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Structure–Activity Comparison in Palladium–N-Heterocyclic Carbene (NHC) Catalyzed Arene C–H Activation-Functionalization

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Dedication: This work is dedicated to Professor Georgiy B. Shul'pin on the occasion of his 70th birthday.

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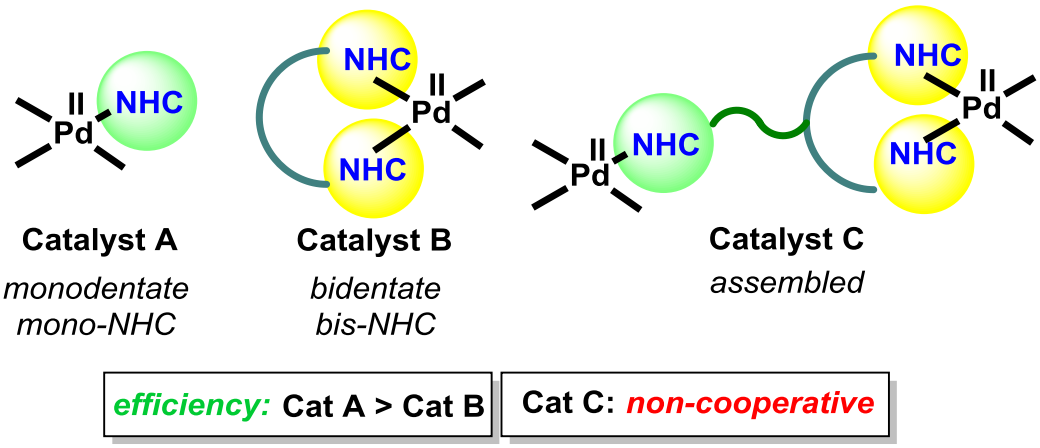
Graphical Abstract



Highlights

- A monodentate mono-NHC palladium(II) complex was developed as efficient arene C-H activation-functionalization catalyst
- The monodentate mono-NHC catalyst was more efficient than a similar bidentate bis-NHC palladium(II) complex
- Kinetics and other mechanistic analyses provided the plausible reason for the observed higher activity of the catalyst

Abstract

A simple and efficient C-H activation catalyst was identified through a model structure-activity screening applied to a noncooperative, nonsymmetric bimetallic palladium(II)-N-heterocyclic carbene complex. Mechanistic studies based on kinetics and DOSY NMR spectroscopy provided the origin of the higher efficiency of the identified catalyst.

Keywords: Arene C-H activation / N-Heterocyclic carbene (NHC) / Palladium / Acetoxylation / Mechanistic study

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1. Introduction

In the field of N-heterocyclic carbene (NHC) chemistry, one of the major focuses has been in the design of new carbenic architectures to offer diverse stereoelectronic properties for fulfilling a plethora of desired functions. Among the various versatile NHC ligand frameworks, bis-, tris- and poly-NHC motifs offer a great deal of coordination multifariousness and modularity—an attribute that benefits the development of bi-/polymetallic catalysis [1]. In line with this, Cowie et al. explored unsymmetrical dicarbenes toward heterodimetallic coordination suitable for tandem catalysis [2], while Peris et al. investigated symmetrical bis- and tris-NHCs for homo-bimetallic/trimetallic catalysis [1a,c,h,i,3]. Orthogonal reactivity and compatibility of each metal centers are required for operating tandem catalysis. On the other hand, cooperative effect among the individual metal centers plays an important role in bi-/polymetallic catalysis which exhibits enhanced activity. However, Peris et al. demonstrated that bi-/polymetallic NHC complexes may [4a] or may not [4b,c] exhibit catalytic cooperative effect depending on the (electronic) communication among the metal centers. Our group has been motivated for developing robust and efficient C-H activation-functionalization catalysts based on NHC ligand framework [5]. Recently, we reported chelating bis-NHC monopalladium(II) complexes for efficient arene C–H acetoxylation catalysis with $PhI(OAc)_2$ as oxidant [6a]. Inspired by the longstanding challenge of developing more active non-directed arene C-H activation catalysts [6b-h], and the success of polymetallic systems in a variety of catalytic reactions [1a,c,2,3,4], a new tris-NHC bound dipalladium(II) catalyst **1** with nonsymmetrically coordinated Pd(II) centers was designed (Fig. 1) and employed by us for anticipated synergistic benefit during oxidative arene C-H acetoxylation catalysis with $PhI(OAc)_2$ as oxidant. Delightedly, the resultant catalytic activity was observed to be higher than that of previously reported chelating bis-NHC monopalladium(II) complexes for the same reaction [6a]. However, no "cooperativity" but only an "additive" effect was observed in the overall catalytic activity. As a part of the assay process with an aim to deconvolute the "additive" effect exhibited by this bimetallic Pd(II) catalyst **1**, two model monometallic Pd(II) partners **2** and **3** (Scheme 1) were synthesized and screened. Interestingly, the relatively simpler, mono-NHC palladium(II) model **3** appeared to be a highly efficient and robust catalyst for the reaction. This finding is significant in the context of a limited number of efficient candidates available in the library of non-directed arene C-H acetoxylation catalysts reported so far [6b,g,h,7].

