Sterically-controlled regioselective *para*-substitutions of aniline†

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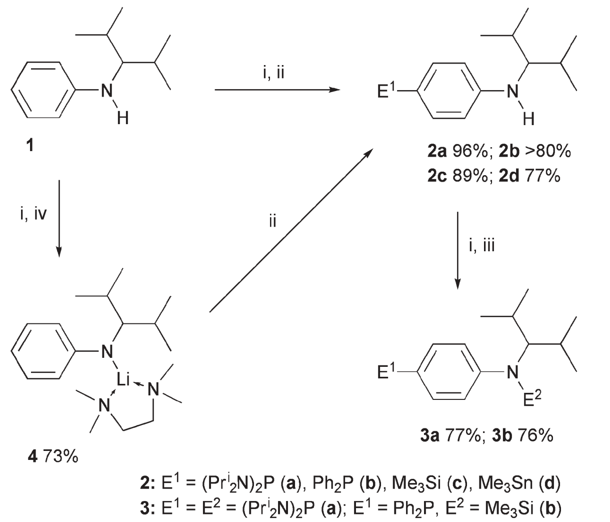
Introduction of sterically demanding 1-isopropyl-2-methylpropyl or triisopropylsilyl groups at the nitrogen of aniline allows high-yielding regioselective *para*-substitution to be achieved using a lithiation/substitution sequence.

Regiospecific preparation of polysubstituted aromatics has been a long-standing challenge in synthetic chemistry. The directed *ortho*-lithiation/electrophilic substitution sequence, which relies on heteroatom (O, N, halogen) directing effects, has become one of the most versatile methodologies, and has grown to be routine in many organic syntheses.[1–5] In contrast, there are few examples of directed *para*-lithiation, this regioisomer usually being favoured by the prior introduction of substituents in the *ortho* and *meta* ring positions or by employing strongly *para*-directing CF_3 groups.[6–8]

Here it is reported that the introduction of bulky 1-isopropyl-2-methylpropyl or triisopropylsilyl (TIPS) substituents at the nitrogen of aniline results in regioselective electrophilic ring substitution by soft electrophiles in the *para*-position, following initial *N*-lithiation.

Treatment of an ethereal solution of (1-isopropyl-2-methylpropyl)-phenyl-amine, **1**,[9] with 1 equiv. of Bu^nLi, followed by the addition of a range of soft electrophiles E^1Cl (E^1 = $(Pr^i{}_2N)_2P$, Ph_2P, Me_3Si, Me_3Sn) affords the *para*-substituted secondary anilines **2a–d** in excellent isolated yields (Scheme 1).‡ Subsequent addition of a second equivalent of Bu^nLi and electrophile leads to the formation of the corresponding *N,N*-difunctionalised *para*-substituted anilines **3a** and **3b** in good yields. The symmetrical derivative, **3a** (89%), can also be prepared in a 'one-pot' procedure, by treating **1** with 2 equiv. of Bu^nLi and then 2 equiv. of chlorophosphine. No reaction was observed between **1** and a range of soft electrophiles in the presence of pyridine or NEt_3.

To probe the course of these reactions, identifying any intermediate lithiated species involved was of interest. Thus, lithiation of **1** was undertaken as above, followed by addition of 1 equiv. of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA). This afforded TMEDA-bound lithium amide, **4** (Scheme 1), which was isolated as air, moisture and light sensitive yellow platelets (73%) and fully characterised (Fig. 1).§ Treating an isolated sample



Scheme 1 Reaction conditions: i. Bu^nLi, Et_2O, −78 °C to RT, 1 h; ii. E^1Cl, Et_2O, −78 °C to RT, 18 h; iii. E^2Cl, Et_2O, −78 °C to RT, 12 h; iv. TMEDA.

