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Ligand-controlled β-selective C(sp^3)–H arylation of *N*-Boc-piperidines†

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We report a general palladium-catalyzed β-arylation of Boc-piperidines, which yields a variety of valuable 3-arylpiperidines in a simple and direct manner. The β- *vs.* α-arylation selectivity was controlled by the ligand, with flexible biarylphosphines providing mainly the desired β-arylated products whereas more rigid biarylphosphines mainly furnished the more classical α-arylated products. The computed reaction mechanism (DFT), studied from the common α-palladated intermediate, indicated that the reductive elimination steps leading to the α- and β-arylated products are selectivity-determining. Moreover, the experimental trend obtained with different ligands was well reproduced by the calculations.

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Introduction

3-Arylpiperidines are important building blocks for drug discovery, as shown by the structures of preclamol, a dopaminergic autoreceptor agonist, and MK-4827, a poly(ADP-ribose)-polymerase (PARP) inhibitor (Fig. 1).[1] Their synthesis usually involves the construction of the piperidine ring or the partial reduction of a 3-arylpyridine precursor,[2] since the inert character of C–H bonds in a β position to the nitrogen atom seems to preclude direct functionalization.

In contrast, the well-established directed lithiation of Boc-piperidines (Boc = *tert*-butyloxycarbonyl) α to the nitrogen atom[3,4] provides an efficient and direct entry into 2-arylpiperidines, *via* transmetalation to zinc and Negishi coupling with aryl electrophiles (Scheme 1a, R = H). This principle was initially implemented on Boc-pyrrolidine by Campos *et al.*,[5] and subsequently transposed to Boc-piperidine by Coldham and co-workers.[6,7] Recently, Knochel and co-workers reported a study on the diastereoselective arylation of substituted Boc-piperidines, which occurred at the usual α position to the nitrogen atom, except with 2-methylpiperidine, which unexpectedly underwent β-arylation (Scheme 1a, R = Me).[8] In this work, the arylation site-selectivity was *substrate-controlled*, since α-arylated products where obtained with the same ligand (Buchwald's RuPhos) from piperidines lacking a 2-Me substituent. We recently described the Pd-catalyzed β C–H-arylation of ester enolates, for which site-selectivity (*i.e.* α- *vs.* β-arylation) was controlled both by the reactants and the ligand.[9,10] This reaction, the mechanism of which was investigated in detail, involves Pd migration

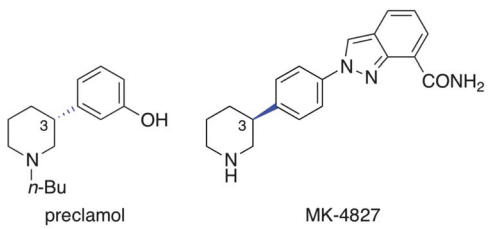
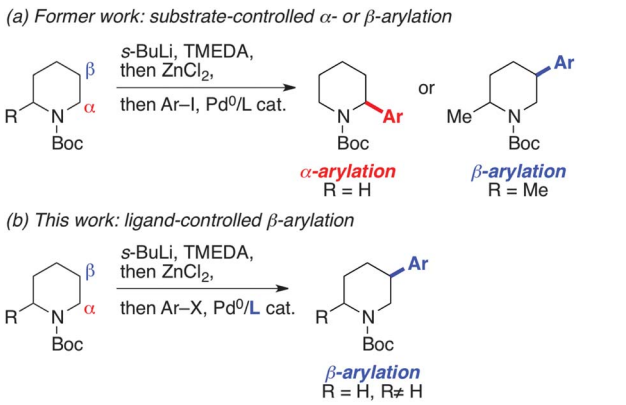


Fig. 1 Examples of bioactive 3-arylpiperidines.



Scheme 1 Substrate *vs.* ligand-controlled arylation of Boc-piperidines.

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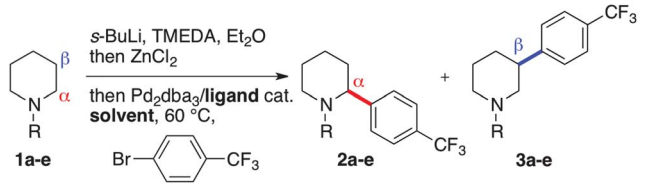
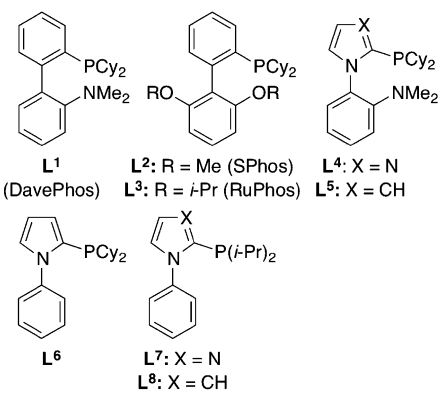
along the alkyl chain by a β-H elimination/rotation/insertion sequence.[9b] By extension, we envisioned that the β-arylation of 2-methylpiperidine observed by Knochel *et al.*, which presumably involves the same Pd migration mechanism,[8] might be extended to other piperidines, including those lacking a C-2 substituent, by a proper choice of the ligand. The development of such a *ligand-controlled* β-arylation of Boc-piperidines (Scheme 1, bottom) is the focus of the current report.