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2. Experimental

2.1. General methods and materials

^{1}H , $^{13}C\{^{1}H\}$, DOSY NMR spectra were recorded on Bruker AVANCE III 400 MHz, 500 MHz and 700 MHz NMR spectrometers. Chemical shifts (δ) are expressed in ppm using the residual proton resonance of the solvent as an internal standard ($CHCl_3$: δ = 7.26 ppm for ^{1}H spectra, 77.36 ppm for $^{13}C\{^{1}H\}$ spectra; DMSO: δ = 2.50 ppm for ^{1}H spectra, 39.5 ppm for $^{13}C\{^{1}H\}$ spectra; CD_3CN: δ = 2.13 ppm for ^{1}H spectra, 118.2 ppm for $^{13}C\{^{1}H\}$ spectra; Toluene: δ = 7.000 ppm for ^{1}H spectra, 137.9 ppm for $^{13}C\{^{1}H\}$ spectra). All coupling constants (*J*) are expressed in hertz (Hz) and only given for ^{1}H-^{1}H couplings unless mentioned otherwise. The following abbreviations were used to indicate multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet) and m (multiplet). ESI mass spectroscopy was performed on a Bruker microTOF QII spectrometer. Dry solvents and reagents were obtained from commercial suppliers and used without further purification. Deuterated solvents were purchased from Aldrich. $Pd(OAc)_2$ was purchased from Johnson Matthey and used as received without further purification. **L1** and **L2** was prepared by following reported literature procedure [6a,8].

2.2. Synthesis of complexes

Complex 1. Complex **1** was synthesized directly from **L1** (50 mg, 0.071 mmol) by refluxing it in acetonitrile with 2 equivalents of $Pd(OAc)_2$ (31.8 mg, 0.142 mmol) in presence of KI (20.6 mg, 0.124 mmol) for 16 h . After column chromatography, pure complex **1** was obtained in 29% yield. Complex **1** can also be prepared from complex **2** by the following procedure. A mixture of **2** (58 mg, 0.071 mmol) and $Pd(OAc)_2$ (15.9 mg, 0.071 mmol) and KI (20.6 mg, 0.124 mmol) in acetonitrile, was refluxed for 9 h under inert atmosphere. After cooling to ambient temperature, mixture was filtered through a pad of celite and solvent was removed under vaccum. The crude solid was purified by column chromatography. Compound **1** was eluted with 8:2 chloroform/acetonitrile solutions. Removal of solvents afforded compound **1** as brown orange solid in 41% yield. ^{1}H NMR (700 MHz, CD_3CN): δ = 8.02 (d, *J* = 8.6Hz, 2H), 7.66 (d, *J* = 1.8Hz, 2H), 7.56 (s, 1H), 7.54 (d, *J* = 8.5Hz, 2H), 7.33 (d, *J* = 1.8Hz, 1H), 7.32 (d, *J* = 1.8Hz, 1H), 7.16 (d, *J* = 1.9Hz, 2H), 3.94 (s, 6H), 3.93 (s, 3H); ^{13}C NMR (175 MHz, CD_3CN): δ = 165.2, 144.8, 140.9, 138.7, 129.0, 127.0, 126.7, 125.8, 124.7, 124.0, 123.1, 66.3, 41.0, 40.3; HRMS (ESI) *m/z* =

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926.6898 $[(M)\text{-}I\text{-}CH_3CN]^+$ (calcd for $C_{19}H_{20}N_6Pd_2I_3^+$: *m/z* = 926.6961). Anal. Calc. for $C_{21}H_{23}N_7I_4Pd_2$, CH_3CN, $CHCl_3$: C, 22.98; H, 2.17; N, 8.93. Found: C, 22.72; H, 2.37; N, 8.82%.

Complex 2. A mixture of ligand precursor **L1** (168 mg, 0.235 mmol) and $Pd(OAc)_2$ (52.5 mg, 0.235 mmol) in 60 mL acetonitrile, was refluxed for 16 h under inert atmosphere. After cooling to ambient temperature, reaction mixture was filtered through celite bed. After filtration acetonitrile was removed in vacuum and yellow residue was washed several times with ether and dried in vacuum to give 173 mg pure complex **2** as yellow powder (Yield 90%).^{1}H NMR (400 MHz, CD_3CN): δ = 9.85 (s, 1H), 8.35 (s, 1H), 8.03 (s, 1H), 7.96 (d, *J* = 1.5Hz, 2H), 7.35 (s, 1H), 7.85 (d, *J* = 8.6Hz, 2H), 7.66 (d, *J* = 8.4Hz, 2H), 7.52 (d, *J* = 1.5Hz, 2H), 3.93 (s, 3H), 3.90 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.6, 138.4, 136.2, 134.9, 128.8, 124.7, 123.5, 122.4, 121.1, 120.5, 113.4 73.6, 40.6, 36.2; HRMS (ESI) *m/z* = 692.8988 $[(M)\text{-}I]^+$ (calcd for $C_{19}H_{21}N_6PdI_2^+$: *m/z* = 692.8954); Anal. Calc. for $C_{19}H_{21}N_6I_3Pd$: C, 27.81; H, 2.58; N, 10.24. Found: C, 28.26; H, 2.729; N, 10.00%.

