Mechanism of the Arene-Limited Nondirected C–H Activation of Arenes with Palladium

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Abstract: Palladium catalysts have recently been discovered that enable the directing group-free C–H activation and functionalization of arenes without requiring an excess of the arene substrate. By overcoming this long standing challenge, the resulting synthetic methods have now become suitable for the functionalization of complex organic molecules. The key to success in several of these transformations has been the use of two complementary ligands, an N-acyl amino acid and an N-heterocycle. Further applications of this design principle will likely require the guidance by a profound mechanistic understanding. This prompted us to engage in a detailed experimental and computational mechanistic study of the two ligand-enabled C–H activation of arenes. Based on comprehensive kinetic experiments, (CID-)MS and DOSY-NMR measurements, and DFT calculations we find that a 1:1:1 complex of palladium and the two ligands is the active species that enables a partially rate-limiting concerted C–H activation as part of a Pd0/Pd2-cycle. Our study highlights the importance of catalyst speciation and allows us to rationalize the role of each ligand as well as the observed regioselectivities. These findings are expected to be highly useful for further method development using this powerful class of catalysts.

Introduction

The prevalence of aromatic cores in natural products and bioactive molecules leads to a continued interest in the development of methods to access such compounds efficiently and, in the case of multiply-substituted arenes, regioselectively. In this context the use of C–H activation has been identified as an enabling technology, often complementing the selectivity patterns obtained in classic aromatic substitution reactions and allowing for the formation of otherwise challenging bond types.[1]

Many methods developed in this field rely on directing effects[2] to address the two critical challenges associated with C–H activation: the low reactivity of C–H bonds and the control of regioselectivity.[3] With unbiased substrates, catalyst design has to be used to achieve the desired reactivity. Such nondirected (non-chelate-assisted) methods offer an inherently orthogonal selectivity pattern and potentially broader applicability due to their independence from directing groups.[4]

However, nondirected methods have faced a long-standing challenge: in order to achieve reactivity, the arene substrate had to be used in excess, often as (co)solvent. Intensive studies over the last two decades have led to the development of methods overcoming this limitation. Seminal work by the groups of Maleczka, Smith and coworkers, as well as Hartwig, Miyaura, Ishiyama and coworkers, enabled the arene-limited nondirected borylation of unbiased arenes. Following this work, a variety of synthetic methods mostly based on Ir- and Rh-catalysis has been reported, which have proven particularly useful for late-stage C–C bond formation and soon found widespread application even on an industrial scale.[5] The regioselectivity of these transformations is governed by a combination of steric and electronic control, which can be tuned by catalyst design, and enables the highly selective synthesis of product motives that are otherwise not easily accessible.[6]

In contrast, Pd-catalysis has remained underdeveloped and until recently no general methods were available that allowed for the arene-limited nondirected formation of aryl-palladium species.

Scheme 1. Milestones for the nondirected arene-limited C–H activation of arenes.

In light of the prominent role of palladium-catalysis for C–C bond forming processes, we became interested in developing a catalyst capable of achieving such an activation and thereby unlocking a synthetic potential complementary to the Ir- and Rh-based methods.

Using the Fujiwara-Moritani reaction as model system,[7] the group of Yu et al. and ourselves recently developed the first broadly applicable palladium catalysts for the arene-limited nondirected C–H activation of arenes.[8] Subsequent studies by the groups of Ritter, Yu, and ourselves demonstrated the generality of these catalyst systems through the development of arene-limited nondirected C–H cyanation reactions suitable for
late-stage benzonitrile synthesis\cite{9, 10}. Recently our group has developed an arene-limited nondirected C–H alkylation.\cite{11} Furthermore, we could recently demonstrate that this design can also be applied to devise sterically controlled heteroarene functionalizations.\cite{12}

These studies hint at the tremendous synthetic potential of a broadly applicable generation of aryl-palladium species through nondirected C(sp^2)–H activation. In order to fully exploit this potential, a detailed understanding of the catalytic systems and reaction mechanisms will be essential. Our catalyst systems, as well as the catalysts used by Fitter et al. for arene cyanation, are based on the use of two complementary ligands acting in concert: an N-acyl amino acid derivative and an N-heterocycle. Interestingly, while catalysts based on either one of these ligand types have been studied extensively,\cite{13-17} so far only few mechanistic details are available on this dual ligand catalysis approach.\cite{3, 11}

Herein we describe combined experimental and theoretical studies on the mechanism of the dual ligand-enabled nondirected olefination of arenes. The results illustrate the generality of dual ligand-enabled C–H activation and lead to a mechanistic model that serves to rationalize the role of each ligand in this process as well as the observed trends in reactivity and selectivity. In light of the rapid development this research field has experienced over the past years, we expect that our studies will prove highly valuable to guide future method development.

