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Mechanistic Characterization of (Xantphos)Ni(I)-Mediated Alkyl Bromide Activation: Oxidative Addition, Electron Transfer, or Halogen-Atom-Abstraction

Justin B. Diccianni, Joseph Katigbak, Chunhua Hu, and Tianning Diao*

Department of Chemistry, New York University, 100 Washington Square East

New York, NY 10003

E-Mail: diao@nyu.edu

ABSTRACT

Ni(I)-mediated single-electron oxidative activation of alkyl halides has been extensively proposed as a key step in Ni-catalyzed cross-coupling reactions to generate radical intermediates. There are four mechanisms through which this step could take place: oxidative addition, outer-sphere electron transfer, inner-sphere electron transfer, and concerted halogen-atom-abstraction. Despite considerable computational studies, there is no experimental study to evaluate all four pathways for Ni(I)-mediated alkyl radical formation. Herein, we report the isolation of a series of (Xantphos)Ni(I)–Ar complexes that selectively activate alkyl halides over aryl halides to eject radicals and form Ni(II) complexes. This observation allows the application of kinetic studies on the steric, electronic, and solvent effects, in combination with DFT calculations, to systematically assess the four possible pathways. Our data reveal that (Xantphos)Ni(I)-mediated alkyl halide activation proceeds via a concerted halogen-atom-abstraction mechanism. This result corroborates with previous DFT studies on (terpy)Ni(I) and (py)Ni(I)-mediated alkyl radical formation, and contrasts with the outer-sphere electron transfer pathway observed for (PPh₃)₄Ni(0)-mediated aryl halide activation. This case study provides insight into the overall mechanism of Ni-catalyzed cross-coupling reactions and offer a basis for differentiating electrophiles in cross-electrophile coupling reactions.

INTRODUCTION

Recent advances in Ni-catalyzed cross-coupling reactions have found important synthetic applications.¹ Historical² and contemporary³ mechanistic studies provide evidence for singleelectron transfer pathways in the presence of Ni(I) and Ni(III) intermediates.⁴ In the catalytic cycles of Ni-catalyzed cross-coupling and cross-electrophile coupling reactions, alkyl halides are proposed to be activated by Ni(I)-halide or Ni(I)-carbyl intermediates via single-electron oxidative activation to form radicals (Scheme 1).³ Capture of the radical by a Ni(II) intermediate gives rise to a Ni(III) species, which undergo reductive elimination to generate the product. The single-electron oxidative activation step and the formation of radical intermediates with Ni(I) catalysts has created opportunities for stereoconvergent coupling of alkyl halides,^{1h,5} and the combination of Ni catalysis with photoredox catalysis has given access to new reactivity.⁶ In addition, electrophile activation is critical to the chemoselectivity and scope of cross-electrophile coupling reactions, when both aryl and alkyl halides are present and competing for activation.^{1h} Therefore, it is crucial to understand the mechanistic details of single-electron oxidative activation of electrophiles mediated by Ni(I) complexes.

Scheme 1. Possible Mechanisms of Ni-Catalyzed Cross-coupling with Ni(I)-Mediated Radical Formation as Key Steps



How are electrophiles activated by Ni(I) species and how are radicals generated? Several different pathways are possible for Ni(I)-mediated radical formation from aryl and alkyl halides (Scheme 2). Ni(I) complexes have been shown to undergo two-electron oxidative addition with MeI to form Ni(III),⁷ from which a radical could be ejected to generate Ni(II) (*Pathway 1*).⁸ Single electron transfer pathways, either outer-sphere (*Pathway 2*) or inner-sphere, via an encounter complex (*Pathway 3*), have been invoked in a number of mechanistic proposals,^{2,3c} and proceed through electron transfer from Ni(I) to the alkyl/aryl halides to form radical anions, followed by subsequent homolytic C–X bond cleavage to eject a radical.^{2,3} Many of these proposals are primarily based on the study of Ni(0)(PEt₃)₄-mediated aryl halide oxidative addition by Kochi and coworkers, who concluded that aryl radicals are formed via outer-sphere electron transfer as the rate-determining step.^{9,10} A macrocyclic Ni(I) complex, relevant to cofactor F430 of methanogenic bacteria, has been proposed to activate alkyl halides via electron-transfer.¹¹ Finally, recent DFT

calculations on a number of Ni(0)¹² and Ni(I)¹³ systems propose the concerted halogen-atomabstraction pathway (*Pathway 4*). In particular, this pathway was found to be operational in (terpy)Ni–Me,^{13a} (PNP)Ni(CO),^{13b} (pybox)NiMe,^{13c} and (py)NiPh^{3h} mediated alkyl halide activation. Although the halogen-atom-abstraction pathway prevails in recent DFT studies, there is limited experimental support. Moreover, despite the observation of stoichiometric radical formation with several well-defined Ni(I) complexes,^{3e,14} there is no systematic experimental study to evaluate all four pathways for Ni(I)-mediated alkyl radical formation.

