Establishing the NHBoc Functionality as *ortho*-Metallating Group for Furan

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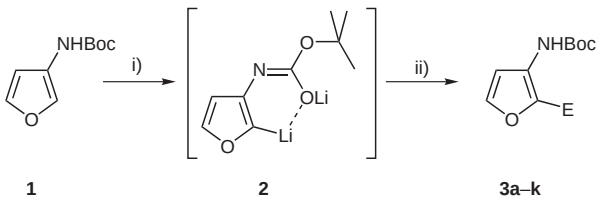
Abstract: The *ortho*-lithiation of *N*-Boc protected 3-aminofuran was investigated. Directed lithiation followed by quenching with an appropriate electrophile led to new 2,3-disubstituted furans. Halogenated compounds obtained by this methodology represent useful intermediates for subsequent cross-coupling reactions.

Key words: *ortho*-lithiation, furans, metallation, ketones, Suzuki cross-coupling reaction

The directed *ortho*-functionalization via lithiation is an attractive process in homo- and heteroaryl chemistry due to the wide range of functional groups which can be incorporated.[1,2] It is known that polysubstituted furans are frequently encountered structural features and represent an important pharamcophore with interesting pharmaceutical properties.[3] In addition, furans can be employed in synthetic chemistry as building blocks and a multitude of reactions have been reported in the past.[4]

The first investigation of the ability of the NHBoc group to act as a directing *ortho*-metallating group (DMG) for phenyl derivatives was carried out by Muchowski.[5] In contrast to homoaryl compounds, heteroaromatic systems possess an inherent difference in acidity of the aromatic protons. Consequently, DMGs can amplify or compensate this intrinsic acidity, as successfully demonstrated in the thiophene series also with NHBoc as directing group.[6] To the best of our knowledge, no principal investigation of this DMG on the furan system has been performed so far. Only in one example, Sato and co-workers subjected 2-*N*-Boc-substituted furan to lithiation conditions for introducing a cyano group.[7] In this case, no directing effect into the 3-position was observed, but rather exclusive introduction of the CN functionality into the intrinsically acidic 5-position.



Scheme 1 *Reagents and conditions*: i) *t*-BuLi (2.5 equiv), TMEDA (2.5equiv), THF, –90 °C to –70 °C, 1–2 h; ii) electrophile (1.2 equiv), dry THF, temperature increased slowly to r.t. overnight.

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We therefore became interested in examining the directing metallation power of the NHBoc group and chose the correspondingly protected 3-amino furan **1** (Scheme 1) as model system. The starting material was prepared in a one-pot reaction from 3-furoic acid via Curtius degradation.[8]

Our investigations started with the determination of appropriate lithiation conditions. The DMG employed here formed a monolithiated amide in the presence of one equivalent of *t*-BuLi. Action of the second equivalent of *t*-BuLi led to complex **2**, where an oxygen atom is loosely bound to the electron-deficient Li atom.[5] In order to achieve comprehensive lithiation, TMEDA was required as additive and THF as solvent turned out to be beneficial. Due to the high reactivity of *t*-BuLi under such reaction conditions, the temperature had to be maintained below –40 °C to avoid attack of the solvent.[9]

N-*tert*-Butylcarbamate **1** was subjected to the optimized directed lithiation procedure[10] followed by quenching with an appropriate electrophile, yielding 2,3-substituted furans **3a**–**k**[11] as summarized in Table 1.

Table 1 Synthesis of 2-Substituted-3-Boc-amino Furans

Entry	Electrophile	E	Product	Yield (%)
1	DMF	CHO	**3a**	51
2	ClCOOEt	COOEt	**3b**	97
3	*t*-BuNCO	CONH*t*-Bu	**3c**	91
4	$ClSiMe_3$	$SiMe_3$	**3d**	52
5	MeI	Me	**3e**	96
6	Cyclohexanone	$C_6H_{10}OH$	**3f**	96
7	Benzaldehyde	PhCO	**3g**	56
8	*p*-Chlorobenzaldehyde	4-ClPhCO	**3h**	62
9	Hexachloroethane	Cl	**3i**	65
10	1,2-Dibromotetrachloroethane	Br	**3j**	96
11	I_2	I	**3k**	53–72[a]

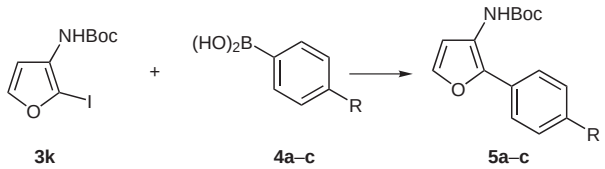
[a] Overall yield determined after Suzuki coupling reaction.

