides in order to avoid the common acetal protection–deprotection sequence of the formyl moiety for the generation of the boronic acids. For added practicality, we were interested in conducting this chemistry at moderately low temperatures (−40 to −20°C).

2. Results and discussion

2.1. Efficacy screen of lithium amides

α-Amino lithium alkoxides are capable not only of protecting the formyl moiety but also of directing subsequent lithiation to the *ortho*-position, a fact which has been exploited in synthetic applications.[8] However, our intention was to identify an efficient protecting agent which would furnish an α-amino lithium alkoxide with low *ortho*-directing propensity. The absence of published studies quantifying these properties prompted us to initiate a systematic screening of aryl aldehyde protecting agents **3**–**9**.

In particular, we were interested in a head-to-head comparison of LDHA (**3**) with literature-precedent lithium amides in regards to protective as well as *ortho*-directing power. Benzaldehyde (**14**), the most fundamental aromatic aldehyde, was chosen as model system for this initial screen (Scheme 2),[2b,9] in which α-amino lithium alkoxides **15** were assessed in THF at −20°C.



Scheme 2.

In a typical experiment, lithium amides **3**–**9** were reacted with benzaldehyde (**14**) to yield their corresponding α-amino lithium alkoxides **15**, which were subsequently treated with 2.3 equiv. of *n*-BuLi for 1–3 h. If a particular α-amino alkoxide moiety functioned not only as a protecting group, but also as an *ortho*-directing group, then *ortho*-lithiation would occur at a rate corresponding to its *ortho*-directing power, to furnish a dianion which could be alkylated by electrophiles. Therefore, to analyze for *ortho*-directing power, the reactions were quenched with iodomethane. The HPLC assessments of the experiments were conducted using meticulous dilution techniques, and showed predominantly three compounds: recovered **14**, 2-methylbenzaldehyde (**16**), and 1-phenyl-1-pentanol (**17**) (Table 1). 1-(2-Methylphenyl)-1-pentanol, the product of both butyl addition and *ortho*-methylation, was only detected by HPLC in a single experiment (entry 7; ca. 0.9% yield-in-solution) and thus omitted from the table. We defined protective power (PP) as the sum of recovered benzaldehydes: PP=% yield-in-solution (**14**)+% yield-in-solution (**16**). The *ortho*-directing power (OP) was directly derived from the amount of *ortho*-methylated benzaldehyde: OP=% yield-in-solution (**16**).

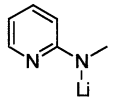
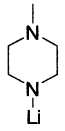
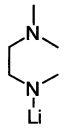
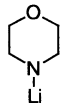
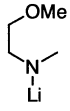
We were pleased to discover that lithium *N*,*O*-dimethylhydroxylamide (LDHA; **3**) not only offered highly efficient in situ protection of the aldehyde moiety, but also that its corresponding α-amino lithium alkoxide displayed minimal *ortho*-directing properties.

In continuation of our initial screen, we evaluated the most efficient non-*ortho*-directing in situ protecting groups, namely LDHA (**3**), lithium 1-methylpiperazide (LNMP; **5**), and lithium morpholide (**7**), at different temperatures (0 and −40°C in THF; entries 2, 3, 9, 10, 16, 17) and with two different solvents (DME and TBME at −20°C; entries 5, 6, and 12, 13). As a result of this study, the efficacy of lithium amides as non-*ortho*-directing benzaldehyde (**14**) protecting agents, represented by the % yield-in-solution of **14**, at temperatures between 0 and −40°C, can be ranked in the following order:

LDHA (**3**)≥lithium morpholide (**7**)≈LNMP (**5**)>lithium diethylamide (**9**)⩾lithium 2-methoxy-*N*-methylethanamide (**8**)>LTMDA (**6**)⩾LMPA (**4**).

Notably, compared to amides **5** and **7**, the use **3** provided significantly higher recovery of **14** at 0°C (entries 3, 10 and 17) or upon prolonged exposure to excess *n*-BuLi at −20°C (3 h vs. 1 h; entries 4 and 11). In addition, the LDHA (**3**)-derived α-amino lithium alkoxide displayed the overall lowest OP properties (entries 1–6), contrasting, as expected, the α-amino lithium alkoxides derived from **6** and **8**, which demonstrated good PP (entries 14, 18) and concurrently strong OP. This, of course, rendered the latter two parent amides less attractive for our purposes as non-*ortho*-directing protecting agents. Finally, a brief look at solvent effects (THF vs DME vs TBME; entries 1, 5, 6, and 8, 12, 13)[11]

Table 1. Composition of mixtures for the reaction **14→15→14+16+17** for various lithium amides

Entry	Lithium amide		Exposure to *n*-BuLi (h)/ temperature (°C)	Corrected % yield-in-solution of **14**[a]	Corrected % yield-in-solution of **16**[a] (=% directing power)	Corrected % yield-in-solution of **17**[a]	% Protective power
1		**3**	1/−20	97.8	0.2	0.0	98.0
2			1/−40	99.4	0.0	0.4	99.4
3			1/0	90.3	0.9	0.0	91.2
4			3/−20	93.9	0.2	0.0	94.1
5[b]			1/−20	96.9	0.7	0.0	97.6
6[c]			1/−20	92.1	0.1	2.1	92.2
7		**4**	1/−20	13.0	0.2	83.4	13.2
8		**5**	1/−20	92.4	0.7	0.0	93.1
9			1/−40	94.3	0.1	0.0	94.4
10			1/0	78.9	3.0	0.0	81.8
11			3/−20	84.7	1.5	0.0	86.2
12[b]			1/−20	90.4	2.6	1.1	93.0
13[c]			1/−20	93.7	0.0	0.0	93.7
14		**6**	1/−20	58.8	35.1	0.0	93.9
15		**7**	1/−20	95.4	0.8	0.5	96.2
16			1/−40	94.8	0.1	0.0	94.9
17			1/0	78.7	3.0	0.0	81.7
18		**8**	1/−20	67.4	17.4	0.0	84.7
19		**9**	1/−20	86.7	0.5	0.0	87.2

Reactions carried out in THF and quenched with MeI followed by AcOH unless otherwise noted. Temperature was not allowed to rise more than 5°C during reagent additions. % Yield-in-solution determined by HPLC.[10]

[a] Corrected for HPLC response factors.

