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Amination with Pd–NHC Complexes: Rate and Computational Studies Involving Substituted Aniline Substrates

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Abstract: The amination of aryl chlorides with various aniline derivatives using the N-heterocyclic carbene-based Pd complexes Pd-PEPPSI-IPr and Pd-PEPPSI-IPent (PEPPSI = pyridine, enhanced precatalyst, preparation, stabilization, and initiation; IPr = diisopropylphenylimidazolium derivative; IPent =diisopentylphenylimidazolium derivative) has been studied. Rate studies have shown a reliance on the aryl chloride to be electron poor, although oxidative addition is not rate limiting. Anilines couple best when they are electron rich, which would seem to discount deprotonation of the intermediate metal ammonium complex as being rate limiting in favour of reductive elimination. In previous studies with secondary amines using PEPPSI complexes, deprotonation was proposed to

Keywords: amination • carbene ligands • catalysis • computational chemistry • palladium be the slow step in the cycle. These experimental findings relating to mechanism were corroborated by computation. Pd-PEPPSI-IPr and the more hindered Pd-PEPPSI-IPent catalysts were used to couple deactivated aryl chlorides with electron poor anilines; while the IPr catalysis was sluggish, the IPent catalyst performed extremely well, again showing the high reactivity of this broadly useful catalyst.

Introduction

Recently we addressed the impact of the electronic properties of the oxidative-addition partner (e.g., Ar-X) on the observed rate of Pd-catalysed amination using N-heterocyclic carbene (NHC) ligands.^[1-3] In the amination catalytic cycle, the metal centre changes its electronic nature from being nucleophilic during oxidative addition (OA), to being electrophilic during amine coordination/deprotonation (Dep) and reductive elimination (RE). As N-heterocyclic carbenes are strong sigma donors,^[4] oxidative addition is seldom a problem and it is generally now believed to be amine coordination and/or deprotonation that is/are rate limiting in amination (or transmetallation in analogous organometallic cross-coupling such as the Negishi reaction).^[5] Consistent with this, we demonstrated that electron-rich aryl halides, once added to Pd, suppress the amination cycle by discouraging amine coordination to the metal and/or subsequent deprotonation of the aryl palladium amide complex. Further, we showed that the Pd-PEPPSI-IPent NHC catalyst (5; PEPPSI = pyridine, enhanced precatalyst, preparation, stabilization, and initiation; IPent = diisopentylphenylimidazoli-

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[b] Dr. R. D. J. Froese um; see Table 1)^[6,7] was suitably electron poor at Pd to still be able to negotiate these steps, while the more electronrich (relatively) Pd-PEPPSI-IPr derivative (4; IPr=diisopropylphenylimidazolium) could not.^[1]

Not unlike the catalyst's metal centre that must walk an electronic tightrope to allow electronically divergent steps to occur, so must the amine. To coordinate Pd, the amine must be electron rich, and yet if it is too basic the pK_a of the aryl palladium amide complex intermediate rises, disfavouring deprotonation; this is especially troublesome when desirable mild bases such as carbonate are used. Herein we investigate how the electronics of the amine interplay with those of the metal centre of Pd–NHC complexes in the pursuit of one catalyst that will have very wide substrate tolerance and high reactivity.

Results and Discussion

Rate studies: Perhaps the most suitable compound family to study the effect of varying amine basicity is aniline.^[9] If we compare the pK_a of a typical secondary amine such as morpholine (~35) with aniline (~25), we would expect aniline to retard coordination to Pd. However, once coordinated, the intrinsic electron-poor nature of aniline, relative to alkyl amines, should dramatically improve deprotonation. Thus, the use of substituted anilines provides a possibility to differentiate amine coordination from deprotonation. Further, this should provide further information on the electronic properties of the Pd centre in the IPr derivative **4** versus the IPent derivative **5**, where one would predict the latter to



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demonstrate higher reactivity on the basis of the extent of positive charge on the metal centre following oxidative addition.

To begin, we varied the electronic properties of the oxidative addition partner to see how the reactivity of unsubstituted aniline compares with that of a typical secondary amine (Table 1, entries 6–10). As for morpholine, Pd-

Table 1. Yield of amination reactions varying both the aryl chloride (1) and aniline (2) for both Pd-PEPPSI-IPr (4) and Pd-PEPPSI-IPent (5).