Complex 3. A mixture of 3-methyl-1-phenyl-1H-imidazolium iodide, **L2** (85.8 mg, 0.3 mmol), $Pd(OAc)_2$ (67.2 mg, 0.3 mmol) and KI (74.7 mg, 0.45 mmol) in 3.5 mL pyridine, was stirred at room temperature for 48 h in Schlenk tube under argon. Reaction mixture was diluted to 18 mL with dichloromethane and was filtered through celite. Solvent was evaporated under vacuum. Crude solid thus obtained was loaded to a silica gel column. Elution with 1:1 hexane/ethyl acetate afforded 115 mg pure compound **3** as orange powder (Yield 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (dd, *J* = 6.3, 1.4Hz, 2H), 8.06-7.98 (m, 2H), 7.66 (tt, *J* = 7.7, 1.5Hz, 1H), 7.56 (dd, *J* = 10.4, 4.8Hz, 2H), 7.48 (t, *J* = 7.4Hz, 1H), 7.26-7.21(m, 2H), 7.18 (d, *J* = 2.0Hz, 1H), 7.10 (d, *J* = 2.0Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 147.8, 139.8, 137.6, 129.1, 128.8, 126.4, 124.5, 123.8, 123.3, 39.8; HRMS (ESI) *m/z* = 469.9321 $[(M)\text{-}I]^+$ (calcd for $C_{15}H_{15}N_3PdI^+$: *m/z* = 469.9346).); Anal. Calc. for $C_{15}H_{15}N_3I_2Pd$: C, 30.15; H, 2.53; N, 7.03. Found: C, 30.29; H, 2.31; N, 7.10%.

*2.3. Catalytic oxidative acetoxylation of arenes with complexes **1**, **2** and **3***

Catalytic acetoxylation of different arenes were performed separately using complex **1**, complex **2** orcomplex **3** as catalyst. Diacetoxyiodobenzene (40.4 mg, 0.125 mmol), catalyst (2.5 mol% w.r.t Pd) and arenes (1.25 mmol) were placed in a sealed tube which was equipped with a magnetic bar.

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1 mL of freshly prepared acetic acid/acetic anhydride (9:1 v/v) mixed-solvent was added to the mixture. Sealed tube was capped tightly and reaction mixture was stirred at 95 °C for 24 h. It was then cooled to room temperature and the yield was calculated by GCMS analysis using PhCl *(added after reaction)* as an internal standard. Following are the yield (%) and corresponding ratios of *o*, *m* and *p*- isomers. In case of acetophenone, *o*-acetoxylated product was formed exclusively. *For evaluating time course of toluene acetoxylation with the complexes **1**, **2**, and **3** the following procedure was followed.* Catalytic acetoxylation of toluene were performed separately using complex **1** (0.2 mol%), complex **2** (0.2 mol%)or complex **3** (0.2 mol%) as catalyst. Catalyst, $PhI(OAc)_2$ (40.4 mg, 0.125 mmol) and toluene (1.25 mmol) were placed in a sealed tube which was equipped with a magnetic bar. 1 mL of freshly prepared acetic acid/acetic anhydride (9:1, v/v) mixed-solvent was added to the mixture. The reaction mixture was stirred at 95 °C. It was then cooled to room temperature and was analyzed at every 6 h interval by GCMS for a total of 24 h.

3. Results and discussion

The complexes were synthesized by heating the corresponding ligands (**L1** or **L2**) and $Pd(OAc)_2$ in acetonitrile (for **1** and **2**) or in pyridine (for **3**) as shown in Scheme 1. The coordination environment of the synthesized assembled dipalladium(II) complex **1** with the tris-NHC ligand was kept distinct at each metal center. Not surprisingly, the coordination environment around a metal center plays a vital role in any catalysis. For every specific catalytic reaction, the significance of metal-coordination environment is different and generally it is closely related to the inherent mechanistic steps involved in the particular catalytic cycle. Thus, in **1**, a chelating bis-NHC scaffold was imposed to one Pd center while the other Pd was coordinated to a tethered mono-NHC ligand. Strong σ-donating ability of NHC ligands was believed to impart robust Pd-NHC bond as required for efficient turnover during oxidative catalysis involving Pd^{II}/Pd^{IV} cycle. Molecular structure of **1** confirmed binding of two Pd centers in different coordination mode within the same ligand backbone (Fig. 2). The six-membered palladaacycle with the chelating bis-NHC preferred a boat conformation exhibiting $C_{carbene}–Pd^{II}–C_{carbene}$ bite angle of 83.9(5)°, and $Pd^{II}–C_{carbene}$ bond distances of 1.991(14) Å and 1.986(14) Å. The other Pd in **1** was bound by one NHC in monodentate coordination mode with a relatively shorter $Pd^{II}–C_{carbene}$ bond length of 1.928(14) Å, and two *trans* iodides. The two Pd metals in **1** were 8.005 Å apart through space.

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When **1** was tested as a catalyst (2.5 mol%) for non-directed C-H acetoxylation of toluene using $PhI(OAc)_2$ as oxidant, it resulted in 64% yield of acetoxytoluene in 24 h of reaction carried out at 95 °C (Fig. 3, A). Some more arenes were used to prove its efficacy which was found to be promising. However, because of the 8 Å distance between two Pd centers in **1**, its catalytic activity seemed not to be due to any cooperativity. This argument prompted us to deconvolute the overall activity of **1**. Thus disassembly of **1** into its monometallic models was sought, which led to the synthesis of **2** and **3** (Scheme 1). Molecular structures of **2** and **3** were confirmed to possess a similar coordination environment around the Pd center along with similar geometric parameters as was present in **1** (Fig. 2). The complexes **2** and **3** were then subjected to catalytic activity test for acetoxylation of the aromatic compounds as above under same conditions. The results were shown in Fig. 3A. It is noteworthy that acetoxylation of all the arenes was not accompanied by any side reaction and maintenance of inert atmosphere was not required for these reactions, which enabled us to compare the performance of all the catalysts quite easily. As is evident from Fig. 3A, the simple mono-NHC complex **3** was proved to be much superior catalyst than **2**. The yields of all the arenes (except bromobenzene) were 60-70% with the use of catalyst **3** which was noteworthy in the context of all the known Pd-based acetoxylation catalysts reported so far [6]. The remarkable difference in the initial rates of the reaction with complex **2** and **3** evaluated by applying a very low catalyst loading (0.2 mol%) was also evident from Fig. 3B. As the complex **3** was found to be superior catalyst, it was applied for a few more oxidative arene C-H acetoxylation and directed halogenation catalysis as shown in Table 1.