[b] Reaction carried out in 1,2-dimethoxyethane (DME).

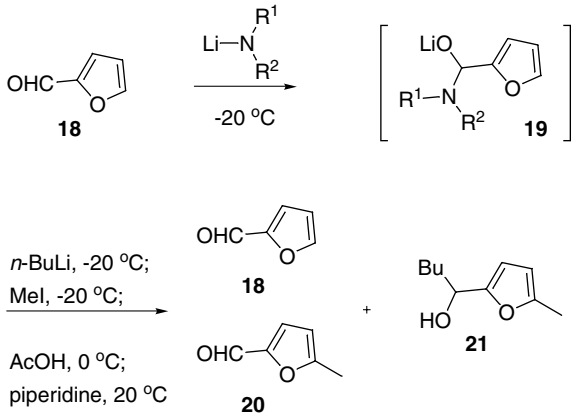
[c] Reaction carried out in *tert*-butyl methyl ether (TBME).

indicated slightly elevated *ortho*-directing aptitudes of the α-amino lithium alkoxides in DME vs THF. Although TBME provided positive results, the use of this solvent was deemed less appropriate due to a significant degree of heterogeneity observed during these experiments.

2.2. Application to 2-furaldehyde

Encouraged by these preliminary findings, we proceeded to examine the practicality and versatility of LDHA (**3**) as an in situ aryl aldehyde protecting agent with two *Glaxo-SmithKline* preclinical drug candidates. The first application entailed the development of a convenient one-pot synthesis of the functionalized pentacyclic core **10** (Fig. 2) of compounds in GlaxoSmithKline's erbB family of protein tyrosine kinase inhibitors,[12] starting from commercially available 2-furaldehyde (**18**). In an earlier disclosure, we described the challenges associated with the development of a practical one-pot synthesis of 5-(4-{3-chloro-4-[(3-fluorobenzyl)oxy]anilino}-6-quinazolinyl)-2-furaldehyde (**10**) via palladium-mediated Suzuki coupling of in situ-generated 5-(diethoxymethyl)-2-furylboronic acid with readily available *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]-phenyl}-6-iodo-4-quinazolinamine (**23**).[13] Although significant cost-savings had been achieved with this procedure, we felt that replacement of 2-(diethoxymethyl)furan with inexpensive **18** could deliver an even more economic approach to 5-formyl-2-furylboronic acid (**12**).[14]

2.2.1. Evaluation of selected secondary lithium amides for in situ protection of 2-furaldehyde. We commenced on this project by evaluating the four most efficient



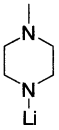
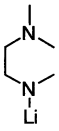
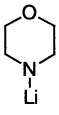
Scheme 3.

protecting groups of the benzaldehyde study (**3**, **5**, **7**, and **9**) with 2-furaldehyde (**18**) in regards to overall efficacy (=% yield-in-solution of **20**; Scheme 3).

Assessment of α-amino lithium alkoxides **19** in THF and DME at temperatures ranging from 0 to −40°C was conducted in the same fashion as the benzaldehyde experiments (see Section 2.1). However, this study targeted the clean formation of 5-methyl-2-furaldehyde (**20**). We found that the α-amino alkoxides **19**, including the one derived from strongly *ortho*-metal directing LTMDA (**6**), functioned as protecting and not as *ortho*-directing groups. This observation agreed with studies by Comins that metalations of **18** via α-amino alkoxides occur exclusively at the 5-position, regardless of the amine component.[3b] The three major products of the reactions were 5-methyl-2-furaldehyde (**20**), recovered **18**, and 1-(5-methyl-2-furyl)-1-pentanol (**21**). The results of these experiments are shown in Table 2.

We were delighted to find that lithium *N*,*O*-dimethylhydroxylamide (LDHA; **3**) excelled as a protecting agent in this series of experiments, yielding 91% of 5-methyl-2-furaldehyde (**20**) in THF at −20°C, a result clearly superior to that of its closest competitors, LNMP (**5**; 79% of **20**; entry 6), and lithium morpholide (**7**, 74% of **20**; entry 10). Lowering the reaction temperature to −40°C seemed to have no significant effect (entry 3), but increasing it to 0°C proved detrimental (entry 4). As with the benzaldehyde series, the use of THF as the solvent consistently provided improved purity profiles and better conversion compared to DME for all tested protecting groups.

