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Combined Theoretical and Experimental Studies of Nickel-Catalyzed Cross-Coupling of Methoxyarenes with Arylboronic Esters via C–O Bond Cleavage

Martin C. Schwarzer,[†] Ryosuke Konno,[†] Takayuki Hojo,[†] Akimichi Ohtsuki,[‡] Keisuke Nakamura,[§] Ayaka Yasutome,[§] Hiroaki Takahashi,[†] Toshiaki Shimasaki,^{‡,¶} Mamoru Tobisu,^{*,‡,§} Naoto Chatani^{*,§} and Seiji Mori^{*,†,#}

[†]Faculty of Science, Ibaraki University, Mito, Ibaraki, 310-8512, Japan

[‡]Center for Atomic and Molecular Technologies, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[§]Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

[#]Institute of Quantum Beam Science, Graduate School of Science and Engineering, Ibaraki University, Mito, Ibaraki 310-8512, Japan

ABSTRACT: Nickel(0)-catalyzed cross-coupling of methoxyarenes through C–O bond activation has been the subject of considerable research because of their favorable features compared with cross-coupling of aryl halides, such as atom economy and efficiency. In 2008, we have reported nickel/PCy₃-catalyzed cross-coupling of methoxyarenes with arylboronic esters, in which addition of a stoichiometric base such as CsF is essential for the reaction to proceed. Recently, we have also found that the scope of the substrate in the Suzuki–Miyaura-type cross-coupling of methoxyarenes can be greatly expanded by using 1,3-dicyclohexylimidazol-2-ylidene (ICy) as the ligand. Interestingly, a stoichiometric amount of external base is not required for the nickel/ICy-catalyzed cross-coupling. To elucidate the mechanism and origin of the effect of external base, density functional theory calculations are conducted. In the nickel/PCy₃-catalyzed reactions, the activation energy for the oxidative addition of the C(aryl)–OMe bond is too high to occur under the catalytic conditions. However, the oxidative addition process becomes energetically feasible when CsF and an arylboronic ester interact with a Ni(PCy₃)₂/methoxyarene fragment to form a quaternary complex. In the nickel/ICy-catalyzed reactions, the oxidative addition of the C(aryl)–OMe bond can proceed more easily without the aid of CsF because the nickel-ligand bonds are stronger and therefore stabilize the transition state. The subsequent transmetalation from an Ar–Ni–OMe intermediate is determined to proceed through a pathway with lower energies than those required for β -hydrogen elimination. The overall driving force of the reaction is the reductive elimination to form the carbon-carbon bond.

INTRODUCTION

Transition metal-catalyzed cross-coupling reactions between aryl halides and organometallic reagents have been recognized as a powerful method for the formation of carbon-carbon bonds.¹ To further improve the utility of cross-coupling methodology, intensive efforts have recently been directed toward the development of catalytic systems that allow the use of inert yet readily available phenol derivatives in place of aryl halides. Studies along this line have revealed that nickel-based catalysts are particularly effective at activating inert phenol derivatives, such as aryl ethers, carboxylates, carbamates and naphthols, which are completely inactive under the conditions used for common palladium-catalyzed cross-coupling reactions.² Despite the considerable progress made in cross-coupling reactions of inert phenol derivatives from the synthetic perspective, their mechanistic aspects largely remain unknown.³ Our interest in the development of nickel-catalyzed cross-coupling of aryl ethers^{4,5} led us to investigate the mechanisms of such reactions; in particular, how the nickel complex cleaves the inert C-O bond.

To date, mechanistic studies of nickel-catalyzed activation of aryl ethers have been reported for four types of reactions.⁶⁻⁹ Wang and Uchiyama have reported a theoretical study on nickel-catalyzed cross-coupling of anisole with phenylmagnesium bromide (Scheme 1a).⁶ They propose that a phenyl nickelate species mediates the C-O bond cleavage via a cyclic transition state (A in Scheme 1a). Gómez-Bengoa and Martin have studied the reductive cleavage of aryl ethers using hydrosilane as a reductant experimentally and theoretically (Scheme 1b).⁷ They demonstrate that the C–O bond cleavage proceeds with the lowest energetic barrier when a silyl-nickel(I) species, rather than nickel(0), mediates the process via a dearomatized intermediate (C in Scheme 1b). Surawatanawong has published a theoretical study on Hartwig's nickel-catalyzed hydrogenolysis⁸ of diphenyl ethers (Scheme 1c).^{9a} In this case, a simple oxidative addition is shown to be possible. Chung and coworkers have also reported a density functional theory (DFT) study on the same transformation.9b They find that excess 'BuOincluded in the reaction mixture facilitates the oxidative addition process by generating an active anionic nickelate species, similar to the complex involved in the Grignard coupling shown in Scheme 1a. Recently, Rueping reported nickel-catalyzed cross-coupling of methoxyarenes with trialkylaluminum (AlR₃) reagents.⁵¹ Their theoretical studies revealed that the use of highly Lewis acidic AlR₃ as nucleophiles considerably lowers the activation barrier for oxidative addition of the C–O bond of aryl ethers by coordination of the ether oxygen atom to an aluminum center (Scheme 1d).