Results and Discussion

Initial Studies. We began by focusing our attention on the key C–H activation step. As documented in literature, four classes of mechanistic pathways are known for the metal-mediated C–H activation: 1) Concerted C–H activations with base assistance spanning the whole spectrum from concerted metalation/deprotonation (CMD)/amphiphilic metal-ligand activations (AMLA), which are used to describe processes that preferentially activate C–H acidic sites, to electrophilicity-driven mechanisms typically denoted as base-assisted internal electrophilic substitution (BIES) or electrophilic CMD (eCMD).\cite{14, 17, 18, 20} 2) σ-bond metathesis.\cite{21, 22} 3) oxidative addition.\cite{23} 4) electrophilic metathesis.\cite{22, 24} Based on detailed mechanistic studies on Pd-catalysis using N-acetyl amino acids as single ligands and the regioselectivities observed in our synthetic methods, we began our studies with the working hypothesis that the C–H activation step proceeds via a concerted C–H activation with base assistance, likely in the BIERS/eCMD regime. This notion was further supported by a computational study, in which Zhang and coworkers find that for Pd\(^{\text{II}}\)/pyridine-catalyzed Fujiwara-Moritani reactions the C–H activation likewise proceeds through a base-assisted concerted mechanism and precedes the reaction of the catalyst with the olefin reaction partner.\cite{25} In order to learn more about the C–H activation of arenes under dual ligand catalysis conditions, we began by probing whether the C–H activation step contributes to the overall rate of the reaction. Ortho-xylene (1a) was chosen as model substrate because (a) only two regioisomers can form, (b) in contrast to toluene no di-olefination was observed, and (c) deuterated ortho-xylene (1a-\(\text{d}_{10}\)) is commercially available. Ligand 2, used under optimized conditions in our initial report on this transformation, was exchanged for ligand 3 in our kinetic studies due to its commercial availability. This substitution is justified, since the two ligands perform almost identically in the model reaction (Scheme 2).

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\text{Scheme 2. The dual ligand-enabled nondirected C–H olefination of arenes as model reaction. Yields and regioselectivities determined by GC-FID. HFIP = 1,1,1,3,3,3-hexafluoropropanol.}
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Parallel and competition kinetic isotope effect (KIE) studies were conducted. The observed rates for the parallel experiments (\(k_{\text{H}}/k_{\text{D}} = 1.8 \pm 0.3\), GC-FID, Scheme 3) and the competition experiment (\(k_{\text{H}}/k_{\text{D}} = 1.9 - 2.0\), NMR, see Scheme S2 in the Supporting Information) between ortho-xylene (1a) and ortho-xylene-\(\text{d}_{10}\) (1a-\(\text{d}_{10}\)) both reveal a small primary kinetic isotope effect. Studies with deuterated ethyl acrylate showed no kinetic isotope effect on the rate of the reaction.

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\text{Scheme 3. Parallel kinetic isotope effect experiments.}
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These results show that the C–H activation contributes to the overall reaction rate and thus, experimental methods can be used to gain knowledge about this step. The comparably small magnitude of the observed KIE, indicates that further steps in the catalytic cycle likely contribute to the rate of the reaction.\cite{26} To obtain further information regarding the steps influencing the reaction rate, we proceeded to assess the kinetic orders of both reaction partners. Initial rates were determined for different starting concentrations of the respective components and the obtained data analyzed using a non-linear least squares fit. As shown in Figure 1, the best fits are obtained for an order in arene of 0.9 and an order in olefin of 0.2.\cite{27}
The fractional order in arene that approaches unity corroborates to the finding from KIE measurements that the C–H activation step is rate-determining. The small fractional order in olefin is remarkable. Typically, a zero order would be expected for a component entering the catalytic cycle after the rate-limiting step.\(^{(25)}\) We interpreted the observed fractional orders to indicate that the C–H activation event is in principle reversible. While most of the C–H activated species proceeds to product formation under the reaction conditions, a small fraction undergoes the reversion to the starting material. Thus, while the C–H activation remains the key step for the observed reactivity, the balance between olefination and retro-C–H activation can be influenced by changes in the olefin concentration.