Scheme 2. Possible Pathways for Ni-Mediated Radical Formation from Alkyl Halides

1. Oxidative Addition

$$\begin{pmatrix} \mathsf{L} \\ \mathsf{N}^{\mathsf{I}} X + \mathsf{R} - \mathsf{B}^{\mathsf{r}} & \longrightarrow & \begin{pmatrix} \mathsf{L} & \mathsf{B}^{\mathsf{r}} \\ \mathsf{N}^{\mathsf{I}} \mathbb{I}^{\mathsf{I}} - \mathsf{R} & \longrightarrow & \begin{pmatrix} \mathsf{L} \\ \mathsf{N}^{\mathsf{I}} \mathbb{I}^{\mathsf{I}} - \mathsf{R} \\ \mathsf{L}' & \mathsf{X} \end{pmatrix} \xrightarrow{\mathsf{R}^{\mathsf{r}}} \begin{pmatrix} \mathsf{L} \\ \mathsf{N}^{\mathsf{I}} \mathbb{I}^{\mathsf{I}} & \mathsf{R}^{\mathsf{r}} \\ \mathsf{L}' & \mathsf{B}^{\mathsf{r}} \end{pmatrix}$$

2. Outer-Sphere Electron-Transfer

$$\begin{pmatrix} \bar{N}_{I}^{I} \cdot X \\ L' \end{pmatrix} \xrightarrow{} \begin{pmatrix} L & I \\ N \\ L' \end{pmatrix} \xrightarrow{+} R - Br \xrightarrow{+} \begin{pmatrix} L & I \\ N \\ L' \end{pmatrix} \xrightarrow{+} R - Br \xrightarrow{+} \begin{pmatrix} L & I \\ N \\ L' \end{pmatrix} \xrightarrow{+} R \xrightarrow{+}$$

3. Inner-Sphere Electron-Transfer

$$\begin{pmatrix} L \\ Ni^{I-X} \\ L' \end{pmatrix} \stackrel{(}{\longrightarrow} \begin{pmatrix} L \\ Ni^{I'} \\ Br_{R} \end{pmatrix} \stackrel{(}{\longrightarrow} \begin{bmatrix} L \\ Vi^{I'} \\ Br_{R} \end{pmatrix} \stackrel{(}{\longrightarrow} \begin{bmatrix} L \\ Vi^{I'} \\ Br_{R} \end{pmatrix} \stackrel{(}{\longrightarrow} \begin{bmatrix} L \\ Vi^{I'} \\ Br \end{pmatrix} \stackrel{(}{\longrightarrow} H) \stackrel{(}{\longrightarrow} H$$

4. Concerted Halogen Atom Abstraction

$$\begin{pmatrix} \mathsf{L} \\ \mathsf{N}\mathsf{i}^{\mathsf{L}}\mathsf{X} + \mathsf{R}\mathsf{-}\mathsf{B}\mathsf{r} \longrightarrow \left[\begin{pmatrix} \mathsf{L} \\ \mathsf{N}\mathsf{i}^{\mathsf{C}}_{\mathsf{X}} \\ \mathsf{L}^{\mathsf{C}} & \mathsf{B}\mathsf{r}_{\mathsf{C}} \\ \mathsf{B}\mathsf{r}_{\mathsf{C}} & \mathsf{R} \end{bmatrix}^{\ddagger} \longrightarrow \begin{pmatrix} \mathsf{L} \\ \mathsf{N}\mathsf{i}^{\mathsf{H}}_{\mathsf{C}} & \mathsf{R} \\ \mathsf{L}^{\mathsf{C}} & \mathsf{B}\mathsf{r} \\ \mathsf{C}^{\mathsf{C}} & \mathsf{B}\mathsf{r} \\ \mathsf{C}^{\mathsf{C}} & \mathsf{B}\mathsf{r} \end{pmatrix}^{\ddagger} + \mathsf{R}^{\bullet}$$