In a first set of experiments, the principal reactivity of the lithiated species **2** was determined by conversion with several carbonyl reagents. Reaction with DMF allowed the introduction of an aldehyde functionality (**3a**).

Carboxylic acid derivatives were prepared by utilizing ethyl chloroformate and *tert*-butylisocyanate as electrophiles, yielding ester **3b** and amide **3c** in excellent yields. Transmetallation was accomplished using TMS chloride to give the silyl species **3d**. Introduction of an aliphatic carbon center was successfully attempted with methyl iodide (**3e**). Evaluation of the scope of the methodology was continued by applying additional carbonyl electrophiles. When cyclohexanone was used the corresponding cyclohexanol derivative **3f** was obtained in excellent yield.

Aromatic aldehydes were also added to the preformed organolithium reagent **2** (entries 7 and 8). While the lithium alkoxide is expected to give an alcohol after acidic workup, we were surprised to obtain the oxidized products **3g** and **3h** almost exclusively. There is precedence in the literature in the thiophene series that such an oxidation can occur upon workup.[12] In particular in related fused homo- and heteroarylic systems aerial oxidations were utilized in combination with lithiation strategies.[13] In addition, a stabilizing effect on adjacent carbonyl groups by the NHBoc group has been reported in context with organometallic transformations, previously.[14]

Halogenated compounds **3i**–**k** were obtained by reaction with halogen donors hexachloroethane and 1,2-dibromotetrachloroethane or with elementary iodine at –80 °C. It should be mentioned that compounds **3i**–**k** displayed a limited stability, in particular in isolated form. Products **3i** and **3j** formed beige solids in pure form, but tend to darken and decompose upon storing at room temperature or in a refrigerator. Iodo derivative **3k** is particularly unstable. It appears as a transparent pale yellow compound in solution, but after complete removal of the solvent the product decomposed within minutes at room temperature in an exothermic reaction. Because of the instability of **3k**, we avoided the isolation and purification of the compound and rather used a solution of the product in a Suzuki cross-coupling protocol as an indirect method to determine its specific reactivity and also to calculate its yield (Scheme 2).



Scheme 2 Suzuki coupling reaction for compound **3k**.

The iodo compound **3k** was submitted to cross-coupling reaction conditions[15] using (4-substituted) phenylboronic acids **4a**–**c** to yield derivatives **5a**–**c**[16] as summarized in Table 2. The resulting products were stable and separated by column chromatography.

In summary we have established the *ortho*-directing properties of the NHBoc group on the furan system. A large variety of electrophiles can be used for the synthesis of 2,3-disubstituted furans. In the case of reaction with aromatic aldehydes, we observed an oxidation process to exclusively give keto products. Iodo compound **3k** was identified as reactive intermediate for cross-coupling reactions and a suitable protocol for this transformation avoiding isolation of **3k** was developed. Currently, further elaboration of this methodology is under investigation in our laboratory.

Table 2 Suzuki Cross-Coupling Reaction of Iodo Derivative **3k**

Entry	R	Boronic acid	Product	Yield (%)
1	H	**4a**	**5a**	68
2	Cl	**4b**	**5b**	53
3	F	**4c**	**5c**	72

Acknowledgment

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(10) **General Procedure for the Lithiation Reaction.**
To a cooled (–90 °C to –70 °C), stirred solution of compound **1** (1.64 mmol) in dry Et_2O or preferable dry THF (25 mL) and TMEDA (4.1 mmol) under argon, a solution of *t*-BuLi in pentane (1.6 M, 4.1 mmol) was added dropwise. The mixture was then stirred for 1–2 h while raising the temperature from –90 °C to –40 °C. After addition of an electrophile (1.97 mmol; as solution in THF if solid) the reaction mixture was stirred for 6 h or overnight with a slow increase of the temperature to r.t. The reaction mixture was then quenched with an excess of aq sat. $NaHCO_3$ (40 mL), and extracted with CH_2Cl_2 (6 × 25 mL). The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated (not completely), under 400–500 mbar at 30–35 °C. The obtained solution was then purified by filtration through a column of silica gel, using CH_2Cl_2 as an eluent. First fractions containing the desired product were collected and the solvent evaporated under reduced pressure (30–35 °C, 400–500 mbar). In the case of the unstable compound **3k** the solvent was not evaporated completely and its yield was calculated indirectly after the subsequent Suzuki coupling reaction.

