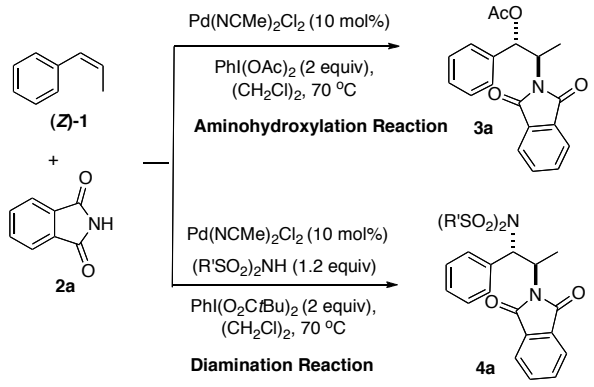
Defined Palladium Phthalimidato Catalysts for Improved Oxidative Amination

Claudio Martínez[a] and Kilian Muñiz*[a,b]

Abstract: New bisphthalimidato palladium(II) complexes have been synthesized, isolated and structurally characterized. As demonstrated for over 30 examples, they constitute superior catalysts for oxidative amination reactions of alkenes with phthalimide as nitrogen source. This work streamlines vicinal difunctionalization of alkenes and provides access to significantly improved and experimentally simplified synthetic protocols.

Defined amination reactions at carbon centers constitute the most versatile approach towards the important class of nitrogenated organic molecules.[1] Within this context, phthalimide has been identified as a particularly versatile ammonia surrogate in organic synthesis. Its potassium salt was originally introduced by Gabriel for amination reactions with broad applicability employing the concept of nucleophilic displacement.[2] In addition to such nucleophilic substitution, the enhanced stability of phthalimide under oxidative conditions has enabled additional seminal transformation of hydrocarbons within this particular area.[3,4]



Scheme 1. Palladium-catalyzed aminoacetoxylation and diamination reactions using phthalimdie as nitrogen source.

Some time ago, the combination of palladium and phthalimide **2a** was found to permit unique intermolecular aminoacetoxylation[5] and diamination reactions,[6] all of which proceed under the conditions of Pd^{II}/Pd^{IV} redox catalysis.[7] This work has generated a synthetic methodology that converts internal alkenes such as **1** into the corresponding difunctionalized products **3a** and **4a** with complete regio-, chemo- and diastereoselectivity (Scheme 1),[6,8] although the structural basis for the involved palladium catalysts has so far remained undetermined. In general, while homogeneous palladium catalysis has reached paramount synthetic applicability over past decades,[9] definite knowledge on the catalyst states involved in individual reactions has often remained missing, in particular when oxidation reactions are concerned.[7,10] Here, we report the isolation of defined bisphthalimidato palladium(II) complexes and present their behavior as tailor-made catalysts in advanced oxidative alkene diamination with phthalimide within significantly simplified experimental protocols.

Our investigation started with the assumption that a transformation of the palladium dichloride source prior to the catalysis should be involved in reactions from Scheme 1. We had identified a preheating period between palladium complexes $(RCN)_2PdCl_2$ and phthalimide as the crucial point in the generation of the active Pd catalyst.[6] For clarification, we studied the reaction between the palladium precursor and phthalimide. First, palladium diacetate reacts readily with phthalimide **2a** or tetrafluorophthalimide **2b** at room temperature in the presence of a nitrile to provide the new complexes **5a-d** as air-stable crystalline solids (Scheme 2).[11] The underlying high stability of the Pd-amide bond is reminiscent to those of peptidic palladium complexes.[12] Complexes **5a-d** form irreversibly and do not revert back to Pd acetate complexes even in the presence of large excesses of the free carboxylic acid.[13] They are equally stable in the presence of hypervalent