The origin of higher activity of **3** than **2** was investigated via mechanistic kinetics study. Kinetic order on each component of complex **2** and **3**-catalyzed acetoxylation of toluene was assessed by initial rate method (Fig. S20-S31, supplementary content). However, surprisingly, the analysis provided the overall rate expression as $rate = k_{obs}[Pd][toluene]$ for both **2**- and **3**-catalyzed reactions (Scheme 2A). The oxidation of Pd^{II} center by $PhI(OAc)_2$ could be excluded to be rate-determining as the order dependency on $PhI(OAc)_2$ was zero in both the cases. Involvement of toluene in the rate expressions suggested its presence in the rds which was again verified by kinetic isotope effect studies (Scheme 2B). Thus, catalytic reactions of toluene and toluene-d_8 with $PhI(OAc)_2$ under identical conditions generated the k_H/k_D value of 4.01±0.14 and 3.47±0.24 in case of **2** and **3** as catalyst, respectively. These primary kinetic isotope effect values indicated that the breaking of arene C-H bond was involved in the rate limiting step [6a,b,h,9]. In situ ESI-MS

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analysis of the reaction of **2** or **3** with $PhI(OAc)_2$ suggested the formation of acetate-bound Pd(II) intermediates such as II and VI (Scheme 2C, 2D) in the reaction mixture. These acetate intermediates could be formed via oxidation of Pd(II) to Pd(IV) followed by reductive elimination of I_2 as supported by qualitative iodine-detection experiment (Fig. S39-S40, supplementary content) [6a].

It has been reported in literature that "Pd^{II}-OAc" species may exist in dimeric, trimeric or other higher order aggregates in solution [6b,10]. Based on this knowledge, a diffusion-ordered spectroscopy (DOSY) NMR experiment was undertaken to assess the catalyst resting state in case of both **2** and **3**-catalyzed reactions [6b], with an aim to complement the mechanistic kinetics information which was alone insufficient to explain the difference in the observed reactivity with **2** and **3**. Thus, the reaction of **2** or **3** with $PhI(OAc)_2$ was performed in CD_3CN and toluene-d_8 in situ in an NMR tube in the presence of some inert reference compounds as molecular weight standards and DOSY spectra were recorded at 298 K. The results of DOSY NMR analysis were found to be significant and suggestive. Within the limits of approximation of these experiments, the molecular weight of the generated "Pd^{II}-OAc" species present in the reaction mixture (essentially the resting states of the catalysts **2** and **3**) was calculated from the plot of log(D) versus log(MW) (D = diffusion coefficient, MW = molecular weight) as shown in Fig. 4. The calculated values of the molecular weight suggested that in case of **2**, the resting state was likely to be a monomeric species **II**, but in case of **3**, the resting state was most likely a dimeric species **VII** or **VIII** (both could be in equilibrium) and unlikely to be a monomeric species **VI** (Fig. 4). A dimeric resting state and a reaction order of 1 on Pd, in case of **3**-catalyzed reaction, actually indicated that the rate- determining transition state also involved a bimetallic Pd species [6b,10b,c,11]. On the other hand, for **2**-catalyzed reaction a monomeric resting state and first order rate dependency on Pd signified a monometallic rate-determining transition state [6b,11]. Based on all these experimental data, the most likely catalytic cycles were proposed for reaction with **2** and **3** (Scheme 3). As per the proposal, the striking difference was in the rate-determining C–H activation step, wherein catalyst **3** exhibited a bimetallic step. The kinetic advantage of bimetallic reaction over monometallic one due to redox cooperativity between two metal centers reducing the activation barrier, can thus explain the more favored and efficient catalysis with **3** than **2**. Ritter et al. reported the argument of kinetic advantage in bimetallic reductive elimination as well as oxidative addition steps over monometallic versions [10b,c]. The favorable acetate-assisted monometallic to

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bimetallic equilibrium for catalyst **3** and the less-favored one for catalyst **2** (as suggested from DOSY data) might be due to favorable π-π stacking interaction arising from a five-membered planar metallacycle in case of **3** as opposed to a six-membered boat-like puckered metallacycle in case of **2** (Fig. S48, supplementary content) [12]. However, it should be mentioned that this justification is speculative only; it requires further analysis. While species **IV** can undergo monometallic reductive elimination to furnish the product ArOAc, **X** is likely to exhibit heterolytic cleavage of Pd–Pd bond to form a Pd^{IV}–Pd^{II} species **XI** according to theoretical and experimental results reported in literature [13], followed by similar reductive elimination of ArOAc.

4. Conclusion

In conclusion, this study featured a structure-activity screening based on the disassembly of a non-cooperative bimetallic Pd-NHC complex into its monometallic model counterparts. Upon full structural characterization of all the complexes followed by comparative catalytic activity studies, eventually it led to the identification of a simple monometallic Pd-NHC-catalyst which was found to be highly efficient in arene C-H activation/functionalization.

Mechanistic navigation with the help of initial rate kinetics, kinetic isotope effects, ESI-MS and DOSY NMR studies suggested that the involvement of Pd–Pd bonded bimetallic intermediate in the rate-determining C–H activation step was the key for the enhanced reactivity of the newly identified catalyst.The kinetic advantage of bimetallic rate-determining step over monometallic one was in line with previous studies on similar oxidative addition and reductive elimination reactions. The presented work is expected to enhance our knowledge-base on the important role of Pd–Pd bimetallic intermediate in the catalytic cycle for designing active monometallic and/or bimetallic Pd complexes for analogous C-H activation catalysis, in general, with similar chelating and non-chelating common organic substrates.

