Dynamic Ligand Exchange as a Mechanistic Probe in Pd-Catalyzed Enantioselective C-H Functionalization Reactions Using Monoprotected Amino Acid Ligands

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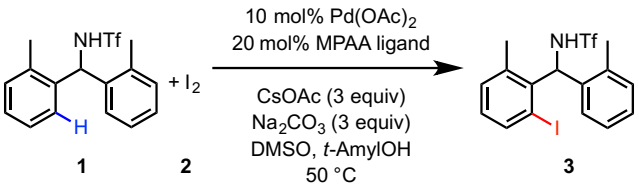
ABSTRACT: A new tool for probing enantioselective reaction mechanisms is introduced. Monitoring the temporal change in product enantiomeric excess after addition of the opposite enantiomer of the ligand during reaction provides a means of probing dynamic ligand exchange in enantioselective C-H iodination catalyzed by Pd with monoprotected amino acid ligands (MPAA). This work has general potential for providing insights about the dynamics of catalyst and ligand molecularity and exchange.

Pd-catalyzed C-H functionalizations employing monoprotected amino acid (MPAA) ligands have emerged as a powerful class of reactions that provide striking ligand-accelerated catalysis, and, in cases of prochiral substrates, highly enantioselective transformations.[1] Both experimental[2] and computational[3] mechanistic studies have contributed to our understanding of these reaction systems, invoking weak coordination of substrates and ligands to Pd. It has been shown that MPAA-ligated Pd catalysts exhibit significant rate accelerations over non-ligated Pd.[1] Most recently, a novel role for Pd(IV) in enantioselective iodination was uncovered in the highly selective desymmetrization of diarylmethylamines via iodination catalyzed by Pd(MPAA)$\left(MPAA\right)$[2c,4] (Scheme 1).

Scheme 1. Iodination of Diarylmethylamines



In the present study, we show how temporal monitoring of product enantioselectivity may be employed as a probe of dynamic ligand exchange in reactions where the opposite hand of the MPAA ligand is introduced as the reaction proceeds. Understanding the capability of the chiral ligand to undergo exchange with different Pd species along the catalytic cycle provides a new tool that uses the reaction itself to probe and report on enantioselective reaction mechanisms.

Our initial studies followed the optimized system developed by Yu and coworkers,[4a] employing benzoyl-protected leucine Bz-Leu-OH as the MPAA ligand. We found that this ligand reacts to produce palladacycle **4** upon mixing with $Pd(OAc)_2$.[2c] Species **4** is an inert precatalyst that is rapidly iodinated to produce **5** upon exposure to the reaction conditions of Scheme 1. Complex **6** was synthesized as an analogous catalyst so that the reaction could be followed by ^{19}F NMR spectroscopy. All three Pd species produce competent catalysts and give similar kinetic profiles in the reaction of Scheme 1. Interestingly, however, we found that none of the species **4**-**6** interacts with substrate **1** in the absence of I_2.[2c] This observation led to ^{19}F-NMR spectroscopic studies as well as electrochemical investigations that implicate a Pd(IV) species **7**, formed from oxidative addition of I_2 to **6**, in the catalytic cycle prior to addition of the diarylmethylamine substrate.

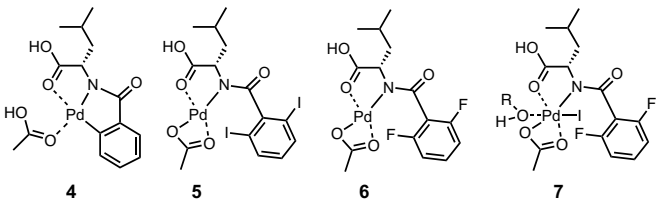


Figure 1 shows that nearly identical rates are observed for Pd:ligand ratios from 1:1.25 to 1:4 in the reaction of Scheme 1. In addition, the reaction exhibits first order kinetics in [Pd] [2c] and no nonlinear effect in ligand enan-

tiomeric excess (Figure 2). Together these observations suggest that the active catalyst is a monomeric Pd(MPAA) species and that neither higher order Pd species nor Pd species with multiple ligands exist either on or off the catalytic cycle.[6]