To support this finding, we probed the reversibility of the C–H activation step. For this purpose the deuterated benzoate substrate \(1\text{b-d}5\) was subjected to the catalyst system without adding the olefin reaction partner (note that a change of model substrate was required, since a background-H/D-exchange is known to occur for more electron-rich substrates).\(^{(11, 28)}\) We observed a substantial degree of H/D-exchange, thus proving the reversibility of the C–H activation step under the reaction conditions. Similarly, we subjected the same substrate to the reaction conditions in the presence of the olefin reaction partner and found that the H/D-exchange in the remaining substrate was strongly reduced. This shows that when the product forming pathway is available the retro-C–H activation is mostly suppressed.

At this stage, we could establish that the C–H activation step is in principle reversible but nevertheless rate-determining (and since the reversion of C–H activation only occurs to a small degree also selectivity-determining) under the reaction conditions.

Stoichiometry Variation Experiments. We proceeded to gather further knowledge about the nature of the catalytically active species. Given that under the optimized reaction conditions an excess of both ligands is employed, we began with stoichiometry variation experiments, in order to determine the composition of the active species.

We thus studied the performance of catalysts generated upon combining different ratios of Pd(OAc)\(_2\), Ac-Gly-OH, and the pyridine-derived ligand in our model reaction (Table 1). Entry 1 shows that there is a significant “background reaction” catalyzed by palladium acetate in the absence of additional ligands.\(^{(26)}\) This can be rationalized considering that \(\text{ortho-xylene (1a)}\), a rather electron-rich arene, can undergo a comparably facile C–H activation with electrophilic Pd\(^{II}\)-catalysts. Adding (only) a pyridine-ligand to the system led to no improvement of the yield or regioselectivity (Entry 2). In contrast, the addition of Ac-Gly-OH improves the yield to 52% and at the same time increases the regioselectivity (Entry 3). Remarkably, when pyridine is added as a third component to the catalytic system, it induces an additional improvement of both yield and regioselectivity relative to the binary Pd:Ac-Gly-OH catalyst (Entry 4). The change from a 1:1:1 ratio to the published reaction conditions (1:3:2) does not further improve the yield in the model reaction with \(\text{ortho-xylene (Entry 5)}\).

The reactions in this table were conducted on a 0.1 mmol scale and yields determined by GC-FID using 1,3,5-trimethoxybenzene as internal standard.

The results in Table 1 show that a higher yielding and more selective catalyst is formed as soon as all three catalyst components are present in at least a 1:1:1 ratio, further equivalents of either ligand have no positive impact on the catalyst performance. However, the substantial product formation observed for Pd(OAc)\(_2\) alone and the binary systems (Entries 1-3) shows that different catalytically active species can form under the reaction conditions. The results obtained with this model system could thus in principle correspond to the superimposition of catalysis by several species, which could in turn hypothetically lead to erroneous conclusions. To eliminate this potential source of error, a second model system was required, in which only the catalyst containing both ligands would show considerable catalytic activity. We reasoned that this might be the case for a substantially more electron-poor substrate such as HFIP benzoate (1b).

We were pleased to find that indeed the reaction with this substrate does not proceed until Pd(OAc)\(_2\) and both ligands are present (Entries 1-4, Table 2). Notably, with this substrate, an improved reaction outcome was observed with the previously optimized ratio of palladium and ligands (Entry 5).
Table 2. stoichiometry variation experiments with HFIP benzoate (1b) as starting material.

| Entry | Rate | Pd Ac-Gly-OH Pyr | Yield (%) | o:m:p |
|-------|------|------------------|-----------|-------|
| 1     | 1:0:0| 4                | -         | -     |
| 2     | 1:1:0| 3                | -         | -     |
| 3     | 1:0:1| 2                | -         | -     |
| 4     | 1:1:1| 37               | 18:70:12  |       |
| 5     | 1:3:2| 49               | 18:71:11  |       |

The reactions in this table were conducted on a 0.1 mmol scale and yields determined by GC-FID using 1,3,5-trimethoxybenzene as internal standard.

