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Role of *N*-Acyl Amino Acid Ligands in Pd(II)-Catalyzed Remote C–H Activation of Tethered Arenes

Gui-Juan Cheng,[†] Yun-Fang Yang,[†,‡] Peng Liu,[‡] Ping Chen,[†] Tian-Yu Sun,[†] Gang Li,[§] Xinhao Zhang,[†] K. N. Houk,*[,‡] Jin-Quan Yu,*[,§] and Yun-Dong Wu*[,†,∥]

[†]Lab of Computational Chemistry and Drug Design, Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, Shenzhen 518055, China

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

[§]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

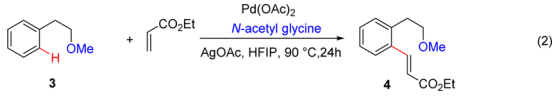
[∥]College of Chemistry, Peking University, Beijing 100871, China

Supporting Information

ABSTRACT: A combined experimental/computational study on the amino acid ligand-assisted Pd-catalyzed C–H bond activation reveals a mechanism in which the amino acid acts as both a dianionic bidentate ligand and a proton acceptor. This new model explains the effects of amino acids on reactivity and selectivity and unveils the dual roles of amino acids: stabilizing monomeric Pd complexes and serving as the internal base for proton abstraction.

Direct activation of C–H bonds provides a sustainable and efficient methodology to synthesize diverse organic molecules from simple hydrocarbon derivatives.[1] Different strategies to improve reactivity and selectivity for C–H activation of arenes have been developed.[2] In the long run, development of ligands to achieve catalyst-controlled selective C–H activation is the most powerful approach, which remains a significant challenge in the field of C–H activation. Recently, Yu et al. discovered that simple, commercially available mono-*N*-protected amino acid (MPAA) ligands lead to improved yields, shorter reaction times, and excellent regio- and enantioselectivities in various Pd-catalyzed C–H activations.[3−6] Numerous applications using MPAA ligands to enable or improve a diverse range of C–H activation reactions with different substrate classes appeared in the literature.[7] Among the most striking examples are the remote C–H activations directed by weakly coordinating functional groups such as nitrile and ethers (eqs 1 and 2).[4,5]

(1)



(2)

In addressing the challenge to achieve *meta*-selective C–H activation of electron-rich arenes,[4,6f,7k,8] Yu et al. reported a class of nitrile-containing end-on templates that direct the activation of remote *m*-C–H bonds of tethered arenes (eq 1).[4] With the assistance of an MPAA ligand, the template overrides the intrinsic electronic and steric biases to achieve up to 96% *meta* selectivity. Similar reaction conditions were applied to *o*-C–H activation employing a weakly coordinating ether as the directing group (DG, eq 2).[5] The MPAA ligand accelerates the reaction substantially, improving the yield from 11% in the absence of MPAA to 92%.[5] Chiral MPAA ligands were employed to achieve the first Pd(II)-catalyzed asymmetric C–H activation of 2-benzhydrylpyridine substrates with up to 90% *ee*.[6a]

Understanding of the effects of MPAA and the mechanism of amino acid-assisted C–H activation is still limited.[9−11] A computational study by Musaev et al. led to the mechanistic proposal involving N–H bond cleavage followed by C–H bond activation.[9] Here we report mass spectrometry (MS) and density functional theory (DFT)[12] studies to reveal a novel mechanism involving monomeric Pd(MPAA) species and the origins of reactivity and regioselectivity. The MPAA not only stabilizes the monomeric Pd catalyst, but also serves as the internal base for proton abstraction by the amidate group.