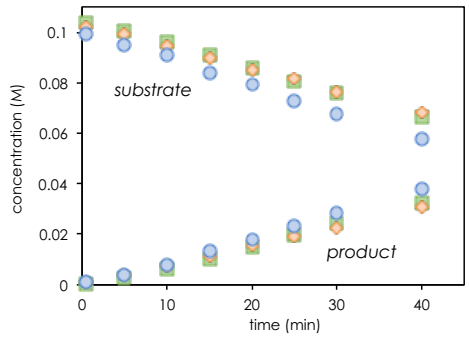


Figure 1. Temporal product formation and substrate consumption in the reaction of Scheme 1 carried out using 10 mol% $Pd(OAc)_2$ Bz-Leu-OH ligand at Pd:L ratios of 1:1.25 (green squares), 1:2 (orange diamonds) 1:4 (blue circles). $[\mathbf{1}]_0$= 0.1 M; $[\mathbf{2}]_0$=0.3 M; 3 equiv. CsOAc, 3 equiv. Na_2CO_3 in DMSO/t-Amyl-OH at 50°C.

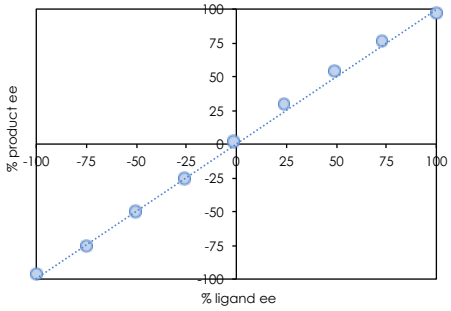


Figure 2. Product ee vs. ligand ee for the reaction of Scheme 1 carried out using 10 mol% $Pd(OAc)_2$ and 20 mol% Bz-Leu-OH ligand. $[\mathbf{1}]_0$= 0.1 M; $[\mathbf{2}]_0$=0.3 M; 3 equiv. CsOAc, 3 equiv. Na_2CO_3 in DMSO/t-Amyl-OH at 50°C.

We aimed to study the dynamic behavior of the chiral ligands in this reaction network by spectroscopic characterization as well as using the reaction itself as a probe. To accomplish the latter, we devised a ligand addition protocol in which we injected the ligand of the opposite chirality into a running reaction after ca. 10% conversion. Because the results in Figs 1 and 2 confirm that monomeric Pd(MPAA) catalysts operate independently from one another in the cycle, we may monitor any temporal change in enantiomeric excess to evaluate whether and how rapidly the ligands exchange (eq 1), where $K_{eq} = k_{on}/k_{off} = 1$.

$$Pd(MPAA)_D + (MPAA)_L \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} Pd(MPAA)_L + (MPAA)_D \quad (1)$$

Ligand exchange reactions were initiated using $Pd(OAc)_2$ and the D-Bz-Leu-OH ligand in a 1:1 ratio, which is immediately converted to catalyst D-**5**.[2c] The reaction of Scheme 1 was then allowed to proceed for 20 minutes, or to ca. 10% conversion (ca. 1 turnover), before addition of 1, 2, or 4 equivalents of ligand of the opposite chirality, L-Bz-Leu-OH. An aliquot taken from the reaction mixture established product ee and conversion just prior to addition of the opposite ligand. Both ee and conversion were monitored for a further 40 minutes, or ca. 4 further turnovers.[5]

Figure 3 shows the results of these experiments plotted as incremental product ee vs. % conversion. "Incremental ee" is defined as the enantiomeric excess of product molecules formed in an interval between two conversion points, which provides a measure of the instantaneous behavior of the catalyst by removing the cumulative effect on ee of product already present in the reaction mixture from earlier reaction times. The dashed horizontal lines in Figure 3 show the expected product ee for a fully equilibrated Pd/ligand mixture in the three cases, 60% ee for D:L=1:4 (red), 33% for D:L=1:2 (blue) and racemic for D:L=1:1 (green). These data show that immediately upon introduction of the opposite hand of the ligand, product ee in the reaction of Scheme 1 begins to reflect its presence, and the system appears to be fully equilibrated within two further turnovers of the catalytic cycle.