Overall, these results confirm that the catalytically active species requires a 1:1:1 ratio of palladium to the two ligands. The identical distribution of regioisomers observed between entries 4 and 5 of both model systems implies that under the optimized conditions the same active species is responsible for product formation as when a 1:1:1 ratio is employed.

At this point several explanations remained possible for the superior yield observed with a 1:3:2 stoichiometry. Either, the concentration of the active species could be increased with this ratio of metal to ligands (improved speciation), or the lifetime of the catalyst could be increased (stabilization). Importantly, these scenarios can be differentiated through initial rate measurements, since an improved speciation would lead to increased initial rates, while a stabilization would not correlate with changes in the initial rate.

We thus proceeded to study the initial rates of reactions conducted with varied catalyst compositions (Figure 2). Based on the observation from Table 1 that for substrate 1a several species are catalytically active, we expected that the more easily interpretable results would be obtained using 1b as the model substrate for these experiments (analogous measurements were also conducted with substrate 1a, for details see the Supporting Information). As expected, based on the results in Table 2, no catalytic activity for the olefination of HFIP benzoate (1b) was observed in absence of either ligand. The initial rate with varied loading of the pyridine-derived ligand (Figure 2A) increased sharply up to a plateau in the range between 0.1 and 0.2 equivalents. Similarly, for Ac-Gly-OH a maximum in catalytic activity is reached at 0.1 equivalents (Figure 2B). The addition of further ligand leads to decreased activities for both ligands.

These results show that a catalyst with a 1:1:1 stoichiometry between palladium and both ligands gives superior results due to an increased catalytic activity, not merely due to an increased catalyst lifetime.

The detrimental effect of adding larger quantities of either ligand can be interpreted as the result of a shift in catalyst speciation away from the active 1:1:1 complex and towards species containing a second equivalent of either ligand. Under the optimized reaction conditions, where a 1:3:2 ratio between the components is employed, such 1:1:2 species (presumably with the pyridine ligand, vide infra) may serve as resting states, thereby contributing to the stability of the catalytic system. In this context it should be noted that the formation of a catalytically inactive species with two pyridine ligands per Pd has been documented for different C–H activation reactions with Pd(OAc)₂ and other catalysts [16, 27, 31, 32]. The introduction of bulky substituents in the ortho-positions of the pyridine can cause a steric clash between the two pyridine ligands and thus shift the equilibrium towards a catalytically active mono pyridine complex [26, 33]. Similarly, this equilibrium can be influenced by electron-withdrawing groups on the pyridine-ligand, which weaken the Pd–N bond [16, 27, 33].

At this stage of our studies, we could establish that the C–H activation is achieved by a catalyst with a 1:1:1 stoichiometry between palladium and the two ligands employed. We could further show that additional ligand can lead to inactive catalytic species, which might serve as resting states under catalytically relevant conditions.

Nuclearity of the Active Species. While the data obtained so far established the stoichiometry of the catalyst, its nuclearity remained to be investigated. It is well documented that Pd₄-based catalysts for C–H activation can adopt a variety of forms, such as monomers, dimers, trimers, and oligomers. The question of nuclearity becomes particularly relevant when N-acetyl amino acids are used as ligands, since they can interact with palladium through a number of known binding modes, the most common of which are the bidentate di-anionic (κ²(−N,O)⁴), the bidentate mono-anionic (κ²(−N,O)⁵), and the bridging mono-anionic (κ¹(−O)⁴) coordination [34]. The potential role of dinuclear Pd₄ species in Pd-pyridine, as well as Pd-N-acetyl amino acid systems, has been investigated intensively with both experimental and computational methods [35, 36]. Depending on the system studied, dinuclear or higher-order complexes have been found both as on-cycle and as off-cycle species [36].