The above theoretical studies indicate that the mechanism involved in the key C–O bond activation process may vary drastically depending on the nature of the nucleophile used. This finding is in sharp contrast to the cross-coupling of aryl halides, in which the mechanism for the activation of Ar–X bonds is oxidative addition with a wide range of nucleophiles. Therefore, it is of great importance to investigate the mechanism of nickel-catalyzed cross-coupling of aryl ether substrates with a series of nucleophiles and clarify the factors that determine the mechanistic pathway for C–O bond activation. We report herein a theoretical study on nickel-catalyzed cross-coupling of aryl ethers with phenylboronic ester (Scheme 1e).¹⁰ As shown in Scheme 1, mechanistic studies on the cross-coupling reactions of aryl ethers with carbon nucleophiles have been limited to two extreme coupling partners: highly nucleophilic ArMgX (Scheme 1a) and highly Lewis acidic AIR₃ (Scheme 1d). Mechanistic insights into this organoboron cross-coupling¹¹ is valuable for the further development of C–O bond activation reactions of aryl ethers using synthetically useful weak nucleophiles.

Scheme 1. Mechanisms for Nickel-Mediated C-O Bond Cleavage of Aryl Ethers Revealed by Computational Studies



COMPUTATIONAL DETAILS

We have performed DFT calculations using the Gaussian 09 program.¹² The BP86-D3^{13,14}density functional, which includes

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dispersion corrections, has been determined suitable by benchmark calculations (see the Supporting Information (SI)). For geometry optimizations and normal coordinate analyses, we have employed the def2-SVP¹⁵ basis set for nickel, the SDD¹⁶ basis set for cesium, and the 6-31G*¹⁷ basis set for the other elements. This combination of double- ζ quality basis sets is denoted as SVBS. Calculations following the intrinsic reaction coordinates (IRC)¹⁸⁻²⁰ from first-order saddle points (transition states) to local minima (reactants, intermediates, and products) has been used to describe the conformation of the reaction pathways; a solid line in the energy profiles denotes these results.

In order to gain a better understanding in the energetics of the reaction, we have performed a series of single-point energy calculations on various density functionals: PBE0,²¹ B3LYP,²² M06L,²³ M06,²³ TPSSh,²⁴ and ωB97X-D.²⁵ For these calculations the more precise def2-TZVP¹⁵ triple-ζ basis set has been used for all atoms. To account for solvent effects, the polarizable continuum model (PCM) with a dielectric constant of 2.3741 (toluene) has been used.^{26,27}

Pure electronic energies, or zero-point energy corrected values are independent of the temperature and do not account for any change in entropy. Thermal corrections to the electronic energies have been estimated at 393.15 K and 1 atm using the normal coordinate analyses at the BP86-D3/SVBS level of theory yielding Gibbs free energies. Translational entropies have also been corrected using the method developed by Whitesides et al. (see SI).²⁸ The discussion of energy barriers is performed within these approximations in order not to neglect temperature dependency and to gain a better understanding of the reaction mechanisms in solution. However, these corrections are based on the gas-phase model and carry an energy penalty as the effects of solvent and pressure on the translational and rotational degrees of freedom are not properly described.²⁹ Reaction energies are often overestimated and a quantitative comparison of barriers in terms of contributions of interacting molecules is not possible. The comparison of relative activation barriers based on complexes that have been validated to lie on one reaction path in qualitative terms is nevertheless possible and reasonable.

We have used 2-methoxynaphthalene **1** as a representative aryl ether substrate^{10a} and 2-phenyl-1,3,2-dioxaborinane **2** as a nucleophile instead of 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane to lower the calculation cost of the study. We have used the PCy₃ conformation determined in the X-ray crystal structure analysis of Ni(PCy₃)₂ coordinated with anthracene.³⁰

Natural Population Analysis (NPA) with the NBO 6.0 program³¹ at the BP86/SVBS level of theory are used to discuss atomic charges, as well as charges from analyses in terms of the quantum theory of atoms in molecules (QTAIM),³² which have been performed with MultiWFN 3.3.8.³³

RESULTS AND DISCUSSION

Experimental Studies. In 2008, we have reported a Ni/PCy₃catalyzed cross-coupling reaction of methoxyarenes with arylboronic esters (Scheme 2a).^{10a} The important features of this reaction are as follows: (1) PCy₃ performs as the only effective ligand among the common series of phosphine ligands. Thus, the use of a simplified model for PCy₃ is not allowed for the subsequent theoretical studies. (2) Addition of excess CsF (4.5 equiv.) is required for this reaction to proceed. No reaction occurred in the absence of CsF. To get some insight into the role of CsF and the fate of the cleaved MeO group, several ¹¹B and ¹⁹F NMR experiments have been conducted. Confirming previous reports,³⁴ 4-CH₃C₆H₄B(pin) forms the corresponding tetraborate species upon treatment with CsF (¹¹B NMR: δ = 7.0 ppm; ¹⁹F NMR: δ = -132 ppm). Spectroscopic analysis of the crude mixture obtained from a Ni/PCy₃-catalyzed reaction of **1** with 4-CH₃C₆H₄B(pin) has revealed that the fluoride adduct of (MeO)B(pin) is present in the reaction mixture (¹¹B NMR: δ = 4.9 ppm; ¹⁹F NMR: δ = -132 ppm).³⁵

In 2014, we have reported that 1,3-dicyclohexylimidazol-2-ylidene (ICy)³⁶ performs as a superior ligand to PCy₃ in nickelcatalyzed cross-coupling through the activation of C–OMe bonds in aryl ethers.^{10c} The use of ICy in place of PCy₃ not only expands the scope of aryl ether substrates in Suzuki–Miyauratype cross-couplings,^{10c} but also broadens the range of nucleophiles that can be coupled with aryl ethers.^{5b-f} Although we have routinely added excess CsF in our initial exploration of the Ni/ICy-catalyzed Suzuki-Miyaura type cross-coupling reactions, we have realized, during the course of our study on a related homocoupling reaction,^{5f} that CsF is not necessary (Scheme 2b).

