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Mechanistic Study on Pd/Mono-N-protected Amino Acid Catalyzed Vinyl−Vinyl Coupling Reactions: Reactivity and *E*/*Z* Selectivity

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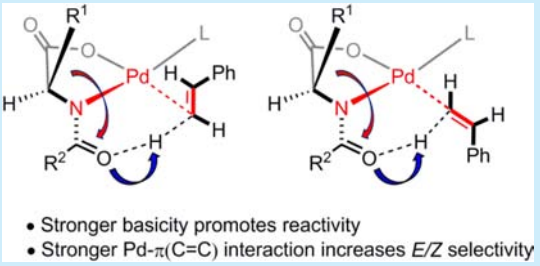
Supporting Information

ABSTRACT: A combined mass spectrometric and computational study of the Pd/mono-N-protected amino acid (MPAA)-catalyzed vinyl−vinyl coupling reactions is reported. Computational study reveals that the reaction is initiated by C−H activation of the styrene followed by the insertion of acrylate. This is supported by mass spectrometry. The MPAA ligand facilitates the cross-coupling reaction between monosubstituted alkenes by stabilizing the active palladium catalyst and offering the N-protecting group as a stronger base than acetate. The *E*/*Z* selectivity is attributed to the stronger d−π interaction between the catalyst and the substrate in the transition state leading to *E* product.

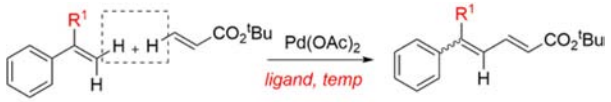


Transition-metal-catalyzed direct C−C bond formation via oxidative C−H coupling is an attractive strategy with which to construct C−C bonds.[1] Compared to traditional coupling reactions that normally involve halogenated substrates, these methods are more atom-economical and cleaner.[2] Oxidative cross-coupling of alkenes by C_{vinyl}−H bond activation is an attractive strategy for synthesis of conjugated dienes, which compose a large class of pharmaceutically active compounds and important natural products.[3] However, compared to the well-explored coupling reactions of (hetero)-arenes with alkenes,[4] direct cross-coupling of simple alkenes by vinylic C−H bond activation to form dienes lags behind. This is mainly due to the inertness of the C−H bonds in unfunctionalized alkenes[5] as well as difficulties in promoting the *E*/*Z* selectivity of the desired product.

Cross-coupling of vinyl carboxylate with acrylates was first reported by Ishii in 2004.[5] Further progress in oxidative cross-coupling reactions of alkenes was achieved next.[6] However, installation of activating functional groups, e.g., carboxylate, at the alkene is usually necessary for these reactions. In 2009, Loh and co-workers reported a $Pd(OAc)_2$-catalyzed cross-coupling reaction between simple olefins and acrylates.[7] However, the substrate was restricted to α-substituted alkenes (Scheme 1a). By increasing the reaction temperature to 110 °C and adjusting the solvent, Liu and co-workers expanded the substrate scope to involve monosubstituted alkenes (Scheme 1b).[8]

Yu and co-workers reported that the reactivity and selectivity of Pd-catalyzed aryl C−H activation is improved with the addition of mono-N-protected amino acid (MPAA) ligands.[9] Inspired by Yu's strategy, Loh and co-workers developed Pd/MPAA-catalyzed direct cross-coupling of a variety of simple olefins with acrylate (Scheme 1c).[10] With an MPAA ligand, the yield and the *E*/*Z* selectivity are improved significantly compared to reactions without MPAA.

Scheme 1. Direct Cross-Coupling Reactions of Alkenes with Acrylates



	ligand	temp	R^1	yield	*E*/*Z*
(a)	—	60 °C	Me	71%	87:13
(b)	—	110 °C	H	56%	90:10
(c)	MPAA	60 °C	H	80%	>99:1

An in-depth mechanistic understanding of how MPAA ligand promotes the reactivity and *E*/*Z* selectivity of alkene−alkene cross-coupling is crucial to the further development of such reactions. In our previous work,[11] we studied Pd/MPAA-catalyzed sp^2 C_{aryl}−H activation reactions and proposed a model in which the MPAA acts as bidentate ligand as well as an internal proton acceptor. In this paper, we report a mechanistic study addressing the following three critical issues of vinyl−vinyl cross-coupling reactions: (1) the mechanism of the reaction, (2) the role of MPAA on reactivity, and (3) the origin of *E*/*Z* selectivity.