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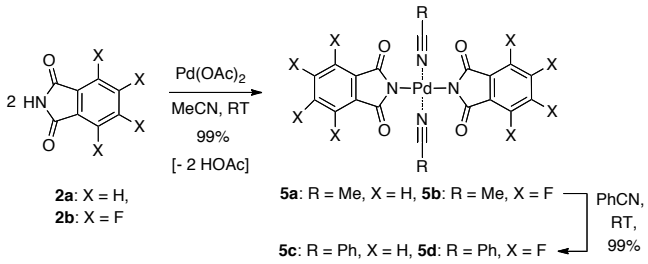
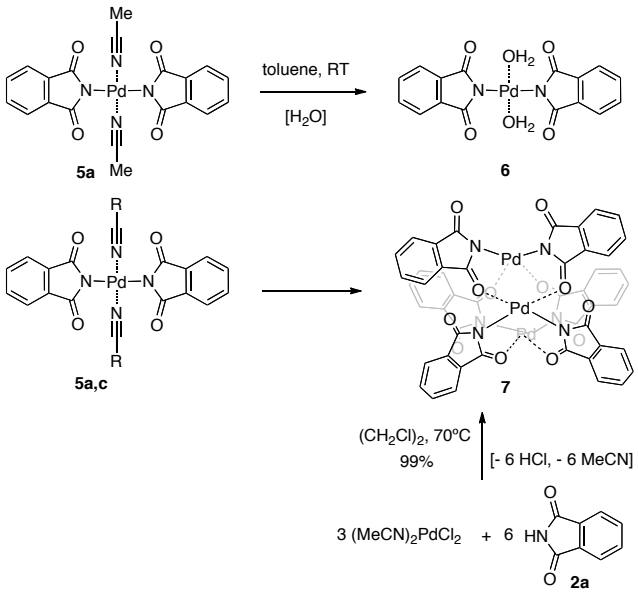
iodine reagents involved in the difunctionalization reactions.[13]



Scheme 2. Synthesis of new palladium-phthalimidato complexes **5a-d**.

Complexes **5a-d** engaged in rapid dissociation of neutral nitrile ligands in solution. Attempts to grow crystals were unsuccessful except for one case, where the structure of the new bis(aqua) complex **6** formed from a toluene solution of **5a** (Figure 1).[14] In a similar manner, alkenes may replace the nitrile ligands in **5a-d**, however, the resulting alkene coordination is again of labile nature and could not be confirmed either by NMR or by X-ray crystallography. Instead, heating of **5a,c** or prolonged standing in solution results in the formation of the unprecedented trimeric complex **7**. The same complex **7** is obtained from $(MeCN)_2PdCl_2$ and free phthalimide under more forcing conditions that resemble the preheating period under the conditions of catalysis.[6]



Scheme 3. Synthesis of advanced palladium-phthalimidato complexes **6** and **7** arising from labile nitrile coordination in complexes **5a-d**.

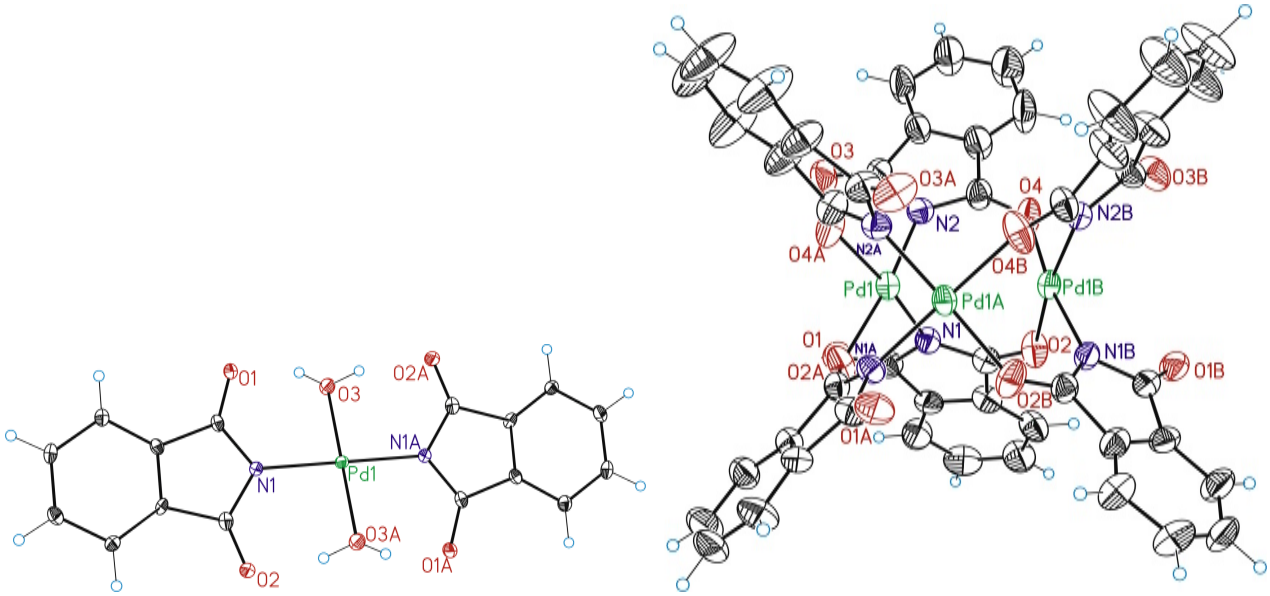
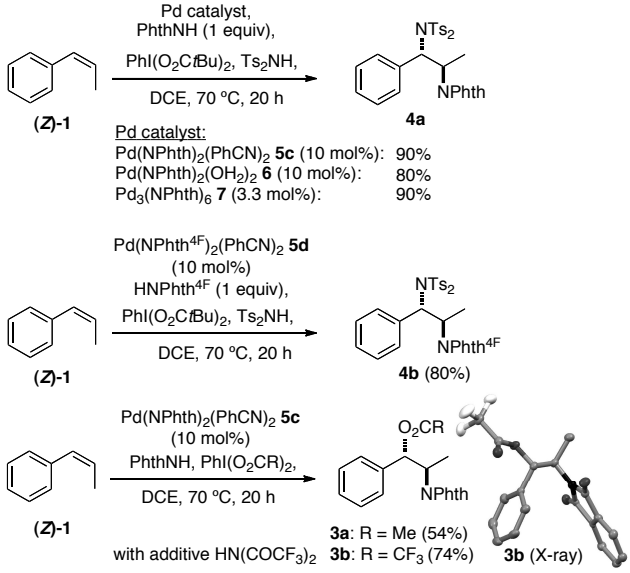


