N,*N*-Diisopropylformamidine (DIFA) Protection of Anilines in Metalation Reactions

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Abstract: A novel *N*,*N*-diisopropylformamidine (DIFA) protecting group for anilines was studied. Metalation is often metal-directed by this weakly coordinating and bulky group, making it complementary to *ortho*-metalation directed by *tert*-butylcarbamate and pivaloylamide groups and to regular electrophilic reactions of anilines. Importantly, DIFA is removed under nucleophilic conditions and is stable toward acids, thus being orthogonal to *tert*-butylcarbamate, *N*-*tert*-butylamide, and other acid-labile protecting groups.

Key words: protecting groups, regioselectivity, metalation, formamidine

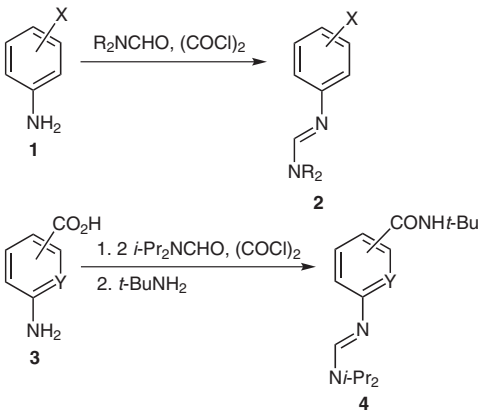
Directed *ortho*-metalation (DOM) reactions are popular and valuable synthetic tools. Aromatic amines protected as pivaloylamides (NHPv) or *tert*-butylcarbamates (NHBoc) are among the most well-researched *ortho*-directing groups.[1] However, to the best of our knowledge, no other protecting groups for anilines, with the exception of silyl groups (NSi),[2] have been systematically studied in DOM reactions.

There were two reasons why we undertook the exploration of alternative protecting groups for anilines. First, the strong *ortho*-orienting character of NHPv and NHBoc groups may be undesirable in some cases; for example, it may lead to mixtures of regioisomers when other strong *ortho*-directing groups are present.[3] Second, the ability to vary regioselectivity of lithiations with a simple change of the protecting group, that is, regiochemical redirection,[1,2] is very useful synthetically.

One of the options we considered was the *N*,*N*-dimethylformamidine (DMFA) protecting group,[4] which is known to *ortho*-direct metal–halogen exchange in polyhalogenated arenes.[5] However, it is also known that the *N*-methyl groups in DMFA and the *N*-alkyl groups in many other *N*,*N*-dialkylformamidines are themselves prone to metalation with various organolithium reagents.[6] Addressing this concern, a novel *N*,*N*-diisopropylformamidine (DIFA) protecting group for aromatic amines, recently introduced by us,[7] has the advantage of greater stability than DMFA and, likely, much lower CH acidity. In this letter, we further compare the DMFA and DIFA groups, present the DIFA group as a useful alternative to the NHPv, NHBoc, and NSi groups in DOM reactions, and show examples of its deprotection and practical use.

DMFA and DIFA derivatives **2a**–**f** were prepared via the reaction of anilines **1** with the corresponding Vilsmeier reagents (Table 1). A one-pot bis-protection of aminobenzoic acids **3** was carried out as described earlier, using two equivalents of the corresponding Vilsmeier reagent[7] to provide, after the subsequent reaction with *tert*-butylamine fully protected derivatives **4** (Table 1).

Table 1 Protection with DMFA and DIFA



Product	R	Substituents	Yield (%)
2a	Me	4-Br	79
2b	*i*-Pr	4-Br	95
2c	Me	3-OMe	88
2d	*i*-Pr	3-OMe	86
2e	*i*-Pr	2-OMe	89
2f	*i*-Pr	4-NHBoc	91
4a	*i*-Pr	3-CONH*t*-Bu, Y = CH	87
4b	*i*-Pr	2-CONH*t*-Bu, Y = CH	89
4c	*i*-Pr	4-CONH*t*-Bu, Y = CH	72
4d	*i*-Pr	4-CONH*t*-Bu, Y = N	61

