Cross-Coupling

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

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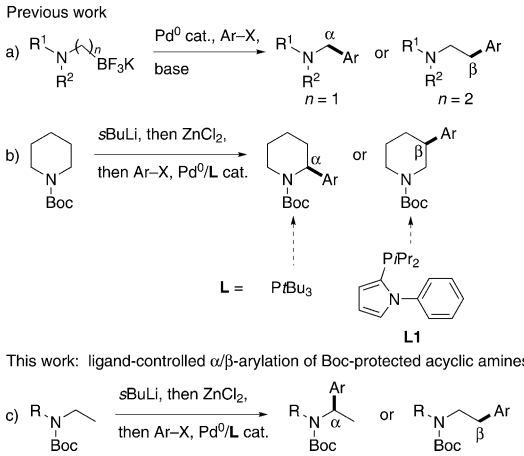
Dedicated to Max Malacria on the occasion of his 65th birthday

Abstract: *The palladium-catalyzed ligand-controlled arylation of α-zincated acyclic amines, obtained by directed α-lithiation and transmetalation, is described. Whereas $PtBu_3$ 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 palladium-catalyzed 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 1a). However, this approach involves the use of 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 α-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 Boc-protected 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 arylmethyl- and arylethylamines from simple precursors.



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

We first studied the arylation of the organozinc reagent, which was generated in situ by α-lithiation of the Boc-protected dimethylamine **1a**[6] and transmetalation with $ZnCl_2$, with *p*-trifluoromethylbromobenzene to give the product **2a** (Scheme 2). A quick optimization[7] revealed that the Pd/P*t*Bu$_3$ 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 *p*-trifluoromethylchlorobenzene 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 (**2l**,**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 (R^1), 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-

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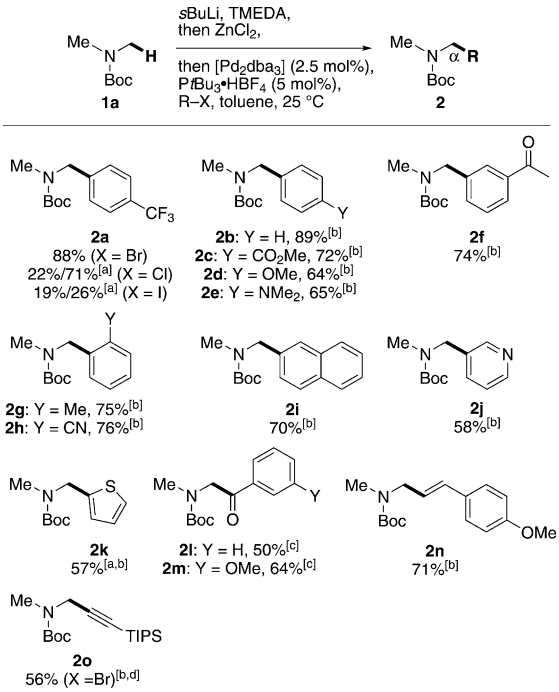
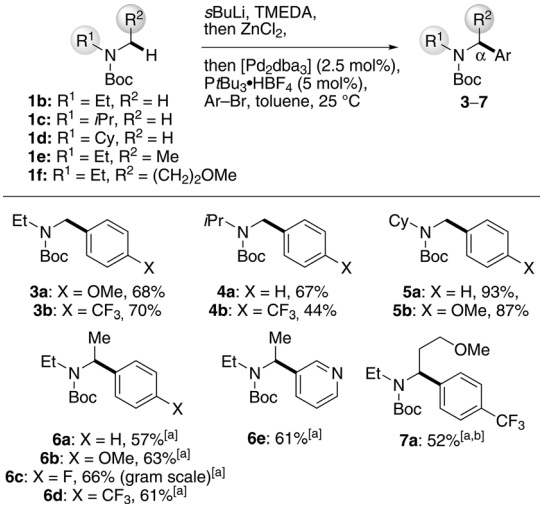


Scheme 2. α-Functionalization of Boc-protected dimethylamine. Reaction conditions: **1a** (1.0 equiv), *s*BuLi (1.2 equiv), TMEDA (1.2 equiv), Et_2O, −60 °C, 1 h, then $ZnCl_2$ (1.2 equiv), −60→20 °C, then removal of volatiles under vacuum, then toluene, [Pd_2dba_3] (2.5 mol%), $PtBu_3{\cdot}HBF_4$ (5 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.

lated with satisfying yields. In addition, the reaction performed equally well on a gram scale (**6c**, 1.77 g, 66%). Of note is that no trace of β-arylation was observed under these reaction conditions. Finally, the α-arylation of the more functionalized **1f** was attempted. The initial α-lithiation occurred regioselectively on the propyl ether fragment, likely as a result of the combined directing effects of the Boc and OMe groups. Subsequent Li–Zn transmetalation and Negishi coupling allowed isolation of the α-arylated product **7a** in moderate yield.

