Cross-Coupling

Ligand-Controlled α- and β-Arylation of Acyclic N-Boc Amines**

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Dedicated to Max Malacria on the occasion of his 65th birthday

Abstract: The palladium-catalyzed ligand-controlled arylation of α -zincated acyclic amines, obtained by directed α -lithiation and transmetalation, is described. Whereas PtBu₃ gave rise to α -arylated Boc-protected amines, more flexible N-phenylazole-based phosphine ligands induced major β -arylation through migrative cross-coupling.

Acyclic arylmethyl and arylethylamines are found in countless bioactive molecules. In addition to classical methods which are employed to access these motifs, the palladiumcatalyzed cross-coupling of α - and β -metalated amines with aryl electrophiles has emerged as an efficient and chemoselective alternative.^[1,2] In particular, the Suzuki–Miyaura coupling of α - and β -aminotrifluoroborates, as developed by Molander and co-workers, has proven effective and versatile (Scheme 1 a). However, this approach involves the use of



Scheme 1. Palladium-catalyzed α - and β -arylation of cyclic and acyclic amines. Boc = *tert*-butoxycarbonyl.

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prefunctionalized amino reagents. In contrast, the directed lithiation of Boc-protected piperidines and pyrrolidines α to the nitrogen atom, with subsequent in situ transmetalation to zinc and Negishi coupling, has been established as a powerful and direct entry into a-aryl nitrogen heterocycles (Scheme 1b).^[3] However, to the best of our knowledge this method has never been extended to acyclic Boc-protected amines. Based on a seminal observation by Knochel and co-workers,^[4] we have recently described the selective β-arylation of Bocprotected piperidines, which occurs through the generation of α -zincated piperidines and ligand (L1)-induced migrative Negishi coupling (Scheme 1b).^[5] Herein, we report the ligand-controlled α - and β -arylation of acyclic Boc-protected amines, which are potentially more challenging substrates for these cross-coupling reactions because of a higher degree of conformational freedom (Scheme 1c). This approach provides a one-step entry into synthetically useful arylmethyland arylethylamines from simple precursors.

We first studied the arylation of the organozinc reagent, which was generated in situ by α -lithiation of the Bocprotected dimethylamine $1a^{[6]}$ and transmetalation with ZnCl₂, with *p*-trifluoromethylbromobenzene to give the product 2a (Scheme 2). A quick optimization^[7] revealed that the Pd/PtBu₃ catalytic system described for the Negishi coupling of Boc-protected piperidines and pyrrolidines^[3] performed exquisitely at 25°C, thus furnishing 2a in 88% yield by using an equimolar amount of 1a and p-trifluoromethylbromobenzene. Aryl bromides were coupled more efficiently than the corresponding chlorides and iodides at 25°C, as shown with 2a. However, upon heating to 40°C ptrifluoromethylchlorobenzene proved a competent coupling partner, thus delivering 2a in 71% yield. A variety of aryl (2a-i) and heteroaryl (2j,k) bromides were coupled successfully, including electrophiles bearing relatively sensitive functional groups (2c,f) or an *ortho*-substituent (2g,h). In addition to (hetero)aryl bromides, acid chlorides (21,m), bromoalkenes (2n), and bromoalkynes (2o) were found to be competent coupling partners, thereby extending the scope of this reaction beyond arylation and allowing access to synthetically useful nitrogenated building blocks.

The α -arylation of other acyclic Boc-protected amines was next studied (Scheme 3). We found that the same reaction conditions could be applied to the Boc-protected alkylmethylamines **1b**–**d** bearing a primary or secondary alkyl group (R¹), thereby delivering the arylmethylamines **3–5** in moderate to high yields. As expected, α -lithiation^[6b] and arylation at the secondary carbon atom of **1e** were found to be more difficult, but upon increasing both the lithiation time (3 h) and the coupling temperature (40 °C), the products **6a–d** were iso-



Scheme 2. α-Functionalization of Boc-protected dimethylamine. Reaction conditions: **1a** (1.0 equiv), sBuLi (1.2 equiv), TMEDA (1.2 equiv), Et₂O, -60°C, 1 h, then ZnCl₂ (1.2 equiv), -60 \rightarrow 20°C, then removal of volatiles under vacuum, then toluene, [Pd₂dba₃] (2.5 mol%), PtBu₃·HBF₄ (5 mol%), R-X (1.0 equiv), 25°C, 17 h. [a] Coupling performed at 40°C instead of 25°C. [b] X=Br. [c] X=Cl. [d] Coupling performed at 80°C instead of 25°C. dba=dibenzylideneacetone, TIPS = triisopropylsilyl, TMEDA=*N*,*N*,*N'*,*N'*-tetramethylethylenediamine.