In order to distinguish between mononuclear and oligonuclear species as active catalysts, kinetic measurements have been established as a highly useful tool [36]. We thus measured the influence of catalyst loading on the initial rate of the reaction using two different approaches. First, we varied the loading of all catalyst components keeping the ratio between them constant as used under the optimized reaction conditions (Figure 3A). The
results were analyzed using a non-linear least squares fit and the order in catalyst was determined to be 0.5. This broken order in catalyst below unity could be caused by (a) mononuclear active species that are in equilibrium with inactive higher order aggregates,[36] or (b) equilibria between mononuclear complexes with one (active) or two (inactive) pyridine ligands bound.[30]

To distinguish between these scenarios, we determined the kinetic order of Pd(OAc)$_2$, by varying only this component and providing a constant excess of both ligands (Figure 3B). Importantly, for equilibria between mononuclear and oligonuclear species, a broken order below unity would again be expected, while for mononuclear complexes with varying metal to ligand ratios, this experimental setup is expected to yield a kinetic order close to unity.

Our experimentally observed order in Pd(OAc)$_2$ of 1.1 thus strongly supports the conclusion that under our reaction conditions a catalytically active species with a 1:1:1 stoichiometry is in equilibrium with a resting state having a 1:1:2 stoichiometry (Scheme 5). It should be noted that analogous findings have been described for Pd(OAc)$_2$-pyridine binary catalysts by Stahl and coworkers.[30]

Scheme 5. Proposed active species and resting state.

HRMS Studies. Having derived the stoichiometries of catalytically active species and resting state from kinetic data, we wondered whether we could obtain experimental evidence for the presence of such species in solution. The mass spectrum obtained from a 1:3:2 mixture of Pd(OAc)$_2$:Ac-Gly-Oh:ligand 2 in HFIP show ions corresponding to mononuclear complexes with 1:0:2, 1:1:1, 1:0:1 and 1:1:2 stoichiometries (Figure 4A). No signals were detected that could be attributed to aggregates or higher order species. The peak assignment was confirmed by matching with the theoretical isotope patterns (see Figure 4B, C and Figure F8-F13 in the Supporting Information).

Figure 3. Non-linear least squares analysis to determine the reaction order in [catalyst] (A) and [Pd(OAc)$_2$] (B) with exponential fits to $y = a x^b$ where $b =$ reaction order.

Figure 4: (A) CID fragmentation analysis of protonated 1:1:2 complex of Pd:Ac-Gly-Oh:ligand 2 in HFIP (collision gas: helium, Ultrap = 15 V). Experimental (top) and theoretical (bottom) isotope patterns for the proposed active species [1:1:1]H$^+$ (B) and resting state [1:1:2]H$^+$ (C). Ions generated from a millimolar HFIP solution of 1:3:2 (A) or 1:1:2 (B and C) stoichiometry (Pd(OAc)$_2$:Ac-Gly-Oh:ligand 2). Ligand 2 is denoted as Pyr$^+$ for simplicity.
To further elucidate the relation between the observed species, collision induced dissociation (CID) experiments were performed. The peak at m/z 692 assigned to the 1:1:2 complex was mass-selected and after analysis by the MS/MS method fragments corresponding to 1:0:2, 1:1:1, 1:0:1 and 0:0:1 stoichiometries could be observed (Figure 4). We furthermore observed a signal that can be explained by the decomposition of Ac-Gly-OH, which loses a COCH3 fragment while remaining bidentately coordinated, a pathway commonly observed for N-acetylated amino acids.[37] These results show that the 1:1:2 complex proposed to be the resting state in our catalytic system readily dissociates one pyridine ligand to give the 1:1:1 complex identified as the active species. They furthermore support the hypothesis that Ac-Gly-OH acts as a bidentate ligand.

When an analogous measurement was conducted using a 1:20:2 ratio of the catalyst components, further mononuclear complexes with 1:2:0, 1:2:1, and 1:2:2 stoichiometries were observed. These data confirm that an excess of either ligand is capable of shifting speciation away from the catalytically active 1:1:1 complex. However, the fact that the species containing two equivalents of ligand 2 was observable with the catalytically relevant ratio of ligands, while a large excess of Ac-Gly-OH was required to detect the corresponding species, implies that the 1:1:2 complex is more prone to serve as the resting state (Scheme 5).

While it should be noted that the observation of a complex in the gas phase alone does not necessarily coincide with relevance for catalysis,[37] these data confirm our finding from kinetic data that mononuclear species dominate the equilibrium in HFIP as solvent. The detection of a 1:1:2 species agrees well with its proposed role as resting state.