MS experiments were carried out to explore the coordination complexes generated from the trimeric precatalyst $[Pd(OAc)_2]_3$ and MPAA ligands.[13] A 1:1 mixture of $Pd(OAc)_2$ and *N*-acetylglycine or *N*-Boc-glycine dissolved in CH_3OH or CH_3CN was analyzed by electrospray ionization MS. No cationic Pd acetate species was observed. Instead, monomeric MPAA-coordinated Pd complexes with two solvent molecules were observed (Figure 1).[14] The two solvent molecules (CH_3OH or CH_3CN) dissociate consecutively from $[Pd(MPAA)(Sol)_2, H]^+$ upon collision with Ar. Isotope pattern and fragmentation analysis via collision-induced dissociation (CID) (Figures S1–S4) suggested that the deprotonated amino acid coordinates with Pd in a bidentate fashion. This provides the first experimental evidence that both acetates in $Pd(OAc)_2$ are replaced upon MPAA coordination. Previously, displacement of one of the acetates[9] or an acetylacetonate[15] from Pd(II) complexes by MPAA was observed by NMR. Monomeric and dimeric Pd acetate species were observed in a mixture of $Pd(OAc)_2$ and benzoquinone in

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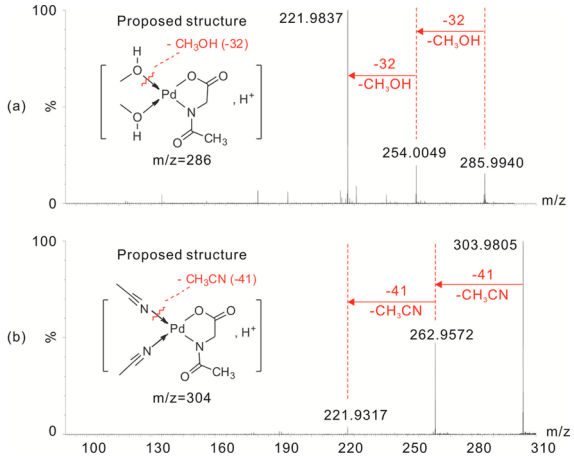


Figure 1. CID mass spectra of (a) $[^{106}PdC_6H_{14}O_5N]^+$ and (b) $[^{106}PdC_8H_{12}O_3N_3]^+$.

AcOH/DMSO (1:1).[16] The present study indicates that MPAA promotes formation of monomeric Pd(II) complexes even without an oxidant or excess AcOH.[17]

Computational studies provide detailed information about the mechanism of C−H activation in the presence of MPAA ligand. DFT calculations[12] were carried out on the dissociation pathways of trimeric $[Pd(OAc)_2]_3$ to form monomeric Pd complexes. As shown in Figure 2, formation of monomeric $Pd(OAc)_2$ (**5-A**) is

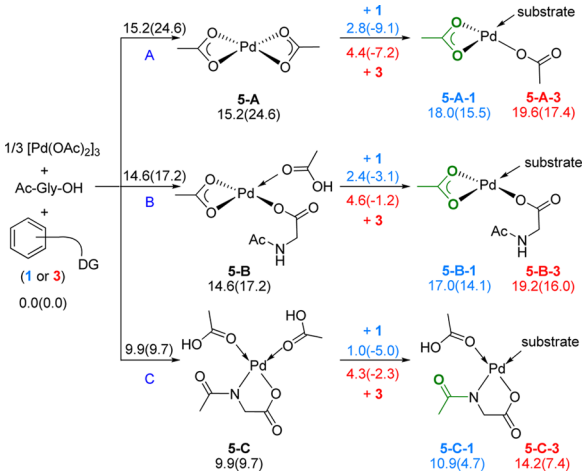
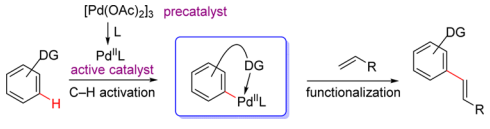


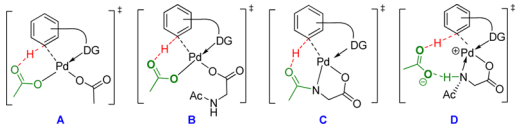
Figure 2. Formation of three possible active monomeric Pd catalysts, **5-A**, **5-B**, and **5-C**, and further complexation with substrate **1** or **3**. Relative free energies (electronic energies in parentheses) with respect to separate reactants are given in kcal/mol.