Table 2. Composition of mixtures for the reaction **18→19→18+20+21** for selected lithium amides

Entry	Lithium amide		Solvent	Corrected % yield-in-solution of **20**[a]	Corrected % yield-in-solution of **18**[a]	Corrected % yield-in-solution of **21**[a]
1		**3**	DME	72.2	2.8	0.7
2			THF	90.7	1.4	1.1
3[b]			THF	90.5	5.4	0.0
4[c]			THF	56.9	2.3	0.4
5		**5**	DME	68.6	4.6	0.5
6			THF	79.2	2.0	0.9
7		**6**	DME	38.6	6.3	0.8
8			THF	40.0	2.2	0.5
9		**7**	DME	69.8	5.0	0.4
10			THF	74.3	3.6	0.1
11		**9**	DME	43.3	7.4	1.0
12			THF	57.7	2.0	0

α-Amino alkoxides were exposed to 2.3 equiv. of *n*-BuLi at −20°C for 1 h unless otherwise noted, and the reactions were quenched with MeI/AcOH. Temperature was not allowed to rise more than 5°C during reagent additions. % Yield-in-solution determined by HPLC.[10,15]

[a] Corrected for HPLC response factors.

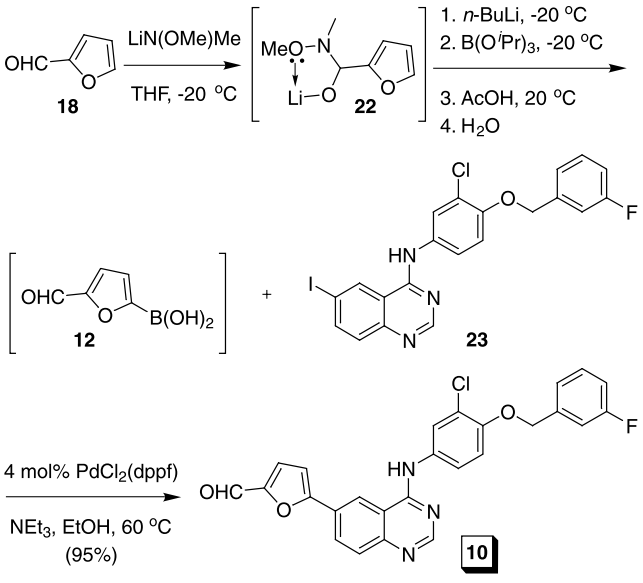
[b] Reaction carried out at −40°C.

[c] Reaction carried out at 0°C.

2.2.2. Safety assessment. At this point, the thermal stability of the new protecting agent **3** and its corresponding protonated versions needed to be assessed,[16] since we intended not only to generate 5-formyl-2-furylboronic acid (**12**), but also to directly advance this compound into the Suzuki coupling step which would likely require elevated temperatures. We found that *N*,*O*-dimethylhydroxylamine hydrochloride exhibited a broad melt at ca. 110°C followed by a large exotherm ranging from 146–239°C with a peak energy yield of 1.4 kJ/g. Assessment of the corresponding free base under pseudo-adiabatic conditions resulted in a thermal runaway event beginning at temperatures above ca. 50°C. Based on this assessment, we targeted a maximum operating temperature of 20°C during operations involving *N*,*O*-dimethylhydroxylamine. Consequently, a low temperature (<20°C) vacuum distillation was used to remove the volatile[17] *N*,*O*-dimethylhydroxylamine following the boronic acid generation and prior to the Suzuki reaction.

2.2.3. One-pot synthesis of an anticancer drug candidate intermediate. Encouraged by the favorable results of the 2-furaldehyde (**18**) study, and considering the thermal instability data of *N*,*O*-dimethylhydroxylamine, we decided to deploy LDHA (**3**) in a one-pot synthesis of the advanced erbB intermediate quinazolinyl-2-furaldehyde **10** (Scheme 4).[18] If successful, this sequence would involve the combination of four distinct chemical transformations, namely: (1) the protection of **18** as α-amino lithium alkoxide **22**, (2) its conversion to the boronate ester, (3) the unmasking of the aldehyde and boronate ester moieties to furnish 5-formyl-2-furylboronic acid (**12**), and (4) the final Suzuki coupling step. Although Suzuki cross-coupling reactions with in situ generated boronic acids have been described by us[13] and others,[19] we found no literature precedent for the combination of boronic acid syntheses via in situ aryl aldehyde protection methodology with Suzuki couplings in a one-pot operation.

We were already aware that it would be challenging to synthesize the seemingly simple furylboronic acid **12**,[20] following reference to publications[21] and patents[22]



Scheme 4.

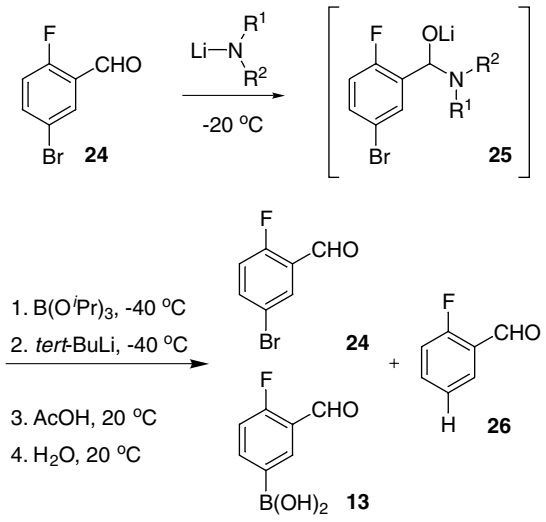
describing its preparation. These reported syntheses typically suffer from low temperature requirements, capricious reproducibility, tedious workup, as well as unsuitably low purity and isolated yields (26–45%). Fortunately, by applying a protocol similar to the one we had developed for the synthesis of 5-(diethoxymethyl)-2-furylboronic acid from 2-(diethoxymethyl)furan,[13] we achieved rapid success and found that formation of 5-formyl-2-furylboronic acid (**12**) was efficient in both DME and THF (91 and 86% uncorrected yield-in-solution by HPLC at $\lambda=280$ nm, respectively). Due to the known difficulties associated with the isolation of this boronic acid, the compound was directly advanced to the Suzuki coupling step. Prior to this, we conducted a vacuum-assisted removal of ca. one-third of the crude boronic acid solution's total volume while maintaining the internal temperature below 20°C, which ensured the safe purge of *N*,*O*-dimethylhydroxylamine (see Section 2.2.2). The Suzuki coupling with *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-iodo-4-quinazolinamine (**23**) was cleaner and more facile in THF and required only 4 mol% of dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) [$PdCl_2$(dppf)] catalyst vs. 8 mol% in DME. In summary, using THF as the reaction solvent, we obtained quinazolinyl-2-furaldehyde **10** in a one-pot operation starting from readily available 2-furaldehyde (**18**) after silica gel flash column chromatography in 95% yield (based on 6-iodo-4-quinazolinamine **23** input).