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Appendix

Supplementary content

Supplementary information containing additional experimental details, kinetics details and spectra are available.

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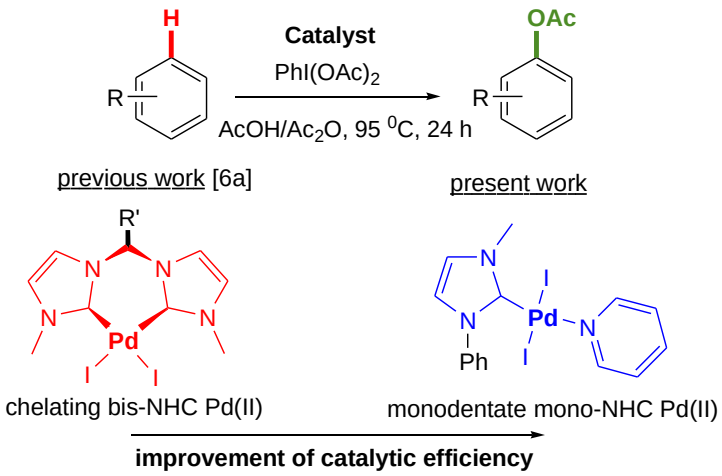

Fig. 1. Development of Pd(II)-NHC catalyst for non-directed arene C-H acetoxylation

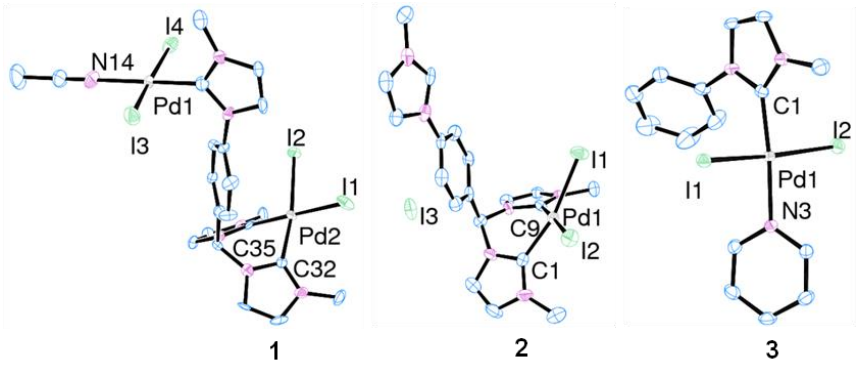

Fig. 2. ORTEP diagrams of complexes **1**, **2** and **3** (30% ellipsoids probability level). Selected bond lengths (Å) and bond angles (°), H atoms were removed for clarity: Complex **1**: C22-Pd1 = 1.928(14); Pd2-C32 = 1.991(14); Pd2-C35 = 1.986(14); Pd2-I1 = 2.6422(15); Pd2-I2 =

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2.6560(14); Pd1-I3 = 2.5919(16); Pd1-I4 = 2.6083(14); Pd1-N14 = 2.061(14); C35-Pd2-C32 = 83.9(5); I1-Pd2-I2 = 95.72(5); I3-Pd1-I4 = 172.61(6). Complex **2**: C1-Pd1 = 1.995(6); Pd1-C9 = 1.979(6); Pd1-I1 = 2.6236(7); Pd1-I2 = 2.6668(7); C9-Pd1-C1 = 83.2(2); I1-Pd1-I2 = 92.14(2). Complex **3**: C1-Pd1 = 1.953(3); Pd1-I1 = 2.6009(3); Pd1-N3 = 2.094(3); I1-Pd1-I2 = 170.531(12). CCDC 1465252, 1465254, and 1465253, contains the supplementary crystallographic data for **1**, **2**, and **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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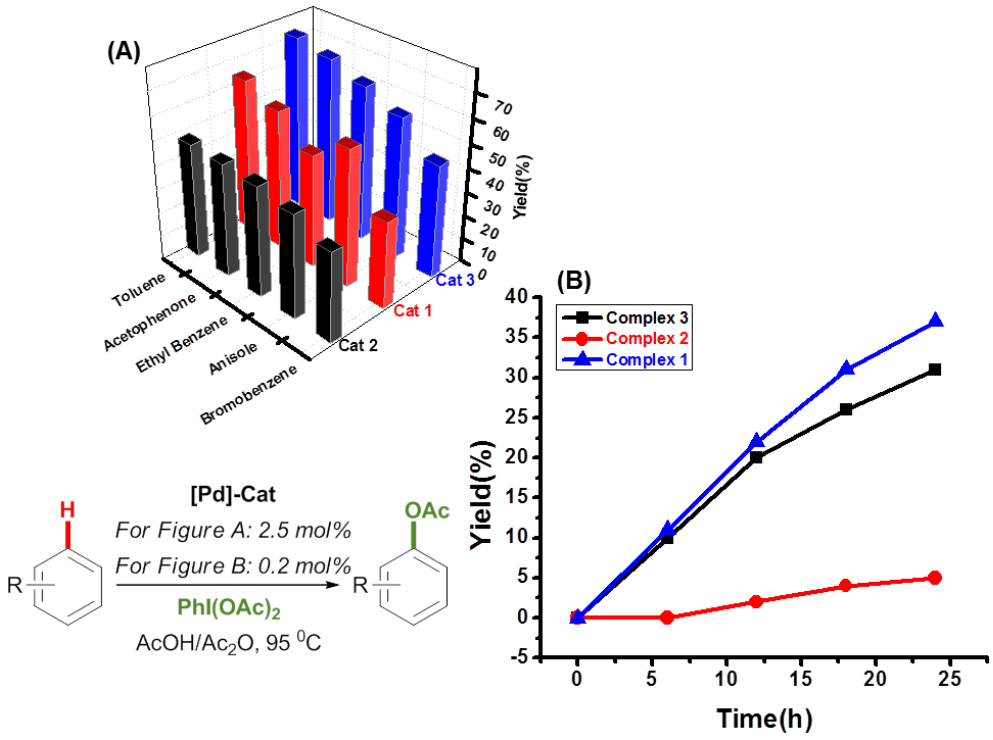
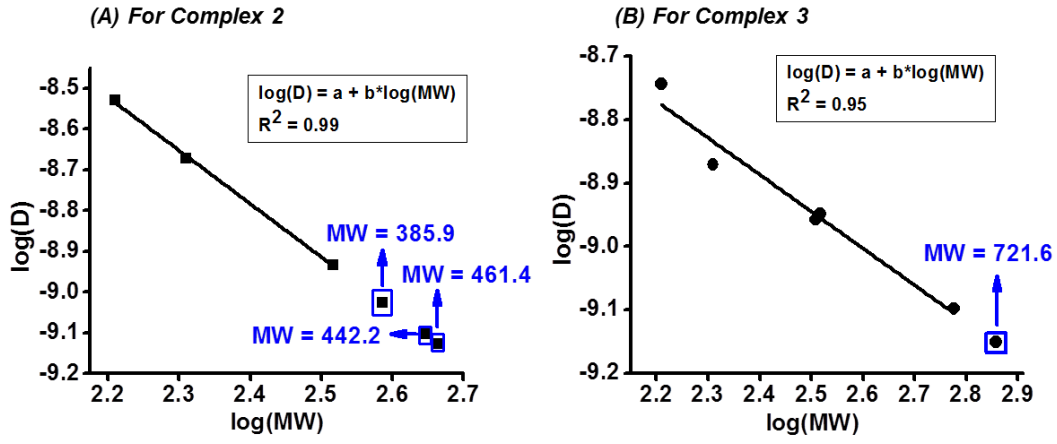