According to the literature, the DMFA group is stable toward Grignard reagents.[5,8] A single reference suggests that it is also stable toward *n*-BuLi at –78 °C.[9] Our first step was to establish the relative stability of DMFA- and DIFA-protected aryllithium species. Compounds **2a** and

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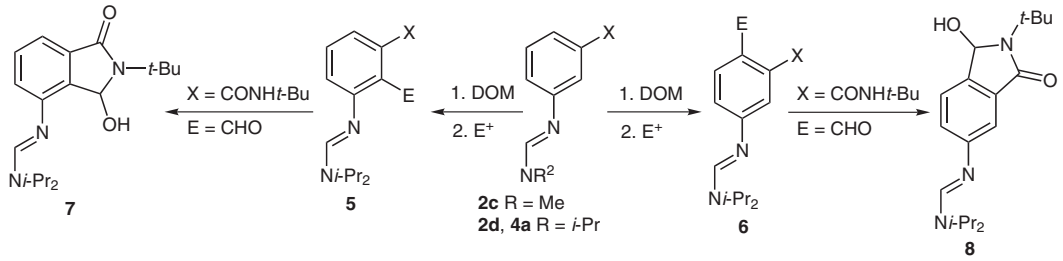
2b were treated with *t*-BuLi at –70 °C, and decomposition of the resulting anions was monitored at progressively higher temperature.[10] The DMFA-protected anion was significantly less stable than the DIFA-protected analogue. The half-life of 4-DIFA phenyllithium derived from **2b** was 8 hours at 20 °C in 0.5 M solution in THF–pentane,[11] while the half-life of 4-DMFA phenyllithium derived from **2a** was only 15 minutes at –30 °C.

Under standard metalation conditions, the instability of the DMFA group is even more pronounced. LTMP was able to deprotonate neither DMFA-protected *m*-anisidine **2c** nor its DIFA analogue **2d** (Table 2, entries 1, 4). However, **2d** remained unchanged, while **2c** decomposed, even though the in situ quench with triisopropyl borate, often successful in the case of unstable anions,[12] was used. Attempted lithiations of **2c** with *n*-BuLi in diethyl ether or THF (entries 2, 3) gave mixtures of unchanged **2c**, deprotection (**1c**) and decomposition products. In the face of these disappointing results, further work with DMFA analogues was stopped.

In contrast to DMFA derivative **2c**, DIFA analogue **2d** could be selectively metalated between the two substituents with *n*-BuLi, albeit in a low yield (entries 5 and 6), mostly due to a low conversion. Applying a stronger co-

Table 2 Metalation of *meta*-Substituted DIFA Derivatives[13]