Table 1 Optimization of the β-arylation of piperidine[a]



Entry	R	Ligand	Solvent	2/3[b]	Yield (%)[c]
1	Boc (**1a**)	L^1	Toluene	61 : 39	68
2	Boc (**1a**)	L^2	Toluene	94 : 6	78
3	Boc (**1a**)	L^3	Toluene	90 : 10	65
4	Piv (**1b**)	L^1	Toluene	85 : 15	—
5	CO(2-pyridinyl) (**1c**)	L^1	Toluene	—	0
6	CO_2i-Pr (**1d**)	L^1	Toluene	—	0
7	CO(2,4,6-*i*-Pr-C_6H_2) (**1e**)	L^1	Toluene	>98 : 2	68[d]
8	Boc (**1a**)	L^1	THF	59 : 41	55
9	Boc (**1a**)	L^1	Me_4THF	71 : 29	68
10	Boc (**1a**)	L^1	MTBE	64 : 36	62
11	Boc (**1a**)	L^1	Mesitylene	73 : 27	54
12	Boc (**1a**)	L^4	Toluene	17 : 83	57
13	Boc (**1a**)	L^5	Toluene	17 : 83	65
14	Boc (**1a**)	L^6	Toluene	10 : 90	44
15	Boc (**1a**)	L^7	Toluene	17 : 83	56[e]
16	Boc (**1a**)	L^8	Toluene	9 : 91	59[e]
17	Boc (**1a**)	—	Toluene	—	0



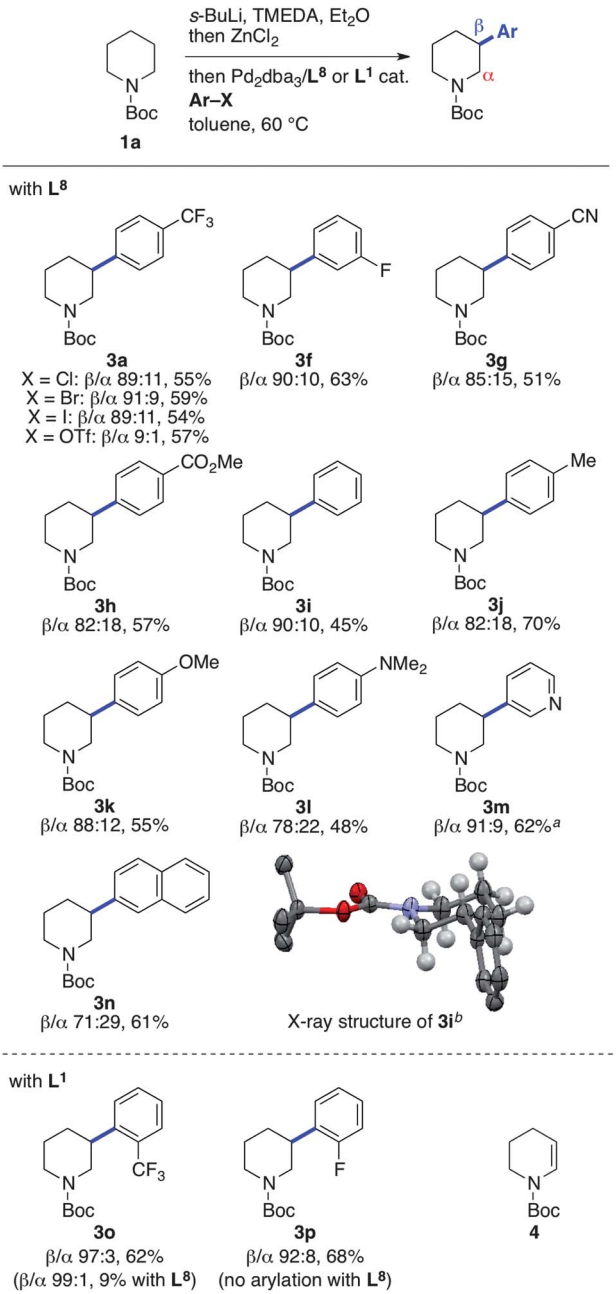
[a] *Reaction conditions*: piperidine (1.0 equiv.), *s*-BuLi (1.2 equiv.), TMEDA (1.2 equiv.), Et_2O, −78 °C, then $ZnCl_2$ (1.2 equiv.), −78 → 20 °C, then removal of volatiles under vacuum, then solvent, $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), ligand (5 mol%), 4-trifluoromethylbromobenzene (0.7 equiv.), 60 °C, 17 h. [b] Determined from ^{1}H NMR or GCMS analysis of the crude mixture. [c] Combined yield of the isolated mixture of **2**/**3** unless otherwise stated. [d] Yield of the isolated α-arylated product. [e] Yield of the isolated β-arylated product. Me_4THF = 2,2,5,5-tetramethyltetrahydrofuran; MTBE = methyl *tert*-butyl ether.