To study each individual step of this reaction and to compare the reactivity of different aryl electrophiles and Boc-protected amines, we turned to the use of in situ 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 *s*BuLi/TMEDA occurred within 2 minutes at −60 °C, as monitored by the disappearance of the $\nu_{C=O}$ 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 $\nu_{C=O}$ 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), *s*BuLi (1.2 equiv), TMEDA (1.2 equiv), Et_2O, −60 °C, 1 h (3 h for **1e**), then $ZnCl_2$ (1.2 equiv), −60→20 °C, then removal of volatiles under vacuum, then toluene, [Pd_2dba_3] (2.5 mol%), $PtBu_3{\cdot}HBF_4$ (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.

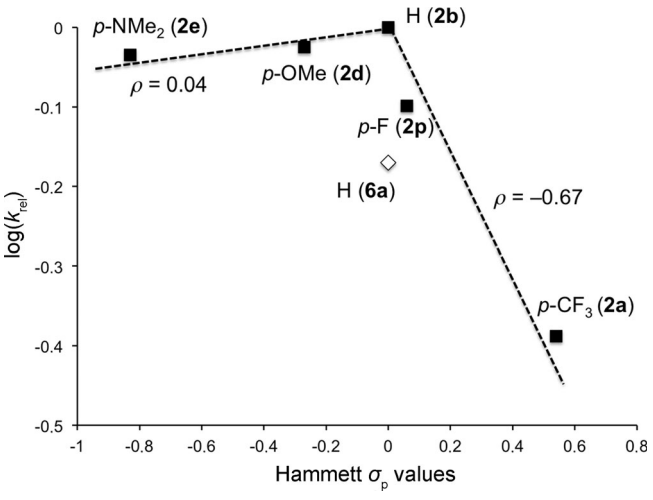


Figure 1. Hammett plot of the relative rates of product formation for the Negishi coupling of α-zincated Me_2NBoc with *p*-substituted aryl bromides, as monitored by in situ IR spectroscopy (■). The relative rate of the coupling of α-zincated Et_2NBoc with PhBr (product **6a**) is also reported on the same plot for comparison (◇). The product **2p** was obtained with 4-fluorobromobenzene as the aryl halide, similar to examples in Scheme 2.

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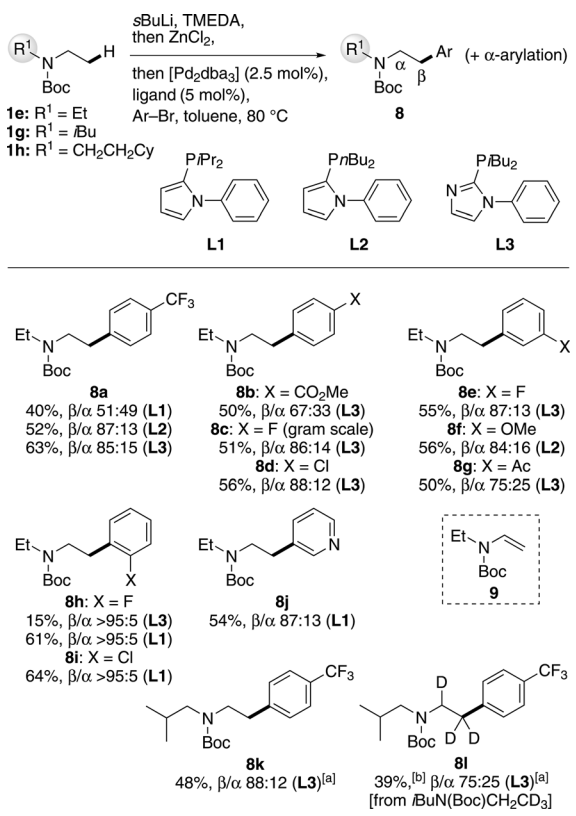
rate-limiting step is reductive elimination with electron-deficient aryl bromides, and transmetalation with electron-rich ones.[11] In addition, the coupling of the α-zincated **1e** and bromobenzene (giving rise to **6a**, Scheme 3) was found to be significantly slower ($k_{rel} = 0.67$) than the coupling 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), *s*BuLi (1.0 equiv), TMEDA (1.0 equiv), Et_2O, −60 °C, 3 h, then $ZnCl_2$ (1.0 equiv), −60→20 °C, then removal of volatiles under vacuum, then toluene, [Pd_2dba_3] (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. **L2** consistently afforded better selectivity albeit often in lower yield than **L3**. 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 *p*-fluorobromobenzene to give **8c** could be performed on a gram scale (0.95 g, 51%; Scheme 4). In contrast, a lower yield was obtained for *ortho*-substituted aryl bromides such as 2-fluorobromobenzene (**8h**) and heteroaryl bromides such as 3-bromopyridine (**8j**), 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 *i*BuN(Boc)Et (**1g**; product **8k**). When the same reaction conditions were applied to *i*BuN(Boc)CH_2CD_3, the corresponding β-arylated product **8l** 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]