1 (1 equiv)

R¹ 2 (1.5 equiv)



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Entry	R	\mathbb{R}^1	Product	Yield ^[a] using 4	Yield ^[a] using 5	
1	NO_2	OCH ₃	3a	90	96	
2	CN	OCH ₃	3b	87	91	
3	Н	OCH ₃	3c	61	99	
4	CH_3	OCH ₃	3 d	17	95	
5	OCH ₃	OCH ₃	3e	0	96	
6	NO ₂	Н	3 f	97	90	
7	CN	Н	3g	79	89	
8	Н	Н	3h	29	93	
9	CH_3	Н	3i	26	92	
10	OCH ₃	Н	3c	0	92	
11	NO_2	CN	3ј	2	96 ^[b]	
12	CN	CN	3k	0	75 ^[b]	
13	Н	CN	3g	0	93	
14	CH_3	CN	31	0	86	
15	OCH ₃	CN	3b	0	49	
16	OCH ₃	CN	3b	0	70 ^[c]	
17	CH ₃	CO ₂ Me	3 m	0	86	
18	OCH ₃	CO ₂ Me	3n	0	79	

[a] Yields are determined on isolated product following silica gel flash chromatography; reactions were performed in duplicate. [b] Significant problems in product isolation were encountered due to the high insolubility of compounds 3j and 3k. [c] 3.0 Equivalents of KtOBu were used instead of Cs₂CO₃.

PEPPSI-IPr displayed a strong reliance that **1** be decorated with electron-withdrawing substituents, while Pd-PEPPSI-IPent possessed sufficient intrinsic reactivity to provide excellent conversion of all aryl chlorides after 24 h. When the rates of these same five transformations were monitored for the IPr derivative **4** (Figure 1 a), it was found that a similar set of curves were produced with aniline as were obtained for morpholine.^[1] Analysis of the kinetic data was complicated by the presence of induction periods that varied with differently substituted aryl chlorides; nevertheless, we endeavoured to obtain initial rates (see Table 2) and these were used to construct the Hammett ρ plot (Figure 1 c). The positive ρ value (2.1) established that groups that withdraw



Figure 1. Comparative rates of amination of various chloroarenes with aniline using a) Pd-PEPPSI-IPr (4) and b) Pd-PEPPSI-IPent (5). c) Hammett plot for amination of various substituted chlorobenzenes with aniline using catalysts 4 and 5.

electron density from the Pd centre strongly increase the rate, whereas electron donors slow the reaction. While the maximum rates for the same five aryl halides were similar with morpholine, with aniline the rates showed a substantial dependence on the substituents, as illustrated by the linear ρ plot (Figure 1 c). The substituent effect for the Pd-PEPPSI-

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Table 2.	Initial rates,	d[P]/dt,	for product	formation	in percent	conversion
per hour	for Pd-PEP	PSI-IPr	(4) and Pd-F	PEPPSI-IP	ent (5).	

-							
<i>p</i> -Substituent on aryl chloride or aniline	Varying s in aryl ch	ubstituents lloride ^[a]	Varying substituents in aniline ^[b]				
	IPr (4)	IPent (5)	IPent (5)				
p-OCH ₃	-	2.18	148.0				
p-CH ₃	0.27	3.93	83.2				
<i>р</i> -Н	1.17	5.11	35.5				
p-CN	29.3	80.8	-				
p-NO ₂	81.1	150.0	-				
p-COOMe	-	-	35.5				
p-COMe	-	-	27.5				

[a] Aryl chlorides (varied) 1 M; aniline (*p*-H) 1.5 M. [b] Aryl chloride (chlorobenzene) 0.1 M; anilines (varied) 0.15 M.

IPent catalyzed reaction was smaller but still appreciable (ρ value 1.8) showing that for both catalysts there is a buildup in electron density at the reaction centre in the rate-determining transition state.