To study each individual step of this reaction and to compare the reactivity of different aryl electrophiles and Bocprotected amines, we turned to the use of insitu IR spectroscopy. This technique has been recently employed to monitor the directed α -lithiation and electrophilic quenching of cyclic Boc-protected amines,^[8] including α-lithiation/ Negishi coupling.^[8a] First, we found that the α -lithiation of 1a with sBuLi/TMEDA occurred within 2 minutes at -60 °C, as monitored by the disappearance of the $v_{C=0}$ band of **1a** at 1701 cm⁻¹ and appearance of a new band at 1655 cm⁻¹, which was ascribed to the organolithium species.^[7] Similarly, upon addition of zinc chloride, transmetalation occurred in less than a minute, as shown with the appearance of a band at 1624 cm^{-1.[7]} An aryl halide was then added, and resulted in the appearance of a $v_{C=0}$ band at about 1700 cm⁻¹, which was ascribed to the coupling product. The reaction was complete in 3-7 hours with the studied aryl bromides. This method was employed to compare the kinetics of the Negishi coupling of 1a with different aryl halides. A Hammett plot was constructed from the individual kinetic curves obtained with aryl bromides bearing various para substituents (Figure 1).^[7,9] The concave-down shape of the plot is indicative of a change in the rate-limiting step of the reaction for the considered substituents.^[10] More specifically, the current trend suggests that the



Scheme 3. α -Arylation of other acyclic Boc-protected amines. Reaction conditions: Boc-protected amine (1.0 equiv), sBuLi (1.2 equiv), TMEDA (1.2 equiv), Et₂O, -60°C, 1 h (3 h for **1e**), then ZnCl₂ (1.2 equiv), -60 \rightarrow 20°C, then removal of volatiles under vacuum, then toluene, [Pd₂dba₃] (2.5 mol%), PtBu₃·HBF₄ (5 mol%), Ar-Br (1.0 equiv), 25°C, 17 h. [a] Coupling performed at 40°C instead of 25°C. [b] Deprotonation performed at -40°C instead of -60°C.



Figure 1. Hammett plot of the relative rates of product formation for the Negishi coupling of α -zincated Me₂NBoc with *p*-substituted aryl bromides, as monitored by in situ IR spectroscopy (**1**). The relative rate of the coupling of α -zincated Et₂NBoc with PhBr (product **6a**) is also reported on the same plot for comparison (\diamond). The product **2p** was obtained with 4-fluorobromobenzene as the aryl halide, similar to examples in Scheme 2.

rate-limiting step is reductive elimination with electrondeficient aryl bromides, and transmetalation with electronrich ones.^[11] In addition, the coupling of the α -zincated **1e** and bromobenzene (giving rise to **6a**, Scheme 3) was found to be significantly slower (k_{rel} =0.67) than the coupling of the α zincated **1a** (giving **2b**), thereby reflecting the greater steric hindrance of **1e** at C_{α} (Figure 1). Although a more complete kinetic analysis should be performed to draw more precise conclusions, these data clearly show how changes in the substitution of both coupling partners affect their reactivity.

We next turned our attention towards migrative arylation at the β position of Boc-protected ethylamines (Scheme 4). Mechanistically, this reaction initially proceeds by formation



Scheme 4. β-Arylation of acyclic Boc-protected amines. Reaction conditions: Boc-protected amine (1.0 equiv), sBuLi (1.0 equiv), TMEDA (1.0 equiv), Et₂O, -60°C, 3 h, then ZnCl₂ (1.0 equiv), -60→20°C, then removal of volatiles under vacuum, then toluene, [Pd₂dba₃] (2.5 mol%), ligand (5 mol%), Ar-Br (0.7 equiv), 80°C, 17 h. Yields refer to the isolated β-arylated product, calculated against the aryl bromide (unless otherwise stated). Ratios of β- and α-arylated products were determined by GCMS analysis of the crude reaction mixture. [a] Deprotonation performed at -40°C instead of -60°C. [b] Yield of the mixture of α- and β-arylated products.

