C–H Activation

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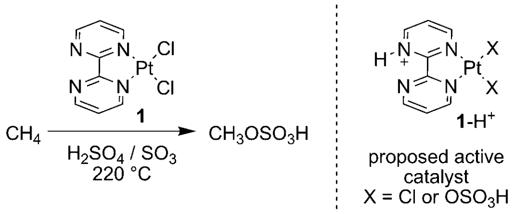
Platinum and Palladium Complexes Containing Cationic Ligands as Catalysts for Arene H/D Exchange and Oxidation**

*Marion H. Emmert, J. Brannon Gary, Janette M. Villalobos, and Melanie S. Sanford**

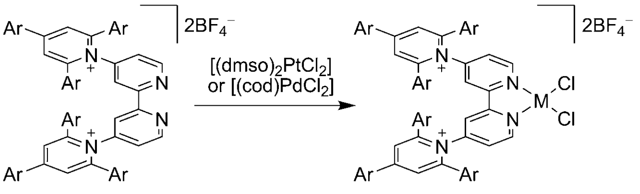
The direct functionalization of C–H bonds has frequently been deemed a “Holy Grail” of organometallic chemistry.[1] A seminal example of this transformation was the demonstration by Shilov and co-workers that platinum(II) salts catalyze the direct oxidation of alkanes into their corresponding alcohols and alkyl halides.[2] Subsequent work in this area has focused on surveying diverse ligands for these reactions in an effort to enhance reactivity and selectivity, slow catalyst decomposition, and replace platinum(IV)-based oxidants with more cost-effective alternatives.[3–5] In a key development, chemists at Catalytica identified [bpymPtCl$_2$] (bpym = bipyrimidine) as a pre-catalyst for the oxidation of CH$_4$ into CH$_3$OSO$_3$H in fuming H$_2$SO$_4$ (Scheme 1).[5] The reaction medium is believed to play several key roles in this system, including acting as a solvent, oxidant, and catalyst activator. Computational studies suggest that the active catalyst (**1**-H$^+$) is formed by in-situ protonation of the ligand backbone, which limits oxidative catalyst degradation and renders the platinum center highly electrophilic and reactive for C–H bond cleavage.[6]



Scheme 1. Oxidative functionalization of methane with pre-catalyst **1**.

Despite this initial success, it remains challenging to develop new generations of Group 10 metal catalysts that display higher turnover frequencies and operate in different, less corrosive media.[3,4] A key goal of our efforts has been to identify ligands that mimic the desirable properties of protonated bipyrimidine but are stable in the absence of strong acids.[7] Herein, we describe the application of dicationic-bipyridine-based ligands in platinum- and palladium-catalyzed arene H/D exchange and oxidation reactions.

We considered dicationic ligands of general structure **2** (Scheme 2) for several key reasons. First, they contain electron-withdrawing quaternized nitrogen substituents, which should render coordinated metal centers highly electrophilic.[8] Second, they are bidentate, sp^2 N-donors, which should allow a direct comparison with other bipyrimidine and bipyridine ligand systems. Third, the quaternized nitrogen atoms are not susceptible to decomposition by dealkylation or deprotonation, which has been problematic in related systems.[5,7] Fourth, substituents can easily be added to the pyridinium ring to tune the solubility of these dications. Finally, ligands **2a** and **2b** are readily available in four steps from commercially available 2,2′-bipyridine (bpy) in 33 % and 24 % overall yield, respectively (for details, see the Supporting Information).[9]



2a (Ar = Ph)
2b (Ar = p-tBuC$_6$H$_4$)

3a (M = Pt, Ar = Ph, 66%)
3b (M = Pt, Ar = p-tBuC$_6$H$_4$, 52%)
3c (M = Pd, Ar = Ph, 84%)

Scheme 2. Synthesis of platinum and palladium complexes **3a–c**. cod = cycloocta-l,5-diene, dmso = dimethyl sulfoxide.