To gain additional mechanistic insight, the electronic character of the aniline (Table 1, entries 1-5 and 11-16 and Figure 2) was also varied by using a variety of *p*-substituents and this provided important information concerning the rate-limiting step of the amination cycle employing NHCbased Pd catalysts. With the strongly electron-donating p-OCH₃ substituent (Table 1, entries 1-5), Pd-PEPPSI-IPent showed a slight improvement to near quantitative conversion over all aryl chlorides, whereas Pd-PEPPSI-IPr saw no significant change in yield (Table 1, entries 6-10 vs. 1-5) except when R = H. However, when the electron-withdrawing p-CN substituent was used, significant differences were seen, in particular for the IPr derivative (Table 1, entries 11-15); regardless of the oxidative addition partner, no amination occurred at all with the IPr catalyst. However, with the IPent catalyst the reaction still proceeded quite well although the effects of an electron-poor aniline became exposed when the chloroarene (1) was electron rich (Table 1 entries 11-15). For example, if the oxidative addition partner is fixed as chloroanisole and one looks at entries 5 and 10 in Table 1 for which the aniline is relatively electron rich, the yields are excellent; a noticeable reduction in yield is observed for the electron-poor aniline in Table 1, entry 15. Of course, this is still quite a remarkable result, as this is one of the worst possible electronic pairings for this transformation and speaks well for the high reactivity of Pd-PEPPSI-IPent for amination.

A study of the rates of reactions of substituted anilines with chlorobenzene provided the Hammett plot in Figure 2c. Despite some scatter in the data points, it is clear that the ρ -value is negative (ca. -0.8), indicating that electron density flows away from the aniline in the rate-determining step. If the deprotonation step is rate determining then electron-withdrawing substituents in *both* the aryl chloride and in the aniline should lead to faster reactions, that is, both ρ -values should be positive with the value associated with the anilines being larger. This is not consistent with the experimental data. The substituent effects are more consistent with reductive elimination being rate determining, as



Figure 2. Comparative rates of amination of chlorobenzene with various substituted anilines using a) Pd-PEPPSI-IPr (4) and b) Pd-PEPPSI-IPent (5). c) Hammett plot for amination of chlorobenzene with various *para*-substituted anilines using Pd-PEPPSI-IPent (5).

previously reported in the formation of diarylamines by reductive elimination from 1,1-bis(diphenylphosphino)ferrocene-ligated aryl palladium amido complexes.^[8]

A study to determine the order of the reactants provided further mechanistic insight into NHC-Pd-cataysed amination involving substituted anilines. The reaction was zero order in aryl chloride, confirming that oxidative addition is fast and not rate-determining for these reactive Pd-NHC cata-

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lysts with their relatively electron-rich metal centres. The reaction rate showed a first-order dependence on the concentration of aniline, implicating it in the rate-determining step. Similarly, the reaction clearly showed a first dependence on the amount of the cesium carbonate base (present as a finely divided solid).

Computational studies: The catalytic cycle for amination was modeled by using density functional theory at the B3LYP level^[9] with the LANL2TZ(f) basis set on $Pd^{[10]}$ and 6-31G*^[11] on the remaining atoms.^[12] Computationally it is difficult to study the deprotonation step using cesium carbonate and we have examined it qualitatively by addition of KOtBu leading to the elimination of KCl and HOtBu. This

provides a thermodynamic assessment of the deprotonation step for different combinations of aryl chlorides, anilines and catalysts. Our goal was to see if the calculations could predict the experimental trends in varying the aryl chloride, varying the aniline, and varying the catalyst from the IPr derivative to the IPent derivative.

Details of the potential energy surfaces are provided in Table 3 and Table 4. The lower parts of these tables are of particular interest as the experimental data indicate that aniline binding and deprotonation may both be kinetically important. As shown in these calculations and also in the experiments, oxidative addition is not rate limiting. Starting with oxidative addition product **11** (see Scheme 1 for structures), formation of the aniline adduct **12** is exothermic and

Table 3. DFT enthalpies (kcalmol⁻¹) relative to compound **8**, Pd⁰Ln, using Pd-PEPPSI-IPr.^[a]

