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Understanding the Differential Performance of $Rh_2(esp)_2$ as a Catalyst for C−H Amination

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The continued development of selective and efficient reaction technologies for C−H amination necessitates a deeper understanding of the factors that affect catalyst stability.[1] Our earliest mechanistic studies on carbamate and sulfamate ester oxidation indicated that dinuclear rhodium-tetracarboxylate catalysts were subject to rapid ligand exchange, a process believed to initiate catalyst decomposition.[2] These findings motivated the design and synthesis of $Rh_2(esp)_2$, a complex derived from two, chelating bis-carboxylate ligands, which exhibits superior performance for C−H amination reactions (Figure 1).[3] While it appears that $Rh_2(esp)_2$ is less prone to ligand exchange than other simple tetracarboxylate systems (e.g., $Rh_2(OAc)_4$), we have noted an alternate pathway for catalyst arrest that involves competing one-electron oxidation to a mixed-valence Rh^{2+}/Rh^{3+} dimer. We now provide evidence that *reduction* of the Rh^{2+}/Rh^{3+} dimer and reconstitution of the active Rh^{2+}/Rh^{2+} catalyst is occurring under the *oxidizing* reaction conditions. The rate of this peculiar reduction event is clearly coupled to catalyst turnover number and reaction efficiency. These data have led us to propose that the differential performance of $Rh_2(esp)_2$ derives from the unusual kinetic stability of the mixed-valence dimer vis-à-vis other dirhodium tetracarboxylate complexes.

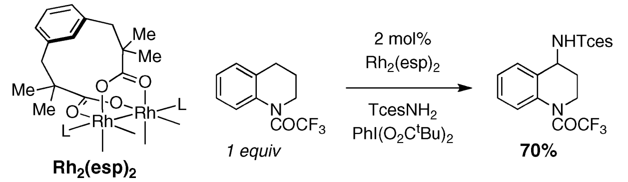

Figure 1. Intermolecular benzylic C−H amination efficiently catalyzed by $Rh_2(esp)_2$. Tces = $SO_2OCH_2CCl_3$.

The advent of $Rh_2(esp)_2$ has enabled the efficient and selective intermolecular amination of benzylic C−H bonds.[4] When this reaction is conducted, a rather striking color change from green to deep red is witnessed as the reagents are mixed. The species responsible for the red color has been identified as a mixed-valence $[Rh_2(esp)_2]^+$ dimer.[4] A large body of circumstantial evidence appears to correlate the formation of this red complex with the reactivity of the C−H bond undergoing oxidation (i.e., $[Rh_2(esp)_2]^+$ forms when the C−H bond is slow to intercept the reactive Rh-nitrene intermediate). Similar phenomena are observed with tetracarboxylate complexes such as $Rh_2(O_2C^nPr)_4$, though the effectiveness of such catalysts for intermolecular amination reactions does not compare with $Rh_2(esp)_2$. Given the nearly identical potentials for one-electron oxidation of $Rh_2(esp)_2$ and $Rh_2(O_2C^nPr)_4$ (1130 mV and 1150 mV vs SCE, respectively), we hypothesized that differences in catalyst performance between these two Rh complexes are linked to differences in the kinetic stability of the respective mixed-valence species. To test this idea, we have generated the one-electron oxidized adduct, $[Rh_2(esp)_2]^+$, by treating $Rh_2(esp)_2$ with $Cl_3CCH_2OSO_2NH_2$ ($TcesNH_2$) and $PhI(O_2C^nPr)_2$ in the absence of substrate.[5,6] UV/visible spectroscopy confirms that this species is persistent in solution for >5 min (Figure 2).[7] Conversely, the solution of mixed-valence dimer derived from $Rh_2(O_2C^nPr)_4$ bleaches to a pale yellow within 60 s of mixing the reactants.[8,9]

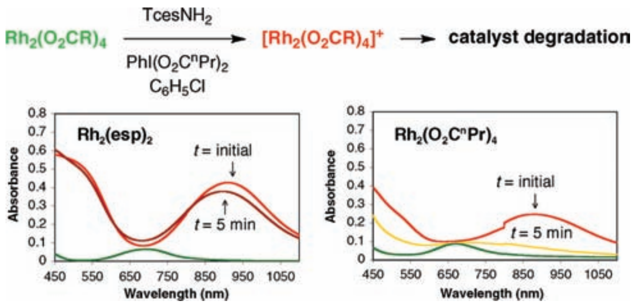

Figure 2. One-electron oxidation of $Rh_2(esp)_2$ and $Rh_2(O_2C^nPr)_4$.