Platinum(II) complexes of **2a** and **2b** were synthesized by reaction of these ligands with [(dmso)$_2$PtCl$_2$] in methanol at 60 °C to afford **3a** and **3b** in 66 % and 52 % yield, respectively, after recrystallization (Scheme 2). The analogous palladium(II) complex **3c** was prepared in a similar fashion by the reaction of **2a** with [(cod)PdCl$_2$] in dichloromethane at room temperature (84 % yield; Scheme 2). All of these complexes were fully characterized by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and elemental analysis.

We first evaluated **3a–c** as catalysts for H/D exchange[10] between [D$_4$]acetic acid and benzene using an assay developed in our laboratory.[10d] Under our standard conditions, (2 mol % [M], 4 mol % AgBF$_4$, 1 equiv C$_6$H$_6$ in 25 equiv of [D$_4$]AcOH, 150 °C), these complexes showed very high catalytic activity, with turnover frequencies (TOFs) of 0.1 s^{-1} (**3a**,**b**) and 0.05 s^{-1} (**3c**) after 15 minutes at 150 °C. For comparison, [dtbpyPtCl$_2$] (dtbpy = 4,4′-di-*tert*-butylbipyr-

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[*] Dr. M. H. Emmert, J. B. Gary, Dr. J. M. Villalobos, Prof. M. S. Sanford
Department of Chemistry, University of Michigan
930 N. University Ave, Ann Arbor, MI 48109 (USA)
Fax: (+1) 734-647-4865
E-mail: mssanfor@umich.edu

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idine), [dtbpyPdCl$_2$], and bipyrimidine catalyst **1** provided TOFs of 0.0002, 0.002, and 0.003 s^{-1}, respectively, under identical conditions.[10d] The catalysts were also compared on the basis of turnover numbers (TONs). Complexes **3a–c** achieved the statistical maximum TON of 242 after 24 hours,[11,12] which is also superior to the results with [dtbpyPtCl$_2$], [dtbpyPdCl$_2$], and **1** (TON = 144 ± 12, 90 ± 18, and 94 ± 13 under analogous conditions).[10d] Lowering the catalyst loading of **3a** to 0.1 mol% resulted in turnovers of 3273 ± 110 after 48 hours at 150 °C, which demonstrates the high activity and stability of this species, even upon prolonged heating at elevated temperatures. Finally, we decreased the reaction temperature to 100 °C. As shown in Figure 1, [dtbpyPtCl$_2$], [dtbpyPdCl$_2$], and **1** promoted very little H/D exchange under these conditions, whilst **3a–c** maintained high activity.

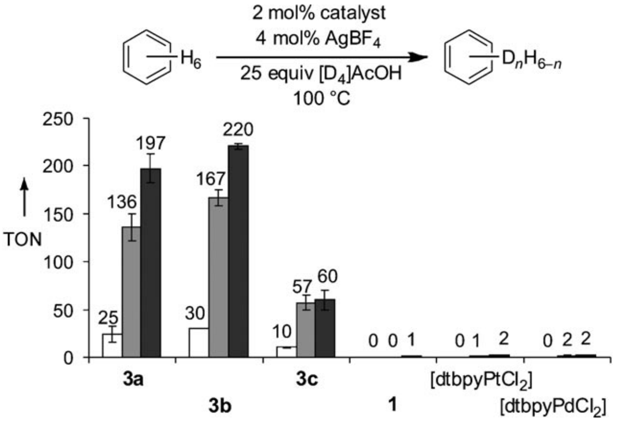
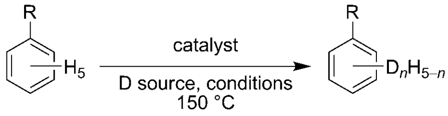


Figure 1. Turnover numbers for H/D exchange between benzene and [D$_4$]AcOH at 100 °C, catalyzed by **1**, **3a–c**, [dtbpyPtCl$_2$], and [dtbpyPdCl$_2$] after 2 h (white), 24 h (light gray), and 48 h (dark gray). Conditions: catalyst (2 mol%, 5 μmol), benzene (22.3 μL, 0.250 mmol), AgBF$_4$ (1.9 mg, 10 μmol), [D$_4$]AcOH (0.37 mL, 6.5 mmol, 25 equiv relative to benzene).