Results and discussion

Experimental results

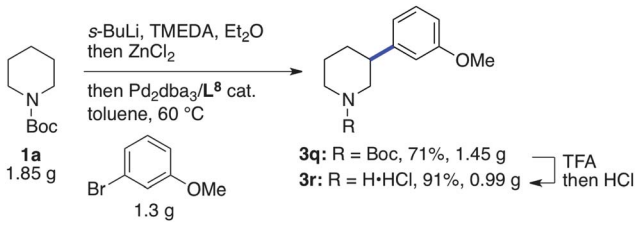
We first examined the arylation of the organozinc reagent, generated *in situ* by α-lithiation of Boc-piperidine **1a** and transmetalation with $ZnCl_2$,[5] with *p*-trifluoromethylbromobenzene (Table 1). This aryl bromide was chosen because the trifluoromethyl group should not introduce a strong electronic bias for the control of the arylation site-selectivity, in light of our previous studies.[9b] In the presence of DavePhos (L^1)[11a] as the ligand and toluene as the solvent, *i.e.* under conditions similar to those developed in our initial work on the β-selective arylation of ester enolates,[9a] a *ca.* 3 : 2 mixture of α- and β-arylated products **2a** and **3a** was isolated in 68% yield (entry 1). By using SPhos (L^2)[11b] or RuPhos (L^3)[11c] as the ligand as in the previous work of Knochel *et al.*,[8] the α-arylated product **2a** was obtained as expected with more than 90% selectivity (entries 2–3). We next studied the effect of the directing group (R) on the piperidine ring,[12] which was expected to have an influence on the α/β selectivity by virtue of electronic and steric effects (entries 4–7). Indeed, this turned out to be the case, but none of the amides and carbamates that were examined resulted in an increase in the selectivity in favor of the β-arylated product. The effect of other solvents was also analyzed (see entries 8–11 for representative examples), but toluene was found to provide the best combination of β-selectivity and yield (entry 1). Next, we turned our attention to the modification of the ligand (entries 12–16). Gratifyingly, analogues of DavePhos bearing an imidazole (L^4) or pyrrole (L^5) ring,[13,14] which gave superior yields and selectivities to DavePhos in a previous study,[9c] reversed the selectivity in favor of β-arylated product **3a** (entries 12–13). Then, we found that the dimethylamino group of these ligands was not required to obtain good β/α selectivity, in contrast to previous work.[9b] Indeed, ligand L^6 provided a slightly enhanced selectivity (entry 14) compared to L^5 (entry 13), albeit with a low conversion and yield. This could be somewhat improved by decreasing the steric bulk at the phosphorus alkyl substituents (entries 15–16), and diisopropylphosphinopyrrole L^8 provided compound **3a** with a 91 : 9 selectivity and a 59% yield after chromatographic separation of the α and β isomers (entry 16). A control experiment without added phosphine ligand (entry 17) gave a low conversion and no arylated product, as expected. Finally, the reaction temperature (60 °C) was found to be optimal through a screening of different temperatures from 20 to 100 °C.

The scope of the β-arylation of Boc-piperidine **1a** with different aryl electrophiles was next evaluated (Scheme 2). The optimized conditions using L^8 as the ligand could be transposed to a variety of aryl electrophiles, to give homogeneously good β/α arylation ratios and isolated yields in the range 45–70% after chromatographic separation to remove the minor α-arylation isomer. As shown with product **3a**, the influence of the aryl leaving group (X) was found to be relatively weak and the usual halides (Cl, Br, I) and triflate of the same arene could be employed with little difference in efficiency and selectivity. Moreover, the reaction tolerated a variety of electron-withdrawing (**3a–h**) and donating (**3j–l**) substituents on the benzene ring as well as other (hetero)arenes (**3m–n**), although the



Scheme 2 Scope of the β-arylation of Boc-piperidine. *Reaction conditions*: see Table 1. Yields refer to the isolated β-arylated product. β/α Ratios were determined from GCMS analysis of the crude mixture. Aryl bromides (X = Br) were used to obtain compounds **3f–p**. [a] Reaction performed at 80 °C. [b] Ellipsoids are drawn at 50% probability; only H atoms of the piperidine ring are shown for clarity.

strongly electron-donating NMe_2 substituent (**3l**) led to somewhat decreased selectivity and reactivity. In addition, similar to the more classical α-arylation of Boc-piperidines,[6,7b,8] relatively sensitive electrophilic groups could be introduced (**3g–h**). In most instances, the conversion of the aryl bromide was incomplete and enecarbamate **4** was formed in variable amounts, at the expense of the desired product. For instance, β-arylated product **3n** was isolated in 61% yield, together with 10% of α-arylated product, 6% of compound **4** and 2-bromonaphthalene (non-quantified). Dehydrogenated products