Entry	Compd	X	Base (equiv),[a] conditions	E^+	E	Ratio (**5/6** or **7/8**)[b]	Product, yield (%)
1	**2c**	OMe	LTMP (2), THF, –70 °C to 0 °C, 0.5 h	$B(Oi\text{-}Pr)_3$	$B(OH)_2$	–	none, –
2	**2c**	OMe	*n*-BuLi (2), Et_2O, –40 °C, 1 h	$C_2F_4Br_2$	Br	–	none, –
3	**2c**	OMe	*n*-BuLi (2), THF, –75 °C, 2 h	$C_2F_4Br_2$	Br	–	none, –
4	**2d**	OMe	LTMP (2), THF, 0 °C, 2 h	I_2	I	–	none, –
5	**2d**	OMe	*n*-BuLi (1.3), Et_2O, 0 °C, 6 h	$C_2F_4Br_2$	Br	>100:1	**5a**, 28[b]
6	**2d**	OMe	*n*-BuLi (1.3), THF, 0 °C, 1 h	$C_2F_4Br_2$	Br	50:1	**5a**, 41[b]
8	**2d**	OMe	*t*-BuLi (1.3), Et_2O, –10 °C, 2 h	$C_2F_4Br_2$	Br	40:1	**5a**, 59[c]
9	**2d**	OMe	*t*-BuLi (1.3), Et_2O, –10 °C, 2 h	$C_2H_4Br_2$	Br	–	**5a**, 1[b]
10	**2d**	OMe	*t*-BuLi (1.3), Et_2O, –10 °C, 2 h	I_2	I	40:1	**5b**, 52[c]
11	**2d**	OMe	*s*-BuLi (2), TMEDA (2), THF, –75 °C, 2 h	CO_2	CO_2H	1.3:1	**5c**, 20;[b] **6c**, 15[b]
12	**2d**	OMe	*s*-BuLi (1.4), TMEDA, Et_2O, –50 °C, 1 h	DMF	CHO	1.4:1	**5d**, 30;[c] **6d**, 27[c]
13	**2d**	OMe	*s*-BuLi (1.5), PMDTA, Et_2O, –55 °C, 1 h	DMF	CHO	13:1	**5d**, 17;[b] **6d**, 1.3[b]
14	**2d**	OMe	*s*-BuLi (1.5), PMDTA, Et_2O, –45 °C, 2 h	DMF	CHO	7:1	**5d**, 39;[b] **6d**, 6[b]
15	**2d**	OMe	*s*-BuLi (3), PMDTA, Et_2O, –42 °C, 2 h	DMF	CHO	17:1	**5d**, 49[c]
16	**4a**	CONH*t*-Bu	*n*-BuLi (2.5), THF, –25 °C to –10 °C, 1 h	$C_2F_4Br_2$	Br	4:1	**5e**, 52;[b] **6e**, 13[b]
17	**4a**	CONH*t*-Bu	*n*-BuLi (2.4), Et_2O, 0 °C, 1.5–2.5 h	DMF	CHO	4:1	**7**, 30–33[c]
18	**4a**	CONH*t*-Bu	*t*-BuLi (2.4), Et_2O, –12 °C, 0.6 h	DMF	CHO	15:1	**7**, 43[c]
19	**4a**	CONH*t*-Bu	*t*-BuLi (2.4), Et_2O, –12 °C, 1.5 h	DMF	CHO	5:1	**7**, 38[c]
20	**4a**	CONH*t*-Bu	*s*-BuLi (2.3), TMEDA, Et_2O, –55 °C, 1 h	DMF	CHO	1:4.5	**7**, 13;[c] **8**, 69[c]
21	**4a**	CONH*t*-Bu	*s*-BuLi (2.3), PMDTA, Et_2O, –55 °C, 1 h	DMF	CHO	1:7	**8**, 50[c]

[a] If different from 1 equiv.
[b] Estimated from LC-MS and/or NMR of crude mixtures.
[c] Isolated yield. Purity > 95% (HPLC area method and ^1H NMR).

ordinating base (*t*-BuLi) increased the conversion. The subsequent quench with electrophiles afforded corresponding bromo- and iodo-derivatives in moderate-to-good yields (entries 8, 10). Interestingly, 1,2-dibromoethane ($C_2H_4Br_2$), a brominating reagent most frequently used in such a quench, gave almost no desired product (entry 9). It appears that more reactive and more expensive 1,2-dibromotetrafluoroethane ($C_2F_4Br_2$) is mandatory in this case (entries 8 and 9).

Unlike the selective metalation observed with *n*-BuLi and *t*-BuLi, comparable amounts of the isomeric products (entries 11, 12) were obtained with a strong complexed base, *s*-BuLi/TMEDA. This result indicates that the coordinating ability of DIFA is responsible for much of its *ortho*-orienting effect. To our surprise, a more hindered complexed base, *s*-BuLi/*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), increased the share of metalation *ortho* to the large DIFA substituent from 1.4:1 to 13:1 (compare entries 12 and 13). *s*-BuLi/PMDTA appeared to behave as a weaker base than *s*-BuLi/TMEDA both kinetically (slower reaction, 96% conversion in entry 12 vs. 38% conversion in entry 13) and thermodynamically (metalation appeared to stop at 58% conversion in entry 14). The literature is equivocal on this issue.[14] To make the *s*-BuLi/PMDTA lithiation practical a large excess of *s*-BuLi had to be used (entry 15).

