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Cluster

DFT Studies Provide Mechanistic Insight into Nickel-Catalyzed Cross-Coupling Involving Organoaluminum-Mediated C–O Bond Cleavage

DFT Calculatio

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Abstract Density functional theory (DFT) calculations were performed to examine the reaction pathway of Ni-catalyzed cross-coupling with organoaluminum through C–O bond cleavage. The results indicate that the strong Lewis acidity of organoaluminums significantly facilitates the transmetalation step, but not the oxidative addition or reductive elimination step.

Key words cross-coupling, C–O bond cleavage, nickel catalyst, organoaluminum, DFT calculation

Synthetic applications of organoaluminum (C-Al) have long been of great interest in both academic research and industry,¹ because C-Al reagents offer many advantages, including low cost, ready availability, low toxicity, high reactivity, and exceptional Lewis acidity. The initial use of C-Al in transition-metal (TM) catalyzed cross-coupling reaction can be traced back to Negishi's reports as early as in 1976,² but in subsequent decades, C-Al was largely neglected in favor of other organometallics (Mg, Zn, B, Sn, etc.).³ Recently, some cross-coupling reactions of C-Al with organic halides have been developed,¹ but few protocols are available for coupling of C–Al with phenol derivatives (ArOX).⁴ Recently, several Ni-catalyzed alkylation reactions of the C-O bond in aryl methyl ether (ArOMe) with trialkylaluminum (R₃Al) were reported by Chatani and Tobisu,^{5a} Rueping,^{5b} and Agapie.^{5c} More recently, we also reported an in-depth experimental study on Ni-catalyzed cross-coupling between organoaluminums and various types of C-O electrophiles, including sulfonates (OMs, OTs, OTf), phosphates, carboxylates (ester, carbamate, carbonate) and ether, which provide a useful and versatile toolbox for synthetic utilization of organoaluminums, as well as for inert bond activation.^{5d} To further understand the reaction mechanism, as well as the role of the aluminum reagent, we carried out a mechanistic study of organoaluminum-mediated C–O cleavage-type cross-coupling based on DFT calculations. It has often been

"Ni(0)" / PCv₃



Scheme 1 Representative results of Ni-catalyzed cross-coupling of aryl carboxylates with aryl aluminum reagents

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speculated that the Lewis acidity of organoaluminum reagents could promote oxidative addition of the C–O bond to Ni(0); however, the results of our computational study clearly indicate that the Lewis acidity of aluminum primarily facilitates the transmetalation step, rather than the oxidative addition step.

All DFT (B3LYP⁶ and M06⁷) calculations were performed with the Gaussian09 program⁸ and GRRM11 program⁹ to clarify the reaction pathway/mechanism. Structure optimization and frequency calculations were carried out with B3LYP/6-31G*(H, C, O, Al, P) & LANL2DZ (Ni). Single-point energy considering the solvent effect of toluene (PCM model¹⁰) was obtained via calculation of the B3LYP geometries with M06/6-311++G**(H, C, O, Al, P) & SDD (Ni). Gibbs free energy (kcal/mol) was used as a basis for discussion. PhOAc and PhAl(OMe₂)Me₂ were employed as model reactants. Ni(PCy₃)₂ was regarded as the active catalyst species based on recent work,¹¹ from which the initial geometry of PCy₃ was also taken. For full citations and details, see the Supporting Information. Natural bond orbital (NBO) analysis was performed with NBO5.9.¹²

The results of several examinations indicated that the reaction pathway of Ni-catalyzed cross-coupling via aluminum-mediated C–O cleavage, as illustrated in Scheme 2 and Figure 1, is the most probable. The cross-coupling basically proceeds according to a catalytic cycle consisting of three elementary steps; namely, oxidative addition, transmetalation, and reductive elimination. In the initial step, Ni(0) catalyst forms a π -arene complex with the aromatic substrate, and then oxidative addition of the C_(Arvl)–O bond to Ni(0) catalyst takes place via **TS1** to generate **CP2-1**, giving the $C_{(Aryl)}$ -Ni(II)–O species with a total activation barrier of 24.3 kcal/mol. The OAc moiety on Ni(II) in **CP2-1** then coordinates to the aluminum reagent to form **CP2-2**, which undergoes transmetalation through **TS2** \rightarrow **CP3** \rightarrow **TS3** to afford Ar₂Ni(II) species **CP4** along the intrinsic reaction coordinate, with release of the Me₂AlOAc moiety. Transmetalation proceeds with a quite low activation barrier (< 12 kcal/mol), without much energy gain. Finally, reductive elimination takes place via **TS4** (ΔG_a = 3.2 kcal/mol), leading to coupling product **PD** and regeneration of the Ni(0) catalyst with large exothermicity. None of the stages in the process involves any energetically unfavorable CPs/TSs with a large overall energy gain (Figure 1).



