Regular Article

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Ethereal C–O Bond Cleavage Mediated by Ni(0)-Ate Complex: A DFT Study

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Density functional theory calculations were performed to explore the mechanism of Ni-catalyzed cross-coupling reactions involving organo-lithium and -zinc reagents through ethereal C–O bond cleavage. Based on this work, together with our previous mechanistic study on ethereal Kumada–Tamao reaction, we identify and characterize a novel catalytic cycle for cross-coupling mediated by Ni(0)-ate complex.

Key words cross-coupling; ether; nickel catalyst; organolithium; organozinc; density functional theory (DFT) calculation

Efficient and selective cleavage and transformation of C–O bonds, particularly by means of cross-coupling methods, has attracted great interest, since compounds containing C–O moieties occur widely in nature and are also extensively utilized in industry. 1–19 Among C–O compounds, ethers are particularly attractive, 1–8 as they offer the advantages of 1) high atom economy/conversion efficiency (the use of ethers as simple as MeO as substrates affords fewer by-products compared with tosylate, mesylate, triflate, phosphate, etc.), 2) environmental compatibility (cleavage of the C–O moiety in ether releases non-halogen-containing waste), and 3) excellent stability, easy accessibility and wide diversity. However, ethereal C–O bonds (C–O) are very unreactive, and most of the well-established Pd-catalyzed C–O bond-cleaving protocols are ineffective for ethers.

On the other hand, Ni-catalysts have proved effective for many types of C–O bond cleavage, including ethers. As early as in 1979, Wenkert et al. 9,10 reported the first Ni-catalyzed Kumada–Tamao type (Mg) 9–23 reaction, in which aryl methyl ether (ArOMe) acted as the electrophilic partner, and this is now recognized as the first example of Ni-catalyzed activation of an inert C–O bond. However, this breakthrough was overlooked for decades, until quite recently. After the development of improved conditions, ArOR can now be used as a coupling partner in several types of transition metal (TM)-catalyzed cross-couplings and related transformations, such as Suzuki–Miyaura-type (B), 24–31 Negishi-type (Zn or Al), 32–36 Murahashi-type (Li), 37–40 and other reactions. 41–50 As a continuation of our work in this area, we reported in 2012 the first ethereal Negishi-type coupling of aryl alkyl ether 36 (Chart 1(1)) and in 2016 we reported a systematic examination of ethereal Murahashi-type reaction 57 (Chart 1(2)). More recently, we also reported an in-depth study of Ni-catalyzed cross-coupling between organoaluminums and various types of C–O electrophiles, including aryl alkyl ether. 52

Results and Discussion

The conventional catalytic cycle for cross-coupling reaction consists of three elemental steps: oxidative addition (OA), transmetalation, and reductive elimination. 51–54 Martin and colleagues reported that direct OA of a 6C–O bond to Ni(0) requires high temperature, based on experimental and theoretical findings. 46 Computational studies by Nakamura and colleagues, 55 Liu and colleagues, 56 Martin and colleagues, 46 and us 44 clearly demonstrated that OA of a 6C–O bond generally involves a very high activation barrier (Chart 2(1)), even considering the Lewis acidity of Mg (Chart 2(2)). This could be attributed to the high stability of the 6C–O bond and the weak interaction between the 6C–O moiety and Ni(0) species. These findings well explain why many reactions that involve breaking 6C–O bonds, such as Suzuki–Miyaura coupling,amination, reduction, and so on, need vigorous heating. However, this understanding seems incomplete, because other Ni-catalyzed ethereal cross-couplings, such as Kumada–Tamao-type, Negishi-type, and Murahashi-type reactions, take place under mild conditions in many cases.

Considering the nucleophilicity of Ni(0) species for the C–O moiety, an anionic [C–Ni(0)]− ate complex would be more reactive than the neutral Ni(0) species. Nakamura and colleagues have found by calculation that the hydroxyphosphine ligand (PO) can form [O–Ni(0)]− ate species, which facilitates addition of the C–O bond of aryl carbamates and phosphates. 55 This catalyst system, however, was ineffective for ether due to insufficient interaction between [O–Ni(0)]− and the 6C–O bond. Chatani and Tobisu and colleagues, 29 Cornella and Martin, 19 and our group 43 have suggested that, instead of the neutral Ni(0) or anionic [O–Ni(0)]− species, the [C–Ni(0)]−-ate species 57–60 is involved. In 2015, we reported the first systematic mechanistic study on the Ni-catalyzed
etheral Kumada–Tamao coupling by means of density functional theory (DFT) calculation (Chart 3), and in particular, we presented a full screen of the reaction pathway of $E$C–O bond cleavage mediated by Ni(0)-ate complex.\textsuperscript{14} The proposed mechanism accounts well for all the experimental findings. Encouraged by this, we next turned to explore the generality of this novel catalytic cycle for cross-coupling reactions. Here, we would like to report the results of computational studies on Ni-catalyzed cross-coupling with organo-lithium and -zinc reagents through ethereal C–O bond cleavage. The purposes of this study are as follows: 1) to investigate the mechanism of the OA step in the Murahashi-type reaction of ethers and to examine whether the mechanism involves the Ni(0)-ate-complex; 2) to analyze the reason why di-anionic organozincate [Ar–ZnMe\textsubscript{3}]\textsuperscript{-} react smoothly with ethers, while normal neutral organozincs such as ArZnX (X=Cl, Br, etc.) show no reactivity in the Negishi-type reaction.\textsuperscript{36}