To the best of our knowledge, DOM of aminobenzoic acids and their derivatives is entirely without a precedent.[15] Hence, we were very happy to observe the metalation of protected 3-aminobenzamide **4a** (entries 16–21) under conditions broadly similar to the ones applied to the protected *m*-anisidine **2d**.

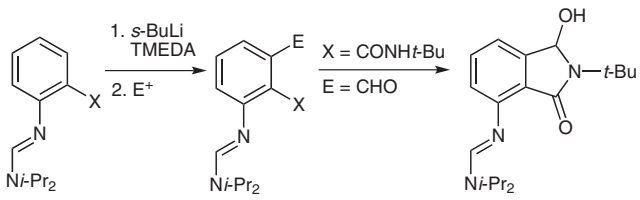
As with **2d**, metalation of **4a** with *n*-BuLi and *t*-BuLi was directed predominantly between the two substituents, affording, after a quench with electrophiles, compounds **5** or **7** in a low-to-moderate yield (entries 16–19).

Switching the base to *s*-BuLi/TMEDA reversed selectivity, and the easily separable by flash chromatography isomer **8** was isolated in a good yield (entry 20). Unlike the examples with anisidine **2d** (entries 13–15), *s*-BuLi/PMDTA further shifted the metalation into the position farthest from the large DIFA substituent (further towards **8**; see entry 21). However, despite the increased selectivity, the amounts of side products and unreacted **4a** were higher with PMDTA, affording a lower isolated yield of **8** (entry 21).

This result is illustrative of the concept of optional site selectivity,[1,2,16] according to which *n*-BuLi or *t*-BuLi preferentially abstract a proton at the position *ortho* to the coordinating substituent (in our case, DIFA group). On the other hand, organolithiums complexed with chelating amines abstract the most acidic and the least hindered proton.

Metalation of less acidic *o*-anisidine-derived analogue **2e** was low-yielding even with activated bases. The deprotection to *o*-anisidine (**1e**) predominated with TMEDA-containing bases (Table 3, entries 1 and 2), while formation of other byproducts was the main direction with LICKOR base (entry 3).

Table 3 Metalation of *ortho*-Substituted DIFA Derivatives[13]



9a X = OMe, E = Br
9b X = OMe, E = PhCHOH
9c X = OMe, E = CHO
9d X = CONH*t*-Bu, E = PhCHOH

Entry	Compd	Base (equiv),[a] conditions	E^+	Product, yield (%)
1	**2e**	*n*-BuLi (2), TMEDA (2), Et_2O, 0 °C, 0.25 h	$C_2F_4Br_2$	**9a**, 10[b]
2	**2e**	*t*-BuLi (1.5), TMEDA (1.5), Et_2O, –35 °C, 1 h	PhCHO	**9b**, 12[c]
3	**2e**	*n*-BuLi (3), KO*t*-Bu (3), THF, –75 °C, 1 h	DMF	**9c**, 19[c]
4	**4b**	*s*-BuLi (2.2), TMEDA, Et_2O, –50 °C, 1 h	PhCHO	**9d**, 65[c]
5	**4b**	*s*-BuLi (2.3), TMEDA, Et_2O, –55 °C, 1 h	DMF	**10**, 64[c]
6	**4b**	*s*-BuLi (2.2), TMEDA, THF, –75 °C, 1 h	PhCHO	**9d**, 32[b]
7	**4b**	*s*-BuLi (2.2), TMEDA, Et_2O, –40 °C, 1 h	PhCHO	**9d**, 31[c]

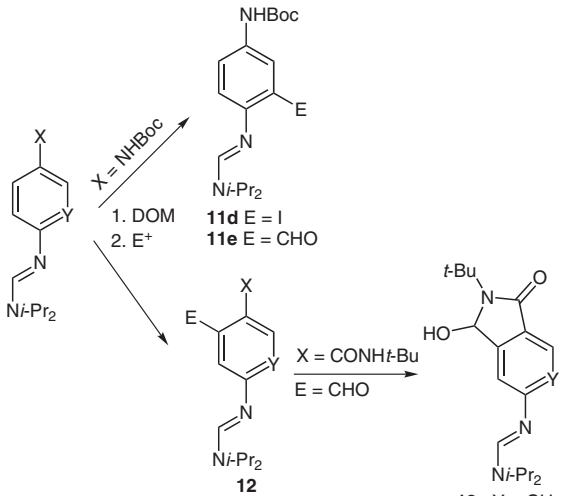
[a] If different from 1 equiv.
[b] Estimated from LC-MS and/or NMR of crude mixtures.
[c] Isolated yield. Purity > 95% (HPLC area method and ^1H NMR).