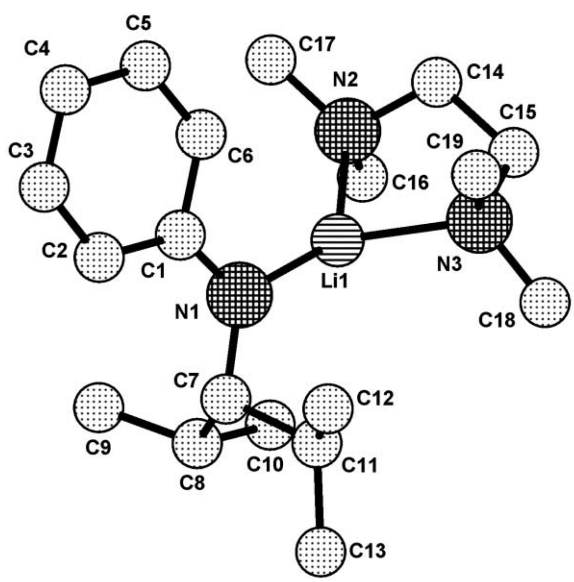


Fig. 1 Molecular structure of **4** (H-atoms omitted). Selected bond lengths (Å) and angles (°): Li(1)–N(1) 1.910(6), Li(1)–N(3) 2.033(6), Li(1)–N(2) 2.077(6), N(1)–C(1) 1.344(3), N(1)–C(7) 1.459(3), N(1)–Li(1)–N(3) 127.9(3), N(1)–Li(1)–N(2) 137.1(3), N(3)–Li(1)–N(2) 89.1(2), C(1)–N(1)–C(7) 119.4(2), C(1)–N(1)–Li(1) 118.4(2), C(7)–N(1)–Li(1) 122.2(3).

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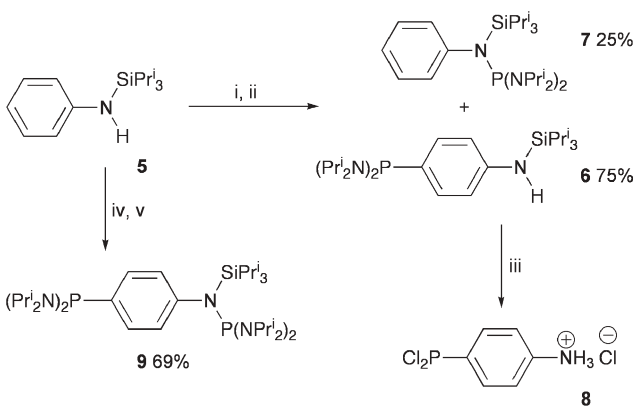
of **4** with E^1Cl generates *para*-substituted aniline **2** in near quantitative yield.

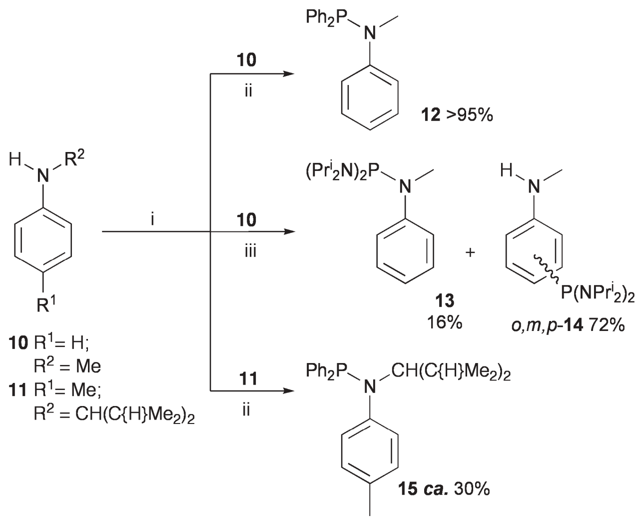
In contrast to the reactions of lithiated **1** with soft electrophiles, the reaction of **1** itself with Bu^nLi, followed by treatment with the hard electrophiles CO_2, acetone or benzaldehyde, led to **1** being recovered in >95% yield in each case, following a H_2O quench. Similarly, attempts to introduce deuterium onto the ring of **1** by sequential reaction with Bu^nLi and either D_2O or CH_3CO_2D were unsuccessful, resulting only in *N*-deuteration. The observed reactivity of **1** with soft electrophiles is consistent with that expected of a soft, C-based nucleophile.

In order to make this overall substitution procedure more attractive from a general synthetic standpoint, it was of interest to try and incorporate a readily cleavable group at nitrogen in the place of the 1-isopropyl-2-methylpropyl substituent, and hence provide access to versatile *para*-substituted primary anilines. Although silyl groups are rarely used for the protection of amines due to the reactivity of the N–Si linkage, it was exactly this feature, combined with their ease of introduction, significant steric demands and commercial availability that led us to explore the use of the TIPS group in this role. Reaction of the sterically-encumbered *N*-TIPS aniline, **5**,[10] with Bu^nLi and $(Pr^i_2N)_2PCl$ under identical conditions to those used for the preparation of **2a**, afforded a mixture of the *para*-phosphino-, **6**, and *N*-substituted, **7**, derivatives in a 3 : 1 ratio (Scheme 2). Subsequent reaction of this mixture of **6** and **7** with excess HCl/Et_2O achieved simultaneous P–N and N–Si bond cleavage, generating the ammonium salt **8**, $Pr^i_2NH_2Cl$, TIPS-Cl and anilinium chloride. The disubstituted compound, **9**, could be isolated in good yield (69%) from a procedure similar to that used to prepare **3a**. Although the regioselectivity of the reactions of **5** is lower than those of **1**, these experiments demonstrate the feasibility of using readily cleavable, bulky silyl groups to effect *para*-substitution in anilines.

