A General Protocol for Addressing Speciation of the Active Catalyst Applied to Ligand-Accelerated Enantioselective C(sp^3)-H Bond Arylation

David E. Hill,[1] Qing-lan Pei,[2] En-xuan Zhang,[2] James R. Gage,[2] Jin-Quan Yu,[1] and Donna G. Blackmond[1*]

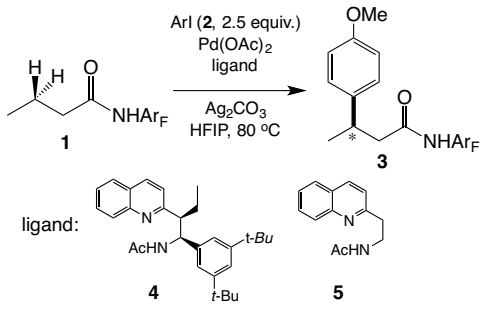
Department of Chemistry, The Scripps Research Institute, La Jolla, CA 92037 USA; [2]New Technology Development Laboratory, Asymchem, Inc., 7 Binhai Xinqu, Tianjin, CN 300457

ABSTRACT: The potential role of dimeric catalyst species on or off the catalytic cycle is considered for a case of Pd-catalyzed C-H functionalization, leading to the development of a general experimental protocol that uses the reaction itself to report on the presence and role of dimeric species in asymmetric catalytic reactions.

Pd catalysis, catalyst speciation, dimer catalysts, nonlinear effects, C-H functionalization

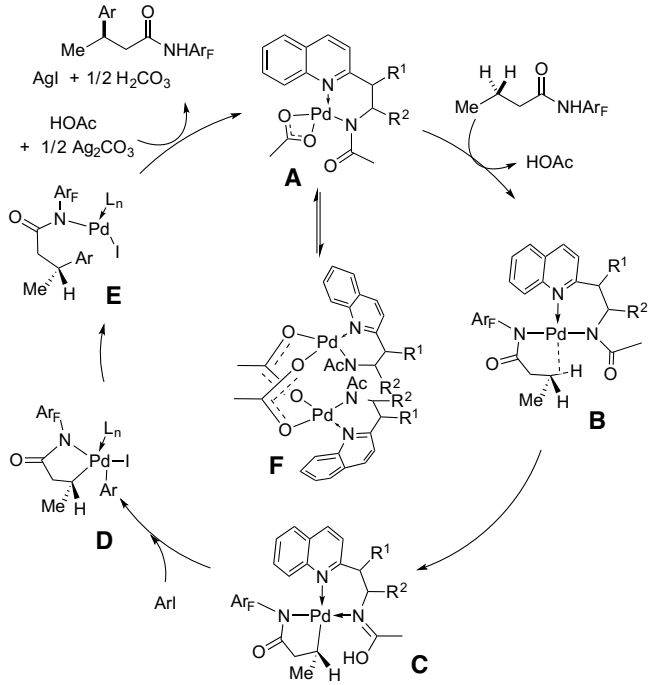
INTRODUCTION

Ligand-accelerated transition metal catalysis coupled with effective differentiation of prochiral carbon-hydrogen bonds via chiral ligands has proved to be a powerful synthetic strategy leading to a wide range of pharmaceutically important chiral compounds.[1] The Yu group has developed a number of ligand systems for activation of C(sp^2)-H and, more recently, C(sp^3-H) bonds, a significant challenge.[2] They showed that the reaction of Scheme 1 proceeds to high yield and high enantioselectivity using acetyl-protected aminoquinoline (APAQ) ligands such as **4**.[3]



Scheme 1. Ligand Accelerated Methylene C(sp^3)-H Arylation.

The origin of rate acceleration in this reaction has been probed in computational studies[4] highlighting the importance of a six-membered chelate structure formed between Pd, the nitrogen of the quinolone ring and the amino group, which alleviates steric repulsion that a five-membered chelate would experience. This work also implicated the formation of stable dimeric palladium-ligand complexes from achiral ligands such as **5**. A proposed mechanism included such dimers as off-cycle species **F** in equilibrium with a monomeric species **A** on the catalytic cycle (Scheme 2). The potential role of dimer species in systems with chiral ligands such as **4** was not included in that computational treatment.