Scheme 2. Effect of the Ligand and Base on Suzuki-Miyaura Type Reaction of 1: Experimental Results



In our previous studies, we have used ICy generated *in situ* by the reaction of ICy·HCl with NaO'Bu, due to its relatively unstable nature. Since a small amount of unreacted NaO'Bu might be present in the catalytic mixture, it may be non-innocent for this cross-coupling.^{9b} To exclude this possibility, we have examined the nickel-catalyzed cross-coupling of **1** with phenylboronic esters using NaO'Bu-free ICy. The product was formed in a good yield. These results clearly indicate that NaO'Bu functions as a base to abstract the proton from ICy·HCl to generate ICy in the cross-coupling. Therefore, there is no need to consider NaO'Bu for the theoretical studies of the reaction mechanism.

The generality of Ni/ICy-catalyzed cross-coupling under CsF-free conditions needs to be addressed, since we have only examined a single set of substrate/boronic esters (Scheme 2b) in our previous study.^{5f} We have examined the cross-coupling of several different aryl ethers and boronic esters (Table 1). In terms of the scope of the organoboron components, both electron-rich (entry 2) and electron-deficient (entry 3) boronic esters successfully undergo the cross-coupling with 1 under CsF-free conditions. In addition to 1, an anisole derivative (entry 4) and a heteroaromatic substrate (entry 5) can be cross-coupled to form the corresponding biaryl products. These results reveal that the use of ICy enables cross-coupling of a

range of methoxyarenes and arylboronic esters in the absence of CsF. On the basis of these experimental studies and those reported in the literature,^{5f,10} the key mechanistic questions on nickel-catalyzed Suzuki-Miyaura type cross-coupling of methoxyarenes are as follows: (1) what is the mechanism for the cleavage of a C(aryl)-O bond; (2) what is the role of CsF when PCy₃ is used as the ligand; and (3) why is CsF not required when ICy is used as the ligand.

Table 1. Ni/ICy-Catalyzed Cross-Coupling of Methoxyarenes with Arylboronic Esters under CsF-Free Conditions^a



 a Reaction conditions: ArOMe (0.30 mmol), boronic ester (0.45 mmol), Ni(cod)₂ (0.030 mmol), ICy·HCl (0.060 mmol) and NaO'Bu (0.060 mmol) in toluene at 120 °C for 12 h.



Figure 1. Gibbs Free Energy Profile of Nickel-Catalyzed Cross-Coupling of 1 with 2 in the Absence of CsF. Calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

Mechanism for the Ni/PCy₃-Catalyzed Reaction in the Absence of CsF. The Ni/PCy₃-catalyzed cross-coupling of **1** with **2** proceeds efficiently only when more than a stoichiometric amount of CsF is added.^{10a} We have investigated the mechanism of the nickel-catalyzed cross-coupling reaction in the absence of CsF to later clarify the role of CsF in the catalytic cycle by comparing the energies of

related reactive intermediates. The most economic pathway without CsF involves ligand exchange (Ni(cod)₂ to Ni(PCy₃)₂), π -coordination of Ni(PCy₃)₂ to 1,³⁷ oxidative addition of the C–O bond to nickel(0) (O2 to INT-O2), transmetalation with 2 (T2 to INT-T2) and reductive elimination of nickel(II) to form the C–C bond (R2 to INT-R2). While the reaction starts with a bis-phosphine/nickel pathway (NiL₂), the transmetalation is lower in energy

for the mono-phosphine/nickel model (NiL). The final reductive elimination again utilizes a NiL₂ pathway (Figure 1). Gómez-Bengoa and Martin have also reported that the transition state for the oxidative addition of 1 to Ni(PCy₃), calculated with the M06 functional is endergonic.⁷ These results are in sharp contrast to the previous theoretical studies on Ni/PCy₃-catalyzed cross-coupling of other inert phenol derivatives, in which the NiL species is responsible for C–O bond cleavage.^{3a,b,d}

Electron-rich, bulky phosphine ligands are generally effective at promoting oxidative addition and reductive elimination processes.³⁸ However, this nickel-catalyzed cross-coupling reaction of methoxyarenes does not proceed when P'Bu₃ is used instead of PCy₃.^{10a} To clarify this discrepancy, we have examined the oxidative addition mediated by the Ni(P'Bu₃)₂ species analogous to **O2**. One P'Bu₃ ligand dissociates from the nickel center in the transition state because of its greater steric bulk than PCy₃, resulting in a path analogous to **O1**, in which the transition state **TS-P'BuO1** has a relative energy of 141.2 kJ/mol. This makes the reaction pathway energetically less favorable than that mediated by either model using PCy₃ as ligand (see SI for details).