2.3. Application to 4-bromo-2-fluorobenzaldehyde

Motivated by the efficient application of lithium *N*,*O*-dimethylhydroxylamide (LDHA; **3**) to the 2-furaldehyde (**18**) process, we set out to explore the versatility of the new protecting agent with a second *GlaxoSmithKline* project. This effort was aimed at a rapid one-pot assembly of the bicyclic compound **11** (Fig. 2), a key intermediate to novel insulin secretion modulator[23] lead compounds, starting from commercially available 5-bromo-2-fluorobenzaldehyde (**24**). Although the reaction sequence leading to formation of 4-fluoro-3-formylphenylboronic acid (**13**) may appear similar to the 2-furaldehyde (**18**) process at first glance, the chemistry required stability of lithium (5-bromo-2-fluorophenyl)[methoxy(methyl)-amino]methoxide (**25**; R^1=Me, R^2=OMe) towards halogen–metal exchange conditions. Literature precedent indicated the viability of this approach as Borchardt had previously utilized Comins' methodology for a one-pot synthesis of hydroxybenzaldehydes, phthalaldehydic acids as well as phthalides via bromine–lithium exchange of in situ protected bromobenzaldehydes.[24] If successful, this second study would significantly broaden the versatility of LDHA (**3**) as a in situ protecting agent for aryl aldehydes.

2.3.1. Evaluation of selected secondary lithium amides for in situ protection of 4-bromo-2-fluorobenzaldehyde. We initially evaluated the four most efficient protecting agents of the benzaldehyde study (**3**, **5**, **7**, and **9**) with 5-bromo-2-fluorobenzaldehyde (**24**) in regards to overall efficacy (=% yield-in-solution of **13**; Scheme 5).

During these studies, we found that the lithiated benzene derived from α-amino lithium alkoxides **25** was inherently unstable and tended to decompose rapidly, even at



Scheme 5.

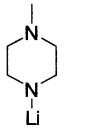
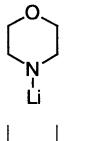
temperatures as low as −78°C. Therefore, triisopropylborate was selected as the electrophile, since this compound could be present in the reaction mixture during addition of the halogen–metal exchange reagent at low temperatures, thereby reducing decomposition by instant trapping of the lithiated species. While *n*-butyllithium at −78°C did afford excellent reaction outcomes and clean formation of 4-fluoro-3-formylphenylboronic acid (**13**), at temperatures more suitable for manufacturing (−40°C and above) addition of *n*-butyllithium to triisopropylborate competed effectively with the desired halogen–metal exchange process. The issue could be alleviated by substituting *tert*-butyllithium for *n*-butyllithium. Therefore, in this sequence of experiments, the α-amino lithium alkoxides (**25**) were treated with 3.0 equiv. of triisopropylborate followed by controlled addition of 3.0 equiv. of *tert*-butyllithium. We assessed the efficacy of α-amino lithium alkoxides **25** in DME and THF at −20 and −40°C by determining the recovery of boronic acid **13**. The two most significant side-products of these transformations were 2-fluorobenzaldehyde (**26**) and recovered **24**. The results of this study are displayed in Table 3.

We determined that lower temperatures provided significantly better results (−40 vs −20°C; entries 1 vs 2), and that DME furnishes increased amounts of **26** (23 vs 8%; entries 3 vs 1). Interestingly, unreacted **24** was only observed as part of the product mixture when lithium *N*,*O*-dimethylhydroxylamide (LDHA; **3**) was used as protecting agent. As in the previous two studies, **3** was at least as efficacious as LNMP (**5**) and lithium morpholide (**7**) and cleanly delivered 4-fluoro-3-formylphenylboronic acid (**13**) in THF at −40°C.

2.3.2. One-pot synthesis of a diabetes drug candidate intermediate. We were now prepared to target the employment of LDHA (**3**) in an one-pot synthesis of the key insulin secretion modulator intermediate 2-fluoro-5-(3-nitro-2-pyridinyl)benzaldehyde (**11**) (Scheme 6). The synthetic sequence would involve the combination of four distinct chemical transformations, including the protection–deprotection sequence of the formyl moiety, generation of the boronic acid, and the Suzuki coupling.