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	Ar-NO ₂		Ar-Cl	N	Ar-H			Ar-Me	Ar-OMe		e			
9	-21.5		-20.4	1	-18.4				-18.0	-18.6				
10	-10.3	-9.6				-6.7					-6.4	-6.2		
11	-34.8		-34.3	3		-31.4					-31.1	-30.8		
Ar-An	NO ₂ /OMe	CN/CN	CN/H	CN/OMe	H/CN	H/CO ₂ Me	H/COMe	H/H	H/Me	H/OMe	Me/OMe	OMe/CN	OMe/H	OMe/OMe
12	-53.5	-49.4	-51.5	-52.8	-46.6	-46.6	-46.3	-48.0	-48.9	-49.0	-48.7	-46.2	-47.5	-48.7
13	-45.8	-46.1	-43.9	-44.4	-43.3	-41.9	-42.4	-39.9	-40.5	-40.0	-40.9	-43.2	-39.3	-40.1
14	-32.7	-30.9	-30.7	-31.1	-26.7	-25.9	-26.1	-25.4	-25.4	-25.8	-25.3	-25.5	-24.1	-24.6
15	-58.2	-51.8	-53.3	-56.2	-51.5	-52.0	-51.5	-53.4	-53.3	-53.0	-54.2	-51.9	-52.4	-53.1
16	-41.6	-37.1	-39.3	-40.5	-35.9	-36.1	-36.1	-36.5	-36.7	-37.1	-36.7	-35.6	-35.6	-35.9
$9 \rightarrow 10$	11.2	10.8	10.8	10.8	11.7	11.7	11.7	11.7	11.7	11.7	11.6	12.4	12.4	12.4
$11 \rightarrow 13$	-11.0	-11.8	-9.6	-10.1	-11.9	-10.5	-11.0	-8.5	-9.1	-8.6	-9.8	-12.4	-8.5	-9.3
$13 \rightarrow 14$	13.1	15.2	13.2	13.3	16.6	16.0	16.3	14.5	15.1	14.2	15.6	17.7	15.2	15.5
$11 \rightarrow 12$	-18.7	-15.1	-17.2	-18.5	-15.2	-15.2	-14.9	-16.6	-17.5	-17.6	-17.6	-15.4	-16.7	-17.9
$11 \rightarrow 14$	2.1	3.4	3.6	3.2	4.7	5.5	5.3	6.0	6.0	5.6	5.8	5.3	6.7	6.2
$12 \rightarrow 13$	7.7	3.3	7.6	8.4	3.3	4.7	3.9	8.1	8.4	9.0	7.8	3.0	8.2	8.6
$12\!\rightarrow\!\!14$	20.8	18.5	20.8	21.7	19.9	20.7	20.2	22.6	23.5	23.2	23.4	20.7	23.4	24.1
11 → 12 +	-5.6	0.1	-4.0	0.1	1.4	0.8	1.4	-2.1	-2.4	-3.4	-2.0	2.3	-1.5	-2.4
13 → 14														

[a] Enthalpies of common species on the potential energy surface include 6 ($-24.4 \text{ kcal mol}^{-1}$), 7 ($-11.2 \text{ kcal mol}^{-1}$) and 8 ($0.0 \text{ kcal mol}^{-1}$). See Table 1 and Scheme 1 for the structures.

Table 4. DFT enthalpies (kcalmol⁻¹) relative to compound 8, Pd⁰Ln, using Pd-PEPPSI-IPent.^[a]