Scheme 2. Proposed Mechanism[4] for the reaction of Scheme 1. R^1=R^2=H for ligand 4; R^1=Et, R^2=$Ar_{di\text{-}t\text{-}butyl}$ for ligand 5.

The potential presence and role of dimeric Pd species, both on and off the active catalytic cycle, has received considerable attention in recent years.[5-8] Ritter has argued that "redox synergy" between Pd(III) centers in

bimetallic complexes aids in reductive elimination processes.[5] Sanford has shown several cases of Pd catalysis with rate-determining C-H bond cleavage where the resting state is an off-cycle Pd dimer.[6] Many of the key experimental observations have been made using well-characterized Pd complexes in stoichiometric reactions where the Pd complex is consumed.[8] In these cases, key questions remain concerning how to extend such conclusions to catalytic systems undergoing reaction turnover, particularly in asymmetric catalysis. Interrogating both the presence of dimeric or higher order species and their potential role on the catalytic cycle remain important considerations in Pd-catalyzed C-H functionalization reactions.

Here we present experimental kinetic and mechanistic studies along with kinetic modeling to provide further insight into the catalyst system of Scheme 1, in particular the molecularity of the active catalyst species. Our work provides a general experimental protocol for probing catalyst speciation under active reaction conditions through a combination of kinetic experiments for both chiral and achiral ligand systems that employ the reaction itself to address the role of dimer and other higher order species in asymmetric transition metal catalysis.

RESULTS AND DISCUSSION

The results of our kinetic investigations for the reaction of Scheme 1 using the chiral ligand **4** in the reaction of Scheme 1 reveal that the system exhibits catalyst deactivation, as shown by the lack of overlay in "same excess" experiments,[6,7] and therefore initial rates from reaction progress profiles are employed to probe concentration dependences. Figure 1 shows that the reaction is positive order in [**1**] and zero order in [ArI] (Ar = *p*-OMe). A competing dehalogenation side reaction depletes the concentration of ArI, rationalizing why several equivalents are required.

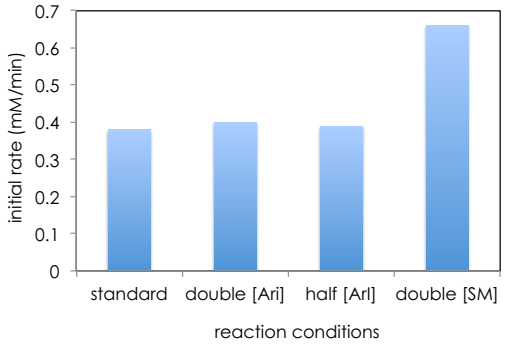


Figure 1. Dependence of initial rate of the reaction of Scheme 1 on reaction variables. Standard conditions: $[\mathbf{1}]_0$=0.09 M; $[\mathbf{2}]_0$=0.20 M (Ar= *p*-OMe); $[Pd(OAc)_2]$=0.01 M; [**4**]=0.02 M; Ag_2CO_3=0.175 M, solvent = HFIP = hexafluoroisopropanol, 80 °C.[6]

Taken together, these observations provide support for the proposed reaction mechanism shown in Scheme 2. Reversible substrate binding to form species **B** followed by rate-limiting C-H activation to form **C** is indicated by positive order kinetics in [**1**]. Zero order kinetics in [ArI] implies that addition of ArI occurs after the rate-determining step.

Further kinetic experiments probing the reaction order, n, in [Pd] are key to providing clues to the nature of the palladium-ligand species present in the active catalyst system. Following the Variable Time Normalization Analysis (VTNA) method of Burés[8] by plotting concentration vs. ([catalyst]^n· time), Figure 2 shows that the reaction is first order in catalyst concentration for the case of the chiral ligand **4**, while the order in catalyst decreases to 0.5 for the achiral catalyst with ligand **5**.