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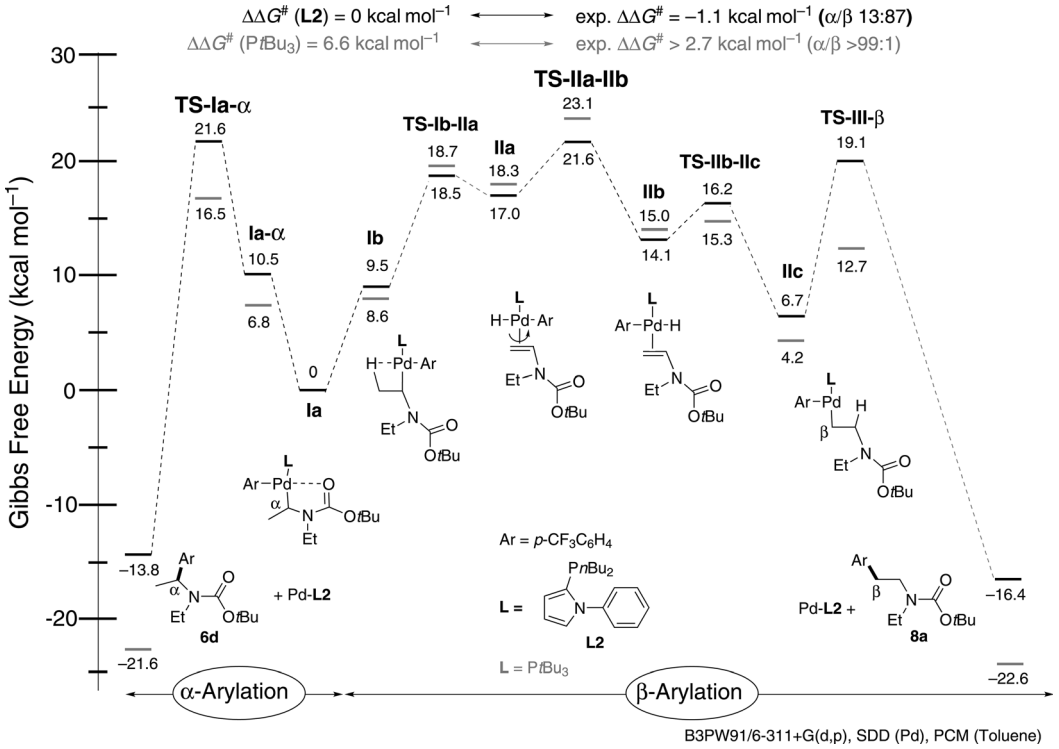

Figure 2. Comparison of the energy profiles for the α- and β-arylation pathways from the complex **Ia** with **L2** and P*t*Bu$_3$ as the ligands.

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 P*t*Bu$_3$ (α-selective) and **L2** (β-selective), and using Et$_2$NBoc and (*p*-CF$_3$)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** ($\Delta G^{\neq} = 21.6$ 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$_\beta$-H 1.14 Å) lead to the intermediate **Ib**. Then, β-hydride elimination from **Ib** via **TS-Ib-IIa** ($\Delta G^{\neq} =$ 18.5 kcal mol^{-1}) leads to the π-complex **IIa**. Rotation of the coordinated olefin through **TS-IIa-IIb** ($\Delta G^{\neq} = 21.6$ kcal mol^{-1}) produces the isomeric π-complex **IIb**. The complex **IIb** is more stable than **IIa** by 2.9 kcal mol^{-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** ($\Delta G^{\neq} = 16.2$ kcal mol^{-1}) leads to the T-shaped β-palladated intermediate **IIc**. The latter is more stable than **Ib** by 2.8 kcal mol^{-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, as shown both by the Pd···C$_{ortho}$ short distance of 2.654 Å and by the incipient piramidalization at C$_{ortho}$ (dihedral angle 7.1°).

Finally, reductive elimination to give the β-arylated product **8a** occurs via **TS-III-β** ($\Delta G^{\neq} = 19.1$ kcal mol^{-1}). The comparison of **TS-III-β** and **TS-Ia-α** shows that the forming C(sp^2)–C(sp^3) bond is shorter (2.02 Å vs. 2.12 Å) and the C(sp^2)-Pd-C(sp^3) angle is smaller (57° vs. 60°) in the former, thus accounting for the observed lower $\Delta G^{\neq}$ value. These calculations suggest that by using **L2** as the ligand, the two selectivity-determining steps are **TS-Ia-α** and **TS-IIa-IIb**, that is, the reductive elimination at the α-carbon atom and the rotation of the π-complex, with a $\Delta\Delta G^{\neq}$ value of 0 kcal mol^{-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 P*t*Bu$_3$ as the ligand, thus leading exclusively to **6d** (Scheme 3). Similar calculations were thus conducted with P*t*Bu$_3$ 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 kcal mol^{-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 kcal mol^{-1}, respectively. This higher energy can be attributed to the increased steric repulsion between the more bulky P*t*Bu$_3$ ligand and the Boc-protected amine substrate. The two other transition states, that is, **TS-IIb-IIc** and especially **TS-III-β**, 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 P*t*Bu$_3$ 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 $\Delta\Delta G^{\neq}$ is 6.6 kcal mol^{-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 P*t*Bu$_3$, and can be mainly attributed to the markedly different rigidity and steric bulk of these ligands.

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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 groundwork for site-selective cross-couplings on other acyclic systems.

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