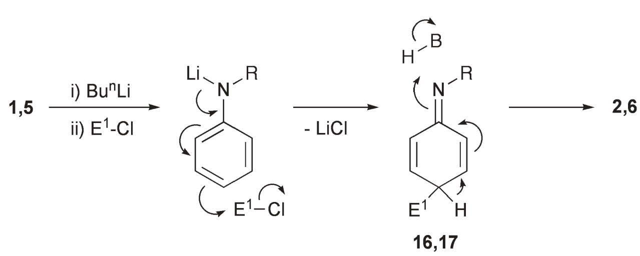
To further explore the substitution chemistry of **1**, two sets of reactions were undertaken (Scheme 3). *N*-methyl aniline, **10**, was treated sequentially with 1 equiv. of Bu^nLi, followed by Ph_2PCl, under conditions analogous to those used for the preparation of **2b**. This quantitatively afforded the known aminophosphine, **12**, according to ^{31}P NMR spectroscopy (δ = 56.8 ppm).[11]



Scheme 2 Reaction conditions: i. Bu^nLi, Et_2O, −78 °C to RT, 1 h; ii. $(Pr^i_2N)_2PCl$, Et_2O, −78 °C to RT, 18 h; iii. HCl, Et_2O, RT; iv. 2 equiv. Bu^nLi, Et_2O, −78 °C to RT, 1 h; v. 2 equiv. $(Pr^i_2N)_2PCl$, Et_2O, −78 °C to RT, 18 h.



Scheme 3 Reaction conditions: i. Bu^nLi, Et_2O, −78 °C to RT, 1 h; ii. Ph_2PCl, Et_2O, −78 °C to RT; iii. $(Pr^i_2N)_2PCl$, Et_2O, −78 °C to RT.



Scheme 4 Proposed mechanism for the formation of *para*-substituted anilines **2** and **6** (B–H = base).

When the *para*-position of the ring of **1** was blocked, *e.g.* in **11**,[12] initial lithiation (Bu^nLi, Et_2O) followed by reaction with Ph_2PCl resulted in a complex, largely intractable mixture of products according to ^{31}P NMR spectroscopy, which contained *N*-phosphinoaniline **15** (^{31}P NMR δ = +54.8 ppm). Treatment of the crude reaction mixture with excess S_8, followed by GC–MS analysis, revealed the thio derivative of **15** to be present as *ca.* 30% of the total products.

Collectively, these results are consistent with *para*-substituted compounds **2** and **6** being formed from secondary anilines **1** and **5** respectively, in a three-step process which may be regarded as an aza analogue of the dienone–phenol reaction (Scheme 4).[13] In this process initial *N*-lithiation occurs, rendering the *para*-position of the ring more nucleophilic, facilitating the subsequent directed electrophilic attack of E^1–Cl. The resulting cyclohexadienyl-idene-amines, **16** and **17**, re-aromatise following deprotonation, to afford **2** and **6** respectively. Given the significant driving force associated with re-aromatisation, it is difficult to identify the base involved in this final step with any certainty. It is possible that residual lithium amide may be transferring a proton catalytically or indeed that **16** and **17** are acting as internal bases.

The role of the bulky substituents, which appear essential for the clean *para*-functionalisation rather than the *N*-substitution of **1** and **5**, is somewhat unclear. However, since the secondary lithium amides that result from the reaction of **1** and **5** with Bu^nLi are extremely sterically hindered, it is presumed that their rate of nucleophilic substitution with E^1Cl is, as a result, retarded. Hence, the rearrangement outlined in Scheme 4 is favoured, giving rise to the observed reactivity in the *para*-position. However, when the ring *para*-position is blocked, as in **11**, a complex mixture of products results, which includes the *N*-substituted compound **15**.

In contrast, the amide resulting from *N*-methyl aniline is considerably less hindered than that from **1** and thus favours reaction at nitrogen. Consistent with this idea is the reaction of lithiated **10** with the bulkier electrophile $(Pr^i_2N)_2PCl$, which gives rise to a mixture of products, including the *N*- and ring-functionalised compounds **13** and **14** respectively (identified by ^{31}P NMR spectroscopy and GC–MS analysis following thiolation).

Additionally, bulky substituents located at nitrogen will effectively 'block' any reaction at the nearby ring *ortho*-positions. The origin of the lower regioselectivity engendered by the TIPS group compared to the 1-isopropyl-2-methylpropyl moiety remains unresolved. However, the greater length of N–Si and C–Si bonds relative to those of N–C and C–C may mean that the steric constraints imposed by the TIPS unit are somewhat lower than those of the more successful hydrocarbon moiety, although the fact that electronic factors may also play a role cannot be ignored.