Scheme 1. Catalytic Process for Ligand-Assisted C−H Functionalization of Tethered Arenes



endergonic by 15.2 kcal/mol. Monodeprotonation of MPAA by one of the acetates leads to monodentate Pd-MPAA complex **5-B**, which is only slightly more stable than $Pd(OAc)_2$. Further deprotonation of the MPAA N−H bond by the other acetate is highly favored,[9] forming a stable bidentate Pd-MPAA complex coordinated with two neutral acetic acid molecules (**5-C**). The

Table 1. Calculated Activation Free Energies (Activation Electronic Energies in Parentheses) of Pathways A−D (kcal/mol) for Substrates 1 and 3



substrate		A	B	C	D
1	*ortho*	30.2(23.3)	30.0(23.6)	25.5(21.4)	44.1(33.6)
	meta	30.5(24.5)	29.2(22.2)	23.6(20.8)	46.4(37.0)
	para	31.1(24.3)	29.1(21.5)	24.1(20.6)	41.0(32.0)
3	*ortho*	34.3(29.1)	33.0(26.9)	28.9(27.3)	43.8(35.9)

N−H deprotonation requires a low barrier of 16.8 kcal/mol with respect to $[Pd(OAc)_2]_3$ (see SI) and the resulting intermediate **5-C** is 5.3 kcal/mol more stable than monomeric $Pd(OAc)_2$ (**5-A**). Here the normally unfavorable deprotonation of the N−H bond in amino acids is promoted by both the *N*-acyl group and the stronger binding of the deprotonated N with Pd, leading to a stable Pd complex with a dianionic bidentate MPAA ligand (**5-C**). This is in agreement with the above MS observations of the stable Pd-MPAA complex. Further complexation of **5-X** with substrate **1** or **3** leads to several possible intermediates, **5-X-1** or **5-X-3** (X: A−C), prior to the C−H bond activation. Similarly, bidentate Pd(MPAA)-substrate complexes **5-C-1** and **5-C-3** are both significantly more stable than the $Pd(OAc)_2$-substrate complexes **5-A-1** and **5-A-3**.

The complete catalytic cycle of reaction 1 was investigated (Scheme 1). The C−H activation was found to be the rate-determining step (Figure S5).[18] In accord with previous studies of Pd-catalyzed C−H activations, the C−H activation occurs through a concerted metalation/deprotonation (CMD) mechanism.[19,20] Other frequently proposed mechanisms, including oxidative addition, electrophilic aromatic substitution, and σ-bond metathesis, all have higher barriers (Figure S6).[10,21]

We explored several variations of the CMD mechanism involving different counterions coordinated to the Pd and employing either the acetate or the *N*-acyl carbonyl to deprotonate the C−H bond (Tables 1 and S1-3). Pathway A involves C−H activation from intermediates **5-A-1/3**, which represents the previously proposed CMD process for $Pd(OAc)_2$-catalyzed C−H activation in the absence of MPAA ligand. In pathway B, C−H activation occurs through monodentate Pd-MPAA complexes **5-B-1/3** and has activation energies similar to those in pathway A. This is consistent with the similar stabilities of the prereaction substrate complexes **5-A-1/3** and **5-B-1/3**. When the MPAA ligand adopts a monodentate binding mode, such as in pathway B, the effects on the metal center are minimal.