All DFT (B3LYP\textsuperscript{61–63} and M06\textsuperscript{64}) calculations were performed with the Gaussian09\textsuperscript{65} program and GRRM11\textsuperscript{66–70} based on Gaussian09. Structure optimization and frequency calculation were carried out with B3LYP/6-31G* (H, Li, C, O, P, Cl) & LANL2DZ (Ni, Zn). Single point energy considering the solvent effect of iPr\textsubscript{2}O (Self-Consistent Reaction Field (SCRF) method using the Polarizable Continuum Model (PCM) model\textsuperscript{71–73}) was obtained via calculation of the B3LYP geometries with M06/6-311++G** (H, Li, C, O, P, Cl) & SDD (Ni, Zn). Gibbs free energy (kcal/mol) was calculated based on M06 single point energy and B3LYP frequency.
Compared with the Grignard pattern, the activation barrier formation, which contains a transmetalation step takes place immediately after TSa-Li. Li(CPb)(OMe)2, and Me2O were employed as reactants and as a simple model of Pr2O (or other ether solvents), respectively. LiBr, Li(OMe)2, and [ClZn(OMe)2]OMe2 were used as co-formed inorganic salts after coupling reactions. Aggregation states for all organometallics and inorganic salts were considered according to the literature. Ni(PCy3)2 was chosen as the active catalyst species based on previous reports. In our previous computational study on Ni-catalyzed etheric Kumada–Tamao-type coupling, we showed that direct OA of the C–OMe bond to Ni(0) has a high activation barrier. Although the counter-cation [MgBr]+ seems to activate the C–OMe bond as a Lewis acid (LA), the activation energy drops only slightly. To understand the reaction mechanism of etheric Murahashi-type coupling, DFT calculation was carried out. The computed conventional OA mechanism for etheral Murahashi-type coupling is shown in Chart 4(1). The initial complex (CP1-Li) and transition state structure (TSa-Li) are essentially the same as the Grignard case, while the transmetalation step takes place immediately after TSa-Li to give CPb-Li, which contains a trans-Ph–Ni–Ph structure. Compared with the Grignard pattern, the activation barrier is somewhat increased to 42.7 kcal/mol, indicating that transformation via this OA pathway is very difficult at ambient temperature. Replacement of PhLi with PhZnCl does not greatly affect the geometrical features of the initial complex (CP1-Zn) and the transition state structure (TSa-Zn), but provides CPb-Zn which contains a cis-Ph–Ni–OMe structure, similar to the Mg’s case. However, the activation energy is still high (34.5 kcal/mol), albeit slightly lower than that for direct OA (TSa) (Chart 2(2)). These results suggest that 1) a simple extension of the traditional OA mechanism cannot account for the experimental facts of C–O bond cleavage under mild conditions, and Lewis acidity of the metal cation in organometallic nucleophiles such as organolithium, organozinc and Grignard reagents cannot efficiently promote C–O bond cleavage. Hence, we next turned to focus on the Ni(0)-ate-complex-mediated reaction mechanism.

The results of several examinations indicated that the most probable reaction pathway of the etheral Murahashi coupling involving Ni(0)-ate complex formation as a key step, shown in Chart 5, is similar to the previously computed Kumada-Tamao-type pathway. The reactants first form initial complex CP1-Li, in which Ni(0) coordinates to the phenyl π-plane and PhLi associates with the OMe group. The formation of CP1-Li causes an energy loss of 18.9 kcal/mol. The intramolecular phenyl shift (from PhLi) to the Ni(0) center then proceeds through TS1-Li with a reasonable activation energy of 24.2 kcal/mol, generating the Ni(0)-ate complex CP2-Li with high stabilization energy (18.8 kcal/mol). Next, cleavage of the C–OMe bond occurs from CP2-Li with an activation energy of 19.4 kcal/mol through TS2-Li, which has a five-membered ring structure, leading to exothermic formation of CP3-Li with release of one Me2O molecule. CP3-Li has a biarylated Ni(II) unit in which one phenyl ring is associated with MeOLi species. The transformation CP2-Li → TS2-Li → CP3-Li is facilitated by a push–pull interaction, in which the leaving ability of the OMe group is improved by coordination of Li cation as a Lewis acidic activator, and the anionically activated [Ph-Ni(0)]–ate moieties inserts into Ph–OMe to form a new σ-C–Ni bond. Different from the case of Mg, the dissociation of MeOLi species in CP3-Li is quite exothermic, leading to CP3, which undergoes normal reductive elimination via TS3 with a very low activation barrier (3.5 kcal/mol) to provide the thermodynamically very stable biphenyl product and regenerate the Ni(0) catalyst. The whole of this route turned out to be kinetically and thermodynamically favorable, in good accordance with the experimental observation that Ni-catalyzed etheral Murahashi-type cross-coupling generally proceeds under mild conditions.