The $Pd(OAc)_2$/Ac-tLeu-OH-catalyzed cross-coupling reaction of styrene with *tert*-butyl acrylate was selected as a model reaction for a detailed mechanistic study. We chose Ac-tLeu-OH, instead of the more reactive Ac-Ile-OH, as the model MPAA to reduce the conformational space of the side chain. All

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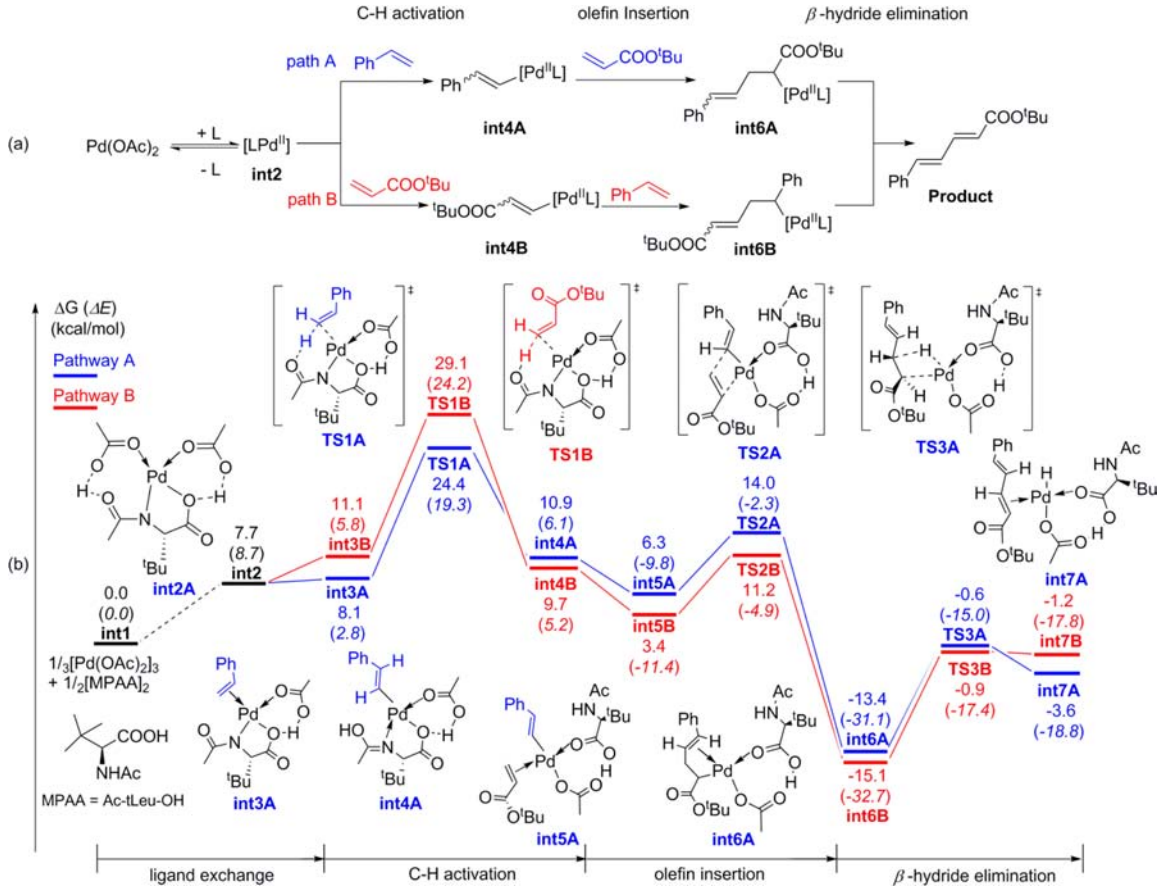

Figure 1. (a) Possible catalytic pathways of cross-coupling reaction. (b) Potential energy surface for the cross-coupling reaction.

the calculations were carried out with the Gaussian 09 package (see the Supporting Information for more details).