(11) ***N*-(2-Formyl-3-furyl)carbamic Acid *tert*-Butyl Ester (3a).**
Pale yellow crystals (51%); mp 58–61 °C. ^{1}H NMR ($CDCl_3$): δ = 1.44 [s, 9 H, $C(CH_3)_3$], 7.16 (br s, 1 H, H4), 7.39 (dd, 1 H, H5, ^3J = 2.0 Hz, ^5J = 0.6 Hz), 8.56 (br s, 1 H, NH), 9.64 (d, 1 H, CHO, ^5J = 0.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 27.2 [q, $C(CH_3)_3$], 80.9 [q, $C(CH_3)_3$], 105.6 (d, C4), 136.0 (s, C3), 137.9 (s, C2), 147.2 (d, C5), 151.2 (s, NHCO), 178.8 (d, CHO).
***N*-[2-(1-Hydroxy)cyclohexyl-3-furyl]carbamic Acid *tert*-Butyl Ester (3f).**
Transparent colorless oil (96%). ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 1.53–1.70 (m, 6 H, H3′, H4′, H5′), 2.09–2.19 (m, 2 H, H2′), 2.24–2.34 (m, 2 H, H6′), 5.94 (br s, 1 H, OH), 6.08 (br s, 1 H, NH), 6.72 (br s, 1 H, H4), 7.11 (d, 1 H, H5, ^3J = 2.0 Hz).
***N*-(2-Benzoyl-3-furyl)carbamic Acid *tert*-Butyl Ester (3g).**
Pale yellow oil (56%). ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 7.23 (br s, 1 H, H4), 7.33–7.44 (m, 4 H, H2′, H3′, H5′, H6′), 8.00 (d, 1 H, H5, ^3J = 2.0 Hz), 8.04 (d, 1 H, H4′, ^4J = 1.6 Hz), 9.39 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 26.2 [q, $C(CH_3)_3$], 79.3 [q, $C(CH_3)_3$], 104.4 (d, C4), 125.5 (d, C3′, C5′), 127.2 (d, C2′, C6′), 130.3 (d, C4′), 134.7 (s, C3), 135.6 (s, C1′), 137.1 (s, C2), 144.2 (d, C5), 150.4 (s, NHCO), 180.5 (s, CO).
***N*-[2-(4-Chlorobenzoyl)-3-furyl]carbamic Acid *tert*-Butyl Ester (3h).**
Colorless crystals (62%); mp 52–55 °C. ^{1}H NMR ($CDCl_3$): δ = 1.53 [s, 9 H, $C(CH_3)_3$], 7.34 (br d, 1 H, H4, ^3J = 2.0 Hz), 7.47 (d, 2 H, H3′, H5′, ^3J = 9 Hz), 7.48 (dd, 1 H, H5, ^3J = 2.0 Hz, ^5J = 0.6 Hz), 8.10 (d, 2 H, H2′, H6′, ^3J = 9.0 Hz), 9.44 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$): δ = 27.1 [q, $C(CH_3)_3$], 80.5 [q, $C(CH_3)_3$], 105.5 (d, C4), 127.6 (d, C3′, C5′), 129.7 (d, C2′, C6′), 134.0 (s, C3), 136.4 (s, C1′), 137.8 (s, C2), 138.5 (s, C4′), 145.4 (d, C5), 151.3 (s, NHCO), 179.8 (s, CO).
***N*-(2-Chloro-3-furyl)carbamic Acid *tert*-Butyl Ester (3i).**
Beige solid which decomposed on storage (65%). ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 6.14 (br s, 1 H, NH), 6.82 (br s, 1 H, H4), 7.12 (d, 1 H, H5, ^3J = 2.0 Hz). ^{13}C NMR ($CDCl_3$): δ = 27.3 [q, $C(CH_3)_3$], 80.0 [q, $C(CH_3)_3$], 107.6 (s, C3), 118.9 (d, C4), 129.6 (s, C2), 139.5 (d, C5), 151.6 (s, NHCO).
***N*-(2-Bromo-3-furyl)carbamic Acid *tert*-Butyl Ester (3j).**
Beige solid which decomposed upon storage (96%). ^{1}H NMR ($CDCl_3$): δ = 1.43 [s, 9 H, $C(CH_3)_3$], 6.23 (br s, 1 H, NH), 6.83 (br s, 1 H, H4), 7.26 (d, 1 H, H5, ^3J = 2.0 Hz).