Having thus clarified the pathway of the present crosscoupling reaction, we next wished to identify the main contributions of organoaluminum reagents to the excellent reactivity. It has been widely accepted, and we also anticipat-



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ed a priori, that the potent Lewis acidity of organoaluminums would promote the oxidative addition of Ni(0) because of the Lewis acidic activation of C-O bond cleavage,^{5b-c,13} but our DFT calculations do not support this view. Three plausible modes of action for oxidative addition with or without O-Al interaction are illustrated in Scheme 3. Unexpectedly, all three transition states lay at almost the same energy level (energetic difference <3 kcal/mol), and the oxidative addition with no assistance of the aluminum reagent (TS1) showed the lowest energy path. This is probably because the interaction from the potent Lewis acidic Al metal center weakens the chelation of the carbonyl group (OAc) to Ni(0), as seen in TS1^{Al-OPh} and TS1^{Al-OAc} (where the Ni-O distances are much longer than that in TS1). NBO analyses of the TSs provides further support for this idea: that is, the contribution from Ni in the NLMO (natural localized molecular orbital) decreases in the order TS1 > TS1^{Al-} ^{OPh} > **TS1**^{Al-OAc}. These findings suggest that the coordination of the OAc moiety to Al decreases electron donation from the carbonyl oxygen to the Ni center, resulting in a more electron-deficient Ni(0) character, and offsetting the activation of C-O by Lewis acid-base interaction.



Scheme 3 Influence of Lewis acidity of aluminum reagent on the oxidative addition process (H atoms are omitted for clarity)

Several mechanistic investigations of Ni-catalyzed cross-coupling of $C_{(Aryl)}$ –O substrates, including esters, carbamates, and sulfonates, have been reported, in which the transmetalation steps are usually energetically unfavorable and rate-determining.¹¹ This is presumably the reason why an excess (≥3 equiv) amount of organo-boron or -zinc reagent is normally needed in such reactions, together with harsh conditions. In contrast, aluminum reagents were required only stoichiometrically or in just slight excess (≤1.5 equiv), and the reaction proceeded at room temperature (or with gentle heating). We speculated that the Lewis acidity of Al reagents facilitates the transmetalation step, and, indeed, this proved to be the case. The energy diagram suggests that the transmetalation step involves two processes,

(1) Ph migration from Al to Ni (**CP2-2** \rightarrow **TS2** \rightarrow **CP3**), and (2) elimination of Me₂AlOAc (**CP3** \rightarrow **TS3** \rightarrow **CP4**) (Scheme 1). The Ph (green) moiety on the Al center in CP2-2 can migrate smoothly to the Ni center (via TS2) to form a disproportionated Ph-Ni(II)-Ph intermediate CP3. This process is facilitated by push-pull synergy through O-Al interaction, which weakens the Ni-O bond and polarizes the Ph-Al bond, as reflected in the bond lengths (a longer Ni-O bond in CP2-2 than CP2-1), NPA charges (more negative charge at carbon in Ni-C-Al moiety) and donor (O)-acceptor (Al) interaction energy (ΔE , a stronger Lewis acid-base interaction in **CP2-2** than that in PhAl(THF)Me₂) (Scheme 4). The complex CP3 undergoes smooth dissociation with very low activation energy (7.0 kcal/mol) owing to the potent Lewis acidity of the aluminum reagent: the Me₂AlOAc moiety of **CP3** is easily detached from the Ni(II) center to give an unsaturated diphenylnickel(II) species, which undergoes rapid reductive elimination to eject the coupling product and to regenerate the Ni(0) species. Thus, the present DFT study has revealed that the potent Lewis acidity of aluminum reagents strongly facilitates the transmetalation step both kinetically and thermodynamically; this may be the reason why the present reaction requires only a small excess of the aluminum reagent and proceeds under mild conditions. It is worth noting that the calculations are in good accordance with the experimental observations^{5d} that: (1) the coupling reaction proceeds much more efficiently in toluene solution than in a coordinative solvent such as THF, and (2) aluminates that have low Lewis acidity, such as [ArAlMe₃]⁻ and [Ar₂AlⁱBu₂]⁻, show lower reactivity. Our findings imply that aluminum reagents may be generally applicable for inert bond cleavage-type cross-couplings via smooth transmetalation.



Scheme 4 NBO analysis of the transmetalation step (ΔE : sum of second-order perturbation energy for O–Al donor–acceptor interaction)

In summary, the present DFT study has revealed the reaction pathway and mechanism of the Ni-catalyzed crosscoupling reactions between organoaluminum and phenol carboxylate derivatives though C–O bond cleavage. In sharp contrast to the widely accepted view that Lewis acid could activate the C–O bond to promote a smooth oxidative addition process, the current theoretical investigations clearly show that the Lewis acidity of organoaluminum reagents primarily facilitates the transmetalation step, rather than

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others such as the C–O bond cleavage or C–C bond-forming step. These results underline the conclusion that novel and interesting mechanisms may hide in well-established reactions that are considered to be fully understood. Our findings open up a new approach for designing novel reagents/reactions/protocols, and may also have implications for other organometallic transformations. Further experimental and theoretical studies on the applicability of this mechanism to other TM-mediated reactions are in progress.

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Supporting Information

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