These results indicate that the oxidative addition of the C–OMe bond is better mediated by NiL₂ than by NiL species. The calculated reaction barrier of the oxidative addition by NiL₂ (Figure 1, **O2** to **TS-O2**) is 137.9 kJ/mol, which is higher than that of similar C–O oxidative addition processes to nickel reported in the literature [95.8 kJ/mol for the activation of aryl esters by Ni(PCy₃),^{3a} 56.5 kJ/mol for the activation of aryl esters by Ni(PCy₃)^{3b} and 122.5 kJ/mol for the activation of aryl esters by Ni(dcype)^{3f}]. The high activation energy required for the oxidative addition of a C-OMe bond is not surprising considering its intrinsic inertness compared with C–O bonds in aryl esters and carbamates. We have examined an alternative pathway initiated by the oxidative addition of the C–B bond of phenylboronic ester 2 to nickel(0). However, this reaction only proceeds via the triplet state and the relative energy is substantially higher than that of a C–O bond (TS- $^{3}B2$ 233.5 kJ/mol, see SI for details). Therefore, we conclude that the oxidative addition of the C–O bond is preferred over that of the C–B bond.

The subsequent transmetalation proceeds with a barrier of 93.8 kJ/mol from the *trans*-bis-phosphine species **T3** via a fourmembered transition state **TS-T3**. In the case of the *cis*-bis-PCy₃ ligand coordination to nickel center, one ligand dissociates in the transition state, because of the steric bulk of PCy₃. The alternative pathway for the NiL model proceeds with a barrier of only 9.4 kJ/mol (**T2** to **TS-T2**) and the relative energy is lower than that of the oxidative addition in the NiL₂ model. This result is in accordance with the experimental observation that the cross-coupling reaction does not proceed when bidentate phosphine ligands such as BINAP are used.^{10a}

The final reductive elimination of the (2-naphthyl)(phenyl)nickel(II) complexes proceeds with a small reaction barrier (12.2–17.2 kJ/mol) regardless of the number of phosphines ligated to nickel. However, the relative free energy is much lower for the bis-phosphine pathway (**R2** to **INT-R2**) than for the mono-phosphine pathway (**R1** to **INT-R1**).

The oxidative addition of the C–O bond of **1** possesses the highest barrier (137.9 kJ/mol) during the whole catalytic cycle, which makes this process difficult to occur in the absence of a co-catalyst at this reaction temperature.



Figure 2. Gibbs Free Energy Profile of Nickel-Catalyzed Cross-Coupling of 1 with 2 in the Presence of CsF. Calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

Mechanism of the Ni/PCy₃-Catalyzed Reaction in the Presence of CsF. Based on experimental observations, CsF has been introduced into the reaction model. Pathways where the external base is not stabilized by the boronic ester are higher in energy than those without CsF.³⁹ The adduct $2 \cdot CsF$ is used to elucidate the role of the external base in the catalytic cycle (Figure 2).⁴⁰ The lowest-energy pathway starts with the ligand exchange (Ni(cod)₂ to Ni(PCy₃)₂), continues with the π -coordination of Ni(PCy₃)₂ to 1, oxidative addition of the C–O bond to nickel(0) (O14 to INT-O14), transmetalation with 2 (T11 to INT-T11), and ends with the reductive elimination from nickel(II) (R12 to INT-R12).

The oxidative addition occurs with the 2·CsF located in the second coordination sphere of the bis-phosphine nickel species (O14 to INT-O14). The calculated activation barrier for oxidative addition is 120.4 kJ/mol, which is 17.5 kJ/mol lower than that of the oxidative addition without CsF (137.9 kJ/mol).⁴¹ A mono-phosphine (NiL) pathway for the oxidative addition in the presence of CsF has also been examined, which is again higher in energy than the NiL₂ pathway (Figure 2, O10 to INT2-O10⁴² vs. O14 to INT-O14).

An alternative pathway initiated by the oxidative addition of the C–B bond of phenylboronic ester **2** to nickel(0) has again a transition state with a relative energy which is substantially higher than that for the C–O bond activation. (**B3** 105.6 kJ/mol, see SI for details).

In the subsequent transmetalation the NiL pathway drops below the bis-phosphine pathway analogous to the unassisted mechanism. The four-membered transition state can only accommodate one ligand due to its size, which is evident as in T15 to INT-T15 one PCy3 molecule is only bound via a weak interaction in the second coordination sphere. Paths where two ligands are directly bound to nickel are much higher in energy (see SI). As a stabilizing factor in TS-T11 the fluoride can occupy the empty coordination site, which allows nickel to maintain its 16 electron configuration. The activation energy from O14 to TS-T14 is 125.3 kJ/mol, which is slightly higher than for the initial oxidative addition (O14 to TS-O14: 120.4 kJ/mol), the relative barrier is much smaller (T11 to TS-T11: 70.0 kJ/mol). Estimating thermodynamic corrections for these kind of reactions in solution is challenging because weakly bound complexes tend to be shallow minima on the potential energy surface. The calculation of absolute barriers, especially when treating dissociations, in a harmonic approximation, may lead to large barriers. For this reason we have performed additional calculations on a range of density functional approximations, which will be discussed at a later point in this paper.

The widely accepted role of an external base in the Suzuki– Miyaura cross-coupling reaction is to accelerate transmetalation by generating a metal–alkoxo complex or a tetracoordinated borate species, although the effect of the base is still being discussed.⁴³ Therefore, we have included the latter possibility in our examinations; which is the transmetalation pathway from **INT-O14** with the retention of the F–B interaction. However, CsF is eliminated from the boron atom in the transition state, resulting in the formation of a four-membered transition state **T12** with CsF located in the second coordination sphere. The relative energy of **TS-T12** is higher than that of **TS-T11** by 43.6 kJ/mol, which makes this transmetalation pathway energetically less favorable than the one where CsF coordinates directly to the nickel(II) center. After the transmetalation process, methoxyboronic ester **3** is eliminated with CsF remaining attached to the nickel(II) center, forming **INT-T11**.