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	Ar-NO ₂		Ar-Cl	N	Ar-H			Ar-Me		Ar-OM	e			
9	-22.0		-20.9)	-18.9					-17.5	-18.6			
10	-10.4		-9.7		-6.7					-6.4	-6.2			
11	-32.2		-31.7	7	-28.4				-28.0	-27.8				
Ar-An	NO ₂ /OMe	CN/CN	CN/H	CN/OMe	H/CN	H/CO ₂ Me	H/COMe	H/H	H/Me	H/OMe	Me/OMe	OMe/CN	OMe/H	OMe/OMe
12	-52.9	-48.9	-51.1	-52.4	-46.2	-46.2	-46.3	-47.6	-48.0	-48.6	-48.3	-45.9	-47.2	-48.2
13	-45.5	-46.6	-44.3	-44.7	-43.7	-42.2	-42.3	-40.5	-40.3	-41.2	-40.7	-43.4	-39.9	-40.5
14	-33.3	-31.3	-30.9	-31.4	-27.1	-26.0	-26.1	-25.4	-25.6	-26.1	-25.5	-25.9	-24.2	-24.8
15	-57.8	-52.0	-55.6	-57.7	-50.1	-51.6	-52.1	-52.9	-53.9	-54.0	-53.7	-51.3	-51.4	-54.0
16	-41.6	-37.1	-39.3	-40.5	-35.9	-36.1	-36.1	-36.5	-36.7	-37.1	-36.7	-35.6	-35.6	-35.9
$9\rightarrow10$	11.6	11.2	11.2	11.2	12.2	12.2	12.2	12.2	12.2	12.2	11.1	12.4	12.4	12.4
$11 \rightarrow 13$	-13.3	-14.9	-12.6	-13.0	-15.3	-13.8	-13.9	-12.1	-11.9	-12.8	-12.7	-15.5	-12.1	-12.6
$13 \rightarrow 14$	12.2	15.3	13.4	13.3	16.6	16.2	16.2	15.1	14.7	15.1	15.2	17.5	15.7	15.7
$11 \rightarrow 12$	-20.7	-17.2	-19.4	-20.7	-17.8	-17.8	-17.9	-19.2	-19.6	-20.2	-20.3	-18.1	-19.4	-20.4
$11 \rightarrow 14$	-1.1	0.4	0.8	0.3	1.3	2.4	2.3	3.0	2.8	2.3	2.5	1.9	3.6	3.0
$12 \rightarrow 13$	7.4	2.3	6.8	7.7	2.5	4.0	4.0	7.1	7.7	7.4	7.6	2.5	7.3	7.7
$12 \rightarrow 14$	19.6	17.6	20.2	21.0	19.1	20.2	20.2	22.2	22.4	22.5	22.8	20.0	23.0	23.4
$11 \rightarrow 12 + $	-8.5	-1.9	-6.0	-7.4	-1.2	-1.6	-1.7	-4.1	-4.9	-5.1	-5.1	-0.6	-3.7	-4.7
$13 \rightarrow 14$														

[a] Enthalpies of common species on the potential energy surface include 6 ($-24.4 \text{ kcalmol}^{-1}$), 7 ($-16.0 \text{ kcalmol}^{-1}$) and 8 (0.0 kcalmol^{-1}). See Table 1 and Scheme 1 for the structures.

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Scheme 1. The proposed mechanism for the coupling of aryl chlorides with aniline (OA = oxidative addition, Dep = deprotonation, RE = reductive elimination).

probably without barrier. The deprotonation step $(12 \rightarrow 13,$ as shown in Scheme 1^[13]) is endothermic, with electron-withdrawing groups in both rings facilitating the reaction. Effects are calculated to be much more pronounced for substituents in the aniline (e.g., for the IPr derivative: CN 3.3, H 8.1, OMe 9.0 kcalmol⁻¹) than in the aryl chloride (e.g., for the IPr derivative: CN 7.6, H 8.1, OMe 8.2 kcalmol⁻¹), as anticipated due to the different proximities of the substituents to the NH₂ group undergoing deprotonation. On all surfaces, structures 12 and 13 lie below 11, while 14, the transition state to reductive elimination, is consistently higher than 11. Furthermore, for any combination of aniline and aryl chloride the enthalpy differences $11 \rightarrow 14$ are always smaller for the Pd-PEPPSI-IPent-catalysed reactions than for the corresponding Pd-PEPPSI-IPr-catalysed ones, suggesting faster reactions for the former.

The energy barriers for $\mathbf{11} \rightarrow \mathbf{14}$ (in kcalmol⁻¹) as a function of the substituent in the aryl chloride for any fixed aniline are always in the order CN < H < OMe; for example, for the parent aniline the barriers are 3.6 for CN, 6.0 for H, and 6.7 for OMe. The most extensive set of data is for the *p*-OMe-substituted anilines for which the barriers for the IPr catalyst are 2.1 for NO₂, 3.2 for CN, 5.6 for H, 5.8 for Me, and 6.2 for OMe. Using these barriers ($\mathbf{11} \rightarrow \mathbf{14}$) as a predictor of relative rates for the aryl chlorides gives the order of reactivity to be NO₂ > CN > H > Me > OMe, the same order as observed experimentally.