In light of the prevalent proposals of Ni(I)-mediated single-electron activation of electrophiles to form radicals in catalytic studies,^{2,3} we herein, report the synthesis and isolation of (*t*Bu-Xantphos)Ni(I)-aryl complexes that enabled a detailed study on the mechanism of Ni(I)-mediated alkyl halide activation to form radicals. Although the vast majority of Ni-catalyzed cross-coupling reactions utilize nitrogen-based ligands, the catalytic reactivity of the Ni/Xantphos system shown here and the analogy of the transition states between (Xantphos)Ni-Ar and (terpy)NiMe^{13a} suggest

 that this work could provide insight into the electrophile activation step in cross-electrophile coupling reactions.

RESULTS

Synthesis and Characterization of (tBu-Xantphos)Ni(I) Complexes. The synthesis and isolation of well-defined Ni(I)-carbyl complexes is a significant synthetic challenge due to the radical, and often unstable, nature of Ni(I) complexes.¹⁵ Previous examples use tridentate ligands to stabilize the Ni(I) oxidation state,^{3e, 14a} whereas only a couple of Ni(I)-carbyl molecules have been reported with bidentate ligands.¹⁶ We reasoned that the large bite-angle of Xantphos would help stabilize Ni(I) complexes. After assessing the effect of substituents on Xantphos, we found that tBu-Xantphos stabilizes Ni complexes better than Ph- and iPr-Xantphos, possibly due to the greater steric protection. Our synthesis started with the preparation of (tBu-Xantphos)NiBr₂ 1 by coordination of tBu-Xantphos to Ni(DME)Br₂ (Scheme 3). Reduction of 1 with KC₈ or NaBHEt₃ afforded (tBu-Xantphos)Ni(N₂) 2. The X-ray crystal structure of 2 shows that N₂ is bridging between two Ni centers, and the N≡N distance is 1.144(3) Å: only slightly elongated from that of free N₂ (1.098 Å) (Figure 1A). The use of Cp₂Co as the reductant gave (*t*Bu-Xantphos)NiBr **3** in 96% yield, which could be further reduced to 2 by KC_8 . The X-ray structure of 3 shows a distorted tetrahedral geometry and a relatively long distance between the O-atom of tBu-Xantphos and Ni (2.434 Å), indicating a secondary O-Ni interaction (Figure 1B). Phenylation of **3** with phenyllithium at -35 °C generated (tBu-Xantphos)NiPh 4 in 55% yield. X-ray crystallography established a secondary interaction between the O-atom of tBu-Xantphos and Ni (2.518 Å) and a distorted tetrahedral geometry (Figure 1C). Broken-symmetry DFT calculations using the ORCA package revealed that the unpaired electron density is concentrated on Ni with a small portion delocalized to the Ar group (Figure 2).¹⁷ Arylation of **3** with a variety of aryllithium reagents gave

a series of (*t*Bu-Xantphos)NiAr complexes **5-11**. The analogous paramagnetic ¹H NMR spectra of

5-11, compared to that of 4, suggest that these compounds have similar electronic structures.

Scheme 3. Syntheses of (tBu-Xantphos)Ni Complexes



Figure 1. X-ray structures of **2** (A), **3** (B), and **4** (C) at 50% probability thermal ellipsoids. Hydrogen atoms are omitted and *t*-Bu groups are truncated for clarity. Selected bond lengths (Å) for **2**: $N(1)\equiv N(2) = 1.144(3)$, $Ni(1)\cdots O(1) = 2.518$. Selected bond length (Å) for **3**: $Ni(1)\cdots O(1) = 2.434$. Selected bond lengths (Å) for **4**: Ni(1)-C(1) = 1.9795(14), $Ni(1)\cdots O(1) = 2.518$.



Figure 2. Spin-density plot of 4.