C−H activation of the bidentate Pd-MPAA complexes **5-C-1/3** involves dissociation of the acetic acid molecule to form a square planar Pd complex in which the DG and the C−H bond on the substrate both bind to the Pd. Traditional CMD mechanism requires an acetate to deprotonate the C−H bond. Since both acetates are replaced by the MPAA ligand and all four coordination sites of the Pd are now occupied by the ligand and the substrate, employing an acetate to activate the C−H bond in this Pd(MPAA)-substrate complex will require either dissociation of the MPAA ligand to an unfavorable monodentate binding mode (pathway B) or outer-sphere deprotonation with an unbound acetate[9] (pathways D and I, see SI). In contrast, the calculations revealed a novel C−H deprotonation mechanism

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involving the bidentate Pd-MPAA catalyst (pathway C). Instead of an external acetate, the *N*-acyl group on the dianionic MPAA ligand is acting as a base to deprotonate the C−H bond. The activation free energies for pathway C are 4−7 kcal/mol lower than those of pathways A and B for both substrates **1** and **3** (Table 1). This is in agreement with the greater reactivities in the presence of MPAA ligand.

The low activation energy of pathway C is attributed to several factors. First, as shown in Figure 2, the MPAA ligand promotes the formation of the active monomeric Pd catalyst. The previously proposed dimeric mechanism[21c] becomes unfavorable in the presence of MPAA ligand (see SI). Stabilization of monomeric Pd complexes may also operate in reactions with other strong σ-donor ligands,[22] such as pyridine.[23] As a dianionic ligand, MPAA replaces the carboxylate anions, and thus does not compete with substrate coordination as in the case of neutral ligands.[23] This advantage enables MPAA to facilitate C−H activation of substrates with weakly coordinating DGs.[5,24] The C−H activation with the Pd-MPAA complex is also promoted by the greater basicity of the *N*-acyl carbonyl (i.e., an amidate) than acetate (e.g., pathways A and B). The smaller bite angle of the MPAA ligand compared to two acetate ligands also leads to less steric hindrance for coordination of the DG. The planar geometry of the dianionic MPAA ligand places the *N*-acyl group in a favorable coplanar orientation to deprotonate the C−H bond while maintaining the square planar geometry of the Pd (Figure 3).

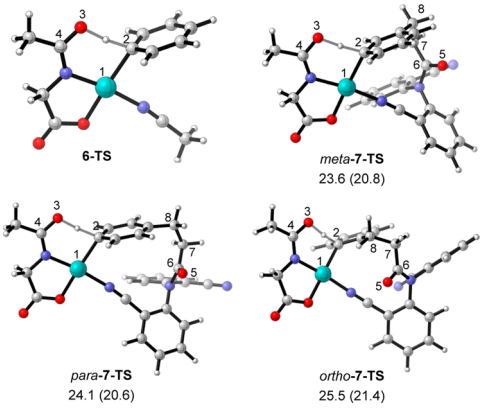
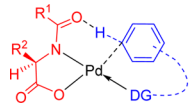


Figure 3. Model transition state **6-TS** with benzene and three most stable conformations of *m*-, *p*-, and *o*-**7-TS** with substrate **1** in pathway C. Activation free energies (activation electronic energies in parentheses) are in kcal/mol.

After determining the role of the MPAA ligand on mechanism, we investigated the regioselectivity. The short linker in substrate **3** apparently prevents the Pd from accessing the *m*- and *p*-C−H bonds in the directed pathways. Thus, we focused on the origin of the unique *meta* selectivity in the reaction with **1**. Systematic conformational searches (details are in Scheme S3) of the transition states (TSs) in reaction with substrate **1** resulted in location of nine, nine, and five TS conformers, respectively, for *o*-, *m*-, and *p*-C−H activations. The most stable *ortho*, *meta*, and *para* transition structures are depicted in Figure 3. The TS leading to the *meta*-product is the most stable, as found in experiment.