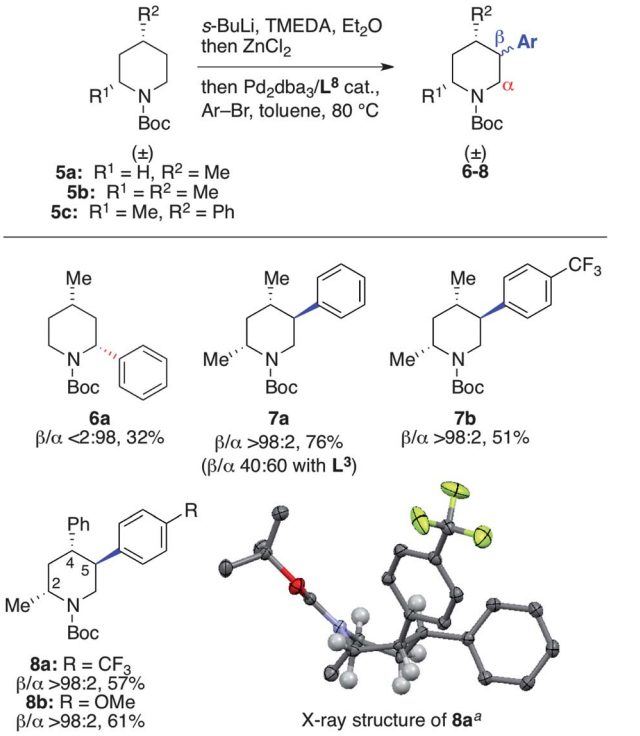


Scheme 3 Formal synthesis of preclamol.

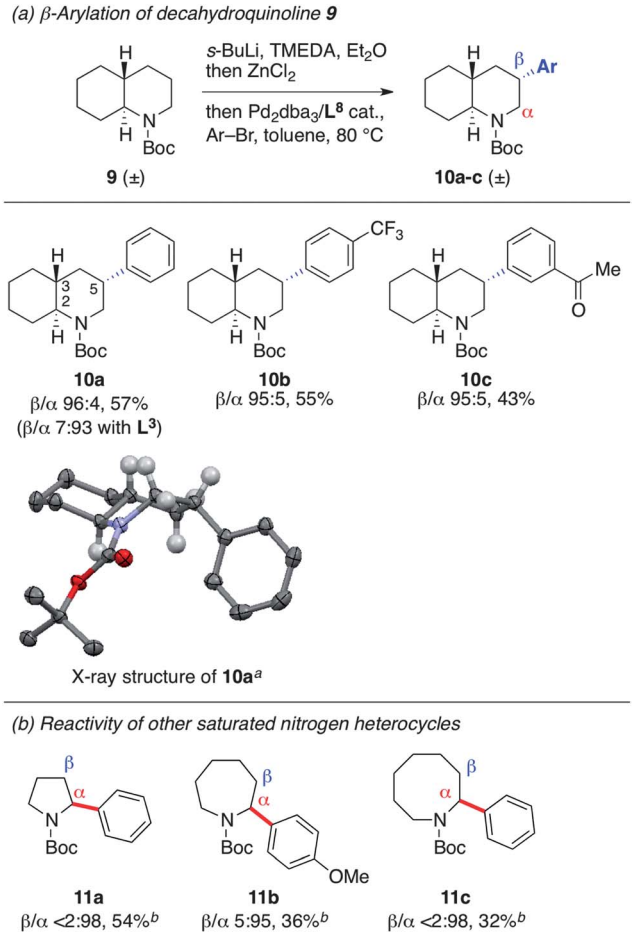
similar to **4**, arising from the decoordination of intermediate palladium π-complexes (*vide infra*), were also observed in the arylation of ester enolates.[9c,15] The X-ray crystal structure of product **3i** could be obtained, showing the chair conformation of the piperidine ring with the phenyl ring in the equatorial position as expected from usual steric effects.† With aryl bromides bearing a strongly electron-withdrawing substituent (F or CF_3) in the *ortho* position, ligand L^8 proved completely inefficient (**3o–p**). In contrast, excellent selectivities and satisfying yields were obtained with DavePhos L^1 as the ligand. We have already shown that *ortho* electron-withdrawing groups introduce an electronic bias by disfavoring C–C reductive elimination.[9a,b] Indeed, large amounts of enecarbamate **4** (64% yield based on aryl bromide) were obtained when ligand L^8 was employed, which might be consistent with this effect. However, it is not yet clear why the use of DavePhos resulted in a counterbalancing of this effect.

This method was applied to the gram-scale formal synthesis of preclamol (Fig. 1, Scheme 3). Indeed, Boc-piperidine **1a** underwent β-selective arylation with 3-bromoanisole under the optimized conditions to give product **3q** in 71% yield. Subsequent cleavage of the Boc group with TFA followed by formation of the known[1a] hydrochloride salt **3r** proceeded efficiently.