For systems that form dimers, the relative concentrations of monomers *PdL* and dimers ***D*** is given by eq 1. First order behavior in total [Pd] may be observed only if the equilibrium in eq 1 between monomers *PdL* and dimers ***D*** is shifted completely towards either monomers or dimers. In those limiting cases either species could be implicated as the active catalyst. The finding of n = 0.5 is in accordance with calculations showing that a stable, off-cycle dimeric species **F** (Scheme 1) is significant in the case of the achiral ligand **5**.[4]

$$PdL + PdL \underset{}{\overset{K_{eq}}{\rightleftharpoons}} D \qquad (1)$$

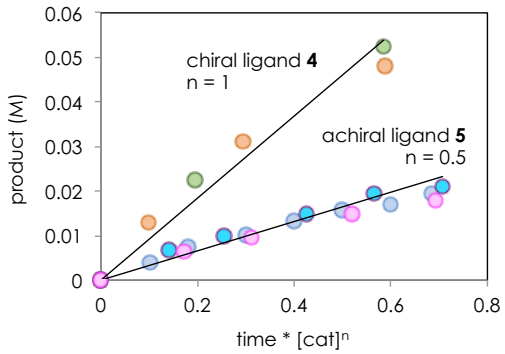


Figure 2. Consumption of substrate **1** under standard conditions plotted as a function of [catalyst]^n· (time) for reactions using chiral ligand **4** (time in min) and achiral ligand **5** (time in hr) at Pd concentrations from 0.01-0.02 M (ligand **4**) and 0.01-0.03 (ligand **5**). Value of n giving overlay between the profiles indicates the order in [Pd].[6]

Reaction simulations[9] may be used to illustrate how to assess cases where both monomers and dimers may be present in non-negligible amounts. Deviation from reaction order of unity in [Pd] is characteristic of cases where both monomers and dimers are present (Figure 3). Importantly, the observed order in [Pd] in the catalytic reaction depends on which species, dimers or mono-

mers, serves as the active on-cycle species. Figure 3 reveals that the observed order in [Pd] will appear to be *lower* than one if monomers are the active catalysts and *greater* than one for dimers as the active catalyst.[6]

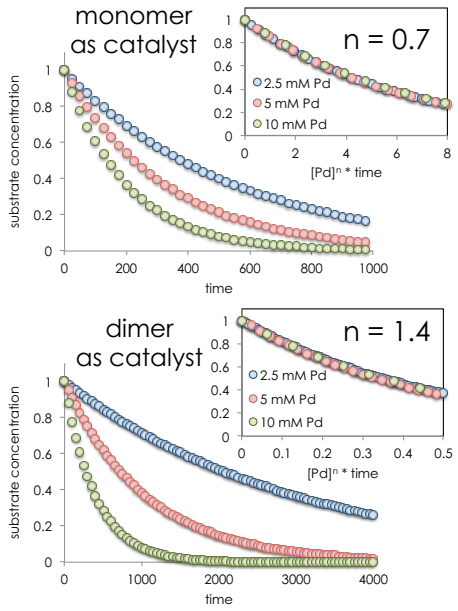


Figure 3. Simulation of reaction profiles to determine the order in [Pd], for an achiral system with an achiral catalyst monomer/dimer equilibrium of eq 1 with K_{eq}=100 M^{-1}. The observed order n is lower than unity if the monomer is the catalyst (top) and greater if the dimer is the catalyst (bottom). Insets show Burés VTNA plots.[9]

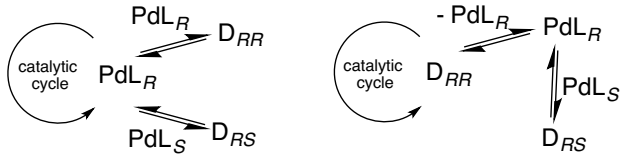
The fraction of catalyst present as monomers is a function of both the absolute catalyst concentration and the dimerization equilibrium constant. For example, in a reaction using an achiral catalyst with K_{eq} = 100 M^{-1} and [Pd] = 0.01 M, 50% of the Pd will be present as monomers and 50% as dimers, while at a fourfold lower [Pd], dimers account for about a quarter of the total Pd. In the case of reactions with achiral ligand **5**, the experimentally determined order of 0.5 supports the mechanism in Scheme 1 and suggests that most of the catalyst is present in the form of an off-cycle dimer species.