Since we had already overcome the hurdle of preparing phenylboronic acid **13** (see Section 2.3.1), we could focus our immediate attention on the in situ advancement of this material to the Suzuki coupling step. For safety reasons (see Section 2.2.2), *N*,*O*-dimethylhydroxylamine was removed in vacuo prior to the palladium-mediated cross coupling. We discovered that EtOH was unsuitable as a Suzuki

Table 3. Composition of mixtures for the reaction **24→25→13+24+26** for selected lithium amides

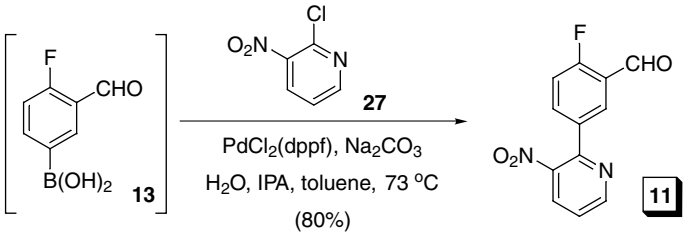
Entry	Lithium amide		Temperature (°C)	Normalized % yield-in-solution of **13**[a]	Corrected % yield-in-solution of **24**[b]	Corrected % yield-in-solution of **26**[b]
1		**3**	−40	80.5	0.3	7.5
2			−20	67.7	7.4	8.0
3[c]			−40	50.3	9.2	23.4
4		**5**	−40	75.7	0	8.7
5		**7**	−40	73.1	0	7.2
6		**9**	−40	38.5	0	5.5

Reactions carried out in THF and quenched with AcOH unless otherwise noted. Temperature was not allowed to rise more than 5°C during reagent additions. % Yield-in-solution determined by HPLC.[10]

[a] Normalized using 2-fluorobenzaldehyde (**26**) as an external standard.[25]

[b] Corrected for HPLC response factors.

[c] Reaction carried out in DME.



Scheme 6.

reaction solvent additive due to its propensity to add directly to the highly electron-deficient 2-chloro-3-nitropyridine (**27**), delivering notable amounts of the undesired 2-ethoxy-3-nitropyridine. This issue was circumvented by the use of the solvent IPA. Furthermore, $PdCl_2$(dppf) in combination with aqueous sodium carbonate, toluene and IPA were identified as appropriate conditions to realize excellent conversion. We thus attained 2-pyridinylbenzaldehyde **11** in a one-pot operation starting from commercially available 5-bromo-2-fluorobenzaldehyde (**24**) in 80% yield after silica gel flash column chromatography (based on 2-chloro-3-nitropyridine (**27**) input).

3. Conclusion

In summary, we have demonstrated lithium *N*,*O*-dimethylhydroxylamide (LDHA; **3**) to be a highly efficient and weakly *ortho*-directing in situ protecting agent for aryl aldehydes at temperatures convenient for large-scale processing. In all three studies evaluating its potential, amide **3** was at a minimum as efficient as its two most effective literature-known counterparts, LNMP (**5**) and lithium morpholide (**7**). Its corresponding α-amino lithium alkoxide was shown to be stable to excess base and halogen–metal exchange conditions. Furthermore, the new protecting agent proved highly useful for the generation of boronic acids **12** and **13**, which were successfully employed in situ for subsequent Suzuki reactions in four-step one-pot operations towards the synthesis of developmental drug candidate intermediates. To our knowledge, these are the first examples of combining boronic acid syntheses via in situ aryl aldehyde protection methodology with Suzuki couplings in one pot. The shortcoming of LDHA (**3**), namely the requirement of two equivalents of *n*-butyllithium for its generation from commercially available *N*,*O*-dimethylhydroxylamine hydrochloride, is offset by the exceptional efficacy of the reagent. Moreover, the low boiling point of *N*,*O*-dimethylhydroxylamine[17] allows for facile removal of the reagent from the reaction mixture by low-temperature vacuum distillation, thus alleviating the thermal hazards associated with its handling. In conclusion, this reagent should prove to be a useful addition to the arsenal of in situ aryl aldehyde protecting groups. Further applications of lithium amide **3** to current *GlaxoSmithKline* projects are ongoing.

4. Experimental

4.1. General

Melting points were determined using a TA Instruments DSC 2910 and a Mettler Toledo DSC 2E, and are uncorrected. IR spectra were recorded on a Nicolet 20DXC FT-IR spectrometer. ^{1}H NMR and ^{13}C spectra were obtained in DMSO-d_6 with Varian INOVA 300 and Varian INOVA 400 NMR instruments, respectively, and chemical shifts are reported in δ values (ppm) relative to the internal reference of DMSO-d_6 (δ 2.49 for ^{1}H and δ 39.5 for ^{13}C spectra). Exact mass data were obtained on a Micromass LCT time-of-flight mass spectrometer. Elemental analyses were performed by Atlantic Microlab. *N*,*O*-Dimethylhydroxylamide hydrochloride, 2-chloro-3-nitropyridine, 5-bromo-2-fluorobenzaldehyde and triisopropylborate were purchased from Avocado, iodomethane from Fluka, *N*-(2-methoxyethyl)methylamine from TCI America, acetic acid and $PdCl_2$(dppf) from Alfa Aesar, MeOH, IPA, acetonitrile and toluene from EM Science, *tert*-butyllithium (as a 2.0 solution in heptane) from FMC Lithium, and *n*-butyllithium (as a 2.5 solution in hexanes), THF, DME, EtOH, 2-(methylamino)pyridine, *N*,*N*,*N*′-trimethylethylenediamine, 1-methylpiperazine, morpholine, diethylamine, triethylamine, the sodium carbonate solution (1.016 M in water) and 2-furaldehyde from Aldrich. All reagents were used without purification or degassing, and all reactions were performed under N_2.