The mechanism of the dehydrogenative vinyl−vinyl cross-coupling reaction involves three key steps: C−H activation, olefin insertion, and β-hydride elimination (Figure 1a). The reaction may be initiated by activation of the C−H bond in styrene followed by the insertion of acrylate (pathway A). Alternatively, it may proceed through the reverse sequence of two olefins (pathway B). The potential energy surface (PES) for the cross-coupling reaction of alkene with acrylate is presented in Figure 1b and Figure S1. The computational results demonstrate that the C−H activation is the rate-determining step in both pathways, in agreement with the reported kinetic isotope effect.[8,10] The C−H activation of styrene (**TS1A**) is more favorable than activation of acrylate (**TS1B**) by 4.7 kcal/mol, indicating electron-rich styrene is more reactive. This finding also accounts for the higher reactivity of α-methylstyrene (Scheme 1a, Figure S2).[7a]

Electrospray ionization mass spectrometry (ESI-MS) proved to be useful in the investigation of the reaction mechanism because of its capability for structural characterization and its high sensitivity.[12] To verify the computational results, an ESI-MS/MS experiment was conducted to examine the competition between styrene and acrylate toward C−H activation. Substrates bearing an amino group, which serves as a charge tag,[13] e.g., 4-aminostyrene (**1**) and *N*,*N*-dimethylacrylamide (**2**), were chosen for the MS study. Ac-Ile-OH was employed as the MPAA. First, a control experiment was performed to test the reactivity of **2**. A mixture of **2**, $Pd(OAc)_2$, and Ac-Ile-OH in acetonitrile was analyzed (Figure 2a). Ions of m/z 204 and 377

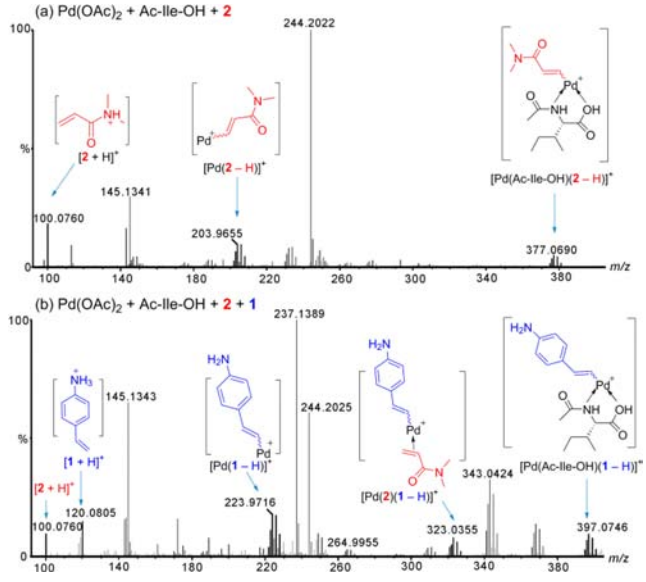

Figure 2. ESI-MS spectra derived from (a) a 5:0.5:2.5 (mM) mixture of **2**, $Pd(OAc)_2$, and MPAA (Ac-Ile-OH) in acetonitrile and (b) a 10:5:0.5:2.5 (mM) mixture of **1**, **2**, $Pd(OAc)_2$, and MPAA (Ac-Ile-OH) in acetonitrile.

were observed, and assigned, respectively, as $[Pd\ (\mathbf{2}), -H]^+$ and $[Pd(Ac\text{-}Ile\text{-}OH)(\mathbf{2}), -H]^+$ (Figures S3 and S4), indicating the C−H bond of **2** can be activated by Pd/MPAA. Then, both **1** and **2** were mixed together with $Pd(OAc)_2$/Ac-Ile-OH to examine their competition. In the presence of **1**, the ions m/z

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204 and 377 were not detected. Instead, the ions m/z 234 and 397, corresponding to [Pd (**1**), -H]$^+$ and [Pd(Ac-Ile-OH)(**1**), -H]$^+$ (Figures S5 and S6), were observed (Figure 2b). The MS experiments suggested that, as indicated by the computational results, the electron-rich styrene species (**1**) are more reactive toward the Pd/MPAA complex.

Compared with the previous results,[7a,8] the application of MPAA ligand significantly promotes the yield of the cross-coupling reaction under mild conditions (60 °C).[10] To unravel the effect of MPAA on reactivity, we compared the relative energies along the C−H activation process. The process involves three steps: the formation of monomeric Pd complex, the binding of styrene, and C−H bond cleavage (Figure 3).