of the α -palladated Boc-amine, which is a common intermediate for α - and β -arylation.^[5] α -Arylation occurs by reductive elimination whereas rearrangement to the β palladated isomer (by the well-characterized β -hydride elimination/rotation/insertion manifold),^[12] and reductive elimination affords the linear β -arylated product.^[13] We initially tested **L1**, which was found to give optimal β/α arylation selectivities and yields with Boc-protected piperidines. However, a 1:1 (approximately) mixture of the β -arylated product **8a** and its α -arylated isomer **6d** was obtained in the coupling of 1e with p-trifluoromethylbromobenzene. In light of previous mechanistic data,^[5] we reasoned that less sterically hindered ligands might further improve the coupling selectivity by disfavoring reductive elimination at the more crowded α position. Indeed, the ligand L2, containing *n*butyl substituents at the phosphorus atom instead of the isopropyl groups as in L1, furnished an improved selectivity (87:13) in favor of 8a, which was isolated in 52% yield after separation from the minor α -arylated isomer. The enecarbamate 9 and trifluorotoluene were also observed in the crude reaction mixture, and consistent with previous work and mechanistic considerations.^[5,14] Further variations of the ligand structure led to the imidazole-based ligand L3 containing isobutyl P substituents of intermediate bulkiness,^[7] and it afforded an enhanced product yield (63%) compared to that of L2. Other reaction parameters such as the molarity of each reagent were also optimized.^[7]

These reaction conditions were applied to different amines and aryl electrophiles (Scheme 4). Both L2 and L3 were tested in each case to obtain optimal yields. L^2 consistently afforded better selectivity albeit often in lower yield than L^3 . It is important to note that in all cases, despite the fact that β/α -isomeric mixtures were obtained, we were able to isolate the major β -arylated isomer in good purity and acceptable yield after standard chromatography. Thus, yields in the 50–63% range were obtained for the β -arylated products 8a-g containing either an electron-withdrawing or electron-donating substituent at the para or meta position, including relatively sensitive or reactive functional groups (8b, 8d, 8g). Moreover, similar to the corresponding α arylation (6c, Scheme 3), the β -arylation of 1e with pfluorobromobenzene to give 8c could be performed on a gram scale (0.95 g, 51 %; Scheme 4). In contrast, a lower vield was obtained for ortho-substituted aryl bromides such as 2-fluorobromobenzene (8h) and heteroaryl bromides such as 3-bromopyridine (8i), and was attributed to the formation of larger amounts of the enecarbamate 9. In these cases, switching back to the bulkier ligand L1 gave a higher efficiency without loss of selectivity, thereby providing the β -arylated products **8h**-j with satisfying yields (54–64%). Electrophiles other than (hetero)aryl halides were also tested, but they mainly gave α -functionalization. The β -arylation of other Boc-protected amines was attempted, but a major limitation came from the initial α -lithiation step, which was found to be very sensitive to steric hindrance. For instance, *i*PrN(Boc)Et and CyN(Boc)Et failed to undergo α -lithiation whereas the α -lithiation/transmetalation/migrative Negishi coupling sequence could be applied to the slightly less crowded iBuN(Boc)Et (1g; product 8k). When the same reaction conditions were applied to iBuN(Boc)CH₂CD₃, the corresponding β -arylated product 81 was obtained with complete transfer of a deuterium atom from the β to the α position. This transfer is consistent with the migrative mechanism involving β -hydride(deuteride) elimination and Pd-H(D)/olefin insertion, which was previously reported with Boc-protected piperidines^[5] and esters.^[12]

as shown both by the

Pd---Cortho short dis-

tance of 2.654 Å and

by the incipient pira-

midalization at Cortho

(dihedral angle 7.1°).

elimination to give

the β -arylated product

8a occurs via TS-III-β

mol⁻¹). The compari-

son of TS-III- β and

TS-Ia- α shows that

the forming $C(sp^2)$ -C-

(sp³) bond is shorter

(2.02 Å vs. 2.12 Å)

and the C(sp²)-Pd-C-

(sp³) angle is smaller

(57° vs. 60°) in the

former, thus account-

ing for the observed

 ΔG^{+}

suggest that by using

L2 as the ligand, the

two selectivity-determining steps are **TS-**Ia- α and **TS-IIa-IIb**,

value.

calculations

lower

These

 $(\Delta G^{\dagger} = 19.1 \text{ kcal})$

Finally, reductive



Figure 2. Comparison of the energy profiles for the α - and β -arylation pathways from the complex **Ia** with **L2** and PtBu₃ as the ligands.