Although the stepwise mechanism for $[Rh_2(O_2C^nPr)_4]^+$ decomposition is not understood at this time, we assume that labilization of one or more of the bridging butyrate ligands is, at least in part, responsible.[2] We have found that both $Rh_2(O_2C^nPr)_4$ and $Rh_2(esp)_2$ are inert at ambient temperature to ligand exchange by carboxylic acids. However, stirring the former complex with $PhI(O_2C^tBu)_2$ (10 equiv) yields within 30 min the tetra-pivaloate species, $Rh_2(O_2C^tBu)_4$. (Figure 3).[10] Binding of $PhI(O_2{}^tBu)_2$ in a two-point fashion to an axial site on the Rh dimer is likely the first step in this exchange event. The initiation of a similar ligand metathesis-type reaction on the mixed-valence dimer, $[Rh_2(O_2C^nPr)_4]^+$, may be responsible for the rapid decomposition of this species. No such ligand exchange reaction is observed between $PhI(O_2{}^tBu)_2$ and $Rh_2(esp)_2$.

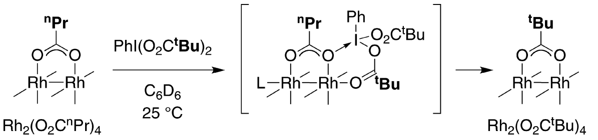

Figure 3. Ligand exchange promoted by iodine oxidant.

An apparent link between reaction performance and the lifetime of the Rh^{2+}/Rh^{3+} dimer raises an intriguing possibility that the mixed-valence species is, in fact, the active catalyst. While this possibility cannot be entirely discounted, there appears to be an operative pathway under the reaction conditions by which $[Rh_2(esp)_2]^+$ is reduced to $Rh_2(esp)_2$. As demonstrated below, the yield of intermolecular amination product is clearly influenced by the rate of this reduction event.

N-Tces-2,2-Dimethylaziridine is obtained as a minor byproduct from intermolecular C−H amination reactions when $PhI(O_2C^tBu)_2$ is employed as the oxidant (Figure 4).[4] The aziridine is presumed to derive from isobutylene, the source of which is $^tBuCO_2H$. We speculate that this cascade of events is initiated by $[Rh_2(esp)_2]^+$-promoted oxidative decarboxylation of $^tBuCO_2H$. Both spectroscopic and mass balance experiments confirm that a reaction ensues between $^tBuCO_2H$ and $[Rh_2(esp)_2]^+$ to furnish the reduced complex, $Rh_2(esp)_2$. Oxidation

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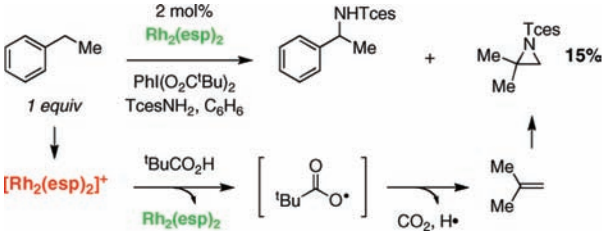

Figure 4. Product analysis gives mechanistic insight.

of $Rh_2(esp)_2$ to the mixed-valence dimer followed by addition of 25 equiv of $^tBuCO_2H$ restores the blue-green color of $Rh_2(esp)_2$• $2(^tBuCO_2H)$ within 15 min (Figure 5). This same sequence of reactions has been performed on a semipreparative scale, and $Rh_2(esp)_2$ is re-isolated in 60% yield. By contrast, no recovered $Rh_2(O_2C^nPr)_4$ is obtained when this complex is subjected to an analogous protocol.

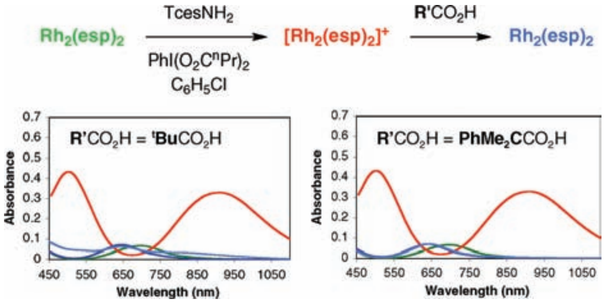

Figure 5. Reduction of $[Rh_2(esp)_2]^+$ by $\mathbf{R'}CO_2H$. $Rh_2(esp)_2$ = (green); $Rh_2(esp)_2$•$2(\mathbf{R'}CO_2H)$ = (dark blue); $[Rh_2(esp)_2]^+$ = (red); recorded UV/visible spectrum following treatment of $[Rh_2(esp)_2]^+$ with $\mathbf{R'}CO_2H$ = (light blue).