Ni(0) and Ni(I)-Mediated Alkyl and Aryl Halide Activation. The isolation of the welldefined (tBu-Xantphos)Ni(N₂), 2, and (tBu-Xantphos)Ni–Ar complexes, 4-11, allowed us to carry out a study on their reactivity towards activating alkyl and aryl halides. In C₆D₆, addition of one equivalent of bromobenzene or chlorobenzene to 2 led to the immediate formation of the corresponding (tBu-Xantphos)Ni–bromide 3 or chloride 13, respectively, with concomitant formation of biphenyl in high yields (Scheme 4). When (bromomethyl)cyclopropane 12 was added to 2, the reaction rapidly formed (tBu-Xantphos) 3 and 1,7-octadiene in 91% yield.

Scheme 4. Ni(0) Complex 2-Mediated Activation of Alkyl and Aryl halides



Subsequently, we examined the reactivity of the Ni(I) complexes. (tBu-Xantphos)Ni-Br **3** does not react with PhBr, PhI, or 12. Next we probed the reactivity of (tBu-Xantphos)Ni-o-Tol, 6, towards aryl and alkyl halides (Scheme 5). When one equivalent of bromobenzene was introduced into a solution of 6 in C₆D₆, no reaction took place after 48 hours. Heating the reaction resulted in decomposition of 6. Addition of CH_3I to 6, in contrast, led to the formation of the corresponding Ni(II) iodide 14 and ethane. Activation of 12 also took place when treated with 6 to form Ni(II) bromide 15 and 1,7-octadiene in high yields. While the iodide of complex 14 is dissociated from the Ni center to give a square planar geometry, as determined by X-ray crystallography (Figure S20), the bromide from complex 15 is bound to Ni to give a distorted trigonal bipyramidal geometry. When 15 was dissolved in a polar solvent, such as acetone, the bromide dissociated from the Ni center to generate the square planar ionic complex. The reaction rate of 6 with 12 is substantially slower than that of 2 with 12. In-situ NMR spectroscopy allowed us to monitor the reaction time-course (Figure 3), as the paramagnetic resonances of $\mathbf{6}$ could be readily integrated (Figure S37). The time-course fits into a second-order kinetic model using COPASI software to give a second-order rate constant (k) of 0.011 $M^{-1}s^{-1}$.¹⁸ When five equivalents of TEMPO were included in the reaction of 6 with 12, the reaction generated a mixture of 16 and 17 as the organic products.

Scheme 5. Ni(I) Complex 6-Mediated Activation of Alkyl and Aryl halides



Figure 3. Kinetic profile of (*t*Bu-Xantphos)Ni-*o*-Tol **6**-mediated ring-opening dimerization of cyclopropylmethy bromide **12**. Reaction conditions: $[6]_0 = 10 \text{ mM}$, $[12]_0 = 12 \text{ mM}$, $C_6D_6 = 0.65 \text{ mL}$, 25 °C. Internal standard = mesitylene.

Steric Effects on Ni(I)-Mediated Alkyl Bromide Activation. The clean kinetic profile of (*t*Bu-Xantphos)Ni-*o*-Tol **6**-mediated alkyl bromide activation and the formation of the resulting (*t*Bu-Xantphos)Ni(II)(*o*-Tol)(Br) **15** as a well-defined molecule provided us a special opportunity to elucidate the mechanism of this single-electron oxidative activation process. We initiated our study by investigating the steric and electronic effects of Ni(I) complexes and alkyl bromides on the reaction kinetics. We first compared the activation rates of **12** with a series of increasingly bulky aryl ligands on Ni(I) (Table 1). The reaction of (*t*Bu-Xantphos)NiPh **4** with **12** proceeded to form 1,7-octadiene with a second-order rate of 0.033 M⁻¹s⁻¹ at 25 °C. Compared to that of **4**, the

rate of (*t*Bu-Xantphos)Ni-*o*-Tol **6**-mediated activation of **12** decreased threefold and no reaction was observed over 12 h with (*t*Bu-Xantphos)Ni-2,6-dimethylphenyl **5**.

Table 1. Steric Effect of the Ar Group on Ni(I)Ar-Mediated Activation of 12^a

P ONil-Ar +		Br C ₆ D ₆ 25 °C	P ONi ^{II-Br} P Ar	
}– Ar		<i>k</i> x 10 ² (M ⁻¹ s ⁻¹)	yield (%)	_
¥—	4	3.3	85	
¥	6	1.1	85	
	5	no reaction	0	

*a*Reaction conditions: $[Ni(I)]_0 = 10$ mM, $[12]_0 = 20$ mM, $C_6D_6 = 0.65$ mL. Internal standard = mesitylene.