There are two possible explanations for the high H/D exchange activity of **3a–c**. The first is that the cationic ligands enhance the reactivity of the coordinated metal center towards arene C–H cleavage to generate metal σ-aryl intermediates (through an organometallic mechanism). An alternative possibility is that the Lewis acidic metal centers promote proton catalysis through an electrophilic aromatic substitution (Ar–S$_E$) pathway. To gain insight into the mechanism for H/D exchange, we examined the site-selectivity of D incorporation with catalyst **3a** for a variety of substituted arenes at partial (ca. 25%) conversion. Table 1 compares the observed selectivity (as determined by ^{1}H NMR spectroscopy) to the product ratio for electrophilic bromination[13,14] (Table 1, entries 1–3); furthermore, the selectivity of DCl/CF$_3$CO$_2$D-catalyzed H/D exchange with bromobenzene is shown in entry 4. In all cases, the site selectivity with **3a** differed dramatically from that observed in Ar–S$_E$. This is strongly suggestive of an organometallic pathway for the platinum/palladium-catalyzed H/D exchange reactions.

Table 1: Comparison of site-selectivity for arene H/D exchange[a,b] at 25% conversion with site-selectivity obtained in electrophilic aromatic bromination.



Entry	R	H/D exchange *ortho/meta/para* (catalyst)	Ar–S$_E$ *ortho/meta/para*
1	Et	1.70:1.33:1 (**3a**)[a]	1.72:0.06:1[c]
2	CO$_2$Et	1.26:2:1.33 (**3a**)[a]	0:2:0[d]
3	Br	2.92:1.19:1 (**3a**)[a]	0.48:0.01:1[c]
4	Br	1.15:0.28:1 (DCl/THF)[b]	0.48:0.01:1[c]

[a] Conditions: **3a** (3.0 mg, 2.5 μmol, 0.5 mol%), AgBF$_4$ (1.9 mg, 5.0 μmol, 1.0 mol%), RPh (0.50 mmol, 1.0 equiv), [D$_4$]AcOH (0.71 mL, 25 equiv), 150 °C. [b] Conditions: BrPh (26.3 μL, 39.3 mg, 0.250 mmol, 1.00 equiv), [D$_1$]TFA (0.51 mL, 0.719 g, 6.25 mmol, 25.0 equiv), DCl in D$_2$O (35%, 0.05 mL), 38 h, 150 °C. [c] See Ref. [13]. [d] See Ref. [14]. TFA = trifluoroacetic acid, THF = tetrahydrofuran.

The substrate scope of H/D exchange reactions catalyzed by **3a** was also investigated. As summarized in Figure 2, naphthalene, veratrole, 1,2-dichlorobenzene, bromobenzene, ethylbenzoate, (H$_3$C)$_3$CCH$_2$Ph, *sec*-butylbenzene, cumene, and trifluorotoluene all underwent extensive (48–98%) aromatic H/D exchange with CD$_3$CO$_2$D. Significant (2–8%) deuteration was also observed at unactivated sp^3 C–H sites along the alkyl chains. In an interesting contrast, substrates that do not bear a tethered aromatic group (e.g. cyclooctane, 2,2,3,3-tetramethylbutane, and methane) did not show H/D exchange reactivity with catalyst **3a** under analogous conditions. This observation suggests that the arene moiety plays a role in directing the catalyst to the unactivated sp^3 sites, likely via cyclometalation[15] or π-coordination.[16] The observation of aliphatic H/D exchange provides further evidence to support an organometallic mechanism, as this side reaction is expected to be negligible under proton catalysis.

