Cation-π Interactions in the Benzylic Arylation of Toluenes with Bimetallic Catalysts

Sheng-Chun Sha, Sergei Tcyrulnikov, Minyan Li, Bowen Hu, Yue Fu, Marisa C. Kozlowski* and Patrick J. Walsh*.

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States.

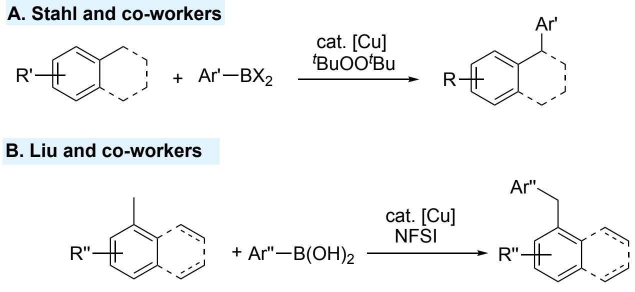
ABSTRACT A method to directly arylate toluene derivatives with aryl bromides to generate diarylmethanes, which are important building blocks in drug discovery, is described. In this method, $KN(SiMe_3)_2$ in combination with a (NIXANTPHOS)Pd catalyst accomplished the deprotonative activation of toluene derivatives to permit cross-coupling with aryl bromides. Good to excellent yields are obtained with a range of electron-rich to neutral aryl bromides. Both electron-rich and electron-poor toluene derivatives are well tolerated, and even 2-chlorotoluene performs well, providing a platform for introduction of additional functionalization. This discovery hinges on the use of a main group metal to activate toluene for deprotonation by means of a cation-π interaction, which is secured by a bimetallic K(NIXANTPHOS)Pd assembly. Mechanistic and computational studies support acidification of toluene derivatives by the K^+–cation- π interaction, which may prove pertinent in the development of other, new reaction systems.

INTRODUCTION

Aromatic hydrocarbons are inexpensive and abundant components of petroleum distillates and have been employed as solvents and reagents on laboratory and industrial scales. They are common starting materials for the preparation of more functionalized and higher value small molecules with applications in synthesis, materials science, and pharmaceutical chemistry.[1,2] Inspired by the challenge of conversion of simple aromatic hydrocarbons into valuable synthetic building blocks, chemists have focused on transition metal promoted C–H functionalizations of aromatic hydrocarbons.

Among catalysts that activate C–H bonds, several different modes of C–H bond cleavage have been documented.[3] Most common are direct oxidative addition of C–H bonds and concerted metallation deprotonation processes.[4-10] These catalysts can be difficult to optimize, because the demands on the catalyst are quite stringent. Furthermore, the arene substrates usually possess multiple types of C–H bonds, giving rise to selectivity problems. Both reactivity and selectivity issues can be addressed by outfitting substrates with directing groups that bear Lewis basic centers to bind to the catalyst and position it in the proximity of the C–H bond of interest.[11-14]

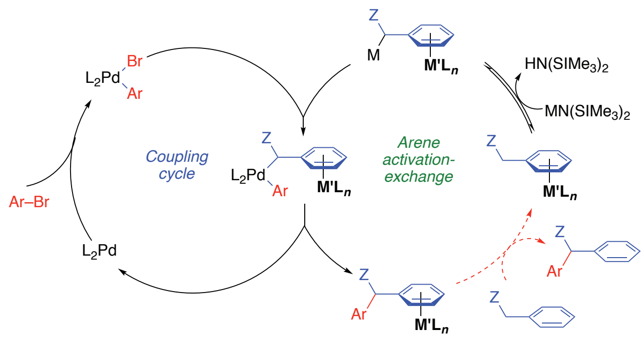
Alternatively, several groups have taken advantage of the decreased bond strength of benzylic C–H bonds over aromatic C–H bonds to achieve selective activation of toluene derivatives via benzylic radical intermediates. Most relevant to this investigation, the groups of Stahl[15] and Liu[16] have developed mild methods for the copper catalyzed arylation of toluene derivatives with arylboronic acids to prepare diarylmethanes (Scheme 1). Toluene derivatives have also been successfully functionalized at the benzylic position via catalytic dehydrogenative cross-coupling methods.[7,8]



Scheme 1. Copper catalyzed activation of toluenes.

We are interested in alternative strategies to selectively arylate weakly acidic (pK_a 25–35) benzylic C–H bonds of arenes and heteroarenes.[17-23] Our strategy relies on reversible deprotonation of the C–H bonds of the benzylic pronucleophile in the presence of the catalyst, which then arylates the substrate. A limitation of this approach is that some benzylic C–H bonds, such as those in toluene, have such high pK_a values (~43 for toluene in DMSO[24]) that appreciable deprotonation in the presence of a transition metal catalyst is difficult. To circumvent this drawback, we sought to increase the acidity of the benzylic C–H, thus facilitating deprotonation. Coordination of arenes to transition metals in an η^6-fashion renders the benzylic C–H bonds more acidic.[3] Based on this idea, we developed the palladium catalyzed arylation of activated toluene derivatives (η^6-C_6H_5–CH_2Z)$Cr(CO)_3$ [Z = H, Ph, OR, NR_2, Scheme 1, M' = $Cr(CO_3)$],[25] including an enantioselective version (Z = NR_2).[26] This strategy was also successful in allylic substitution reactions with toluene derivatives activated with $Cr(CO_3)$.[27,28] While these reactions were successful, they required generation of a stoichiometric, stable metal arene adduct. The ultimate goal, however, is to develop a dual catalytic cycle wherein the arene activating metal, M' (Scheme 2), functions catalytically by exchanging from the product to a new starting arene. Reactions incorporating this concept have proven challenging,[29-32] despite the great potential impact of this strategy.