Our examination of the effect of the alkyl halide was carried out using (*t*Bu-Xantphos)Ni(I) complex **8** as the model molecule (Table 2). Reaction of **8** with 1-bromopropane proceeded with a second-order rate constant of $1.4 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ at 25 °C. The reaction with secondary alkyl bromide, 2-bromopropane, was about 4 times faster. The more hindered 4-bromoheptane led to a slightly decreased rate relative to that of 2-bromopropane.

Table 2. Steric Effect of Alkyl Bromides on Ni(I)-Mediated Activation^a



^{*a*}Reaction conditions: $[\mathbf{8}]_0 = 10 \text{ mM}$, $[R-Br]_0 = 20 \text{ mM}$, $C_6D_6 = 0.65 \text{ mL}$. Internal standard = mesitylene. Electronic Effect on Ni(I)-Mediated Alkyl Bromide Activation. The electronic effect of the Ni(I) complexes on the rate of alkyl bromide activation was investigated with a series of parasubstituted (tBu-Xantphos)NiAr complexes, 6-11 (Table 3). The electronic effect of each Ni(I) complex was parameterized by the electrochemical potentials of the oxidation and reduction in THF solutions. The cyclic voltammetry (CV) of 6 showed quasi-reversible oxidation and reduction waves at -2.70 V (vs. Fc/Fc⁺) and -1.51 V (vs. Fc/Fc⁺) with a scan rate of 250 mV/s, which are assigned to Ni(0)/Ni(I) and Ni(I)/Ni(II) transitions, respectively (Figure 4). With a scan rate of 25 mV/s, the quasi-reversible Ni(0)/Ni(I) transition became irreversible. We attribute this phenomenon to a reversible electron transfer event followed by an irreversible chemical reaction (ErCi).¹⁹ The irreversible chemical reaction rate varies as the electronic nature of the Ni(I) complex changes (cf. Figures S23-S28). The time-courses of the (tBu-Xantphos)NiAr, 6-11, mediated single-electron oxidative activations of 12 were monitored by in-situ NMR spectroscopy, and fit into a second-order kinetic model (Figures S1-S7). The E_{1/2} values for the Ni(I)/Ni(II) transition

in Table 3.

Table 3. Electronic Effect on Ni(I)-Mediated Alkyl Bromide Activation



Х	σ_p	E _{1/2} (Ni ^{1/II}) (V vs. Fc ⁺ /Fc)	<i>k</i> x 10 ³ (M ⁻¹ s ⁻¹)
NMe ₂ 7	-0.83	-1.60	27
OMe 8	-0.27	-1.54	14
Me 9	-0.17	-1.59	11

and the second-order rate constants, k, for each (*t*Bu-Xantphos)NiAr complexes are summarized



Figure 4. Cyclic Voltammetry of **6** in THF. [6] = 1 mM, $[Bu_4NPF_6] = 0.4$ M. (A) scan rate = 250 mV/s; (B) scan rate = 25 mV/s. Internal standard = ferrocene.

The second-order rate constants, *k*, for the oxidative addition and dimerization of **12** with various (*t*Bu-Xantphos)NiAr complexes show a linear-free-energy relationship with the Hammett parameters to give a slope (ρ) of -0.72 (Figure 5). The ΔG^{\ddagger} of each reaction was calculated with *k* using the Eyring equation. The ΔG^{0} of each reaction was estimated with the E_{1/2}(Ni(I)/Ni(II)) and the Nernst equation. The ΔG^{\ddagger} varied linearly as a function of ΔG^{0} , with R² of 0.86 and a slope of 0.22 (Figure 6).







Figure 6. Correlation of the activation energy ΔG^{\ddagger} (kJ/mol) versus ΔG^{0} (kJ/mol).

Solvent Effect. The effect of solvent on the rate of **8**-mediated activation of isopropyl bromide was investigated with four solvents (Table 4). Monitoring the reactions in pentane- d_{12} , benzene d_6 , DME- d_{12} (dimethoxyethane), and acetone- d_6 revealed similar rates despite the different dielectric constants of the solvents. The reduced rates in polar solvents could be attributed to their coordination to Ni, hindering the approach of the alkyl bromides. The rate in THF- d_6 decreased dramatically, and a black precipitate was formed from the reaction. We attribute this outlier to a side-pathway triggered by the coordination of THF to **8**. Our attempts to examine the reaction in other polar solvents, including CH₂Cl₂, were complicated by the decomposition of complex **8** in halogenated solvents.