The final reductive elimination occurs with the lowest activation barrier, 11.6 kJ/mol, from the bis-phosphine complex **R12** with CsF bound to **3** in the second coordination sphere of nickel(II). The formation of the product complex proceeds with a large energy release from the starting materials, as well as the precursor complex **O14**, and can be considered the driving force of the whole reaction.

In intermediate O14, there is an interaction between the hydrogen atoms of the methoxy group and the fluorine atom, as evidenced by the F-H distances of 2.46 to 2.81 Å (the sum of the van der Waals radii of F and H is 3.21 Å⁴⁴) (Table 2, Figure 4). The cesium atom is located close enough to the carbon atoms of the naphthalene ring and the oxygen atom of the methoxy group to interact with them during the course of oxidative addition. The distance between the cesium atom and carbon atoms of the naphthyl group in O14 is between 4 and 6 Å, indicating a weak interaction.⁴⁵ As the oxidative addition proceeds, the cesium atom and carbon atoms of the naphthalene ring move closer to each other, becoming a formal interaction in TS-O14 (Cs…C distance: 3.6 to 4 Å; sum of the van der Waals radii of Cs and C: 5.13 Å). An analogous interaction is observed in INT-014 as evidenced by the Cs…C distances of around 4 Å. A weak interaction exists between the oxygen atom of the methoxy group and the cesium atom, with a decreasing distance as the oxidative addition proceeds (Cs-O: 3.24 Å in O14 to 3.15 Å in TS-O14 to 3.05 Å in INT-O14; sum of the van der Waals radii of Cs and O is 5.01 Å⁴⁴). These weak interactions have been investigated with an analysis in terms of the quantum theory of atoms in molecules,³² which supports their existence (see SI for details).

Table 2. Selected Atomic Distances for Structures O14 to INT-O14 in angstrom. Calculated at the BP86-D3/SVBS Level of Theory.

Parameter	014	TS-014	INT-O14
Ni-C2	2.79	3.11	1.93
Ni-C3	1.99	1.96	2.80
Ni-C4	2.07	2.76	4.13
Ni-O	3.57	2.01	2.02
O-C2	1.38	1.70	2.52
H-F	2.46	2.58	2.81
Cs-F	2.85	2.93	2.96
Cs-O	3.24	3.15	3.05
Cs-C(cent.)	5.13	3.74	3.83
Cs-C1	5.13	3.74	3.83
Cs-C2	5.11	4.06	4.16
Cs-C3	4.30	3.61	4.03
Cs-C4	5.57	3.93	4.03
Cs-C5	6.33	4.30	4.05
Cs-C6	6.16	4.33	4.12

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Figure 3. Optimized Structures for O14, TS-O14 and INT-O14. Calculated at the BP86-D3/SVBS Level of Theory. Cyclohexyl moieties omitted for clarity.

To gain deeper insight into the effect of CsF in the oxidative addition process, we have performed an energy decomposition analysis⁴⁶ for **O14**, **TS-O14** and **INT-O14**. These structures have been divided into two fragments: (A) the complex of nickel, PCy₃, and methoxynaphthalene, and (B) CsF and boronic ester (Scheme 3). The changes in the electronic energy of interaction, E_{int} , have been calculated as the difference of the total electronic energy, *E*, and the energy of the non-optimized fragments, $E_{A/B}$:

$$E_{\rm int} = E - (E_{\rm A} + E_{\rm B})$$

The deformation energy has been calculated as the difference of the energy of the non-optimized and the optimized fragments, $E_{A/B}$ ':

$$E_{\text{def, A/B}} = E_{\text{A/B}} - E_{\text{A/B}}'$$

 $E_{\text{def}} = (E_{\text{A}} + E_{\text{B}}) - (E_{\text{A}}' + E_{\text{B}}')$

The optimization of the fragments A leads to the same structures as the complexes without the external base, **O2**, **TS-O2**, and **INT-O2**, hence E_A ' is the total electronic energy of these. The total electronic energy of fragment B for the optimized phenylboronic ester complexed with CsF, E_B ', is the adduct **2**·CsF. As the oxidative addition proceeds, the deformation energy increases by 6.8 kJ/mol (**TS-O14**) and 16.4 kJ/mol (**INT-O14**) relative to that of **O14**:

$$\Delta E_{\rm def} = E_{\rm def}(\mathbf{TS} - \mathbf{O14} / \mathbf{INT} - \mathbf{O14}) - E_{\rm def}(\mathbf{O14})$$

This indicates that the oxidative addition step is unfavorable in terms of E_{def} . In contrast, the difference of the interaction energy between the fragments relative to **O14** decreases from -30.8 kJ/mol (**TS-O14**) to -42.5 kJ/mol (**INT-O14**).

$$\Delta E_{\text{int}} = E_{\text{int}}(\text{TS-O14}/\text{INT-O14}) - E_{\text{int}}(\text{O14})$$

The transition state **TS-O14** and the intermediate **INT-O14** are stabilized by strong interactions between these two fragments. This is also evident from the decreasing distances of the cesium to the oxygen, and the naphtyl moiety. The change in the interaction energy overcompensates the destabilization that is induced by the deformation, and is therefore the major contributing factor that the C–O bond cleavage is energetically feasible.