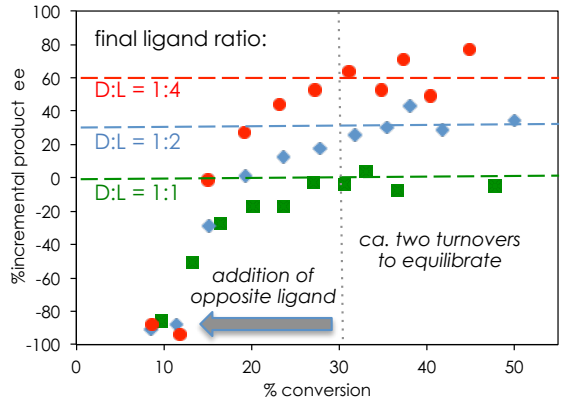


Figure 3. Incremental product ee vs. conversion for the reaction of Scheme 1 carried out using 10 mol% $Pd(OAc)_2$. Reactions initiated with 1 equiv. D-Bz-Leu-OH ligand, with L-Bz-Leu-OH added at ca. 10% conversion to give the ligand enantiomeric ratios shown in the graph. $[\mathbf{1}]_0$= 0.1 M; $[\mathbf{2}]_0$=0.3 M. 3 equiv. CsOAc, 3 equiv. Na_2CO_3 in DMSO/t-Amyl-OH at 50°C. Horizontal lines show product ee values expected from fully equilibrated mixtures of ligands.

Based on the reaction kinetics in Figure 1 coupled with simulations of the reaction of eq 1, we may estimate the value of k_{on} and k_{off} to be ca. 0.1 $M^{-1}s^{-1}$.[5,7] This indicates a relatively rapid exchange mechanism between Pd and ligand on the time scale of the catalytic reaction. The reaction's instantaneous selectivity thus provides an excellent reporter of this ligand exchange.

Figure 4 showing ^{19}F NMR of Pd(MPAA) catalysts with the 2,6-difluorobenzoyl protecting group reveals a shift in the Pd-bound ligand as increasing amounts of iodine are added to the system. In accordance with our

previous studies, this suggests that the catalytic species shifts from **6** in the absence of iodine to predominantly **7** under catalytic concentrations of I_2. The two peaks corresponding to diastereotopic F atoms are shifted closer in **7**, suggesting more rapid exchange or less hindered rotation in **7** compared to **6**.

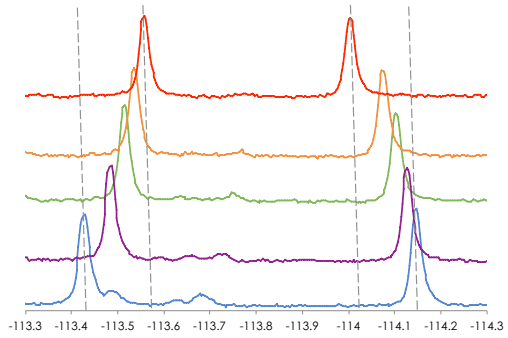


Figure 4.[19]F NMR spectra of $Pd(OAc)_2$ and the 2,6-difluoro Bz-Leu-OH ligand at Pd:L = 2:1 and 30 equiv. CsOAc with increasing amounts of I_2. blue: no I_2; purple: 0.05 M I_2; green: 0.10 M I_2; orange: 0.16 M I_2; red: 0.33 M I_2. Spectra acquired after heating to 50 °C in d_6-DMSO/t-Amyl-OH.

A key question to address is the nature of the species in the active catalytic cycle that are implicated in this ligand exchange. Dissociation of ligand from Pd(II) species **5** or **6** could occur at the close of each turnover in the cycle. Ligand exchange might occur via dissociation of ligand from a Pd(IV) species, either **7** or the subsequent species formed from binding to substrate **1**, both of which were implicated as resting states in the cycle from the observation of saturation kinetics in [**1**].[2c] We employed [19]F NMR spectra to monitor exchange between species **5** and **6** and between species **7** and its diiodo counterpart **8**, as shown in Scheme 2.

Scheme 2. Proposed MPAA Ligand Exchange from either Pd(II) or Pd(IV) Species.