Table 4. Solvent Effect of 8-Mediated Isopropyl Bromide Activation

	Me Br +	k $O \sim NiII - Br$ 22 °C P Ar	+ //
Solvent	Dielectric constant	<i>k</i> x 10 ³ (M ⁻¹ s ⁻¹)	Yield
Pentane- <i>d</i> ₁₂	1.8	5.3	80

Benzene- d_6	2.3	6.0	95
$1,2$ -DME- d_{10}	7.2	1.8	88
THF- d_6	7.5	0.17	85
Acetone- d_6	21	4.3	84

DFT Calculations. Computational studies were performed and compared with the experimental data. We evaluated the four possible pathways (Scheme 2) for the single-electron oxidative activation of EtBr by (tBu-Xantphos)Ni(Ph) 4, using spin-unrestricted formalism of DFT calculations with the B3LYP functional and the LANL2DZ basis/pseudopotential for the nickel centers and 6-31G(d) for the main-group elements, phosphorus, and bromine. The Gibbs free energy change (ΔG) of -15.6 kcal/mol suggests that the single-electron oxidative activation is exergonic. Optimization for the oxidative addition pathway converged to an S_N^2 -type mechanism with an activation energy of 17.0 kcal/mol (Figure S57). The outer-sphere electron transfer mechanism was modeled using the Marcus-Hush theory, and resulted in a high barrier of 82.8 kcal/mol, suggesting an unfavorable pathway. Evaluation of the inner-sphere electron transfer pathway failed to locate a stable encounter intermediate between 4 and EtBr. Calculations for the halogen-abstraction pathway converged to a concerted transition state 18 with an activation energy of 9.91 kcal/mol (Figure 7A). The geometry of the Ni center in 18 is distorted to a square pyramidal geometry with the phenyl group lifted as the bromide approaches Ni, giving a nearly linear geometry for the C(Ph)-Ni-Br-CH₂CH₃ atoms with a Ni---Br---Et angle of 169°. The spin density plot of 18 shows that the unpaired electron density is distributed on Ni and CH_2CH_3 (Figure 7B). Within the context of the halogen-abstraction mechanism, we examined the steric effect of the electrophile on the rate of single-electron oxidative activation. When *i*PrBr was used instead of EtBr, the ΔG of the reaction decreased to -16.3 kcal/mol, while the activation energy decreased to 8.53 kcal/mol. Finally, in order to unravel the lack of reactivity of Ni(I) with any halides, we

calculated the ΔG for phenyl radical generation from PhBr with (*t*Bu-Xantphos)Ni(Ph) **4**. The ΔG of 1.15 kcal/mol suggests that the activation of sp² electrophiles is slightly uphill.



Figure 7. (A) Reaction coordinate for single-electron oxidative activation of EtBr by **4** via concerted halogen-abstraction. Relative Gibbs free energy values were calculated with DFT B3LYP/LANL2DZ/6-31G(d). (B) Spin-density plot of transition state **18**.

Catalytic Reactivity. While the majority of Ni-catalyzed cross-coupling reactions utilize nitrogen-based ligands, phosphine ligands, such as Xantphos, are competent in a number of cross-coupling reactions.²⁰ We explored the catalytic relevance of Xantphos ligands to the cross-coupling of alkyl halides. Kumada coupling of benzyl bromide **19** with PhMgBr benefited from the use of a Ph-Xantphos ligand to afford the cross-coupling product **20** in 60% yield, whereas the reaction without a ligand gave **20** in 24% yield (Scheme 6A). Use of the bulkier *t*Bu-Xantphos afforded **21** in 30% yield, suggesting activation of **19**, but unsuccessful cross-coupling. Unactivated neopentyl iodide underwent cross-coupling with PhMgBr to give **23** in 83% yield,

whereas the reaction with no ligand afforded **23** in 5% yield. Cross-electrophile coupling of **19** with PhI proceeded to generate the desired cross-coupling product **20** in 20% yield with considerable homo-coupling by-products (Scheme 6C). These observations clearly reveal a strong ligand effect on the reactivity and selectivity of the reaction.