Scheme 3. Energy Decomposition Analysis of the CsF-Assisted Oxidative Addition.





Figure 4. Gibbs Free Energy Profiles of the Comparison of the Transmetalation and β -Hydrogen Elimination in the Presence (Purple Line) and Absence (Black Line) of CsF. Calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

Mechanisms of the competing β-hydrogen elimination. Gómez-Bengoa and Martin have reported that an attempt to synthesize ArNi(OMe)(PCy₃)₂ by treatment of ArNiCl(PCy₃)₂ with NaOMe resulted in the formation of Ni(CO)(PCy₃)₂.⁷ They propose that the expected Ni–OMe species is prone to a β-hydrogen elimination/decarbonylation sequence to form the corresponding Ni(CO) complex. We have reported that the β -hydrogen elimination of the postulated Ar-Ni-OMe complex proceeds to form Ar-H in the Ni/NHC-catalyzed reaction of aryl methyl ethers in the absence of a reducing agent.5c To examine the potential involvement of β -hydrogen elimination from the Ni-OMe intermediates as a competing pathway in the Suzuki-Miyaura-type cross-coupling, we have investigated the energy profiles for these processes from the intermediates generated by C-O oxidative addition in both, the presence and absence of CsF.

In the absence of CsF, **INT-O2** is generated via oxidative addition of the C–O bond to the nickel center (Figure 1). A possible β -hydrogen elimination occurs from the mono-ligated isomer **H1** with concomitant C–H bond-forming reductive elimination to deliver formaldehyde complex **INT-H1** via **TS-H1**. Although the calculated activation energy for this β -hydrogen elimination is only 10.8 kJ/mol, the relative energy of the transition state **TS-H1** (84.0 kJ/mol) is comparable with the transmetalation **TS-T2** (82.7 kJ/mol). This can be lead back to the instability of **H1** as it necessitates the dissociation of one phosphine ligand, making the nickel center electron deficient. The bis-coordinated pathway does not suffer from this, but the relative energy of its transition state is higher (**TS-H2**, 113.3 kJ/mol) and the reaction therefore less likely.

Both of these pathways are higher in energy than the most economic mechanism for the transmetalation in the presence of CsF (**TS-T11**, 62.5 kJ/mol). A possible β -hydrogen elimination aided by the base may occur from **INT-O12** via ligand dissociation to form the mono-phosphine species **H4**. The proceeding reaction is very unlikely as the transition state **TS-H4** is 44.6 kJ/mol higher in energy than the corresponding transmetalation **TS-T11** (Figure 4).

Our calculations demonstrate that a β -hydrogen elimination can be ruled out due to unfavorably high activation energies.

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Comparison of the energies of the most economic reaction paths according to different levels of theory. For the chosen level of theory BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS the transmetalation is 4.9 kJ/mol higher in energy than the oxidative addition for the most economic pathways in the presence of CsF (TS-O14, TS-T11), while in the absence of the base the barriers are reversed (TS-O2, TS-T2) though consistently higher in energy (Figures 1, 2, S4 in SI, and Table 3).

For a general verification of the reaction energies and in order to obtain more insight which step is rate-determining we have performed additional calculations on other density functionals.

Gómez-Bengoa and Martin have already reported that B3LYP fails at predicting the correct stabilities of the ligand exchange Ni(cod)₂ to Ni(PCy₃)₂.⁷ The latter is described more stable than the former, which is not supported by experimental evidence. The relative energy of the calculated structures varies with the level of theory, but the overall agreement of the reaction barriers is very good. For all investigated functionals, except BP86, the oxidative addition is the rate determining step by about 30-40 kJ/mol. The reaction in the presence of CsF is consistently lower in energy by about 20 kJ/mol. The trend for the competing β -hydrogen elimination is also supported by all functionals. Therefore we conclude that the overall lowest lying reaction pathway proceeds in the presence of CsF via the transition states **TS-O14**, **TS-T11**, and **TS-R12** (Table 3 and SI).

 Table 3. Relative Gibbs Energies of the Most Economic Pathways for Selected Density Functionals.^a

	BP86 ^b	PBE0 ^{b,c}	M06L ^{b,c}	ω B97X-D ^{b,d}
Ni(cod) ₂	0.0	0.0	0.0	0.0
Ni(PCy3)2	38.8	42.7	44.3	13.5
		Absence of	CsF	
02	-48.1	-13.0	-18.2	-49.2
TS-02	89.8	143.0	122.7	117.9
INT-O2	32.1	61.0	43.5	21.3
T2	73.3	76.0	84.5	42.3
TS-T2	82.7	91.4	96.8	58.8
INT-T2	39.9	45.3	48.4	6.8
R2	-41.2	-5.9	-14.7	-49.9
TS-R2	-29.0	21.1	7.6	-14.6
INT-R2	-109.6	-52.7	-74.6	-86.9
		Presence of	CsF	
014	-62.8	-14.3	-19.2	-102.1
TS-014	57.6	121.1	107.8	37.1
INT-O14	-1.8	45.0	31.6	-52.5
T11	-7.5	-14.3	-18.6	-98.5
TS-T11	62.5	79.4	73.1	6.7
INT-T11	-27.8	-19.8	-24.2	-118.1
R12	-83.2	-42.3	-42.7	-145.9
TS-R12	-69.4	-22.9	-30.2	-118.5

INT-R12	-151.8	-86.6	-106.7	-159.2				
β-Hydrogen Elimination								
H1	73.1	49.3	48.4	16.5				
TS-H1	84.0	90.0	87.6	60.1				
INT-H1	14.5	38.0	4.6	4.8				
H4	88.1	89.2	93.0	-1.1				
TS-H4	107.1	126.0	131.4	40.8				
INT-H4	69.6	102.5	81.4	11.3				

^{*a*} For more functionals see SI. ^{*b*} Thermal corrections are estimated on the optimized geometries at the BP86-D3/SVBS level of theory (T = 393.15 K, p = 1 atm). ^{*c*} Level of Theory Functional in the table head XX+D3(PCM)/def2-TZVPP//BP86-D3/SVBS. ^{*d*} ω B97X-D (PCM)/def2-TZVPP//BP86-D3/SVBS.