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(15) **General Procedure for the Suzuki Cross-Coupling Reaction.**
To a solution of dioxane–water (4:1) in a three-necked round-bottom flask (150 mL) equipped with condenser, thermometer and argon inlet, a solution of **3k** (ca. 10.0 mmol; estimated from **1**) in THF was added. Boronic acids **4a–c** (12.1 mmol) and K_2CO_3 (22.0 mmol) were added to the system. The flask was flushed with argon and then $Pd(PPh_3)_4$ (0.272 mmol) was added (2.2 mol%). The reaction mixture was heated at 70–80 °C keeping the inert atmosphere until the TLC showed complete reaction (usually 17–56 h) then the obtained mixture was quenched with aq sat. $NaHCO_3$ (40 mL), extracted with CH_2Cl_2 (4 × 100 mL), and the organic layers were dried over Na_2SO_4. After solvent evaporation the residue was purified by flash column chromatography using PE–EtOAc (10:1) as eluent. The products **5a–c** were obtained in an overall yield varying between 53–72%, calculated from compound **1**.

(16) ***N*-(2-Phenyl-3-furyl)carbamic Acid *tert*-Butyl Ester (5a).**
Yellow oil (68%). ^{1}H NMR ($CDCl_3$): δ = 1.41 [s, 9 H, $C(CH_3)_3$], 6.27 (d, 1 H, H4, ^3J = 2.0 Hz), 6.76 (br s, 1 H, NH), 7.10–7.18 (m, 1 H, H4′), 7.23 (d, 1 H, H5, ^3J = 2.0 Hz), 7.24–7.33 (m, 2 H, H3′, H5′), 7.49 (d, 2 H, H2′, H6′, ^3J = 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ = 27.2 [q, $C(CH_3)_3$], 79.7 [q, $C(CH_3)_3$], 108.4 (d, C4), 119.7 (s, C3), 122.7 (s, C1′), 123.7 (d, C2′, C6′), 126.1 (d, C4′), 127.8 (d, C3′, C5′), 129.5 (s, C2), 139.7 (d, C5), 152.4 (s, NHCO).
***N*-[2-(4-Chlorophenyl)-3-furyl]carbamic Acid *tert*-Butyl Ester (5b).**
Pale yellow solid (53%); mp 89–93 °C. ^{1}H NMR ($CDCl_3$): δ = 1.42 [s, 9 H, $C(CH_3)_3$], 6.15 (br s, 1 H, NH), 6.73 (br s, 1 H, H4), 7.26 (d, 1 H, H5), 7.25–7.32 (d, 2 H, H3′, H5′, ^3J = 9.0 Hz), 7.43–7.47 (d, 2 H, H2′, H6′, ^3J = 9.0 Hz). ^{13}C NMR ($CDCl_3$): δ = 27.2 [q, $C(CH_3)_3$], 79.9 [q, $C(CH_3)_3$], 108.9 (d, C4), 119.2 (s, C1′), 120.0 (s, C3), 124.8 (d, C2′, C6′), 127.9 (d, C3′, C5′), 129.0 (s, C2), 131.7 (s, C4′), 140.0 (d, C5), 152.4 (s, NHCO).
***N*-[2-(4-Fluorophenyl)-3-furyl]carbamic Acid *tert*-Butyl Ester (5c).**
Pale yellow crystals (72%), mp 68–71 °C. ^{1}H NMR ($CDCl_3$): δ = 1.41 [s, 9 H, $C(CH_3)_3$], 6.18 (br s, 1 H, NH), 6.69 (br s, 1 H, H4), 7.00 (d, 2 H, H2′, H6′, ^3J = 9.0 Hz), 7.23 (d, 1 H, H5, ^3J = 2.0 Hz), 7.48 (dd, 2 H, H3′, H5′, ^3J = 9.0 Hz, $^3J_{H-F}$ = 3.5 Hz). ^{13}C NMR ($CDCl_3$): δ = 28.2 [q, $C(CH_3)_3$], 80.8 [q, $C(CH_3)_3$], 109.8 (d, C4), 115.8 (d, C3′, C5′, $^2J_{C-F}$ = 21.6 Hz), 120.2 (s, C2), 122.2 (s, C3), 126.4 (d, C2′, C6′, $^3J_{C-F}$ = 13.1 Hz), 126.7 (s, C1′, $^4J_{C-F}$ = 4.1 Hz), 140.6 (d, C5), 153.6 (s, NHCO), 161.8 (d, C4′, $^1J_{C-F}$ = 247.4 Hz).