Scheme 6. (Xantphos)Ni-Catalyzed Cross-Coupling Reactions

(A) Kumada Coupling of benzyl bromide

	PhMgBr (2 equiv)			
	Br (L)Ni	Br ₂			
	(10 m	<u>∽ ∧</u>		+ ^r ~ + ^	Ar
$0 \sim$	THF, 2	2°C 7	00 FI	• Al II • A	vr ~
(Ar Br)	19		20	21	22
. ,	L	additive		yields (%) ^a	
	none	ZnCl ₂	24	0	0
	<i>t</i> Bu-xantphos	none	trace	30	0
	Ph-xantphos	none	38	0	30
	Ph-xantphos	ZnCl ₂	60	0	15
^a Yields det	ermined by ¹ H N	IMR with r	nesitylene	e as the interna	l standard.
(B) Kumada (Coupling of unac	tivated alk	yl iodide		
	NiB	r ₂ (DME) (10 mol%)		
	+ PhMqBr — Ph-;	kantphos (10 mol%)	→ tBu [^] Ph	
		THF, 22 °C	, 12 h	23	
				83% yield	
				5% (no ligar	nd)
(C) Cross-ele	ctrophile couplir	ng			
19 + Phl.	NiBr ₂ (DME) (Ph-xantphos (10 mol%) 10 mol%)	<u> </u>	22 + Ph_Ph	
	Nal (0.5 equiv), THF, 22 °C	Zn (5 equi , 12 h	v) 20%	31% 35%	

DISCUSSION

The Ni(0) complex (*t*Bu-Xantphos)Ni(N₂) **2** undergoes facile single-electron oxidative activation of aryl and alkyl bromides to form (*t*Bu-Xantphos)NiBr **3** (Scheme 4). This observation is reminiscent of previous studies on (PEt₃)₄Ni(0).⁹ In contrast, Ni(I) complex (*t*Bu-Xantphos)Ni– *o*-Tol **6** selectively activates alkyl halides, but is inactive towards aryl halides (Scheme 5). We attribute the lack of reactivity with aryl bromides to the instability of aryl radicals, which results in a positive ΔG for the reaction, as determined by DFT calculations. This selective activation of alkyl bromides activation over aryl bromides has important implications in controlling selectivity

in cross-electrophile coupling reactions, when both sp² and sp³ electrophiles are present.^{1h} The reaction of (*t*Bu-Xantphos)Ni–*o*-Tol **6** with radical clock **12** forms 1,7-octadiene, indicating a radical-mediated ring opening that precedes the dimerization of the homoallylic radical (Scheme 5). Such radical dimerizations have been extensively observed in catalytic reactions proceeding through radical intermediates.²¹ This assignment is supported by the trapping experiment of the cyclopropylmethyl radical with TEMPO to form **16** and **17**. The ratio of **16** to **17** is dependent on the relative rates of cyclopropylmethyl radical ring-opening and trapping by TEMPO.²²

Four different mechanisms were postulated for the activation of alkyl halides by Ni(I) complexes (Scheme 2), and the results described above provide evidence to distinguish among these possibilities. The slower rate with primary alkyl bromides relative to secondary alkyl bromides (Table 2) rules out the oxidative addition pathway (Scheme 2, *Pathway 1*). This interpretation is consistent with DFT calculations, which show an activation energy of 17.0 kcal/mol for the S_N2 type oxidative addition: substantially higher than that of the halogen abstraction pathway (9.91 kcal/mol). The faster rate of secondary bromide activation, relative to primary bromide activation, is reproduced by DFT calculations on the halogen-atom-abstraction pathway, and can be attributed to the formation of a more stable secondary radical which has a higher driving force compared to the formation of a primary radical.

The steric effect of aryl groups on Ni and the slope of the linear correlation of ΔG^{\ddagger} with ΔG^{0} , according to Marcus theory, provides evidence against an outer-sphere electron transfer pathway (Scheme 2, *Pathway 2*). Increased steric hindrance of the Ni complexes significantly reduced the reaction rate (Table 1), whereas outer-sphere electron transfer rates are unlikely to be subject to steric effects.²³ According to Marcus theory,²⁴ the activation barrier (ΔG^{\ddagger}) of electron transfer would exhibit a linear-free-energy relationship with ΔG^{0} and a slope of 0.5 (eq 1).²⁵ The observed

slope of 0.22 for the correlation of ΔG^{\ddagger} to ΔG^{0} significantly deviates from 0.5 (Figure 6), which is inconsistent with the outer-sphere electron transfer pathway. Corroborating this analysis, DFT calculations on the outer-sphere electron transfer pathway returned a very high activation energy of 82.8 kcal/mol.