Next, we studied the β-arylation of substituted Boc-piperidines (Scheme 4). The above reaction conditions were first applied to the coupling of 4-methylpiperidine **5a** and bromobenzene, but only *cis*-configured α-arylated product **6a** was formed in low yield.[8] In this case, β-arylation is highly disfavored, likely because this would involve the formation of an organopalladium intermediate in the β-position *cis* to the 4-methyl substituent. In contrast, *cis*-2,4-dimethylpiperidine **5b**, which was obtained by directed lithiation/methylation of **5a**,[3a] underwent exclusive β-arylation with bromobenzene to give trisubstituted piperidine **7a** in good yield as a single *cis*,*trans* diastereoisomer. In this case, β-arylation is sterically allowed by the *trans* relationship between the 4-methyl group and the incoming 5-phenyl group. Compared to unsubstituted piperidine **1a**, a higher temperature (80 °C) was required to achieve a satisfying conversion. Of note, when RuPhos L^3 was employed as ligand instead of L^8, α-arylation occurred predominantly (β/α 40 : 60). These results show that the use of ligand L^8 allows the inherent preference for substrate **5b** to undergo α-arylation to be overridden. Similarly, compounds **5b** and **5c** underwent highly regio- and diastereoselective β-arylation with two different aryl bromides to give products **7b** and **8a–b** in moderate yields.



Scheme 4 Diastereoselective β-arylation of 2,4-disubstituted Boc-piperidines. *Reaction conditions*: see Table 1. Yields refer to the isolated β-arylated product. β/α Ratios were determined from GCMS analysis of the crude mixture. [a] Ellipsoids are drawn at 50% probability; only H atoms of the piperidine ring are shown for clarity.



Scheme 5 Diastereoselective β-arylation of *trans*-decahydroquinoline (a) and reactivity of other *N*-heterocycles (b). *Reaction conditions*: see Table 1. Yields refer to the isolated β-arylated product. β/α Ratios were determined from ^{1}H NMR or GCMS analysis of the crude mixture. [a] Ellipsoids are drawn at 50% probability; only H atoms of the piperidine ring are shown for clarity. [b] Yield of the isolated α-arylated product.

The X-ray crystal structure of **8a** revealed that in this case the piperidine ring adopts a twist-boat conformation, which avoids both the 1,3-allylic strain between the 2-Me and the Boc groups and the 1,3-diaxial interaction between the 2-Me and the 4-Ph groups.†[3c,d] This twist-boat conformation is compatible with the Pd migration involved in the β-arylation mechanism (*vide infra*).

The reactivity of *trans*-decahydroquinoline **9** was also studied (Scheme 5a), to assess the applicability of the current approach to bicyclic systems.[16] Under the same conditions as above (Scheme 3), the arylation of **9** with three different aryl bromides proved both highly β-selective and diastereoselective (β/α ≥ 95 : 5, 1 observed diastereoisomer). However, the yields of the corresponding products **10a–c** were moderate, especially for **10c** bearing the sensitive acetyl group. With RuPhos **L^3** as the ligand instead of **L^8**, a complete reversal of selectivity was obtained for **10a** (β/α 7 : 93), consistent with the preceding results (Table 1, Scheme 4). The X-ray structure of compound **10a** was obtained and showed again a twist-boat conformation for the piperidine ring, together with a *cis* relationship between the C-3 methylene and C-5 phenyl substituents.† This conformation allows 1,3-allylic strain between the C-2 methylene substituent and the Boc group to be avoided while maintaining a diequatorial arrangement for the C2, C3-fused cyclohexane ring, and is again compatible with the β-arylation mechanism.

Finally, the reactivity of saturated nitrogen heterocycles of different ring size (5, 7, 8) was also examined (Scheme 5b). However, in all cases α-arylation[5,6] occurred predominantly despite the use of ligand **L^8**. These results indicate that the β-arylation mechanism cannot accommodate the conformational constraints of these rings, at least under the current conditions.

Computational mechanistic study

We assumed that the current reaction involves the same overall mechanism as previously reported with ester enolates.[9] The competition between α- and β-arylation in the reaction of 2-zincated Boc-piperidine with bromobenzene was addressed computationally using DFT(B3PW91) calculations (Fig. 2–4, see also the ESI† for the geometries of all intermediates and transition states).[17] In the initial palladium complex [Pd(**L^8**)(Ph)Boc-piperidine] **Ia**, which results from the Zn–Pd transmetalation step, the Pd atom is attached to the piperidine ring in the equatorial position (Pd–C = 2.060 Å) and coordination of the Boc group to Pd (Pd···O 2.192 Å) completes the square-planar geometry around Pd^{II} (Fig. 3), in line with previous calculations.[8]