Scheme 2. Ideal Dual Catalytic Cycle for Toluene Activation



In studies with bimetallic catalysts based on van Leeuwen's NIXANTPHOS[33,34] (Figure 1A) some clues toward achieving this goal were discovered. Namely, we observed under basic conditions the ligand's N–H (pK_a ~22)[24] is deprotonated and there is a main group metal (Li, Na, K) associated with the ligand backbone.[18] Furthermore, based on experimental and computational studies, cooperativity between the main group element and transition metal leads to unprecedented reactivity.[18,21,35] Specifically, C3 arylation was observed with 2-benzylfurans using $KN(SiMe_3)_2$, and (NIXANTPHOS)Pd-based catalyst exclusively furnishing the C-3 arylated product with excellent yield (93%, Figure 1B and 1C). Addition of 18-crown-6, which entrains the cation, resulted in a dramatic switch in the selectivity favoring benzylic arylation with exclusion of the C-3 product. Finally changing to $LiN(SiMe_3)_2$ in the presence of 12-crown-4 resulted in selective formation of the benzylic arylation product (91% isolated yield) and none of the C-3 arylation product detected. Thus, near perfect selectivity could be obtained simply by changing the base and additive. The preponderance of the C-3 arylation product was proposed to arise from a cation-π adduct between K^+ and the phenyl of the 2-benzylfuran (Figure 1D).

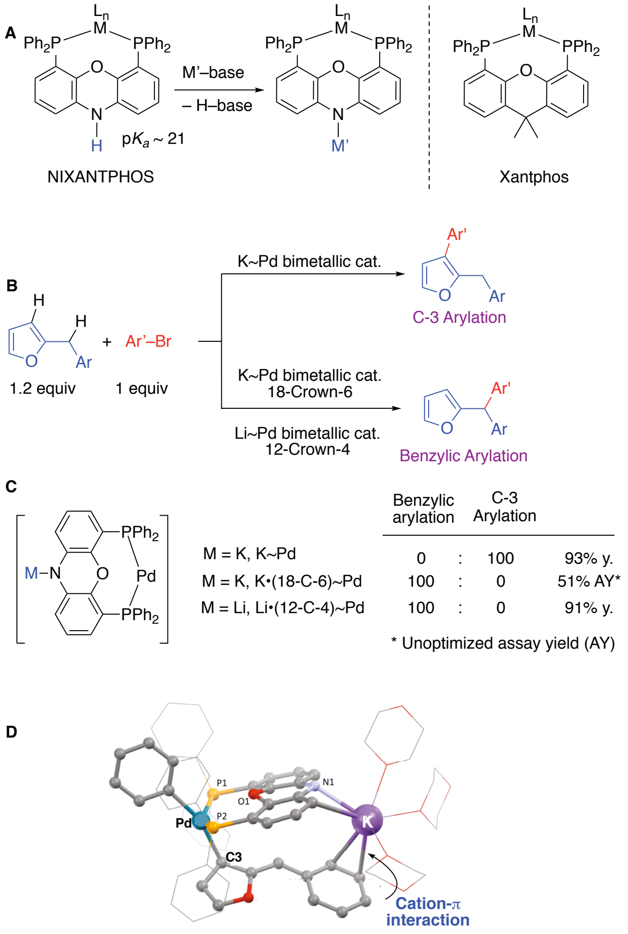
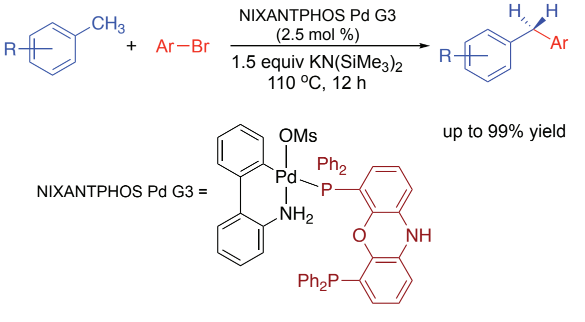


Figure 1. A) Structures of neutral and deprotonated NIXANTPHOS and Xantphos, B–C) Arylation of 2-benzylfuran, cation and crown ether dependent selectivity and D) Calculated cation-π interaction.

Juxtaposing these two projects, we were motivated to investigate cation-π interactions[36-38] of the type in Figure 1 for the deprotonation of toluene derivatives.[39] Herein, we present our findings in the catalytic and selective *mono*arylation of toluene derivatives using $KN(SiMe_3)_2$, aryl bromides, and a K(NIXANTPHOS)Pd catalyst (eq 1). A computational study points to cation-π interactions facilitating the deprotonation/arylation of toluene.



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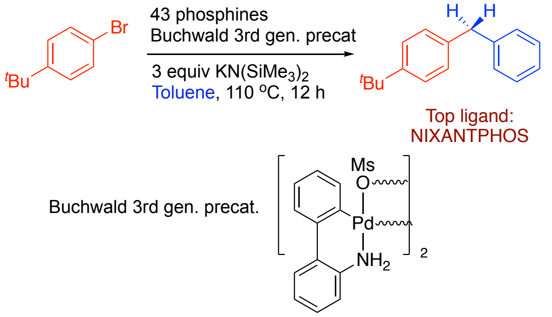
RESULTS AND DISCUSSION

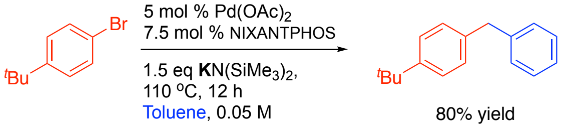
Initial Studies in Toluene Arylation. At the outset of our study, we performed a ligand screen to examine a range of phosphines in the arylation of toluene. Thus, 43 well-known mono- and bidentate phosphines (2 µmol for monodentate ligands and 1 µmol for bidentate ligands) and the Buchwald 3rd-generation palladium precatalyst dimer (0.5 µmol) were combined with 4-*tert*-butylbromobenzene (10 µmol) and $KN(SiMe_3)_2$ (15 µmol) in 100 µL of toluene (eq 2). The reaction mixtures were heated to 110 °C for 12 h before cooling to rt, quenching, addition of biphenyl internal standard, and analysis by HPLC. Of the ligands screened, NIXANTPHOS gave the highest assay yield (AY) of the diphenylmethane derivative by a factor of 2 (see Supporting Information for tabulated ligands and results). Interestingly, XANTPHOS,[34] which is similar in its ligand framework but does not possess the deprotonatable N–H (Figure 1A), and thus cannot form a bimetallic catalyst, did not generate any diphenylmethane product.