The computational reaction pathway of Ni-catalyzed cross-coupling between PhOMe and PhZnCl will be discussed next (Chart 6). Although the geometrical features of the transition structures and intermediates are essentially the same as in the cases of PhLi and PhMgBr, the energy profiles are very different (Chart 7). Most CPs/TSs in this pathway are energetically less favorable than those in pathways using PhLi or PhMgBr, and the reaction is therefore much less likely to take place, at least at ambient temperature. It is noteworthy that the formation of Ni(0)-ate complex CP2-Zn from PhZnCl proceeds kinetically, but is thermodynamically unfavorable. Further, the next step of C–O bond cleavage needs a very high activation barrier (total 33.2 kcal/mol). Hence, C–O bond cleavage cross-
Chart 5. DFT Calculation of the Reaction Pathway for Ethereal Murahashi-Type Coupling Involving Ni(0)-Ate Complex-Mediated C–O Bond Cleavage (G: Gibbs Free Energy, kcal/mol)

Chart 6. DFT Calculation of the Reaction Pathway of Ethereal Negishi-Type Coupling with ArZnX Species Involving Ni(0)-Ate Complex-Mediated C–O Bond Cleavage (G: Gibbs Free Energy, kcal/mol)
coupling pathways with neutral organozinc species (PhZnCl) are kinetically and thermodynamically unfavorable in both the conventional OA mechanism and the Ni(0)-ate complex pathway. These computations provide a reasonable explanation of why ArZnX fails to react with ArOMe under mild conditions.36) To understand in depth the origin of the energy differences in these mechanisms, Natural Bond Orbital (NBO) calculation was performed for the key intermediate CP2 (Chart 8). In this Ni(0)-ate complex, two interactions mainly contribute to gathering the three SM molecules (Ph–[M], Ni, and PhOMe) and stabilizing the whole complex: 1) σ-coordination from the phenyl anion in Ph–[M] to the Ni(0) (ΔE1) and 2) π-complexation between Ni(0) and the phenyl ring of PhOMe (bonding interaction: ΔE2, back-bonding interaction: ΔE3). The NBO analysis indicated that the σ-coordination from the Ph anion in PhZnCl to Ni(0) is much weaker than those in PhLi and PhMgBr. The π-complexations between Ni(0) and the Ph ring of PhOMe in the three CP2s are all similar, though CP2-Zn also shows the lowest value. This could be attributed to the less polar character of the C–Zn bond, compared to the C–Li and C–Mg bonds, which causes poor σ-donation from PhZnCl to Ni and consequently weak back-bonding donation from Ni to PhOMe. Thus, the stability of the Ni(0)-ate complex appears to be mainly determined by the σ-donation ability of the organometallic nucleophiles R–[M]. In our previous reports, we have found that in organozincates77–85) the anionic character of C–Zn bond could be drastically enhanced (Table 185). Therefore, di-anion-type zinicate [Ar–ZnMe2]2− should form more stable Ni(0)-ate complexes compared with neutral PhZnCl or mono-anion-type zinicates. These results are consistent with the experimental findings that the use of di-anion-type zinicate [Ar–ZnMe2]2− led to smooth cross-coupling under mild conditions. In general, these results strongly suggest that the Ni(0)-ate complex-mediated OA process is a key step in TM-catalyzed C–O bond cleavage. Currently, mechanistic study on the Ni-catalyzed cross-coupling of organo-zinicate [Ar–ZnMe3]2− with ether via ΔC–O bond cleavage by means of both experimental and theoretical methods is in progress.

Conclusion

In conclusion, we performed DFT calculations for etheric Murahashi-type and Negishi-type cross-couplings, in comparison with the Kumada–Tamao-type reaction. The results indicate that the reaction pathway involving the Ni(0)-ate complex is a new and general mechanism for ethereal cross-coupling reactions, which can well explain the experimental findings for several ΔC–O bond cleavage couplings. Further, NBO analysis indicated that σ-coordination from the organometallic nucleophiles R–[M] to Ni(0) plays a critical role in both formation and stabilization of the Ni(0)-ate complex. The present work also suggests that the anionic character of organometallic nucleophiles can change OA mechanisms/pathways, which may provide new reactivity and selectivity. These results should be helpful for designing new reagents/reactions/protocols for inert bond activations and may also have implications for other organometallic transformations. Further experimental and theoretical studies aimed at applying this mechanism to other TM-mediated reactions are in progress.

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