Fig. 3. Comparison of catalytic activity of **1**, **2**, and **3** in non-directed arene C-H activation reaction.



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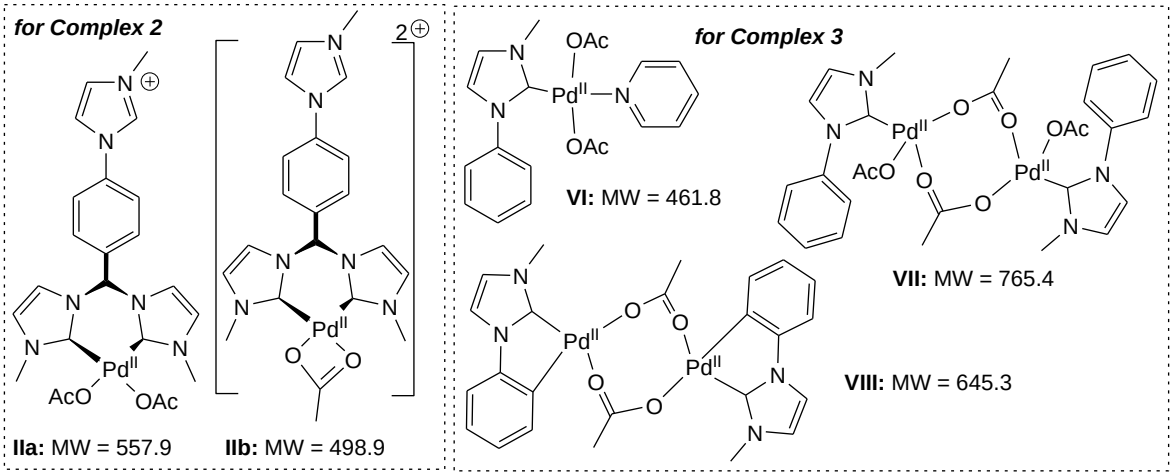
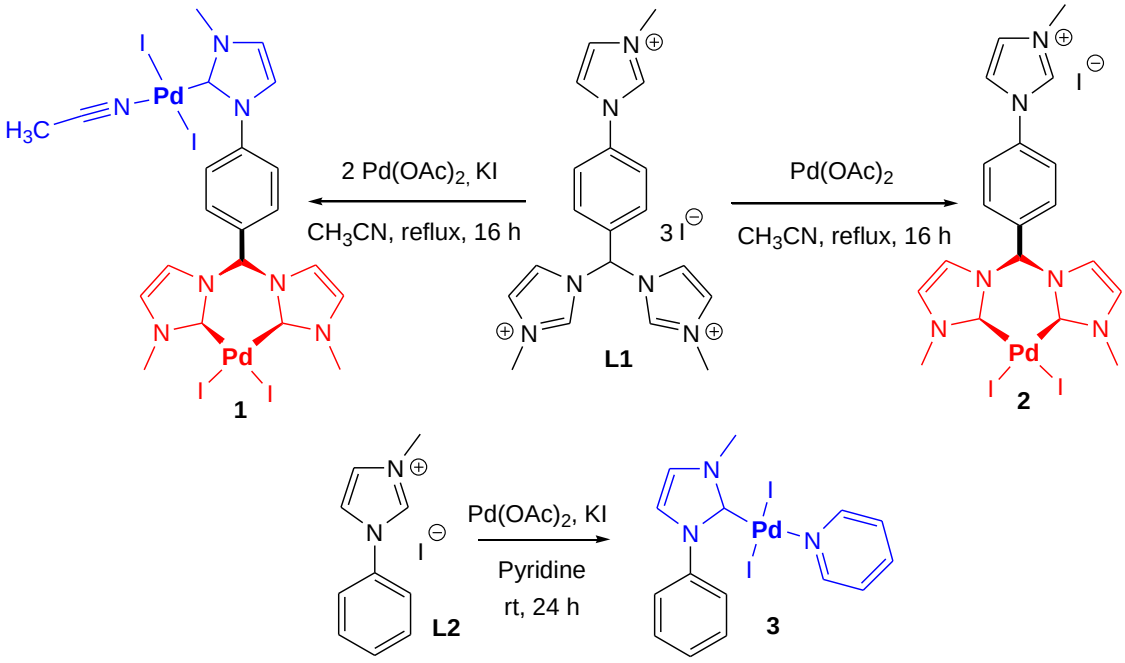