(2)

There are several features about this reaction that are remarkable. First, conventional protocols for deprotonation of toluene require much stronger bases than $KN(SiMe_3)_2$, such as super bases.[40-42] The pK_a of the $MN(SiMe_3)_2$ conjugate acid $[HN(SiMe_3)_2$, pK_a 26 in THF][43] is much lower than the generally accepted pK_a value of toluene (43 in DMSO).[24] Second, the selectivity of the catalyst for the conversion of toluene and aryl bromide to diphenylmethane with little or no generation of the triarylmethane is especially notable since the diarylmethane is considerably more acidic (pK_a ~33 in DMSO) than toluene.[24] In addition, a similar Pd(NIXANTPHOS)-derived catalyst is amongst the most efficient for the arylation of diphenylmethane derivatives with aryl bromides or chlorides to give triarylmethanes. Unlike the reaction in eq 2 in toluene solvent, ethereal solvents, like cyclopentyl methyl ether, were employed in the synthesis of triarylmethanes.[17,18,23] Of course, etheral solvents will coordinate to the potassium of the K(NIXANTPHOS)Pd-based catalyst and will impact the ability of the potassium to participate in cooperative interactions with palladium and the substrate.

Our previous findings, discussed in the introduction, led us to attribute the observed unusual reactivity to the effect of the base counterion that is coordinated to the deprotonated NIXANTPHOS ligand. This hypothesis is supported by the acidity of the N–H of the NIXANTPHOS (pK_a ~22, DMSO),[24] which will be deprotonated during the reaction causing the counterion to be associated with the reactive complex. The deprotonated ligand has been characterized crystallographically.[18] To probe this premise, we examined different counterions of $M[N(SiMe_3)_2]$ (M = K, Na, Li) in the present reaction. Arylation of toluene with $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ bases resulted in conversion to the diarylmethane in 80 and 58% assay yields (AY, determined by ^1H NMR of the unpurified reaction mixtures), respectively (eq 3–4). In contrast, use of $LiN(SiMe_3)_2$ led to Buchwald-Hartwig reaction to furnish 4-*tert*-butyl aniline after workup in 67% assay yield (eq 5). No product was observed in control experiments lacking either $Pd(OAc)_2$ or NIXANTPHOS.



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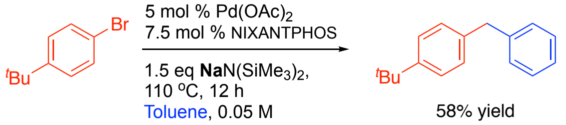

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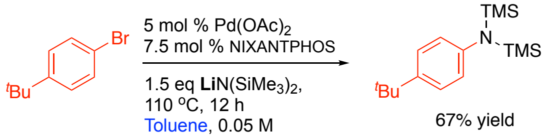
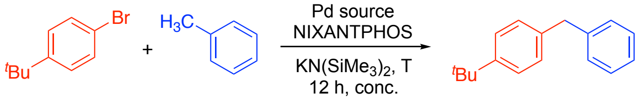


(5)

Further optimization revealed that decreasing the amount of $KN(SiMe_3)_2$ from 3 to 1.5 equiv did not significantly impact the AY (Table 1, entries 1–2). Increasing the concentration from 0.05 M to 0.1 M caused a drop in the yield to 68% (entry 3), decreasing the concentration to 0.033 or 0.025 M resulted in slightly higher AY (entries 4–5). Changing from $Pd(OAc)_2$ to the Buchwald NIXANTPHOS precatalyst had the largest impact, increasing the AY to 95%. Lowering the temperature from 110 to 80 °C under the same conditions was not beneficial (71%, entry 7) and no product was seen at ambient temperature (entry 8). With the precatalyst, further lowering the amount of base to 1.2 equiv resulted in only 65% AY (entry 9). Finally, reducing the loading of the precatalyst to 2.5 and 1.0 mol % resulted in 93 and 75% yield, respectively (entries 10–11).

Table 1. Optimization of Pd-Catalyzed Arylation of Toluene[a]



2a (1 equiv)