Starting from intermediate **Ia** (Fig. 3), the α-arylated product (*i.e.* **2i** still coordinated to Pd through the aromatic ring) is obtained by reductive elimination through **TS-Ia-α** associated with $\Delta G^{\#} = 31.2$ kcal mol^{-1} (Fig. 4). **TS-Ia-α**, in which the Pd atom is still coordinated to the oxygen atom of the Boc group, is reminiscent of a tetrahedral ML_4 geometry. In addition, the forming C(sp^2)–C(sp^3) bond (1.929 Å) is associated with a lengthening of both Pd–C bonds (Pd–C(sp^2) from 1.996 Å in **Ia** to 2.040 Å in **TS-Ia-α**; Pd–C(sp^3) from 2.060 Å in **Ia** to 2.273 Å in **TS-Ia-α**), and a concomitant decrease of the C(sp^2)–Pd–C(sp^3) angle from 87.7° (**Ia**) to 52.8° (**TS-Ia-α**). The Pd···O interaction observed in **Ia** (2.192 Å) is weakened in **TS-Ia-α** (2.524 Å). However, this interaction is still sufficiently important to induce an out-of-plane motion of the Pd-bound phenyl ring, as illustrated by the variation of the dihedral angle C_{ipso}–P–Pd–C(sp^2) from 118.2° in **Ia** to 152.4° in **TS-Ia-α** (C_{ipso}: *ipso* carbon atom of the phenyl ring in **L^8**). This results in a geometry of **TS-Ia-α** featuring the Pd-bound phenyl ring in a pseudo *trans* geometry with respect to the phenyl ring of **L^8**. Consequently, the shortest Pd···C bond distance of 3.374 Å in **Ia** between the phenyl ring of **L^8** and Pd elongates to 3.556 Å in **TS-Ia-α**.

The β-arylation pathway involves the following sequential steps: (1) decoordination of Pd···O, ring-flipping to the twist-boat conformation **Ib** ($\Delta G = 10.9$ kcal mol^{-1}) and formation of a β-CH agostic interaction (C_β–H 1.143 Å, H···Pd 2.034 Å, Fig. 3); (2) β-H elimination from the agostic C–H bond *via* **TS-Ib-IIa** ($\Delta G^{\#} = 9.2$ kcal mol^{-1}) leading to π-complex **IIa**; (3) two subsequent 90° rotations of the coordinated olefin, *via* **TS-IIa-IIb** ($\Delta G^{\#} = 1.8$ kcal mol^{-1}) and **TS-IIb-IIc** ($\Delta G^{\#} = 4.2$ kcal mol^{-1}) leading to π-complex **IIc** (Fig. 3); (4) insertion of the olefin into the Pd–H bond through **TS-IIc-III** ($\Delta G^{\#} = 1.8$ kcal mol^{-1}) with the formation of the Pd–C_β bond in an axial position of the piperidine ring which has flipped back to the chair conformation (intermediate **III**, Fig. 3); (5) reductive elimination to give the β-arylated product (**3i**) *via* **TS-III-β** ($\Delta G^{\#} = 15.9$ kcal mol^{-1}, Fig. 4). In **TS-III-β**, the Pd–C(sp^3) bond has elongated to 2.275 Å, a value similar to that obtained in **TS-Ia-α**. The Pd–C(sp^2) bond is shorter in **TS-III-β** (2.025 Å) compared to the value in **TS-Ia-α** (2.040 Å) and the forming C(sp^2)···C(sp^3) bond is longer (1.984 Å *vs.* 1.929 Å). The essential difference between **TS-Ia-α** and **TS-III-β** is the lack of Pd···O interaction in the latter, which is reminiscent of a T-shaped ML_3 geometry. Consequently, the Pd-bound phenyl ring does not experience the out-of-plane motion observed in **TS-Ia-α**. The C_{ipso}–P–Pd–C(sp^2) dihedral angle has even decreased compared to the value in **Ia** (90.0°, **TS-III-β**; 118.2°, **Ia**). As a result, the interaction between the phenyl ring of **L^8** and Pd has increased in **TS-III-β** with a shortest C···Pd distance of 3.304 Å. This final reductive elimination step furnishes the β-arylated product with the phenyl group in the axial position of the piperidine ring in the chair conformation, which interconverts to