Effect of the ligand on oxidative addition. One of the key questions in nickel-catalyzed Suzuki-Miyaura type reaction of methoxyarenes is the crucial role of CsF in the presence of PCy₃ and no salt needed in the presence of ICy. To better understand the effect of an ICy ligand in cross-coupling reactions, we have performed calculations on the oxidative addition process of 1 mediated by a Ni/ICy complex, because the oxidative addition has the largest energy barrier in this cross-coupling (Figure 1). Optimization of the structure of a free ICy molecule allowed us to identify eleven conformers \mathbf{a} - \mathbf{k} , which are generated by rotation around the C–N axis (See SI for details).

The ligand exchange of Ni(cod)₂ with ICy is exergonic by -30.8 kJ/mol (Figure 6), which is in sharp contrast to the ligand exchange with PCy₃ (endergonic by 38.8 kJ/mol; Figure 1). Transition states for one and two ligand models have been explored; the energetically most favorable pathways for the Ni(ICy)- and Ni(ICy)₂-mediated oxidative addition have been further investigated (Figure 6, and see SI for details). Analogous to the Ni/PCy3-mediated system, a bis-ligated Ni(ICy)2 pathway (ICyO2aa to INT-ICyO2aa) proceeds through a lower energy surface than a mono-ligated Ni(ICy) pathway (ICyO1c to INT2-ICyO1c).⁴⁷ The nickel atom is coordinated differently in the precursor complexes O2 and ICyO2aa, but their analogues have also been considered (Figure 7 and SI). The calculated activation energy for the oxidative addition with Ni(ICy)₂ is 106.8 kJ/mol, which is much lower than the barrier with Ni(PCy₃)₂ (TS-O2 139.9 kJ/mol, Figure 1) and even lower than that in the presence of CsF (TS-O14 120.4 kJ/mol, Figure 2). These results are in good agreement with the experimental observations summarized in Scheme 2.



Figure 5. Gibbs Free Energy Profile of Nickel-Mediated Oxidative Addition with one (black line) and two (purple line) ICy Ligands Calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

The partial charges reveal the character of the initial steps of the reaction clearly as an oxidative addition as the charge of the nickel atom becomes more positive while the naphthyl carbon becomes more negative. In the PCy₃ system the nickel is slightly less positive than in the ICy system. The key difference is in the bonded atom of the ligands. The phosphorus carries a large positive charge as opposed to the carbon of the ICy ligand, which is only moderately positive (Table 4). This suggests that the Ni-P bond is more polarized than the Ni-C_{ICy} bond.

The electron density at the bond critical points (QTAIM analysis) of the ligand-nickel bonds is lower for the PCy_3 supported reaction compared to the ICy system (Table 4 and SI). This indicates that the former bond is weaker. The stronger nickel-ligand bond stabilizes the backbone of the catalyst and therefore reduces the relative energy of the transition state, which results in a lower activation barrier.

To elucidate this difference we have also performed an energy decomposition analysis, separating the molecules into the ligands (one fragment each) and the remaining nickel and methoxy naphthalene fragment (Scheme 5). The interaction energy between the nickel fragment and the ICy ligands is about 60 kJ/mol more stabilizing than in the PCy₃ case. Additionally the deformation energy within the ligands is about 8 kJ/mol less destabilizing for the ICy ligands. In both system the remaining nickel fragment is almost the same (Table 5). This supports the findings from the QTAIM analyses.

Further studies into the bonding nature of these compounds have to be performed to elucidate the reasons for these discrepancies.



Figure 6. Optimized Structures of the Intermediates and Transition States Involved in the Oxidative Addition Reactions Using PCy₃ (top) and ICy (bottom) Calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

Table 4. Selected Partial Charges (NPA) in atomic units, Bond Distances in Angstrom, and Electron Density Values at the Bond Critical Points of the Structures Involved in the Oxidative Addition for the Bis-Ligated Reaction Pathways calculated at the BP86-D3(PCM)/def2-TZVP//BP86-D3/SVBS Level of Theory.