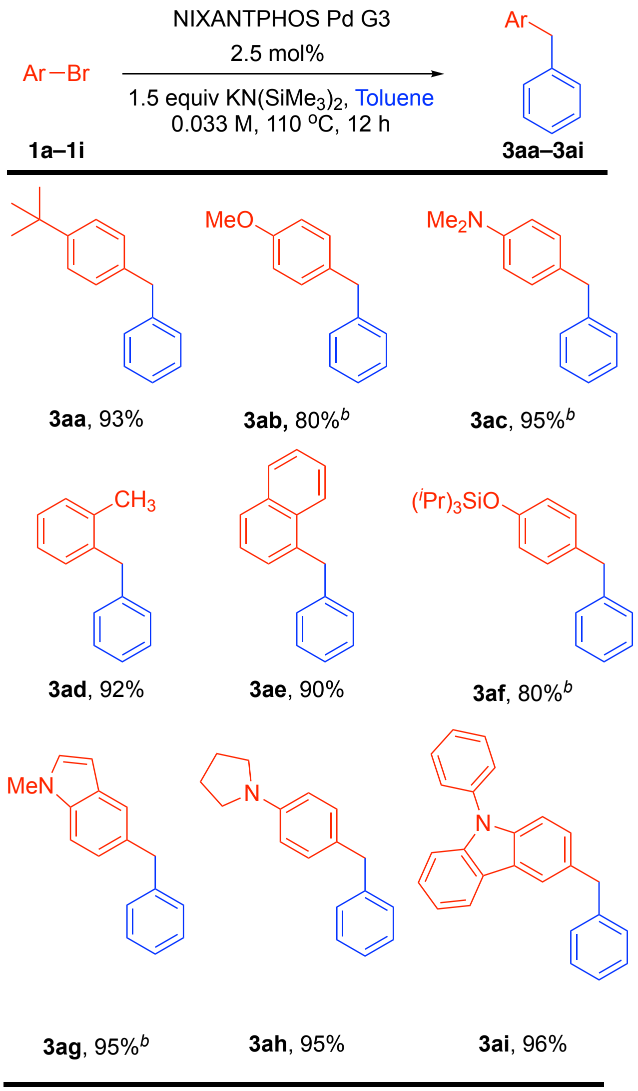
entry	base (equiv)	T (°C)	Pd source	Pd (mol %)/ ligand (mol %)	conc (M)	AY (%)[b]
1	3	110	$Pd(OAc)_2$	5/7.5	0.05	80
2	1.5	110	$Pd(OAc)_2$	5/7.5	0.05	81
3	1.5	110	$Pd(OAc)_2$	5/7.5	0.10	68
4	1.5	110	$Pd(OAc)_2$	5/7.5	0.033	84
5	1.5	110	$Pd(OAc)_2$	5/7.5	0.025	83
6	1.5	110	Pd precat[c]	5	033	95
7	1.5	80	Pd precat[c]	5	033	7
8	1.5	24	Pd precat[c]	5	033	0

9	1.2	110	Pd precat[c]	5	033	65
10	1.5	110	Pd precat[c]	2.5	033	93
11	1.5	110	Pd precat[c]	1	033	75

[a] Reaction conducted on a 0.1 mmol scale [b] Assay yields (AY) determined by ^{1}H NMR spectroscopy of the reaction mixture [c] NIXANTPHOS Pd G3 used.

Substrate Scope. Diarylmethanes are core structures in a number of bioactive compounds, and their synthesis has attracted significant attention.[44,45] In general, they are prepared by cross-coupling with either aryl[46-57] or benzylic[58-63] organometallic reagents, although cross electrophile coupling reactions are growing in importance.[64] Preparation of diarylmethanes from inexpensive feed stocks, such as toluene derivatives, is potentially the most economical. With these considerations in mind, we set out to explore the scope of the arylation of toluene with aryl bromides (Scheme 3). Aryl bromides bearing electron donating groups, such as 4-*tert*-Bu (2.5 mol% Pd), 4-OMe (5 mol% Pd) and 4-*N,N*-dimethyl (5 mol% Pd) were excellent substrates (**3aa**–**3ac**, 80–95% isolated yield). Sterically hindered 2-bromotoluene and 1-bromonaphathalene reacted efficiently at 2.5 mol% catalyst loading, providing product **3ad** and **3ae** in 90–92% yield. The TIPS protected 4-bromophenol underwent arylation at 5 mol% catalyst loading to provide the coupled product **3af** in 80% yield. Indoles are amongst the most common substructures in natural products chemistry. Thus, 5-bromo-1-methyl-1*H*-indole was found to be a good coupling partner, affording the product **3ag** with 5 mol% Pd in 95% yield. Other heterocycle containing substrates, such as 1-(4-bromophenyl)pyrrolidine and 3-bromo-9-phenyl-9*H*-carbazole also furnished monoarylation products in ≥ 95% yield. Unfortunately, aryl bromides bearing electron-withdrawing substituents proved recalcitrant, decomposing under the reaction conditions [including aryl bromides with 2-Cl, 4-F, 4-CN, 3-CF$_3$, 4-CF$_3$, 3,5-(CF$_3$)$_2$]. Furthermore, we did not observe product formation with aryl iodides or triflates bearing electron withdrawing groups. Overall, the protocol proved to be robust with various aryl bromides bearing electronically neutral or electron donating groups undergoing arylation with Pd loadings as low as 2.5%.

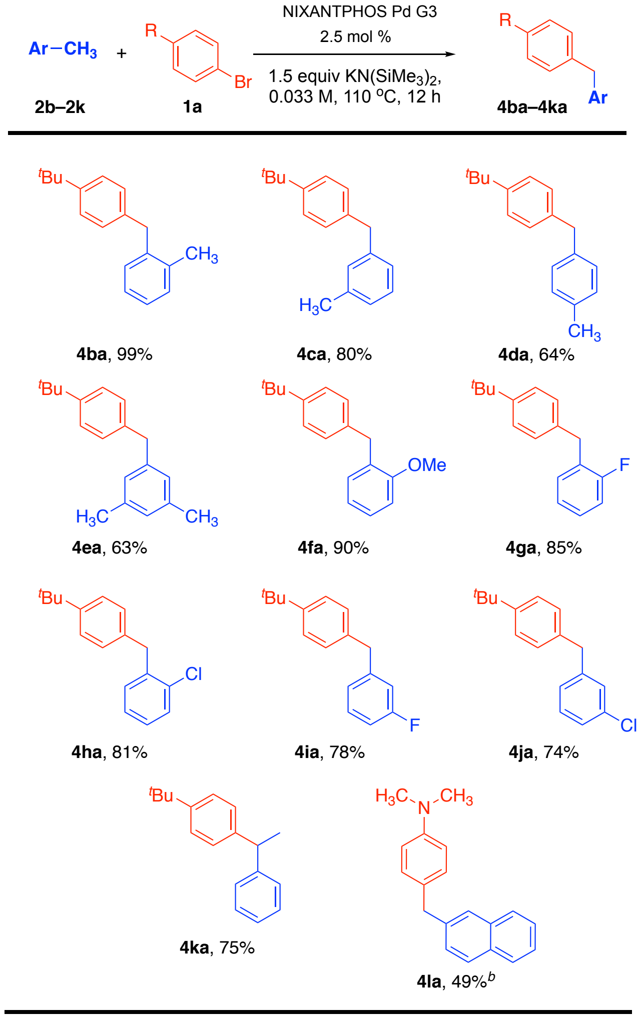
Scheme 3. Arylation of Toluene with Aryl Bromides[a]