The standard reaction conditions used with the protected *meta*-benzamide **4a** (*s*-BuLi, TMEDA, Et_2O) also worked well for the *ortho* analogue **4b** (entries 4 and 5). It is important to keep the reaction temperature between –60 and –50 °C because metalation is too slow at lower temperature (conversion 54% in entry 6), while **4b** is prone to deprotection to *tert*-butylanthranylamide at higher temperature (20% of deprotection in entry 7). Notably, for all of the *ortho*-substituted DIFA derivatives lithiation occurred exclusively next to the stronger directing group X (OMe or CONH*t*-Bu).[17]

Metalation of the protected 4-aminobenzamide **4c** was also successful, although a somewhat higher temperature and longer time were required to drive it to completion (Table 4, entry 1). Metalation of the 6-aminonicotinamide derivative **4d** with *t*-BuLi proceeded in low yield because of competing ring addition reactions (entry 2); however, metalation with the magnesiate base 'LiMg*t*-BuTMP_2'[18] (a mixture of *t*-BuMgCl and 2 LTMP) was successful (entries 3, 4). As above, a single regioisomer directed by the CONH*t*-Bu group was formed.

The relative strength of the *ortho*-directing ability of NHBoc and DIFA groups is illustrated by DOM reactions of differentially protected 4-phenylenediamine **2f**. Metalation with *t*-BuLi in diethyl ether gives a mixture, in which the *ortho*-NHBoc regioisomer **12c** predominates (entry 5, 4:1 ratio). The reaction can be made synthetically useful by employing *s*-BuLi/TMEDA (entry 7). Higher temperature, more base and longer time were needed for carbamate **2f** (entry 6, conversion 7%; entry 7, conversion 75%) as compared with *tert*-butylamide analogue **4c** (entry 1, conversion 96%). Metalation *ortho* to the DIFA group was observed only as a minor side reaction (entry 7). Excess TMEDA increased the regioselectivity of the reaction; however, the isolated yield did not increase (entry 8) because the conversion was also lower (65%). This

Table 4 Metalation of *para*-Substituted DIFA Derivatives[13]

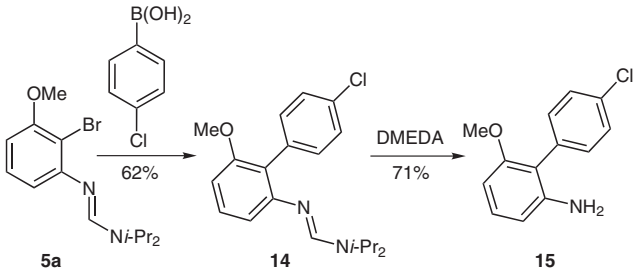


Entry	Compd	Base (equiv),[a] conditions	E^+	Product, yield (%)
1	**4c**	*s*-BuLi (2.3), TMEDA, Et_2O, –45 °C, 1.5 h	DMF	**13a**, 84[c]
2	**4d**	*t*-BuLi (2.4), THF, –70 °C, 1.5 h	$C_2F_4Br_2$	**12a**, 10[b]
3	**4d**	LiMg*t*-BuTMP_2 (1.5), THF, 0 °C, 0.5 h	I_2	**12b**, 73[c]
4	**4d**	LiMg*t*-BuTMP_2 (1.5), THF, 0 °C, 0.5 h	DMF	**13b**, 73[c]
5	**2f**	*t*-BuLi (2.5), Et_2O, –14 °C, 1.5 h	I_2	**11c**, 8;[b] **12c**, 32[b]
6	**2f**	*s*-BuLi (2.3), TMEDA, Et_2O, –55 °C, 1 h	DMF	**12d**, 2[b]
7	**2f**	*s*-BuLi (3), TMEDA, Et_2O, –37 °C, 3 h	DMF	**11d** 8;[d] **12d** 46[c,e]
8	**2f**	*s*-BuLi (3), TMEDA (3), Et_2O, –33 °C, 3 h	DMF	**12d** 47[c,f]