For asymmetric reactions employing chiral scalemic ligands, the possibility of forming both homochiral (***D*****$_{RR}$** and ***D*****$_{SS}$**) and heterochiral (***D*****$_{RS}$**) dimers with two Pd atoms and two chiral ligands, as in the case of species **F** in Scheme 1, leads to the expansion of eq 1 to eqs 2-4. As in the achiral case, deviation from reaction order of unity similarly implicates the role of dimer species either as active catalysts on the catalytic cycle or as spectator species connected to the cycle, as shown in Scheme 3.

$$PdL_R + PdL_R \overset{K_{homo}}{\rightleftharpoons} D_{RR} \quad (2)$$

$$PdL_S + PdL_S \overset{K_{homo}}{\rightleftharpoons} D_{SS} \quad (3)$$

$$PdL_R + PdL_S \overset{K_{hetero}}{\rightleftharpoons} D_{RS} \quad (4)$$



monomer as catalyst homochiral dimer as catalyst

(analogous cycles for PdL_S and D_{SS} not shown)

Scheme 3. Dimer Species On and Off the Catalytic Cycle for Pd with Chiral Ligands.

The asymmetric reaction offers a further probe of the nature of the Pd-ligand species for the chiral catalyst system by examining the effect on product enantiomeric excess of varying the enantiomeric excess of ligand **4**.[12] Probing asymmetric catalyst systems using a mixture of the two enantiomeric ligands further helps deconvolute the potential presence and role of dimer species. If dimers are present, a nonlinear effect in product enantiomeric excess as a function of catalyst enantiomeric excess will be observed under all circumstances except in two singular cases: 1) if the dimers are off-cycle species and are formed in a statistical distribution between ***D*****$_{RR}$**, ***D*****$_{SS}$**, and ***D*****$_{RS}$**; and 2) if the dimers are the active species on-cycle and the heterochiral dimer ***D*****$_{RS}$** exhibits identical reactivity to that of the homochiral dimers ***D*****$_{RR}$** and ***D*****$_{SS}$**. Absent these special cases, a lack of an observed nonlinear effect indicates the absence of dimers.

Figure 4 establishes that product ee in the reaction of Scheme 1 varies linearly with catalyst ee. Taken together, the results shown in Figs. 2 and 4 for the case of asymmetric ligand **4** – first order kinetics in [Pd] coupled with the absence of a nonlinear effect in catalyst enantiomeric excess – confirm: 1) the absence of Pd dimers or other higher order Pd species either on or off the cycle; and 2) the absence of multiple ligands bound to a single Pd atom.

While the calculations of Ref. 4 for the system of Scheme 1 did not address the chiral ligand system **4**, the order in catalyst n = 1 shown in Figure 2 coupled with the lack of a nonlinear effect strongly indicate that the dimeric off-cycle species **F** proposed in the reaction mechanism of Scheme 2 may be neglected in the case of reaction with the asymmetric ligand **4**.

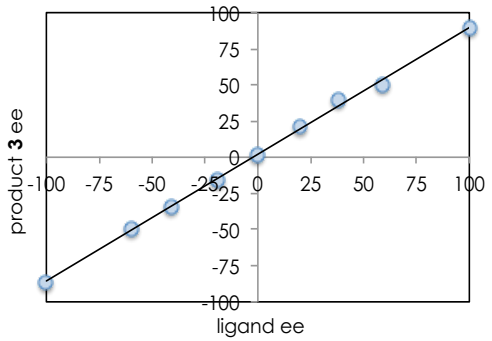


Figure 4. Product **3** enantiomeric excess as a function of ligand **4** enantiomeric excess for reactions run under standard conditions.[9]

As an illustration of a case where dimers are formed with chiral ligands, we may expand the example described above for dimers with $K_{eq} = K_{homo} = 100\ M^{-1}$. If the heterochiral dimer exhibits higher stability and is itself inactive as a catalyst, a nonlinear effect will be observed for either the monomer or the dimer as catalyst, as shown in Figure 5, where the effect is more pronounced for dimers.