[a] Reactions conducted on a 0.1 mmol scale [b] 5 mol % Catalyst was used.

We next set out to examine toluene derivatives as substrates (Scheme 4). The isomeric xylenes exhibited surprisingly different reactivity under the arylation conditions. For example, *ortho*-xylene reacted with 4-*tert*-butyl bromobenzene to form desired product **4ba** in 99% yield. The yield dropped with *meta*-xylene and *para*-xylene (**4ca**, **4da**) to 80 and 64%, respectively. Mesitylene was also subjected to the reaction conditions and formed the arylation product **4ea** in 63% yield. Toluene derivatives with electron donating and electron withdrawing groups at the *ortho*-position gave high yields of 90% (2-OMe, **4fa**), 85% (2-F, **4ga**) and 81% (2-Cl, **4ha**). Interestingly, no byproduct derived from the oxidative addition of 2-chlorotoluene was found, despite the known ability of K(NIXANTPHOS)Pd catalyst to oxidatively add aryl chlorides (in cyclopentyl methyl ether solvent).[18] Ethyl benzene underwent arylation at the benzylic position to give the branched product **4ka** in 75% yield. Interestingly, alkyl substituted benzene derivatives with longer alkyl chains were unreactive, suggesting that there may be a restrictive pocket size in the deprotonation step that is responsible for the high selectivity in the formation of diarylmethanes over triarylmethanes (as discussed later). The coupling between 2-methylnaphthalene, a solid at room temperature (melting range 32–35 °C), and 4-bromo-*N,N*-dimethylaniline provided the product in 49% yield. Overall, common toluene derivatives were well tolerated under the reaction conditions.

Scheme 4. Arylation of Toluene Derivatives[a]

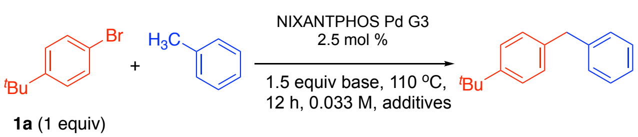


[a] Reactions conducted on a 0.1 mmol scale

[b] Reactions conducted with 1:1 mixture of Buchwald Pd G3 dimer and NIXANTPHOS.

Mechanism. With the optimized reaction conditions in Table 1 (entry 10), we investigated the cation effect with $KN(SiMe_3)_2$ in the presence of crown ether additives. As noted in the Introduction, addition of crown ethers to the arylation of 2-benzyl furans (Figure 1C) with the bimetallic K(NIXANTPHOS)Pd catalyst changed the regioselectivity from C-3 arylation to benzylic arylation (Figure 1B–C). We hypothesized that sequestration of the potassium, as was observed in the solid state structure of K-18-Crown-6•(NIXANTPHOS),[18] inhibited cooperativity between the palladium and potassium centers. In the present case, the arylation of toluene with aryl bromide **1a**, suffered a decrease in yield from 93% without crown ether to 64 and 20% upon addition of 1.5 and 3.0 equiv of 18-crown-6, respectively (Table 2, entries 1–3). Likewise, use of 1.5 and 3.0 equiv of 15-crown-5 caused a decrease in yield from 93% without crown ether to 35 and 10%, respectively (entries 4–5). These results can be interpreted as indirect evidence that the arylation of toluene requires the K(NIXANTPHOS)Pd catalyst to have a potassium that is not exhaustively coordinated.

Table 2. Impact of Additives on the Arylation of Toluene[a]

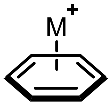


entry	base	additives	equiv	yield (%)[b]
1	$KN(SiMe_3)_2$	–	–	93
2	$KN(SiMe_3)_2$	18-crown-6	1.5	64
3	$KN(SiMe_3)_2$	18-crown-6	3.0	20
4	$KN(SiMe_3)_2$	15-crown-5	1.5	35
5	$KN(SiMe_3)_2$	15-crown-5	3.0	10

[a] Reaction conducted on a 0.1 mmol scale [b] Yield determined by ^1H NMR spectroscopy of the crude reaction mixture.

To gain insight into the catalyst substrate interactions that enable this unusual reactivity of toluene derivatives, we initiated computational studies. In particular, we searched for interactions mediated by NIXANTPHOS that would be absent in unreactive catalyst analogs (i.e. the XANTPHOS derivative). Knowing that π-activation of toluene, as seen with chromium activated toluene derivatives,[25,26] is an important potential modality, computational methods were needed that could capture such interactions. CCSD(T) calculations in combination with large basis set are among the most accurate ab-initio methods available today, but were not tractable for the larger system in hand. Thus, B3LYP/6-31G(d) and M06/6-311+G(d,p)[65] methods were benchmarked against CCSD(T)/6-311++G(2d,2p), which has been reported to reproduce cation-π interaction energies and geometries (Table 3).[37] For lithium, the M06 method was found to be closest to the experimental and CCSD values of the interaction energy, while both B3LYP and M06 gave reasonable agreement for potassium. For geometries, good agreement between the calculated B3LYP and CCSD distance was observed. As such, B3LYP was used for geometry optimization whereas energies were generated with M06 single point calculations on the B3LYP geometries.