4.2. Efficacy screen of lithium amides

4.2.1. Benzaldehyde (14) series—typical procedure.[26] To a 3-necked, 100 mL round-bottom flask equipped with an electrical overhead stirrer and internal thermocouple was added the amine (5.87 mmol) and solvent (THF or DME; 30 mL). The flask was cooled to the desired internal temperature using a Cryocool-controlled IPA bath. *n*-Butyllithium (2.5 M solution in hexanes; 4.70 mL, 11.75 mmol for generation of **3**; 2.35 mL, 5.87 mmol for the generation of **4**–**9**) was added at a rate to maintain the internal temperature within 10°C of the setpoint. The mixture was then stirred for 30 min, followed by addition of benzaldehyde (**14**; 0.50 mL, 4.89 mmol) and stirring for 15 min. *n*-Butyllithium (2.5 M solution in hexanes; 4.50 mL, 11.26 mmol) was added, and the mixture was stirred for 1–3 h. Iodomethane (1.53 mL, 24.47 mmol) was added, the mixture was stirred for 30 min, and then treated with acetic acid (0.34 mL, 5.87 mmol). The mixture was warmed to 0°C, at which time piperidine (2.43 mL, 24.47 mmol) was added to quench the excess iodomethane. The resulting exotherm rapidly increased the internal temperature to ca. 20°C. The mixture was diluted successively with CH_3CN (40 mL), MeOH (5.00 mL) and DI water (5.00 mL). A 5.00 mL sample was removed from the resulting clear yellow-orange solution and diluted with DI water (5.00 mL) and CH_3CN (40 mL) to a total volume of

50 mL in a volumetric flask. This solution was used directly for HPLC analysis. While benzaldehyde (**14**) and 2-methylbenzaldehyde (**16**) were evaluated at 250 nm, 1-phenyl-1-pentanol (**17**) was evaluated at 220 nm (corresponding to their λ_{max} values). The % yield-in-solution obtained for each of the three products was corrected for response factors derived from standard solutions of known concentrations.[27]

4.2.2. 2-Furaldehyde (18) series—typical procedure.[26] The secondary lithium amides were generated according to the method described in Section 4.2.1, using 6.24 mmol of amine, 30 mL of solvent (THF or DME) and the corresponding amount of *n*-butyllithium (2.5 M solution in hexanes; 5.00 mL, 12.49 mmol for generation of **3**; 2.50 mL, 6.24 mmol for the generation of **5**–**7** and **9**). The mixture was treated with 2-furaldehyde (**18**; 0.43 mL, 5.20 mmol) and then stirred for 15 min. *n*-Butyllithium (2.5 M solution in hexanes; 4.80 mL, 11.96 mmol) was added and the mixture was stirred for 1 h. Iodomethane (1.62 mL, 26.00 mmol) was added, the mixture was stirred for 30 min, and then treated with acetic acid (0.36 mL, 6.24 mmol). The mixture was warmed to 0°C, at which time piperidine (2.57 mL, 26.00 mmol) was added to quench the excess iodomethane. The resulting exotherm rapidly increased the internal temperature to ca. 20°C. In preparation for the HPLC assay, the mixture was diluted as described in Section 4.2.1. While 2-furaldehyde (**18**) and 5-methyl-2-furaldehyde (**20**) were evaluated at 280 nm, 1-(5-methyl-2-furyl)-1-pentanol (**21**) was evaluated at 220 nm (corresponding to their λ_{max} values). The % yield-in-solution obtained for each of the three products was corrected for response factors derived from standard solutions of known concentrations.[28]

4.2.3. 5-Bromo-2-fluorobenzaldehyde (24) series—typical procedure.[26] The secondary lithium amides were generated according to the method described in Section 4.2.1, using 6.24 mmol of amine, 25 mL of solvent (THF or DME) and the corresponding amount of *n*-butyllithium (2.5 M solution in hexanes; 5.00 mL, 12.49 mmol for generation of **3**; 2.50 mL, 6.24 mmol for the generation of **5**, **7**, and **9**). The mixture was treated with 5-bromo-2-fluorobenzaldehyde (**24**; 5.20 mmol, 6.41 mL of 16.8 wt% solution in THF or DME)[29] and then stirred for 15 min. Triisopropylborate (3.67 mL 15.60 mmol) was added, resulting in a white precipitate. During addition of *tert*-butyllithium (2.0 M solution in heptane; 7.80 mL, 15.60 mmol), the mixture briefly turned bright yellow upon contact with the base. Upon completion of addition, acetic acid (0.895 mL, 15.60 mmol) was added, and the yellow mixture was allowed to stir for 5 min. The mixture was warmed to 15°C, at which time DI water (0.47 mL, 26.02 mmol) was added to hydrolyze the boronic ester. The resulting exotherm increased the internal temperature to ca. 20°C. The mixture was stirred for 30 min and then diluted with CH_3CN (40 mL), MeOH (5.00 mL) and DI water (5.00 mL). In contrast to the previous sets of experiments (see Sections 4.2.1 and 4.2.2), a yellow-orange slurry containing a white inorganic precipitate was formed. Thus, stirring of the reaction vessel was suspended to allow for settlement of the particles. A 5.00 mL sample was extracted from the supernatant and diluted with DI water (5.00 mL) and CH_3CN (40 mL) to a total volume of 50 mL in a volumetric flask. This solution was used directly for HPLC analysis. The % yield-in-solution thus obtained for 4-fluoro-3-formylphenylboronic acid (**13**) was calculated using 2-fluorobenzaldehyde (**26**) as an external standard. This compound, as well as the side-products, 5-bromo-2-fluorobenzaldehyde (**24**) and 2-fluorobenzaldehyde (**26**), were evaluated at 245 nm (λ_{max} for these materials). The % yield-in-solution of the latter two products was corrected for response factors derived from standard solutions of known concentrations.[30]