 $\Delta G^{\ddagger} = 0.5 \Delta G^0 + \text{constant} \qquad (1)$

The difference between the inner-sphere electron transfer (Scheme 2, *Pathway 3*) and the concerted halogen-atom-abstraction pathways (Scheme 2, *Pathway 4*) mainly rests on whether a caged ionic pair is formed as an intermediate. Polar solvents are expected to accelerate the rates of reactions going through an ionic intermediate.⁹ In this Ni(I)-mediated single-electron oxidative activation, DME and acetone gave slightly slower rates than those in pentane and benzene (Table 4). We attribute the reduced rates with polar solvents to their coordination to Ni, which hinders the approach of the alkyl bromides. This solvent effect is inconsistent with the inner-sphere electron transfer pathway.

Halogen-atom-abstraction is fully supported by experimental and computational data. The high susceptibility of the rate to the steric effect of the Ni complex (Table 1) indicates association of Ni with the alkyl bromide in the rate-determining step. Such a steric effect is corroborated by the faster rate for 2-bromopropane relative to 4-bromoheptane (Table 2). The encounter of the Ni(I) with the alkyl bromide could be viewed as nucleophilic donation of electron density from Ni(I) to the σ^* orbital of the C–Br bond.²⁶ TS **18** is stabilized by delocalizing electrons among three atoms, Ni, Br, and CH₂CH₃, and forming a three-center-three-electron bond (eq 2). The nearly linear geometry of **18**, with a Ni---Br---Et angle of 169°, is reminiscent of TS **24** identified for (terpy)NiMe-mediated activation of iodopropane.^{13a} In contrast, halogen-abstraction by (py)Ni(Ph) was calculated to have a bent TS **25**.^{3h} The activation barriers for **24** and **25** were determined to be

18 and 7.3 kcal/mol, respectively. The barrier of 9.91 kcal/mol for **18** is in between of the two systems. The *trans*-geometry of the aryl group on Ni to the incoming bromide in TS **18** is expected to enhance the electronic effect on the rate. The Hammett correlation of the rates with *para*-substituted Ni-aryl complexes indicates a build-up of partial positive charge on Ni in transition state (TS) **18**. A similar electronic effect has been proposed for **24**.^{13a} The slope of -0.72 is similar to previous reactions going through a concerted mechanism.²⁷ The Marcus dependence of ΔG^{\ddagger} as a function of ΔG^{0} shows an unusually shallow slope of 0.22. A comparable slope has been reported in a C–H oxidation reaction, going through concerted PCET (proton-coupled-electron-transfer).²⁸ While the origin of the moderate slope is unclear in either system, studies to explain it are underway.

$$Ni - Br - CH_2CH_3 \xrightarrow{\parallel 0^+ 0^-} Ni - Br - CH_2CH_3$$
 (2)



SUMMARY

We prepared a series of (*t*Bu-Xantphos)Ni(I)–Ar complexes that selectively activate alkyl halides over aryl halides via single-electron oxidative activation to eject alkyl radicals. Kinetic studies on the steric, electronic, and solvent effects, in combination with DFT calculations, reveal that the single-electron oxidative activation of alkyl halides proceeds via a concerted halogen-atom-abstraction mechanism, in contrast with the previous proposal of outer-sphere electron transfer for Ni(0)-mediated aryl halide activation⁹ and consistent with recent DFT calculations on Ni(I) systems.¹³ Corroborated by the stoichiometric study, Xantphos is shown to promote catalytic cross-coupling of unactivated alkyl halides. The selective reactivity of (Xantphos)Ni(I) toward

alkyl halides, relative to aryl halides, and the elucidation of the mechanism, as a case study, provide insight into the mechanism of Ni-catalyzed cross-coupling reactions. However, whether the mechanism could be generalized remains to be seen, and the insight obtained here should be cautiously applied to other systems.

ASSOCIATED CONTENT

Supporting Information

All experimental procedures, additional figures, details of DFT calculations, NMR spectra, and crystallographic data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

diao@nyu.edu

Notes

The authors declare no competing financial interest.

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