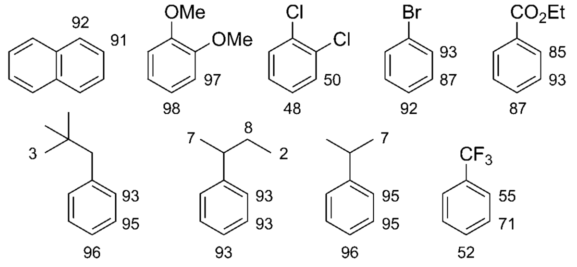


Figure 2. Substrate scope of H/D exchange catalyzed by **3a**; numbers in small font are %D incorporation. Conditions: **3a** (3.0 mg, 2.5 μmol, 2.0 mol%), substrate (0.125 mmol, 1.00 equiv), AgOTf (5.0 μmol, 4.0 mol%), [D$_4$]AcOH (0.36 mL, 0.40 g, 6.25 mmol, 50 equiv), 48 h (naphthalene, veratrol, PhBr) or 168 h (other substrates). Tf = trifluoromethanesulfonyl.

The H/D-exchange experiments probed the reactivity of **3a–c** in C–H bond cleavage, which is only the first step of a potential C–H functionalization process. Thus, it was important to determine whether the high reactivity and stability of these new complexes for arene H/D exchange correlated to catalytic activity in arene oxidation. To test this, we conducted preliminary studies of the effect of ligand **2a** on the $Pd(OAc)_2$-catalyzed acetoxylation of arenes with $PhI(OAc)_2$.[17,18] As illustrated in Figure 3, the use of $Pd(OAc)_2$/**2a** for the oxidation of benzene resulted in a significantly enhanced reaction rate compared to the best catalysts reported to date for this transformation ($Pd(OAc)_2$[17] or $Pd(OAc)_2$/bpy 2:1[18]). Similarly enhanced turnover frequencies were obtained in the C–H acetoxylation of naphthalene, 1,2-dichlorobenzene, chlorobenzene, bromobenzene, ethylbenzoate, and α,α,α-trifluorotoluene using $Pd(OAc)_2$/**2a** (for full details, see the Supporting Information). These initial results show that ligand **2a** can be used to generate robust, highly active palladium C–H oxidation catalysts.

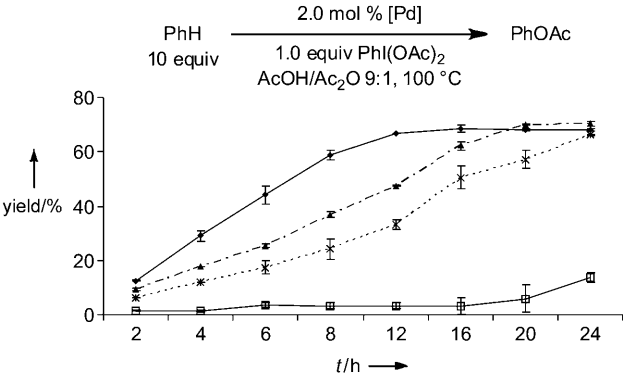


Figure 3. Pd^{II} catalyzed acetoxylation of benzene. Catalysts [Pd]: (◆) $Pd(OAc)_2$/**2a** 2:1; (*) $Pd(OAc)_2$/bpy (2:1); (×) $Pd(OAc)_2$; (☐) $Pd(OAc)_2$/bpym (2:1).

In conclusion, the application of cationic pyridinium substituted ligands of general structure **2** for Group 10 C–H functionalization catalysis has been described. Both platinum and palladium complexes of these ligands display high catalytic activity for arene H/D exchange; furthermore, the combination of $Pd(OAc)_2$/**2a** shows enhanced activity for arene acetoxylation, compared with the best previously reported catalysts.[17,18] Further applications of late transition metal complexes of **2a** and **2b** in C–H functionalization reactions are currently underway in our laboratory.

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