Figure 1. X-ray structures of complexes **6** (top) and **7** (bottom). Selected bond lengths (A) and angles (°): Pd1-O3 2.018(3), Pd1-N1 2.046(4), O3-Pd1-O3 180.0, O3 Pd1 N1 90.25(15), O3-Pd1-N1 89.75(15) (complex **6**) and Pd1-N1 1.992(4), Pd1-N2 1.975(5), Pd1-O2 2.017(4), Pd1-O4 2.026(4), N2-Pd1-N1 91.67(19), N2-Pd1-O2 170.44(17), N1-Pd1-O2 87.6(2), N2-Pd1-O4 88.6(2), N1-Pd1-O4 169.32(17), O2-Pd1-O4 90.3(2) (complex **7**).

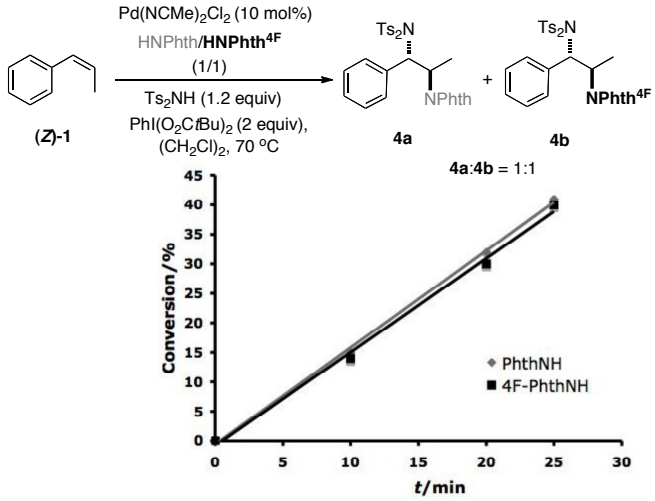


Scheme 4. Reactivity of palladium-phthalimidato complexes. HNPhth = phthalimide, $HNPhth^{4F}$ = tetrafluorophthalphthalimide.

The isolated phthalimidato complexes of palladium **5a-d** and **7** are versatile catalysts for the diamination and aminooxygenation of alkenes using phthalimides as nitrogen sources, as exemplified with the internal alkene (*Z*)-β-methylstyrene as substrate (Scheme 4). For the corresponding diamination reaction to **4a**, all three new catalysts **5c**, **6** and **7** provide complete selectivity and high isolated yields of 80-90%. The same observation is made for a diamination with tetrafluorophthalimide in the presence of catalyst **5d**. Finally, aminoxygenation to **3a** proceeds with yields comparable to previous in situ protocols, while addition of bistrifluoroacetamide provides a new aminooxygenation variant to **3b** in 74% yield.

The formation of **5a-d** and **7** upon its concomitant complete loss of the chloride atoms also lends an explanation to the absence of any alkene isomerization pathway over the course of the difunctionalization reactions from Schemes 1 and 4. Alkene isomerization is known to be rapid with $(RCN)_2PdCl_2$[15] and completely suppressed upon formation of the phthalimidato complexes of type **5**.[13] Moreover, the nature of the phthalimide[16] does not alter the course of the reaction (Scheme 5). An internal competition experiment demonstrates equal product formation for both phthalimide and tetrafluorophthalimide from **(*Z*)-1**; kinetic control experiments confirm equal rates for the two individual reactions.