Table 3. Benchmarking Computational Methods



Interaction energy, kcal/mol

	Method A	Method B	Method C	exp
M=Li	42.6	34.7	35.8	38.5
M=K	18.8	16.5	16.5	18.0

Equilibrium distance, Å

	A	C
M=Li	1.87	1.90
M=K	2.81	2.90

^{a} A: B3LYP/6-31G(d); B: M06/6-311+G(d,p)//B3LYP/6-31G(d); C: CCSD(T)/6-311++G(2d,2p).

Using these methods, we analyzed the energetics of deprotonation of toluene with $KN(SiMe_3)_2$ base where H_3Si served as a model for Me_3Si (Figure 2). Several possible reaction pathways with different deprotonation modes and a dimeric aggregation state of the base were considered. The latter is essential since $KN(SiMe_3)_2$ exists primarily in the oligomeric form in low polarity solvents.[66] Our findings indicate that coordination of potassium to the π-system of toluene significantly lowers the activation energy for deprotonation. Thus, **TS B** is about 10 kcal/mol lower in energy than **TS A**. In **TS B**, π-activation of toluene is provided internally, where the activating potassium atom is a part of the deprotonating base dimer. External π-coordination by a second base dimer provides similar activation for deprotonation of the toluene (**TS C**). Using the non-simplified base structure (with Me_3Si fragments) and additional coordinated solvent molecules in calculations did not have a significant effect on the relative energies of the transition states (See Supporting Information for details).

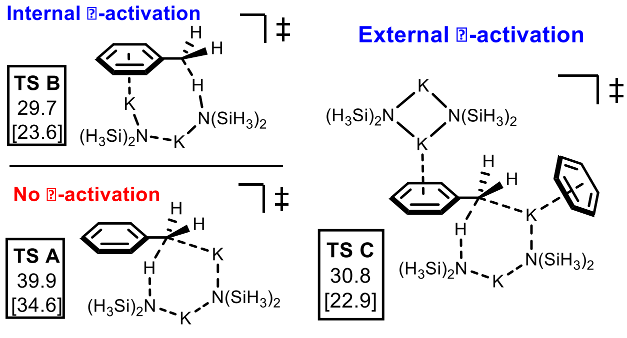


Figure 2. Relative Gibbs free energies and enthalpies (in brackets) for deprotonation of toluene relative to corresponding oligomeric intermediates, kcal/mol. Values calculated with SMD-toluene-M06/6-311+G(d,p)//B3LYP/6-31G(d).

Using the structure of **TS C** as a reference, the energy of the corresponding transition state where toluene is deprotonated by K[NIXANTPHOS] rather than $K[N(SiMe_3)_2]$ was analyzed (Figure 3). Comparison of the energies of transition states **TS 1** and **TS C** indicates substantial stabilization of **TS 1** due to the interaction of ligand with the outer-sphere potassium atom. Both deprotonations are endothermic. However, the corresponding K_{eq} value for deprotonation of toluene via **TS 1** is ~10^{10} times more favorable than that for deprotonation of toluene via **TS C**. Overall, the deprotonation via **TS 1** is faster, and it results in the formation of higher concentration of the tolyl anion. Moreover, the formed tolyl anion is in proximity to the Pd center, allowing immediate transmetallation to occur. These three factors combined, are proposed to substantially accelerate the overall coupling process compared to the case of a noninteracting, "innocent" ligand (e.g. Xantphos).

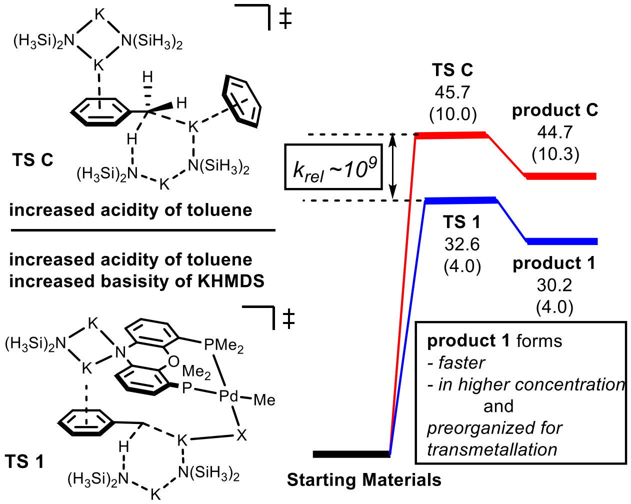


Figure 3. Relative Gibbs free energies and enthalpies (in parenthesis) of ligand-assisted deprotonation of toluene, kcal/mol. Values calculated with SMD-toluene-M06/6-311+G(d,p)/ Pd:LANL2DZ //B3LYP/6-31G(d)/Pd:LANL2DZ relative to the isolated dimeric base units, toluene and deprotonated ligand.

Since the system exists in some highly aggregated state, it is also important to consider the activation energies calculated relative to oligomeric species. Such analysis suggests that while deprotonation with assistance by ligand is facile, the unassisted deprotonation is still possible, albeit slower. This important result suggests that under harsh reaction conditions, silylamide bases are capable of establishing acid-base equilibirum for deprotonation of low-acidic benzylic positions.