The data in Tables 3 and 4 also allow us to study the effect of varying the substituent in the aniline with one particular aryl chloride. The barriers show a much smaller dependence on the substituent in the aniline than was calculat-

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ed for the aryl chlorides. For the reaction of the parent aryl chloride (i.e., chlorobenzene) catalyzed by the IPr derivative, the calculated barriers for $11 \rightarrow 14$ are CN 4.7, CO₂Me 5.5, COMe 5.3, H 6.0, Me 6.0 and OMe 5.6, a range of only 1.3 kcalmol⁻¹. If these barriers determine the relative rates, then the reactivities would all be similar (as indicated in Table 4).

Experimentally, the reaction is first order in aniline and base; thus, the rate-limiting step is most likely the process of aniline binding (11 \rightarrow 12), deprotonation (12 \rightarrow 13), and reductive elimination (13 \rightarrow 14). This process, 11 \rightarrow 14, accurately predicts that the IPent catalyst is more reactive than the IPr catalyst and correctly predicts the order of reactivity of the aryl chloride as CN > H > OMe. However, $11 \rightarrow 14$ does not discern the small differences in the aniline substituents. One can accurately estimate the reactivity of the aniline by disregarding the deprotonation term and using the $(11 \rightarrow 12) + (13 \rightarrow 14)$ term (final entry in Tables 3 and 4). It may be that the simple deprotonation model used is not sufficient. It should be pointed out that this energetic parameter also predicts that the IPent catalyst is faster than the IPr catalyst and predicts the correct order of reactivity of the aryl chlorides.

Reaction scope studies: The scope of aniline-based amination was investigated by using the IPent catalyst 5 and these runs were compared directly with those with the IPr catalyst 4 to see how much 'value added' there is using this bulky, and presumed-to-be more reactive catalyst. Table 5 also includes some of the reactions outlined in Table 1 for comparison sake and completeness. Our rate studies have clearly shown a negative effect on catalyst performance when the oxidative addition partner is electron rich; electron-deficient aniline derivatives also slow the rate. Thus, to show maximally the differences in catalytic ability, we focused largely on examples that have electron-rich aryl chlorides and electron-poor anilines. In every single case, the IPent catalyst out-performed the IPr catalyst and in most situations the IPr catalyst either had no turnovers or very few. Additionally, substrates possessing various levels of steric hindrance (e.g. 18, 19, 20 and 21) were also investigated and again there was a significant improvement in yield using the IPent catalyst.

Conclusion

In this study, the NHC-based catalyst Pd-PEPPSI-IPent was examined in the coupling of aniline derivatives with aryl chlorides and compared head-to-head with Pd-PEPPSI-IPr. In rate studies, electron-withdrawing groups on the aryl chloride accelerated the rate, whereas electron-withdrawing groups on the aniline made the reaction slower. While the former result is consistent with deprotonation being rate-determining, the latter one is not. Because the groups on aniline are directly conjugated with the aniline proton, and can therefore play a more direct role in deprotonation than the CHEMISTRY

Table 5. Scope study of amination reaction with challenging substrates using Pd-PEPPSI-IPr (4) and Pd-PEPPSI-IPent (5).



[[]a] Conditions: Cs_2CO_3 with DME at 80 °C. [b] Conditions: Cs_2CO_3 with toluene at 110 °C.

aryl chloride substituents can, this suggests that deprotonation is not problematic for aniline-based substrates. That electron-donating groups on the aniline increase the rate, while electron-withdrawing groups on the aryl chloride also increase the rate is more consistent with reductive elimination being rate limiting. This was not the case for the coupling of secondary alkyl amines using NHC catalysts where deprotonation was clearly the slow step.^[1]

The IPent ligand is clearly far more reactive in the coupling of aniline derivatives than the IPr ligand, as it was for secondary alkyl amines, despite the appearance that the rate-determining step is different for the two transformations. The IPent catalyst effectively couples electron-rich aryl chlorides with electron-poor anilines, while the IPr catalyst is essentially inactive. Further, sterically challenging substrates appear to pose no concern for IPent.

DFT calculations were performed and supported the lower barrier for oxidative addition compared to the latter steps. While experiments predicted a reaction dependent on aniline and base, the computed energy differences predicted more facile reactions only if the reductive elimination was also included. Computed energy differences were found that correctly predicted the order of reactivity of the aryl chloride substituents, the aniline substituents, and the IPr versus IPent catalysts.

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