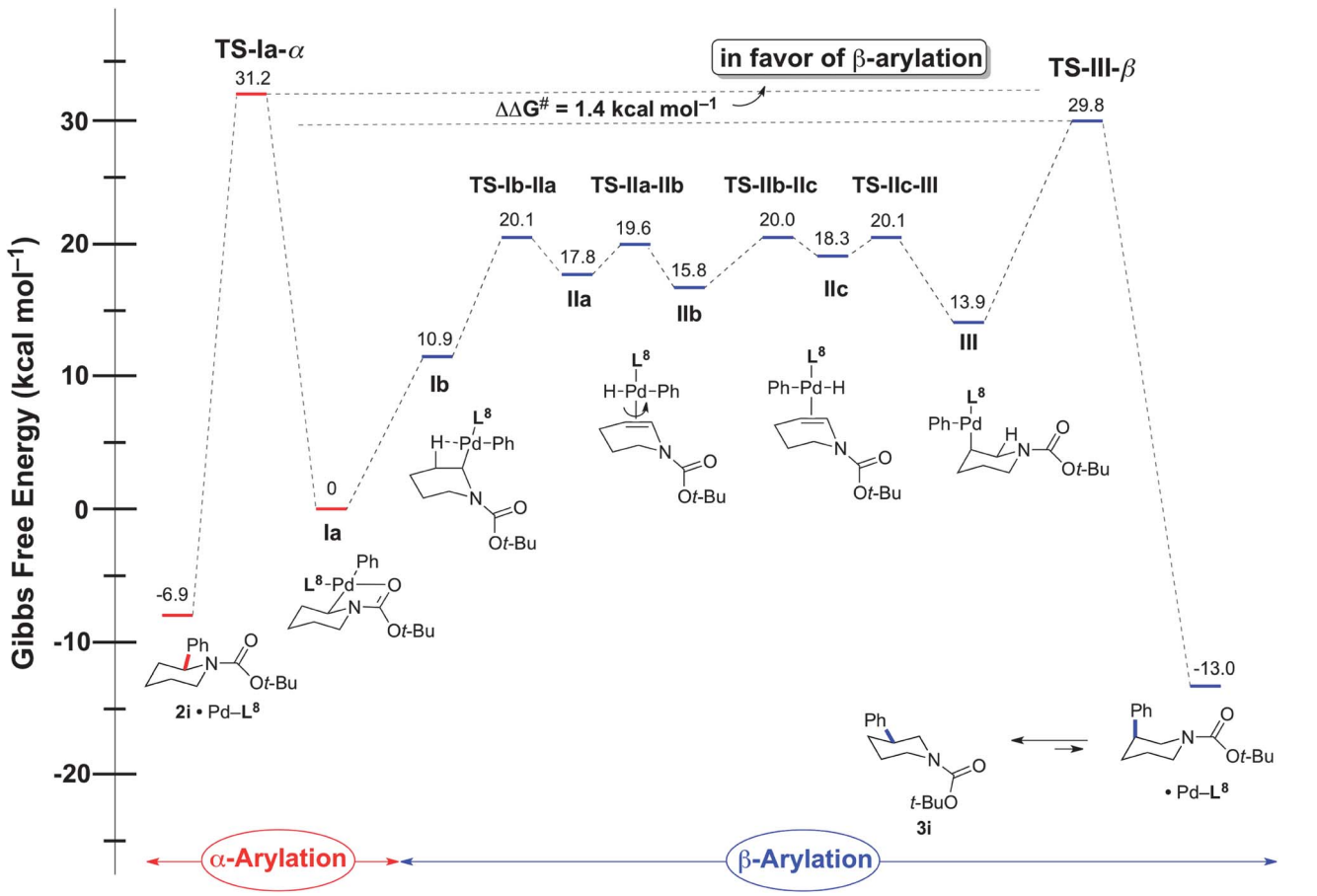


Fig. 2 Comparison of the energy profiles for the α- and β-arylation pathways from complex **Ia** with **L^8** as the ligand.

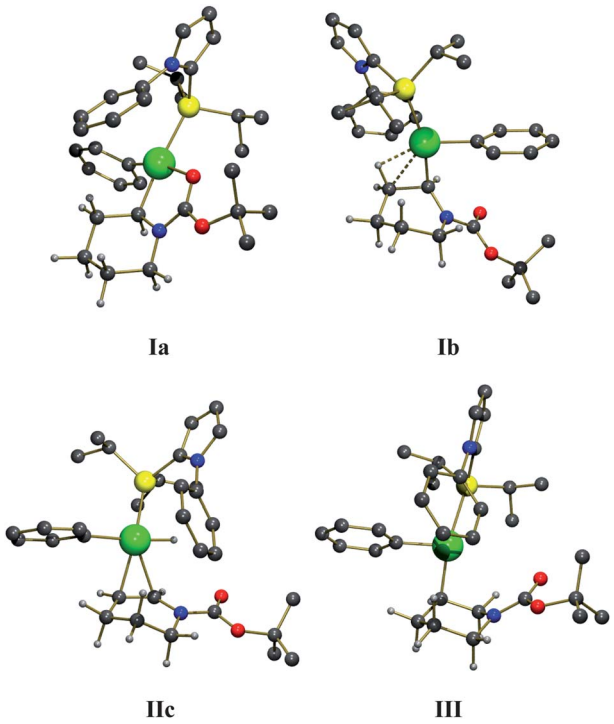


Fig. 3 Selected intermediates in the α- (**Ia**) and β-arylation (**Ib**, **IIc** and **III**) pathways. Only H atoms of the piperidine ring are shown for clarity.

put the phenyl group in the thermodynamically favored equatorial position (Fig. 2). The latter conformation was indeed found to be more stable by 3.2 kcal mol^{-1} than the former, in line with the above X-ray structure of **3i** (Scheme 2).