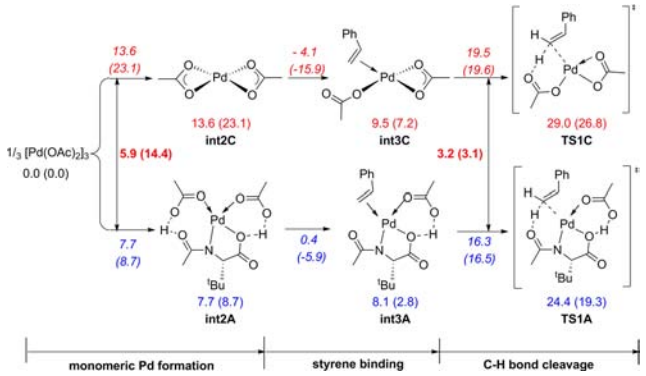

Figure 3. Free energy (kcal/mol) profiles (electronic energies in parentheses) for the C−H activation step catalyzed by Pd(OAc)$_2$ and Pd/MPAA, respectively. Barriers are shown in italics.

As shown in Figure 3, the intermediate **int2A** is 5.9 kcal/mol more stable than monomeric Pd(OAc)$_2$ (**int2C**), suggesting that MPAA stabilizes the active monomeric Pd species. For the C−H bond cleavage step, **int3A** overcomes a barrier of 16.3 kcal/mol, which is 3.2 kcal/mol lower than the barrier for **int3C** because the N-protecting group is a stronger base than an acetate group. As a consequence, the promotional effect on the reactivity of MPAA can be attributed to the stabilization of the monomeric palladium catalyst and the stronger basicity of the N-protecting group.

On the basis of these findings, it could be expected that varying the N-protecting group might result in different reactivities.[11c] In fact, it was reported by Loh and co-workers that use of Piv-, Tf-, Bz-, and Boc-protected valines as the ligand dramatically decreases the yield of the coupling reaction.[10]

To investigate the different behaviors of these N-protecting groups, we conducted a comparative density functional theory (DFT) analysis on three valines bearing Ac, Piv, and Boc protecting groups which can be compared with the Loh's experiments (Figure 4). The reaction energy profile of Ac-Val-OH is regarded as a reference for comparison. In the case of Boc-Val-OH, the energy demands for the monomeric Pd formation and styrene binding are similar to those of Ac-Val-OH, but the C−H bond cleavage with Boc-Val-OH has a higher barrier than that with Ac-Val-OH by 4.1 kcal/mol. The reason for this is that the σ-electron-withdrawing *tert*-butoxyl group decreases the basicity of the carbonyl group involved in the deprotonation process. In the case of Piv-Val-OH, the barrier for C−H bond cleavage is comparable to that for Ac-Val-OH, but the monomeric Pd complex (**int2_Val_Piv**) is 6.7 kcal/mol less stable than **int2_Val_Ac** and thus increases the

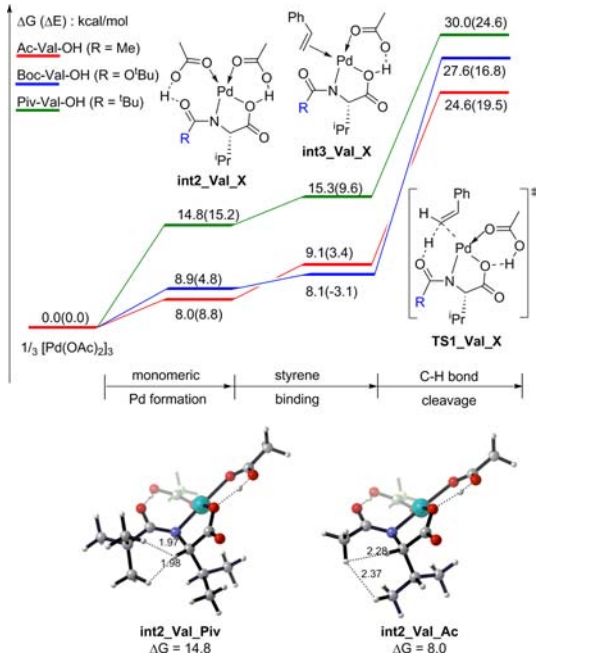

Figure 4. Free energy (kcal/mol) profiles (electronic energies in parentheses) for the C−H activation step catalyzed by different MPAA ligands. Structures of **int2_Val_Piv** and **int2_Val_Ac**.

overall activation free energy. As shown in Figure 4, the bulky pivaloyl group induces significant steric hindrance in **int2_Val_Piv**, destabilizing the bidentate binding of MPAA ligand. These results are in agreement with experiments and are evidence that the N-protecting group acts as a proton acceptor.