Fig. 4. DOSY NMR spectroscopic results (shown at the top) to evaluate the most probable species (shown at the bottom) generated from the reaction of **2** and **3** with $PhI(OAc)_2$ via approximate molecular weight determination method. See supplementary content for details.



Scheme 1. Synthesis of the complexes.

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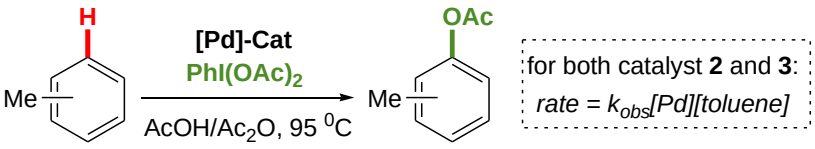
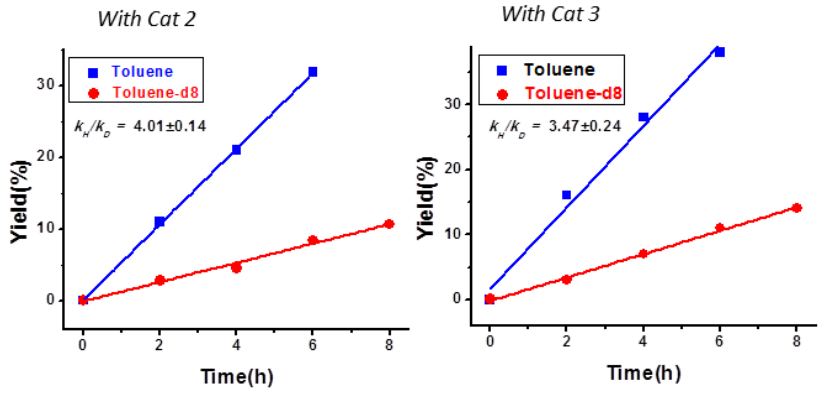
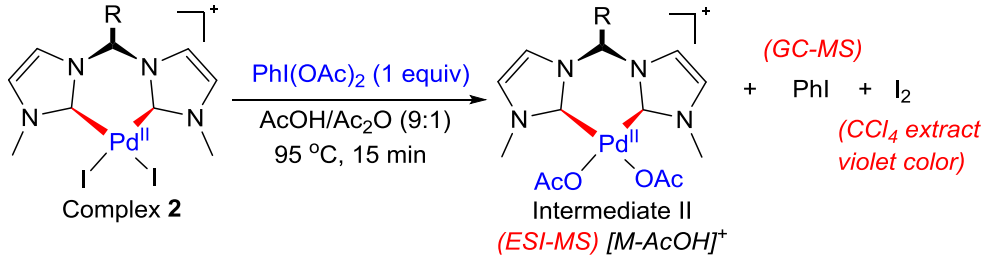
(A) Initial rate studies



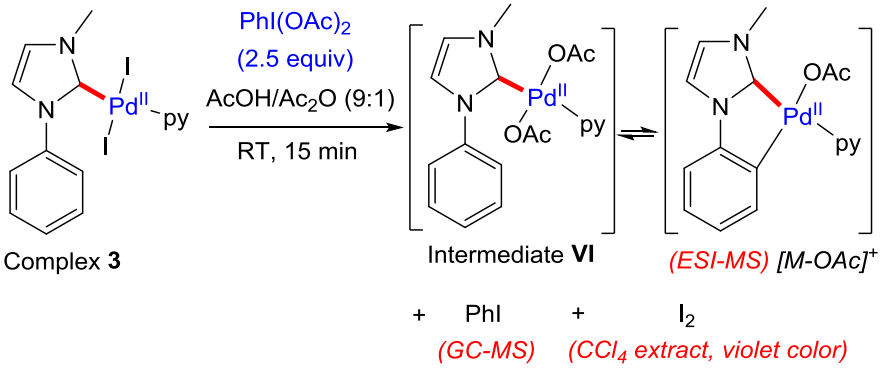
(B) Kinetic Isotope effects



(C) Control study with complex **2**



(D) Control study with complex **3**



Scheme 2. Kinetics for order determination, isotope effect, and other control studies.