On this basis, DFT calculations were employed to study the ligand effect on the α/β selectivity (Figure 2).^[15] To this purpose, the reaction mechanism was computed both with PtBu₃ (α -selective) and L2 (β -selective), and using Et₂NBoc and (p-CF₃)PhBr as coupling partners (the corresponding products being 6d, Scheme 3, and 8a, Scheme 4). Results obtained with L2 are discussed first. The initial α -palladated intermediate Ia, resulting from the Zn-Pd transmetalation step, is coordinated to the Boc group (Pd-O 2.179 Å), as observed previously with Boc-protected piperidine.^[5] In the present case, the pathway leading to α -arylated product **6d** involves decoordination of the Boc group from palladium, thus leading to the T-shaped ML_3 complex Ia- α , with reductive elimination occurring via **TS-Ia-** α ($\Delta G^{+} = 21.6$ kcal mol⁻¹). In contrast, the β -arylation pathway involves several sequential steps. First, decoordination of the Boc group from palladium and the establishment of a β-CH agostic interaction (Pd···H 2.025 Å, C_8 -H 1.14 Å) lead to the intermediate **Ib**. Then, β -hydride elimination from **Ib** via **TS-Ib-IIa** ($\Delta G^{\dagger} =$ 18.5 kcalmol⁻¹) leads to the π -complex **IIa**. Rotation of the coordinated olefin through **TS-IIa-IIb** ($\Delta G^{\pm} = 21.6$ kcal mol⁻¹) produces the isomeric π -complex **IIb**. The complex **IIb** is more stable than **IIa** by 2.9 kcalmol^{-1} , and this is possibly a result of lower steric constraints in the former. Insertion of the olefin into the Pd-H bond via TS-IIb-IIc $(\Delta G^{\dagger} = 16.2 \text{ kcal mol}^{-1})$ leads to the T-shaped β -palladated intermediate IIc. The latter is more stable than Ib by 2.8 kcalmol⁻¹, even though no stabilizing agostic interaction is present in IIc. This stability could be due to stronger interactions between the phenyl group of L2 and palladium,

the rotation of the π -complex, with a $\Delta\Delta G^{\dagger}$ value of 0 kcalmol⁻¹. This value is consistent with the observed experimental α/β ratio of 13:87, when considering the uncertainties of the computational method. We experimentally observed that the α -arylation pathway was favored using $PtBu_3$ as the ligand, thus leading exclusively to **6d** (Scheme 3). Similar calculations were thus conducted with PtBu₃ as the ligand, and allowed analysis of the impact of the ligand on the different steps of the mechanism. First, reductive elimination occurring via **TS-Ia-** α is significantly favored (5.1 kcalmol⁻¹) compared to the case of L2. Along the β -arylation pathway, two transiton states, TS-Ib-IIa and TS-IIa-IIb, were found to be higher in energy by 0.2 and 1.5 kcalmol⁻¹, respectively. This higher energy can be attributed to the increased steric repulsion between the more bulky PtBu₃ ligand and the Bocprotected amine substrate. The two other transition states, that is, **TS-IIb-IIc** and especially **TS-III-\beta**, were found to be lower in energy compared to the case of L2. The known propensity of bulky and rigid ligands to favor C-C reductive elimination^[16] is translated into the lower **TS-Ia-** α and **TS-III-** β observed with PtBu₃ compared to L2. Importantly, the two selectivity-determining steps are TS-Ia- α and TS-IIa-IIb as in the above-mentioned case for L2, but now the $\Delta\Delta G^{\dagger}$ is 6.6 kcalmol⁻¹ in favor of α -arylation, and is in accordance with the observed experimental selectivity. Overall, the calculations reproduce well the selectivity difference observed experimentally with L2 and PtBu₃, and can be mainly attributed to the markedly different rigidity and steric bulk of these ligands.

that is, the reductive elimination at the α -carbon atom and

In conclusion, we have reported for the first time the direct α - and β -arylation of acyclic Boc-protected amines proceeding by a sequence of directed α -lithiation, transmetalation with zinc, and palladium-catalyzed cross-coupling, with the latter occurring under the normal or migrative mode in a ligand-controlled manner. These studies lay the ground-work for site-selective cross-couplings on other acyclic systems.

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