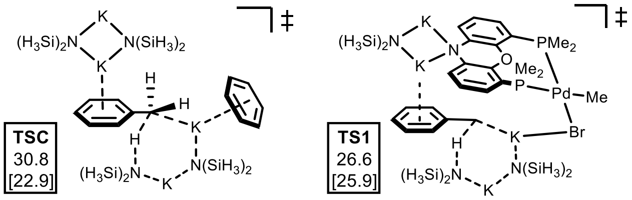
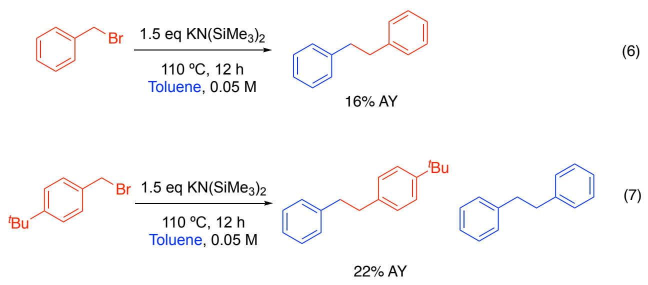


Figure 4. Relative Gibbs free energies and enthalpies (in brackets) of ligand-assisted deprotonation of toluene, kcal/mol. Values calculated with SMD-toluene-M06/6-311+G(d,p)/ Pd,Br: LANL2DZ //B3LYP/6-31G(d)/Pd,Br: LANL2DZ relative to corresponding oligomeric intermediates

This prediction was confirmed experimentally. Under the reaction conditions, tolyl anion can be trapped with benzylbromides, furnishing corresponding product in low yields (Scheme 5, eq 6 and 7, unoptimized conditions).

Scheme 5. Deprotonation Study - Benzylation



Another interesting aspect of this coupling is that aryl chlorides are inert in this transformation (see Scheme 4), which is unexpected as oxidative addition to aryl chlorides occurs with M(NIXANTPHOS)Pd catalysts at room temperature.[18] Since potassium–halogen interactions were identified as mediating the deprotonation of toluene (**TS 1**, Figure 3), the low reactivity of aryl chlorides was hypothesized to arise from a weaker K–Cl interaction in the deprotonation transition state. Examination at the corresponding transition states revealed that activation energies for deprotonation step in both cases are very similar (~32 kcal/mol, Figure 5). However, further analysis revealed a cumulative impact of both the oxidative addition and the deprotonation on the reactivity (Figure 5). Namely, oxidative addition of the chloride is uphill such that the deprotonation transition state moves to an inaccessibly high level on the overall reaction coordinate diagram.

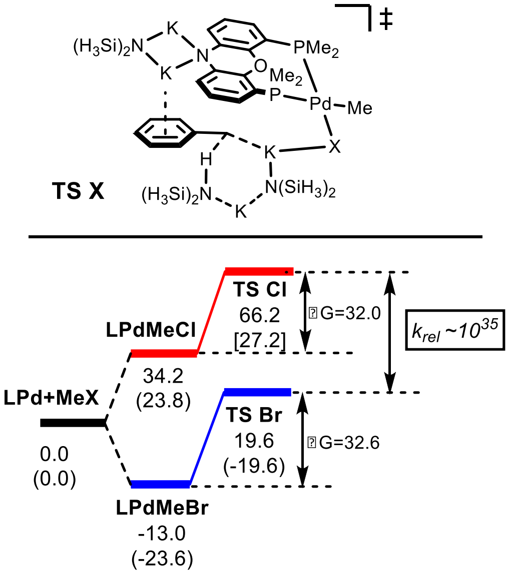


Figure 5. Relative Gibbs free energies and enthalpies (in parenthesis) of deprotonation of toluene in Br and Cl systems, kcal/mol. Values calculated with SMD-toluene-M06/6-311+G(d,p),Pd:LANLl2DZ//B3LYP/6-31G(d),Pd:LANL2DZ