	02	O2-iso	TS-02	INT-O2	ICyO2aa- iso2	ICyO2aa	TS- ICyO2aa	INT- ICyO2aa
Grel/kJ mol ⁻¹	-48.1	-9.4	89.8	32.1	-67.1	-73.7	33.1	-51.8
Ni	0.28	0.28	0.38	0.55	0.41	0.41	0.50	0.61
0	-0.45	-0.49	-0.60	-0.80	-0.45	-0.52	-0.58	-0.78
C2	0.31	0.11	0.04	-0.19	0.31	0.10	0.08	-0.17
P7/C7	0.91	0.90	0.98	1.04	0.11	0.10	0.11	0.21

P8/C8	0.91	0.90	0.87	0.96	0.10	0.11	0.05	0.15
Distances / Å			,					
Ni-C2	2.83	2.01	1.95	1.92	2.85	2.01	1.93	1.93
Ni-O	3.65	2.96	1.98	1.91	3.65	2.77	1.99	1.95
O-C2	1.38	1.42	1.73	2.76	1.38	1.43	1.67	2.66
Bond Critical Poi	nts, Electron dens	ity ρ / a.u.						
Ni-C2	n.a.	0.094	0.113	0.122	n.a.	0.096	0.117	0.122
Ni-O	n.a.	n.a.	0.084	0.098	n.a.	n.a.	0.081	0.091
O-C2	0.281	0.260	0.133	n.a.	0.280	0.225	0.150	n.a.
Ni-P7/C7	0.091	0.088	0.098	0.094	0.121	0.121	0.130	0.126
Ni-P8/C8	0.094	0.094	0.085	0.078	0.120	0.120	0.108	0.101

Scheme 5: Fragmentation for the Energy Decomposition Analysis of the Structures Involved in the Oxidative Addition with Different Ligands.



 Table 5: Energy Decomposition Analysis of the Structures Involved in the Oxidative Addition with Different Ligands at the BP86-D3(PCM)/def2TZVP/BP86-D3/SVBS level of theory.

	02	O2-iso	TS-02	INT-O2
Eint	-493.9	-477.7	-464.2	-446.1
Edef (A)	2.3	2.9	2.5	3.6
Edef (B)	14.6	15.4	17.3	18.7
Edef (Ligands)	16.9	18.3	19.8	22.3
Edef (C)	0.1	14.7	25.1	53.2
	ICyO2aa-iso2	ICyO2aa	TS-ICyO2aa	INT-ICyO2aa
Eint	-527.1	-525.9	-522.8	-544.6
E _{def} (A)	3.9	3.7	3.8	7.5
Edef (B)	8.3	8.1	7.7	8.3
Edef (Ligands)	12.2	11.9	11.5	15.7
Edef (C)	0.6	20.2	24.9	60.6

CONCLUSION

The mechanism of nickel-catalyzed cross-coupling of methoxyarene **1** with phenylboronic ester **2** is elucidated utilizing DFT (Scheme 4). In the reaction using PCy₃ as a ligand, oxidative addition of a C–OMe bond to Ni(PCy₃)₂ requires an activation energy of 137.9 kJ/mol. This energy barrier is lowered by 17.5 kJ/mol through the formation of a quaternary complex consisting of Ni(PCy₃)₂/CsF/**1**/**2** (**TS-O14**), thereby making this process energetically feasible. The CsF-assisted oxidative addition mechanism clearly explains the experimental observation that addition of CsF is essential for the cross-coupling to proceed. The reaction employing ICy as a ligand proceeds with a calculated activation barrier of 106.8 kJ/mol for the oxidative addition of the C–OMe bond to Ni(ICy)₂. This value is 31.1 kJ/mol lower than the most economic path for the Ni(PCy₃)₂ system. This lower barrier is in good agreement with the experimental observation that stoichiometric base is not required for the cross-coupling when ICy is used as the ligand. A β -hydrogen elimination cannot compete with the cross-coupling reaction under the catalytic conditions used in the experimental studies, as any of the observed transition states are at least 20 kJ/mol higher in energy than the most economic transmetalation pathway (**TS-T11**).

The analysis on different density functionals identify the oxidative addition as the rate determining step, which has not only the highest activation barrier, but also the highest lying transition state relative to the reactants. The overall driving force of the reaction is the large energy release through the carbon-carbon bond formation in the reductive elimination step.

Although the Ni/PCy₃ is used in most cross-coupling reactions of aryl ethers reported to date, oxidative addition of a C–OMe

bond via the classical three-centered transition state is energetically unfavorable,⁷ and several non-classical pathways come into play depending on the nature of the nucleophile used (see Scheme 1). Our calculations reveal the pivotal role of CsF to facilitate the oxidative addition process in the case of an organoboron nucleophile. In contrast, the carbene type ICy ligand allows the oxidative addition of C–OMe bonds to occur via the classical pathway, so cross-coupling reactions can proceed without external base. The bonding interactions between the ligands and the nickel center are much more stabilizing in the ICy case, while the ligands itself have a smaller deformation penalty, as compared to the PCy₃ mechanism.

We anticipate that these insights into the mechanism of C–O activation by nickel species will stimulate further development of catalytic transformations of aryl ethers.

Scheme 4. DFT-Revealed Mechanism for the Cleavage of C(aryl)-O Bond in the Nickel-Catalyzed Cross-Coupling of Aryl Ethers with Arylboronic Esters



ASSOCIATED CONTENT

Supporting Information. Details of computational results, Gibbs free energies, total electronic energies, imaginary frequencies, Cartesian coordinates of the calculated compounds, and related experimental results are available free of charge via the Internet at <u>http://pubs.acs.org</u>.

AUTHOR INFORMATION

Corresponding Author

*tobisu@chem.eng.osaka-u.ac.jp; chatani@chem.eng.osakau.ac.jp; seiji.mori.compchem@vc.ibaraki.ac.jp

Present Addresses

¹Department of Life and Environmental Sciences, Faculty of Engineering, Chiba Institute of Technology, Narashino, Chiba 275-0016, Japan

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