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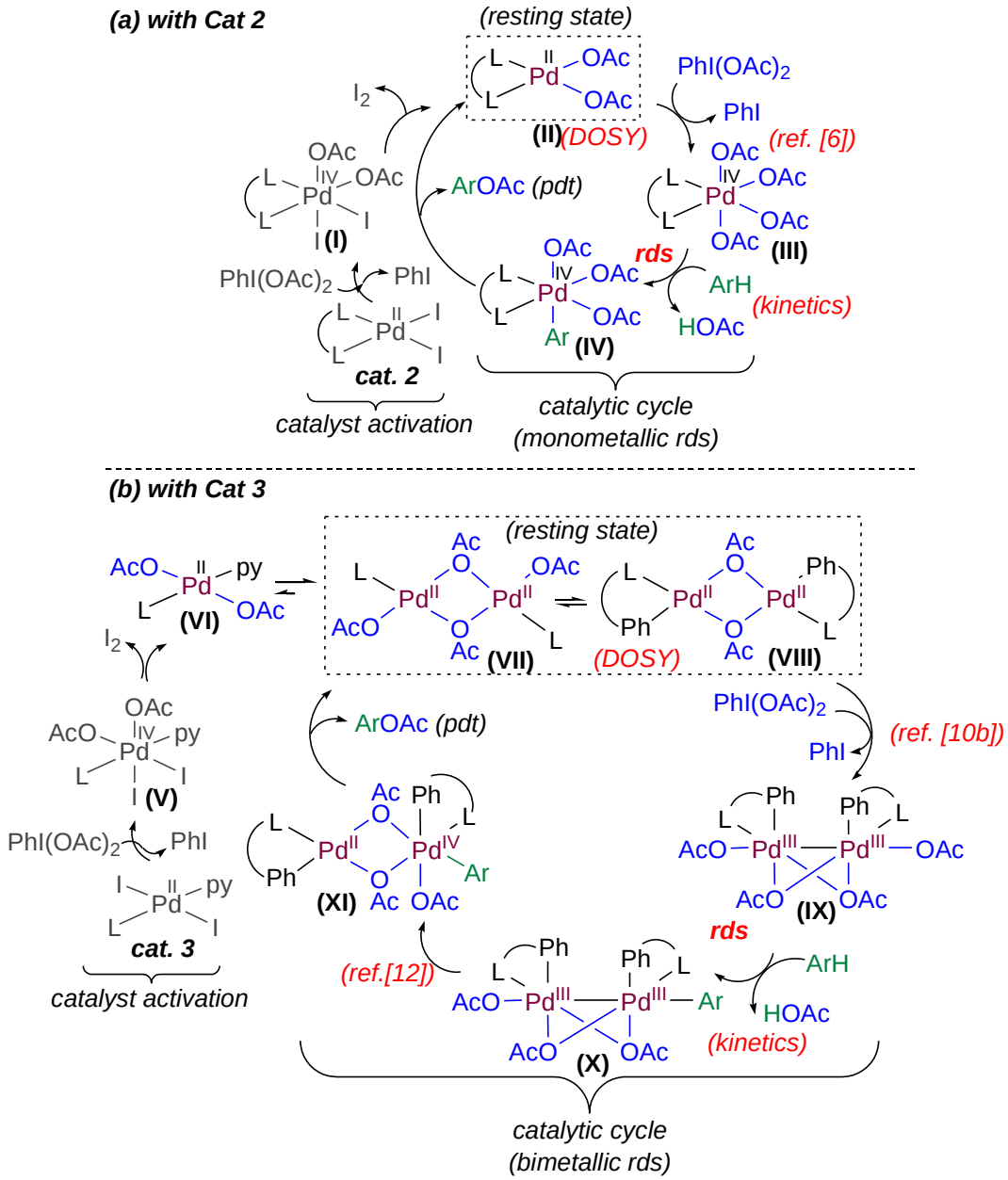

Scheme 3. Plausible catalytic cycles for **2**- and **3**-catalyzed reactions.

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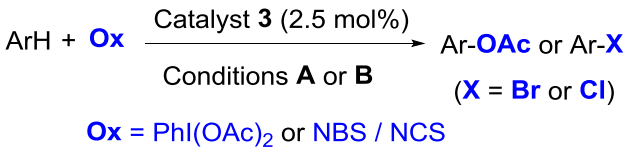
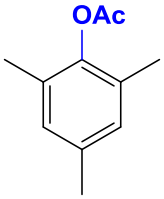
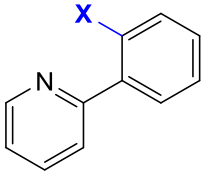
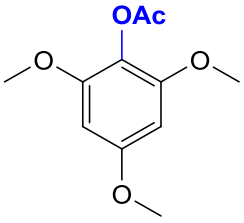
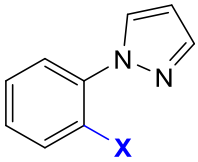
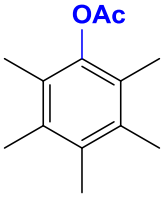
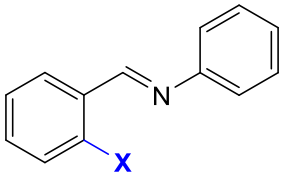
Table 1 Complex **3**-catalyzed arene C-H acetoxylation and directed halogenation reaction.



Ar-OAc	%Yield	Ar-X	%Yield (X= Br)	%Yield (X= Cl)
	39		72	81
	95		79	77
	70		50	44

[a]Reaction conditions **A**: ArH (1.25 mmol), $PhI(OAc)_2$ (0.125 mmol), Catalyst **3** (2.5 mol%), $AcOH/Ac_2O$ (1 mL; 9:1, v/v), 95 °C, 24 h. Reaction conditions **B**: ArH (1.25 mmol), NBS or NCS (0.125 mmol), Catalyst **3** (2.5 mol%), CH_3CN (1 mL), 95 °C, 24 h. Yields (based on the oxidant, **Ox**) were calculated by GCMS using chlorobenzene as internal standard added after the reaction was over.