NMR Studies. To further investigate the nature of the active species in solution NMR studies were conducted. Considering that HFIP proved to be crucial for the performance of the catalyst system meaningful results could not be expected from experiments conducted in another solvent. Since deuterated HFIP is not commercially available all NMR experiments were conducted in regular HFIP with acetone-d6 in a coaxial tube for external locking. As expected based on our findings detailed above, the presence of multiple interconverting species rendered a full spectroscopic characterization of the catalytically relevant species impossible. However, we expected that NMR-spectroscopy could nevertheless deliver valuable information regarding the nuclearity of the catalytically relevant species.

Diffusion ordered NMR spectroscopy (DOSY) emerged as a powerful tool to determine the molecular weight of complexes in solution since the diffusion constant (D) depends on the size and is proportional to the MW using the relationship log MW ∝ log D.[37, 38]

While 1H-DOSY has been used extensively for absolute diffusion information to estimate the size of molecules and aggregates, the catalyst shown in Scheme 2 proved to be too complex for a determination of diffusion constants (D) by 1H-NMR. We envisaged that applying heteronuclear 19F-DOSY with a 19F-labeled pyridine ligand would allow us to analyze the different catalytic species in solution separately due to the large chemical shift dispersion of 19F compared to 1H and the reduced overall number of peaks. 19F-DOSY has been applied to determine monomer/dimer equilibria and molecular weights (MW) of complexes in solution.[39]

In order to introduce fluorine into the catalyst, 3,5-difluoropyridine was used instead of ligand 2 or 3. A control experiment with this ligand revealed that, while not delivering optimal results, the use of this ligand resulted in catalytic activity, and thus meaningful data could be obtained through this replacement. The 19F-NMR of a 1:1:2 Pd(OAc)2·Ac-Gly-OH·3.5-difluoropyridine mixture in HFIP gave a complex but well-resolved spectrum, showing the presence of several pyridine-containing complexes. To avoid hydrogen bonding to the solvent as a potential source of error in our DOSY measurements, six fluorinated molecules without hydrogen bond acceptors were selected as internal standards.

The MW calculated from the diffusion constants of the pyridine-containing palladium complexes by internal standard reference 19F-DOSY are slightly above the ones of simple mononuclear complexes, but at the same time drastically too low for analogous dinuclear species (Figure 5).

We hypothesized that the overestimation of the MW could be explained by unspecific hydrogen bonding between the palladium complexes and HFIP. Analogous hydrogen bonding has been observed numerous times, for example between HFIP and amino acids.[40] While such hydrogen bonding would not result in stable catalyst-HFIP adducts via specific bonds, the dynamic forming and breaking of hydrogen bonds would slow diffusion and thus lead to higher measured molecular weight. In accordance with this proposal, the MW calculated for mononuclear complexes with an average of one hydrogen bond to HFIP (1:1:2·HFIP) lies well within the range of measured diffusion constants.

To further validate the hypothesis of hydrogen bonding between HFIP and the catalyst, model compounds with and without hydrogen bond acceptor sites were studied and an increase in the measured MW was observed for molecules bearing H-bond acceptors, while compounds lacking such sites delivered the correct MW value. As expected based on these findings, the MW measured for free pyridine ligand was also found to exceed the theoretical value (see the Supporting Information for details).

In agreement with our findings from kinetic measurements and mass spectrometry, the above 19F-DOSY results indicate that...
mononuclear complexes are the predominant species formed from the three catalyst components in HFIP. The NMR results thus corroborate to identification of these mononuclear complexes as the relevant resting states and catalytically active species.

**Experimental Data on the Mechanism of C–H Activation.** Based on the above experimental results, the following statements can be derived regarding the mechanism of dual ligand-enabled C–H activation:

(a) The C–H activation step, although in principle reversible, is rate-limiting and selectivity-determining under the reaction conditions.
(b) Palladium and both ligands are part of the catalytically active species.
(c) The active species is mononuclear and has a stoichiometry of 1:1:1 between palladium and the ligands.
(d) The active species is in equilibrium with a mononuclear resting state that has a 1:1:2 stoichiometry between palladium, Ac-Gly-OH, and the pyridine-derived ligand.