From these calculations, the highest points in the α- and β-arylation pathways are **TS-Ia-α** and **TS-III-β**, respectively (Fig. 2), and therefore the C–C reductive eliminations are selectivity-determining. Moreover, **TS-Ia-α** is 1.4 kcal mol^{-1} higher than **TS-III-β**, and although intermediate **Ia** is more stable than **Ib** by 10.9 kcal mol^{-1}, the β-arylated product is the kinetically favored product by virtue of the Curtin–Hammett principle. One should point out that the highest point in the β-arylation pathway is the Ar–C_β reductive elimination in the present case, whereas it was found to be the insertion of the olefin into the Pd–H bond with the formation of the Pd–C_β bond

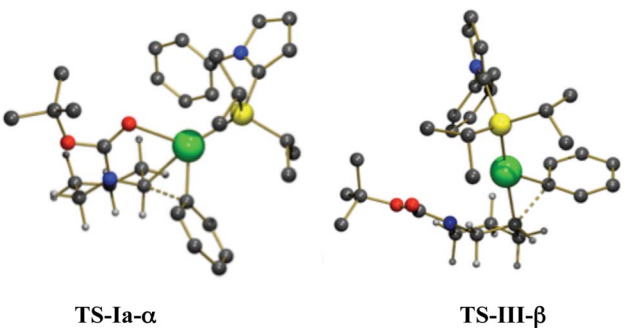


Fig. 4 Transition states for the reductive elimination step in the α- (**TS-Ia-α**) and β-arylation (**TS-III-β**) pathways. Only H atoms of the piperidine ring are shown for clarity.

Table 2 Comparison of calculated and experimental α/β-arylation selectivities in the reaction of 2-zincated Boc-piperidine with bromobenzene

Entry	Ligand	$\Delta G^{\#a}_{\alpha}$	$\Delta G^{\#a}_{\beta}$	$\Delta\Delta G^{\#}_{calcd}{}^{b}$	α/β_{calcd}	$\alpha/\beta_{exp}{}^{c}$
1	$\mathbf{L^8}$	31.1	29.6	−1.5	9 : 91	10 : 90
2	$\mathbf{L^7}$	30.5	30.2	−0.3	39 : 61	20 : 80
3	$\mathbf{L^1}$	26.3	26.3	0.0	50 : 50	50 : 50
4	$\mathbf{L^2}$	23.5	24.4	0.9	80 : 20	97 : 3

[a] Calculated values (kcal mol^{-1}) at 333 K, expressed relative to intermediate **Ia**. [b] $\Delta\Delta G^{\#} = \Delta G^{\#}_{\beta} - \Delta G^{\#}_{\alpha}$. A negative value indicates that the β-arylated product is kinetically preferred. [c] Experimental ratios (333 K), determined from ^{1}H NMR analysis of the crude mixture. The latter differ only slightly from those obtained with *p*-trifluoromethylbromobenzene (see Table 1).

in the β-arylation of ester enolates.[9b] A possible explanation could be that both the α and the β carbons in Boc-piperidine are secondary, while in the ester case the α carbon was tertiary and the β carbon primary, thereby reducing the activation energy for the Ar–C_β reductive elimination.

Finally, as the nature of the ligand proved to be crucial with regard to the α/β selectivity, we computed the activation barriers of the two rate-limiting steps, *i.e.* $\Delta G^{\#}_{\alpha}$ (**TS-Ia-α**) and $\Delta G^{\#}_{\beta}$ (**TS-III-β**), with selected ligands (Table 2).[18] The trend observed experimentally for the competition between α- and β-arylation was qualitatively well reproduced by the calculations ($|\Delta\Delta G^{\#}_{calcd} - \Delta\Delta G^{\#}_{exp}| \leq 1.3$ kcal mol^{-1}). In particular, imidazole- and pyrrole-based ligands $\mathbf{L^7}$–$\mathbf{L^8}$ (entries 1–2) give opposite selectivities compared to DavePhos $\mathbf{L^1}$ and SPhos $\mathbf{L^2}$ (entries 3–4), as observed experimentally. In addition, the comparison of $\Delta G^{\#}_{\alpha}$ and $\Delta G^{\#}_{\beta}$ values indicates that more flexible and less sterically hindered ligands such as $\mathbf{L^7}$ and $\mathbf{L^8}$ disfavor the reductive elimination at the less crowded C_β to a lesser extent than at C_α, thus favoring the β-arylated product. Conversely, the more bulky and rigid SPhos ligand ($\mathbf{L^2}$) favors reductive elimination to a higher extent at the more sterically hindered C_α compared to C_β.[19]

Conclusions

In conclusion, we have reported a general palladium-catalyzed β-arylation of Boc-piperidines, leading to a variety of valuable 3-arylpiperidines in a regioselective and highly diastereoselective manner. The β- *vs.* α-arylation selectivity was essentially controlled by the ligand, with flexible biarylphosphines providing the desired β-arylated products whereas more rigid biarylphosphines furnished the more classical α-arylated products. The computed (DFT) reaction mechanism indicated that the reductive elimination steps leading to the α- and β-arylated products are selectivity-determining, and the experimental trend obtained with different ligands was well reproduced by the calculations. The extension of these results and mechanistic data to other synthetically relevant systems will be reported in due course.

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