[a] If different from 1 equiv.
[b] Estimated from LC-MS and/or NMR of crude mixtures.
[c] Isolated yield. Purity > 95% (HPLC area method and ^1H NMR).
[d] Isolated yield. Purity = 83% (HPLC area method).
[e] Ratio **11/12** = 1:4 in crude reaction mixture.
[f] Ratio **11/12** = 1:17 in crude reaction mixture.

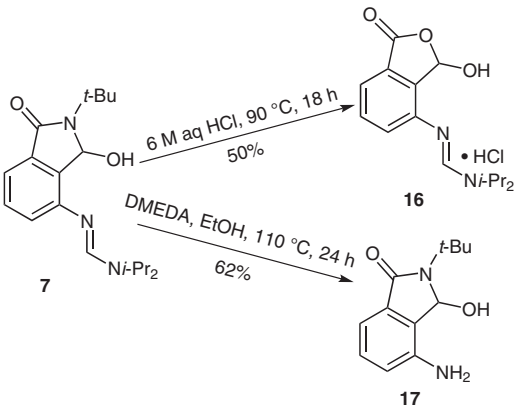
result is consistent with the literature, which notes that excess TMEDA may either decrease[14] or increase[14] metalation rates.

To illustrate the practical use of DIFA-protected derivatives, bromide **5a** was converted into **15**, a precursor of a potent corticotrophin-releasing factor receptor antagonist,[19] via a Suzuki reaction followed by deprotection with *N*,*N*′-dimethylethylenediamine (DMEDA; Scheme 1).



Scheme 1 Practical use of DIFA protection

The two synthetically important properties of the DIFA group are its stability under acidic conditions and its ability to be deprotected by nucleophilic DMEDA. This opens a multitude of possibilities for the orthogonal protection with acid-sensitive groups and for the following selective deprotection. For example, *tert*-butylamide in compound **7** can be selectively hydrolyzed to **16** under acidic conditions while DIFA stays unchanged (Scheme 2). On the other hand, DIFA can be selectively deprotected to **17** with DMEDA without disturbing *tert*-butylamide and the masked aldehyde group (Scheme 2).



Scheme 2 Selective deprotections of DIFA and CONH*t*-Bu groups

In conclusion, the use of a novel *N*,*N*-diisopropylformamidine (DIFA) protecting group for aromatic amines in directed *ortho*-metalation reactions was established. DIFA is a large group with only weak *ortho*-orienting properties. In many cases, it is *meta* directing. This allows changing the usual *ortho*-directing regiochemistry observed with NHBoc/NHPv groups via a simple change of the amine protecting group to DIFA. The other important property of DIFA is that it is stable to acids and can be removed by nucleophilic DMEDA, thus being orthogonal to many acid-labile protecting groups.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are detailed experimental procedures and spectra for isolated compounds **2a**–**f**, **4a**–**d**, **5a**,**b**,**d**, **6d**, **7**, **8**, **9b**,**c**, **10**, **11d**, **12b**,**d**, **13a**,**b**, and **14**–**17**.

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(10) An aliquot of the reaction mixture was quenched with 5% AcOH in H_2O, and the HPLC areas of des-Br **2a** or des-Br **2b** were compared with those for decomposition products.

(11) The anion of **2b** obtained using *n*-BuLi had a half-life of only 1 h at –30 °C due to its reaction with 1-bromobutane, a side product of the metal–halogen exchange. After warming to r.t., *N*′-(4-butylphenyl)-*N*,*N*-diisopropylformamidine could be isolated in 90% yield (see Supporting Information for details).

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