Recently, the regioselective *para*-bromination of certain primary anilines has been achieved with varying degrees of success by using a 'one-pot' procedure, involving the sequential treatment of the amine with equimolar quantities of Bu^nLi, Me_3SnCl and elemental bromine.[14] It was proposed that this reaction proceeded *via* formation of a tin amide (through a salt elimination reaction between the lithium amide and Me_3SnCl), which activated the *para*-position of the aromatic ring towards direct electrophilic bromination. In light of the results presented here, this pathway was to be expected, rather than direct stannylation as for **2d**, since no sterically demanding groups were present at nitrogen.

Overall, the approach of using bulky *N*-substituents to direct regioselective substitution affords a ready means of preparing a range of variously-functionalised, *para*-substituted anilines. In particular, aromatic amines bearing the Me_3Sn moiety are accessible—compounds that are of potential utility in Stille cross-coupling reactions. Work is ongoing to enhance the regioselectivity of the reaction by involving a sterically demanding, yet readily cleavable group at nitrogen.

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Notes and references

‡ Representative synthesis of **2a**: To a solution of **1** (5.12 g, 2.68 × 10^{-2} mol) in Et_2O (40 mL) at −78 °C was added Bu^nLi (1.6 M, hexane, 17.6 mL, 2.81 × 10^{-2} mol) dropwise, the resulting mixture then being allowed to slowly warm to RT with stirring over 1 h. The re-cooled (−78 °C) solution was added to a suspension of $(Pr^i_2N)_2PCl$ (7.15 g, 2.68 × 10^{-2} mol) in Et_2O (40 mL) at −78 °C. Following reaction at RT for 18 h, removal of volatiles *in vacuo* and extraction with hexane, prolonged cooling (−30 °C) afforded **2a** as white crystals (5.61 g, 96%). Found: C, 71.14; H, 11.59; N, 9.95. $C_{25}H_{48}N_3P$ requires C, 71.21; H, 11.47; N, 9.97%; δ_H (250.13 MHz, $CDCl_3$) 7.98 (2 H, dd, $^3J_{HH}$ 8.7, $^3J_{PH}$ 6.7 Hz, *m*-C_6H_4), 6.53 (2 H, dd, $^3J_{HH}$ 8.7, $^4J_{PH}$ 1.9 Hz, *o*-C_6H_4), 3.42 (4 H, d sept., $^3J_{HH}$ 6.7, $^3J_{PH}$ 2.5 Hz, PNC*H*), 2.99 (1 H, br d, $^3J_{HH}$ 10.1 Hz, N*H*), 2.84 (1 H, m, CNHC*H*), 1.58 (2 H, overlapping sept., $^3J_{HH}$ 6.4 Hz, CC*H*), 1.29 (12 H, d, $^3J_{HH}$ 7.0 Hz, $NCH(CH_3)_2$), 1.27 (12 H, d, $^3J_{HH}$ 7.0 Hz, $NCH(CH_3)_2$), 0.83 (6 H, d, $^3J_{HH}$ 6.7 Hz, $CH(CH_3)_2$), 0.76 (6 H, d, $^3J_{HH}$ 6.7 Hz, $CH(CH_3)_2$); $\delta_C\{^1H\}$ (62.90 MHz, $CDCl_3$) 150.1 (s, *ipso*-C_6H_4), 133.1 (d, $^1J_{PC}$ 21.9 Hz, *ipso*-C_6H_4), 131.1 (s, C_6H_4), 112.9 (d, $^2J_{PC}$ 5.6 Hz, C_6H_4), 64.4 (s, N*C*H), 48.2 (d, $^2J_{PC}$ 11.7 Hz, N*C*H), 31.8 (s, *C*H), 25.1 (d, $^3J_{PC}$ 7.6 Hz, N*C*H), 25.0 (d, $^3J_{PC}$ 7.1 Hz, N*C*H), 21.3 (s, $CH(CH_3)_2$), 18.4 (s, $CH(CH_3)_2$); $\delta_P\{^1H\}$ (101.26 MHz, $CDCl_3$) 59.4 (s); *m/z* (EI): 421 (M^+).

§ Crystal data for **4**: $C_{19}H_{36}LiN_3$, M = 313.45, orthorhombic, space group *P2(1)2(1)2(1)*, a = 9.1878(18), b = 14.344(3), c = 15.575(3) Å, V = 2052.7(7) $Å^3$, Z = 4, μ(Mo-Kα) = 0.059 mm^{-1}, T = 150(2) K, crystal size 0.26 × 0.25 × 0.15 mm, 13076 reflections collected, 3619 independent reflections (R_{int} = 0.0849), R_1 = 0.0563 [$I > 2\sigma(I)$], wR_2 = 0.1090, R_1 = 0.0976, wR_2 = 0.1297 for all data. CCDC 236521. See http://dx.doi.org/10.1039/b506824j for crystallographic files in CIF format.

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