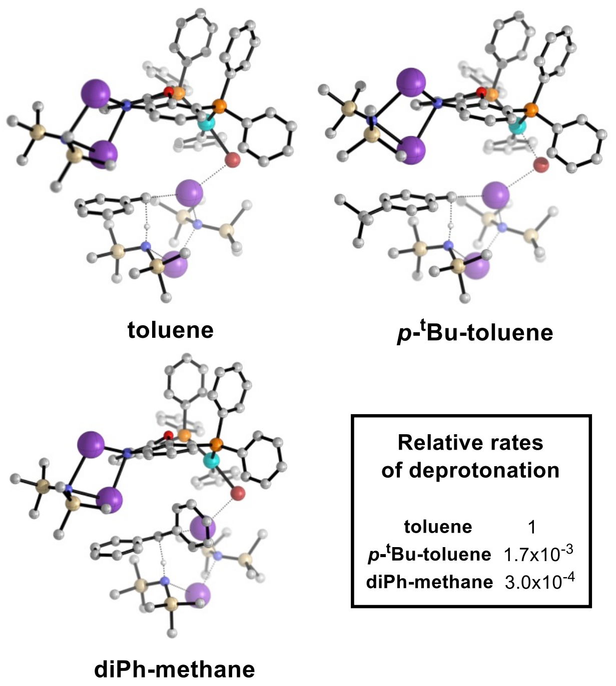


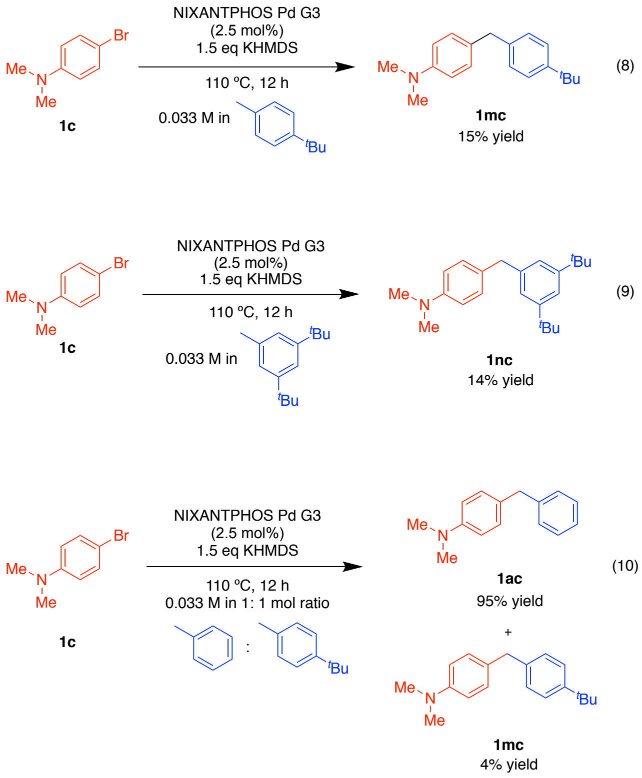
Figure 6. PM6-optimized transition states of deprotonation of toluene derivatives. The relative values of rate constants are provided.

We applied our model to rationalize the observed low reactivity of diphenylmethane. Based on the optimized geometry of **TS 1**, we constructed the corresponding non-truncated transition state and used semi-empirical calculations to optimize it, leaving the deprotonation 6-membered transition state core intact (Figure 6). The calculations indicated that one of the phenyl groups undergoes steric interactions with the NIXANTPHOS ligand raising the energy for deprotonation. This destabilization manifests in a much higher activation energy and correspondingly slower reaction rate (Figure 6).

As a further test of the validity of this model, we decided to analyze its predictive ability. Using the semi-empirical modeling approach described above, we examined the reactivity of the 4-*tert*-butyltoluene in the coupling reaction. Our calculations revealed steric interactions between the *tert*-butyl group and the silyamide groups of the potassium that undergoes π-interaction with the arene of 4-*tert*-butyltoluene. These interactions should significantly lower the rate of the corresponding couplings as indicated by the values of relative rate constants (Figure 6). Subsequent experiments confirmed this prediction. Coupling of 4-*tert*-butyltoluene with 4-bromo *N,N*-dimethylaniline (used to facilitate isolation) resulted in very low conversion under the standard conditions (15% yield, Scheme 6, eq 8). Likewise, 3,5-di-*tert*-butyltoluene exhibited similar reactivity (Scheme 6, eq 9). In a competition experiment, equimolar amounts of toluene and 3,5-di-*tert*-butyltoluene were subjected to the standard coupling conditions with 4-bromo *N,N*-dimethylaniline. The product derived from toluene arylation formed in 95% AY, while the arylation of 3,5-di-*tert*-butyltoluene furnished <5% AY (Scheme 6, eq 10). These results support the computational model that the size of the group(s) positioned far from the reacting methyl group have a significant impact on the deprotonation transition state. Without the proposed model, such results would be surprising given that the *tert*-butyl groups are located distal relative to the methyl substituent undergoing deprotonation.

Based on these models, we hypothesize that the ligand and the oligomeric base fragments create a cavity that allows only certain toluene derivatives to successfully 'dock' and take advantage of the π-activation that facilitates deprotonation.

Scheme 6. Reactivity of the 4-*tert*-butyltoluene



CONCLUDING REMARKS

In summary, we have developed a method to directly arylate toluene derivatives with aryl bromides to generate diarylmethanes, which are important building blocks in drug discovery. Entry to these adducts in good to excellent yields from toluene derivatives, many of which are readily available solvents, has the potential to be more efficient overall since steps to add halide or organometal functionalities are not required. Mechanistic and computational studies point to activation of the toluene by means of η^6-coordination with a main group element. The resultant adduct is more acidic than the parent, such that a base normally ineffective in the deprotonation of toluene derivatives, such as $KN(SiMe_3)_2$, can be employed. This activation is facilitated by the use of alkane rather than ethereal solvents and also takes advantage of a bifunctional ligand that positions the activating main group element in proximity to the palladium catalyst allowing rapid transmetallation after deprotonation. The concepts described herein provide a basis for construction of systems to allow deprotonation and selective reaction in other contexts.

We are currently applying cation-π interactions to activate benzylic C–H' s to other reactions and working to reduce the equivalents of toluene derivatives by examining other reaction solvents.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational procedures and data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Patrick J. Walsh, pwalsh@sas.upenn.edu
Marisa C. Kozlowski, marisa@sas.upenn.edu

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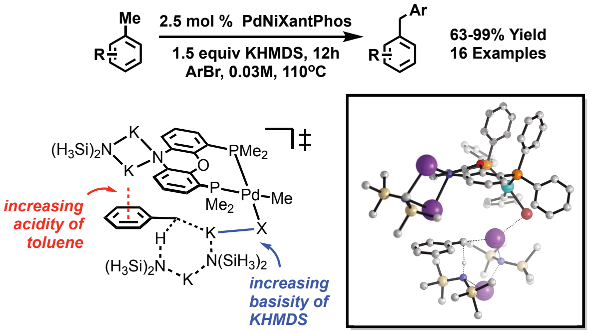
(67) Since the system exists in some highly aggregated state, values of activation entropies relative to isolated materials are not meaningful and may lead to erroneous conclusions. To avoid this entropy contribution overestimation, we also evaluated activation free energies and enthalpies calculated relative to IRC-obtained starting materials. These

calculations also point to the stability of TS C (see Supporting Information for details).

TOC GRAPHIC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R
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1.5 equiv KHMDS, 12h
ArBr, 0.03M, 110ºC
Ar
R
63-99% Yield
16 Examples
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K
K
N
O
PMe2
‡
P
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Pd
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X
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