Experimental methods cannot deliver detailed information about the subsequent steps of the catalytic cycle, since these steps occur after the rate-limiting step. In analogy to literature reports we expected the reaction to continue with a ligand exchange, bringing the olefin into the coordination sphere of the Ar–Pd species.\cite{14,17,25,41} Given that we observe a small broken order in the olefin, these steps must, as observed in previous studies, proceed through activation barriers that are lower but in the same order of magnitude than that of the C–H activation step and do not contribute significantly to the rate or selectivity of the overall process.\cite{17,41}

**DFT Studies.** In order to obtain further insights into the reactivity and selectivity determining transition state, we proceeded to study the C–H activation step computationally. We started the theoretical investigation by determining the free energy of intermediates and transition states using benzene (1c) as substrate. Computational studies were performed using the TURBOMOLE program.\cite{42} Structures were optimized with the hybrid functional PBE0-D3 and electronic energies calculated with the hybrid meta GGA functional PW6B95-D3.\cite{43} Solvation free energies at T = 363 K were obtained with COSMO-RS using the COSMOTHERM program package.\cite{44} A reaction profile for the dual ligand-enabled C–H olefination of benzene is shown in Figure 6.

The resting state of the catalyst system 5, a complex with a stoichiometry of 1:1:2 (Pd:Ac-Gly-OH:pyridine) is significantly more stable than the active state 6 in which one pyridine is dissociated. The active complex 6 is stabilized by an interaction between palladium and the amide carbonyl group of the N-acetyl amino acid ligand. The free energy of dissociation is +14.6 kcal/mol. The association of benzene 1c to form the pre-reactive complex 8 is slightly endergonic (+2.2 kcal/mol). From here, the formation of the CMD-transition state 9 requires an additional free energy of activation of +4.8 kcal/mol. The total energy barrier for the C–H activation of benzene thus amounts to ΔG‡$\text{363}$(5→9) = 21.6 kcal/mol.

![Figure 6: Reaction coordinate [free energy profile, ΔG‡$\text{sol}$ in kcal/mol computed with PW6B95-D3/PBE0-D3/def2-TZVP+COSMO-RS(HFIP)] for the arene-limited nondirected C–H activation of arenes with palladium. All energies are given in Table S17 of the Supporting Information.](image-url)

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The formation of the aryl-palladium intermediate 7 is endergonic with respect to the catalyst resting state by 8 kcal/mol, which is in good agreement with the observation that the C–H activation step is generally reversible. In order for the reaction to proceed to product formation, a ligand exchange bringing the acrylate into the coordination sphere of palladium is required, leading to intermediate 10. We found that the transition state for a carboxapalladation from intermediate 10 was substantially above the transition state of C–H activation, which would be incompatible with the C–H activation constituting the rate-determining step of the overall process. However, further ligand exchange processes in which Ac-Gly-OH becomes a monodentate ligand (10′) or is replaced by two acetic ligands (10″) can enable substantially lower barriers for the subsequent carbometalation step (11′/11″) with 22.0 kcal/mol and 22.9 kcal/mol respectively, which are very close to the activation barrier of the C–H activation step (21.6 kcal/mol). This is in good agreement with the broken orders kinetic in arene and olefin indicating that both steps contribute to the overall rate of product formation. Through this step the carboxapalladation products 12' and 12'' are formed in an overall exergonic process. It should be noted that for intermediate 12'' the subsequent steps of β-hydride elimination and reductive elimination have been studied by Zhang and coworkers and were found to be highly exergonic and proceed through very low activation barriers, which leads to the conclusion that the formation of 12' and/or 12'' occurs irreversibly.[24]

Since our kinetic data implied that the C–H activation step is the main rate-determining step, we argued that the relative activation barriers of this step for the different positions of substituted arenes should correlate with the experimentally observed regioselectivities and reactivities of these arenes. We thus studied a series of substituted arenes with varied steric and electronic properties and determined the respective barriers of activation (Figure 7).

![Figure 7](image-url)

**Figure 7.** Computed barriers of activation for different positions in representative substituted arenes and experimentally observed regioselectivities.