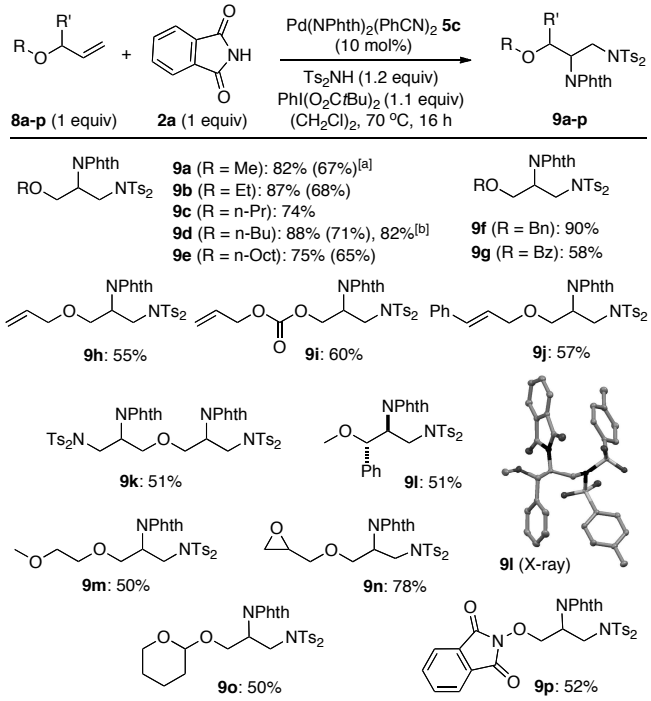
Further kinetic control experiments suggest **7** to be a precatalyst, particularly in the absence of loosely coordinating ligands such as nitriles.[17] For the transformation of **(*Z*)-1** to **4a**, a first order dependence on catalyst was observed confirming a monomeric catalyst state.[13] In line with these observations, participation of phthalimidato complexes of palladium sets the basis for the chemoselectivity in catalytic diamination reactions, which kinetically override the potentially competing stoichiometric background reaction based on $PhI(NTs_2)_2$. This particular reaction had previously been investigated by us.[18] Indeed, this background reaction does become dominant in the presence of ligands that exercise stronger coordination to palladium than nitriles, where the alkene oxidation proceeds exclusively throughout the iodine(III)-mediated channel.[18] The mechanistic conclusion is that a free coordination site at palladium is required for alkene coordination within the initial aminopalladation.[8b,c]



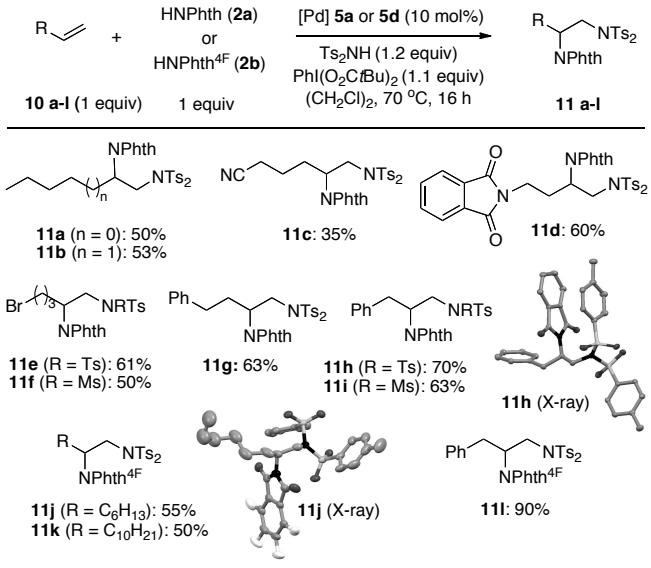
Scheme 5. Role of the phthalimide source in diamination of **(*Z*)-1** (above) and individual rates for diamination of **(*Z*)-1** with **5a** and HNPhth and $HNPhth^{4F}$, respectively.