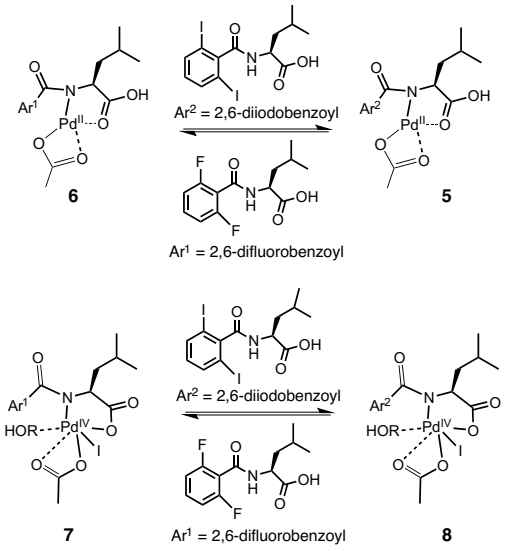


Figure 5 plots the time evolution of the PdL species **5** and **7** as the difluorobenzoyl ligand exchanges with the diiodobenzoyl ligand in the processes shown in Scheme 2. The results are in good agreement with the estimated chiral ligand exchange rates from the reaction results in Figure 3. Further, the difference in the time courses support the suggestion from the NMR shifts in Figure 5 that ligand exchange is more rapid between species **7** and **8** than between **5** and **6**.

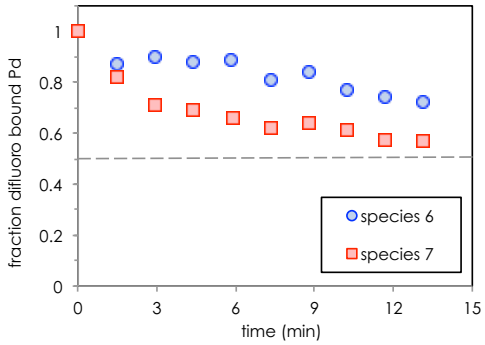


Figure 5. Fraction of PdL species with MPAA system containing the substituted benzoyl protecting group (Ar^1 = 2,6 difluorobenzoyl) over time after exchange with the substituted benzoyl protecting group (Ar^2 = 2,6 diiodobenzoyl) as monitored by [19]F NMR spectroscopy. Initial Pd:L (with Ar^1) = 1:1; 1 equiv. ligand (with Ar^2) added at t=0. 30 equiv. CsOAc in d_6-DMSO/t-Amyl-OH at 50 °C.

The observation of rapid exchange of ligands on and off the Pd center in the catalyst both during the working catalyst cycle as well as at rest is all the more striking given the high enantiomeric excess values achievable in this reaction. This result reiterates the power of ligand-accelerated catalysis in this system, since high ee indicates that the reaction appears to be completely shut down in the "ligand off" state. It also suggests that probing the dynamics of exchange between enantiomeric ligands by temporal monitoring of product enantiomeric excess may be used as a tool for future catalyst design and mechanistic evaluation. Systems exhibiting facile ligand exchange coupled with high enantiomeric excess are good candidates for successful ligand-accelerated asymmetric catalysis. Understanding which species on the catalytic cycle are capable of undergoing ligand exchange may add support to a proposed reaction mechanism and may aid in future catalyst design.

Calculations provide support for the mechanistic details of ligand exchange proposed from the experimental data.[2c] Figure 6 investigates the reaction coordinate for exchange between difluoro and diiodo ligands for Pd(II) and Pd(IV). Protonation/deprotonation steps are not calculated due to uncertainties in the mechanism, which could proceed through number of different possible routes including both inter- and intramolecular bases. Assuming that protonation/deprotonation steps are not rate-determining, the results reveal that the Pd(IV) pathway (species **7** to species **8**) is more favorable than the Pd(II) (species **6** to species **5**).