Interestingly, the computed barriers reflect the experimentally observed relative reactivities well. Anisole (1d) is predicted to be the most reactive substrate, followed by benzene (1c) and tert-butylbenzene (1e), the electron-poor methyl benzoate (1f) being the least reactive. Indeed, we experimentally observe a large degree of overreaction with anisole, leading to low isolated yields. For the same reason, no reliable ratios of regioisomers can be reported, since the primary products undergo overreaction to a different degree, such that small changes in conversion, acrylate loading or temperature substantially alter the observed ratios. We furthermore considered that for this highly reactive substrate a different step might potentially become selectivity-determining and thus focused on tert-butylbenzene (13) and methyl benzoate (1f) as substrates. In both of these cases the relative barriers of activation correlate well with the observed regioselectivities. For tert-butylbenzene the barriers of activation for the meta and para positions are 21.0 kcal/mol and 21.1 kcal/mol respectively, the barrier of activation for the ortho position being substantially higher (23.8 kcal/mol), which is in good agreement with the experimentally observed ratio of m:p = 58:42 with no ortho product being formed. Analogously, the barrier of activation for the meta position of methyl benzoate (23.4 kcal/mol) is computed to be substantially lower than those for the ortho and para positions (24.4 kcal/mol and 25.7 kcal/mol), which fits with the experimental ratio of o:m:p = 13:70:17. Qualitatively, the computations confirm the experimental observation that this catalyst system favors the electron-rich positions of a given substrate. This can also be rationalized considering the bond orders in the transition states, which are consistent with a highly synchronous yet somewhat electrophilic concerted C–H activation mechanism (BIES/eCMD, for further discussion, see the Supporting Information).[20][18]

**Proposed Catalytic Cycle.** Based on the kinetic investigation, spectroscopic and spectrometric data, and the theoretical analysis presented above, as well as analogies to related literature reports, we propose the catalytic cycle shown in Scheme 8.

![Scheme 8](image-url)

**Scheme 8.** Proposed Catalytic Cycle.

Accordingly, the C–H activation of the arene by the active species 6 is preceded by an equilibrium with the resting state 5. The arenne coordinates to palladium to form the pre-reactive complex 8. The regio-determining C–H activation proceeds through a concerted 6-membered transition state to form the Ar–Pd intermediate 7. Subsequent ligand exchange processes bring the olefin and...
acetate into the coordination sphere of palladium and render the amino acid ligand monodentate giving intermediate 10. As can be deduced from Figure 6 an alternative pathway would involve the complete replacement of the amino acid ligand to give 10'. From 10', the carbopalladation would take place through a second comparably high transition state to give the carbopalladated product 12 in the first overall exergonic step. It has already been established for the analogous 12' that a subsequent sequence of β-hydride elimination giving 13 and product liberation can take place through a pathway involving very low barriers, such that the formation of 12'12' is expected to be irreversible. The resulting Pd(II)-hydride species would then, again in analogy to the literature, undergo reductive elimination followed by a re-oxidation to Pd(II) by the silver salt as terminal oxidant, thereby closing the catalytic cycle. The involvement of the silver salt after the product forming step of the catalytic cycle was probed experimentally: In a reaction without silver salt but with a stoichiometric amount of Pd(OAc)2, Ac-Gly-OH, and ligand 3, the HFIP-benzolate 1c could be very similar to the one observed under catalytic conditions (o:m:p = 20:59:21). The amide carbonyl group of AcOH facilitates the C—H olefination of the arene functionalized in 39%, as can be deduced from Figure 6 an alternative pathway would take place through a second comparably high transition state to give the carbopalladated product 12, which supports the observed steric control of the regioselectivity.

**Conclusion**

We have conducted a combined experimental and computational investigation of the arene-limited non-directed C—H olefination of arenes by dual ligand-enabled palladium catalysis. Using techniques including kinetic measurements, (CID)MS, (DOSY)-NMR, and DFT studies has allowed us to propose a catalytic cycle that readily explains the role of both ligands used to enable remarkably high catalytic activities and regioselectivities that complement other existing technologies. Dual ligand catalysis has only recently been recognized as a highly useful tool to achieve the non-directed C—H activation of arenes with the arene as the limiting reagent. The potential of such catalysts to enable valuable methods for late-stage modification is reflected by a rapidly increasing number of applications of dual ligand catalysis. We expect that the insights into the underlying mechanism presented herein will prove highly useful in the rational development of novel catalysts and synthetic methods.

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**Keywords:** arenes • C—H activation • Fujiwara-Moritani reaction • reaction mechanisms • DFT calculations

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