In addition to the identification of complexes **5** and **7** as the catalysts providing the observed chemoselectivity, these complexes also improve existing diamination reactions. For example, the isolated palladium phthalimidato complexes catalyze the diamination of allylic ethers (Scheme 6). In comparison to earlier work,[20] which employed phthalimide as limiting agent with an excess of two oxidants (NFSI and hypervalent iodine), under the optimized protocol the reaction only requires phthalimide and a hypervalent iodine. In addition, the reaction can now be conducted with a limiting amount of alkene, which significantly improves the reaction attractiveness from an economic point of view. For all reactions, yields under the present conditions are superior to previous ones,[19] and even surpass those from an *in situ* catalyst formation. As demonstrated for substrate **8d**, the reaction can be up-scaled conveniently. Besides common allylic substrates **8a-g**, the scope could be enhanced to selective monodiamination of dienes (**9h-j**) or to the corresponding tetraamination reaction (**9k**). The reaction can be conducted with complete diastereoselectivity (**9l**). Higher-functionalized allylic ethers including epoxides and acetal substituents are also tolerated (**9m-p**).

More importantly, terminal alkenes, which according to our previous protocols required the use of saccharine as a nitrogen source,[20] can now be employed in the palladium-catalyzed diamination with more readily removable[13] phthalimide (Scheme 7). Examples include representative aliphatic alkenes **10a,b** for phthalimide and **10j,k** for tetrafluorophthalimide, respectively.



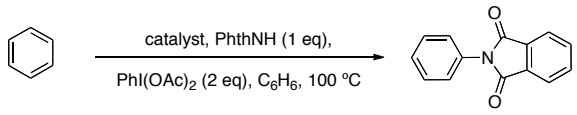
Scheme 6. Palladium catalyzed diamination of allylic ethers employing preformed phthalimidato complexes. [a] Yields in brackets refer to the outcome from the *in situ* conditions. [b] Yield from a 4 mmol scale reaction.



Scheme 7. Palladium catalyzed diamination of terminal alkenes employing preformed phthalimidato complexes.

Functionalized alkenes are equally tolerated (**11d-g**), including the nitrile **10c**. The latter is entirely non-reactive without preformed catalyst resulting in an alkene consumption by the iodine(III)-mediated background reaction.[18] Although still low in rate, the present reaction with **5a** occurs selectively within the Pd oxidation manifold. Finally, allyl benzene was employed as a substrate to demonstrate again that the present reaction conditions proceed without any detectable alkene isomerization. As a result, the present protocol substitutes the former saccharine variant, with the particular advantage of milder deprotection conditions for phthalimide.[13] All these examples demonstrate the advantage of preformed palladium phthalimidato catalysts in the difunctionalization of alkenes, where they currently provide the best protocols. Moreover, the new complexes should also be of value in additional catalytic transformations. The direct C-H amination of benzene was chosen to explore this assumption, and treatment of benzene with preformed complex **5a** led to clean formation of *N*-phenyl phthalimide **12** as the C-H amination product in 70% yield. This compares

favorably to a related transformation with a combination of palladium acetate and tris(*tert*-butyl)phosphine as catalyst, which provides **12** in only 30% yield (Scheme 8).[21]



catalyst:	**14**
$Pd(OAc)_2$(10 mol%)/P*t*Bu_3 (10 mol%), 24h	30%
$Pd(NPhth)_2(PhCN)_2$ **5a** (10 mol%), 12h	70%

Scheme 8. Palladium catalyzed C-H amination of benzene.

In summary, we have succeeded in the isolation and structural characterization of new palladium phthalimidato complexes and have demonstrated that these complexes greatly improve the scope of palladium catalyzed oxidative amination reactions.

Acknowledgements

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Keywords: alkenes • diamination • palladium • phthalimide • oxidation

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[13] See Supporting Information for details.

[14] X-ray crystallographic data for compounds **3b, 6**, **7**, **9l**, **11h** and **11j** have been deposited with the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under codes CCDC 885869 (**9l**), 885868 (**11h**), 885870 (**11j**), 1447007 (**3b**), 1447008 (**6**) and 1447009 (**7**), respectively.

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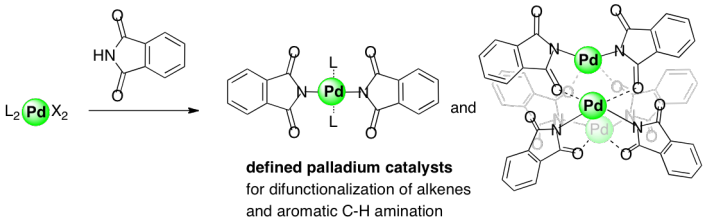

Coordination mission completed: free phthalimide forms stable monomeric or trimeric coordination compounds with palladium. These complexes serve as defined palladium catalysts for oxidative amination reactions with phthalimide as nitrogen source. Examples include the diamination and aminooxygenation of alkenes and the C-H amination of benzene.