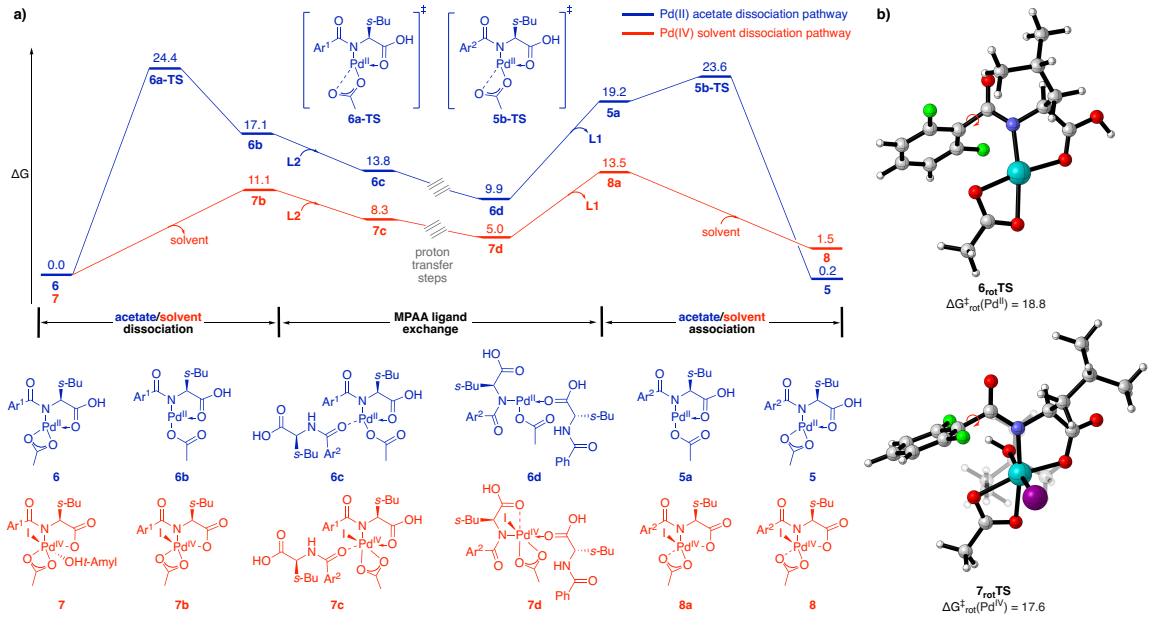


Figure 6. Left: Free energy profile for dissociative MPAA ligand exchange. The Pd(II) acetate dissociation pathway is shown in blue, and the Pd(IV) solvent dissociation pathway is shown in red. M06/SDD(Pd,I)-6-311++G(d,p) energies are reported as ΔG in kcal/mol; Right: Transition states and energy barriers of rotation of the aryl group on the benzoyl protecting group for complex **6** (top) and **7** (bottom). Activation free energies are given in kcal/mol. [5]

Figure 6b reveals that the energy barrier for rotation of the aryl group of the difluoro ligand for the Pd(II) species **6** is 1.2 kcal/mol higher than that for the Pd(IV) species **7**. Both computational results are in accord with the experimental NMR data of Figures 4 and 5.

In conclusion, we present a protocol for probing dynamic ligand exchange in asymmetric catalytic reactions applied to the Pd(MPAA)-catalyzed iodination of diarylmethylamines. Monitoring the temporal product enantiomeric excess after addition of the opposite enantiomer of the MPAA ligand allows assessment of the dynamics of ligand exchange in the system. While this system exhibits Pd:ligand = 1:1 and the lack of a nonlinear effect, it may be imagined that valuable information concerning the dynamics of ligands might also be obtained in systems exhibiting more complex catalyst speciation. Combining such experiments with spectroscopic characterization and an understanding of the ligand and metal molecularity provides a detailed protocol for comprehensive mechanistic understanding of the catalytic system. Further studies probing the generality of this protocol in other asymmetric catalytic systems of import are underway.

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Supporting Information. Details of kinetic, spectrsocpic, and computational measurements.

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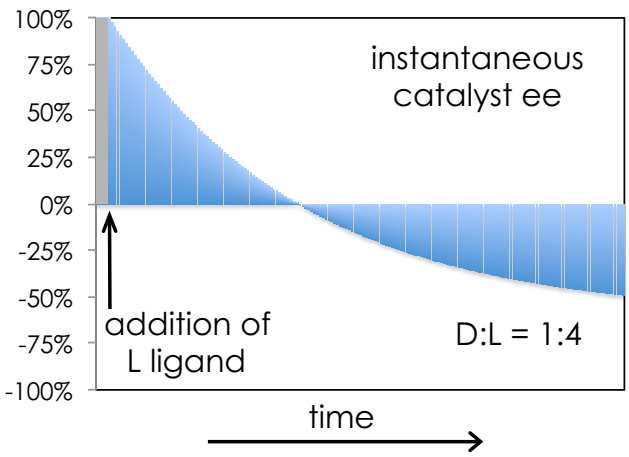
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