4.3. Practical applications

4.3.1. 5-(4-{3-Chloro-4-[(3-fluorobenzyl)oxy]anilino}-6-quinazolinyl)-2-furaldehyde (10). In a 100 mL, 3-necked round-bottom flask equipped with an overhead stirrer and internal thermocouple, *N*,*O*-dimethylhydroxylamine hydrochloride (623 mg; 6.26 mmol) was suspended in THF (30 mL), and the flask was cooled to −20°C (internal temperature; Cryocool-controlled IPA bath). *n*-Butyllithium (2.5 M solution in hexane; 5.00 mL, 12.49 mmol) was added dropwise while maintaining the internal temperature below −10°C. The reaction mixture was stirred at −20°C for 30 min before adding 2-furaldehyde (0.43 mL; 5.20 mmol) at a rate to maintain the temperature below −15°C. *n*-Butyllithium (2.5 M solution in hexanes; 2.70 mL, 6.76 mmol) was added dropwise to this solution while maintaining the internal temperature below −15°C. After complete addition, the pale yellow mixture was allowed to stir at −20°C for 75 min. Triisopropylborate (1.84 mL, 7.81 mmol) was added dropwise, maintaining the internal temperature below −15°C. The reaction mixture was stirred for 15 min before adding acetic acid (0.75 mL, 13.00 mmol) and warming to 15°C. DI water (470 μL, 26.02 mmol) was added, which resulted in an exotherm that caused the internal temperature to rise to ca. 20°C. The resulting pale yellow slurry was stirred for 10 min. Approximately 10–15 mL of volatiles were removed under vacuum, and the mixture was diluted to its original solvent level with THF. The crude slurry of 5-formyl-2-furylboronic acid (**12**) was analyzed for purity by HPLC (in CH_3CN plus one drop DI water at λ=280 nm; 85.7%) and then directly carried forward to the Suzuki coupling reaction.

To the crude boronic acid solution (4.46 mmol of **12** assuming 85.7% conversion) was added *N*-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-iodo-4-quinazolinamine (**23**) (1.12 g, 2.23 mmol). The resulting mixture was treated successively with EtOH (15 mL), NEt_3 (930 μL, 6.69 mmol), and dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) (76 mg, 0.0892 mmol), heated to 60°C (internal temperature), and stirred at this temperature until completion of reaction was determined by HPLC (using CH_3CN plus one drop DI water at λ=220 nm). The reddish black mixture was cooled to 20°C, directly loaded onto silica gel and purified by flash column chromatography (silica gel, 200–400 mesh, 60 Å) using 80% EtOAc–hexane containing 0.1% (v/v) NEt_3. The eluants were concentrated in vacuo to afford 0.96 g (95% yield) of 5-(4-{3-chloro-4-[(3-fluorobenzyl)oxy]anilino}-6-quinazolinyl)-2-furaldehyde (**10**) as a yellow crystalline solid. An analytically pure sample was obtained after re-slurry of the compound in

hot EtOAc (60°C). Mp 229–231°C. IR (neat): ν=3399, 1672, 1490, 1382, 1259, 777 cm^{-1}. ^1H NMR (300 MHz): δ=10.09 (s, 1H, N*H*), 9.66 (s, 1H, C*H*O), 8.94 (s, 1H, N=C*H*–N), 8.58 (s, 1H, furan-C–C*H*=C–C(–NHAr)=N), 8.29 (d, 1H, *J*=8.7 Hz, furan-C=C*H*–CH), 7.97 (d, 1H, *J*=1.9 Hz, Cl–C=C*H*), 7.84 (d, 1H, *J*=8.7 Hz, furan-C=CH–C*H*), 7.74 (d, 1H, *J*=3.7 Hz, OHC–C=C*H*–CH), 7.71 (dd, 1H, *J*=8.8, 1.9 Hz, ArHN–C=C*H*–CH), 7.46 (q, 1H, *J*=8.3 Hz, F–C=CH–C*H*), 7.40 (d, 1H, *J*=3.7 Hz, OHC–C=CH–C*H*), 7.23–7.37 (m, 3H, ArHN–C=CH–C*H*, F–C=CH–CH=C*H*, F–C–C*H*=C(–CH_2)), 7.18 (bt, 1H, *J*=8.3 Hz, F–C=C*H*–CH), 5.25 (2H, Ar-O–CH_2). ^{13}C NMR (100 MHz): δ=177.9, 162.2 (d, *J*=244.2 Hz), 157.8, 157.6, 155.3, 152.1, 150.2, 150.0, 139.6 (d, *J*=6.9 Hz), 132.8, 130.6 (d, *J*=8.4 Hz), 129.6, 128.8, 126.3, 125.8, 124.6, 123.3 (d, *J*=3.1 Hz), 122.8, 121.0, 119.5, 115.3, 114.7 (d, *J*=20.6 Hz), 114.2, 114.0 (d, *J*=21.4 Hz), 109.8, 69.4. HRMS (ES pos.): *m/z* calcd for $C_{26}H_{18}ClFN_3O_3^+$ ($M+H^+$): 474.1021. Found: 474.1007. Anal. calcd for $C_{26}H_{17}ClFN_3O_3$: C, 65.90; H, 3.62; Cl, 7.48; F, 4.01; N, 8.87. Found: C, 65.66; H, 3.56; Cl, 7.42; F, 3.89; N, 8.88.