Compared with previous work summarized in Scheme 1a,b),[7a,8] the E/Z ratio in the products was significantly improved, up to >99:1, in the presence of MPAA.[10] DFT studies were conducted to elucidate the origin of E/Z selectivity. The activation energy difference between **TS1C_E** and **TS1C_Z**, which leads to E- and Z-products with Pd(OAc)$_2$, is 0.6 kcal/mol, indicating a moderate E/Z selectivity. The activation energy difference is increased to 1.7 kcal/mol when Ac-tLeu-OH is employed as the ligand, and this is consistent with the improved E/Z selectivity observed experimentally.

Transition structures of C−H activation catalyzed by Pd/Ac-tLeu-OH or Pd(OAc)$_2$ are shown in Figure 5. In **TS1A_E** and **TS1A_Z**, the N-protecting group significantly bends below the coordination plane of Pd due to steric repulsion from the bulky *tert*-butyl group. The downward N-protecting group orients the substrate to engage in the C−H bond activation. In **TS1A_E**, the C−C double bond is almost perpendicular ($\alpha 1 = -83.4°$) to the coordination plane of Pd, presumably benefiting by the Pd-π(C═C) interaction (Table S1), while in **TS1A_Z**, the corresponding dihedral angle $\alpha 1$ is 138.1°, which weakens the back-donation. In the case of Pd(OAc)$_2$, both **TS1C_E** and **TS1C_Z** can adopt a geometry that the C−C double bond is nearly perpendicular to the coordination plane of Pd to achieve a good Pd-π(C═C) interaction. Therefore, the energy difference between the two TSs catalyzed by Pd(OAc)$_2$ is not significant, and the E/Z selectivity is moderate. A distortion−interaction analysis[14] of **TS1A_E** and **TS1A_Z** (Table S2) demonstrates that it is the interaction energy between substrate and catalyst that contributes to the preference of the E product.

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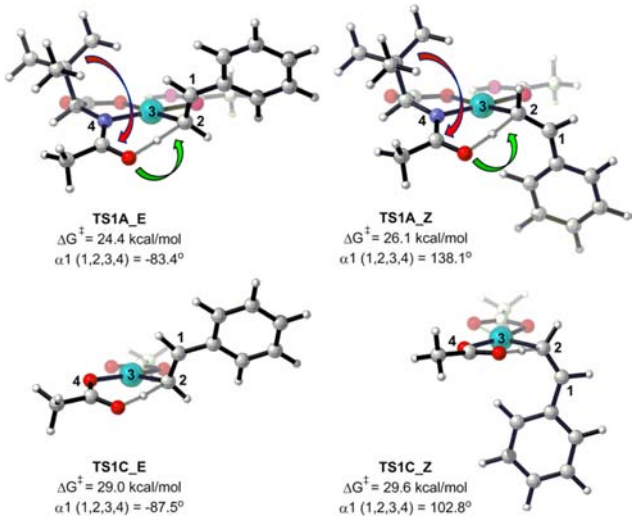

Figure 5. Transition structures of C−H activation catalyzed by Pd/Ac-tLeu-OH or $Pd(OAc)_2$.

This combined DFT and MS study reveals the reaction mechanism as well as the effect of MPAA on both reactivity and *E*/*Z* selectivity in Pd-catalyzed alkene−alkene cross-coupling reactions. The strong binding of the MPAA to Pd and basicity of the N-protecting group facilitate the C−H bond activation, while the *E*/*Z* selectivity is mainly attributed to the interaction energy between catalyst and substrate.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02542.

More details about MS and DFT calculations (PDF)

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Notes

The authors declare no competing financial interest.

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