To reveal the origins of the template-controlled *meta* selectivity, we compared the geometries of the *o*-, *m*-, and *p*-TSs to a model C−H activation TS without the constraint of the linker, i.e., a TS with benzene and acetonitrile (**6-TS**, Figure 3). The structure of **6-TS** is perfectly planar with Pd1, C2, O3, and C4 atoms in the same plane ($\alpha 1_{\text{Pd1-C2-O3-C4}} = 0°$). This places the *N*-acyl group to an ideal orientation to deprotonate the benzene C−H bond. The benzene plane is perpendicular[19e] to the coordination plane of Pd ($\alpha 2 = 90°$) in order to achieve the optimum orbital overlap between the π orbital of benzene and the *d* orbital of the Pd. The planarity of the *N*-acyl group and the perpendicular orientation of the benzene ring are reasonably well preserved in *m*-**7-TS** ($\alpha 1 = 0°$ and $\alpha 2 = 88°$). Slight deviation from this optimum geometry was observed in *p*-**7-TS** ($\alpha 1 = -6°$ and $\alpha 2 = 84°$). More significant distortion was observed in *o*-**7-TS** ($\alpha 1 = 17°$ and $\alpha 2 = 81°$). Superimposing the regioisomeric TSs with **6-TS** indicates rmsd's of 0.19, 0.10, and 0.42 Å for the *o*-, *m*-, and *p*-TSs, respectively (Figure S7). This also indicates that the *m*-TS better mimics the nonconstrained model. In addition, the template itself is also less distorted in the *m*-TS compared to *o*- and *p*-TSs. It is well-known that the C−C single bond adjacent to carbonyl (O5═C6−C7−C8) prefers a *syn*-planar geometry ($\alpha 3 = 0°$).[25] This dihedral angle is −7° in reactant **1**, increasing to −27°, −42°, and −60° in *m*-, *p*-, and *o*-**7-TS**, respectively. This indicates stronger template distortions in the *p*- and *o*-TSs.

Scheme 2. Effects of Substituents on the MPAA Ligand



Ligand	Yield	Calc. $\Delta G^{\ddagger}$ ($\Delta E^{\ddagger}$) kcal/mol
R^1 = Ac, R^2 = H	95%	23.6 (20.8)
R^1 = Boc, R^2 = H	10%	26.3 (24.0)

Electronic and steric properties of the substituents (R^1 and R^2 groups, Scheme 2) on the bidentate MPAA ligand are expected to alter the electrophilicity of Pd and the proton affinity of the *N*-carbonyl group, and thus affect the rate of C−H activation. For example, replacing Ac-Gly-OH (R^1 = Ac, R^2 = H) with Boc-Gly-OH (R^1 = Boc, R^2 = H) in the reaction with **1** leads to a significant decrease in the experimental yield from 95% to 10%.[4] Our calculations indicate that the barrier of C−H bond activation with the Boc-Gly-OH ligand is 2.7 kcal/mol higher than with the Ac-Gly-OH ligand. The agreement between theory and experiment further supports the proposed mechanism. By properly introducing effective R^2 groups on the rigid chelating MPAA skeleton, it is possible to create a chiral environment for asymmetric C−H bond activation.[6] A long linker between coordinating group and active site of C−H bond enable substrates to achieve remote functionalization.[26] Based on the monomeric TS model, the linker in substrates can be adjusted to accomplish site-selective functionalization of remote C−H bonds in various arenes and heteroarenes.

In summary, the reaction mechanism of amino acid-assisted remote C−H bond activation was investigated with MS and DFT calculations. Our study provided experimental support for the formation of monomeric Pd(MPAA) complexes and uncovered a novel CMD mechanism in which the basic *N*-protecting group of the dianionic amidate ligand participates in the deprotonation of the C−H bond. This mechanism accounts for improved reactivity and selectivity in C−H activation reactions with MPAA ligands. The direct involvement of dianionic MPAA as the proton acceptor in C−H activation opens new avenues for ligand and template design.

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■ ASSOCIATED CONTENT

Supporting Information

More details about MS and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

houk@chem.ucla.edu; yu200@scripps.edu; wuyd@pkusz.edu.cn

Notes

The authors declare no competing financial interest.

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