4.3.2. 2-Fluoro-5-(3-nitro-2-pyridinyl)benzaldehyde (11). 4-Fluoro-3-formylphenylboronic acid (**13**) was prepared according to the procedure described in Section 4.2.3, using *N*,*O*-dimethylhydroxylamine hydrochloride (622 mg; 6.25 mmol) and THF (25 mL) at −40°C. After warming the boronic ester solution to 15°C, it was treated with 1.016 M aqueous Na_2CO_3 solution (10.2 mL, 10.40 mmol). The resulting exotherm increased the internal temperature to 25°C. The mixture was stirred for 1 h and then diluted with IPA (15 mL), followed by vacuum-assisted removal of approximately 15 mL of volatiles. The crude slurry of phenylboronic acid **13** was analyzed for purity by HPLC (in CH_3CN plus one drop DI water at λ=220 nm; 93.8%) and directly carried forward into the Suzuki coupling step.

To the 100 mL, 3-necked round-bottom flask containing the crude solution of 4-fluoro-3-formylboronic acid (**13**; 4.87 mmol assuming 93.8% conversion) were added, at ambient temperature, 2-chloro-3-nitropyridine (0.65 g, 4.06 mmol), dichloro[1,1′-bis(diphenylphosphino)-ferrocene]palladium(II) dichloromethane adduct (100 mg, 0.12 mmol), and toluene (15 mL). The orange slurry was heated to 73°C (internal temperature; reflux) and stirred until completion of reaction was indicated by HPLC (using CH_3CN plus one drop DI water at λ=220 nm). Addition of a second batch of the $PdCl_2$(dppf) catalyst (100 mg, 0.12 mmol) after ca. 2–3 h was required to complete the reaction. The reddish black mixture was cooled to 20°C, directly loaded on silica gel and purified by flash column chromatography (silica gel, 200–400 mesh, 60 Å) using 30% EtOAc–hexane containing 0.1% (v/v) NEt_3. The eluants were concentrated in vacuo to furnish 0.80 g (80% yield) of 2-fluoro-5-(3-nitro-2-pyridinyl)benzaldehyde (**11**) as a pale beige crystalline solid. An analytically pure sample was obtained after recrystallization from warm toluene–hexane (1:1; 60°C). Mp 151–152°C. IR (neat): ν=3077, 1684, 1604, 1515, 1494, 1446, 1400, 1350, 1262, 1225, 1175, 1118, 843, 766 cm^{-1}. ^1H NMR (300 MHz): δ=10.25 (s, 1H, C*H*O), 8.95 (dd, 1H, *J*=4.7, 1.4 Hz, C=N–C*H*), 8.53 (dd, 1H, *J*=8.3, 1.4 Hz, N=C–C(–NO_2)=C*H*), 8.02 (dd, 1H, *J*=6.6, 2.5 Hz, CF–C(–CHO)–C*H*), 7.92 (ddd, 1H, *J*=8.6, 5.0, 2.5 Hz, CF–CH=C*H*), 7.74 (dd, 1H, *J*=8.3, 4.7 Hz, C=N–CH=C*H*), 7.54 (dd, 1H, *J*=10.2, 8.6 Hz, CF–C*H*=CH). ^{13}C NMR (100 MHz): δ=187.4 (d, *J*=4.6 Hz), 163.7 (d, *J*=260.2 Hz), 152.9, 149.6, 145.6, 136.3 (d, *J*=9.9 Hz), 133.6 (d, *J*=3.8 Hz), 133.4, 129.1 (d, *J*=2.3 Hz), 124.2, 123.8 (d, *J*=9.2 Hz), 117.3 (d, *J*=21.4 Hz). HRMS (ES pos.): *m/z* calcd for $C_{12}H_8FN_2O_3^+$ ($M+H^+$): 247.0519. Found: 247.0510. Anal. calcd for $C_{12}H_7FN_2O_3$: C, 58.54; H, 2.87; F, 7.72; N, 11.38. Found: C, 58.12; H, 3.00; F, 7.59; N, 11.28.

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26. All reagent additions, following generation of the lithium amides, were conducted at such a rate not permitting the internal temperature to rise more than 5°C.
27. Benzaldehyde (**14**), 2-methylbenzaldehyde (**16**), and 1-phenyl-1-pentanol (**17**) reference solutions were obtained by diluting 0.50 mL of the respective commercial compound with CH_3CN (90 mL), extracting a 5.00 mL sample, and diluting it with CH_3CN (45 mL) in a 50 mL volumetric flask.
28. 2-Furaldehyde (**18**) and 5-methyl-2-furaldehyde (**20**) reference solutions were obtained by diluting 0.43 and 0.52 mL of the respective commercial compound with CH_3CN (90 mL), extracting a 5.00 mL sample, and diluting it with CH_3CN (45 mL) in a 50 mL volumetric flask. The 1-(5-methyl-2-furyl)-1-pentanol (**21**) marker was obtained by reacting 2-furaldehyde (0.43 mL; 5.20 mmol) with *n*-butyl-lithium (2.5 M solution in hexanes; 2.50 mL, 6.24 mmol) in THF (30 mL) at −78°C. The reaction was quenched with AcOH (0.39 mL, 6.76 mmol), warmed to 20°C, diluted with CH_3CN (40 mL), DI water (5.00 mL) and MeOH (5.00 mL). A 5.00 mL sample was extracted and diluted with DI water (5.00 mL) and CH_3CN (40 mL) in a 50 mL volumetric flask.
29. Preparation of this solution prevented solidification of the reagent during addition.
30. 5-Bromo-2-fluorobenzaldehyde (**24**) and 2-fluorobenzaldehyde (**26**) reference solutions were obtained by diluting 2.98 mL of a 16.8 wt% solution of **24** in THF and 0.50 mL of **26**, respectively, with CH_3CN (85 and 90 mL, respectively), extracting a 5.00 mL sample from these solutions, and diluting each sample with CH_3CN (45 mL) in a 50 mL volumetric flask.