Recorded cyclic voltammograms for a series of α-substituted carboxylic acids show a clear correlation between oxidation potential and the stability of the incipient carbon-center radical that is formed following CO_2 loss.[11] As we and others have noted, higher catalyst turnover numbers and product yields are obtained in intermolecular C−H amination reactions conducted with $PhI(O_2C^tBu)_2$ instead of $PhI(OAc)_2$.[12] The reason for this discrepancy is now clear—the byproduct, $^tBuCO_2H$, is significantly more effective than AcOH for reducing $[Rh_2(esp)_2]^+$ to $Rh_2(esp)_2$. Accordingly, the kinetic stability of $[Rh_2(esp)_2]^+$ is critical to the overall success of the reaction. On the basis of this mechanistic model, oxidants such as $PhI(O_2CCMe_2Ph)_2$ might give way to higher catalyst turnover numbers than $PhI(O_2C^tBu)_2$. The carboxylic acid produced, $PhMe_2CCO_2H$, is more reducing than $^tBuCO_2H$; the larger thermodynamic driving force for reduction of the mixed-valence dimer is also coincident with a faster kinetic event.[13] UV−visible spectroscopy indicates that reaction between $[Rh_2(esp)_2]^+$ and $PhMe_2CCO_2H$ is complete within seconds of mixing and $Rh_2(esp)_2$ is restored (Figure 5).

Oxidation of ethylbenzene with $TcesNH_2$ and $PhI(O_2CCMe_2Ph)_2$ yields 62% of the amination product, a substantial improvement in overall reaction efficiency when contrasted against results obtained using other hypervalent iodine derivatives (Figure 6).[14,15] Importantly, the experimental protocol does not take recourse to slow, dropwise addition of any of the components.[4] These data bolster our supposition that $Rh_2(esp)_2$ is the working catalyst and not the one-electron oxidized form.

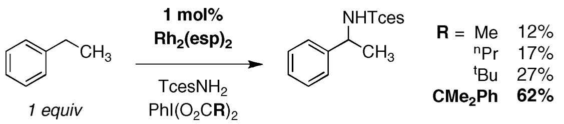

Figure 6. Improved reaction performance using an alternative hypervalent iodine oxidant.

Our results suggest that the high performance displayed by $Rh_2(esp)_2$ for catalytic C−H amination is in part due to the kinetic stability of its mixed-valence dimer toward further oxidative damage. The carboxylic acid generated as a byproduct under the reaction conditions serves a critical role as a reducing agent to return $[Rh_2(esp)_2]^+$ to a catalytically active neutral form. Our understanding of the details of this complex process has resulted in the development of a new iodine oxidant, $PhI(O_2CCMe_2Ph)_2$ and a significant improvement in the performance of intermolecular C−H amination reactions. These findings also raise intriguing questions regarding the specific mechanistic details by which $[Rh_2(esp)_2]^+$ is formed, the answers to which will likely result in further methods advances.

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Note Added after ASAP Publication. The version of this paper published on May 14, 2009, had an error in the fifth paragraph. The version published on May 19, 2009, has the correct information.

Supporting Information Available: General experimental protocols and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Use of $PhI(O_2C^nPr)_2$ is preferred over $PhI(OAc)_2$ for mechanistic studies given its greater solubility in organic solvents.

(6) In the absence of $TcesNH_2$, no catalyst oxidation is observed. The measured potential of $PhI(OAc)_2$ is −0.9 V vs SCE, see: (a) Kokkinidis, G.; Papadopoulou, M.; Varvoglis, A. *Electrochim. Acta* **1989**, *34*, 133–139.

(7) After ∼5 min the λ_{max} of $[Rh_2(esp)_2]^+$ is blue-shifted by ∼75 nm from the initial recording, likely the result of axial coordination of butyric acid or $PhI(O_2C^nPr)_2$ to one or both Rh centers. Under the reaction conditions, the red color of $[Rh_2(esp)_2]^+$ persists for >12 h.

(8) Although we assume that the extinction coefficients of $[Rh_2(esp)_2]^+$ and $[Rh_2(O_2C^nPr)_4]^+$ are similar, the rapid decomposition of $[Rh_2(O_2C^nPr)_4]^+$ precludes observation of its maximum UV−vis absorbance.

(9) Oxidative degradation of a mixed-valence Rh^{2+}/Rh^{3+} dimer to give monomeric Rh^{3+} species under bulk electrolysis conditions has been described, see: Best, S. P.; Nightingale, A. J.; Tocher, D. A. *Inorg. Chem. Acta.* **1991**, *181*, 7–9.

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(14) $PhMe_2CNHTces$ has been isolated from the reaction mixture, the product of $PhMe_2CCO_2H$ decarboxylation and amination of $PhMe_2CH$.

(15) Use of $PhI(O_2CCPh_3)_2$ affords comparable results to reactions performed with $PhI(O_2CCMe_2Ph)_2$.

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