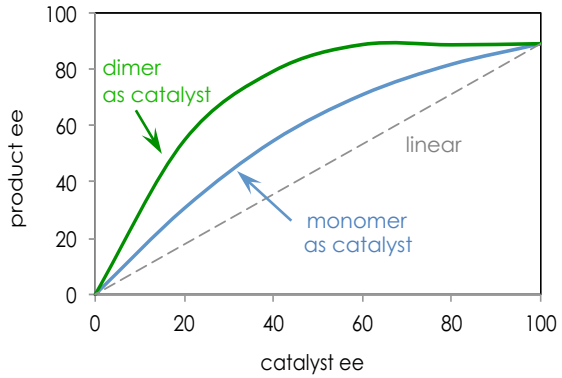


Figure 5. Simulation of the nonlinear effect predicted for a reaction in which the catalyst with chiral ligands forms monomer/dimer equilibria as in eqs 2-4 with K_{homo}=100 M^{-1} and K_{hetero}=1000 M^{-1}. The nonlinear effect is given in green for dimers as the active catalyst (with inactive heterochiral catalyst) and in blue for monomer-active catalysts.

The example in Figure 5 presents only one of many possible scenarios for nonlinear effects,[8b] the magnitude of which will depend on both the absolute and relative magnitudes of K_{homo} and $K_{hetero.}$ We may, however, summarize general observations expected for different scenarios involving the presence and role of dimers in catalytic systems. Table 1 considers cases whether the active catalyst is a monomer or a dimer, whether dimers $\boldsymbol{D_{RR}}$, $\boldsymbol{D_{SS}}$, and $\boldsymbol{D_{RS}}$ are formed in a statistical vs. non-statistical distribution in eqs 2-4, and whether the heterochiral dimer exhibits activity equal or unequal to that of the homochiral dimers as active catalysts. The final two entries treat the cases where the system consists of exclusively monomers or exclusively dimers.

These studies demonstrate that the catalytic reaction itself serves as a probe of catalyst speciation. It is worthy of note, as is seen in the comparison of chiral and achiral ligands **4** and **5**, that dimer species may predominate in one ligand system and play little or no role in another, even for similar ligands in the same catalytic reaction. Caution should be exercised in attempting to apply mechanistic conclusions from study of an achiral catalyst to those of a chiral catalyst, or even between two chiral ligand systems, without first assessing catalyst speciation in reaction experiments as described here.

Table 1. Protocol for Predicting the Presence and Potential Role of Dimers in Asymmetric Catalysis.

active catalyst	non-1st order in [cat]?	nonlinear effect?
monomer (statistical)	✔	✗
monomer (non-statistical)	✔	✔
dimer (statistical) equal activity	✔	✗
dimer (statistical) unequal activity	✔	✔
dimer (non-statistical) equal activity	✔	✗
dimer (non-statistical) unequal activity	✔	✔
monomer (exclusively)	✗	✗
dimer (exclusively) unequal activity	✗	✔

CONCLUSION

In summary, an experimental protocol uses the behavior of the reaction itself to provide a decisive answer to the question of whether dimer species are present and, if so, whether they play a role on the catalytic cycle or are off-cycle spectator species in asymmetric catalytic reactions. Further studies to assess the role of dimer species in other Pd-catalyzed enantioselective C-H functionalization reactions are underway.

Blackmond@scripps.edu

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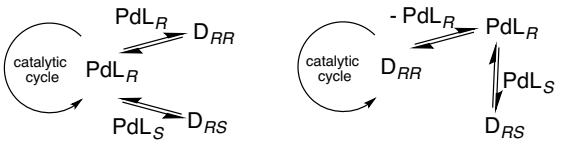

monomer as catalyst homochiral dimer as catalyst